Scuola Dottorale di Ateneo
Graduate School

Dottorato di ricerca
in Scienze Chimiche
Ciclo XXVII
Anno di discussione 2015

GREEN TRANSFORMATIONS OF BIO-BASED CHEMICALS

Tesi in co-tutela con The University of Sydney, Australia

SETTORE SCIENTIFICO DISCIPLINARE DI AFFERENZA: CHIM/06
Tesi di Dottorato di Alessio Caretto, matricola 825138

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ABSTRACT

This thesis work was focused on the development of green chemical technologies for the upgrading of platform molecules obtainable from renewable feedstocks through a biorefinery scheme. The feedstocks were chosen among those considered as the most promising for the development a new, sustainable, chemical industry.

Levulinic acid (LA) can be converted into new derivatives with a higher degree of oxigenation (methyl levulinate and its 4,4-dimethyl ketal, dimethyl succinate and dimethyl 3-methylsuccinate), without actually using oxidizing agents. This result was achieved by using dimehtyl carbonate (DMC), a green reagent and solvent, in conditions of basic catalysis (K_2CO_3).

Bio-derived lactones such as gamma-valerolactone, gamma-butyrolactone, delta-valerolactone and epsilon-caprolactone were reacted with three dialkylcarbonates (DMC, diethyl- and dibenzylcarbonate). The five-membered ring lactones yielded the corresponding alpha-alkylated derivatives with high selectivity and yields. The six- and seven-membered ringed lactones afforded highly oxygenated acyclic monomeric derivatives otherwise hardly accessible by previous chemistry.

Gamma-valerolactone was chosen as a model to study acid catalyzed ring-opening reactions. A novel reactivity of the molecule was discovered in the presence of DMC. The 4-methoxy pentanoyl moiety was thus accessible by a green route. A reaction mechanism, supported by experimental and computational data, was proposed. The reaction was then extended to a continuous flow process, with solid acid catalysts. In such conditions, the selectivity towards methyl 4-methoxy pentanoate or methyl pentenoate, monomer for the production of polymers, can be tuned by optimising the operating parameters.

Bio-derived diols were efficiently upgraded using organic carbonates in tandem with ionic liquids as organocatalysts. The study investigated the parameters that control the selectivity towards cyclic- or linear di-carbonates.

The derivatisation of fatty acids methyl ester in conditions of on-water catalysis was investigated whilst at the University of Sydney, with the aim of developing a green

strategy to reduce the cloud point of biodiesels. A new branched additive was synthesised, the thermal characteristics of which were analysed, both pure and blended with biodiesel.

The study of on-water catalysis continued by investigating the mechanism and the effect of reagent structure on on-water catalysis. It was demonstrated, by using the model reactions between cyclopentadiene (cp) and alkyl vinyl ketones, that little changes of the alkyl chain of a reactant have a dramatic influence on the catalytic effect. In particular, the reaction between ethyl vinyl ketone and cp was demonstrated to be on-water catalysed. When vinyl ketones bearing a longer or bulkier alkyl chain were tested, the catalytic effect was not observed, and the reactions were as fast as in neat conditions.

List of abbreviations

AE	Atom economy
AFEX	Ammonia Fiber Explosion
AFRL	U.S. Air Force Research Laboratory
APR	Aqueous Phase Reforming
BPR	Back pressure regulator
CE	Carbon efficiency
CF	Continuous flow
CFPP	Cold filter plugging point
CI	Cost index
CLA	Conjugated linoleic acid
CLAME	Conjugated linoleic acid methyl ester
COSY	Correlation Spectroscopy
CP	Cloud point
cp	cyclopentadiene
DA	Diels-Alder
DABCO	diazabicyclooctane
DALA	aminolevulinic acid
DAlC	Dialkyl carbonate
DBnC	Dibenzyl carbonate
DBU	Diazabicycloundecene
DEC	Diethyl carbonate
DFT	Density Function Theory
DMC	Dimethyl carbonate
DMFum	Dimethyl fumarate
DSC	Differential scanning calorimetry
DVL	δ-Valerolactone

E	Environmental factor
ECL	ε-Caprolactone
EG	Ethylene glycol
ESI	Electrospray ionization
EU	European Union
EWG	Electron withdrawing group
FAME	Fatty acid methyl ester
FCC	Flash column chromatography
GBL	γ-Butyrolactone
GC	Gaschromatography
GOST	Green Organic Syntheses Team
GVL	γ-Valerolactone
HMBC	Heteronuclear Multiple Bond Correlation
HMF	Hydroxymethylfurfural
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High pressure liquid chromatography
IL	Ionic liquid
LA	Levulinic acid
LA	Linoleic acid
LD	Lethal dose
LDA	Lithium diisopropylamide
MOF	Metal-organic framework
MS	Mass spectrometry
NAcS	Nucleophilic acyl substitution
NBA	N-bromoacetamide
NBM	N-butylmaleimide
NMR	Nuclear Magnetic Resonance
NPM	N-Phenylmaleimide
NPrM	N-propylmaleimide

NREL	National Renewable Energy Laboratory
NSW	New South Wales
OAME	Oleic acid methyl ester
P8881	Methyl-tri-n-octylphosphonium
PCC	Pyridinium chlorochromate
PET	Polyethylene terephthalate
PP	Pour point
PTSA	*p*-toluenesulfonic acid
PTT	Polytrimethylene terephthalate
RME	Reaction mass efficiency
ROP	Ring opening polymerisation
rt	Room temperature
S-1	Mass index
SA	Sorbyl acetate
SEM	Scanning electron microscope
SPR16	Slurry phase reactor
t,t-CLA	*trans,trans*-conjugated linoleic acid
t,t-CLAME	*trans,trans*-conjugated linoleic acid methyl ester
THF	Tetrahydrofuran
US DOE	United States Department of Energy
WCED	World Commission on Environment and Development

CONTENTS

1 | INTRODUCTION

1.1. Towards a new chemistry

It is doubtless that the global chemical industry is based on crude oil. It might be sometimes hard to recognize this fact, especially for those not in the field, but considering all the chemicals and materials produced, the conclusion is univocal. Concerns of the long term sustainability of our oil-based society have been raised in the last decades, mostly in view of peak oil production occurring in the near future; however crude oil running out is not the only issue directly related to its exploitation. As will be discussed in the following paragraph, various other issues are connected to petroleum, including social, economic (and political), and environmental ones. A simple example of the effect of oil prices on economics is represented by the ubiquitous plastic bottles. The price of their material (PET) depends directly on the price of crude oil, generating upheavals in the world of bottled drinks.

Figure 1.1. PET chip price in 2010.

This is the relatively small example; however the economy of any kind of industry is directly or indirectly connected to crude oil, being the latter the main source of energy and materials. Thus, the economy of entire nations may be shocked by significant changes in the crude oil price, also taking into account that reserves distribution is uneven.

The crude oil issue also poses another not immediately intuitive fact: many chemicals and materials are organic, *i.e.* based on carbon, and can therefore be produced only starting from either of two sources, fossil ones (crude oil, coal and natural gases) and biomass. Both of these resources are composed of organic material; the first generated by geological processes, while the second formed continuously, in a "renewable" way (see next paragraph). Until technology will be able to fix CO_2 efficiently, these two are the only options we have for the synthesis of organic chemicals. In this context, the transition from a fossil-based chemical industry to a renewable-based one is strongly advocated.

1.1.1. Crude oil and related issues

Crude oil prompted the industrial revolution and is at the basis of all the innovations that contribute to a higher standard of living. As already stated, it is doubtless that most organic materials and products that make our life better today derive from crude oil, either directly or indirectly. However, its exploitation is getting more and more problematic for a series of reasons, all connected with one another, which are summarised below.

- **Social reason: sustainability.**

"Sustainability" is a general term with many facets that should become a widespread concept. Over and above the intuitive meaning, an accepted definition was formulated during the World Commission on Environment and Development (WCED, also informally known as the Brundtland Commission), whose mission was to unite countries to pursue sustainable development together. The commission ended with the publication of the report "Our Common Future" (Figure 1.2), where the following definition was contained: *"Humanity has the ability to make development sustainable to ensure that it meets the needs of the present without compromising the ability of future generations to meet their own needs"*.[1] In this sense sustainability includes social, economic and environmental aspects.

In this context we want to point out the difference in sustainability between crude oil as a non-renewable feedstock and other, renewable, sources. The extensive use of petroleum that is not able to replace itself within the cycle of human generations belongs to a non-sustainable society. Crude oil demand has in fact been continuously increasing, in parallel with the human population and with the degree of industrialisation. Some argue

that peak oil has in fact been reached in 2005 (see Figure 1.3) and that production might decline in the forthcoming future.

Figure 1.2. Front cover of the report "Our Common Future". [1]

Even allowing that new sources of fossil organic feedstocks may be found (*e.g.* shale gas), the alternative is the use of renewable biogenic sources, and the development of technologies that will allow transformation and processing of these chemical feedstocks into useful products.

- **Economic reason: fluctuating price.**

Crude oil price has always fluctuated, in dependence of historical events which involved oil-producing countries or of major upheavals in the financial markets.[2] Such instability can cause financial problems; *e.g.* the price of oil is likely to have been a large contributor to the Euro crisis in southern Europe in 2007-08.[2-3] A powerful example of the effect of increasing oil prices can be seen in Italy. In 1999 the country's annual trade surplus was $22 billion. Thirteen years later the deficit was of $36 billion. Although many reasons contributed to this decline (including the rise of imports from China), the increase in oil price was the most important. Despite a decrease in imports of 388,000 barrels per day compared with 1999, Italy now spends about $55 billion a year on imported oil, up from $12 billion in 1999. That difference is close to the current annual trade deficit.[3]

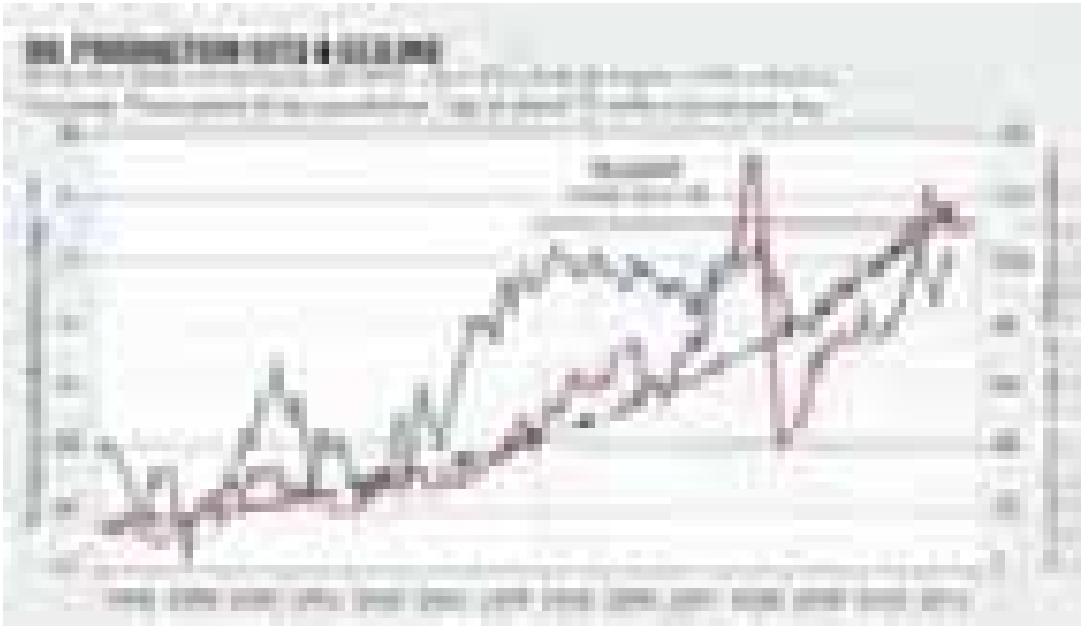


Figure 1.3. Crude-oil production and price between 1998 and 2011.[3]

Despite crude oil price affects primarily energy generation and transports, it must be consider the consequent impact on any activity. Besides this, all those companies that transform oil derivatives are strongly affected by fluctuant prices (an example was given in the first paragraph with the PET price).

- **Environmental reason: minimisation of wastes.**

Crude oil is the main world energy source, and in the past it boosted the industrialisation and the transportation sectors.

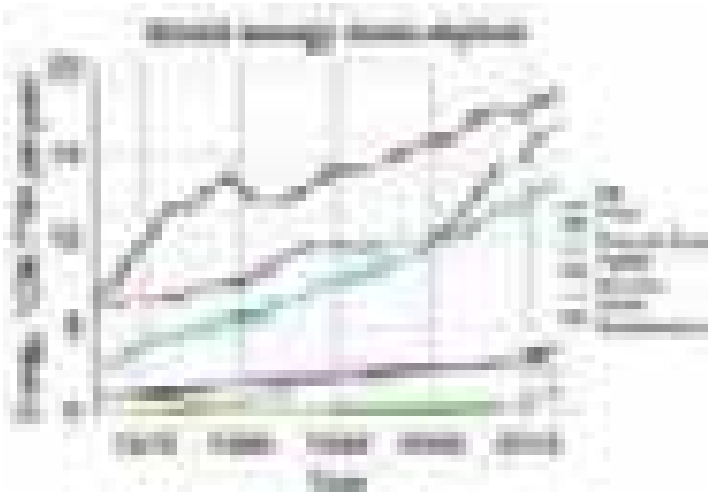


Figure 1.4. World energy consumption by source.[4]

Moreover it can be said that the development of organic chemistry itself went hand in hand with the discovery of petroleum and the development of the petrochemical

industry. The latter is intended as the conversion of individual compounds obtained from petroleum into different compounds, via various synthetic processing steps. To date most of the organic chemical industry is based on crude oil and its derivatives.[5] Crude oil as a source has two main environmental issues: (i) the inevitable release of CO_2, the main greenhouse gases, when it is used as an energy source; (ii) the necessity for dangerous and pollutant chemicals in many chemical transformations.

i. Crude oil, as well as coal and natural gas, is not a renewable source. It was formed over millions of years from organic material, remained trapped beneath the Earth surface, which underwent high pressure and high temperature conditions in absence of oxygen. It is basically a reservoir of hydrocarbons. Its combustion quickly oxidises the hydrocarbons, releasing large amounts of CO_2 in the atmosphere that cannot be all fixed by nature. It is estimated that since the beginning of the Industrial Revolution, the burning of fossil fuels (together with the extensive clearing of native forests) has contributed to a 40% increase in the atmospheric concentration of CO_2.[6-8]

ii. Being the crude oil components exclusively hydrocarbons, any other atom need to be introduced separately. Among all the possible chemical transformations, the most commonly performed are controlled oxidations, and these are the ones that generally use the most dangerous and polluting reagents. It is attractive to move away from such reactions.

1.1.2. Biofuels and bio-based chemicals

1.1.2.1.Biofuels

All the issues related to crude oil have directed research towards the exploitation of alternative feedstocks for energy and chemicals. Sustainability requires that these alternative sources should be renewable. Consequently energy research expanded to all the feedstock that could generate energy: solar power, water splitting, wind and hydro power, etc. However there is a limit in all the cited applications: they are all suited to produce electricity. This, coupled with the fact that the density (by volume and by weight) of energy storage in batteries is about two orders of magnitude lower than that of the fuels used currently in vehicles,[9] implies that efficiency of these renewable energy feedstocks is bound to be low.[10] Despite intense research into this field (developing flow-batteries[11-13]

and innovative Li-ion batteries[14] are likely to reduce the above mentioned gap by one order of magnitude),[10] the problem is not likely to be solved in the immediate future, even if issues directly connected to the energy production were disregarded.[11, 14-15] This is one of the reasons why biofuels have become very attractive in the last decades, inducing governments, *e.g.* in the EU, to enact laws in their support (Under the Directive 2009/28/EC on the promotion of the use of biofuels or other renewable fuels for transport, EU established the goal of reaching a 5.75% share of renewable energy in the transport sector by 2020 every Member State in 2020).[16] Another reason is the perspective for a country to achieve the energy independence, avoiding to depend from others that hold the great majority of fossil sources. A third reason why biofuels are attractive is that they consist of mixtures obtained by the transformation of biomass (biomass is organic renewable material like plants and algae; it will be described in detail in the next chapter), such as biodiesel (manufactured from vegetal oils) and bioethanol (generated from sugar). As such, biofuels have the advantage of being useable directly in the existing engines, or at least in blend with the traditional fuels.

Nonetheless, the ones mentioned (biodiesel and bioethanol) are considered as first-generation biofuels because they are made from crops that could potentially be food resources (see paragraph 1.2.2). Therefore ethical reasons make their use unattractive, if not outright unacceptable, in the long term. To sidestep this approach, which is contrary to the issue of world hunger, research is now focusing on non-food biomass as feedstocks. However there are a few issues even in this case: (i) enough land-based biomass for large volume production is not available; (ii) the production of biofuels is not economically advantageous yet; (iii) biofuels are not currently considered to be sufficient to satisfy the demand. Despite all of these points, it is still important to develop biofuels, as explained in the following section.

1.1.2.2. Biofuels as stepping stones towards new bio-based chemicals and products

Biofuels are compatible with existing internal combustion engines and represent therefore a short-term viable alternative to fossil-based fuels, in addition they may in principle contribute to an ideal closed carbon cycle, making them attractive from an environmental point of view (see Figure 1.5).[17]

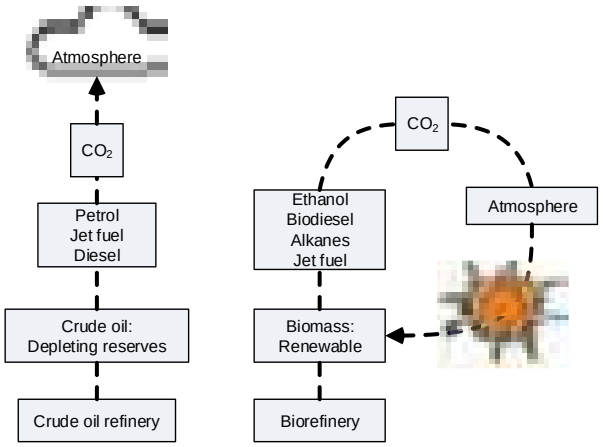


Figure 1.5. Comparison of the carbon cycle for oil-derived fuels and bio-derived ones.

A second more important point to be considered is the "chemical value" of biomass, *i.e.* its importance not only from an energetic point of view, but also considering a possible production of chemicals from renewable biomass sources.[18] It was suggested that by coupling the production of biofuels with the production of bio-based chemicals the economic problem could be overcome.[19] This concept is often described as the "integrated approach", and it is recognised as the final goal of the whole research on the topic of the use of renewable biomass feedstocks in substitution of fossil ones.[20] The integrated approach underlies this entire PhD project: biomass is the only existing source of renewable fixed carbon, *i.e.* in the future it will be the only available source for producing organic chemicals. Biomass research cannot however focus exclusively on its transformation into chemicals because there is the need for the short term economic incentive provided by biofuels. In fact, research on bio-derived chemicals gives significant results over the time, and very often it is not of immediate application, making this research less attractive for funding and investments. On the other hand, second generation biofuels do not appear to be economically sustainable by themselves. So the general concept of the paragraph is that biofuels are important as the economic driver that will promote research in the field of bio-based chemistry.

1.1.2.3.Bio-based chemistry

The rapid development of a new bio-based chemistry is challenged by two main facts, identified and described by Bozell and Petersen.[19]

1. "Lack of conversion technology". The bottleneck for development is the lack of conversion technologies for the chemical species obtainable from renewable

resources. It is the most difficult and least developed chemical technology, especially when compared to the technology underlying current petrochemistry.

2. "Over-abundance of targets". Research is still trying to identify a core group of primary chemicals that serve as the basis for the whole development. A rational selection processes for sorting the different opportunities needs to be developed.

A possible way to pursue the development of the new bio-based chemistry is to employ a target-based approach. At first sight the pre-identification of specific molecular structures appears like the simplest method, particularly in an industrial context. It has several advantages, such as identifying opportunities when prioritising research funds, and it can address "what if" questions when preliminary process variables are estimated. Indeed this approach was successful in the research on fuels, where a wide number of technologies were investigated in order to obtain a single target product by a "convergent" approach (see Figure 1.6, top).[19]

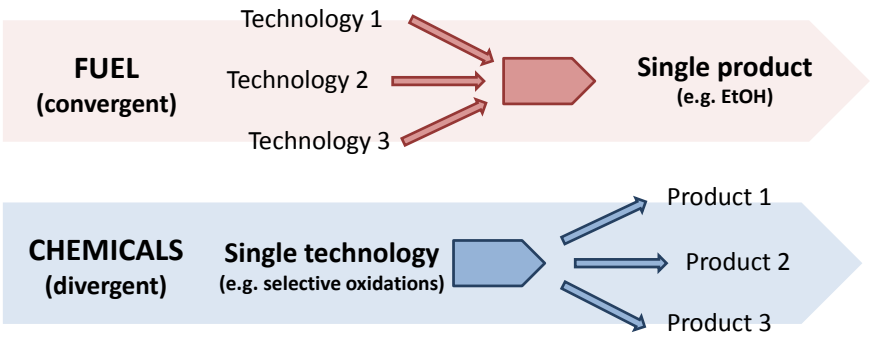


Figure 1.6. Research approaches towards the production of fuels and chemicals.[19]

On the contrary, the experience of the chemical industry shows that the complexity of the possible outputs is better handled by developing general technologies to produce multiple outputs in a "divergent" approach. The previous considerations suggested addressing research on bio-based chemicals via the development of general conversion technologies, which can be applied to wide a range of molecules. This is exactly the approach that we decided to apply to develop this research project.

1.1.3. Biomass

The word "biomass" has become quite popular in the last decades, in particular since alternative renewable sources for the production of energy and chemicals became a hot topic. However this term is often misused or, in case, used reductively. When looking for

"biomass" in a dictionary, one finds two definitions. The traditional meaning refers to the amount of living organisms per area, and is mostly used in environmental sciences. The second definition was introduced to account for the emerging concept of renewables. Here is how it appears in the Collins dictionary:[21-22]

"2. Vegetable matter used as a source of energy".

It is apparent that this is a very reductive definition which derives from the early use of vegetal sources in combined heat and power plants (so called biomass cogeneration plants). Biomass is better defined as:

"The biological material derived from living or recently living organisms".[23]

This basically includes all life forms on Earth (see Figure 1.7). This wide range can be refined focusing on the eukaryote domain, that includes plants, which we are more able to take advantage of (*n.b.* here we refer to the most recent classification according to Cavalier-Smith,[24] which is currently the most widely accepted).

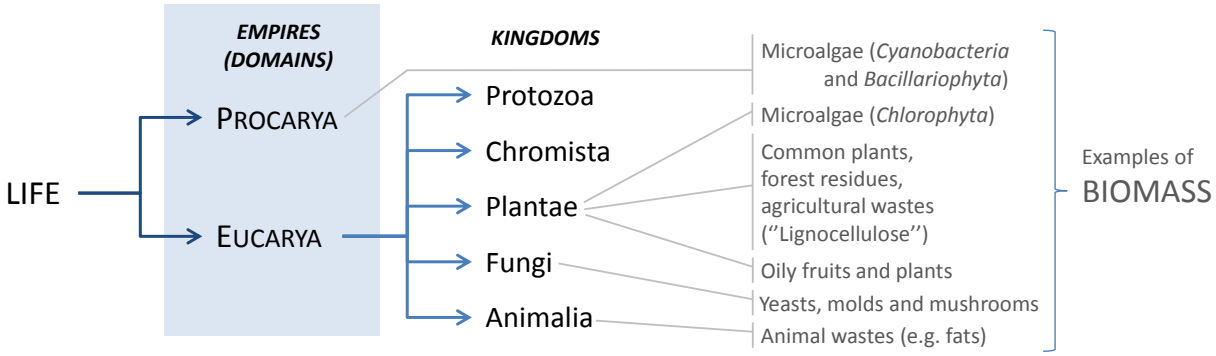


Figure 1.7. Life domains and kingdoms, with some examples of biomass sources.

Within the eukaryote domain, the majority of biomass derives from plants (kingdom *Plantae*), and is more precisely defined as "lignocellulosic biomass", in view of its structure that will be later described. Within this kingdom are also included aquatic plants, among which microalgae are becoming more and more attractive for biodiesel production. Microalgae include different classes of organisms: prokaryotes (*Cyanobacteria*), eukaryotes (*Chlorophyta*) e diatoms (*Bacillariophyta*). They are all characterised by their high lipid content, ranging from 20 to 70%, with some species reaching 90%. These photosynthetic microorganisms, thanks to their simple structure, are able to grow quickly and to live in various aquatic environments. In addition, since they grow in water they are not in competition with land-based crops. From these considerations it appears clear the interest

for this kind of biomass. Finally, even animal wastes represent a source that can be valorised, as well as fungi. This description should make evident that biomass is a wide concept, and that it cannot be reduced to vegetable matter. Nonetheless, as we already stated, the lignocellulosic biomass is at the moment the most abundant, easily available, and the most versatile. The next section describes its structure.

1.1.3.1.Lignocellulosic biomass

Lignocellulosic biomass is named after its major components: lignin, cellulose and hemicellulose. The relative abundance of these three polymeric components varies widely depending on the source (see Table 1.1). They form the constitutive structure of all the vegetal matter, being the substances of which the vegetal cells walls are formed. Each of them has a particular function, but the final aim is common: to give shape to the cells, together with robustness and good mechanical properties.[25]

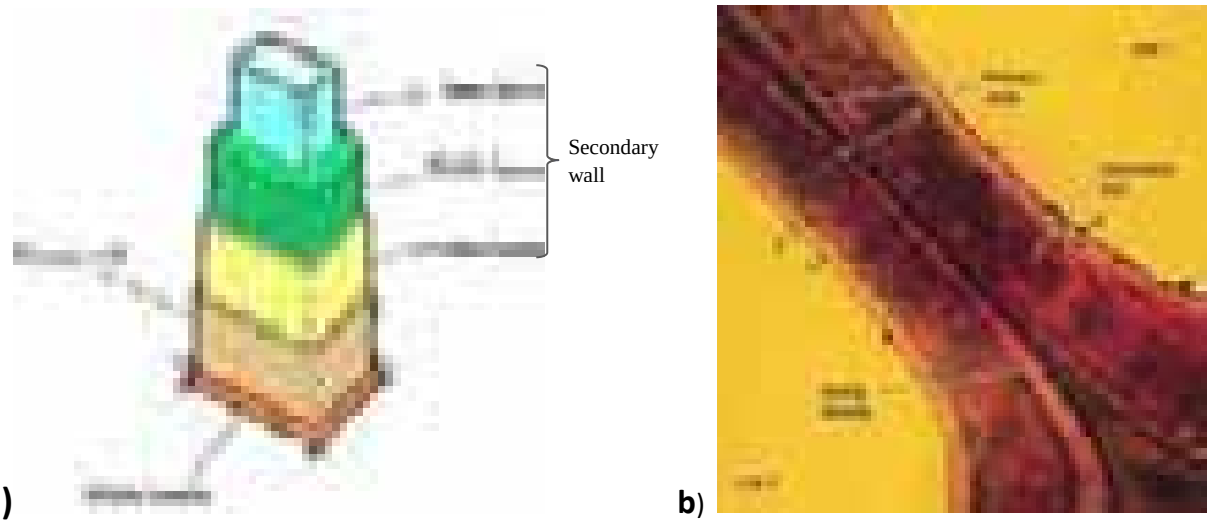


Figure 1.8. a) Exploded of the vegetal cell wall;[26] b) SEM image of the vegetal cell wall section.[27]

Cellulose, the main component of vegetal cell walls (and the most abundant biopolymer on Earth), is made exclusively of glucose (a hexose). The long polyglucosidic chains are interlinked by a multitude of H-bonds, giving to it a crystalline structure.[25] Thus, cellulose microfibrils (beams of polyglucosidic chains) act as supporting props of the cell. Such a structure makes cellulose very resistant to transformation. Cellulose can be broken down chemically into its glucose units by treating it with concentrated acids at high temperature (see paragraphs 1.2.3 and 1.2.4).[15, 28]

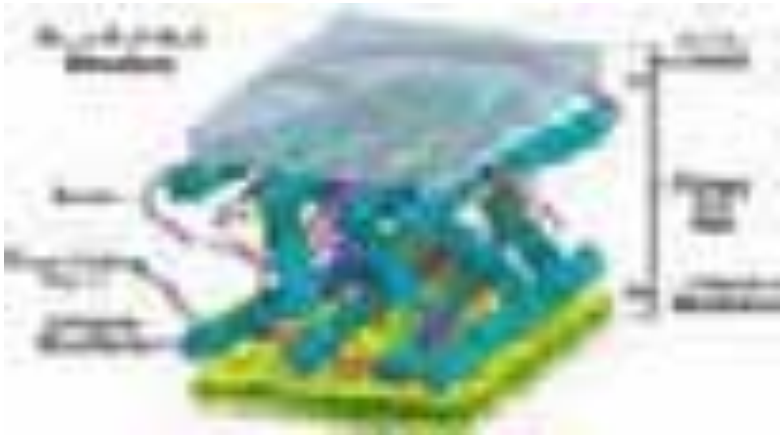


Figure 1.9. 3D cross-section of the vegetal cell wall (membrane and primary cell wall).

The term "**hemicellulose**" defines different saccharidic heteropolymers (for instance its sugar monomers can include xylose, mannose, galactose, rhamnose, and arabinose), which are branched and keep together the cellulose microfibrils. Its function is to increase the tensile strength of the cellulose, with the ability to resist compression.[25] While cellulose is crystalline, strong, and resistant to hydrolysis, hemicellulose has a random, amorphous structure with little chemical strength. It is easily hydrolysed by dilute acid or base as well as by numerous hemicellulase enzymes.[15, 28]

The last main component, **lignin**, is a phenolic polymer (monomeric units are called monolignols), that is located in the secondary cell wall (see Figure 1.8). It provides strength and rigidity to plant walls, while providing resistance to diseases, insects, cold temperatures, and other stresses. Also, lignin plays a crucial part in conducting water in plant stems.[25] It is the second most abundant biopolymer, exceeded only by cellulose.

Table 1.1. Percentage by weight of the three lignocellulose components in some materials.[29]

Material	Lignin (%)	Hemicellulose (%)	Cellulose (%)
Sugar cane bagasse	20	25	42
Sweet sorghum	21	27	45
Hardwood	18-25	24-40	40-55
Softwood	25-35	25-35	45-50
Corn cobs	15	35	45
Corn stover	19	26	38
Rice straw	18	24	32
Nut shells	30-40	25-30	25-30
Newspaper	18-30	25-40	40-55
Grasses	10-30	25-50	25-40
Wheat straw	16-21	26-32	29-35
Banana waste	14	15	13
Bagasse	23	16	55
Sponge gourd fibres	15	17	67

Lignin exploitation is not trivial because of its heterogeneity and lack of a defined primary structure. Nonetheless it is the only renewable source of aromatics, and research is currently focusing on its depolymerisation and transformation.[15, 28]

To conclude, Table 1.1 (see previous page) shows an example of the distribution of the bio-polymers here described in some common renewable materials.

1.2. The biorefinery concept

One approach to using biomass as a source of fuels and chemicals involves applying established concepts to the development of new technology and new products. An example is the concept of "biorefinery", in an analogy to the oil refinery.[30-31] In the oil refinery, crude oil, a complex mixture of hydrocarbons, is transformed into various derivatives in a facility that involves different transformation processes. The biorefinery uses new technologies to transform biomass (a complex mixture of carbohydrates and biopolymers) into a range of derivatives (see Figure 1.10).

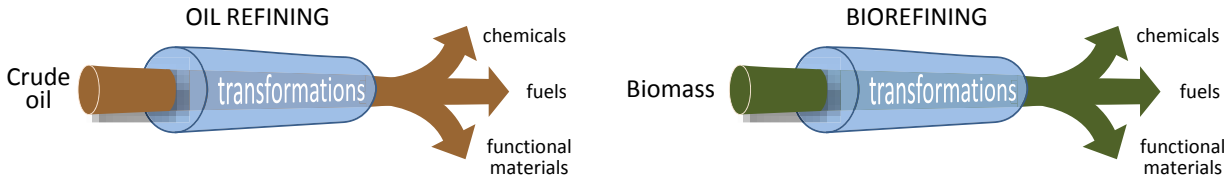


Figure 1.10. Schematic comparison of oil- and bio-refining.

This simple concept is attractive; however it is of difficult execution because, despite of the very similar approach of the two refineries, their transformation technologies will be very different. In addition in the case of biomass they still need to be optimised. At any rate, this concept should have as its final aim to develop a biomass-based chemistry: to develop technologies that can transform efficiently biomass feedstock into valuable products, such as chemicals, materials and fuels.[15, 19-20]

1.2.1. Biorefining vs crude oil refining

Taking a closer look at oil and biomass refining we can identify other similarities. The whole process can be divided in blocks:[32]

- Treatment and separation – They are needed at first for fractioning the initial material into simpler mixtures, subsequently to prepare a particular stream for

additional processing and prepare finished products. In the classic refinery they are just physical processes, which do not alter the molecular structure. On the other hand, in the biorefinery a little alteration of the molecular structure is needed from the beginning, being generally lignocellulose components kept together by chemical bonds. However the very first processes in the biorefinery scheme are aimed to the mere separation of the subunits, so they can be conceptually included here and compared to the distillations that are carried out in the classic refinery.

- Chemical conversion – These alter molecular structure to produce a wide range of products.[32] They include:
  - Fragmentation – the output is composed by molecules smaller than the input. In the classic refinery an example would be thermal and catalytic cracking; in the biorefinery depolymerisation.
  - Isomerisation (rearranging) – the output products have the same formula of the input, but their structure is different. This is carried out in the isomerisation and reforming units of the classic refinery.
  - Upgrading – the output products are more complex molecules than the input. It may happen through alkylation and polymerisation in the classic refinery; it could be the same in the biorefinery.[33-34]

The parallelism between oil refinery and biorefinery can be illustrated as in

Figure 1.11. At first the starting mixtures need to be separated into their components. This is achieved by distillation for crude oil, where the different fractions are classified depending of their boiling points. Biomass has to be first fractionated into its major components, cellulose (carbohydrate parts), lignin (phenolic part) and proteins. After this first step, chemical conversion follows through the processes briefly outlined above. Which pathway is followed depends on the target. It is beyond the scope of this thesis to describe each pathway of this complicated scheme. However it should be stressed that such an approach is functional to the development and implementation of the integrated biorefinery concept also from an economic point of view, because the possibility of obtaining different products makes it more profitable and resilient to fluctuation of the market demand.

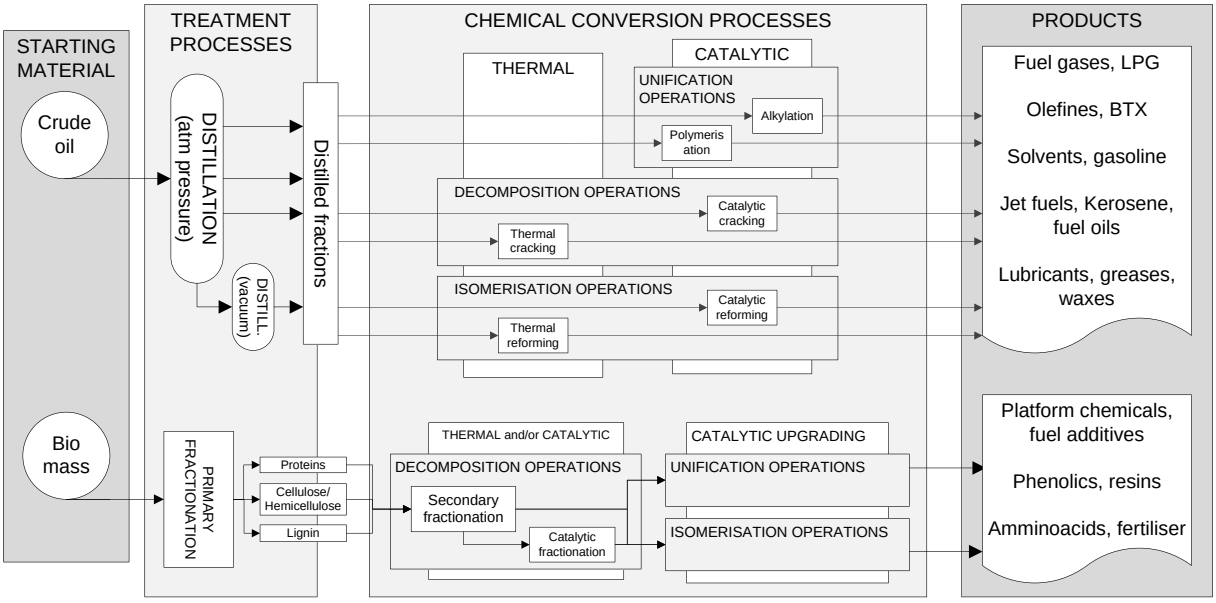


Figure 1.11. Schematic comparison of an oil refinery and a biorefinery.

As already mentioned above, the major difference between lignocellulosic biomass and crude oil is the degree of oxidation: while oxygen is almost absent in oil, it makes up about 40% the mass of a generic lignocellulose (Table 1.2). The molecular complexity and the high oxygen content of biomass derived chemicals can be seen as the main challenges in their handling and upgrade, but also as part of the work already done by mother nature. While selective oxidations are required to obtain chemicals from oil (Figure 1.12), on the contrary biomass is already highly oxygenated. Its exploitation allows the direct use of highly oxygenated molecules, while saving time, energy and money, as well as reducing risk and pollution.[5]

	Biomass (lignocellulose)[35]	Crude oil[36]
C	40-50%	84%
H	5-6%	14%
O	36-45%	<1%
N	0.5-3%	<1%
S	0.1-0.7%	1-3%
C	0.1-1%	<1%

Table 1.2

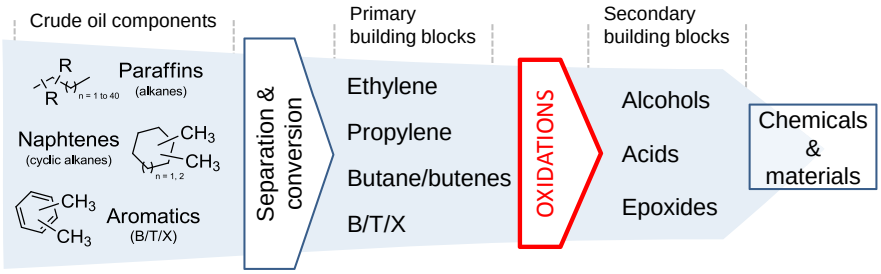


Figure 1.12.

Table: Comparison of the elemental analysis of a generic lignocellulosic biomass and a generic oil. Figure: Oxidation step in the pathway from crude oil to chemicals and materials.

1.2.2. Biorefinery: feedstocks

Even if the biorefinery concept is quite recent, it has already evolved since its first formulation (see Figure 1.13). This evolution has depended principally on the starting materials. The first biorefinery was designed around one type of a renewable feedstock to produce a defined product via an ad hoc process. This is considered the **phase 1 biorefinery**.[20]

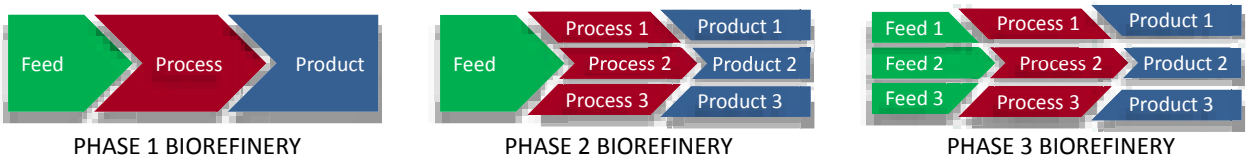


Figure 1.13. Evolution of the biorefinery concept.

Subsequently it was realised that such an approach was neither versatile nor sustainable enough from an economic point of view. The natural conclusion was that a facility should be able to produce more than one product to be competitive. To do so, a variety of different processes needed to be implemented within the same biorefinery. This is the **phase 2 biorefinery**.[20]

However the ideal refinery should also be able to process different sources, taking into account that one feedstock could be discontinued in favour of another, and that by including waste as a feedstock the feed composition could be variable. A facility that processes different feeds to obtain numerous products is called **phase 3 biorefinery**.[20]

The simple flow scheme shown below (Figure 1.14) will be used to facilitate understanding of where each component fits into the whole biorefining process.

Starting Materials

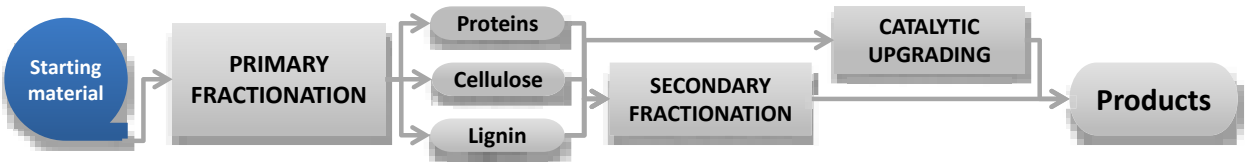


Figure 1.14. Biorefinery flow scheme: starting material.

Concerning the starting materials (Figure 1.14 in blue), a preliminary description was already given above while describing biomass. Here following we present a more detailed picture, by attempting to classify various feedstocks in function of their main product/s, uses, and origin.[18]

Table 1.3. Various sources of biomass, along with their main components and possible uses.

Class of biomass		Major components	Potential applications
Algal		triglycerides	Fuels and glycerol
Animal and vegetable oil wastes		triglycerides	fuels and glycerol
Vegetal	- Oily fruits and plants	triglycerides	fuels and glycerol
	- Easy processable carbohydrates	carbohydrates	ethanol and chemicals
	- Complex lignocellulosic	carbohydrates and phenolics	chemicals and fuel additives

Algae, and especially microalgae, have elicited attention in the last few years, in consideration of their high content of lipids, ease of processing (compared to other feedstock) and growth rates. Advances in biological (growth and harvesting) and engineering research (extraction and treatment) will likely make this feedstock very attractive in the future for the production of biodiesel.

A small portion of available biomass is represented by oily wastes. In particular vegetable oil waste and animal fats can be a good source of fatty acids for the production of biodiesel.

Vegetal biomass can also contribute as a source of triglycerides. It is well known that many fruits and seeds are high in these substances, and their processing is already well established. Besides that, some plants are intrinsically high in triglycerides, e.g. eucalyptus.

Vegetal biomass is of course primarily a good source of carbohydrates. These can be divided into two groups: easily processable and complex carbohydrates. The first group includes edible sources, like sugar cane and corn starch. These can be directly fermented or chemically processed after minor treatment. The second group includes the vast variety of lignocellulosic biomass, such as: agricultural crop residues, forest residues, industrial wastes (*e.g.* from the pulp and paper industry), energy plantations (*i.e.* fast growing trees and grasses that require low maintenance; examples are miscanthus and switch grass).

The competition with food sources

Table 1.3 shows a simple classification of biomass feedstock, obtainable from different sources. However some of these biorefinery feedstocks are actually also edible resources for humans. This represents an ethical issue as long as food shortage is still a major worldwide problem. Therefore, the development of new chemistry based on edible feedstocks must be considered as an ethical issues as well.[37] This concern can also be extended to the depletion of forest heritage and to the transformation of landscape due to the cultivation of crops for biofuels, and should be considered in a wider sustainability scenario. Nonetheless, it should be underlined that fundamental research must start from simple models that will allow to gain the necessary understanding of the underlying scientific aspects, in order to be able to deal with more complex substrates in the future. Thus, glucose contained in sugar and starch, and oils derived from fruits and seeds, should be considered as the necessary stepping stone toward the future development of the next generations of biofuels. In this context, a different classification was originally proposed for the biorefinery concept, based on the output, *i.e.* the obtainable biofuels:

- First generation biofuels - are produced directly from food crops, by extracting and processing the lipids or by producing ethanol through fermentation.
- Second generation biofuels - are produced from non-food crops (*e.g.* wood, food crop waste).
- Third generation biofuels - are based on improvements in the production of biomass. Examples are specially engineered energy crops such as algae.

More recently another generation was proposed:

- Fourth generation biofuels - are engineered energy crops aimed not at only producing sustainable energy, but also at capturing and storing CO_2 for their growth.[38]

This classification should not be confused with the previously discussed classification of the biorefineries.

1.2.3. Biomass primary treatment

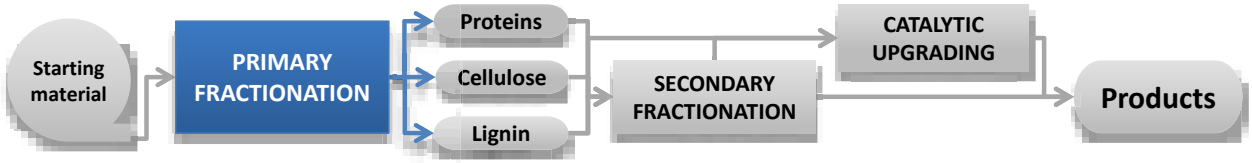


Figure 1.15. Biorefining flow scheme: primary fractionation.

The first biomass processing steps strongly depend on the nature of the feedstock and on the final product/s to be achieved. Any process involves an initial preparation step (grinding, drying, extracting, etc.). Next comes the core of the process, *i.e.* conversion of the pretreated biomass by thermo-chemical, bio-chemical and chemo-catalytic methods (this is generally referred as pretreatment or primary fractionation). The variety of pretreatment and conversion processes is very wide depending on the feedstock, thus we will focus on lignocellulosic biomass processing.

Lignocellulose processing. As lignocellulosic biomass is a complex mixture of materials it requires a set of diverse processing steps. In the simplest case, when lignocellulose is used solely to produce energy or fuels, thermal processing can quite readily provide the desired outcome. This is the case of pyrolytic treatments, in which temperatures in the 600-800 °C range are applied. Depending on the conditions, different types of pyrolysis, gasification and torrefaction are used to produce gaseous, liquid or solid fuels.[39] The selectivity of the mentioned processes is generally low: for example, the liquid produced in pyrolysis, so called "bio-oil", is an acidic combustible liquid containing more than 300 compounds.[39-40] In these cases the products are intermediates that have to be further upgraded to fuels via catalytic treatments, *e.g.* hydroprocessing, cracking, reforming, methanation, Fischer-Tropsch.[15]

In alternative, lignocellulose can be degraded by a pool of hydrolytic and oxidative enzymes.[41] In this case however rate is too slow for industrial application. Bio-chemical technologies become more important in the further steps, when simpler conversions are performed, and high selectivity towards particular products are desired.

When a physical or chemical pretreatment of lignocellulose is instead considered, its role must be to alter the physical features and chemical composition of the feedstock, along with its reactivity and solubility, in order to make the product stream prone to further transformations (see Figure 1.16).

Different transformations of the native lignocellulose, yielding different product streams can be achieved, by different pretreatment technologies. The kind of pretreatment depends on what is required for the next steps of the process. Generally any pretreatment will aim at obtaining any of the following conditions: separating or altering lignin, separating hemicellulose, altering the crystalline structure of cellulose, removing the acetyl groups from hemicellulose, reducing the degree of polymerisation in cellulose and swelling the structure to increase pore volume and internal surface area.

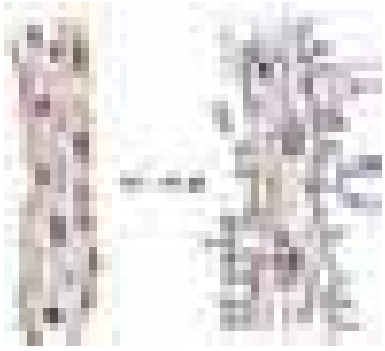


Figure 1.16. Representation of the pretreatment effect on the lignocellulose structure.

Typically, a combination of physical and chemical treatment is required to obtain these results. Below are listed the most common pretreatment methods.[15, 42]

- Acid hydrolysis – A dilute acid in combination with high temperature is commonly used. Treatments based on concentrated acid/low temperature are being abandoned due to the related issues. Industrially a dilute sulfuric acid process is widely used (acid conc. 0.5-1.5%, 120-180 °C, residence time 5-30 min, pressure 5-15 atm). Acid treatments are effective on hemicellulose solubilisation, while cellulose and lignin need further treatment (either acid again or different).

- Hydrothermal – There is a variety of technologies. Some based on autohydrolysis, that takes place when biomass is heated in the presence of steam-saturated water and of the acids are generated *in situ* a temperatures in the range 200-250 °C. Among these treatments, steam explosion is a popular one. When autohydrolysis is followed by rapid pressure release, the liquid water inside the biomass explosively vaporises, shredding the material and increasing the surface area. Generally these processes remove most of the hemicellulose and alter the lignin structure.

- Alkaline – These can be divided into two major groups: those that use hydroxides (sodium, potassium or calcium), and those that use ammonia. Calcium hydroxide

(lime) is the most economic method. Low-lignin biomass (12-18%) is fractionated by simply boiling in saturated lime water solution. A higher content of lignin requires more severe conditions.[43-44] This first series of processes are mainly effective on lignin solubilisation. In the "ammonia fiber explosion" process (AFEX) the alkali is used in combination with the steam explosion. [45-46] This process is less effective than hydroxides in lignin solubilisation, but it alters the crystalline structure of cellulose, rendering it more digestible.

- Wet oxidation – a mixture of water, oxygen and a base (typically NaOH), is used at high temperatures and pressures, causing the selective removal of lignin and hemicellulose. The latter and cellulose however generally remain in their solid polymeric form, and need further processing.[47-49]

As a general rule, alkali-based processes are more effective for lignin solubilisation, whereas acid or hydrothermal processes exhibit high hemicellulose solubilisation (rendering it in oligomeric form) and some cellulose depolymerisation.[15] Enzymatic treatments are an alternative to process the oligosaccharides obtained from hemicellulose or cellulose, provided that the latter was altered enough from the previous treatment. Figure 1.17 briefly summarises the pretreatment technologies described above. The flow chart on the left shows the viable pathways for biomass fractioning, while the area chart on the right shows an approximate polymeric composition after the described pretreatments.[42]

a b

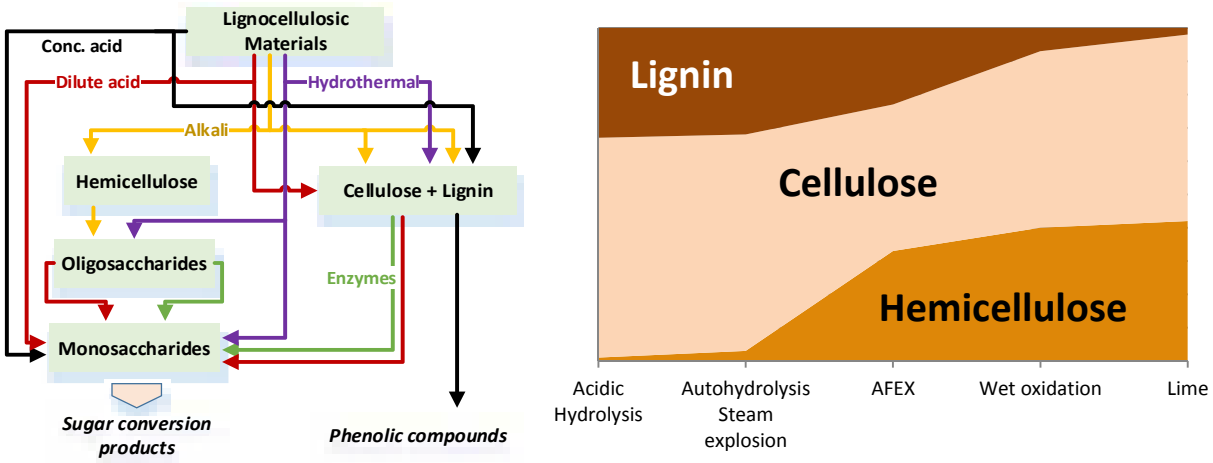


Figure 1.17. a) Main options for hydrolysis processes in biomass fractionation; b) Typical polymeric solids composition after biomass pretreatment as a function of reaction pH.[42]

1.2.4. Biomass secondary treatment

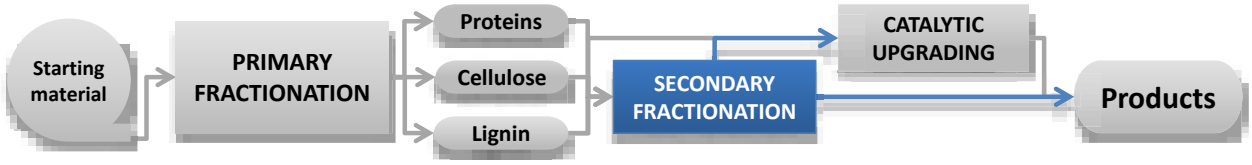


Figure 1.18. Biorefining flow scheme: secondary fractionation.

The second important process in a biorefinery aims to further simplify the mixture deriving from the primary fractionation. This is accomplished mainly via depolymerisation of the various components previously separated in the pretreatment. For this reason it is known as secondary fractionation. Every component requires a separate dedicated process, being their structure different. Cellulose and hemicellulose are converted to small oligomers and sugars, together with furans, via catalytic depolymerisation/hydrolysis. Lignin instead is generally separated from the mixture. As it was previously described, its structure is significantly different form the two sugar polymers, hence it requires a dedicated process to be transformed in phenolic compounds or eventually used as source of energy. For example, currently lignin can take to form of "black liquor" as in the Kraft process and be burnt for energy. Hemicellulose and cellulose can be efficiently depolymerised, and the current transformation processes are getting more and more efficient. Instead, good technologies for lignin conversion are still under study and development. The major problems come from its widely variable composition of the polymeric fraction, which leads to a plethora of phenolic compounds. Despite this issue it is a very attractive source of renewable aromatics.

Cellulose can be hydrolysed in water by attack of the electrophilic hydrogen atoms in the H_2O molecule on the glycosidic oxygen. This reaction is slow, hence an acidic catalyst needs to be used. Nonetheless, the crystalline structure is very resistant to water penetration, and this is the main reason why high temperatures (and consequently pressures) are applied in the acid hydrolysis of cellulose. Currently diluted sulfuric acid is the catalyst that provides better results. Other solid acid catalysts have around half of the

activity of H_2SO_4 (Figure 1.19). Other materials having an improved contact with cellulose, in order to improve the performances, are a hot research topic.

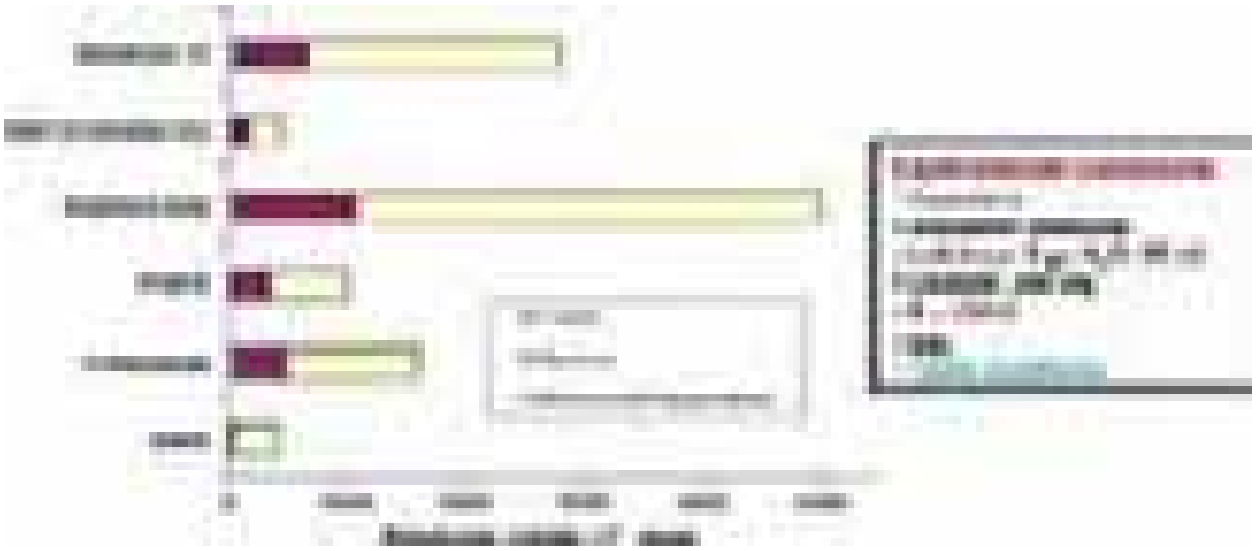


Figure 1.19. Product yields in the hydrolysis of crystalline cellulose in water using different acid catalysts.

The depolymerisation of cellulose and hemicellulose gives oligomers, sugars and furfural as products, while lignin, treated separately, can give phenolics. The first can already be efficiently produced. Moreover, considering that among the sugars glucose is the most abundant, the possible outcomes are limited and generally simple to be further processed. On the other hand, lignin is formed by many different subunits of substituted phenols. This fact, in parallel with the complicated depolymerisation step, makes it more difficult to be exploited. As a matter of fact, while research on sugars conversion is already in an advanced stage, lignin conversion is still in its early days. For these reasons, in the next paragraph the description will be focused on sugar derivatives, which were chosen for most of this thesis work.

1.2.5. Platform chemicals from biomass

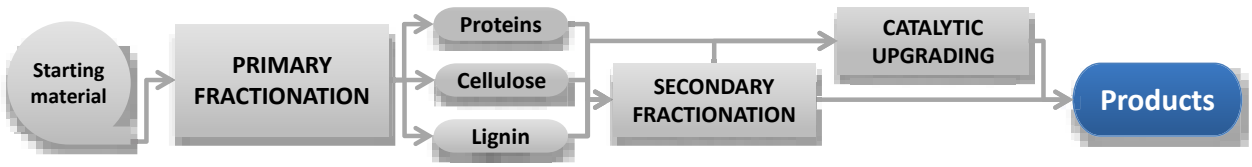


Figure 1.20. Biorefining flow scheme: products.

The intermediates obtained by the primary and secondary treatments (sugars for the great majority) can be further processed to yield a series of small molecules. These are called "platform chemicals". Such a name indicates molecules that can be used directly as commodity chemicals, and they can serve as platforms for further upgrading to other value added compounds.

There are three main pathways to convert this pool of sugars and polyols obtained from secondary fractionation: (1) fermentation, (2) chemical dehydration and (3) aqueous phase reforming (APR).

(1) Fermentation processes

Fermentation of the sugars can lead to two main groups of compounds: alcohols and carboxylic acids. A list of the main products is reported in Table 1.4.

Table 1.4. Chemicals obtainable from saccharides by fermentation. In bold the most promising ones.

PLATFORM CHEMICALS				
Acids and alcohols				
C2 Acetic acid Ethanol Oxalic acid *C3* 1,2-propanediol 1,3-propanediol **1,3-hydroxypropionic acid** **Lactic acid** Propionic acid	*C4* 1,4-butanediol 3-hydroxybutyrolactone Acetone Aspartic acid Butanol Fumaric acid Malic acid **Succinic acid**	*C5* **Itaconic acid** Levulinic acid Xylonic acid *C6* 2,5 Furandicarboxylic acid Citric acid Gluconic acid Sorbitol	*Amino acids* **L-glutamic acid** L-lysine L-threonine L-tryptophan *Other Chemicals* Acetone Vitamins Pigments Long chain dicarboxylic acids	

These compounds are formed by the metabolism of microorganisms such as bacteria and saccharomycetes (yeasts), which includes fermentation and cellular respiration. Both are oxidative processes, needed for the production of energy. The difference is that in the first one the final electron acceptor is an organic compound (mostly carbohydrates), while in the second one it is an inorganic species (if oxygen it is called aerobic respiration, if another species, e.g. sulphate ion or nitrate ion, it is called anaerobic). However all the processes to produce chemicals via microbial activity are commonly defined as

"fermentation processes". The generation of a single molecule is maximised by choosing a particular microorganism or by genetically engineering a suitable organism.[50-52]

(2) Chemical dehydration processes

Thermo-chemical dehydration of pentoses and hexoses in acidic media leads to the formation of two important chemicals: furfural (2-furancarboxaldehyde) arising from the loss of 3 water molecules from pentoses, 5-hydroxymethylfurfural (HMF) arising from the loss of 3 water molecules from of hexoses (Figure 1.21). This is the "furfural fraction".

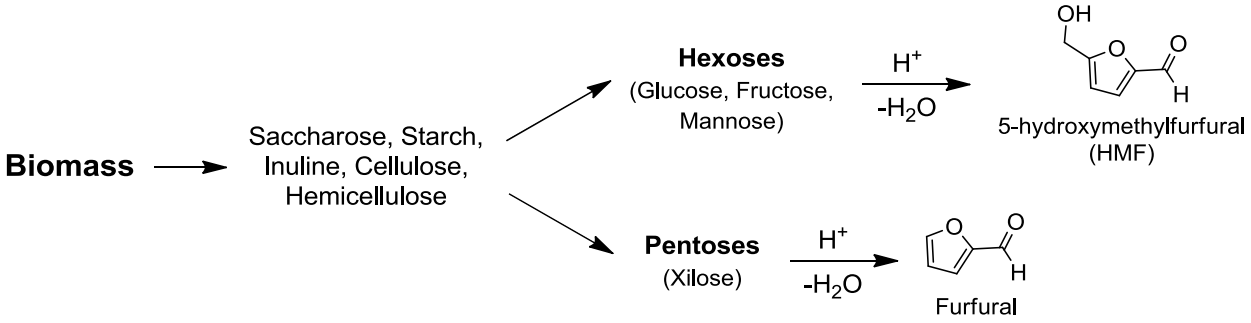


Figure 1.21. Acid dehydration of hexoses and pentoses leads to HMF and furfural respectively.[28]

Being hexoses the most naturally abundant sugars, the deriving HMF has been widely studied in its mechanism of formation and in its production methods.[53-55] HMF formation is formed through a triple dehydration process, either via the linear form of glucose (path I, Figure 1.22) or via the furanosidic form of fructose (path II, Figure 1.22).[53, 56-58]

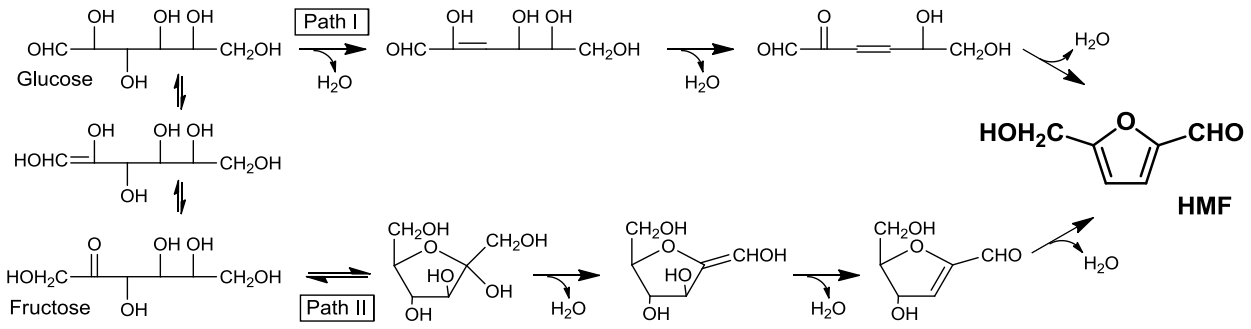


Figure 1.22. Acid mediated dehydration of glucose/fructose to HMF.[28]

HMF can be further converted to levulinic acid, one of the platform chemicals that attracted our attention, in view of its reactivity and wide field of application.[59] This molecule, its production and its possible uses will be discussed in a dedicated chapter (see chapter 2). Table 1.5 summarises the platform chemicals obtainable via chemical

conversion of glucose/fructose (glucaric acid and sorbitol are obtained via catalytic oxidation of saccharides, however they were included in this group being a chemo-catalytic process as well).

Table 1.5. Chemicals obtainable via chemical conversion of sugars. In bold the most promising ones.

PLATFORM CHEMICALS	
C4 3-hydroxybutyrolactone	*C5* **Levulinic acid** **Furfural**
C6 2,5 Furandicarboxylic acid **5-Hydroxymethylfurfural**	Glucaric acid Sorbitol

(3) Aqueous phase reforming (APR)

Water soluble sugars can be catalytically converted to liquid alkanes via aqueous phase processing. Liquid fuels are thus produced, equivalent to those currently derived from petrol. APR of sugars is typically carried out at lower temperatures (*e.g.* 230 °C) compared to pyrolysis, liquefaction or gasification. However, whereas these latter can operate with complex substrates, APR is only suitable for simple mixtures of sugars or polyols. When starting from lignocellulose, the pretreatments described above are strictly necessary in order to prepare a proper feed solution (that is why we chose to mention the process in this section). On the other hand the ease of separation of the alkanes from the aqueous feed boosts the process efficiency.[60-62] Virent Inc. has developed the BioForming® process[63] that is based on a combination of APR with catalytic processing. In March 2010 Virent and Shell built a demonstration plant (declared productivity of 38000 l/y), based on the BioForming® process, in Madison (WI). In May 2013 Virent announced the delivery of 380 l of its bio-based jet fuel to the U.S. Air Force Research Laboratory (AFRL) for testing purposes.[64] Finally, Licella developed a process that uses a supercritical water technology (Cat-HTR®) to transform lignocellulose (e.g. Radiata Pine sawdust) in what they call "Bio-Crude oil"; the latter can be processed into traditional refineries blended with normal crude oil.[65] Their pilot plant, opened in Somersby (NSW) in 2011, has been running for over three years.[66]

1.2.5.1. Most promising platform chemicals from biomass

In paragraph 1.1.2.3, "Bio-based chemistry", a desirable approach towards a new chemistry based on biomass derivatives was described. It was stated that among the limitations to a rapid development, was the overabundance of targets, i.e. it is not clear towards which products it is more convenient to direct research yet. Some efforts were made in this sense, in an attempt of sorting out the complex scenario of all the compounds obtainable from biomass. A first, important screening was commissioned by the US DOE (United States Department of Energy) to the Pacific Northwest National Laboratory (PNNL) and the National Renewable Energy Laboratory (NREL). In 2004 the report "Top value added chemicals from biomass" was published.[67] It was the first time that a systematic and detailed classification of the potential platform chemicals was made. A series of criteria were progressively evaluated, following a precise flow schemed selection strategy.

US DOE's screening was the only report of its kind until 2010, when Bozell and Petersen published a review with the subtitle "the US Department of Energy's Top 10 revisited", proposing a new list in consideration of advances in bio-based product development since 2004.[19] Table 1.6 shows a comparison between the two lists of the most promising chemicals obtainable from biomass. Differences are shown in italic.

Table 1.6. Comparison between US DOE's and Bozell & Petersen's top bio-derived chemicals.

US DOE top platforms[67]	Bozell & Petersen revision[19]
Aspartic acid	
2,5-Furan dicarboxylic acid	*Biohydrocarbons (e.g. isoprene)*
3-Hydroxybutyrolactone	*Ethanol*
3-Hydroxypropionic acid	Furans (e.g. furfural, HMF, etc.)
Glucaric acid	Glycerol and derivatives
Glutamic acid	Hydroxypropionic acid/aldehyde
Glycerol	*Lactic acid*
Itaconic acid	Levulinic acid
Levulinic acid	Sorbitol
Sorbitol	Succinic acid
Succinic, *fumaric and malic acids*	Xylitol
Xylitol/*arabinitol*	

1.3. Green chemistry to drive the change

Sustainable development should be an unavoidable human endeavour. Until this point focus has been mainly on the sustainability of the sources, thus on the concept of "renewable" (see paragraph 1.1.1). However sustainability is not only matter of sources, but also of means. More explicitly, the use of renewable sources will not be sustainable unless transformation processes will be sustainable as well. From the chemical point of view this issue is taken into account by "green chemistry". Green chemistry has been defined as a philosophy of chemical research and engineering that targets the design of products and processes that minimises the use and generation of hazardous substances.[68-69] The concept can be further generalized by saying "… that minimises the use and generation of substances", and more simply it could become "a philosophy of chemical research and engineering that strives to obtain the best with the least, avoiding hazardous species". This discipline is not just a definition: precise principles (the so called "twelve principles of green chemistry" and "twelve principles of green engineering") were listed as a set of rules to follow when doing chemistry or designing a chemical process. In order to underline the general philosophy of optimisation, the 24 principles were condensed in the mnemonic acronyms of "IMPROVEMENTS" and "PRODUCTIVELY".[70]

Table 1.7. The 12 principles of Green Chemistry and the 12 principles of Green Engineering.

	Principles of Green Chemistry		**Principles of Green Engineering**
P-	Prevent wastes	**I-**	Inherently non-hazardous and safe
R-	Renewable materials	**M-**	Minimise material diversity
O-	Omit derivatisation steps	**P-**	Prevention instead of treatment
D-	Degradable chemical products	**R-**	Renewable material and energy inputs
U-	Use safe synthetic methods	**O-**	Output-led design
C-	Catalytic reagents	**V-**	Very simple
T-	Temperature, Pressure ambient	**E-**	Efficient use of mass, energy space & time
I-	In-Process monitoring	**M-**	Meet the need
V-	Very few auxiliary substances	**E-**	Easy to separate by design
E-	E-factor, minimise feed in product	**N-**	Networks for exchange of local mass&energy
L-	Low toxicity of chemical products	**T-**	Test the life cycle of the design
Y-	Yes it's safe	**S-**	Sustainability throughout product life cycle

Therefore by combining the green chemistry approach with the use of renewable feedstocks one would be moving towards the green biorefinery concept . Figure 1.23 shows a simple diagram, where green chemistry intersects oil refining and biorefining.

While the intersection with the first allows to obtain a more sustainable petrochemistry, the second intersection indicates the green biorefinery.

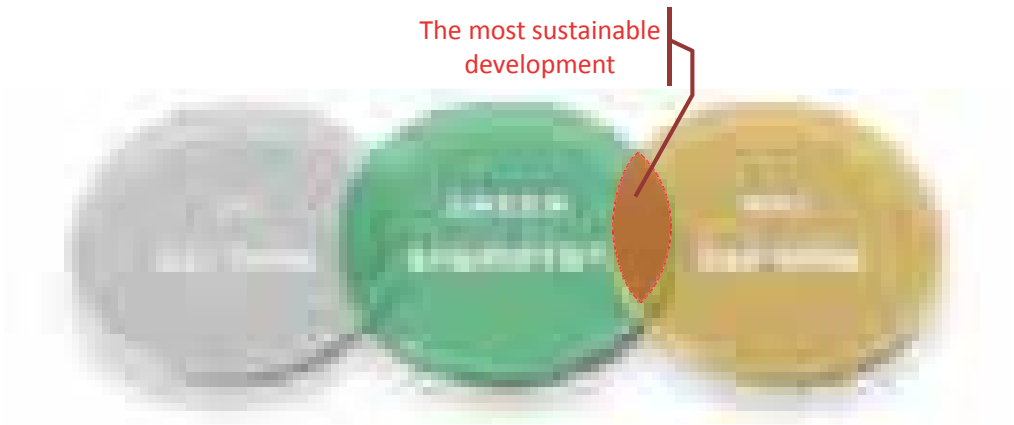


Figure 1.23. The interplay between green chemistry and the refining technologies.

Green chemistry has developed over the last two decades, and as a result a very large "toolbox" of green technologies is now available, based 24 principles, as well as on green metrics, green reagents, green processing technologies, green solvents, etc.. some of the green chemistry tools employed in this PhD thesis research project are described below.

1.3.1. The green chemistry toolbox

1.3.1.1.Metrics

Before introducing the actors on the green chemistry stage, it is worth to define some practical guidelines that allow to better evaluate the greenness of a reaction/process. The 24 principles give some general guidelines for the development of a green process, however they are mainly qualitative. For this reason mathematical methods were developed for a more quantitative evaluation. They were successively called green chemistry metrics, since they can be used as a measure of the greenness of a transformation, and, more important, to compare different transformations that aim to the same result. The most commonly used are listed in Table 1.8.

Most metrics are a ratio between the amounts of reagents and the quantity of product. Thus, atom economy (AE) considers the molecular weights and the reaction stoichiometry,[71] while the reaction mass efficiency (RME) is based on all the involved masses in kg.[72] The carbon efficiency (CE) does the same thing, but using only the element carbon in the calculation.[72]

Table 1.8. Most common green chemistry metrics.

Metric		Formula
Atom economy[71]	**AE**	$\mathrm{AE} = \frac{\text{M. W. product}}{\sum \text{M. W. reagents}} \cdot 100$
Reaction mass efficiency[72]	**RME**	$\mathrm{RME} = \frac{\text{mass of product [kg]}}{\sum \text{mass reagents [kg]}} \cdot 100$
Carbon efficiency[72]	**CE**	$\mathrm{CE} = \frac{\text{carbon mass in product [kg]}}{\sum \text{carbon masses in reagents [kg]}} \cdot 100$
Mass index[73]	**S^{-1}**	$S^{-1} = \frac{\sum \text{reagents} + \text{solvents} + \text{catalysts [kg]}}{\text{product [kg]}}$
Environmental factor[74]	**E**	$\mathrm{E} = \frac{\text{total waste [kg]}}{\text{product [kg]}}$
Cost index	**CI**	$\mathrm{CI} = \frac{€}{\text{kg}}\text{ of product}$

All these metrics are expressed as a percentage, and basically express how much matter is preserved passing from the reagents to the products. Differently, the last three metrics in the table are indexes, normalised per kilogram of product. The first one, mass index (S^{-1}; also referred as mass intensity, MI), considers all the matter used in the whole process to make the final product, thereby including not only the reagents but also solvents, catalysts and everything else necessary.[73, 75] On the other hand, the environmental factor (E) measures the amount of waste generated while preparing a product.[74] Finally the cost index (CI) expresses the cost of a kilo of product.

1.3.1.2. Organic carbonates

Over the last two decades, organic dialkylcarbonates have gained attention as green reagents, starting from dimethyl carbonate (DMC), the parent of this class of compounds.

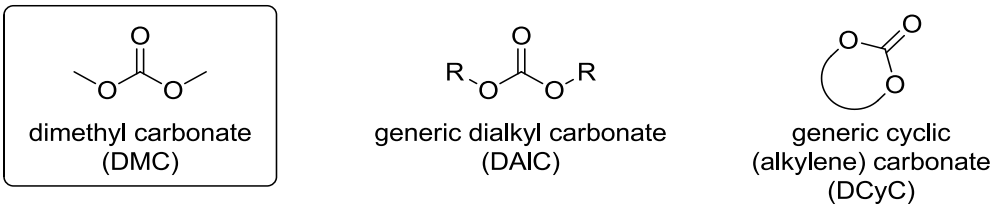


Figure 1.24. DMC and examples of generic alkyl carbonates.

The interest in these compounds derives from their properties, which can be categorized as follows:

- ❖ safety and toxicological properties;
- ❖ reactivity and production;
- ❖ physical and solvent properties.

All these factors contribute in making DMC and the higher homologues attractive from a green perspective.

Safety and toxicological properties

Organic carbonates generally have low toxicity, mostly when compared with other reagents used for similar reactions. DMC in particular is non-toxic (Table 1.9), and is merely classified as flammable.

Table 1.9. Eco-toxicological data of DMC.

oral acute toxicity (rats)	LD50 13.8 g/Kg
acute toxicity per contact (cavy)	LD50>2.5 g/Kg
acute toxicity per inhalation (rats)	LD50 140 mg/L; (4 h)
mutagenic properties	none
irritating properties (rabbits, eyes, skin)	none
biodegradability (OECD 301 C)	> 90% (28 days)
acute toxicity (fish) (OECD 203)	NOEC 1000 mg/L
acute toxicity on aerobial bacteria of wastewaters (OECD 209)	EC50> 1000 mg/L

Other carbonates that were used in this work are diethyl carbonate and dibenzyl carbonate. Their toxicity data are not as good as DMC, nor as complete. Nonetheless DEC (liquid) is classified as flammable and irritating but not toxic, while DBnC (solid) is harmful if swallowed (its toxicity was assessed as category 4, LD ~ 2 g/kg, so still low).

Reactivity and production

The early success of DMC was due to its properties as methylating and carboxymethylating agent. Conventionally such reactions are carried out using methyl iodide or dimethyl sulphate in the first case, phosgene in the second(Scheme 1.1).

Methylation

$$NuH + CH_3I + MOH \longrightarrow NuCH_3 + MI + H_2O$$

$$NuH + (CH_3)_2SO_4 + MOH \longrightarrow NuCH_3 + MCH_3SO_4 + H_2O$$

Carbonylation

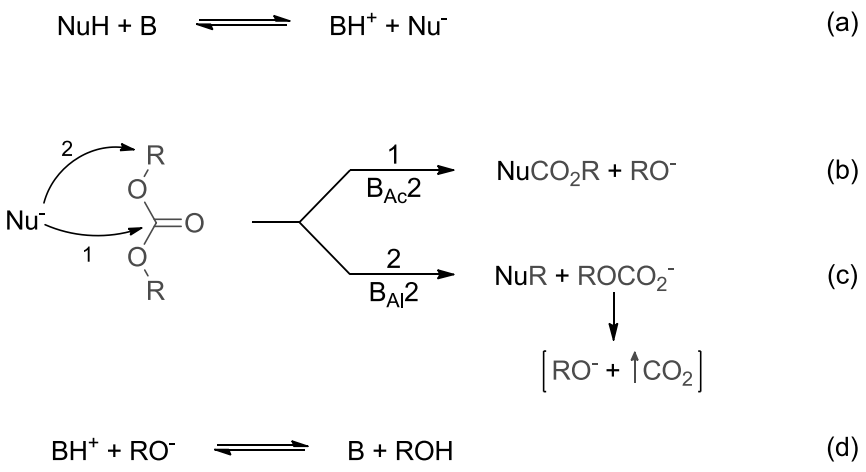
$$NuH + COCl_2 + MOH \longrightarrow NuCOCl + MCl + H_2O$$

Scheme 1.1. Classical methylation methodologies.

However these procedures have several drawbacks which make them undesirable from a green point of view: i) the methylating and carbonylating compounds are highly toxic and corrosive; ii) stoichiometric amounts of bases are needed, with the consequent

production of stoichiometric amounts of salts; iii) organic solvents are required to ensure homogeneity and heat-control; iv) the reactions are highly exothermic, and an accurate control is needed. [76]

On the other hand DMC can be efficiently used to methylate and carboxymethylate numerous nucleophilic substrates, overcoming the issues listed above. Organic carbonates have a dual reactivity, since they bear two electrophilic sites: the carbonyl and the first alkyl carbon (Scheme 1.2).[77]



Scheme 1.2. Dual reactivity of dialkyl carbonates.[77]

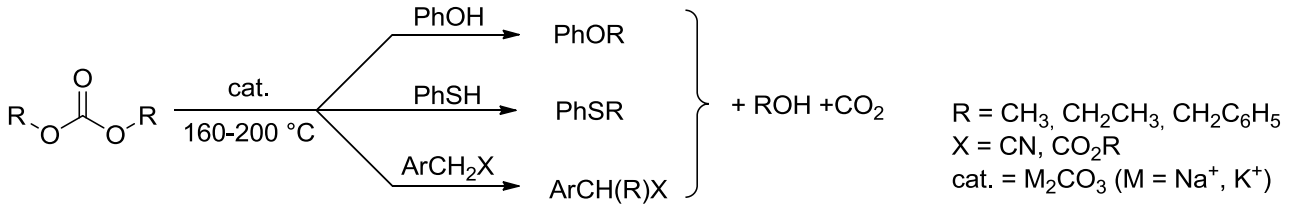
A base (B) is generally needed to generate an activated nucleophile (Nu^-) (eq. a). Successively the latter can follow one of the mentioned pathways:

1) attack the carbonyl, giving the carboxyalkylated product and the alkoxide RO^- (eq. b; $B_{Ac}2$ mechanism);

2) attack the alkyl chain, giving the alkylated derivative and the alkylcarbonate anion $ROCO_2^-$ (eq. c; $B_{Al}2$ mechanism). Generally the carbonate anion is unstable in the reaction conditions, and decomposes to form the alkoxide RO^- and CO_2.

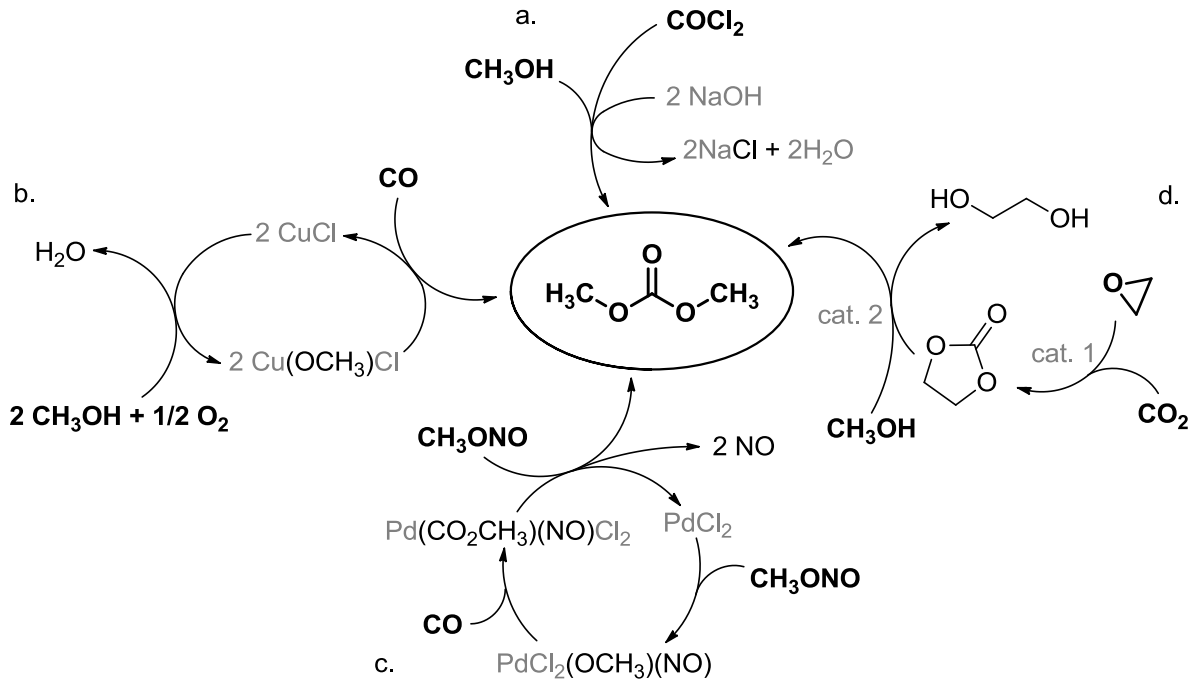
Both the pathways lead to the formation of the alkoxide RO^-, which is neutralised by the protonated base BH^+ to form the corresponding alcohol and the initial base that is regenerated as a catalyst. It must be pointed out that most of the time the catalyst is a solid that can be recovered and re-used.[78] This dual reactivity can be tuned by optimising the

reaction conditions, in particular temperature and nature of the catalyst.[77] Below are listed some examples of selective alkylation reactions.



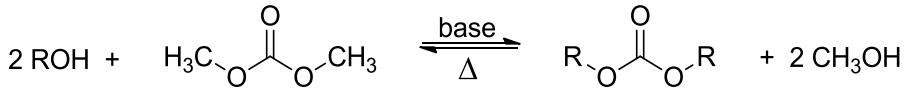
Scheme 1.3. Examples of selective alkylation reactions via dialkylcarbonates.

Recent evolution in the chemical synthesis of DAlCs has prompted renewed interest on these compounds. The classical route was based on phosgene and methanol to produce DMC. This process is obviously far from green: the starting substrate is a very toxic gas, and an organic waste NaCl is formed in a 2:1 ratio with respect to the product (NaOH is needed to neutralise the forming HCl; see Scheme 1.4, a). Since the mid-80s the safer Enichem and UBE processes have become the preferred industrial production routes. The first is based on a copper catalyst, and is based on an oxidative carbonylation of methanol, with water as the only by-product (Scheme 1.4, b).[79] The UBE process is based on a palladium catalyst, and uses two molecules of methyl nitrite to produce DMC and two moles of nitrogen monoxide as a by-product (Scheme 1.4, c).[80] Other approaches, like CO_2 insertion, are currently under investigation and development (Scheme 1.4, d).[81-82]



Scheme 1.4. Routes for the industrial production of DMC.

Higher homologue DAlCs can be prepared via base promoted transesterification of DMC with the desired alcohol, by removing methanol continuously via distillation to drive the equilibrium.[83]



Scheme 1.5. Transesterification of DMC with alcohols to yield other dialkylcarbonates.

As expected the electrophilic reactivity of the alkyl position decreases significantly with the increase in length of the chain making the higher homologues of DMC less reactive.

Solvent properties

Many organic carbonates, including DMC and DEC, have another important characteristic that makes them desirable while designing a green reaction or process: they are good organic solvents. They solubilise most of the common organic compounds and, moreover, even inorganic bases such as K_2CO_3 are slightly solubilised at the higher temperatures.[77] This makes the catalytic process described in Scheme 1.2 easier. For this reason many reactions involving DAlCs as reagents are also carried out using the same DAlC as the reaction medium, acting both as a solvent and a reagent. The fact that an additional organic solvent is often not needed, adds to the safety and to the ease of the final work-up. Generally, the carbonate has a lower boiling point than the product, and can simply be distilled out. The alcohol co-produced during the reaction (see again Scheme 1.2) can be separated by fractional distillation of the mixture. When an insoluble inorganic base is used it can be simply filtered at room temperature, recycled and re-used.

1.3.1.3.Water

Water has always been a Janus-faced solvent for a chemist: many important reactions need water to occur, and its importance in the isolation and purification (work-up) processes is doubtless. On the other hand, due to its reactivity, many compounds react with water and, most importantly, the great majority of organic compounds is insoluble in water. Because of these reasons it has had limited applications for organic reactions. However, if one considers how life evolves and proliferates on our planet, we cannot avoid asking ourselves whether we could take advantage efficiently of water as a solvent

for organic reactions. In this regard it is worth to cite a thought from Prof. Engberts (University of Groningen, The Netherlands):

"Traditionally, water is not a popular solvent for organic reactions. The limited solubility of many organic substrates and reagents as well as the fact that a variety of functional groups is reactive towards water have contributed to this lack of popularity of water as a reaction medium. On the other hand, the chemistry of all life processes occurs in aqueous media and few people will doubt the high quality and efficiency of these transformations!"[84]

In the context of green chemistry water has attracted much attention, in view of its possible use as a solvent or, better, as a reaction medium. Undeniably water has many advantages which are briefly listed in Table 1.10.

Table 1.10. Water as a solvent: advantages and disadvantages.

Advantages	Disadvantages
Non-toxic - Non-flammable	Contaminated waste streams may be difficult to treat
Opportunity for replacing VOCs	
Naturally occurring - Inexpensive	High specific heat capacity – difficult to heat or cool rapidly - distillation is energy intensive
High specific heat capacity – exothermic reactions can be more safely controlled	

Water has two main disadvantages: the treatment of waste streams and the high heat capacity. The latter, according to the situation, can be positive (thermal control is made easier), or negative (energy is needed to change its temperature).

The main issue to overcome when using water a solvent for organic chemistry is the poor solubility of many organic molecules. On the other hand, this lack of solubility brings along an important consequence: the hydrophobic effect. This effect is the tendency of nonpolar molecules to aggregate when they are placed in water. This attraction might appear very strong at first sight, however it is not because the Van Der Waals interactions between two hydrocarbons is weaker than the that between a hydrocarbon and a water molecule (the former is only a dispersion force, while the latter is a dipole-induced dipole interaction). This implies that the hydrophobic effect is actually favoured from an entropic

point of view. Within the solid aqueous lattice, every water molecule tends to form 4.0 hydrogen bonds (accepting two and donating two). In the liquid state every molecule is engaged in approximately 3.0-3.5 hydrogen bonds, maintaining therefore a certain degree of freedom. When a hydrophobic species is introduced, water molecules tend to arrange so as to maintain the highest total degree of freedom. This situation is verified when a number of water molecules are "sacrificed" to create a cage, or cavity, around the nonpolar species, and keeping the usual lattice outside in the bulk.[85-86]

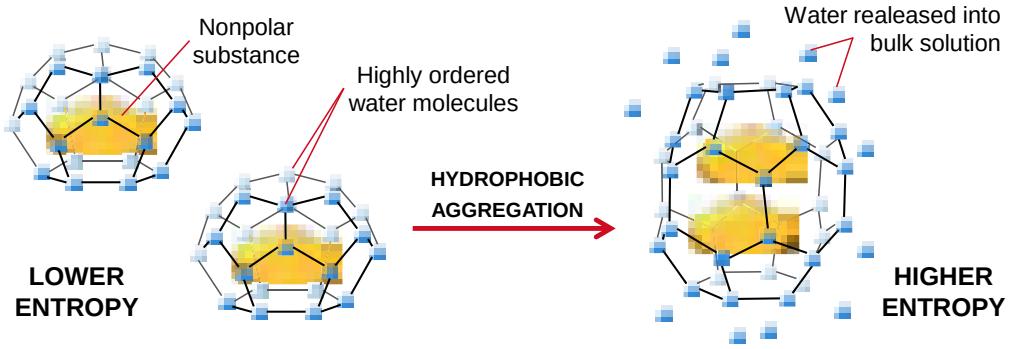


Figure 1.25. Schematisation of the hydrophobic effect.

The disruption caused by the nonpolar molecules is minimised when they are grouped together, and the exposed aqueous surface is minimised. What seems like a more ordered situation is actually the most chaotic, *i.e.* favoured, for the water lattice.[86]

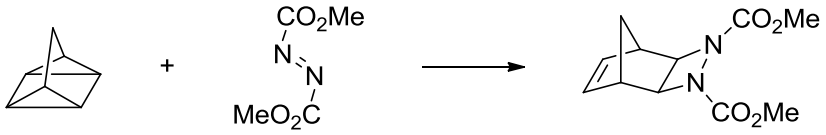
In the past it was observed that some reactions between hydrophobic organic molecules were accelerated when performed as a suspension in water. Breslow studied the acceleration of some Diels-Alder reactions in dilute aqueous and attributed the acceleration shown to the hydrophobic effect.[87-89] At this time the field on-water catalysis was still 25 years into the future, nonetheless, the hydrophobic effect remains an important consideration and the anomalous reactions found during the course of these investigations are the progenitors of the on-water catalysis.

1.3.1.4.On-water catalysis

The approach described above was extended by Sharpless *et al.* who introduced the term "on-water", pointing out that a "unique reactivity of organic compounds" was observed in aqueous suspension.[90] Since then this particular field of research flourished, involving both the mechanistic and synthetic chemists.

Features of on-water catalysis

In their landmark paper Sharpless *et al.* identified the main features of on-water catalysis. Among the reactions they considered the cycloaddition between quadricyclane and dimethyl azodicarboxylate in detail (see Scheme 1.6 and Table 1.11).[90]



Scheme 1.6. Cycloaddition between quadricyclane and dimethyl azodicarboxylate.[90]

Table 1.11. Cycloaddition between quadricyclane and dimethyl azodicarboxylate.[90]

Line	Solvent	Conc. [M]	Time to completion
1	Toluene	2	>120 h
2	EtOAc	2	>120 h
3	CH_3CN	2	82 h
4	CH_2Cl_2	2	72 h
5	DMSO	2	36 h
6	MeOH	2	18 h
7	Neat	4.53	48 h
8	On C_6F_{14}	4.53	36 h
9	On D_2O	4.53	45 min
10	On H_2O	4.53	10 min
11	H_2O/MeOH (3:1, heterogeneous)	4.53	10 min
12	H_2O/MeOH (1:1, heterogeneous)	4.53	10 min
13	H_2O/MeOH (1:3, homogeneous)	2	4 h

A few observations can be made.

- The reaction is faster the more polar the solvent. This is in agreement with a polar transition state which can be better stabilised by a polar solvent.
- The reaction is tremendously accelerated when the reactants are stirred as an aqueous emulsion (on-water conditions).
- The observed acceleration is neither due to a high concentration nor to the heterogeneous conditions. In fact both the neat reaction and the reaction in perfluorurate solvent are much slower than the on-water one.

- The addition of methanol to water did not affect the rate enhancement, as long as the mixture remains heterogeneous. When dissolution occurs, the rate enhancement drops.
- The use of deuterium oxide in place of water leads to a smaller rate enhancement.

All these observations led researchers to formulate the following hypothesis, which would have been confirmed in the following years:

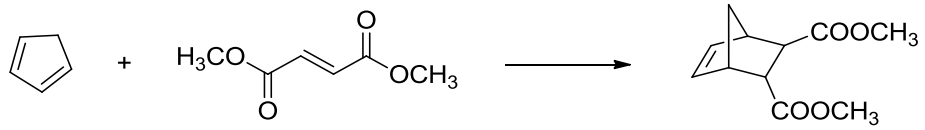
❖ A heterogeneous mixture is needed – i.e. the reactants have to be insoluble in water.

❖ It must be a surface effect – when the stirring is insufficient (i.e. the dispersion is not good) the effect drastically diminishes.

On-water catalysed reactions

Various reactions have been recognised as accelerated under on-water catalysis conditions. There are examples of unimolecular and multimolecular reactions, including rearrangements, cycloadditions and displacements. The most abundant class of examples can be grouped in the following classes.

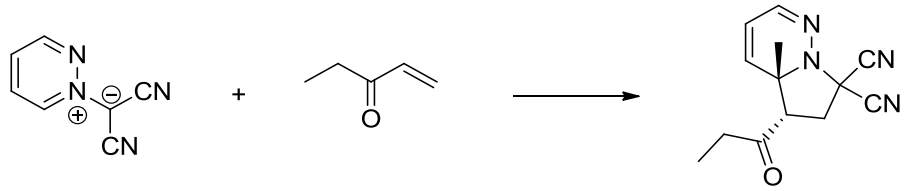
Diels-Alder cycloaddition



Scheme 1.7. The [4+2] cycloaddition reported by Beattie and McErlean.[91]

The Diels-Alder reaction was the first reaction known to be accelerated as an aqueous emulsion. Generally its selectivity is higher towards the *endo* product; in some cases the *endo*/*exo* ratio is extremely high.

Dipolar cycloadditions

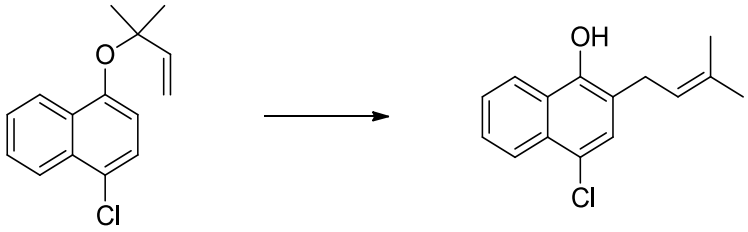


Scheme 1.8. The aqueous dipolar cycloaddition performed by Butler.[92]

Dipolar cycloadditions which are inhibited in organic solvents have been found to proceed quickly in the presence of water.[92] It has also been found that a large range of

dipoles and dipolarophiles benefit from this form of catalysis.[93] It is also known that water facilitates some Huisgen azide/alkyne 1,3-dipolar cycloadditions.[94]

Claisen rearrangement



Scheme 1.9. An on-water Claisen rearrangement reported by Sharpless.[90]

Claisen rearrangements are a class of on-water catalysed reactions. A first example was reported by Grieco;[95] successively several new ones were found by Sharpless et al., and the catalysis has been found to be general.[96]

Mechanism of on-water catalysis

Experimental evidence requires validation by a coherent theoretical framework in order to be explained. This allows to understand the interactions occurring at the molecular level and to have a better control of the reaction outcome. Secondly, this insight allows to predict new applications and the feasibility of each transformation. Although on-water catalysis has become popular, the field still suffers the absence of a theoretical model able to account for all the evidence. The currently most accepted model was proposed by Marcus and Jung in 2007, and is known as the "dangling hydrogen bonds theory".[97] More recently (2010) Beattie and McErlean refined the previous model, proposing a new one based on the properties of the oil-water interphase.[91] These two models will be briefly described.

The dangling H-bonds theory

All the experimental observations consistently suggested that the interphase between water and the hydrophobic substance/s has a fundamental role.[90] It was proposed that there was a formation of H-bonds at the interphase between water and the hydrophobic substrates, and that such an interaction could have been somehow responsible for the observed acceleration. Marcus and Jung tried to rationalise this assumption by proposing a model based on a computational approach.[97] They chose the cycloaddition between quadricyclane and dimethyl azodicarboxylate, thouroghly investigated experimentally by Sharpless et al, as a sample reaction, being the one that shows the greatest acceleration

amongst the known on-water reactions. A DFT modelling was performed (using the UB3LYP/6-31G* method), considering three explicit water molecules to represent the aqueous phase. It was already known that at the interphase between water and a non-polar material approximately 25% of the water molecules have free OH groups (dangling gropus) in consequence of the disruption of the water network (see hydrophobic effect).[98] Computational data were in agreement with the formation of hydrogen bonds between the dangling OH groups and dimethyl azodicarboxylate, which lead to a stabilisation of the transition state and a consequent reduction of the activation energy. The magnitude of the acceleration predicted by this model was found to be consistent with that observed by Sharpless.

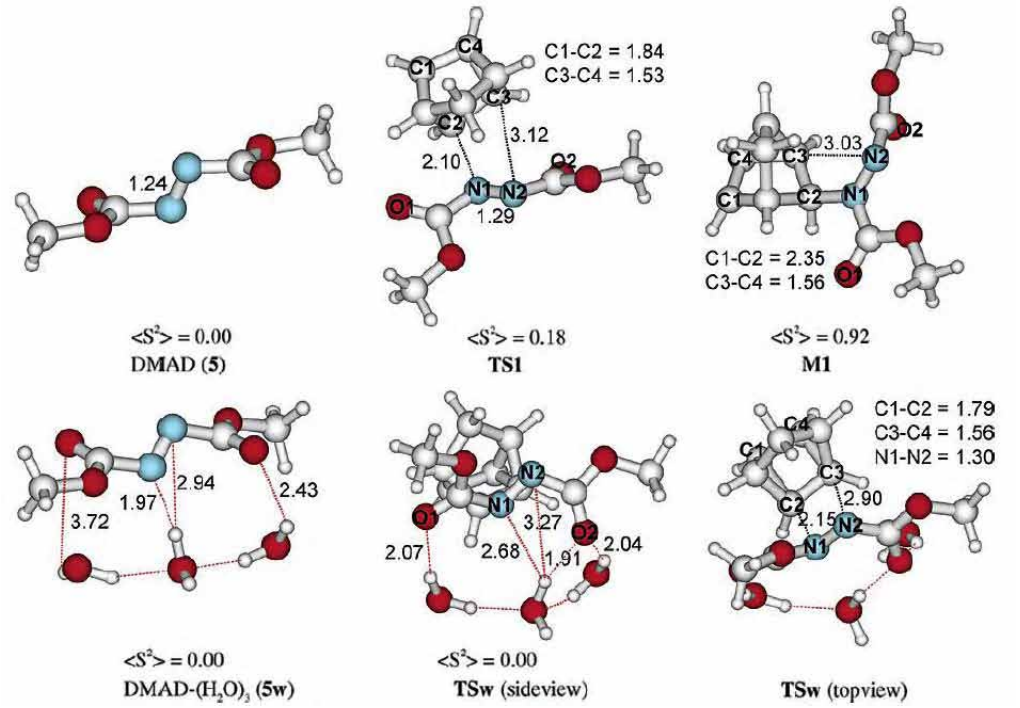


Figure 1.26. Transition states calculated by Marcus and Jung with three explicit water molecules, compared with the same in absence of water.[97]

Jung and Marcus' theory gained wide success and to date is the most widely accepted. This is probably due to its ease of comprehension, at least in the general meaning, its plausibility (H-bonds showed many important implications) and nonetheless the fact that it was the very first theory to propose a model supported by proper calculations.[97] Eventually, the compatibility with Sharpless' experimental data seemed to make it definitive. However in the early years after it was proposed, some weak points were identified.

The protonation theory

The most recent alternative theory was proposed by Beattie and McErlean in 2010.[91] In their paper they gathered together all the criticisms to the dangling H-bonds model with an additional observation: *"all the reactions that have been described as accelerated by the on-water effect […] are also known to be subject to acid catalysis"*. Thus, they proposed the hypothesis that acid-base chemistry, which evidently occurs at the interphase, might be governing the observed rate enhancements. To support this idea they offered as proof that a transfer of protons into the organic phase would be facilitated by the strong propensity of the hydroxide ions to adsorb at the interface between water and low dielectric constant materials. Evidence that such an interface is negatively charged in neutral water have been available for decades.[99] It was found that the charges derived from the hydroxide anions formed from water autolysis, which are preferentially and strongly adsorbed at the interface (Beattie reported a surface charge density of -5 to -7 uC/cm^2, which corresponds to one hydroxide anion for every 3nm^2).[99] The cause of this accumulation was explained once again with an entropic advantage. When an anion has to be solvated, a highly ordered network is formed around it, meaning an overall entropic loss for the solvent (Figure 1.27, left).[100] On the other hand, a non-polar material will not become organised in proximity of the anion; hence, a proximity between them would reduce the number of dipoles which had to be ordered in the previous situation (Figure 1.27, right). Despite the diversity of the situation, the driving force is exactly the same with which the hydrophobic effect is explained.

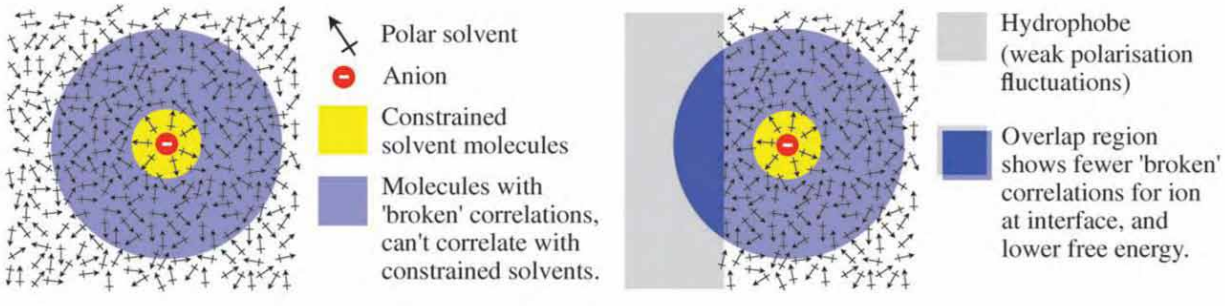


Figure 1.27. Reason that hydroxide is stabilised at the surface.[100]

This data might seem as opposed to the hypothesis of an acidic catalysis at first, but it becomes reasonable when the whole scenario is imagined, as schematised in Figure 1.28.

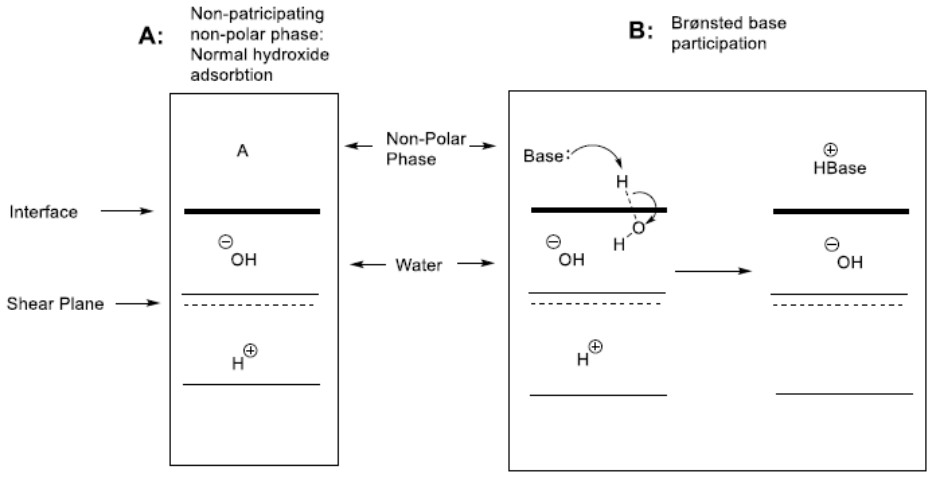


Figure 1.28. Interfacial water molecules become acidic.

In the absence of groups participating in hydrogen bonding in the non-polar phase, the hydroxide ions are balanced by the proton counter ions in the double layer. Instead, when a Brønsted base is present in the non-polar phase, the stabilisation of the hydroxide manifests itself as an increase in the acidity of the interfacial water molecules (to a pKa of 4 to 5), by making hydroxide a good leaving group.

Taking into account all of these data, Beattie and McErlean proposed a mechanism that consists in a simple acid-base equilibrium, which takes place at the interphase.[91] A substrate with Brønsted base character can be there protonated, and will be activated toward reaction.

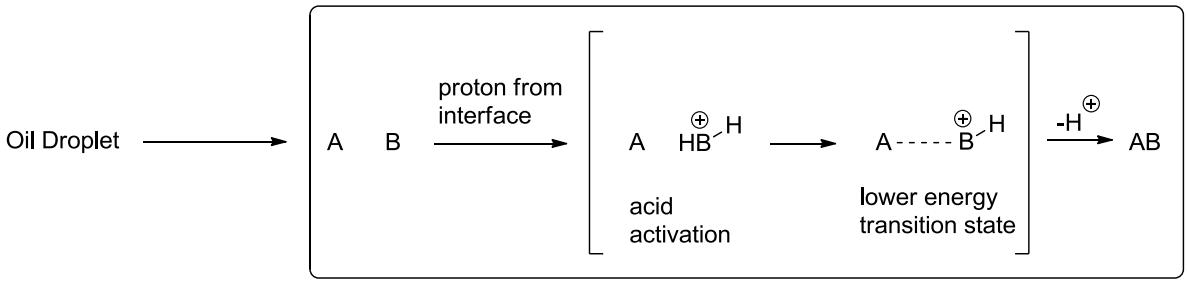


Figure 1.29. Mechanism of acid catalysis during on-water catalysis according to Beattie *et al*.

In essence, this mechanism describes a means of stabilisation and immobilisation of hydroxide ions at the interface which renders interfacial water molecules acidic and able to participate in reactions. This theory also reconciles the ostensibly conflicting facts in the literature that the surface of water is negatively charged[99, 101-102] (suggesting adsorption of hydroxide) but acidic[103-104] (which would ordinarily suggest adsorption of hydronium).

1.4. Aim of the PhD project

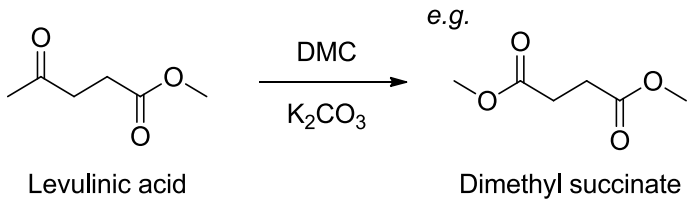
This research project has been developed within a PhD cotutelle agreement between Università Ca' Foscari Venezia and The University of Sydney. It was carried out in the laboratories of the Green Organic Synthesis Team (GOST; Venice) and the Laboratory of Advanced Catalysis for Sustainabilty (Sydney). Both the research groups have a long-standing interest in the green and sustainable chemistry, and have been collaborating in other research projects over the years. GOST focuses on the development of green organic transformations, while in Sydney new catalyst design and renewable feedstock processing are the key research topics. These competencies of the two groups are complementary, therefore transfer and integration of the respective knowledge has become key for the development of new scientific breakthroughs.

The general aim of this research project has been the development of green chemical technologies for the upgrading of platform molecules obtainable from renewable feedstocks through a biorefinery scheme. The feedstocks were chosen among those considered as the most promising for the development a new, sustainable, chemical industry, based on availability and potential. The transformations were developed based on the wide experience of the two research groups in two important areas of green chemistry: the use of organic carbonates as green reagents and solvents (Venice, chapters 2 to 5), and the use of water as reaction medium (Sydney, chapters 6 and 7). Taking advantage of the know-how of the two research groups for these technologies, these were applied to the derivatisation of chosen platform chemicals, generating a set of green procedures for a sustainable upgrading of renewable feedstocks.

The description of the work has been divided into six chapters, each one focused on a particular platform chemical (or class of platform chemicals) and a particular transformation.

- **Chapter 2: Upgrading of levulinic acid with DMC as solvent/reagent**

The reaction of the platform chemical levulinic acid, one of the most interesting platform chemicals, with DMC was studied in conditions of basic catalysis. The aim was to obtain derivatives with a higher degree of oxygenation, without actually using oxidising agents (Scheme 1.10).

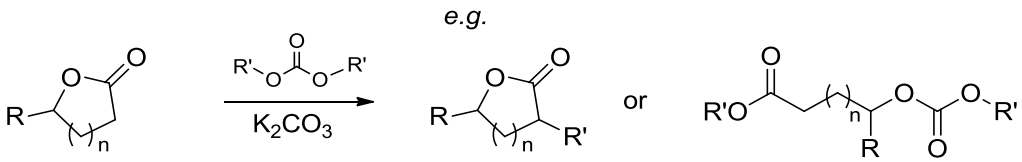


Scheme 1.10. Example of a reaction between Levulinic acid and DMC in basic catalysis.

Such transformation was pursued by applying the reaction of ketones to yield methyl esters previously described in the GOST research group.[105]

❖ Chapter 3: Derivatisation of bio-based lactones

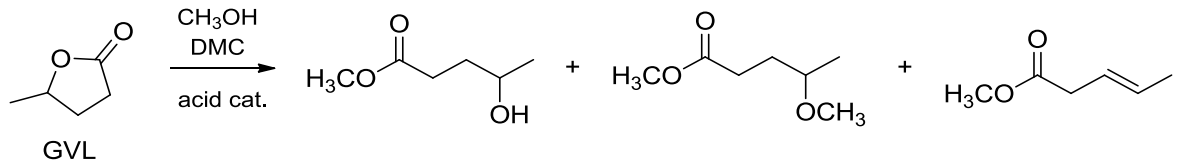
Four renewable lactones, γ-butyrolactone (GBL), γ-valerolactone (GVL), δ-valerolactone (DVL) and ε-caprolactone (ECL) were studied in their reaction with three dialkylcarbonates (dimethyl, diethyl and dibenzylcarbonate). A preliminary report indicated that α-methyl-γ-butyrolactone was formed in the base-catalysed reaction of γ-butyrolactone with DMC. Now, the possibility to develop this catalytic technology and apply it to bio-based platform chemicals, has become of interest, and was here applied to obtain an interesting array of compounds.



Scheme 1.11. Example of reactions between lactones and dialkylcarbonates in basic catalysis.

❖ Chapter 4: Ring opening of bio-based lactones

Gamma-valerolactone was chosen as a model to study acid catalysed ring-opening reactions of lactones (Scheme 1.12). These transformations are useful to synthesise many valuable compounds. However, to date the selectivity is low, and dangerous and pollutant reagents are needed. In such context the presence of DMC as a promoter to direct the selectivity was studied.

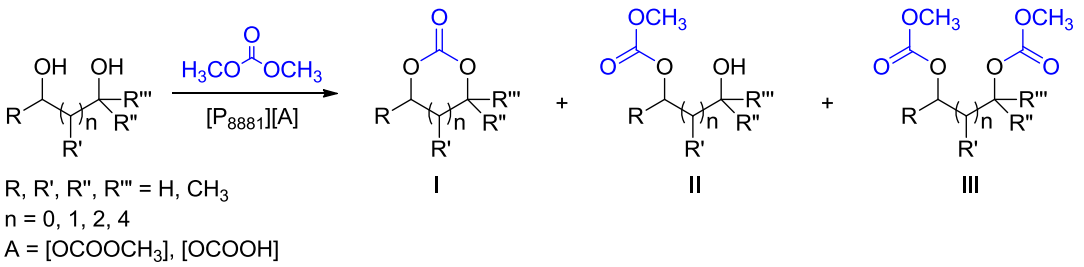


Scheme 1.12. Example of GVL ring opening in presence of methanol, DMC and an acid catalyst.

The chapter is divided in two main parts: in the first one the mechanism of the reaction was investigated, while in the second a continuous flow process was developed.

❖ Chapter 5: Diols as a route to linear and cyclic carbonates

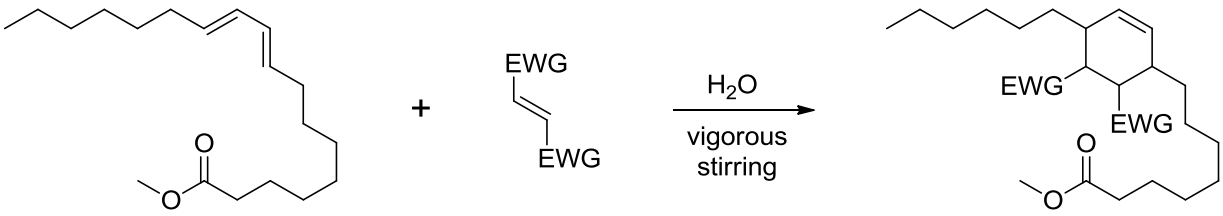
The synthesis of eco-friendly organic carbonates as intermediates has triggered a massive research activity for the synthesis of dialkyl carbonates. These can be produced via catalytic transesterification starting from the simplest homologue DMC via catalytic transesterification with alcohols or polyols. In this chapter the transesterification reaction was applied to bio-derived diols, using organic carbonates in tandem with ionic liquids as organocatalysts (Scheme 1.13). The study of possible effects of the chain length and the degree of substitution of the carbon backbone of diols was carried out.



Scheme 1.13. Example of reactions between diols and DMC, in the presence of ILs as catalysts.

❖ Chapter 6: On-water modification of FAMEs to improve cold flow properties of biodiesel

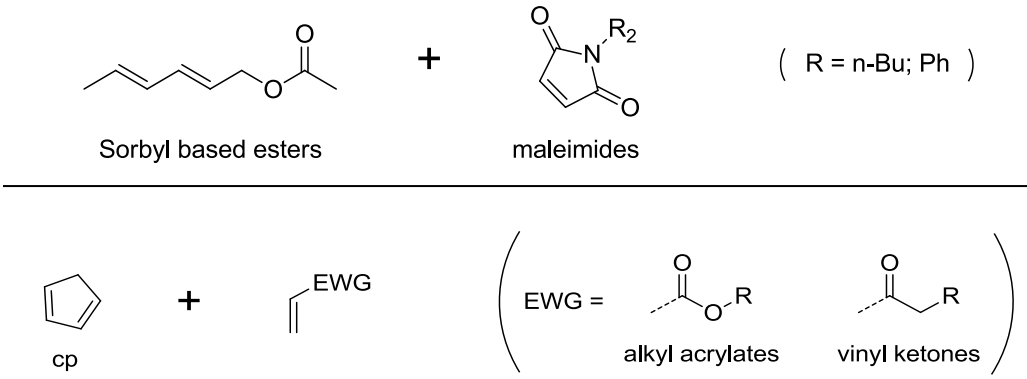
A major problem associated to the wide use of biodiesels, consist in their cold flow properties, which are generally worse than those of common petro-diesels. For instance, the cloud point (temperature at which first crystals are formed in the bulk of the fuel) of biodiesels is generally too high (between 4 and 14 °C) for their use in cold climates. Here, the derivatisation of fatty acids methyl esters in conditions of on-water catalysis was investigated whilst at the University of Sydney, with the aim of developing a green strategy to reduce the cloud point of biodiesels.



Scheme 1.14. Example of cycloaddition between a fatty acid methyl ester and an activated dienophile (EWG = electron withdrawing group)

- **Chapter 7: On-water catalysis of Diels-Alder reactions: Influence of the structure of the reagents**

Based on the outcome of the previous chapter, the study of on-water catalysis continued by investigating the mechanism and the effect of reagent structure on on-water catalysis. In particular, the Diels-Alder reaction was studied with the aim to determine the influence on the outcome due to the different lengths of the alkyl chains, i.e. lipophilicity, of the diene and dienophile. Examples of investigated dienes and dienophiles include: sorbyl acetate, alkyl acrylates and alkyl vinyl ketones.



Scheme 1.15. Examples of reactants chosen for the study.

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2 | UPGRADING OF LEVULINIC ACID WITH DMC AS SOLVENT/REAGENT

2.1. Introduction

2.1.1. Levulinic acid from biomass

Levulinic acid (LA) represents a precious bio-based C5 feedstock. Its wide availability, low price, renewable origin, as well as its interesting reactivity make it a valuable platform molecule for chemical transformations. In particular, it represents an alternative renewable C5 building block that can be used in place of fossil derived homologues. Unlike succinic acid, which is prepared mainly by biochemical transformations, LA can be synthesized very efficiently by an exclusively chemical sequence starting from biomass. The Biofine process reportedly achieves a 50% weight yield of LA based on cellulose as feedstock, it was developed originally in the US, and a 50 tons/day plant was commissioned in Caserta (Italy) using a mixed lignocellulosic feedstock.[1-2]

2.1.2. Chemistry of Levulinic acid

LA can be utilized, still in principle, as a platform molecule of renewable origin in alternative to fossil building blocks. For example LA can be transformed into butanone[3], instead of starting from heavy naphta as in the traditional Fischer-Tropsch process. However, LA represents primarily a self-standing platform for a variety of different molecules, as exemplified in figure 2.1.[4-5]With the added advantage that among all these possible products, some have already been identified as having the potential for the market, *i.e.* 2-methyltetrahydrofuran (2-Me-THF), γ-valerolactone(GVL),[5] 1,4-pentadiol, diphenolic acid, δ-aminolevulinic acid (DALA), ethyl levulinate, and succinic acid.[1]

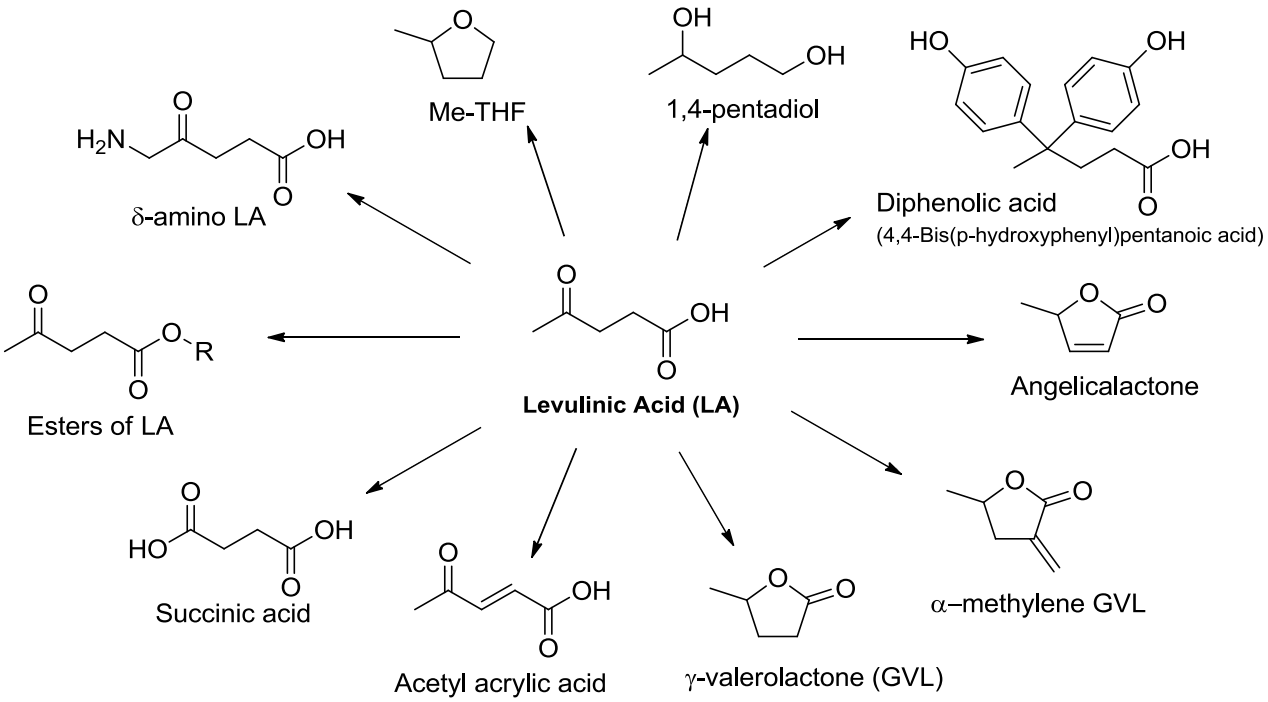
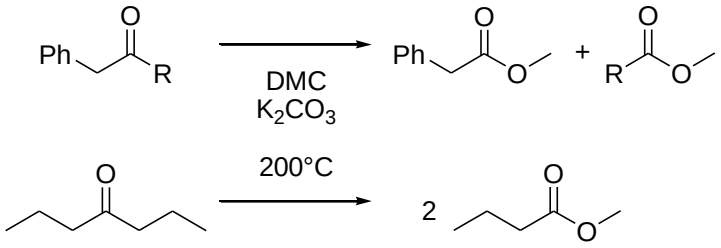


Figure 2.1. Some products derived from levulinic acid (LA).

It is apparent that most of the products in figure 2.1 can be obtained following a reductive pathway, and in fact such pathways are described frequently in the scientific literature. In this work, instead, attention was focused on a formally oxidative approach to LA upgrading, by aiming towards the "oxidized" derivatives of figure 2.1. In particular, the attention was focused on succinic acid esters. Traditionally these are obtained from LA through classical oxidation procedures such as by vanadium catalysed oxidation with oxygen,[6] or oxidation by *N*-bromoacetamide (NBA) in perchloric acid with mercuric acetate and ruthenium chloride as catalyst,[7] followed by esterification.

2.1.3. Aim

Based on the experience of the research group, in which this thesis work was developed, in the use of dimethylcarbonate as a green reagent[8] it was decided to investigate its reaction with LA to yield LA methyl ester and succinic acid methyl ester. The latter could be approached by applying the reaction of ketones to yield methyl esters previously described in the same research group group,[9] depicted in scheme 2.1. It consists of the formal splitting of a ketone, *e.g.* a benzyl-alkyl ketone or dialkyl ketone, to yield the corresponding benzylic acid methyl ester and alkyl carboxylate methyl ester. Albeit not high yielding and somewhat energy intensive, particularly for aliphatic ketones,[9] this transformation appeared to be a novel interesting strategy to upgrade LA.



Scheme 2.1. Reactions of ketones with DMC in the presence of K_2CO_3 at 200 °C.

Here it is described the development of new DMC-based chemical technology to transform LA into target compounds. This work however was organised to go one step further and also screened reactions for novel and unexpected outputs by following a more curiosity-driven approach, analogously to a recent work performed, within the same research group, on lignin.[10] The expectation was that this kind of broad-based method could lead to the discovery of new reactions (selective reductions, oxidations, bond making/breaking processes, catalysis, *etc.*), that could pave the way to unexpected new compounds. This approach was key, for example, in the development of the fossil-based chemical industry, that prospered when efficient transformations were discovered, that in turn made available a variety of new molecules, that successively found multiple applications.[11]

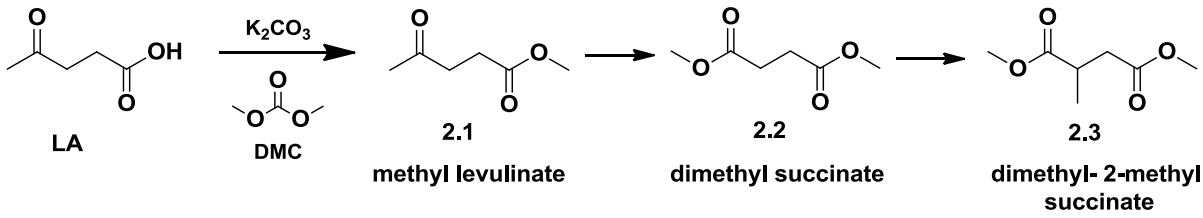
In the present case, by understanding the reaction sequences, the products, and the selectivity that were obtained by the reaction of LA with DMC under alkaline conditions, it was possible to pinpoint an uncommon base-promoted acetalisation reaction that yielded the unexpected compound **2.4** (methyl levulinate dimethyl-ketal).

2.2. Results

2.2.1. Effect of the temperature.

LA and DMC were placed in a stainless steel autoclave with K_2CO_3 (molar ratio K_2CO_3:LA = 2:1) and heated with stirring at temperatures ranging from 160 to 220 °C (depending on the temperature and on the reactor volume, pressures in a range between 15 and 30 atm were observed). DMC was always used as reagent in a 20-fold excess respect to LA, and thus also acted as solvent for the reaction. The temperature screening (table 2.1) indicated that at 160 °C the reaction was selective for the formation of methyl levulinate **2.1**; while at higher temperatures selectivity decreased. For example, gas-

chromatographic (GC) analysis after 4 hours at 200 °C indicated the formation of methyl levulinate **2.1** (9%), dimethyl succinate **2.2** (16%), and dimethyl-2-methylsuccinate **2.3** (3%) (scheme 2.2), along with a large amount (> 70%) of unidentified by-products. Above 180 °C, dimethylsuccinate **2.2** was the major product.



Scheme 2.2. Products of the reaction of LA with DMC in the presence of K_2CO_3 at 200 °C for 4 hours.

Table 2.1. Product distribution of the reaction of LA with DMC in the presence of K_2CO_3 at different temperatures.

Entry[a]	Temp. (°C)	Time (h)	Conv.[b] (% GC)	Products (% GC)[b]			
				2.1	2.2	2.3	Others[c]
1	160	4	100	99	-	-	1
2	180	4	100	12	10	1	77
3	200	4	100	9	16	3	72
4	220	3	100	0	17	5	78

[a]All reactions were performed at 200 °C for a time of 6 hours, using a molar ratio LA:DMC = 1:20. [b]Conversion and product percentages in the final mixture were determined by GC/MS analysis. [c]Others means all the products whose structure is unknown.

By prolonging the reaction time, the selectivity towards the desired dimethyl succinate **2.2** increased and went through a maximum (21%) after 6 hours, then decreased as the product reacted further. The product dimethyl succinate **2.2** was isolated through distillation under reduced pressure, achieving an isolated yield of 18%.

2.2.2. Effect of the catalyst.

Three strong organic bases were tested in place of K_2CO_3 under the best operative conditions for the reaction of LA with DMC (200 °C, 6 h), including: diazabicyclooctane (DABCO), diazabicycloundecene (DBU), and trioctylmethylphosphonium methyl-carbonate ($[P_{8,8,8,1}][CH_3OCO_2^-]$).[12] The results are summarized in table 2.2. A blank test without catalyst, performed to rule out spontaneous reactions between LA and DMC (entry 1, table 2.2), indicated only 16% conversion to the methyl ester.

Table 2.2. Reaction of LA 1 with DMC using different base catalysts.

Entry[a]	Base	Base/LA[b] (mol/mol)	Conv.[c] (% GC)	Products (% GC)[c]			
				2.1	2.2	2.3	Others[d]
1	none	-	17	16	-	-	1
2	K_2CO_3	2	100	1	21	5	73
3	DABCO	2	100	3	10	2	85
4	DBU	2	100	-	14	26	60
5	$[P_{8,8,8,1}][CH_3OCO_2^-]$	0.025	100	96	-	-	4

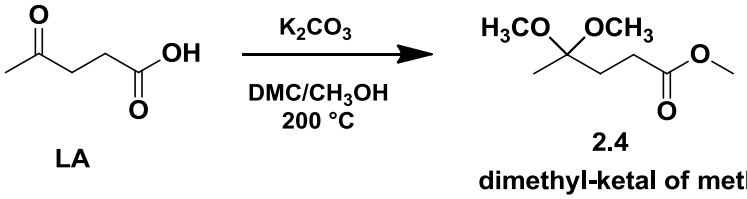
[a]All reactions were performed at 200 °C for a time of 6 hours, using a molar ratio LA:DMC = 1:20. [b]Molar ratio between base and LA. [c]Conversion and product percentages in the final mixture were determined by GC/MS analysis. [c]Others means all the products whose structure is unknown.

All the bases prompted complete conversion, albeit with poor selectivity and conspicuous amounts of by-products. The only exception being $[P_{8,8,8,1}][CH_3OCO_2^-]$ (entry 5) that, even just in catalytic amounts (2.5% molar respect to LA), promoted selective conversion to methyl levulinate **2.1**. DABCO and DBU did not improve on the performance (conversion or selectivity) obtained with potassium carbonate and were not used further. DBU (entry 4) showed significant amounts (26%) of dimethyl-2-methyl succinate **2.3** as the major identifiable product.

2.2.3. Effect of added solvent.

Further attempts to improve the selectivity towards the desired dimethylsuccinate **2.2** were made using DMF and methanol as co-solvents at 200 °C. DMF caused an increase in the amounts of unidentified by-products and was immediately abandoned.

Addition of methanol (molar ratio MeOH:DMC = 1:1) promoted the unexpected formation of the dimethylketal of methyl levulinate **2.4** (scheme 2.3), whose structure was confirmed by isolation and comparison with an independently synthesized sample.[13]



Scheme 2.3. Product of the reaction of LA with DMC and methanol in the presence of K_2CO_3.

In an attempt to improve the yield of **2.4**, a set of reactions run with progressively higher amounts of methanol showed the parallel increase in the formation of the ketal (figure 2.2), up to 40% by GC at a 1:1 MeOH-DMC ratio.

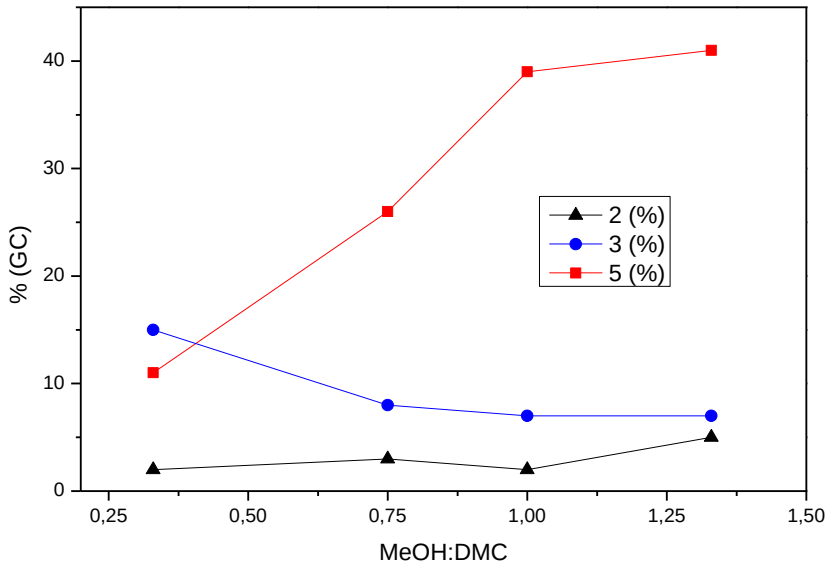
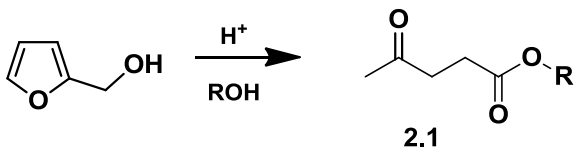


Figure 2.2. Product distribution *vs.* MeOH:DMC ratio in the reaction of LA with DMC and MeOH after 6 hours at 200 °C with K_2CO_3.

Pure ketal **2.4** could be isolated from methyl levulinate **2.1** and dimethyl succinate **2.2** (as well as from other higher boiling compounds**)** by flash column chromatography followed by distillation. Ketal **2.4** was thus obtained in high purity (≥ 95%), in a 20% yield with respect to LA.

2.3. Discussion

Methods for the synthesis of methyl levulinate are currently of widespread interest. For example a direct pathway from furfuryl alcohol (scheme 2.4) was recently reported.[14] However, the esterification of easily accessible LA to yield methyl levulinate **2.1** is a more established approach,[15] and it can be carried out under acidic conditions, either by using methanol,[16-17] or dialkyldicarbonates as esterification reagents.[18-19]



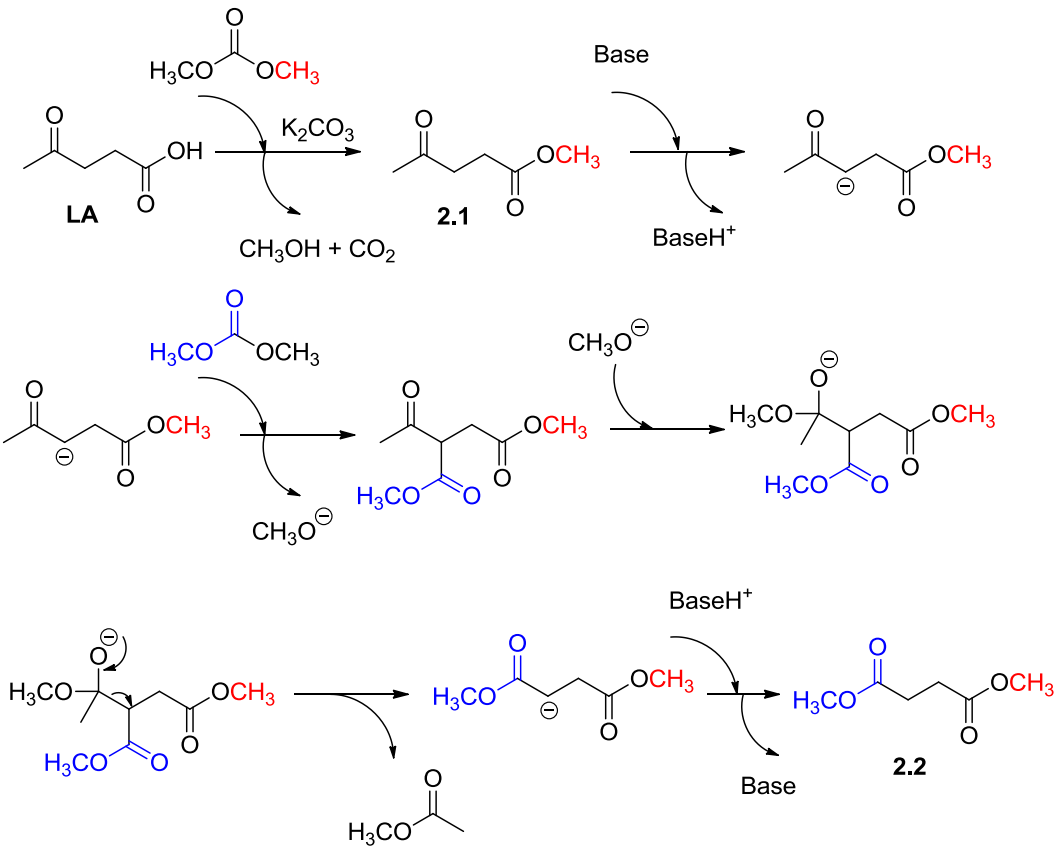
Scheme 2.4. Alkyl levulinates from furfuryl alcohol.

An alternative esterification reagent for the catalytic synthesis of methyl carboxylates[20] is dimethylcarbonate (DMC), that is considered a green reagent[8] as well as a green solvent.[21] With DMC catalysts are usually basic, and can be NaY zeolites as well as inorganic bases such as K_2CO_3.

Here it is demonstrated that DMC can be used as solvent/reagent for the synthesis of methyl levulinate from LA in the presence of catalytic amounts of K_2CO_3 (T = 160 °C, t = 4 h, table 2.1, entry 1).

At higher temperature and in the presence of K_2CO_3, the reaction gave instead rise to three main products: methyl levulinate **2.1**, dimethyl succinate **2.2**, and 2-methyl dimethyl succinate **2.3**, accompanied by the formation of sizeable amounts of unknown by-products.

Based on a previous paper[8] it was reasonable to assume dimethyl succinate was produced by a mechanism such as the one depicted in scheme 2.3.



Scheme 2.3. Mechanism for the formation of dimethyl succinate 2.2 from LA and DMC.

Methyl levulinate **2.1**, formed by transesterification with DMC, underwent deprotonation by the base, generating a nucleophile able to add to the carbonyl carbon of

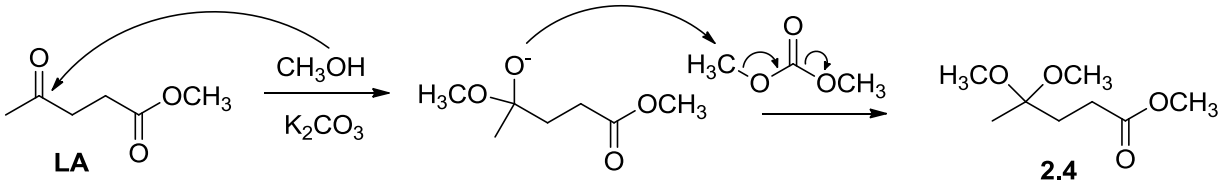
DMC. The resulting species was now set up to undergo nucleophilic attack on the ketone carbonyl by methoxide, thereby generating a species able to eliminate methyl acetate, thus yielding dimethyl succinate **2.2**. Further reaction of **2.2** with DMC accounted for the formation of 2-methyl dimethyl succinate **2.3**, likely by a mechanism described elsewhere for the base-promoted methylation of an activated CH_2.[22-23] Fine tuning of the reaction conditions followed by vacuum distillation allowed to obtain pure dimethyl succinate **2.2** in around 20% yield, a result consistent with previous reports[24] that may serve as benchmark for further developments.

Gaschromatographic analysis showed a discrete number (15-20) of unidentifiable higher boiling by-products that accounted for up to 70% of the mass balance. The mass spectra of these compounds showed some common features, such as evidence of longer aliphatic chains, as well as the presence of methyl ester groups. These allowed to presume levulinate oligomeric structures, based on the fact that levulinic esters are prone to aldol-type condensation reactions under the present alkaline conditions. No further attempts to isolate or characterize these compounds was made.

With a view to improve the selectivity of the reaction, three strong organic bases were tested as catalysts at a lower temperature (100 °C). While selectivity with DABCO was far worse than with K_2CO_3, DBU instead appeared to prompt formation of dimethyl succinate **2.2** and 2-methyl-dimethyl succinate **2.3** (14 and 26% respectively by GC). Both catalysts however were poorly selective as well and caused large amounts of by-products to form. Finally, $[P_{8,8,8,1}][CH_3OCO_2^-]$, that was previously demonstrated by our group to be a strong basic organicatalyst,[25-28] was selective (96%) towards the formation of methyl levulinate **2.1**, even when used in only 2.5% molar amount respect to LA. It did not however catalyse formation of the succinate derivatives **2.2** and **2.3**, and was therefore not considered further.

A far more interesting result was obtained by attempting to improve selectivity towards dimethyl succinate **2.2** by means of added solvents. Methanol in particular, promoted the totally unexpected formation of the dimethyl-ketal of methyl levulinate **2.4** (Scheme 2.3). Ketones undergo reversible acid- or base-catalysed addition of one mole of alcohol to yield the hemiketal. Dehydration followed by addition of a second molecule of alcohol gives a ketal. The second step of the process can be catalysed only by acids since elimination of water from the intermediate is needed,[29] and in fact this step often requires

a water-scavenging agent such as trimethylorthoformate.[30] To best of knowledge, here it was observed a unique case of base-promoted formation of a ketal. A mechanistic hypothesis might involve the excess of methanol acting as proton source to promote dehydration of the hemiketal as proposed by others,[30] with DMC helping by acting as a dehydrating agent. However, in our opinion it was more likely that under the harsh conditions (200 °C) here employed, a role was played by dimethylcarbonate as methylating agent of the hemiketal (scheme 2.6), as was recently reported in the case of glycerol derivatives.[31] In addition, given that ketal formation is an equilibrium that can be driven forward by removing water to prevent hydrolysis, DMC likely acted as water scavenger in this hypothesis as well, thus preventing the reaction from being reversible.[32]



Scheme 2.6. Mechanistic hypothesis for the formation of ketal 2.4 under basic conditions.

2.4. Conclusions

The results presented in this chapter indicate that the platform chemical levulinic (LA) acid can produce interesting derivatives when treated by alternative methods with respect to the commonly investigated reductive ones, and that is possible to establish suitable conditions for its catalytic upgrading. For the time being, the reported reactions are clean and selective only for the synthesis of methyl levulinate **2.1**, nonetheless access to dimethyl succinate **2.2** and ketal **2.4** has been demonstrated as well. In this sense, the investigation is not a target-oriented catalytic study *per se*, rather the paper wishes to illustrate broad reactivity trends and the most promising avenues that lead to LA-based chemicals.

In the simplest instance, the reaction of LA with DMC in the presence of K_2CO_3 at 160 °C yields selectively levulinic acid methyl ester **2.1**. Alternatively **2.1** could be obtained with high selectivity at 200°C by using $[P_{8,8,8,1}][CH_3OCO_2^-]$ as a base. At higher temperatures (200 °C) the reaction became less selective but afforded dimethyl succinate **2.2** in up to 20% isolated yield by a previously described formally "oxidative" mechanism. Addition of methanol to the reaction of LA with K_2CO_3 and DMC at 200 °C prompted the

unexpected formation of ketal **2.4**, this was tentatively rationalized by invoking the harsh conditions that may lead to somewhat unconventional chemistry taking place, as well as to the role of DMC that may act as a sacrificial water scavenger.

Despite the energy intensity required for these reactions, several green aspects can be recognised.

1. DMC is non-toxic and used both as a reagent and solvent;
2. potassium carbonate used as catalyst is safe and can be recovered, reactivated, and re-used;
3. methanol and CO_2 are the only by-products, and can be recycled to form DMC;
4. LA is a renewable, environmentally friendly feedstock.

Thus, not only it is demonstrated the potential of LA to develop new chemistry by using broad-based technologies to produce multiple outputs, but it is also implemented the use of a green reagent and green solvent (DMC) within these new methodologies.

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3 | UPGRADING OF BIO-BASED LACTONES

3.1. Introduction

3.1.1. Lactones from biomass

Current advances of research on the synthesis of biorefinery-derived chemicals have demonstrated that useful lactones can be obtained from biomass (Figure 3.1).

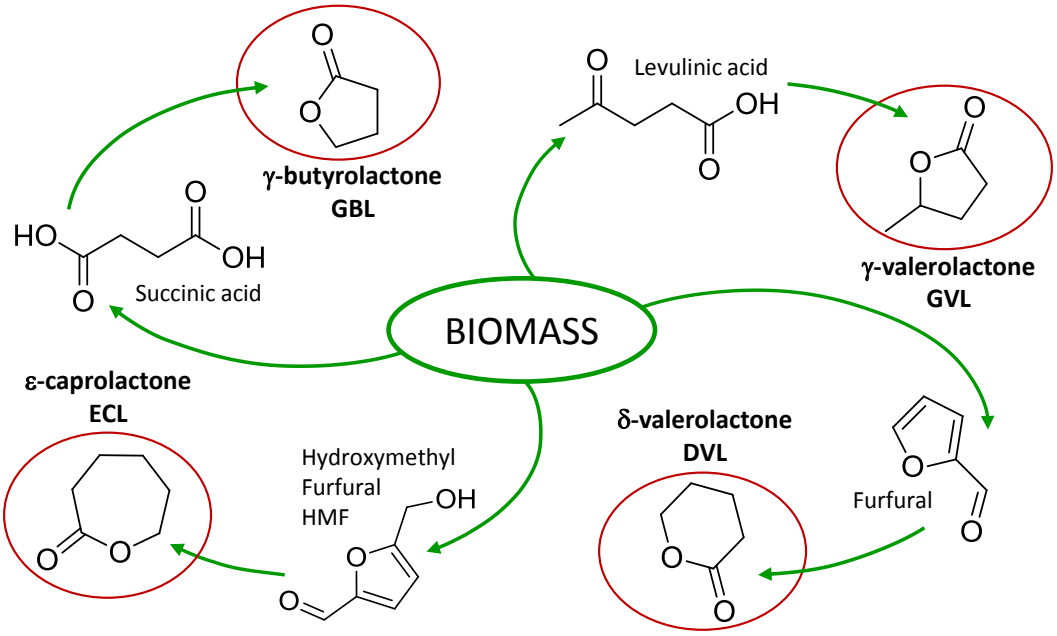
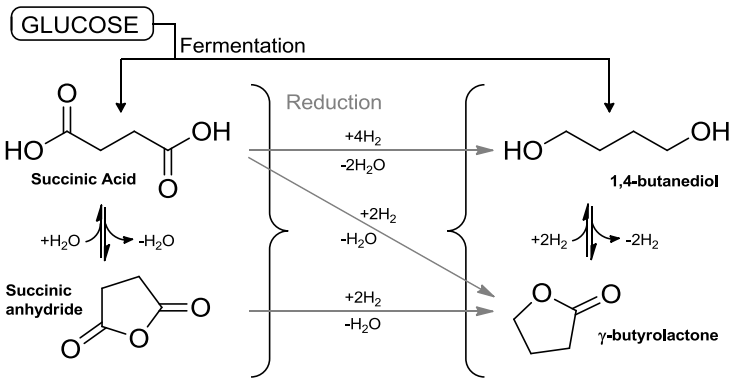


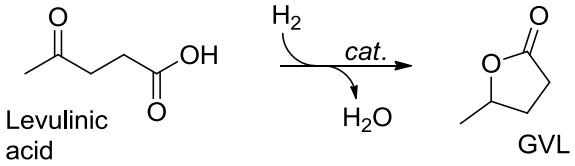
Figure 3.1. Routes to lactones from biomass.

For example, γ-butyrolactone (GBL) can originate reductively[1-3] from succinic acid (Scheme 3.1), that is one of the most promising bio-based chemicals[1, 4-6] obtainable from glucose via a fermentative pathway[7-11] GBL has recently been subject of widespread interest as solvent and intermediate.



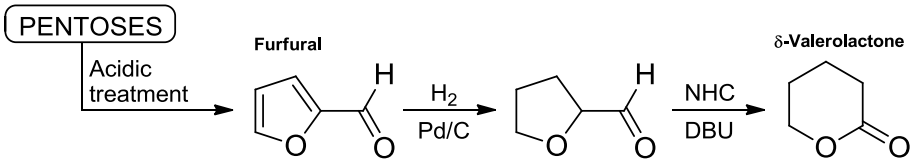
Scheme 3.1. γ-Butyrolactone (GBL) from succinic acid.

γ-Valerolactone (GVL) is directly obtainable in high yields by hydrogenation of levulinic acid (LA) (Scheme 3.2).[1] The latter is the main platform chemical obtained from the chemical transformation (acidic digestion) of cellulose and hemicelluloses. Processes for its production have already been patented,[12-15] proving also the economic feasibility of the whole transformation. This fact, together with the ease of LA lactonisation,[1617-18] has made GVL the most promising lactone obtainable from biomass. GVL research was addressed to its possible use for the production of biofuels[18-19] (valeric biofuels) and new solvents,[20] making it a hot topic of study.

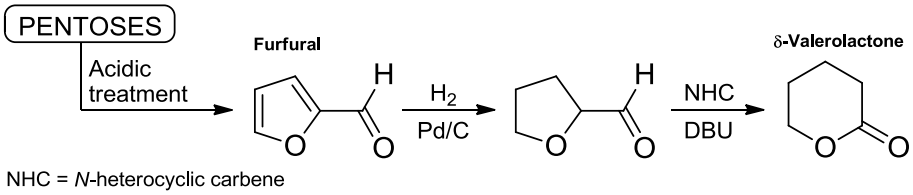


Scheme 3.2. γ-Valerolactone (GVL) from levulinic acid.

The production of six-membered ring δ-valerolactone (DVL) from biomass is still not as studied as GBL and GVL. However it is likely to become of greater interest, given its well-known use as a monomer.[21-25] One of the bio-based production processes starts from furfural (another platform chemical, obtained from acidic treatment of pentoses) by reduction to tetrahydrofurfural, followed by ring-expansion to DVL by means of an *N*-heterocyclic carbene (NHC = *N*-heterocyclic carbene



Scheme 3.3).[26] Another possible pathway to DVL involves reduction of glutamic acid to 1,5-pentanediol.[1] The latter can then undergo oxidation and lactonisation, as described in a recent paper.[27]



Scheme 3.3. Bio-based synthesis of δ-valerolactone.

Finally, it was recently demonstrated that also ECL can be obtained by a biobased route starting from hydroxymethylfurfural (HMF) in four steps, involving as intermediates 2,5-THFdimethanol (THFDM), 1,2,6-hexanetriol (1,2,6-HT), and 1,6-hexanediol (1,6-HD).[28]

3.1.2. Chemistry of lactones

Lactone structures are often present in natural compounds[29] and bio active molecules[29], such as sesquiterpene lactones[30] and some lignans[31] (Figure 3.2, left), and as a consequence their structure appears in many drugs such as macrolides (used as antibiotics[32] and anti-cancer agents[33])as well. Because of these reasons they have been the subject of fundamental as well as applied chemical research, the latter concerning especially polymers (Figure 3.2, right). Worth to be cited here are γ-butyrolactone, commonly used as a solvent or precursor for synthesis, and ε-caprolactone, widely used in the production of polymers).[34] The derivatisation of lactones has played and still plays an important role in the broadening of their possible uses.

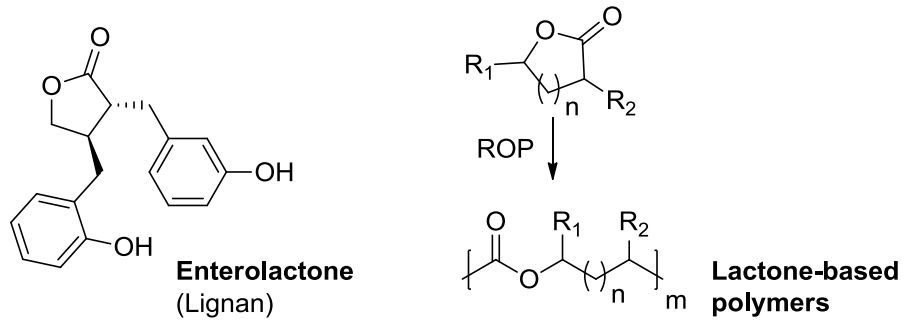
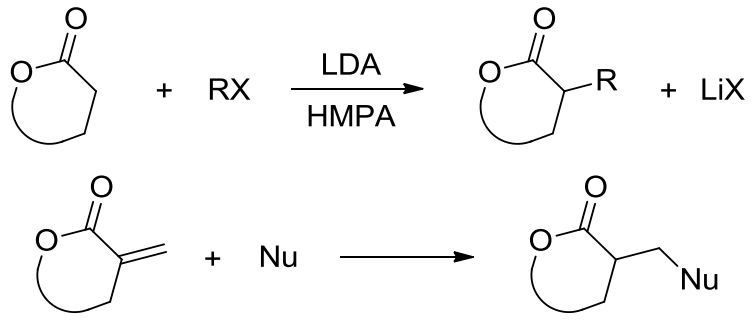


Figure 3.2 Examples of bio-active lactones.

Alpha-alkylation is one of the common methods used to modify lactones, but it generally involves the use of undesirable chemicals (dangerous to handle as well as for health and the environment) such as alkyl halides (Scheme 3.4, top),[35] sulfates, as well as of bases (generally lithium and potassium salts of organic bases[36-37]), whose use generates stoichiometric amounts of unwanted salts.



Scheme 3.4. Synthetic strategies towards alpha-alkyl lactones.

Another method used to obtain alpha-alkyl derivatives of lactones starts from the corresponding alpha-alkylidenes which are reacted with a suitable nucleophile (eventually generated in situ) in a Michael reaction (Scheme 3.4, down). However the production of alkylidenes from the corresponding lactones is generally not straightforward, due to the necessity of catalysts which are prone to deactivation.[38,39]

An alternative greener reagent was shown to be dimethyl carbonate (DMC), that acts as a methylating agent for several nucleophile, including alcohols, amines, and CH_2-active compounds under catalytic conditions.[40] In 1991 a preliminary report indicated that α-methyl-γ-butyrolactone was formed in the base-catalysed reaction of γ -butyrolactone with DMC.[41] More recently, Semak et al. also reported the synthesis of α -methyl-γ-butyrolactone by alkylation with DMC and K_2CO_3 at 210 °C.[42] Now, the possibility to develop this catalytic technology and apply it to bio-based platform chemicals, has become of interest. Not only are dialkylcarbonates generally regarded as safe chemicals, but the by-products of their reactions are CO_2 and the corresponding alcohol, both intrinsically easier to deal with than the salts originated by conventional alkylating agents (see above). It is noteworthy that DMC can be used both as reagent as well as reaction medium, implying that no additional solvent is required.

3.1.3. Aim

One of the crucial factors for the development of a competitive biorefinery industry will involve integrating the production of fuels (low added-value, short term revenue) with the development of new technologies for the production of chemicals.[6,43] Herein we propose new synthetic options for the upgrading of four bio-based lactones, with a view on obtaining alkylated derivatives and of demonstrating new chemical pathways for their catalytic transformation in an array of new products. To this strategy we also couple the use of green chemical technologies as we consider that the use of chemical reagents

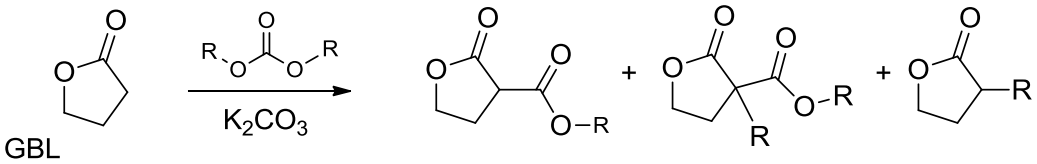
derived from renewable resources must go hand in hand with greener reaction protocols in order to be truly sustainable. To this end, in the past two decades, dialkylcarbonates have been extensively studied for greener reactions from bulk industrial to lab scale chemistry.[44-46] The tuneable reactivity and the low toxicity of dialkylcarbonates, particularly of lighter dimethyl and diethyl carbonate ($ROCO_2R$; R = Me, Et; DMC and DEC, respectively), have been key for their successful use as green reagents in place of hazardous reagents, such as phosgene and alkyl halides.[40] In this context, the reactivity of GBL, GVL, and DVL with organic carbonates ($ROCO_2R$; R=Me, Et, Bn) was examined under basic conditions. An array of compounds was obtained, some with excellent yields and selectivity.

3.2. Results

The reactions of γ-butyrolactone (GBL), γ-valerolactone (GVL), δ-valerolactone DVL), and ε-caprolactone (ECL) with dimethylcarbonate or diethylcarbonate (DMC or DEC: bp of 90 and 126 °C, respectively) were carried out in sealed steel autoclaves, using the organic carbonate as reagent as well as solvent and potassium carbonate as the base. The choice of K_2CO_3 as base was dictated by our previous experience on these kinds of alkylation reactions and by its easy separation and recovery from the final reaction mixture. For dibenzylcarbonate (DBnC, bp of 180-190 °C at 2 mmHg), the reactions could be conducted using standard glassware. The reaction temperatures were chosen in the range 180-220 °C, and the reaction times between 12 and 72 hours. The five-membered ring lactones GBL and GVL behaved similarly and are discussed together, while the six-membered lactones DVL and ECL are discussed separately.

3.2.1.1. Five-membered ring γ-butyrolactone and γ-valerolactone

γ-Butyrolactone. The products of the reactions of the five-membered GBL with three different dialkylcarbonates, in the presence of K_2CO_3 as catalyst, are summarized in Scheme 3.5.



3.1	R = CH_3 (DMC)	**3.1a**	**3.1b**	**3.1c**
3.2	R = CH_2CH_3 (DEC)	**3.2a**	**3.2b**	**3.2c**
3.3	R = CH_2Ph (DBnC)	**3.3a**	**3.3b**	**3.3c**

Scheme 3.5. Products of the base-catalysed reaction of γ-butyrolactone GBL with DMC, DEC and DBnC.

GBL and DMC. In order to establish experimentally viable conditions for the base-catalysed reaction between γ-butyrolactone and DMC, a range of reactions was run at 180 and 200 °C over different times. The results are summarized in Table 3.1.

Table 3.1. Reactions of GBL with DMC in the presence of K_2CO_3.

Entry[a]	Temp. (°C)	Time (h)	GBL:K_2CO_3 (mol/mol)	Conv.[b] (%)	Products (%)[b]			
					3.1a	3.1b	3.1c	Others[c]
1	180	3	1:1	76	38	33	1	4
2		12	1:1	99	14	30	35	20
3	200	6	1:1	99	4	28	39	28
4		20	1:1	100	0	13	51	36
5		24	1:0.2	100	0	22	64	14

[a]All reactions were performed using a molar ratio GBL:DMC = 1:15.[b]Conversions and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

At 180 °C, complete conversion of GBL was reached after 12 h (run 2) with a widely dispersed product distribution (**3.1a** : **3.1b** : **3.1c** = 14 : 30 : 35) accompanied by sizeable amounts (20%) of unidentified by-products. By raising the temperature to 200 °C complete conversion was achieved already after 6 h. In this case selectivity towards the methylated product **3.1c** appeared to become favoured. By prolonging the reaction time to 20 h at 200 °C, selectivity towards products **3.1a** and **3.1b** decreased down to 0 and 13% respectively and a selectivity of 51% to **3.1c** was observed. Larger amounts of unidentified heavier products were however also observed (36%). The product distribution profile for the reaction of line 4 of Table 3.1 is shown in Figure 3.3. The graph indicates that **3.1a** and **3.1b**

show intermediate-like behaviour and that **3.1c** is the main product. **3.1c** was isolated from the reaction of line 4 of Table 3.1, with a final yield of 45%.

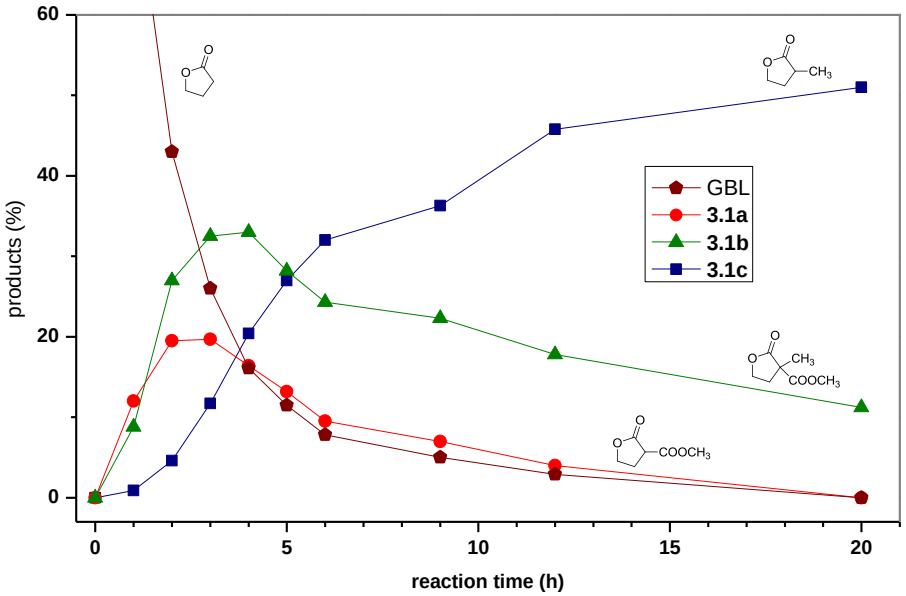


Figure 3.3. Reaction between GBL and DMC in the presence of K_2CO_3 at 200°C.

In order to confirm the catalytic nature of the reaction, an experiment was also run in the presence of sub-stoichiometric amounts of K_2CO_3 (20% molar with respect to GBL). Under these conditions, 100% conversion was reached after 24 h, and products **3.1b** and **3.1c** were obtained with 22% and 64% selectivity, respectively (entry 5).

GBL and DEC. The reaction between γ-butyrolactone GBL and DEC was conducted under the same experimental conditions than with DMC. However, being the reaction slower in this case, higher temperatures were also tested. The results are listed in Table 3.2.

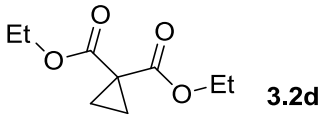
Table 3.2. Reactions of GBL with DEC in the presence of K_2CO_3.

Entry[a]	Temp. (°C)	Time (h)	Conv.[b] (%)	Products (%)[b]			
				3.2a	3.2b	3.2c	Others[c]
1	180	24	80	41	17	2	20
2	200	12	92	33	34	2	23
3	210	72	100	0	5	56	39
4	220	48	100	0	4	52	44

[a]All reactions were performed using a molar ratio GBL:DEC = 1:12 and GBL:K_2CO_3 = 1:1. [b]Conversion and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

At 180 °C, 80% conversion was reached after 24 h, with moderate (41%) selectivity towards the carboxymethylated product **3.2a**. At 200 °C almost quantitative conversion was achieved after 12 h with poorer selectivity (33 and 34% of **3.2a** and **3.2b** respectively), while at 210-220 °C, the selectivity towards **3.2c** was up to 52-56% at complete conversion (entries 3-4). Compound **3.2c** was isolated in a 45% yield.

Among major co-products of the reaction between GBL and DEC (Table 3.2, entry 4), diethyl cyclopropane-1,1-dicarboxylate (**3.2d**) was isolated in a 8% yield. (Figure 3.4).



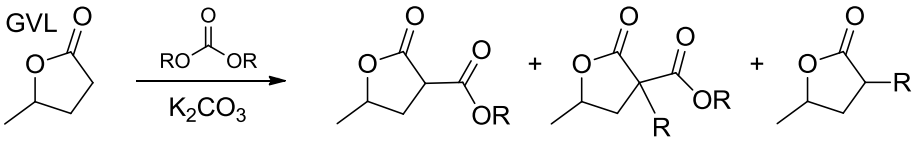
3.2d

diethyl cyclopropane-1,1-dicarboxylate

Figure 3.4. Co-product of the reaction between GBL and DEC.

GBL and DBnC. The reaction between GBL and DBnC was conducted at 200 °C for 12 hours, using a molar ratio GBL:DBnC = 1:1.1 and GBL:K_2CO_3 = 1:1. A 90% gaschromatographic yield of **3.3c** was obtained. The purification of compound **3.3c** required distillation at reduced pressure followed by FCC. The product was isolated in 50% yield.

γ-Valerolactone. The products of the reactions of γ-valerolactone GVL with the three different dialkylcarbonates, in the presence of K_2CO_3, are summarized in Scheme 3.6.



4	R = CH_3 (DMC)	**4a**	**4b**	**4c**
5	R = CH_2CH_3 (DEC)	**5a**	**5b**	**5c**
6	R = CH_2Ph (DBnC)	**6a**	**6b**	**6c**

Scheme 3.6. Products of the base-catalysed reaction of GVL with DMC, DEC and DBnC.

GVL and DMC. Based on the results with GBL, the reaction between γ-valerolactone and DMC was run directly at the higher temperatures of 200 and 220 °C (Table 3.3).

Table 3.3. Reactions of GVL with DMC in the presence of K_2CO_3.

Run[a]	T (°C)	Time (h)	Conv.[b] (% GC)	Products (% GC)[b]			
				3.4a	3.4b	3.4c	Others[c]
1	200	16	89	4	43	39	3
2		24	98	3	26	68	1
3		32	100	2	15	80	3
4	220	24	100	0	8	90	2

[a]All reactions were performed using a molar ratio GVL:DMC = 1:15 and GBL:K_2CO_3 = 1:1. [b]Conversions and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

GVL reacted much more cleanly with DMC than GBL. At 200-220 °C, the conversion reached 100% after 32 and 24 hours, respectively, with very high selectivity (80-90%) towards the mono-methylated product **3.4c (**runs 3 and 4). Unidentified by-products were in only 2-3% amounts. The profiles of reaction conversion and product distribution *vs* time are shown in Figure 3.5.

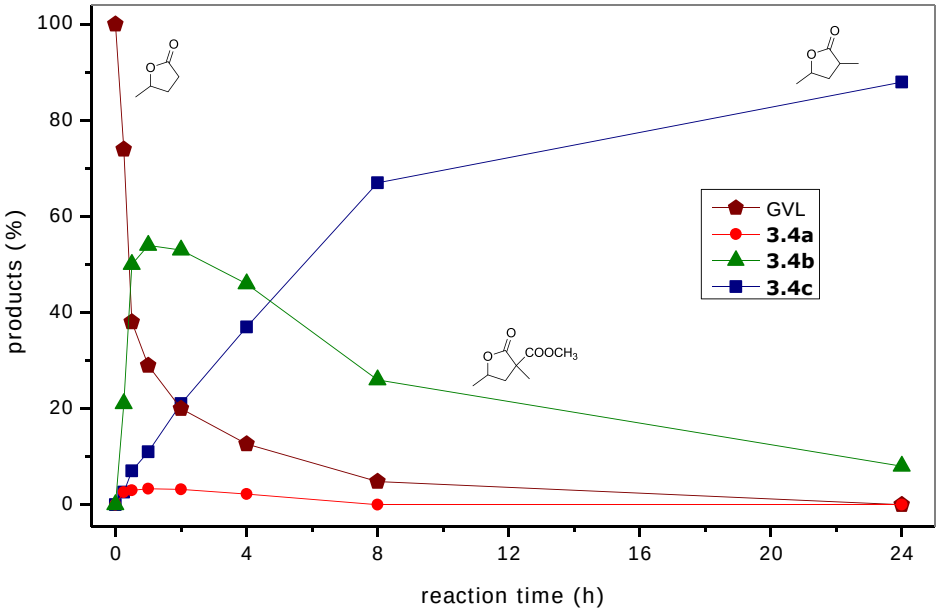


Figure 3.5. Reaction between GVL and DMC in the presence of K_2CO_3 at 200°C.

The α-methylated product **3.4c** was distilled under reduced pressure and it was isolated in 82% yield (purity >95%).

GVL and DEC. The K_2CO_3 [illegible] -valerolactone GVL and DEC was slower than with DMC. Table 3.4 describes the mixture compositions after different reaction times at 220 °C.

Table 3.4. Reactions of GVL with DEC in the presence of K_2CO_3.

Entry[a]	Time (h)	Conv.[b] (% GC)	Products (% GC)[b]			
			3.5a	3.5b	3.5c	Others[c]
1	16	88	2	62	24	0
2	24	94	1	60	32	1
3	48	100	0	34	56	10
4	72	100	0	4	71	25

[a]All reactions were performed at 220°C using a molar ratio GVL:DEC = 1:12 and GVL:K_2CO_3 = 1:1. [b]Conversions and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

Selectivity towards **3.5c** increased with time, although at complete conversion by-products started to ensue. After 72 hours 71% of the ethylated product was observed along with 25% of unwanted compounds. The α-ethylated product **3.5c** was distilled under reduced pressure and it was isolated in a 50% yield (purity >95%).

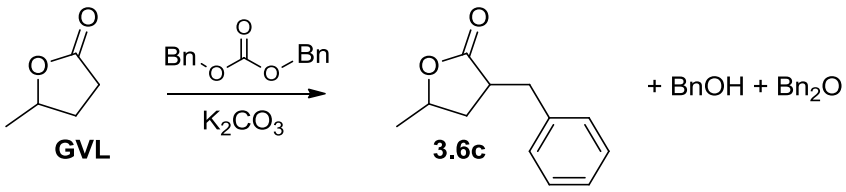
GVL and DBnC. The K_2CO_3 catalysed reaction of GVL with dibenzylcarbonate took place cleanly at lower temperature (see Table 3.5).

Table 3.5. Reactions of GVL with DBnC in the presence of K_2CO_3.

Run[a]	Temp. (°C)	Base/GVL (mol/mol)	time (h)	Conv.[b] (%)	Products (%)[b]	
					3.6c	Others[c]
1	200	1	24	98	92	8
2		0.5	24	98	91	9
3	170	1	24	64	98	2

[a]All reactions were performed using a molar ratio GVL:DBnC = 1:1.1. [b]Conversion and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

After 24 h, and at 64% conversion, a selectivity of 98% was observed already at 170 °C. By raising the temperature to 200 °C conversion reached 98% with 92% selectivity towards the benzylated lactone **3.6c** after 24 h. Benzyl alcohol and dibenzyl ether were also observed in the reaction mixture (Scheme 3.7). No intermediate products were present.

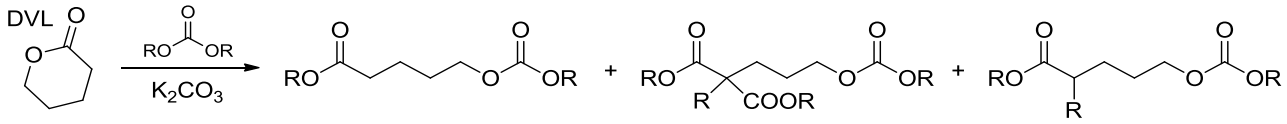


Scheme 3.7. Reaction of GVL with dibenzylcarbonate.

Since the purification of compound **3.6c** required distillation at reduced pressure followed by FCC, it could be isolated in only a 65% yield (purity >98%).

3.2.1.2. Six-membered ring δ-valerolactone

δ-Valerolactone. The products of the reactions of six-[redacted]-valerolactone DVL with three different dialkylcarbonates, in the presence of K_2CO_3 as catalyst, are summarized in Scheme 3.8.



7	R = CH_3 (DMC)	3.7a	3.7b	3.7c
8	R = CH_2CH_3 (DEC)	3.8a	3.8b	3.8c

Scheme 3.8. The base-catalysed reaction of δ-valerolactone DVL with DMC and DEC.

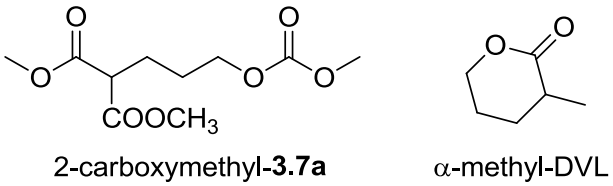
DVL and DMC. The K_2CO_3 catalysed reaction of δ-valerolactone with DMC was initially performed on small scale (0.27 g, 2.69 mmol of substrate). Scheme 3.7 summarises the results obtained running the reactions for different times at 200 °C. Molar ratios were the same as above: DVL:DMC = 1:15 and DVL:K_2CO_3 = 1:1.

Table 3.6. Reactions of DVL with DMC in the presence of K_2CO_3.

Entry[a]	DVL (g)	Time (h)	Conv.[b] (% GC)	Products (% GC)[b]			
				3.7a	3.7b	3.7c	Others[c]
1	0.27	1	99	78	12	2	6
2		4	99	67	18	7	7
3		6	99	63	16	10	10
4		12	99	40	11	36	12
5		24	>99	18	5	64	13
6	2.00	4	99	94	3	>1	2
7		24	100	34	19	29	18

[a]All reactions were performed at 200 °C using molar ratios DVL:DMC = 1:15 and DVL:K_2CO_3 = 1:1. [b]Conversions and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

After one hour conversion was already quantitative. The major component of the mixture was 4-(methoxycarbonyl)butyl methyl carbonate **3.7a** that derived from a ring-opening transesterification reaction. By prolonging the reaction time (as well as by increasing the temperature) sizeable amounts of its α-methyl derivative **3.7c** were formed (Scheme 3.8). The third major component was not isolated. However, it was identified as intermediate **3.7b** by GC-MS and ^{1}H-NMR analyses of the crude mixture. MS spectra also suggested that by-products labelled as "others" were most likely the 2-carboxymethyl-**3.7a**, and α-methyl-DVL (Figure 3.6).



2-carboxymethyl-**3.7a** α-methyl-DVL

Figure 3.6. Plausible by-products of the reaction between DVL and DMC.

In order to monitor the reaction progress, a larger-scale reaction was set up and sampled at time intervals (see experimental section). Figure 3.7 shows the profiles of the reactant DVL, and the major products **3.7a** and **3.7c**, respectively, over time. The reaction was slower than the ones of Table 3.6, due to the higher amounts involved. Nonetheless, the trend was consistent: the ring-opening transesterification product **3.7a** was obtained first (0 to 4 hours, Figure 3.7); followed by the alpha methylation derivative **7c** (4 to 48 hours, Figure 3.7). Product **3.7a** was isolated in 80% yield from the reaction of Table 3.6, run 6, by distillation under reduced pressure (b.p. 70 °C at 150 Pa). Product **3.7c** was isolated in 44% yield from the reaction of Table 3.6, run 5, by FCC (see Experimental section).

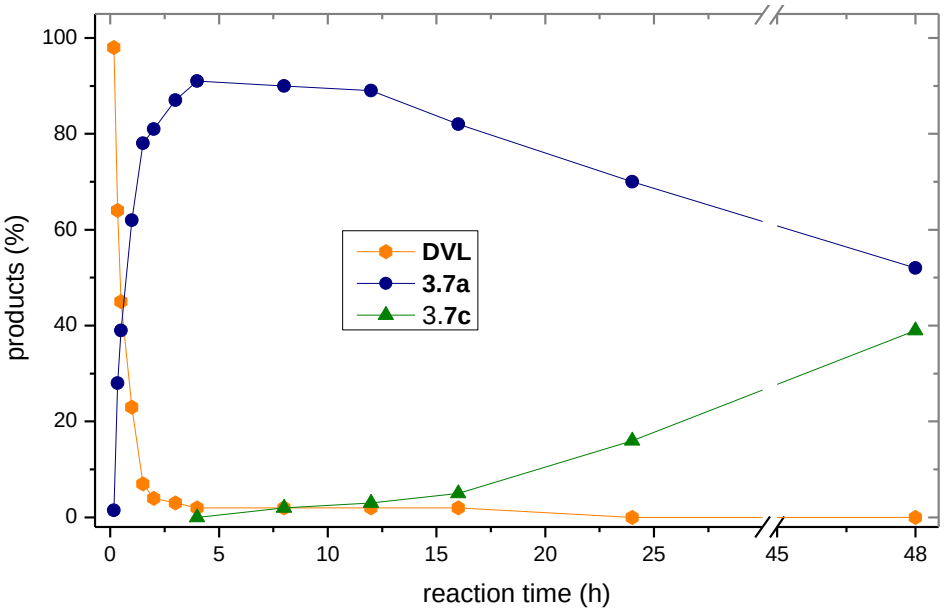


Figure 3.7. Reaction between DVL (4 g, 39.95 mmol) and DMC in the presence of K_2CO_3 as catalyst at 200°C.

DVL and DEC. The reaction of DVL with DEC was carried out under conditions similar to those used with DMC (Table 3.7). An analogous trend was observed: the ring-opening transesterification product **3.8a** was obtained first. It was then consumed in favour of **3.8c**. The overall process went through the intermediate **3.8b** (identified by GC-MS). Plausible by-products were the corresponding ethyl-derivatives of compounds in Figure 3.6.Product **3.8a** was isolated by distillation under reduced pressure (b.p. 81 °C at 0.8 mmHg) in 75% yield from the reaction of Table 3.7, entry 2.

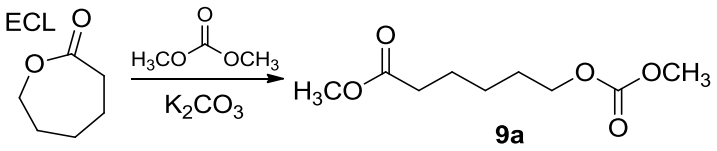
When the K_2CO_3 catalysed reaction of DVL with DBnC was attempted, none of the above ring-opening or alkylation products were observed, rather DBnC was always present in the final reaction mixture, accompanied by BnOH and Bn_2O as side products. This led us to postulate extensive polymerisation of DVL.[47]

Table 3.7. Reactions of DVL with DEC catalysed by K_2CO_3.

Entry[a]	DVL (g)	time (h)	Conv.[b] (%)	Products (%)[b]			
				3.8a	3.8b	3.8c	Others[c]
1	0.27	6	100	53	25	5	17
2	2.00		97	90	5	>1	2

[a]All reactions were performed at 200°C using molar ratios DVL:DEC = 1:15 and DVL:K_2CO_3 = 1:1. [b]Conversions and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

ε-Caprolactone. In order to confirm the reactivity observed for δ-valerolactone, the K2CO3 catalysed alkylation reaction of the seven-membered ring ε-caprolactone was carried out with DMC. The reaction was performed on a 2.00 g (17.52 mmol) scale, using the same molar ratios as above (DVL:DMC = 1:15 and DVL:K2CO3 = 1:1), at 200 °C for 6 h. The observed product was methyl-6-((methoxycarbonyl)oxy)hexanoate **3.9a**, the analogue of **3.7a** obtained previously for DVL (Scheme 3.9).

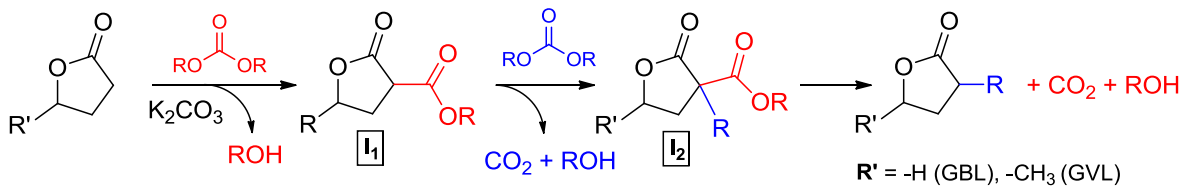


Scheme 3.9. Reaction of ECL with DMC.

3.3. Discussion

The K_2CO_3 catalysed reaction of 5-membered ring lactones with dialkylcarbonates used as reagent and solvent proceeded to yield the α-alkylated homologues. The reaction pathway was similar to one reported elsewhere.[41] It involved three steps and consumed 2 moles of dialkylcarbonate $ROCO_2R$ per mole of lactone, as determined by previous investigations[48] and confirmed in our case by the intermediates observed in the reactions of γ-valerolactone and γ-butyrolactone. In the first step the carboxyalkyl derivative I_1 was formed by a $B_{AC}2$ (Base catalyzed, ACyl-oxygen bond breakage, 2 refers to the bimolecular nature)attack of the nucleophilic α-carbon of the lactone to $ROCO_2R$; in the second step the alkyl-carboxyalkyl derivative I_2 was formed by a $B_{AL}2$ reaction (Base catalyzed, Alkyl-oxygen bond breakage, bimolecular)with a second molecule of $ROCO_2R$; then, in the third and final step, decarboxylation afforded the α-alkylated lactone plus a third molecule of ROH (

Scheme 3.10).



Scheme 3.10. Base catalysed alkylation of 5-membered ring lactones with dialkyl carbonate.

The reactions required relatively high temperatures in order to be practical: 200 °C for GBL with DMC and 220 °C for GVL with DMC. In the case of diethyl carbonate (DEC) a poorer reactivity was expected with respect to DMC: accordingly, the reaction was slower even at a higher temperature. Though, by prolonging the reaction up to 72 hours, it was still possible to obtain good yields of the desired alpha-ethyl substituted lactone for both GBL and GVL. In analogy to previous findings,[49] a higher reactivity was observed for dibenzyl carbonate (DBnC): the reaction was much faster, possibly due to the activated benzylic position of the carbonate. No intermediate species were observed for DBnC, although these were still probably formed under the reported conditions. In all cases, the co-products of the alkylation reactions were CO_2 and the corresponding alcohol ROH. Other possible by-products were the ethers (ROR) obtained by decarboxylation of the dialklycarbonates, but these were ignored out based on a previous investigation[50] where the extent of DMC decarboxylation was measured in the presence of different catalytic materials. At that time we observed that in the presence of K_2CO_3, after 6 h at 200 °C, the extent of DMC that was converted to the corresponding dimethylether was limited to 4%. The low extent of decarboxylation measured under the previously reported conditions prompted us to neglect this possible by-product in the present investigation.

The reaction of the 5-membered ring lactones with the three carbonates DMC, DEC and DBnC could be pushed to yield the mono–α-alkylated products **3.1c**-**3.6c** with good to high selectivity (50-90%) and isolated yields (40-80%) as summarized in Table 3.8.

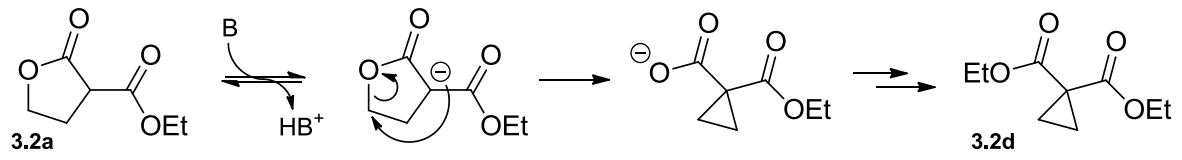
Table 3.8. Comparison between the reactions of GBL and GVL.

Product	Time (h)	conv.[a] (%)	% (GC/MS)	Yield[b] (%)	Others[c] (%)
3.1c	24	100	51	45	38
3.2c	72	100	56	40	39
3.3c	12	100	88	50	12
3.4c	24	100	90	82	2
3.5c	72	100	76	50	16
3.6c	12	98	85	65	15

[a]Conversions and product percentages in the final mixture were determined by GC/MS analysis. [b]isolated yield, [c]"Others" refers to products, the majority of which were not identified.

It should be highlighted that all the reported reactions were catalytic transformations. This was here further demonstrated *una tantum* by reacting GBL in the presence of a catalytic amount of K_2CO_3(20 mol% with respect to GBL, entry 5 of Table 1), and observing that 100% conversion of the substrate was achieved, with 64 and 22% selectivity towards **3.1c** and **3.1b** respectively. In all the other cases, albeit used in stoichiometric amounts, K_2CO_3 acted as a catalyst. This was confirmed by the fact that in its absence the reaction was inhibited, that its presence accelerated the reaction, that it was not consumed, and that at the end of the reaction it could be recovered unchanged and filtered off to be re-used. An accurate mass balance of recovered K_2CO_3 was not repeated here since previous work, as recent as 2012,[51] had indicated that its recovery was quantitative and its activity unchanged for successive cycles. Other authors have proposed methoxide (CH_3OK) as the active alkaline species for this transformation, formed in the reaction environment by disproportionation of K_2CO_3 in the presence of DMC at T > 200 °C.[42] Although this possibility is plausible, it should be noted that the nucleophilic activation of phenylacetonitrile by K_2CO_3 was observed previously at temperatures as low as 140 °C,[48] where the formation of methoxide is likely to be disfavored.

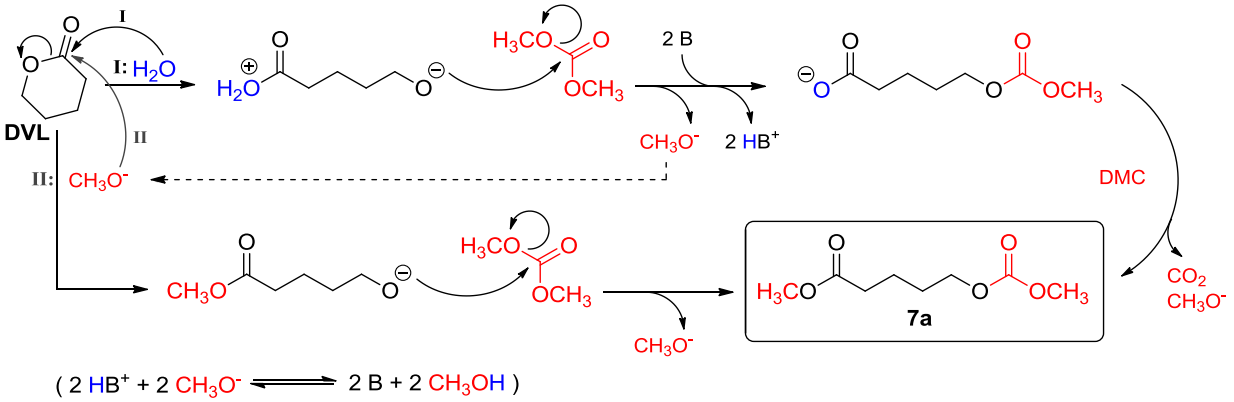
It was readily apparent that the reactions of GBL with DMC and DEC (products **3.1c** and **3.2c** of Table 3.8) suffered from the formation of by-products. On the contrary the reactions of GVL were in general high yielding and selective. Our hypotheses to explain this different behavior were based on two facts. First, the inherent chemical stability of GVL due to its low ring strain[47] makes it likely less prone to parallel side reactions. Secondly, GBL is likely to undergo nucleophilic attack at the gamma as well as at the alpha positions. The higher reactivity of GBL and its easier ring-opening could therefore lead to a plethora of compounds. This was confirmed by some of the observed by-products, the MS spectra of which suggested the formation of dimers. The observed side product **3.2d** shown in Figure 3.4 also lends support to this analysis: the formation of **3.2d** can be explained by ring contraction of intermediate **3.2a** obtained *via* intramolecular nucleophilic attack as shown in Scheme 3.11. This cyclization can be classified as *3-exo-tet* according to Baldwin,[52] and is therefore favoured.



Scheme 3.11. Hypothesis of mechanism for 3.2d formation.

GVL on the other hand reacted very cleanly and selectively with dialkylcarbonates, especially DMC. The methyl group protects the gamma position from further reactions, and directs the selectivity towards the alpha attack. Interest in this renewable lactone, coupled with the use of a safer greener reagent such as DMC and of a catalytic protocol, exemplify in our view a pathway towards the development of a truly sustainable reaction.

Six- and seven-membered ring DVL and ECL were subjected to the same reactions as the other lactones, but the outcome was markedly different. Rather than giving alpha-alkylated lactones, both these substrates underwent a ring-opening reaction that yielded highly oxygenated acyclic products **3.7a**, **3.8a**, and **3.9a**, bearing an ester and a carbonate group at each end. In our hypothesis, ring opening of DVL and ECL was favoured by the presence of traces of water (path I, Scheme 3.12). The open compound reacted then twice with DMC, releasing methoxide, which could in principle continue ring-opening *via* the second pathway (II) shown in Scheme 3.12.



Scheme 3.12. Hypothesis of mechanism for the K_2CO_3 catalysed reaction between DVL and DMC.

This ring-opening behaviour was due to the higher reactivity of the six- and seven-membered ring lactones respect to the five-membered ones,[53] as confirmed also by the fact that DVL and ECL are widely used monomers for ring opening polymerization. In this context it is worth underlining that DVL transforms into linear polyesters merely on storage at room temperature.[47] Therefore, a reaction such as the one here described that allows to trap DVL and ECL in a monomeric form may provide a useful synthetic perspective, particularly in view of the high oxygen content of product **3.7a** and **3.9a**. It should also be noted that few examples exist in the literature in which a carbonate formally acts as an oxidant.[54] While ring-opening of DVL was extremely fast, still traces of α-methyl DVL were observed in the reaction mixture by GC-MS, thus confirming the

reactivity of organic carbonates with lactones. Ring-opened products **3.7a** and **3.8a** reacted further with DMC under the present alkaline conditions and formed the alkylated products **3.7c** and **3.8c** analogously to what was observed in previous studies.[41]

3.4. Conclusions

This work highlights potential upgrading pathways of four lactones (GBL, GVL, DVL, ECL) obtainable from a renewable biorefinery scheme, by using a set of green and safe compounds such as dimethyl-, diethyl-, and dibenzylcarbonates, and catalytic reactions. Carbonates not only displayed a double reactivity as alkylating and carboxyalkylating agents of lactones, but they also served as solvents. Accordingly, in the presence of K_2CO_3 as a base, the product distribution of the investigated reactions could be tuned by variations of temperature and time. Based on kinetic profiles, some insight is obtained as to the reaction mechanisms.

The overall balance of the reaction yields one mole of α-alkyl-lactone, three of alkyl-alcohol and two of CO_2 starting from one mole of lactone and two moles of dialkyl carbonate (Scheme 3.13). The alcohol can in principle be re-used to synthesize the starting carbonate, and K_2CO_3 is recovered unchanged at the end of the reaction.

Overall reaction:

$$\text{Lactone} + 2\text{ROCO}_2\text{R} \xrightarrow[\text{Cat.}]{\Delta} \alpha\text{-R-Lactone} + 3\text{ROH} + 2\text{CO}_2$$

Scheme 3.13. Overall reaction for the alkylation of lactones.

Finally, heterogeneous catalysis itself represents one of the strongholds of green chemistry as it allows to intensify the process, reduce the energy demand, improve selectivity, and accelerate reaction rates. In this context, the catalyst used (K_2CO_3) is a safe and easily recoverable and recyclable compound. Moreover, in perspective, the overall procedure is perfectly suited to be intensified by moving to continuous flow catalytic conditions. The intrinsic value of these kinds of transformations can therefore epitomise a green and sustainable processes towards new bio-based chemicals.

3.5. Bibliography

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4 | RING OPENING OF BIO-BASED LACTONES

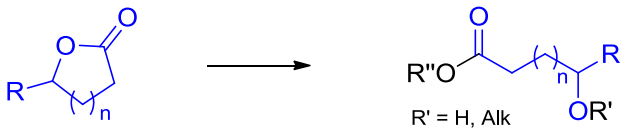
4.1. Introduction

In the previous chapter the alpha alkylation of the most promising bio-derived lactones based on the use of dialkyl carbonates in conditions of basic catalysis has been described. Here it is described another opportunity to transform bio-derived lactones, into a different set of compounds. In this case the derivatives, originated by ring-opening of the lactonic ring, are generated in conditions of acid catalysis. The selectivity is shown to be mediated by the presence of dimethyl carbonate (DMC), which plays an important role never observed before. A study of a continuous flow process, carried out using solid acid catalysts, completes this chapter, demonstrating the applicability of our methodology.

4.1.1. Lactone derivatives

4-alkoxybutanoyl and 5-alkoxypentanoyl moieties for the synthesis of fine chemicals

Lactones can be used as starting materials for the synthesis of the corresponding alkoxy opened form (Scheme 4.1).



Scheme 4.1. Ring opening of a generic lactone to yield the corresponding alkoxy derivative.

In particular, 4-methoxy-butanoyl and 5-methoxy-pentanoyl moieties have been used for decades in the design of biologically active molecules, such as: antibiotics,[1-2] prostaglandins[3-5] and their antagonists, analgesics,[6] bronchodilators,[7-8] antiarrhythmics,[9] and flavourants[10] (see some examples in Figure 4.1).

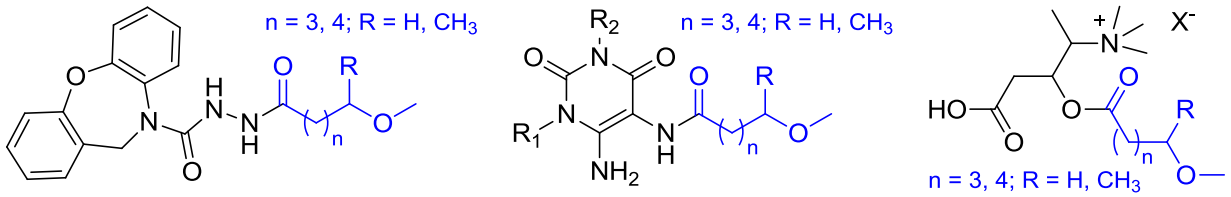
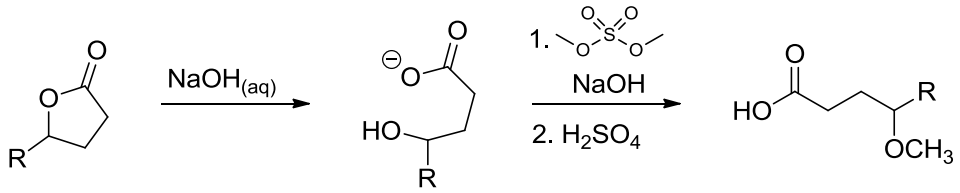


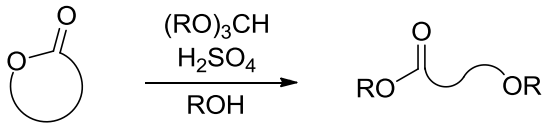
Figure 4.1. Bioactive molecules containing the 4-methoxbutanoyl- and 5-methoxypentanoyl- moieties.

Lactone ring opening to yield 4-alkoxybutanoyl and 5-alkoxypentanoyl moieties is commonly achieved via the classical methodology developed by Reppe, which starts with the alkaline hydrolysis of the lactone followed by methylation with dimethyl sulfate and neutralisation (Scheme 4.2).[11]



Scheme 4.2. Reppe's route to alkoxy carboxylic acids.

Despite its use of dangerous chemicals (*e.g.* dimethyl sulfate is very toxic, fatal if inhaled, carcinogenic and a suspect mutagen), this is still the favourite production route, in consideration of its simplicity and its high yields. One of the most accredited alternatives is the route developed by King, which performs the ring opening via alcoholysis, mediated by orthoformates, in acidic catalysis (see Scheme 4.3).[12]



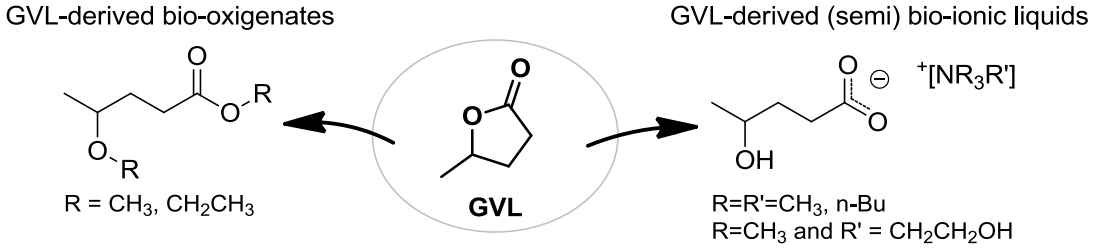
Scheme 4.3. King's route to alkoxy esters.

This allows to achieve good yields starting from a series of lactones. However safety and storage concerns are only reduced, being orthoformates generally irritating and reactive.

Alternative solvents

Bio-derived lactones, besides being considered as renewable building blocks (see previous chapter), are currently investigated as alternative solvents. Especially γ–valerolactone (GVL) received much attention from this point of view: its physical and chemical properties make it an excellent candidate as a renewable, non-toxic and

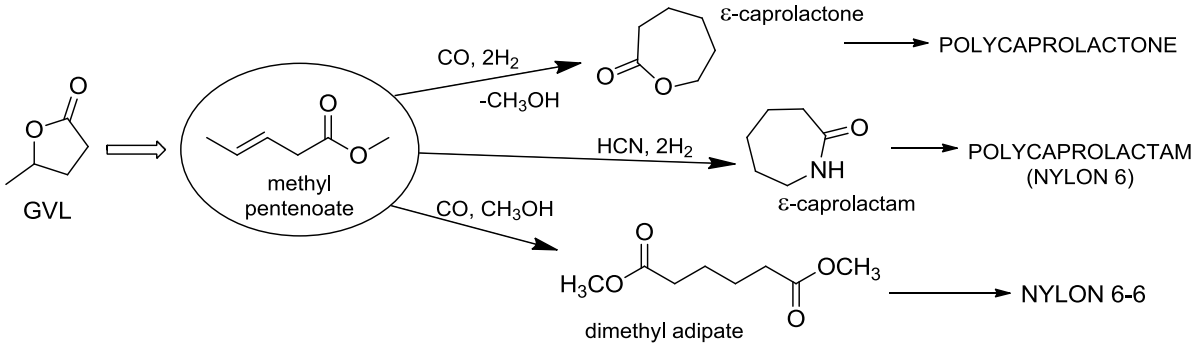
biodegradable solvent. Recently some of its derivatives (again the alkoxyesters, and novel ionic liquids; see Scheme 4.4) started to be investigated as oxygenated solvents and for other applications. The first in particular exhibited a lower vapour pressure, sometimes desirable, than other commonly used oxygenated solvents, while the new ionic liquids exhibited properties (viscosity, conductivity and vapour pressure) in line with those of other known ones.[13]



Scheme 4.4. GVL as source of alternative solvents as proposed by Horváth *et al.*[13]

Alternative sources of monomers

GVL has also been investigated for the synthesis of pentenoates, from which various monomers can be prepared: ε-caprolactone, ε-caprolactam or adipates can be obtained via hydroformylation, hydrocyanation or hydroxycarbonylation respectively.[14-15]

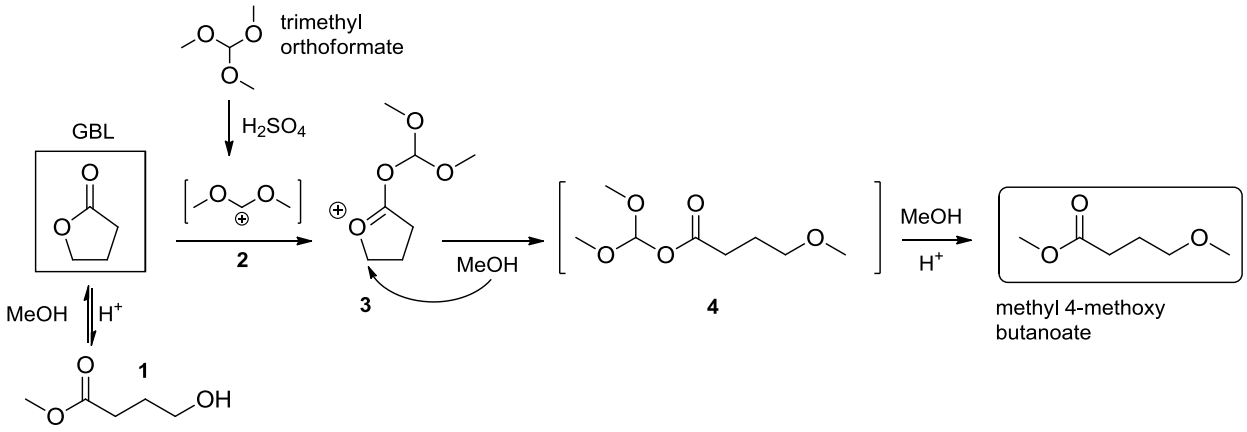


Scheme 4.5. Possible monomers deriving from GVL.

4.1.2. An innovative (green) route to ring-opened GVL derivatives

The synthesis of ring-opened derivatives of lactones has been briefly described in the previous paragraph. While the alcohols can be obtained via basic hydrolysis, the preparation of the corresponding alkoxy-derivatives is not trivial. The best choices are the classical route that uses dangerous compounds (see Scheme 4.2), and an alternative pathway that uses orthoesters[12] that are safer than dimethylsulfate, but fairly unstable and quite expensive. Based on the observed mode of action of orthoesters for lactone ring opening (see scheme 4.5) an analogous route for GVL alcoholysis using dimethylcarbonate

(DMC) as a mediator, in conditions of acidic catalysis, was envisaged. While DMC and its homologues dialkylcarbonates can be efficiently employed for alkylation and carboxyalkylation reactions in basic catalysis, very few examples of the reactivity of DMC in acidic conditions are known. Among these, anyway, the reactivity is the classical one: the nucleophilic substitution at the carbonyl (described in chapter 1, paragraph 1.3.1.2 "Organic carbonates"). The hypothesis was that DMC could exhibit a reactivity analogous to the one of orthoesters proposed in King's work.[12] In that paper a mechanism was proposed, on the basis of various tests and of the documented formation of the species 2 in acidic conditions (see Scheme 4.6).



Scheme 4.6. Mechanism proposed by King for the synthesis of 4-methoxy butanoate from GBL.[12]

The proposed mechanism involves the formation of cation 2, generated by the orthoester in the presence of an acid. This acts as a Lewis acid by coordinating the carbonyl and activating the 4 position rather than the carbonyl of the lactonic ring, thereby promoting nucleophilic substitution of methanol and the observed ring opening. The hypothesis was that dimethyl carbonate would behave similarly to trimethylorthoformate. Its carbonyl is polarisable in the presence of an acid thereby enhancing the electrophilic character of the carbonyl carbon. Thus, in principle, protonated DMC should behave analogously to the cationic species 2 in the mechanism proposed by King. This possibility introduces the aim of the present work.

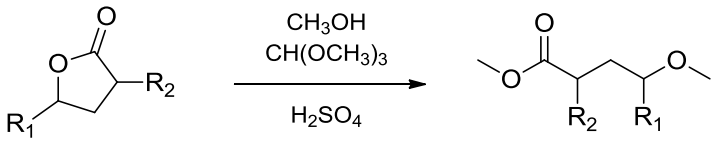
4.1.3. Aim

GVL was chosen as a model lactone to study the acid-promoted ring-opening reactions. Based on the working hypothesis outlined above, the research was initially focused on the selective opening of GVL to 4-methoxy-pentanoate **4.2**, rather than the corresponding alcohol (4-hydroxy-pentanoate, **4.1**). For this purpose we investigated the

methanolysis of GVL with DMC in acidic conditions. Such conditions were never investigated before, and they led to an outcome that seems to confirm our initial hypothesis of DMC as a mediator to direct the selectivity. The proposed theory was supported both by experimental data as well as by computational calculations, and a mechanism was proposed. The possibility of generating alkoxy-ester moieties by using the green reagent DMC in place of the exotic orthoesters or, especially, the toxic dimethylsulfate is intriguing. To further develop our technology, and to give it an even greener character by using solid acid catalysts in place of inorganic/organic acids, we undertook a study of the same reaction in continuous flow conditions. In such environment the generation of pentenoates, **4.3**, (see paragraph 4.1.1) was also considered.

4.2. Results

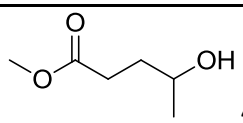
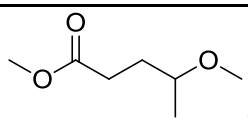
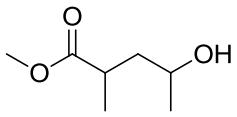
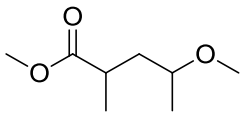
Reference compounds for analytic comparison were prepared by the method described by King[12] (see introduction) to open the lactonic rings. Lactones were added to a mixture of methanol, trimethylorthoformate and a catalytic amount of sulfuric acid, and then heated to reflux for the required time (see experimental part).



Scheme 4.7. Ring-opening of lactones via orthoester-mediated methanolysis.

The corresponding alcohols were synthesised via basic hydrolysis of lactones, followed by esterification. All the reference compounds obtained are summarised in Table 4.1.

Table 4.1. Compounds obtained from ring opening of lactones.

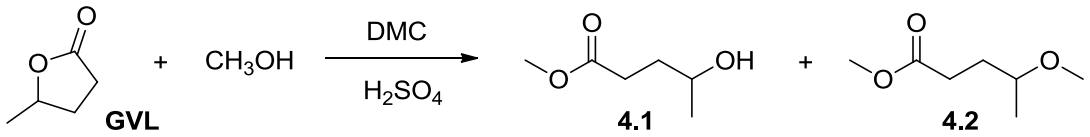
Lactone	Hydroxy derivative	Methoxy derivative
$R_1 = CH_3$, $R_2 = H$ (GVL)	 **4.1** methyl 4-hydroxypentanoate	 **4.2** methyl 4-methoxypentanoate
$R_1 = CH_3$, $R_2 = CH_3$ (α-Me GVL)	 **4.4** methyl 2-mehtyl-4-hydroxypentanoate	 **4.5** methyl 2-mehtyl-4-methoxypentanoate

Next a series of reactions was carried out using DMC in place of orthoesters. All the experiments aimed at the determination of the reaction conditions and of the mechanism were carried out in batch reactors (stainless steel autoclave for high temperature reactions, 150 °C; r.b. flask for low temperature reactions, >90 °C). Next a continuous flow process was investigated .

4.2.1. Batch conditions

Atmospheric pressure (temperature >90 °C)

γ-valerolactone (GVL) was chosen as a model compound for the whole study. Its ring-opening reaction in the presence of methanol, DMC and catalytic sulfuric acid, was first investigated at atmospheric pressure. The reaction carried out according to Scheme 4.8, afforded two major compounds: 4-hydroxy- and 4-methoxypentanoate methyl esters (**4.1** and **4.2** respectively).



Scheme 4.8. Reaction of GVL with CH_3OH and DMC (acidic catalysis).

Based on the hypothesis that selectivity for the formation of **4.1** and **4.2** could be tuned by the presence of DMC, a set of three reactions was carried out in order to determine the boundary conditions determined by the absence of one of the reagents. In the first, methanol was present while DMC was omitted, in the second DMC was present and methanol omitted, in the third both DMC and methanol were present. The results are summarised in Table 4.2.

Table 4.2 Reaction of GVL with MeOH and DMC in the presence of H_2SO_4.

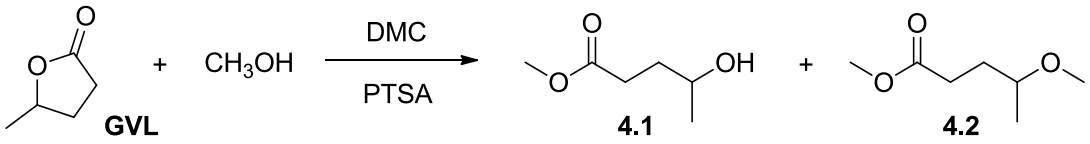
Entry[a]	CH_3OH (mol/mol GVL)	DMC (mol/mol GVL)	Temp. (°C)	Conv.[b] (%)	Products[b] (%)		
					4.1	4.2	others[c]
1	30	-	65	41	40	1	-
2	-	30	90	1	-	1	-
3	30	2	65	40	35	5	-

[a]Time = 40 hours. All the reactions were carried out using xx mol% of H_2SO_4. [b]Conversion and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

In the absence of DMC and with methanol the conversion stopped at around 40%, with almost complete selectivity for **4.1** (entry 1, Table 4.2). Without methanol and by using only DMC the reaction was inhibited as expected, and produced only traces of **4.2** and some unidentified products (entry 2, Table 4.2). When the reaction was carried out using 30 mol of MeOH and 2 mol of DMC per mole of GVL (entry 3, Table 4.2), the conversion was again around 40%, but with an increase in the selectivity towards **4.2** compared to the reaction of entry 1.

High temperature (150 °C)

In order to reach higher temperatures, reactions were then carried out into sealed steel autoclaves. Sulfuric acid was replaced by *p*-toluenesulfonic acid (PTSA) to prevent corrosion (0.08 mol/mol GVL). Reactions were carried out at 150 °C for 24 hours, varying the methanol/DMC ratio. Results are summarized in Table 4.3.



Scheme 4.9. Reaction between GVL and methanol in the presence of DMC and PTSA.

Table 4.3. Reaction of GVL with MeOH, in presence of DMC and PTSA.

Entry[a]	CH_3OH (mol/mol GVL)	DMC (mol/mol GVL)	Conv.[b] (%)	Products (%)[b]		
				4.1	4.2	others
1	30	none	68	22	43	3
2	30	2	70	10	60	-
3	15	10	85	7	78	-
4	10	10	84	6	72	6
5	2	30	20	10	6	4
6	none	30	4	4	-	-

[a]T = 150 °C , time = 24 hours. PTSA = 0.08 mol/mol GVL. [b]Conversion and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

In this case also, two reactions were carried out again as "blanks", using only either methanol or DMC (entries 1 and 6). It was observed that by increasing the amount of DMC the selectivity towards 4.2 increased while the selectivity towards 4.1 decreased. The ratios methanol/DMC that led to higher conversions and selectivity towards **4.2** were those of

entries 3 and 4 of Table 4.3, about equimolar. The reaction of entry 3, performed using 15 equivalents of methanol and 10 of DMC (ratio methanol/DMC = 1.5), gave the highest selectivity towards **4.2** and was consequently repeated for a longer time with the aim of maximizing the conversion. Thus, a conversion of 92% and a selectivity towards 4.2 of 93% were obtained running the reaction at 150 °C for 30 hours, using a molar ratio GVL:methanol:DMC:PTSA = 1:15:10:0.08.

Catalysis test

In order to exclude any catalysis due to metal leaching from the walls of the autoclave (slight corrosion was observed), the reaction of entry 3, Table 4.3, was repeated twice in a Teflon lined autoclave. Results are summarised in Table 4.4 (entry 2 and 4), where they are compared with the previous results obtained in steel autoclaves (entry 1 and 3). The results indicated that any unwanted metal catalysis due to leaching could be ruled out.

Table 4.4. Comparison of results obtained in steel autoclaves and teflon lined ones for the reaction between GVL and MeOH, in presence of DMC and PTSA.

Entry[a]	Material	Time (h)	Conv.[b] (%)	Products[b] (%)		
				4.1	4.2	others[c]
1	Steel	24	85	7	78	-
2	Teflon		90	5	83	2
3	Steel	30	92	2	85	3
4	Teflon		93	1	90	2

[a]T=150 °C , time =24 hours. Starting GVL = 1.0 g. Molar ratio MeOH:DMC:GVL = 15:10:1. PTSA = 0.08 mol/mol GVL. [b]Conversion and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

Lewis acid test

A Lewis acid was tested in place of the Brønsted ones: two experiments were run using scandium triflate. As done previously, in the first experiment only methanol was used as a reactant, while in the second one the mixture methanol/DMC was used with the same molar amount, over GVL, of entry 3, Table 4.3. Results are summarized in Table 4.5. In both the cases conversion and selectivity were higher than in the corresponding experiments where PTSA was used as an acidic catalyst. By using the sole methanol an

almost 80% conversion was obtained, with a selectivity towards **4.2** of 87%. With the use of DMC in the mixture the conversion went to completion, with total selectivity towards **4.2**.

Table 4.5 Reaction between GVL and methanol, in the presence or absence of DMC, using scandium triflate as an acidic catalyst.

Line[a]	CH_3OH (mol/mol GVL)	DMC (mol/mol GVL)	Conv.[b] (%)	Products (%)[b]		
				4.1	4.2	others[c]
1	30	none	79	10	69	-
2	15	10	>99	traces	98	2

[a]T=150 °C , time =24 hours. Starting GVL = 1.0 g. Scandium triflate = 0.08 mol/mol GVL. [b]Conversion and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" refers to products, the majority of which were not identified.

4.2.2. Continuous flow conditions

Continuous flow (CF) reactions of GVL with methanol in the presence of DMC and a solid acid catalyst were carried out using an apparatus consisting in: an HPLC pump, a tubular reactor thermostated inside a GC oven, and a backpressure regulator. See the experimental section for a simplified scheme of the apparatus and for further details.

The reaction mixture consisting of GVL, methanol and, where present, DMC was pumped by means of the HPLC pump through a tubular reactor contained in the GC oven, which allowed to control the temperature. The product mixture was collected after the back pressure regulator, at the end of the apparatus. A solid acid catalyst or an inert material was loaded inside the tubular reactor.

4.2.2.1. Acidic alumina

Acidic alumina was loaded in the tubular reactor and tested as a solid acid catalyst for the reaction between GVL and methanol. the first set of experiments were run using a reactor of about 3 ml internal volume, with a typical catalyst loading of about 2 g. A mixture of GVL and methanol (0.05 mol/mol) was pumped through the reactor thermostated at three different temperatures. The same reactor was also loaded with an equal volume of inert material (sand) and the reaction monitored under the same conditions. Results are summarized in Table 4.6, and shown in Figure 4.2. The reaching of a steady state was monitored by GC-MS analysis of fractions collected at appropriate time intervals.

Table 4.6. Comparison of sand and acidic alumina for promoting the reaction between GVL and MeOH at various temperatures.

		SAND[b]				ACIDIC ALUMINA[b]			
Entry[a]	Temp (°C)	Conv. (%)	Products (%)			Conv. (%)	Products (%)		
			4.1	4.2	4.3		4.1	4.2	4.3
1	200	6	6	0	0	17	16	1	0
2	250	8	7	1	0	27	6	20	1
3	300	18	6	10	1	64	2	45	10

[a]Reactions were carried out pumping a mixture of GVL:MeOH (1:20 mol/mol) at a flow of 0.05 ml/min; pressure was kept at 60 bar. [b]Conversions and product percentages in the final mixture were determined by GC/MS analysis.

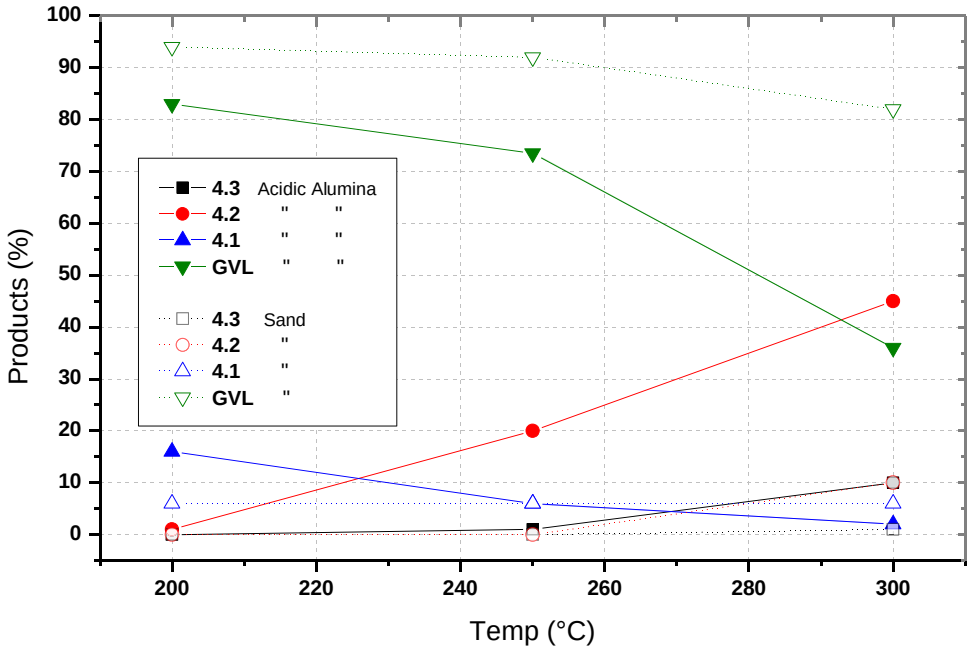


Figure 4.2. Compounds distribution for the CF reaction between GVL and MeOH.

At 200 °C (entry 1, Table 4.6) the conversion over alumina was low (16%) and the alcohol **4.1** was the prevalent product. Conversion on sand was even lower (6%) and only compound **4.1** was observed. Increasing the temperature by 50 °C conversion on alumina increased slightly (10% more), but with an opposite trend in products distribution: the ether **4.2** was the most abundant compound (20%), while **4.1** drastically decreased (from 16 to 6%) and traces of compounds **4.3** were observed. No significant change was observed using sand: conversion barely increased, and first traces of **4.2** were observed. Rising the temperature up to 300 °C, conversion on alumina increased significantly (64%). Compound **4.2** was still the most abundant (45%), while compound **4.1** became a minor product. Compounds **4.3**, previously only observed in traces, were produced in a 10%

amount under such conditions. Sand gave again quite low conversion (18%) with a similar distribution of **4.1** and **4.2**. At the highest temperature (300 °C), considerable amounts of gas were observed at the outlet of the apparatus (at the same time, smaller volumes of liquid than those provided by the flow rates were collected). This was attributed to the formation of dimethyl ether from methanol self-condensation.

Further experiments were run in a larger 4.5 cc volume reactor, where a typical catalyst loading was about 4 g. Various parameters were investigated, including: different methanol/DMC ratios (MeOH only, MeOH/DMC = 3, MeOH/DMC = 1); flow rates (0.25, 0.10, 0.05 ml/min); temperatures (180-250 °C). Obtained data are summarised in Table 4.7 (see following page).

Methanol only

In the absence of DMC, conversion was always very modest, ranging from a minimum of 7/8% (entries 1 to 3) to a maximum of 22% in the best case. Selectivity was generally oriented towards the alcohol **4.1**; only at a low flow rate of 0.1 ml/min at 250 °C , product **4.2** started forming.

Methanol/DMC = 3/1

With a ration MeOH/DMC = 3/1 again modest conversions were observed at the lower temperatures (180-200 °C), with **4.1** as the major product. In tihs base, this selectivity started changing at 220 °C where, despite the low conversion, products **4.1** and **4.2** were produced in similar amounts. At 250 °C the conversion increased drastically up to 29% at 0.25 ml/min and 41% at 0.10 ml/min flow rates, with sizeable amounts of **4.2** being observed (23 and 35% respectively).

Methanol/DMC = 1/1

The equimolar mixture of MeOH and DMC also afforded low conversion at the lower and medium temperatures, however compound **4.2** started to be produced in small quantities already at 200 °C , becoming the major compound at 220 °C. Again at 250 °C conversions substantially increased: 43% at 0.25 ml/min, 52% at 0.10 ml/min and 55% at 0.05 ml/min. Selectivity was definitely shifted towards **4.2**, ranging from 90 to 94%.

Table 4.7. Reaction between GVL and methanol over acidic alumina. Data collected at various flow rates and temperatures, in presence or absence of DMC.

Entry	mix. composition	FLOW (ml/min)	T (°C)	Conv.[b] (%)	Prod.[b] (%)		
					4.1	4.2	4.3
1	*MeOH only*	**0.25**	180	7	7	<1	0
2			200	7	7	<1	0
3			220	8	5	3	0
4			250	14	9	5	0
5		**0.1**	180	15	14	<1	0
6			200	15	14	1	0
7			220	15	12	3	0
8			250	22	9	13	0

	mix. composition	FLOW (ml/min)	T (°C)	Conv.[b] (%)	Prod.[b] (%)		
					4.1	4.2	4.3
9	*MeOH:DMC =3:1*	**0.25**	180	8	7	1	0
10			200	8	7	1	0
11			220	10	6	4	0
12			250	29	5	23	1
13		**0.1**	180	10	10	<1	0
14			200	13	11	2	0
15			220	16	8	8	0
16			250	41	5	35	1

	mix. composition	FLOW (ml/min)	T (°C)	Conv.[b] (%)	Prod.[b] (%)		
					4.1	4.2	4.3
17	*MeOH:DMC = 1:1*	**0.25**	180	7	6	1	0
18			200	7	5	2	0
19			220	14	5	9	0
20			250	43	2	40	1
21		**0.1**	180	8	11	<1	0
22			200	11	9	2	0
23			-	-	-	-	-
24			250	52	2	48	2
25		**0.05**	250	55	2	52	1

[a]Reactions were carried out at a pressure of 60 bar. [b]Conversions and product percentages in the final mixture were determined by GC/MS analysis.

In an attempt to increase the conversion, a reactor with a bigger volume was assembled, in order to slow the flux and increase the contact time of the mixture. About 30 g of acidic alumina were loaded in a column with id of 7.75 mm and length of 420 mm. Initially the reaction was conducted in the absence of DMC with the mixture of GVL in methanol (0.05 mol/mol); temperatures ranging from 200 to 260 °C were tried, alongside with different flow rates. Results are summarized in Table 4.8 and shown in Figure 4.3.

Table 4.8. Reaction between GVL and MeOH over acidic alumina in CF conditions (20 ml reactor).

		FLOW RATE											
		0.25 ml/min				0.10 ml/min				0.05 ml/min			
Entry[a]	Temp. (°C)	Conv.[b] (%)	Products (%)[b] 4.1	4.2	4.3	Conv.[b] (%)	Products (%)[b] 4.1	4.2	4.3	Conv.[b] (%)	Products (%)[b] 4.1	4.2	4.3
1	200	20	10	9	1	26	9	17	0	-	-	-	-
2	240	40	6	30	4	52	5	41	2	59	4	46	9
3	250	-	-	-	-	60	4	48	8	-	-	-	-
4	260	-	-	-	-	63	3	45	15	-	-	-	-

[a]Reactions were carried out pumping a mixture of GVL:MeOH (1:20 mol/mol); pressure was kept at 60 bar. [b]Conversions and product percentages in the final mixture were determined by GC/MS analysis.

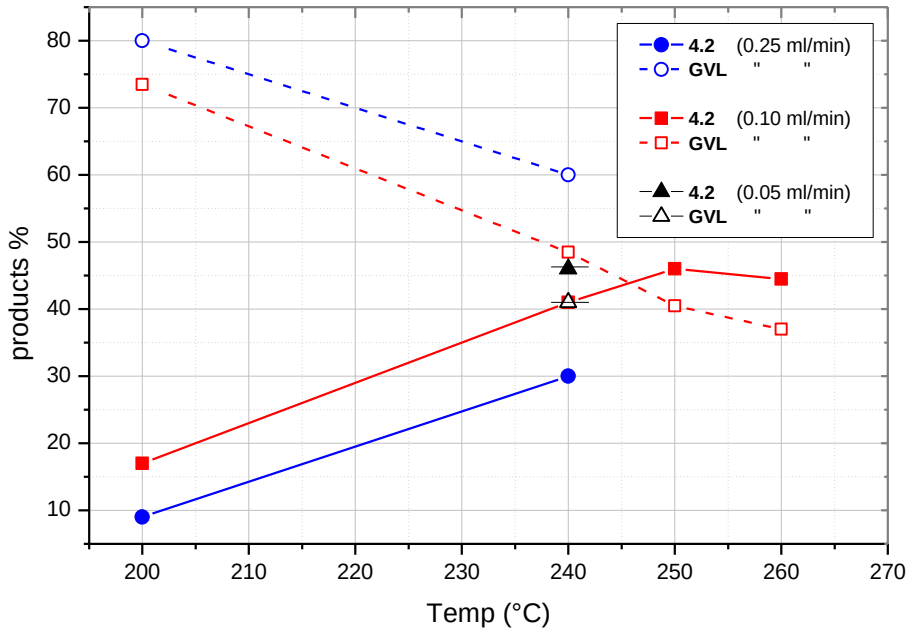


Figure 4.3. Selectivity towards 4.2 as a function of the temperature and flow rate (data from Table 4.8).

In another series of experiments a new reacting mixture was employed: DMC was added, to obtain a final composition of GVL:MeOH:DMC = 1:10:10. Two temperatures were tested, using a flow ratio of 0.25 ml/min. Results are summarized in Table 4.9.

Table 4.9. Reaction of GVL with MeOH over acidic alumina in presence of DMC

Entry[a]	Temp. (°C)	Conv.[b] (%)	Products (%)[b]		
			4.1	4.2	4.3
1	200	44	5	37	2
2	240	64	3	56	5

[a]Reactions were carried out pumping a mixture of GVL:MeOH:DMC (1:10:10 mol/mol) at a flow rate of 0.25 ml/min; pressure was kept at 90 bar. [b]Conversions and product percentages in the final mixture were determined by GC/MS analysis.

4.2.2.2. HY zeolites

The second type of solid acid catalyst investigated was the HY type of zeolites. It was prepared by calcination of NH_4Y zeolite, preloaded into the 4.5 cc volume reactor, with a typical catalyst loading of about 1.6 g. As with alumina, the effect of different parameters was investigated: temperature, flow rate and methanol/DMC ratio. All the data are listed in Table 4.10 (see following page).

Methanol only

The mixture of methanol and GVL gave conversions ranging from 45 to 66%. At a flow rate of 0.25 ml/min conversion increased with the temperature, from a 45% at 180 °C to a 63% at 250 °C. Selectivity was high towards **4.2** up to 220 °C, then **4.3** became the major compound at 250 °C, with a 68% selectivity. At 0.10 ml/min the maximum conversion (59%) was achieved at 200 °C, then it dropped down to 50% at 220 °C to increase slightly at 250 °C. The tendency to produce **4.3** at high temperatures was observed again: its selectivity was low until 200 °C, 36% at 220 °C and 68% at 250 °C. Finally using a flow rate as low as 0.05 ml/min a conversion of 66%, with selectivity towards **4.2** of 91%, was achieved at 180 °C.

Methanol/DMC = 3/1

With a ratio MeOH/DMC = 3/1, GVL conversion was good as well (42 to 76%). At 0.25 ml/min conversion increased again with the temperature, from 42% at 180 °C to 74% at 250 °C. Selectivity behaved similarly to the previous case as well: higher selectivity towards **4.2** up to 220 °C (from 88% at 180 °C to 75% at 220 °C), then higher towards **4.3** at 250 °C (69%). At 0.10 ml/min there was again a conversion increase from 180 to 200 °C (56 to 74%), with a slight drop going from 220 to 250 °C (71 and 65%). At 250 °C the selectivity was again high towards **4.3** (81%). A conversion peak of 76% was reached at 0.02 ml/min and 180 °C; selectivity towards 2 was 92%.

Methanol/DMC = 1/1

The data collected using the third mixture showed trends consistent with the previous ones, with conversions generally slightly higher. At 0.25 ml/min conversion increases with the temperature from 45 to 76%. Maximum selectivity towards **4.2** was achieved at 200 °C (90%), while maximum selectivity towards **4.3** was achieved at 250 °C (82%). At 0.10 ml/min conversion increased (60 to 76%) passing from 180 to 200 °C, then remained more or less constant (72% - 74%) at 220 °C and 250 °C respectively. At the lower flow rates, 0.05 and 0.02 ml/min, high conversions were obtained already at 180 °C (66 and 81% respectively), with selectivity towards **4.2** of 91 and 90% respectively.

Table 4.10. Reaction between GVL and methanol over HY zeolites. Data collected at various flow rates and temperatures, in presence or absence of DMC.

Entry		FLOW (ml/min)	T (°C)	Conv.[b] (%)	Prod.[b]		
					4.1	4.2	4.3
1	*MeOH only*	**0.25**	180	45	6	37	2
2			200	57	3	48	6
3			220	57	2	43	12
4			250	63	2	18	43
5		**0.1**	180	51	6	41	4
6			200	59	4	46	9
7			220	50	4	28	18
8			250	53	2	8	43
9		**0.05**	180	66	6	60	>1

		FLOW (ml/min)	T (°C)	Conv.[b] (%)	Prod.[b]		
					4.1	4.2	4.3
10	*MeOH:DMC =3:1*	**0.25**	180	42	5	37	<1
11			200	60	4	53	3
12			220	69	3	56	10
13			250	74	1	21	51
14		**0.10**	180	56	4	52	2
15			200	74	3	66	5
16			220	71	2	53	16
17			250	65	1	7	53
18		**0.02**	180	76	3	70	3

		FLOW (ml/min)	T (°C)	Conv.[b] (%)	Prod.[b]		
					4.1	4.2	4.3
19	*MeOH:DMC = 1:1*	**0.25**	180	45	4	40	1
20			200	63	1	57	5
21			220	71	1	53	17
22			250	76	<1	12	62
23		**0.1**	180	60	4	55	1
24			200	76	2	66	8
25			220	72	2	56	14
26			250	74	1	7	65
27		**0.05**	180	66	2	60	3
28		**0.02**	180	81	2	73	6

[a]Reactions were carried out at a pressure of 60 bar. [b]Conversions and product percentages in the final mixture were determined by GC/MS analysis.

4.3. Discussion

4.3.1. Batch conditions and study of the mechanism

The initial experiments run in batch at atmospheric pressure showed appreciable differences in running the reaction with added DMC rather than with the sole methanol. As shown in Table 4.2, by adding 2 equivalents of DMC to the GVL/MeOH mixture (entry 3) an increase from 1% to 5% in the formation of compound **4.2** was observed compared to using only MeOH (entry 1). Alternative reaction pathways between GVL and DMC were excluded by running an experiment without methanol(Table 4.2, entry 2). By increasing the reaction temperature up to 150 °C, higher conversions were obtained (Table 4.3). Under such conditions not only better conversions were achieved, but selectivity towards compound **4.2** was favoured respect to **4.1**. While, improved selectivity for 4.2 was observed at higher temperature even using only methanol (entry 1); however the addition of DMC caused a further increase in conversion and selectivity towards **4.2**. The methanol/DMC ratio was also shown to be of critical importance in to maximize both conversion and selectivity towards the desired compound (see Figure 4.4 below). Under

batch conditions, the best results were obtained when the two reagents were used in approximately equimolar amounts (15:10 and 10:10 mol/mol GVL, entries 3 and 4 respectively), affording conversions of 84-85% and selectivity towards **4.2** of 86-92%. The best conditions for the formation of 4.2 (methanol/DMC = 15/10 mol/mol GVL, entry 3) were chosen to run a reaction for a longer time, aiming to further increase the lactone conversion. With a reaction time of 30 hours a 90% conversion was achieved, along with 85% selectivity towards **4.2**. Any possible interference by metals (possibly leaching from the autoclaves) was excluded by running test reactions in Teflon lined autoclaves. These gave results almost identical to the previous reactions (conversion and selectivity even improved slightly; this can be explained considering that all the acidic catalyst is available for the reaction, not being involved in corrosion phenomena).

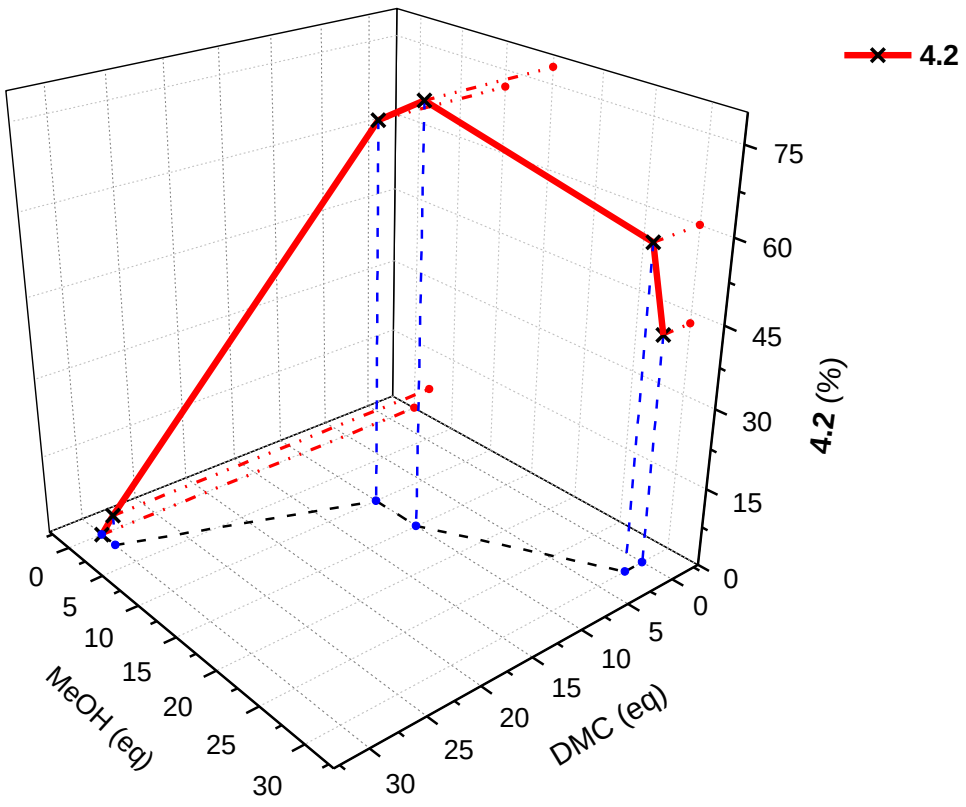
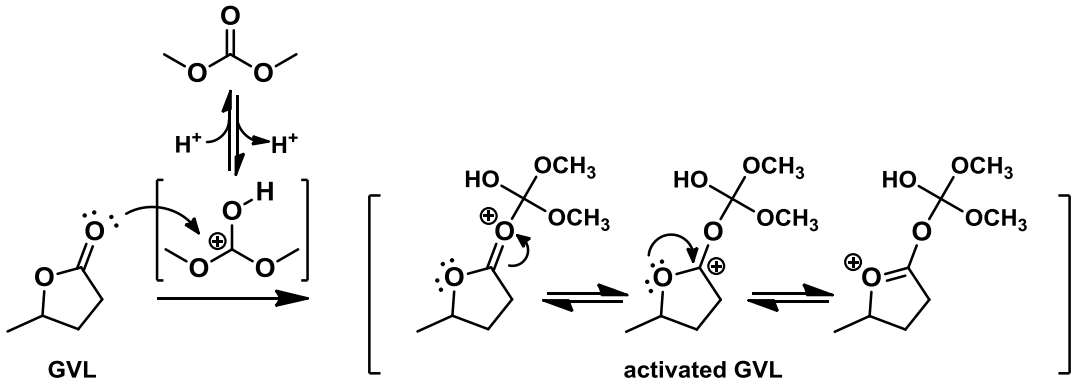


Figure 4.4. Yield of 4.2 as a function of the molar ratio MeOH/DMC (from data reported in Table 4.3).

Such results suggested that DMC played an important role in the reaction.

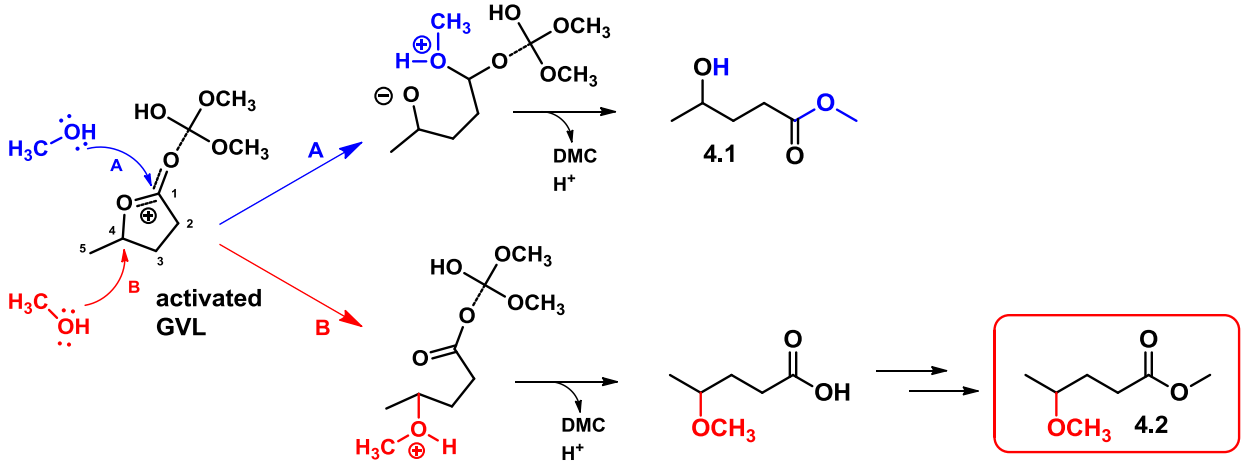
Having excluded the possibility of unwanted reactions between GVL and DMC, we propose a mechanism whereby DMC acts similarly to what already described for

orthoesters (see introduction).[12] We hypothesised that in acidic conditions DMC can be protonated, thereby polarizing the carbonyl bond and enhancing its electrophilic character, and behave like a Lewis acid. The protonated DMC species would be susceptible to coordinate the lactone carbonyl group (see Scheme 4.10). Such coordination would generate a cationic intermediate species, in which the positive charge is delocalized by resonance onto the lactone.



Scheme 4.10. Resonance structures of the proposed intermediate for the DMC-mediated methanolysis of GVL in acidic conditions.

The activated intermediate will be activated towards nucleophilic attack by methanol in two positions, C1 and C4. The first has a positive charge due to the resonance, the second is partially positively charged as well, due to an inductive effect of the vicinal oxygen. The mechanism and possible outcome due to attack of methanol on each of the two positions is shown in the following Scheme 4.11.



Scheme 4.11. Proposed mechanism for the DMC-mediated methanolysis of GVL in acidic conditions.

In pathway A, nucleophilic attack of methanol at the carbonyl carbon C1, leads to the compound **4.1.** In pathway B, nucleophilic attack of methanol at the ring carbon C4, leads

to the compound **4.2**. It appears plausible, analogously to what proposed for orthoformates, that coordination of DMC to the lactone would favour pathway B due to the steric hindrance around the carbonyl and the carbon C1 itself.

4.3.2. Computational calculations

Computational calculations seem to support the mechanism proposed. The energies relative to the proposed intermediate and the orthoformate derived one were calculated and compared, giving very similar values. Table 4.11 shows a comparison of the partial charges at the C1 (carboxylic carbon) and C4 (carbon vicinal to the methyl) in the adducts of GVL with the carbocations $[CH(OMe)_2]^+$ and $[C(OH)(OMe)_2]^+$ (see Figure 4.5. Equilibrium geometries of the adducts between GVL and the two carbocations, $CH(OMe)_2$ (left) and $C(OH)(OMe)_2$ (right).). The interaction between GVL and the two carbocations happens only at the carbonylic oxygen of the former. No stable equilibrium geometries were obtained for the adducts between the carbocations and the lactonic ring oxygen. From this point of view, thus, the two considered species behave similarly.

Table 4.11. Partial charges (a.u.) on C1 (GVL carbonylic oxygen) and C4 (which bears the methyl group).

Species	6-31G** - gas	6-31G**- MeOH	6-31+G** -gas
Adduct [**1c**-$CH(OMe)_2$]$^+$	C1 0.863 C4 0.085	C1 0.848 C4 0.089	C1 0.847 C4 0.127
Adduct [**1c**-$C(OH)(OMe)_2$]$^+$	C1 0.856 C4 0.086	C1 0.846 C4 0.089	C1 0.840 C4 0.127

Figure 4.5 shows the minimum energy geometries for the considered systems.

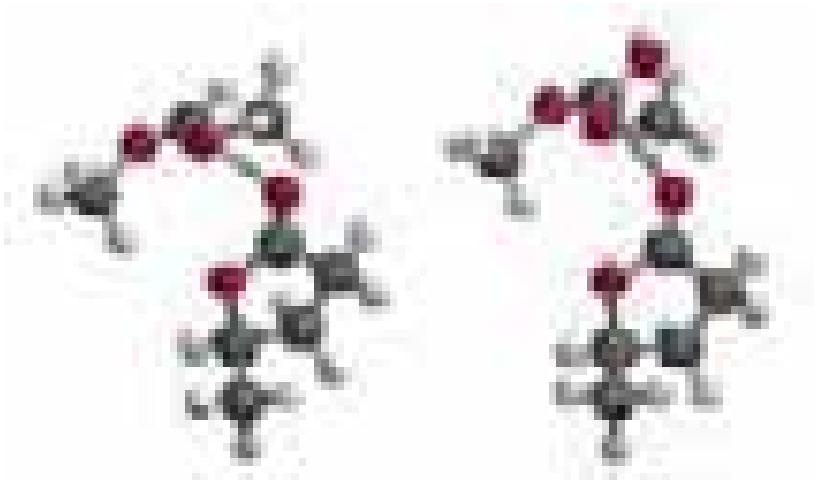


Figure 4.5. Equilibrium geometries of the adducts between GVL and the two carbocations, $CH(OMe)_2$ (left) and $C(OH)(OMe)_2$ (right).

A comparison between the partial charges on the carbons C1 and C4 of the proposed activated intermediate and the intermediate reported in the literature (see Table 4.11) indicates minor differences. In particular the partial charges on the carbon C4 were identical in three different experiments.

In another set of calculations, the two carbocations interacted similarly with the carbonylic oxygen: for $CH(OMe)_2$ it was calculated an interaction energy of 21 Kcal/mol, against 19 Kcal/mol found for $C(OH)(OMe)_2$.

Other experiments were ran by considering the transition state (shown in Figure 4.6) of the possible reaction in which methanol attacks at the carbon C4 the species formed by GVL and $C(OH)(OMe)_2$. It was possible to calculate an activation energy of 32 Kcal mol^{-1}. This value seems to indicate the feasibility of this mechanism, taking into account that chemical reactions values are commonly in the range 10-20 kcal/mol. Moreover it is evident from the calculations the tendency of the carbon C4 to change hybridisation state, from sp3 to sp2. Finally, calculations indicate that for the species formed by GVL and $C(OH)(OMe)_2$ the attack of methanol to the carbon C1 is unfavoured.

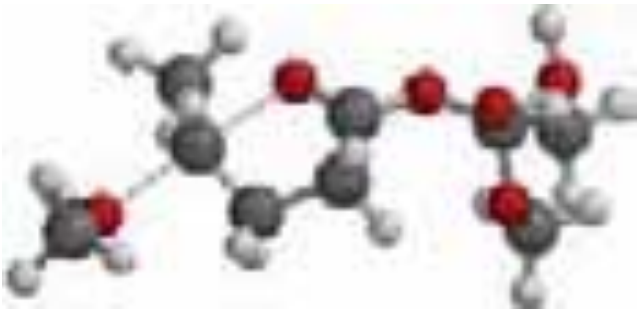


Figure 4.6. Transition state for the reaction between GVL (centre) and MeOH (left), mediated by DMC (right).

All the computational data confirm the possibility of formation for an intermediate between GVL and the DMC-carbocation $C(OH)(OMe)_2$, similar to the adduct proposed in the literature. On the other hand the distance between the sp2 carbon of the carbocation and the carbonylic oxygen of the lactone appears higher for $C(OH)(OMe)_2$ (2.612 Å) than for $CH(OMe)_2$ (2.439 Å). This means that with DMC the steric hindrance is lower compared to orthoformate and can explain a lower selectivity with DMC at 90 °C, temperature at which trimethylorthoformate is already efficient.

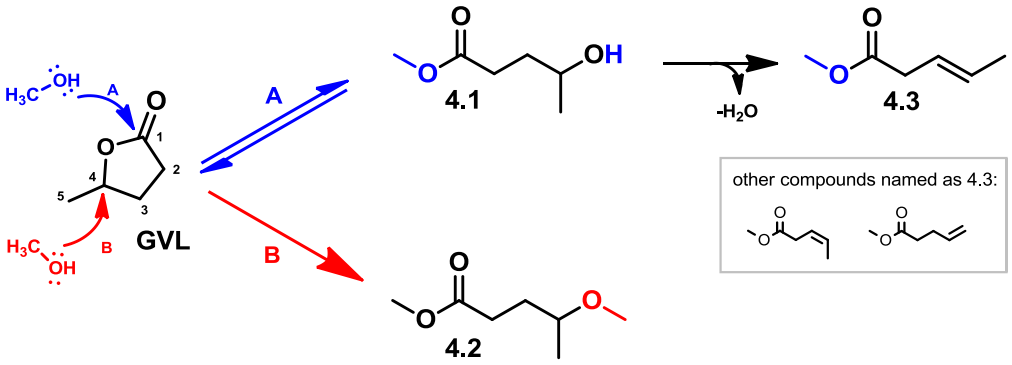
What can be inferred from these calculations is that the attack at the C1 rather than C4 is energetically equivalent because the electron density of the two positions is similar.

What discriminates between C1 and C2 opening is therefore the steric accessibility for the nucleophile. The C1 carbonyl is more hindered and possibly in a less favourable geometry to undergo nucleophilic attack. *Vice-versa*, the C4 carbon is more easily accessible because it is farther from the coordinated DMC moiety.

4.3.3. Continuous flow process

The applicability of this DMC-promoted GVL methanolysis reaction was also demonstrated in continuous flow. The objective was to show that a solid acid catalysts can substitute a homogeneous one, in flow, with all the benefits involved. In this set-up the reagents flow over a catalyst bed confined in a tubular reactor (see experimental section for details), that can be easily replaced and/or reactivated. In addition, in such conditions higher temperatures can be used, being the corrosion issue, relevant when using protic soluble acids, avoided. At higher temperatures a faster kinetic profile was obtained and a consequent reduction in reaction time. Before proceeding with the discussion it is important to point out a few mechanistic aspects that govern selectivity. The first reaction of pathway A in Scheme 4.12, is reversible (intramolecular nucleophilic attack of the alcohol at the carbonyl, with subsequent elimination of methanol)and leads to the formation of alcohol **4.1**,. On the other hand, the reaction of pathway B is not an equilibrium, and product **4.2** is therefore the thermodynamically favoured product, whereas **4.1** is the kinetically preferred one, a sit is formed faster and at lower temperatures. Another product that will be important in the next part of the discussion are the isomers of **4.3** (product **4.3** includes three different isomers, shown in Scheme 4.12; they are grouped together to make the discussion easier, so from here in advance they will just be described as "products **4.3**"). These alkenes were observed in the preceding set of batch reactions only in small amounts and included into products labelled as "others", and originate at high temperatures by irreversible dehydration of alcohol **4.1**.

Two different heterogeneous acidic catalysts were tested for the methanolysis of GVL: acidic alumina and HY zeolites.



Scheme 4.12. Reaction between GVL and MeOH and its products observed in continuous flow conditions.

Acidic alumina

Initially only methanol was used in mixture with GVL (20:1 mol/mol). The first objective was to demonstrate that the thermal reaction is not efficient in our range of conditions. This was achieved comparing the conversion over sand and over acidic alumina in a 3 ml reactor. As it is clear from Table 4.6, the conversion due to the sole thermal reaction is negligible up to 250 °C (8% with an almost complete selectivity towards 4.1), and still low (18%) at 300 °C. On the other hand acidic alumina did not initially show a very good activity, being the conversion quite low until 300 °C, temperature at which it increased to 64%. However at such a temperature methanol self-condensation to dimethyl ether starts to be relevant, making a possible process less desirable from an economic and sustainable point of view. For this reason we tried to increase the conversion by means of a larger reactor. Another set of experiments using the mixture GVL:methanol = 1:20 mol/mol was performed using a 3.65 ml volume reactor (Table 4.7). Again conversion was not satisfactory, being maximum 22% at 250 °C (flow rate = 0.10 ml/min). Using a much bigger reactor (volume = 20 ml) it was possible to obtain 60% conversion with a selectivity towards **4.2** of 80% (entry 3, 0.10 ml/min, Table 4.8). The addition of DMC to the mixture (first in a 1/3 volumetric ratio to methanol, then in a 1/1 volumetric ratio) did not cause relevant changes at the lower temperatures (180-200 °C). At 220 °C conversions had a small increase, as well as selectivity towards **4.2**. At 250 °C the DMC effect was very relevant (Figure 4.7): using it in a 1/3 ratio over methanol conversion doubled in respect to the sole methanol, both at 0.25 and 0.10 ml/min flow rates. Using a 1/1 ratio conversions further increased up to 43% at 0.25 ml/min (almost three times higher compared to the sole methanol) and up to 52% at 0.10 ml/min. Selectivity towards **4.2** improved parallel to conversions. Starting from 36% and 59% using the sole methanol

(0.25 and 0.10 ml/min respectively), we obtained a 79-85% with a methanol/DMC ratio 3/1 (0.25 and 0.10 ml/min respectively) and a 93-92% with a methanol/DMC ratio 1/1 (0.25 and 0.10 ml/min respectively).

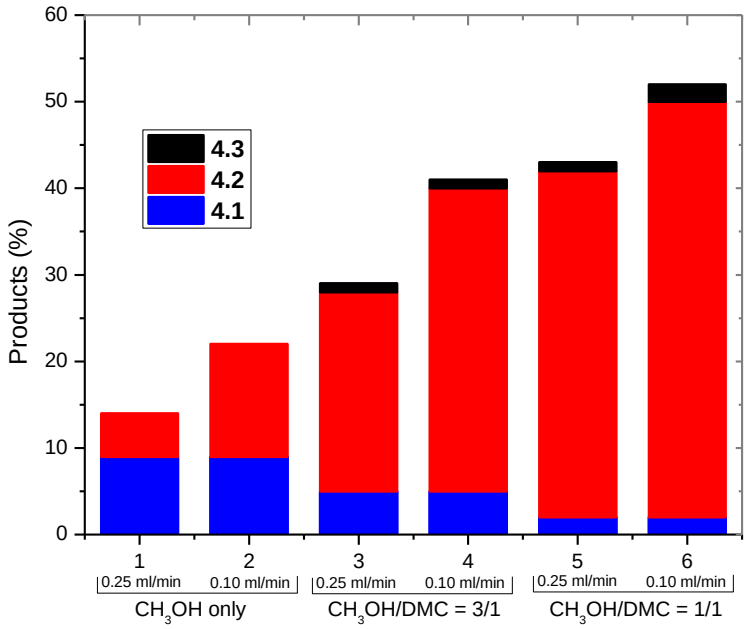


Figure 4.7. Conversions and products distributions of GVL ring opening using different methanol/DMC rations at 250 °C in continuous flow conditions over acidic alumina.

Table 4.12. Conversions and products distributions of GVL ring opening using different methanol/DMC rations at 250 °C in continuous flow conditions over acidic alumina.

mix. composition	Flow (ml/min)	Conv.[b] (%)	Prod. (%)[b]		
			4.1	4.2	4.3
MeOH only	**0.25**	14	9	5	n
	0.10	22	9	13	n
MeOH:DMC 3:1	**0.25**	29	5	23	1
	0.10	41	5	35	1
MeOH:DMC 1:1	**0.25**	43	2	40	1
	0.10	52	2	48	2

[a]The reactions were carried out at 250 °C. [b]Conversion and product percentages in the final mixture were determined by GC/MS analysis.

These results are consistent with our hypothesis and with the proposed mechanism of Scheme 4.11, in which DMC plays a crucial role as a promoter of the investigated reaction. Its addition under acidic conditions boosts both conversion and selectivity towards **4.2**.

HY zeolites

HY zeolites showed a higher activity than acidic alumina. The mixture GVL/MeOH reacted with good conversions and selectivity even in the absence of DMC and even at a temperature as low as 180 °C, at which acidic alumina was inefficient. The graph in Figure 4.8 shows conversions and selectivity towards the compounds **4.2** and **4.3** at different temperatures and flow rates, using GVL:MeOH = 1:20 mol/mol as a reacting mixture.

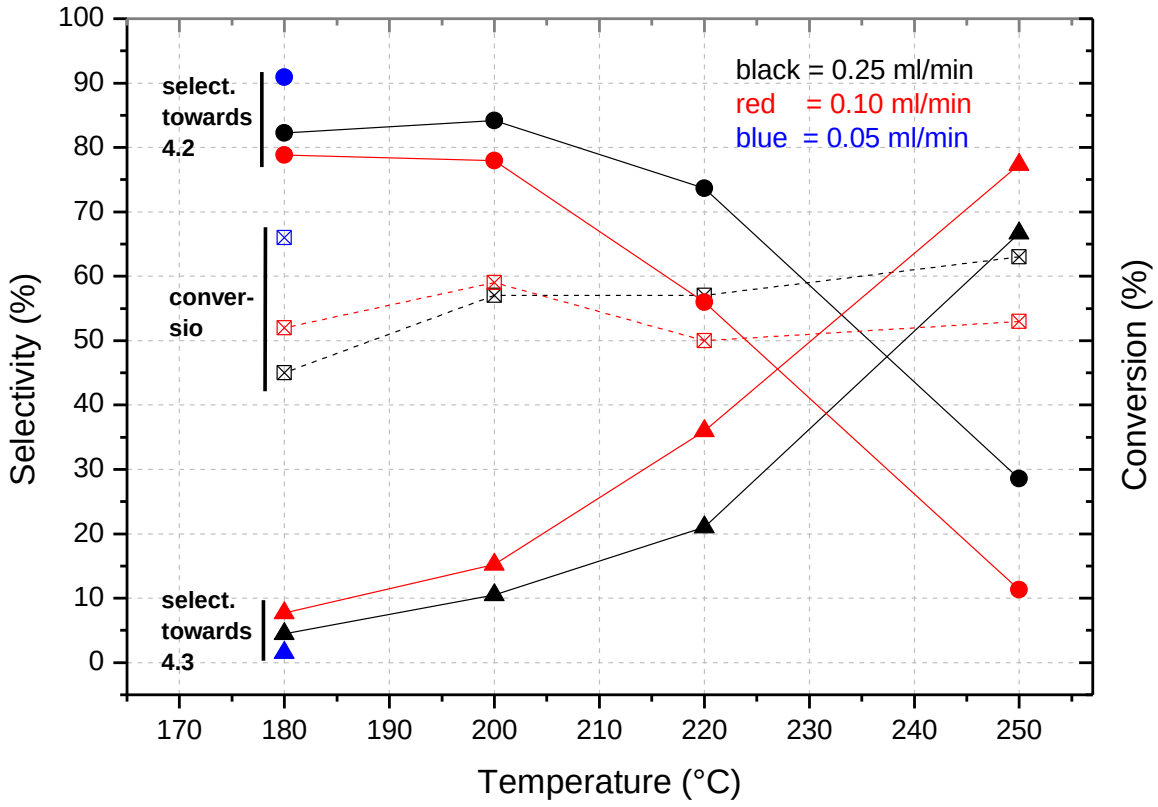


Figure 4.8. Reaction of GVL with MeOH over HY zeolites at various temperatures and flow rates.

The graph above is very significant: at lower temperature (180-200 °C) the selectivity is high towards **4.2**, ranging between 80 and 90%. By increasing the temperature, conversion remains more or less constant, while the selectivity is reversed being **4.2** consumed in favour of **4.3**. The effect of the different flow rates of 0.25 and 0.10 ml/min (black and red lines respectively) indicates that higher contact times (*i.e.* lower flows) favour formation of **4.3**. When DMC was added to the mixture, higher conversion and selectivity were observed again, although less relevant than with alumina. The results are condensed in Figure 4.9 divided by temperature in column graphs, in which the x axis represents the ratio DMC/MeOH. Moreover the x axis was divided in the two main flow rates employed. Each column shows the overall conversion and the product distribution for the particular set of conditions to which it refers.

As a general trend, a bigger fraction of DMC into the mixture consistently improved the conversion. This held true at all the investigated temperatures. The effect of added DMC was more significant at the lower flow rates (*i.e.* longer contact times) and at the higher temperature. This seems to indicate that DMC acts as a mild promoter of the reaction.

From Figure 4.9, we can observe that the highest selectivity towards **4.2** were obtained at 180 and 200 °C. At 180 °C **4.2** was obtained with a conversion of 76% and selectivity of 92%, using a flow rate as low as 0.02 ml/min (residence time ~100 min) for the mixture MeOH/DMC = 3. By increasing the temperature, the selectivity shifted towards the unsaturated compounds **4.3**, and this could prove to be potentially important in a view of producing monomers from bio-derived compounds. The highest conversion and selectivity towards **4.3** were obtained using the mixture MeOH/DMC = 1; the former were 76 and 74%, while the latter were 82 and 88% respectively.

The effect of DMC can be rationalized by considering the reactions of scheme 4.12. By rising the temperature and increasing the contact time a competition ensues between the two pathways A and B. On one side the ether-ester **4.2** becomes favoured thermodynamically over the alcohol-ester **4.1**. This is reflected in Figure 4.9 by observing that **4.2** increases with respect to **4.1** passing from 180 to 200 °C (top graphs). On the other hand, by rising the temperature, dehydration of **4.1** to yield **4.3** becomes competitive, and drives the reaction towards the preferential formation of **4.3**. This was observed at 220 °C, and more so at 250 °C where **4.3** is the main product. The higher temperature favours the kinetically preferred product **4.1** that immediately dehydrates to yield **4.3**. The data collected under batch conditions and the continuous flow results are therefore in agreement.

The observed difference in the effect of DMC with acidic alumina and HY zeolites can be explained considering the structures of the catalysts. The typical cages of the zeolite lattice have already demonstrated to be able to direct the selectivity, when a reaction can follow different pathways, in function of the geometry of the transition state. In our case it can be imagined that the cage is itself hindering partially the active site at the lactone carbonyl (the same effect that we propose is given by DMC), making the C4 position more favourable to undergo nucleophilic substitution.

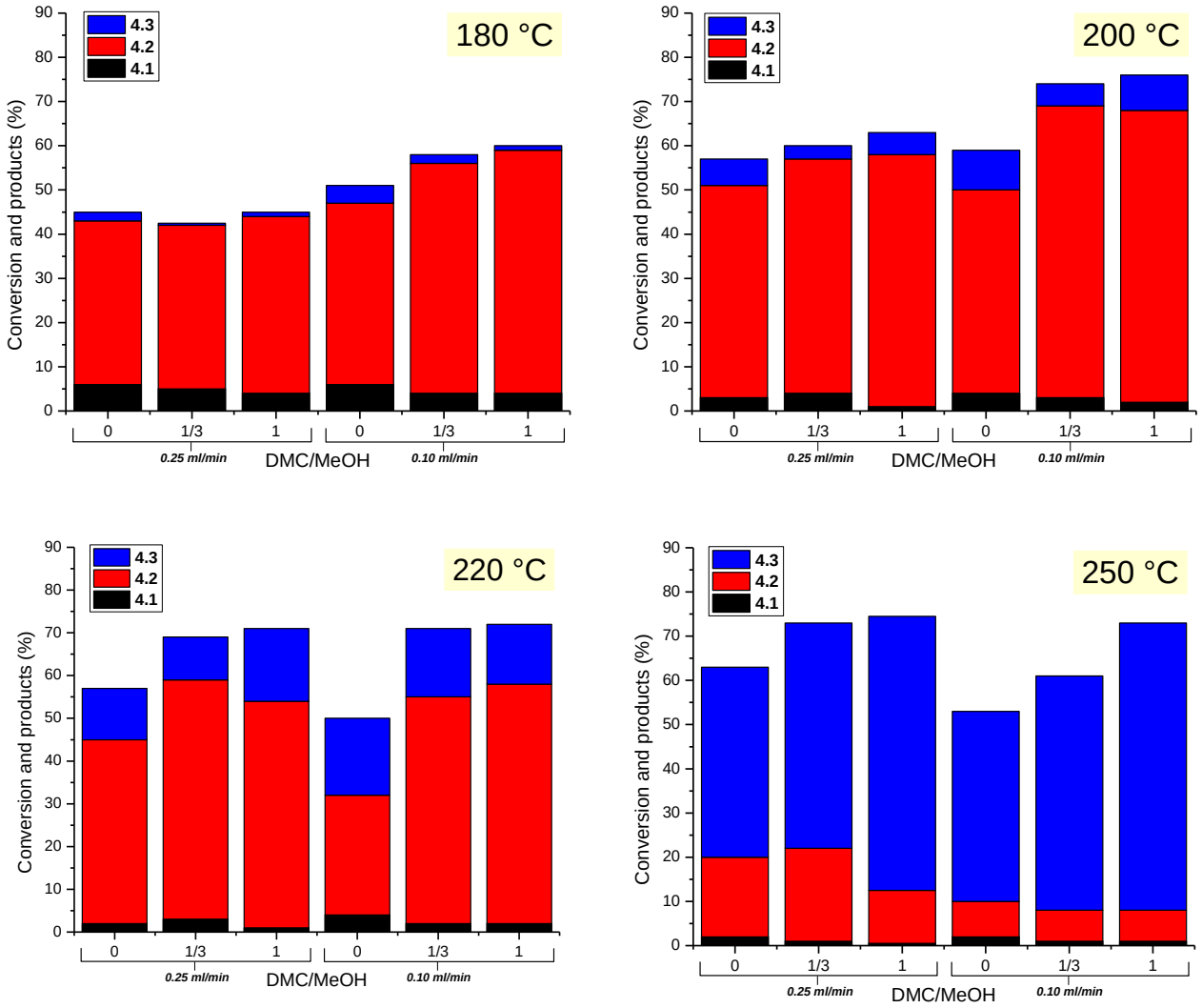


Figure 4.9. Column graphs showing conversion and products percentages for the reaction between GVL and MeOH (in presence or not of DMC) at various temperatures and flow rates.

4.4. Conclusions

This chapter described the investigation on the acid promoted ring-opening of GVL; the latter chosen as a model lactone. It was shown that the acidic alcoholysis of the lactonic ring, in batch conditions at 150 °C, leads to two main compounds: 4-hydroxy- (**4.1**) and 4-methoxy-pentanoate (**4.2**). In particular the latter moiety finds application in many sectors of the chemical industry, from fine chemicals to commodities. Dimethylcarbonate (DMC) was used as a reaction mediator, and it was demonstrated to direct the selectivity towards **4.2**. The use of organic carbonates in acidic conditions is an almost unexplored field, and the few examples reported in the literature concern their known behaviour (transesterification at the carbonyl). This novel reactivity was investigated through

dedicated experimental tests and computational calculations, both in agreement with the proposed mechanism. The GVL ring opening reaction was studied in continuous flow conditions, using two different solid acid catalysts (acidic alumina and HY zeolites). In such conditions we investigated a wider range of temperatures, showing that methyl pentenoate (**4.3**) can be produced as the major compound in the more drastic conditions. Selectivity towards the three possible products can be tuned by modifying the set of parameters, including: temperature, flow rate (contact time), presence of DMC (mostly using acidic alumina), catalyst, reactor dimensions. To conclude, we demonstrated that various ring-opened derivatives can be obtained selectively from GVL via a greener methodology, which involves the use of DMC and/or solid acid catalysts in a continuous flow process. Moreover a novel reactivity of DMC was discovered, widening the range of applicability of such compound.

4.5. Bibliography

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5 | DIOLS AS A RESOURCE FOR LINEAR AND CYCLIC CARBONATES

5.1. Introduction

5.1.1. Diols from biomass

Diols are chemicals obtainable through the transformation of bio-derived platform chemicals that have an interesting synthetic potential. The precursors are generally (di)carboxylic acids (or the corresponding esters) that can be reduced to the corresponding (di)ols either by chemo-catalytic or biocatalytic processes. Figure 5.1 shows the most interesting diols, to date, which can be manufactured from biomass feedstock.

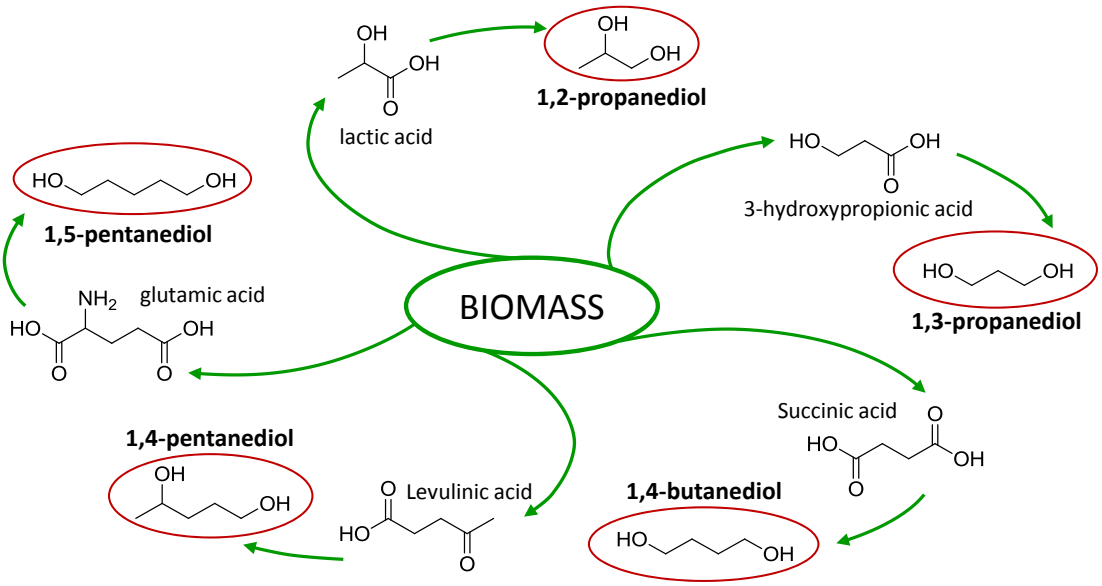
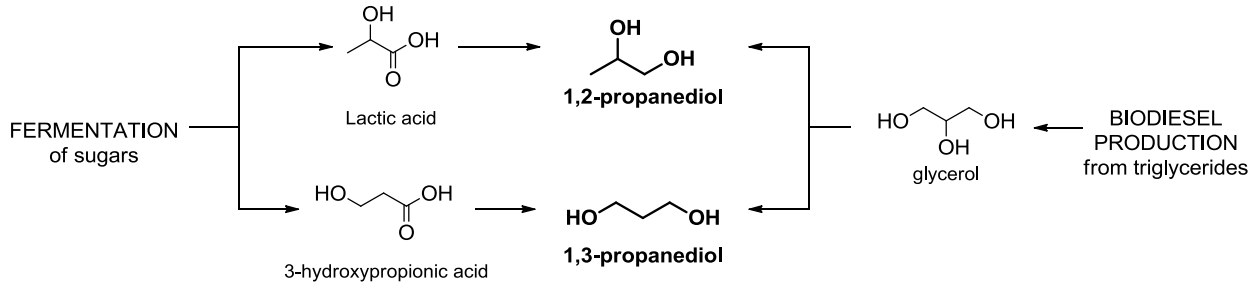


Figure 5.1. Routes to diols from biomass.

1,2-propanediol, or propylene glycol (PG), is a commodity chemical with a variety of applications, including for the production of unsaturated polyester resins (about 45% of PG produced is employed for this purpose), as solvent in the production of many pharmaceuticals (e.g. oral, injectable and topical formulations); as humectant, solvent and preservative in food; de-icing fluid.[1] It is traditionally manufactured via hydration of

either propylene oxide or chlorohydrin. However several routes for its production from renewable feedstock have been developed. Currently the most efficient processes consist in the biotransformation of sugars or polyols, in anaerobic and aerobic batch fermentation; yet some chemo-catalytic pathways are available as well, and innovative ones are continuously being developed. A first important route is the reduction of lactic acid and lactates. Another route consists in the hydrogenolysis of glycerol. This is of particular interest in view of utilising the large surplus of glycerol generated in biodiesel production plants (see Scheme 5.1).[2]



Scheme 5.1. Production of propanediols (1,2- and 1,3-) from biomass-deriving platform chemicals.

1,3-propanediol used to be a high-price speciality glycol until 1999, when Shell Chemicals developed a new cost-efficient process and marketed it at a competitive price. As an industrial intermediate it can be formulated into composites, adhesives, laminates, powder and UV-cured coatings, mouldings, novel aliphatic polyesters, co-polyesters, solvents, anti-freeze, and other end uses. The main use has become its polymerisation with methyl terephthalate to produce polytrimethylene terephthalate (PTT). This polymer is employed in the manufacture of a large variety of products, from fibres to thermoplastics, challenging PET its high-volume relative. The success of this new polymer stimulated the research in the bio-chemicals field, and recently DuPont has patented both the production of 1,3-PD from a fermentation process and the consequent production of a bio-1,3-PD based PTT (Sorona®). At the moment various new processes, both chemo-catalytic and biological, for 1,3-PD production from renewables are under development.

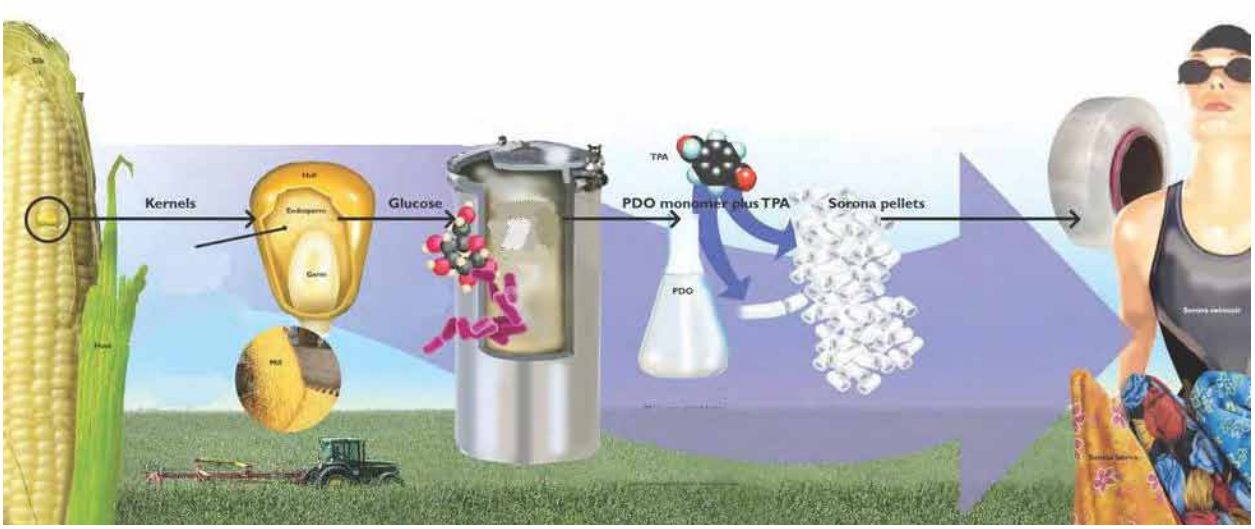


Figure 5.2. DuPont process for bio-1,3-PD production, followed by its polymerisation to PTT Sorona®.

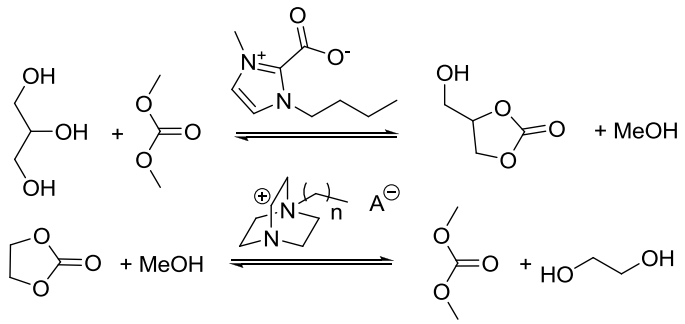
Hydrogenation of succinic acid and its derivatives (succinic anhydride and succinates) leads to the formation of a family of products, including: γ-butyrolactone (see chapter 3), tetrahydrofuran and 1,4-butanediol (BD). The latter is of great interest, once again for the production of important polymers such as polyesters, polyurethanes and polyethers. Polybutylene terephthalate is recognised as a possible substitute of PET, as already seen above for PTT. BD production does not suffer from the lack of catalysts for its synthesis, being the family of succinic acid and its derivatives currently obtained through the production process of maleic anhydride and derivatives, on which an extensive literature exists. The bottleneck of a hypothetical inclusion in a biorefinery scheme is succinic acid production that still needs to be optimised.

At last, two interesting pentanediols (PnD) can be generated from platform chemicals: the 2,5-PnD from levulinic acid (LA), and 1,5-PnD from glutamic acid (GA). It has been already mentioned that levulinic acid can be converted into γ -valerolactone; the latter can be further hydrogenated to 1,5-PnD. Little work has been done instead on glutamic acid, which can lead to 1,5-PnD once again via hydrogenation.

5.1.2. Diols for the production of carbonates

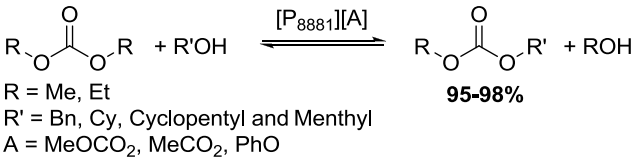
In the past two decades the growing demand for eco-friendly organic carbonates as intermediates for pharmaceuticals, lubricants, fuels, solvents, and polymers, has triggered a massive research activity for the synthesis of both diaryl and dialkyl carbonates.[3-7] As already described in chapter 1, various carbonates can be produced starting from a common precursor, such as dimethylcarbonate, via its catalytic transesterification with

alcohols or polyols. Patent and open literature offers a plethora of catalytic methods to accomplish these processes. Catalysts more often include bases such as phosphines and tertiary amines, alkali metal hydroxides, alkoxides, halides, and inorganic carbonates, alkali metal exchanged faujasites, and hydrotalcites,[6-19] but acid compounds (sulfonated Amberlyst resins and Zn-based MOF) are reported as well.[20-24] A great potential is envisaged also by using versatile organocatalysts such as ionic liquids (ILs); yet, the use of these compounds represents a largely unexplored area. Among few reported examples, two recent remarkable ones are shown in Scheme 5.2 where the synthesis of glycerol carbonate and dimethyl carbonate is described via transesterification processes catalysed by task-specific (basic) ILs as 1-*n*-butyl-3-methylimidazolium-2-carboxylate (top) and DABCO-derived systems (bottom), respectively.[25-26]



Scheme 5.2. Transesterifications of organic carbonates catalysed by ionic liquids

Even more recently, new weakly basic phosphonium salts, namely methyltrioctylphosphonium methyl carbonate (**5.1a**: $[P_{8,8,8,1}][MeOCO_2]$) and methyl trioctylphosphonium bicarbonate (**5.1b**: $[P_{8,8,8,1}][HOCO_2]$), were shown to act as efficient transesterification catalysts as well as catalytic precursors.[27] In this case, the reaction of both dimethyl and diethyl carbonate (DMC and DEC, respectively) with model primary, secondary and tertiary alcohols proceeded towards the selective formation of unsymmetrical dialkyl carbonates (Scheme 5.3).



Scheme 5.3. Synthesis of unsymmetrical dialkyl carbonates via transesterifications catalysed by phosphonium salts.

Major advantages associated with compounds **5.1a-b** include the following. i) An excellent catalytic activity. Beyond transesterification processes, salts **5.1a-b** can be used

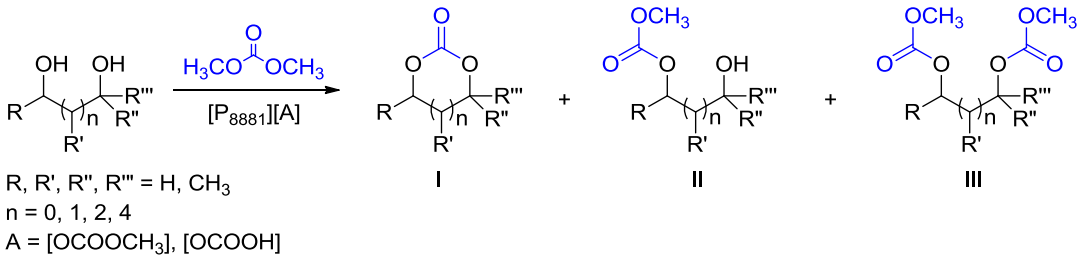
for fundamental C-C bond forming reactions such as Michael, Henry, and Baylis-Hillman transformations, where they exhibit performances comparable to those of organic superbases such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and phosphazeneP1–tBu.[27-30] ii) The availability of a green method for their preparation. The key step of the synthesis of **5.1a-b** involves a simple halide-free methylation of an alkyl phosphine with non-toxic dimethyl carbonate (DMC).[28-30] iii) Versatility. Carbonate onium salts, particularly **5.1a**, serve as catalysts as such, or they may be anion exchanged with a variety of acids (HA: A=NO_3, AcO, CF_3CO_2,TsO, $ArCO_2$, etc.) to generate libraries of derivatives ([$P_{8,8,8,1}$][A]) in a highly pure form. By-products of these reactions are only MeOH and CO_2. iv) Finally, compounds **5.1a-b** show a good thermal stability.

5.1.3. Aim

As a part of our the interest for the implementation of green protocols based on organic carbonates and ILs as organocatalysts,[3, 27-33] we decided to further explore the behaviour of carbonate salts **5.1a-1b** to catalyse the transesterification of DMC and DEC with different 1,n-diols (n = 2, 3, 4, and 6). The research was not only aimed at investigating the feasibility of the reaction, but also at studying possible effects of the chain length and the degree of substitution of the carbon backbone of diols. For this reasons, 1,2-diols such as 1,2-propane- and 1,2-ethane- diol (**5.2** and **5.3**, respectively), 1,3-diols such as 1,3-butanediol (**5.4**), 2-methyl-1,3-propanediol (**5.5**), 1,3-propanediol (**5.6**), 2,2-dimethyl 1,3-propanediol (**5.7**), and 2-methyl 2,4-pentandiol (**5.8**), and other 1,n-diols such as 1,4-butanediol (**5.9**) and 1,6-hexanediol (**5.10**) were used. While some of the listed diols can be produced by renewable feedstocks, on the other hand the main goal of this work was not to study the synthesis of their derivatives, rather to reach a good comprehension of which products can be obtained in dependence of the structure of the starting molecule (i.e. length of the diol and degree of branching), and to develop a technology to tune the selectivity towards one species rather than another one whenever possible. Such a technology would benefit the development of a new chemistry, in which bio-derived diols will plausibly represent important building blocks.

Here we demonstrate that, in the presence of salts **5.1a-b**, reactions proceeded with complete conversion towards the formation of transesterification products, *i.e.* cyclic and linear carbonates (I, II and III, respectively; Scheme 5.4 illustrates the model case of DMC). Even more interestingly, depending on the substrate and reaction conditions, experiments

proved that the product distribution could be largely controlled: the selectivity could be shifted from cyclic to linear di-carbonates (I and III), which were isolated in good-to-excellent yields (70->90%).



Scheme 5.4. The transesterification of dimethylcarbonate with diols, catalysed by carbonate phosphonium salts.

Beside the effect of diol structures, other reaction parameters such as the reactant molar ratio and the catalyst loading were examined. This investigation prompted some general considerations on the synthetic scope of the method and on the mechanism at the basis of the competition between ring-closing transesterification to yield carbonates I, and the formation of linear mono- (II) and di-carbonates (III).

5.2. Results

5.2.1. Catalysts

Methyltrioctylphosphonium methylcarbonate (**5.1a**: $[P_{8,8,8,1}][MeOCO_2]$) and methyltrioctylphosphonium bicarbonate (**5.1b**: $[P_{8,8,8,1}][HOCO_2]$) were used as organocatalysts. These compounds were prepared through a reported procedure.[28] Accordingly, at 150 °C, *n*-trioctyl phosphine (20.8 g) was initially methylated by DMC (30 mL) in the presence of MeOH as a co-solvent (30 mL). This allowed to isolate compound **5.1a** in quantitative yield. In a second step, compound **5.1a** (3.0 g) was mixed with water (1.0 mL) at 40 °C. A rapid hydrolysis of the methylcarbonate anion ($MeOCO_2$) took place with the formation of salt **5.1b** (>99%) and the release of MeOH as a co-product. Both salts **5.1a** and **5.1b** were stable colourless liquids at r.t., and were used as such without any further purification. (Additional synthetic details are in the experimental section).

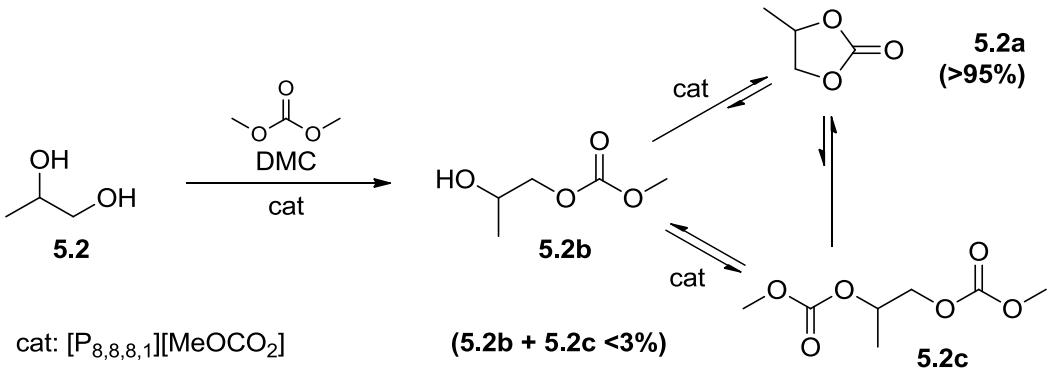
5.2.2. 1,2-Diols

The study of transesterification reactions started by using 1,2-diols such as 1,2-propanediol and 1,2-ethanediol (**5.2** and **5.3**, respectively).

1,2-propanediol

The reaction of **5.2** with DMC was initially examined: effects of the temperature, the catalyst loading, and the DMC:**5.2** molar ratio, respectively, were explored. A mixture of **5.2** (837 mg, 11.0 mmol), DMC and [$P_{8,8,8,1}$][OCO_2Me] in a 1: 20: 0.01 molar ratio, respectively, was set to react at three different temperatures of 90, 70 and 50 °C, for 6 hours. Then, under the same conditions, two additional experiments were performed at 90 °C: in the first, the catalyst amount was halved (**5.2**:[$P_{8,8,8,1}$][OCO_2Me]=1:0.005 molar ratio), while in the second one, a blank reaction was run in the absence of the onium salt.

At intervals, samples of the reaction mixtures were collected and analysed by ^1H NMR and GC/MS. Cyclic propylene carbonate (4-methyl-1,3-dioxolan-2-one, **5.2a**) was by far, the major product (>95%). Two by products were detected in trace amounts (total: ≤3%): these two compounds were supposed to be the corresponding mono- and di-transesterified derivatives (**5.2b** and **5.2c**, respectively; Scheme 5.5). NMR evidence was consistent with this hypothesis, although it was not possible to isolate them in pure form due their very low concentration. The conversion profiles of **5.2** at different temperatures and at different catalyst loadings are reported in Figure 5.3.



Scheme 5.5. Transesterification of 1,2-propanediol with DMC catalysed by [$P_{8,8,8,1}$][OCO_2Me]

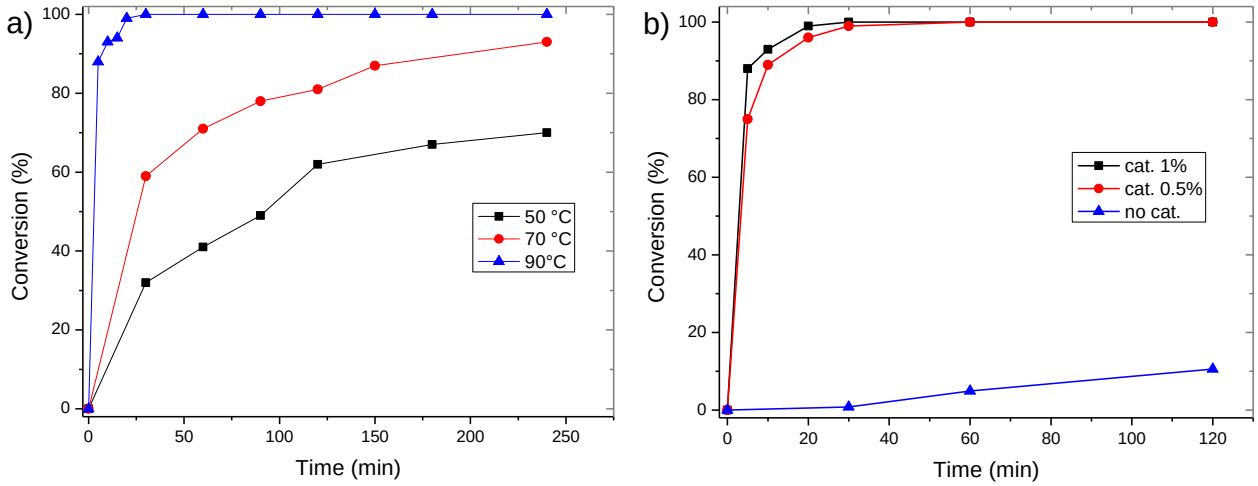


Figure 5.3. Conversion of 1,2-propanediol in the reaction with DMC catalyzed by [$P_{8,8,8,1}$][OCO_2Me]. a)Effect of the reaction temperature (molar ratio 2:DMC:[$P_{8,8,8,1}$][OCO_2Me]=1: 20: 0.01, respectively); b) Effect of the catalyst amount (90 °C; molar ratio 2:DMC=1: 20; [$P_{8,8,8,1}$][OCO_2Me]: 0 to 0.01 equivalents with respect to 2).

At 90 °C (boiling point of DMC), **5.1a** was a highly active catalyst: after 30 min, the conversion of 1,2-propanediol was quantitative even when the amount of the phosphonium salt was as low as 0.5 mol% (Figure 5.3 b, red profile). By contrast, the non-catalytic reaction was of no practical significance (Figure 5.3 b), blue profile). The decrease of the temperature from 90 to 50 °C produced a remarkable reduction of the conversion (Figure 5.3 a); nonetheless, the selectivity towards propylene carbonate (**5.2a**) was always very good (> 95%).

Further experiments were carried out to evaluate possible effects of the DMC/**5.2** molar ratio. Based on the results of Figure 1, reactions were performed at 90 °C, in the presence of 0.5 mol% (with respect to **5.2**) of [$P_{8,8,8,1}$][OCO_2Me] as the catalyst. Under such conditions, 1,2-propanediol (837 mg) was set to react with variable amounts of DMC: in particular, the DMC/**5.2** molar ratio was progressively decreased from 20 to 2. Results are reported in Figure 5.4 where the conversion profiles of **5.2** with time are shown at the different reactant molar ratios.

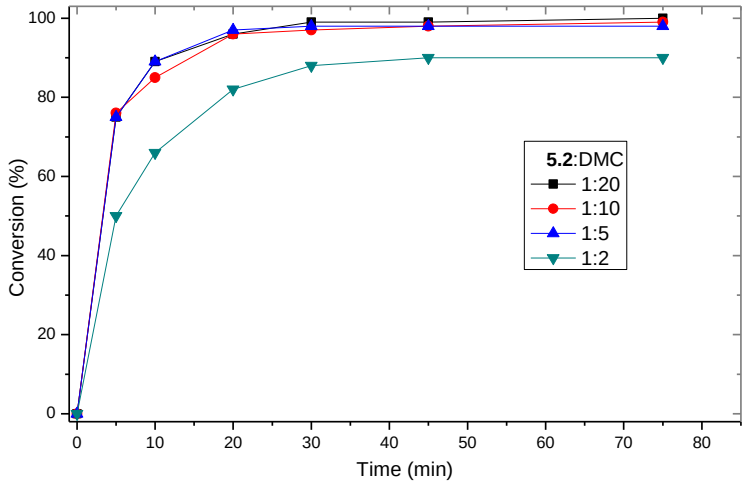


Figure 5.4. The reaction of 1,2-propanediol (2) with DMC catalyzed by [$P_{8,8,8,1}$][OCO_2Me] (90 °C; molar ratio 2:cat= 1:0.005). Effect of DMC:2 molar ratioon the reaction conversion. For convenience, some results of Figure 5.3 (b) are also shown (black profile, DMC:2=20).

The reduction of the DMC/**5.2** molar ratio from 20 to 5 had no dramatic consequences on the reaction outcome: after 30 min, the conversion of 1,2-propanediol was quantitative in all cases (black, red and blue profiles). When the DMC amount was further decreased (DMC/**5.2** = 2), the diol conversion was still satisfactory (around 90 %); though, a remarkably slower reaction was observed (green profile). No appreciable changes were noted in the product distribution: propylene carbonate was always obtained with very high selectivity (up to 95%).

Under the conditions of Figure 5.4 (molar ratio DMC/**5.2** = 5), catalyst recycle was also explored. Accordingly, the same catalytic sample was reused for three subsequent reactions of DMC and **5.2** at 90 °C for 60 min. Once the first experiment was complete, the excess of DMC and the co-product MeOH were removed by rotary evaporation. Next, propylene carbonate was recovered by distillation under vacuum (65 °C @ 200 Pa). To the residual catalyst **5.1a** was added a fresh aliquot (4.6 mL) of DMC and **5.2a** (in a 5:1 molar ratio, respectively). The mixture was then set to react at 90 °C for 60 min. The same reaction/catalyst reuse cycle was repeated a third time. The three tests showed an excellent reproducibility: in all cases, the conversion of **5.2** was 98-99% and the selectivity towards the formation of propylene carbonate was >95%. The stability and recyclability of the catalyst was thus confirmed.

Overall, the preliminary experiments proved that: i) the transesterification of DMC with 1,2-propanediol was efficiently catalysed by [$P_{8,8,8,1}$][OCO_2Me], and ii)

notwithstanding the different conditions investigated, the cyclic carbonate **5.2a** was always the preferred, if not the exclusive, product; iii) a reaction intensification was possible. Particularly, the amount of DMC could be reduced from 20 to 5 molar equivalents with respect to the limiting diol.

The behaviour of 1,2-propanediol was further explored in the transesterification with both DMC and DEC catalysed by methylcarbonate and bicarbonate phosphonium salts, **5.1a** and **5.1b**, respectively. Since DEC was expected to be less reactive than DMC,[34] transesterification processes were carried out under the most favourable conditions of previous experiments from Figure 5.3 and Figure 5.4. Accordingly, a mixture of **5.2** (837 mg), dialkyl carbonate (either DMC or DEC) and the catalyst (either **5.1a** or **5.1b**) in a 1:20:0.005 molar ratio, respectively, was set to react at 90 °C. The results are reported in Table 5.1. Experiments confirmed the previously observed trend for the product distribution: at complete conversion, all reactions were highly selective towards the formation of the cyclic propylene carbonate (**5.2a**). The product was distilled under reduced pressure (65 °C @ 200 Pa) and isolated in 86-92% yields (entries 1 and 3). Both carbonate onium salts proved to be effective transesterification catalysts: they showed a comparable activity when DMC was used (entries 1 and 2), while in the case of DEC, $[P_{8881}][OCOOCH_3]$ (**5.1a**) was more efficient than $[P_{8881}][OCOOH]$ (**5.1b**) (entries 3 and 4).

The reproducible behaviour of transesterifications with DEC was further verified by four repeated reactions: two of them were run under the conditions of entry 3, and two others were performed under the conditions of entry 4 (Figure 5.5, black and red profiles, respectively).

Table 5.1. The transesterification of DMC and DEC with 5.2, catalysed by 5.1a and 5.1b.

Entry	Carbonate	Catalyst	Time (h)	Product 5.2a (%)	
				NMR [b]	Isolated [c]
1	DMC	$[P_{8,8,8,1}][OCOOCH_3]$	0.5	99	92
2	DMC	$[P_{8,8,8,1}][OCOOH]$	0.5	99	-
3	DEC	$[P_{8,8,8,1}][OCOOCH_3]$	3	95	86
4	DEC	$[P_{8,8,8,1}][OCOOH]$	3	74	-

[a]All reactions were carried out at 90 °C, using **5.2**, dialkyl carbonate (either DMC or DEC) and the phosphonium salt in a 1:20:0.005 molar ratio. [b]% Amount of **5.2a** determined by ^{1}H-NMR analyses; [c] Isolated yield of **5.2a**. Product was isolated from reactions scaled to 22 mmols.

After 180 min, the formation of **5.2a** was 93% and 73% for the reaction catalysed by **5.1a** and **5.1b**, respectively. No clear reasons accounted for such a substantial difference: a similar effect was never observed in previous comparisons of salts **5.1a** and **5.1b** as organocatalysts for both transesterification processes and Michael- or Henry-type nucleophilic additions.[27-33]

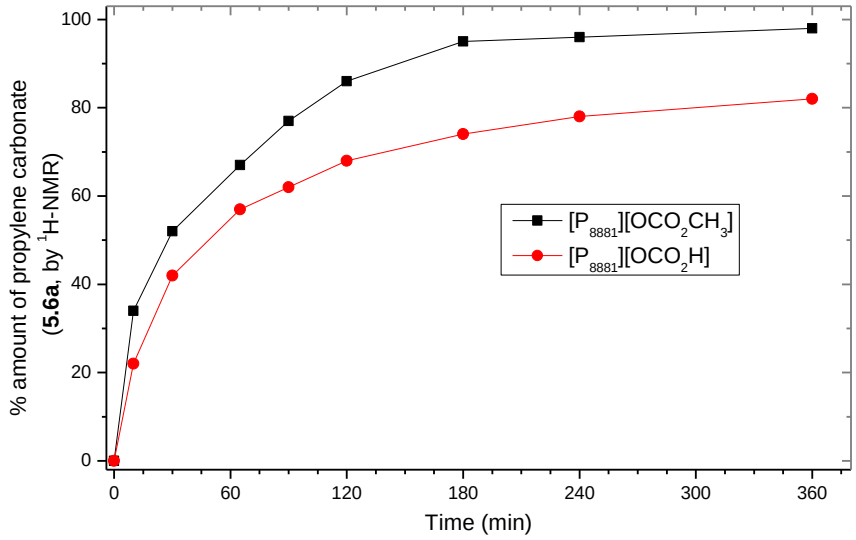


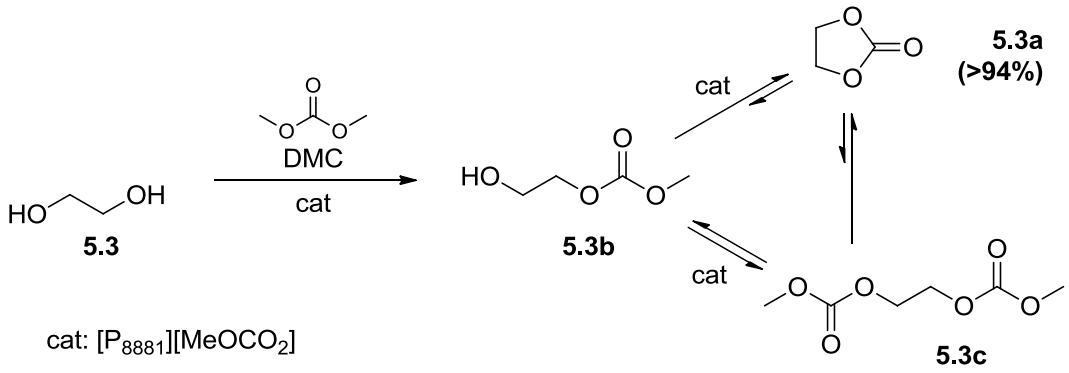
Figure 5.5. The formation of propylene carbonate during the transesterification of DEC with 1,2-propanediol catalysed by [P_{8881}][OCO_2CH_3] (5.1a) and [P_{8881}][OCOOH] (5.1b) (black and red profiles, respectively). In each profile, points indicated the average % amount of propylene carbonate (5.2a, by ^{1}H-NMR analysis) measured in two reactions repeated under identical conditions. Experiments were highly reproducible: at the chosen time intervals, amounts of 5.2a did not differ by more than 7% from each other.

In the presence of **5.1a** as a catalyst, the scale-up of the reaction of propylene glycol (**2**) to propylene carbonate with DMC was also investigated. An experiment was carried out on 200 g (2.63 moles) of **5.2**, adding 474 g of DMC (5.26 moles, DMC/**5.2** = 2) and 6.48 g of **5.1a** (13.1 mmol, **5.1a**/**5.2** = 0.005). After 1 hour at reflux, the MeOH/DMC azeotrope was removed by distillation. Then, the excess of DMC was removed by rotary evaporation and propylene carbonate **5.2a** was distilled (65 °C @ 200 Pa) yielding 258 g of pure product (96 %).

1,2-Ethanediol

The transesterification of DMC with ethylene glycol (**5.3**) was examined under the conditions of Figure 5.4 previously reported for 1,2-propanediol. At 90 °C, a mixture of **5.3** (683 mg, 11 mmol), and [$P_{8,8,8,1}$][OCO_2CH_3] in a 1: 0.005 molar ratio, was set to react with two different amounts of DMC (1.98 and 4.95 g; the molar ratio DMC/**5.3** being 2 and 5,

respectively). All experiments were carried out for 4 hours. Two further transesterification tests were also considered: in the first one, the co-product methanol was continuously distilled off throughout the experiment; in the second reaction, a higher temperature of 120 °C was used. This required a stainless-steel autoclave since the operating temperature was above the boiling point of DMC. ^{1}H-NMR analyses of the reaction mixtures indicated the formation of the cyclic carbonate – ethylene carbonate (1,3-dioxolan-2-one, **5.3a**) – as the major product (up to 94%). In analogy to 1,2 propanediol (Scheme 5.5), the other minor compounds were, most probably, the corresponding mono- and di-transesterified derivatives (**5.3b** and **5.3c**, respectively) shown in Scheme 5.6.



Scheme 5.6. Transesterification of 5.3 with DMC catalysed by [P$_{8,8,8,1}$][OCO$_2$Me].

The experimental results are reported in Table 5.2.

Table 5.2. Transesterification of 1,2-ethanediol with DMC.

Entry[a]	DMC:5.3 (mol:mol)	Temp. (°C)	Conversion[b] (%)	Products[b] (%)			3a (Y,%)[c]
				3a	3b	3c	
1	2	90	88	83	15	2	
2	5	90	95	74	19	7	
3[d]	2	90	100	94	3	2	86
4	2	120	100	88	12		

[a] All reactions were carried out in the presence of [P$_{8,8,8,1}$][OCOOCH$_3$] as a catalyst (molar ratio **5.1a**/**5.3** = 0.005). [b]The reaction conversion and the product distribution were determined by ^{1}H-NMR: reported values were obtained after 4 hours. [c] Isolated yield of the carbonate **5.3a**. Product was isolated from reactions scaled to 22 mmols. [d] A continuous distillation of the co-product methanol (at 70°C) was carried out.

In general, [P$_{8,8,8,1}$][OCO$_2$Me] acted as an efficient catalyst also for the transesterification of DMC with ethylene glycol (**5.3**). Compound **5.3** however, was

remarkably less reactive than 1,2-propanediol (**5.2**): under comparable conditions, conversions of **5.2** and **5.3** were 100% and 95%, after 30 min and 4 hours, respectively (Figure 5.4, blue profile and Table 5.2, entry 2). Moreover, the amount of ethylene carbonate (**5.3a**) did not exceed 83% (entry 1), while propylene carbonate (**5.2a**) was obtained with a much higher selectivity (≥95%, Figure 5.4). This trend was confirmed also by the reaction carried out at 120 °C: although the increase of the temperature allowed a quantitative conversion of **5.3**, the formation of the cyclic carbonate was only slightly improved (88%, entry 4).

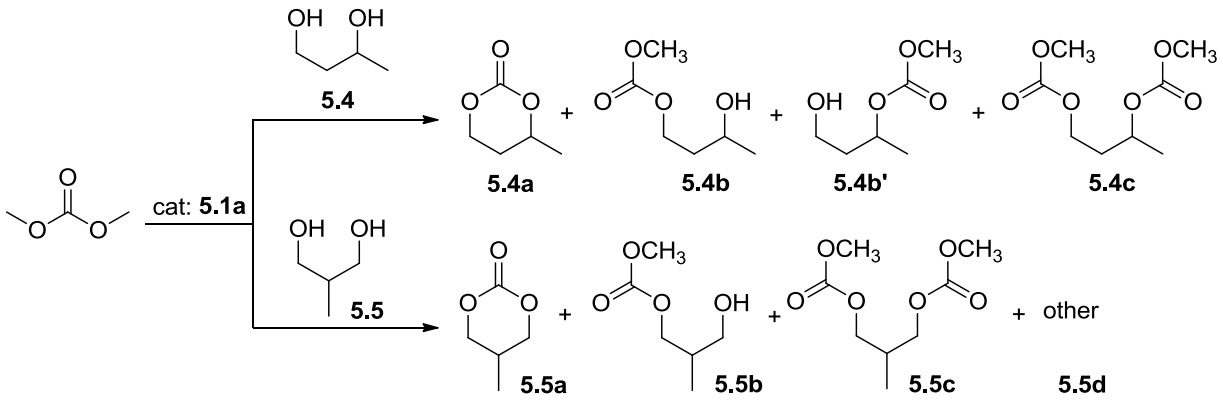
Better results were achieved when the co-product methanol was continuously removed by distillation: this expedient allowed to boost the selectivity towards the formation of **5.3a** up to 94% (entry 3). Once the reaction was complete, product **5.3a** was distilled under vacuum (78 °C @ 200 Pa) and isolated in 86% yield.

5.2.3. 1,3-Diols

1,3-Butanediol (**5.4**) and 2-methyl-1,3-propanediol (**5.5**) were chosen as model compounds. Initial experiments were carried out under the conditions previously explored for 1,2-diols: a mixture of **5.4** or **5.5** (991 mg, 11 mmol), DMC (18.5 mL), and [$P_{8,8,8,1}$][OCO_2Me] in a 1:20:0.005 molar ratio, respectively, was set to react at 90 °C, for 12 hours. At intervals, samples of such a mixture were withdrawn and analysed by both ^{1}H-NMR and GC-MS. In the reaction of compound **5.4**, four products were observed: the cyclic carbonate (4-methyl-1,3-dioxan-2-one, **5.4a**), the double-transesterification derivative (butane-1,3-diyl dimethyl dicarbonate, **5.4c**) and other two compounds most likely derived from mono-transesterification (3-hydroxybutyl methyl carbonate, 4-hydroxybutan-2-yl methyl carbonate, **5.4b**, **5.4b'**, respectively) (Scheme 5.7, top). Four products were detected also in the reaction of **5.5**: the corresponding cyclic carbonate (5-methyl-1,3-dioxan-2-one, **5.5a**), the mono- and di-carbonate derivatives [3-hydroxy-2-methylpropyl methyl carbonate and dimethyl (2-methylpropane-1,3-diyl) dicarbonate, **5.5b** and **5.5c**, respectively], and another unidentified compound (other **5.5d**) (Scheme 5.7, bottom).

Since compound **5.5b** formed in a reasonable amount (up to 20% at the beginning of the reaction), an additional transesterification reaction of DMC with **5.5** was carried out to isolate such product. The experiment was set up under the above described conditions and it was stopped after the first 10 minutes by quenching the reaction with aq. HCl.

Compound **5.5b** could be purified by f.c.c., and isolated in a 12% yield. NMR analyses fully confirmed the structure of **5.5b** reported on Scheme 5.7.



Scheme 5.7. The transesterification of DMC with 1,3-butanediol (5.4) (top) and 2-Methyl 1,3-Propanediol (5.5) (bottom), catalysed by 5.1a.

Figure 4 illustrates the results achieved in the reaction of DMC with compounds **5.4** and **5.5**: the conversion of both diols and the corresponding product distributions are plotted as a function of time.

In the case of 1,3-butanediol (**5.4**) (Figure 4, top), the experiment showed that after the first hour, the conversion was substantially quantitative and a mixture of all products **5.4a-c** was obtained. As the reaction proceeded further, the amount of compounds **5.4a-b/b'** progressively decreased in favour of the formation of **5.4c** that reached ~90% after 12 hours (green profile). Product **5.4c** was recovered by vacuum distillation (70 °C@ 120 mbar) and isolated in a 72 % yield.

A similar behaviour was displayed by the reaction of 2-methyl-1,3-propanediol (**5**) (Figure 4, bottom). Also in this case, after an initial formation of products **5.5a-d**, the reaction mixture reached an equilibrium composition in which the dicarbonate derivative **5.5c** was by far, the most abundant compound (85%, purple profile); **5.5c** was distilled under vacuum (70 °C @ 100 Pa) and isolated in 75% yield.

The product **5.5d** was not identified; however, its spectroscopic (GC-MS) analysis and the bell-shaped profile of its formation (magenta curve, Figure 5.6, right) suggested a backbone compatible with a high molecular weight carbonate obtained via a reversible reaction.[35] A plausible structure for **5.5d** was then hypothesised via a multiple transesterification process of DMC with **5.5** (Scheme 5.8).

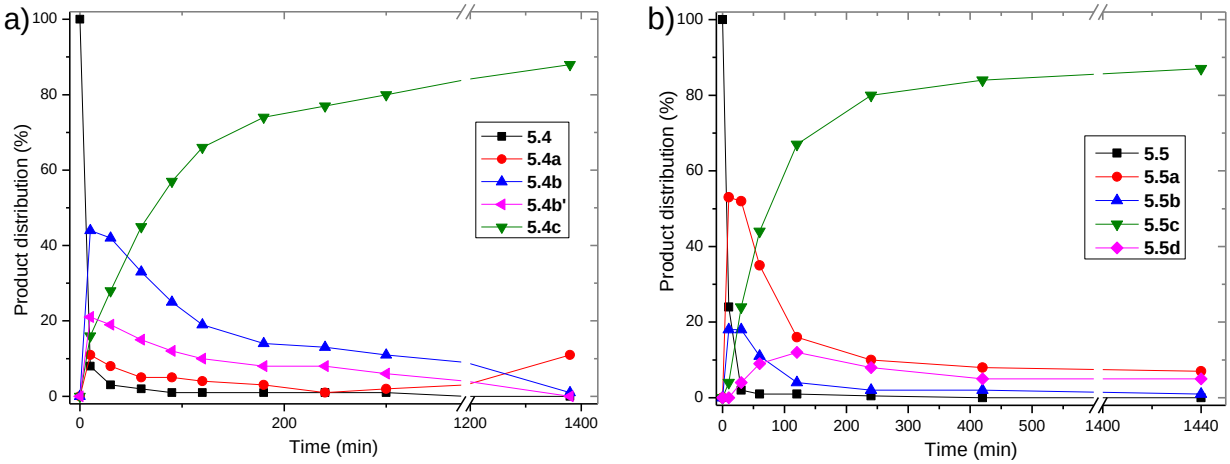
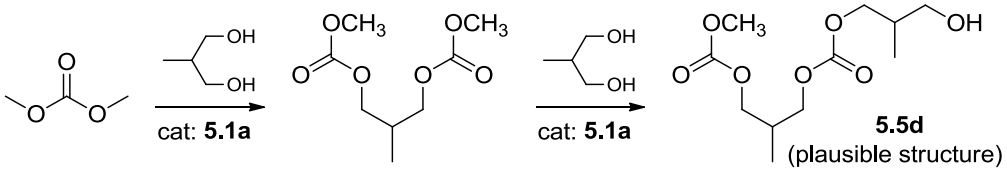


Figure 5.6. The product distribution observed for the reaction of DMC with 1,3-butanediol (5.4) (a) and 2-methyl-1,3-propanediol (5.5) (b); (90 °C, molar ratio 1,3-diol:DMC:[$P_{8,8,8,1}$][OCOOMe] = 1:20:0.005).

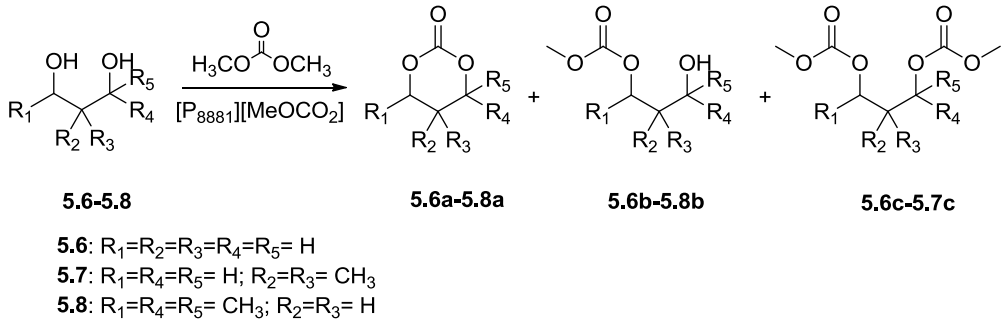


Scheme 5.8. Proposed structure for product 5.5d.

Overall, the results of Figure 5.6 indicated that: i) the catalyst ([$P_{8,8,8,1}$][$OCOOCH_3$]) efficiently activated both the primary and secondary OH groups of **5.4** and **5.5** for the transesterification with DMC; ii) a striking difference was manifest between 1,3-diols (**5.4** and **5.5**) and 1,2-diols. Under comparable reaction conditions, the former (**5.4** and **5.5**) preferentially gave linear dicarbonates **5.4c** and **5.5c**, while the latter (**5.2** and **5.3**) yielded the corresponding cyclic carbonates (**5.2a** and **5.3a**, respectively) with selectivity ≥ 95%. The selectivity towards linear products **5.4c** and **5.5c** was particularly noteworthy since such compounds, once formed, were expected to react further to give oligomers and finally, polycarbonates. The latter however, were never observed, not even in trace amounts.

This behaviour was confirmed by additional experiments carried out with 1,3-butanediol, in which the molar ratio DMC/**5.4** was varied between 2 and 20 and the temperature was increased up to 120 °C (in a stainless-steel autoclave). [$P_{8,8,8,1}$][OCO_2Me] was always used in 0.005 molar equivalents with respect to **5.4**. In all cases, the initial formation of mixtures of **5.4a-d** was followed by the progressive increase of the dicarbonate **5.4d** which was recovered in amounts ranging from 50 to 90% after 7 and 23 hours of reactions, respectively.

Other 1,3-diols such as 1,3-propanediol (**5.6**), 2,2-dimethyl 1,3-propanediol (**5.7**), and 2-methyl 2,4-pentandiol (**5.8**) were then used in the reaction with DMC. Conditions were those most frequently employed for the above described tests: accordingly, a mixture of the selected diol (**5.6**, **5.7** and **5.8**: 11 mmol; 0.84, 1.15, and 1.30 g, respectively), DMC (19.8 g, 220 mmol,), and $[P_{8,8,8,1}][OCO_2Me]$ in a 1:20:0.005 molar ratio, respectively, was set to react at 90 °C, for 12 hours. At intervals, samples of such a mixture were collected and analysed by both ^{1}H-NMR and GC-MS. In the case of compounds **5.6** and **5.7**, three products were observed: they were the corresponding cyclic carbonates (**5.6a** and **5.7a**), and the derivatives of mono- and double-transesterification of the reacting diol (**5.6b**-**5.6c**, and **5.7b**-**5.7c**, respectively) (Scheme 5.9). In the case of compound **5.8**, only the cyclic carbonate (**5.8a**) and the monocarbonate (**5.8b**) were detected (Scheme 5.9).

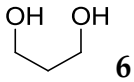
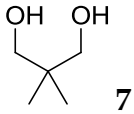
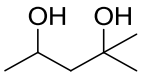


Scheme 5.9. The transesterification of DMC with 1,3-propanediol (5.6), 2,2-dimethyl 1,3-propanediol (5.7), and 2-methyl 2,4-pentadiol (5.8), catalyzed by 5.1a.

Results are reported in Table 5.3. For each substrate (**5.6-5.8**), the conversion and the product distribution are shown after 0.5 and 12 hours of reaction. The behaviour of diols **5.6** and **5.7** paralleled the one of compounds **5.4** and **5.5**: once the equilibrium was reached, the corresponding linear dicarbonates **5.6c** and **5.7c** were obtained as major products in amounts >80% (entries 2 and 4). Both **5.6c** and **5.7c** were recovered by vacuum distillation and isolated in 85 and 70% yields, respectively. A different outcome was observed for 2-methyl 2,4-pentandiol (**5.8**). In this case, the formation of the cyclic carbonate was highly favoured: after 12 hours, compound **5.8a** was the sole reaction product (96%, entry 6). This was purified by sublimation under reduced pressure (~100 °C @ 200 Pa), and isolated in a 95% yield. Notably, the experiment proved that during the reaction: i) only one of the two expected monocarbonate derivatives was observed. A ^{13}C-NMR analysis (see appendix) confirmed the presence of product **5.8b** resulting from the exclusive transesterification of DMC with the secondary hydroxyl group of **5.8** (@ C4). The tertiary OH function (@ C2)

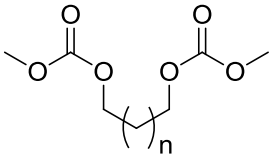
was totally unreactive; ii) not even trace amounts of the dicarbonate derivative were detected.

Table 5.3. The transesterification of DMC with 1,3-propanediol (5.6), 2,2-dimethyl 1,3-propanediol (5.7), and 2-methyl 2,4-pentadiol (5.8).[a]

Entry	1,3-Diol	Time (h)	Conv. (%)[b]	Products (%, NMR)[b]			Y (%)[c]
				5.6a	**5.6b**	**5.6c**	
1	 **6**	0.5	93	3	51	34	-
2		12	>99	<1	11	89	85
				5.7a	**5.7b**	**5.7c**	
3	 **7**	0.5	86	19	51	12	-
4		12	>99	1	18	81	70
				5.8a	**5.8b**	-	
5	 **8**	0.5	43	21	22	-	-
6		12	>99	96	3	-	95

[a]All reactions were carried out at 90 °C, using a mixture of 1,3-diol, DMC, and $[P_{8,8,8,1}][OCO_2Me]$ in a 1:20:0.005 molar ratio, respectively. [b]The reaction conversion and the product distribution were determined by ^{1}H-NMR. [c] Isolated yields of carbonates **5.6c**, **5.7c**, and **5.8a**, respectively. Products were isolated from a reaction scaled to 22 mmols.

Other 1,n-diols. To conclude the investigation, the reactions of DMC with 1,4-butanediol (**5.9**) and 1,6-hexanediol (**5.10**) were explored. Experiments were carried out at 90 °C, using a mixture of the diol (**5.9** or **5.10**: 1.0 or 1.3 g, 11mmol), DMC (19.8 g, 220 mmol), and $[P_{8,8,8,1}][OCO_2Me]$ in a 1:20:0.005 molar ratio, respectively. Under such conditions, both primary hydroxyl groups of **5.9** and **5.10** underwent an exhaustive transesterification that gave the corresponding linear dicarbonates (Figure 5.7: **5.9c** and **5.10c**, respectively): after 12 hours of reaction, these products were purified by distillation and isolated in 72% and 78% yields, respectively. Not even traces of oligomers or polycarbonates were detected.



5.9c: n = 2
5.10c: n = 4

Figure 5.7. Dicarbonate products from the transesterification of DMC with 1,4-butanediol (5.9) and 1,6-hexanediol (5.10).

5.3. **Discussion**

5.3.1.1. Effect of diol structure

The analysis of the investigated transesterification reactions proves that the structure and the relative OH-positions of the diols affect both the reaction conversion and the product distribution. Three aspects summarize the most salient results obtained so far with dimethyl carbonate:

i) for 1,2-diols, the main products are cyclic C5-carbonates with yields and selectivity up to 96% and >99%, respectively. Ethylene glycol however, is definitely less reactive than 1,2-propanediol (Figure 5.4 and Table 5.2);

ii) for 1,3-diols (**5.4**-**5.7**), although reactions are slower with respect to 1,2-diols, they afford linear dicarbonates **5.4c**-**5.7c** as preferential, if not exclusive, products once the equilibrium is reached (Figure 5.6 and Table 5.3). It should be noted that to date, a high yielding procedure for the syntheses of such linear derivatives is not described elsewhere via transesterification methods because the competitive formation of polycarbonates occurs preferentially over classical base-catalysts (see also below). A particular case is represented by 2-methyl-2,4-pentandiol (**5.8**) that possesses a tertiary OH group, the reaction of which with DMC does not occur; notwithstanding this, the occurrence of an exhaustive transesterification process involving both hydroxyl functions of **5.8** is substantiated by the formation of the cyclic C6-carbonate **5.8a** (95%, Table 5.3);

iii) for 1,n-diols (**5.9** and **5.10**), only linear dicarbonates **5.9c** and **5.10c** are obtained with not even trace amounts of cyclic derivatives. Polycarbonate formation is never observed.

A literature survey may offer different starting points to discuss such results. For one thing, the formation of cyclic carbonates *vs* linear products should be considered. Although Baldwin rules would predict that n-exo-trig type ring-closing processes (such as those involved for C5- and C6-cyclic carbonates) are favoured,[36] it has been often observed that exo double bonds in cyclic products tend to stabilise 5-membered rings and destabilise 6-membered rings, respectively.[37-39] Specifically, for carbonate derivatives, the

comparison of the chemical reactivity of C5- and C6-cyclic carbonates leaves few doubts on the higher stability of the former (C5) compounds.[12, 37, 39-40] This behaviour has been rationalized through thermochemical and computational data as well as by measures of activation energies which support and predict a larger ring strain for C6-cycles with respect to C5-rings. Conformational effects due to the interactions between lone pairs of carbonate oxygen atoms and ring methylene hydrogens have been postulated: these (effects) should not have consequences in quasi-planar 5-rings, but they would produce 6-ring chair structures with unfavourable energies. Whatever the reason, the thermodynamic stability may also substantiate our evidence for the preferred formation of C5-cyclic carbonates with respect to the corresponding C6-derivatives. Moreover, the intramolecular nature of cyclization processes plausibly accounts for the favourable kinetic of C5-ring closing reactions (Figure 5.4) over the double (bimolecular) transesterification reactions necessary for linear dicarbonates **5.4c**-**5.7c**, and **5.9c**-**5.10c**, respectively (Figure 5.6).

There are however two manifest discrepancies between our results and literature reports. The first one pertains to the presence of alkyl substituents in the carbon chain of the diol. According to different authors,[38, 41] when these substituents are located on alkyl chains tethering two reacting (hydroxyl) centres of a diol, intramolecular transesterification reactions are facilitated and small carbonate rings are obtained. These observations are often described within the many variations proposed for the so called "gem-disubstituent effect": the concept - originally formulated by Thorpe and Ingold[42] has been reviewed in 2005 by Jung and Piizzi,[43] that offered an analysis of fascinating early and recent theories based on the mutual repulsion of substituents (valency deviation), and the effect of reactive rotamers. In our case, although such notions may explain the easier formation of propylene carbonate with respect to ethylene carbonate (Figure 5.4), they hardly apply to account for the results of Table 5.3 and Figure 5.6. Except for 2-methyl 2,4-pentandiol (**5.8**), the investigated diols (**5.4**-**5.7**) produce the corresponding linear dicarbonates **5.4c**-**5.7c**: in other words, in our case methyl substituents located on the alkyl chains do not favour cyclic products at all.

The second question concerns the formation of polycarbonates. The literature well describes that in the presence of conventional organic and inorganic bases (amines, alcoxides, hydroxides, etc.) as catalysts, the transesterification of diols with light dialkyl

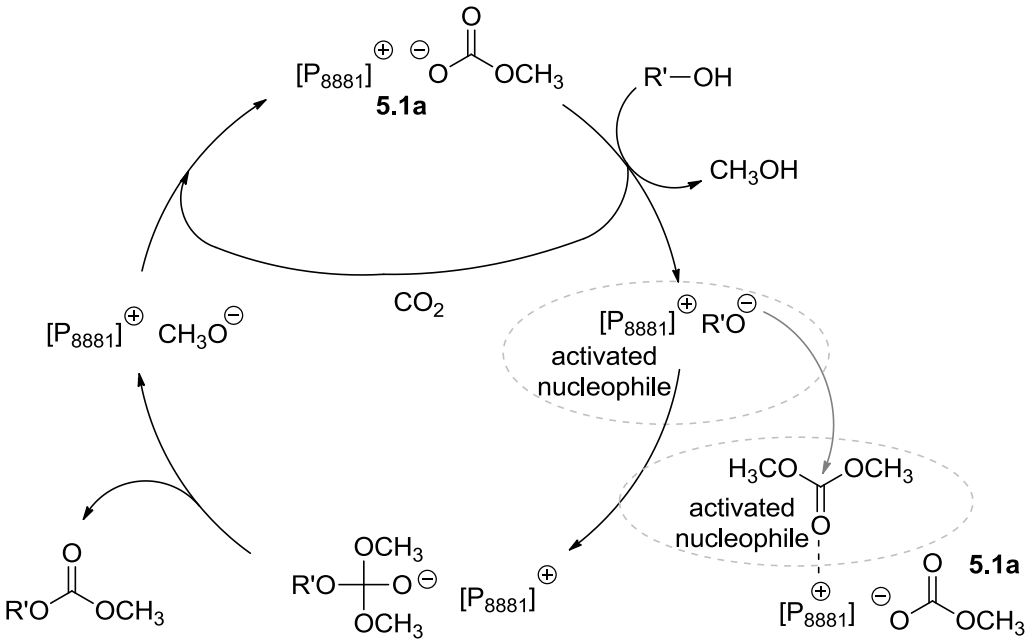
carbonates (both DMC and DEC) suffers from the competitive formation of the corresponding polycarbonates.[12, 44] In general, the reaction of 1,X-diols with X= 3 affords mostly mixtures of cyclic molecules and polymers, while with X≥4, polycarbonates are the almost exclusive products. By contrast, our results (Figure 5.6, Table 5.3, and Figure 5.7) show that linear dicarbonates **5.4c**-**5.7c** and **5.9c**-**5.10c** are obtained, without any trace of polymers even in the case of 1,4-butanediol and 1,6-hexanediol (**5.9** and **5.10**, respectively).

To complete the picture, two very recent reports should be here mentioned. In the first one,[45] the reaction of 1,4-diols with DMC and NaOMe as a catalyst, has been described under conditions by which five-membered cyclic ethers are the final products. However, not even traces of such derivatives (particularly of tetrahydrofuran) were detected by us during the reaction of 1,4-butanediol catalysed by **5.1a**. In the second paper, the selective formation of linear dicarbonates (including some compounds of Schemes 5.7 to 5.9 and Table 5.3) from 1,3-diols and DMC has been achieved only under biocatalytic conditions, in the presence of a lipase enzyme.[46]

In our case, the observed behaviour finds a plausible explanation in the nature of the organocatalysts used for the transesterification processes.

5.3.1.2. The role of carbonate phosphonium salts as catalysts

As was mentioned in the introduction, phosphonium ionic liquids such as salts **5.1a** and **5.1b**, are excellent catalysts not only for transesterification processes, but also for several C-C bond forming reactions.[27, 31-33] Of particular note is the fact that although these salts possess poorly basic anions (*i.e.* methylcarbonate and carbonate), their performance is comparable to that of organic superbases. This behaviour has been explained through the concept of ambiphilic (both nucleophilic and electrophilic) catalysis by which ILs act as catalysts via ion pairs.[27, 30, 47] In particular, our previous investigation on model transesterification reactions of primary and secondary alcohols with dialkyl carbonates,[27] highlighted two effects: i) an electrophilic activation due to the coordination of the P^+ centre of the catalyst (as a Lewis acid) to the basic carboxylic oxygen of dialkylcarbonates; ii) a nucleophilic activation due to an acid-base reaction between the alcohol and the basic anion of the catalyst (Scheme 5.10).



Scheme 5.10. Ambiphilic catalysis for transesterification reactions in the presence of carbonate phosphonium salts (the model case of methyl trioctylphosphonium methyl carbonate 5.1a is shown).

The first equilibrium of Scheme 5.10 is to the left, however once the activated nucleophilic alcoxide [P8,8,8,1][R'O] forms, it is immediately captured by DMC that is electrophilically activated by a second molecule of catalyst, driving the reaction forward. The electrophile and the nucleophile, triggered by the catalyst, react according to the usual pattern of nucleophilic acyl substitutions (NAcS) to yield the transesterification product CH_3OCO_2R' and restore the initial ionic liquid **5.1a** by incorporating CO_2 back into the anion. A further support to this mechanistic hypothesis comes also from an additional experiment in which an equimolar mixture of salt **5.1a** (500 mg) and 1,2-propanediol (77 mg) has been set to react at 90 °C for 21 hours. Under such conditions, NMR analyses have proved that the catalyst structure does not change and not even traces of the cyclic carbonate **5.2a** are formed. In short, the methylcarbonate anion of the catalyst does not possess any carbonylating activity. The large steric bulk of the phosphonium compared to the reactants accounts for two other facts already described by us:[27] (i) the exclusive formation of mono-transesterification products ($ROCO_2R'$). With respect to DMC (or DEC), once bulkier mono-transesterification derivatives are obtained, any catalytic activation and reaction are inhibited; (ii) the higher reactivity of primary OH groups with respect to secondary ones. The effect of the progressive crowding at the OH functions becomes so relevant that for tertiary alcohols, the corresponding transesterification reaction is no longer possible over ILs catalysts.

This analysis may offer a basis to discuss the product distribution observed for the transesterification of DMC with diols **5.4-5.10**. In this case, the influence of the steric bulk of the reactants on their activation by onium salts (Scheme 5.10) as well as the non-favourable energetics of C6-ring closing (see above) should be considered: the two effects plausibly contribute to drive the reaction towards mono-transesterification products (linear dicarbonates **5.4c**-**5.7c** and **5.9c**-**5.10c**), and to preserve these compounds from further reactions that would yield polycarbonates. Figuratively, the large phosphonium carbonate ion pair mimics the active binding site of an enzyme: the synergic catalytic effect of the cation and anion of the salt results in a high reaction rate even when a very low catalyst loading is used, and an unusual selectivity compared to other more conventional catalysts.

The cooperative catalysis mechanism may also help to discuss the selective formation of the cyclic carbonate (**5.8a**) from 2-methyl 2,4-pentandiol (**5.8**) (entries 5 and 6, Table 5.3). A hypothesis is that the lack of an efficient nucleophilic activation of the tertiary OH group and the (difficult) approach/coexistence of sterically encumbered sites on both the diol **5.8** and the intermediate monocarbonate **5.8b**, favours an intramolecular transesterification reaction of **5.8b** which affords the cyclic derivative **5.8a** as the preferred product.

5.3.1.3. Different dialkyl carbonates and catalysts

The results of Table 5.1 indicate that the synthetic scope of the procedure may be extended to different dialkyl carbonates of which DMC and DEC are model examples. In the presence of 1,2-propanediol, the lower transesterification rate observed for DEC with respect to DMC, parallels a trend already reported in comparative kinetic analyses of several other alkylations and carboxyalkylations mediated by organic carbonates:[10] in general, the heavier the (dialkyl) carbonate, the poorer its reactivity.

As far as salts **5.1a** and **5.1b**, it is not surprising that their very similar structures may allow comparable catalytic performances. This behaviour has been observed by us in previous applications of such catalysts,[27-33] and it is confirmed by the results of Table 5.1 when reactions of DMC are considered (entries 1 and 2). By contrast, the minor activity shown by **5.1b** in the reaction of DEC (Table 5.1, entry 4; Figure 5.5), has presently no clear reasons.

5.4. Conclusions

This investigation proposes a high-yielding procedure for the synthesis of both C5-cyclic carbonates and linear dicarbonates **5.4c**-**5.7c** and **5.9c**-**5.10c**. In addition, it rationalises the parameters that control product distribution during the transesterification of dialkyl carbonates with diols. In this respect, the structures of diols, as well as the nature of the organocatalysts, play a crucial role. The preference for ring closing reactions shown by 1,2-diols is most plausibly due to the greater stability of C5-membered cycles. Instead, the (preferred) occurrence of bimolecular processes for 1,n-diols (n ≥ 3) can be ascribed to two effects: on one hand, the less favourable energetics of C6-ring closing processes, on the other, the influence of the steric bulk of the reactants on their activation by the catalytic onium salts, that derives from a cooperative catalysis mechanism. This last observation further corroborates the choice of carbonate-exchanged phosphonium salts as catalysts for this study: since compounds **5.1a** and **5.1b** operate through a cooperative nucleophilic-electrophilic activation of the reagents and since they are effective for primary and secondary OH groups, therefore they may be used as a powerful tool to tune the access to cyclic or linear products, and to prevent polycarbonate formation. It should be noted that linear dicarbonates are not otherwise accessible in good yields or selectivity by other conventional base catalysed methods.

A final mention goes to the green features of the procedure that makes use of: i) non-toxic dialkyl carbonates, particularly DMC, for both the synthesis of ILs catalysts and the transesterification step, and ii) stable and recyclable catalysts that are so efficient to be used in amounts as low as 0.5 mol% (with respect to the limiting diols).

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6 | ON-WATER MODIFICATION OF FAMES TO IMPROVE COLD FLOW PROPERTIES OF BIODIESEL

6.1. Introduction

Lipids are one of the most abundant components of biomass. Among them triglycerides are the major form of energy storage both in plants and animals, as they allow to accumulate a larger amount, per weight unit, than carbohydrates or proteins (9 Kcal/g against 4 Kcal/g).[1]

Figure 6.1. a) Structure of a generic triglyceride: a saturated fatty acid moiety (blue), a mono-unsaturated (green) and a triple-unsaturated (red) one are connected to the central glycerol moiety (black). b) 3D model of trimyristine, a saturated triglyceride.

Triglycerides are stored mainly in oily fruits and seeds of plants, some species of algae and fatty tissues of animals. Their competitive cost, widespread availability, and built-in functionality make them attractive for numerous commercial applications. As a matter of fact vegetable oil derivatives are being investigated as plastics[2] and thermoplastics, plasticizers, hydraulic fluids, lubricants, surfactants, adhesives and fuel additives. Since their aliphatic chains chemically not very different from certain petroleum fractions, a large effort has been devoted in the past few years to the conversion of fats into fuels.

6.1.1. Biodiesel

The possibility of using vegetable oils as fuels has been known for decades, since Rudolf Diesel's engine was run on peanut oil at the Exposition Universelle in 1900. Diesel's foresight is evident from his words: "the use of vegetable oils for engine fuels may seem insignificant today but such oils may become, in the course of time, as important as petroleum and the coal-tar products of the present time".[3] Fuel mixtures based on fatty acids were then called "bio-diesel", being suitable for the use, in blend with crude oil-derived diesel, in the corresponding engines. Soon fatty acids started to be esterified with methanol to produce "fatty acids methyl esters" (FAMEs), that are free from glycerol, and that consequently possess improved physical behaviour. This process has been optimized over the years. Nowadays FAMEs biodiesel is the dominant biofuel in Europe.[4] Its success derives from the renewable character of the starting materials, as well as the lower emissions of carbon monoxide, hydrocarbon and particulate when it is used in place of petrodiesel, both as pure and as biodiesel blends. Its use is supported by the EU biofuel support policy.

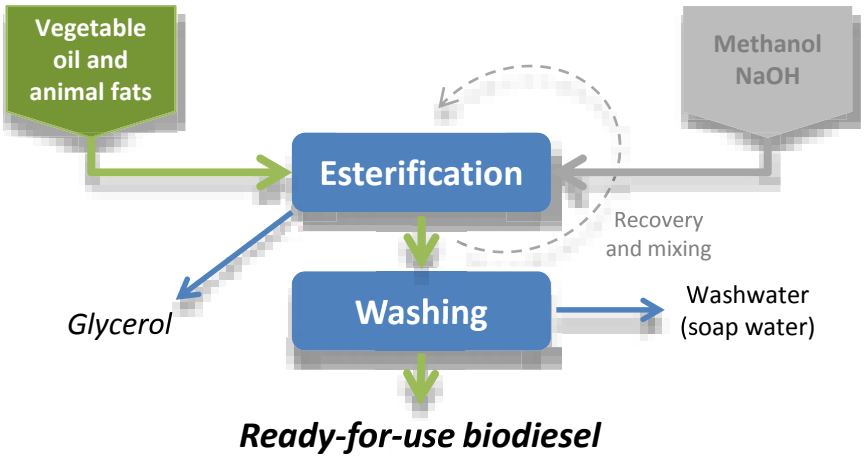


Figure 6.2. Production scheme of FAMEs.

Despite the ease of production of FAMEs, research towards new production processes and alternative starting materials is still in progress. Regarding the first point, improved or better new technologies are needed to meet the increasing demand pushed by new laws in support of renewable fuels (e.g. in the UE and in the US).[5-6] In the context of starting materials, the current aim is to avoid the use of food sources, which represents an ethical problem (see chapter 1, paragraph 1.2.2: "The competition with food sources").[7] Moreover, it has to be considered that biodiesel cost is strongly influenced by the feedstock, which makes up 70-80% of the whole production cost.[8-9] In this sense the trend

is to employ lower value feedstocks such as used cooking oils, sewage, animal waste streams and unconventional oilseed crops, while as a long-term objective microalgae represent an interesting perspective. [8]

6.1.2. Cold flow properties of biodiesels

The main problem connected to the extensive use of biodiesels is represented by their cold flow properties, which determine their geographical applicability. Fuel blends for cold climates obviously must maintain flowing properties at lower temperatures compared to blends for warmer regions. The most common cold flow properties are listed in Table 6.1, together with their description.

Table 6.1. Standard cold flow properties of diesels.

Parameter	Acronym	Definition
Cloud point[10]	CP	Temperature at which wax crystals first appear in the liquid.
Cold filter plugging point	CFPP	Lowest temperature at which a given volume of fuel still passes through a standard filtration device.
Pour point	PP	Temperature at which the fuel can no longer be poured due to gel formation.

Upon cooling a sample of biodiesel, its phase diagram, shows first the insurgence of the CP, followed by CFPP, then PP. Commonly FAMEs mixtures exhibit worse cold flow properties than petrodiesel, and the problem becomes more relevant when using low value feedstocks and/or animal waste (see Table 6.2), due to the increased concentration of saturated fatty acids.

Table 6.2. Cold flow properties for various diesel and biodiesel mixtures.

Substance	Cloud point (°C)	Cold filter plug point (°C)	Pour point (°C)
Cold flow improved diesel[11]	-5	-27	-47
Untreated diesel[11]	-5	-15	-23
Canola methyl ester[12]	-3	-4	-4
Soy methyl ester[12]	3	-2	-4
Yellow grease methyl ester[12]	8	11	6
Lard methyl ester[12]	13	11	13
Edible tallow methyl ester[12]	19	14	16

Cold flow properties are strongly dependent by the fatty component distribution in the mixture: a high content of unsaturated alkyl chains leads to better values, whereas a high content of saturated chains has an opposite effect. This happens because the unsaturation is naturally produced with *cis* geometry, causing a certain degree of disorder in the mixture, certainly higher than the linear saturated chains (Figure 6.3).

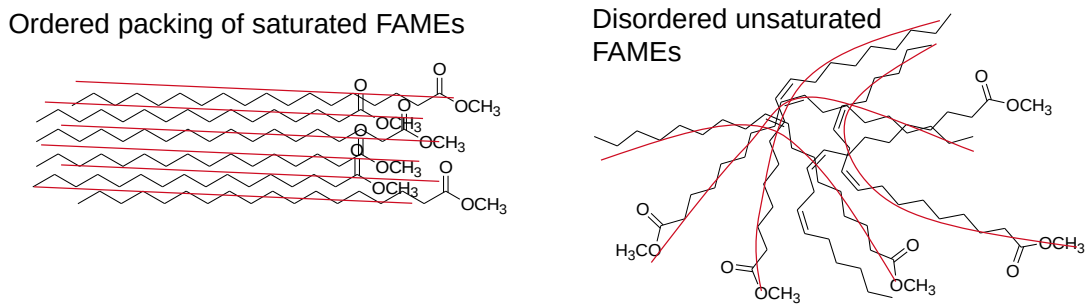


Figure 6.3. Visual simplification of the difference behaviours of saturated and unsaturated FAMEs.

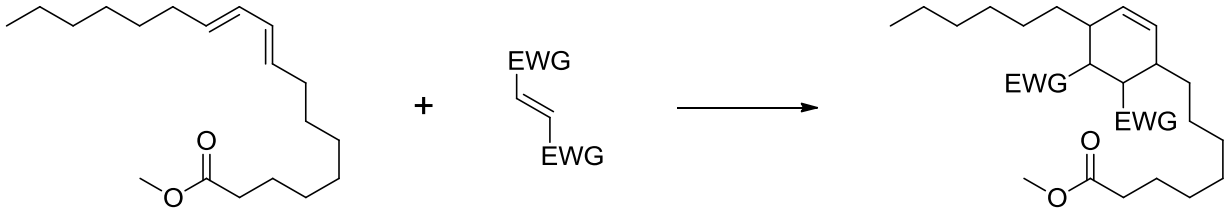
At any rate, as already stated above, poor cold flow properties strongly limit the applicability of biodiesels, both as pure and blends. Thus, methods to improve such properties are highly desirable. While CFPP generally determines the lowest feasible operating temperature for diesel fuels, research suggests that the best improvement in biodiesel cold flow is obtained by strategies that improve CP.[13] All the possible strategies can be grouped as follows: i) methods to change the molecular structure or the mixture composition, which are effective but generally relatively expensive as they involve the bulk modification of the fuels; ii) methods involving the use of additives. Despite the urgent need, the latter is underdeveloped for biodiesels, even though it seems particularly attractive, as it has already been applied with good results to fossil biodiesels.[14]

6.1.3. Aim

The work presented here was aimed at using the unsaturated fraction of the biodiesel itself as a molecular platform to prepare an *in-situ* additive. The modification consisted in the Diels-Alder (DA) addition of a chosen molecule to the olefinic part of the fatty chain (Scheme 6.1). The resulting molecule would be more highly substituted, thus potentially able to reduce the CP in a biodiesel mixture.

Added value as far as sustainability is concerned is was represented by the use of water as a reaction medium, aiming at the development of an on-water catalysed reaction as the key step in the strategy for reducing biodiesels CP. As it was described in the first

chapter (see paragraph 1.3.1.5 "On-water catalysis"), on-water catalysis has been successfully applied to DA cycloadditions allowing to carry out efficient reactions. In order to provide access to improved biodiesel fuels, the following points were considered in the present investigation.



Scheme 6.1. General scheme for the generation of a substituted fatty acid molecule from an unsaturated FAME via Diels-Alder reaction (EWG = electron withdrawing group).

- The transformation strategy avoids the use of organic solvents and of any other chemical except the two reactants (see Scheme 6.1) and water, giving an additional green character to the process;
- Water is already present during biodiesel production (see Figure 6.2), thus the additional proposed transformation would not significantly alter the existing process;
- By using a bio-derived molecule to react with the FAMEs a completely renewable-based process is envisaged.

The study was focused on the FAMEs corresponding to the most abundant unsaturated fatty acids in vegetable oils and animals fats: oleic acid and linoleic acid; the first being the main compound of the C18:1 class (eighteen carbons, one unsaturation) and the second the main compound of the C18:2 class (eighteen carbons, two unsaturated bonds) (see Table 6.3). We started by testing the reactivity of oleic acid methyl ester (OAME) first, moving then on linoleic acid methyl ester (LAME).

Table 6.3. Percentage distribution of fatty acids in the lipid fraction of various substances.[15]

Source	Saturated	Unsaturated			Others
		C18:1	C18:2	C18:3	
Sunflower oil	5-16	14-40	48-74	1	-
Soybean oil	17	23	58	1-2	-
Canola oil	7	63	28	1-2	-
Olive oil	8-20	55-83	4-21	1-2	-
Corn oil	13	28	58	1	-

Lard	41	46	9	0.3	3.7
Tallow	43	50	3	1	3
Chicken fat	33	41	20	2	4

6.2. Results

6.2.1. Methyl oleate

Methyl oleate was the first FAME chosen for derivatisation. The free fatty acid was avoided because it was prone to H-bonding with water molecules, a behaviour which is undesirable for on-water reactions. As already described in the introduction, the aim was to perform a Diels-Alder (DA) functionalisation of the FAME with a suitable diene. Three different dienes were tested (Figure 6.4): the first two, methyl sorbate and furan, involved an inverse electron demanding DA reaction; cyclopentadiene instead involved a normal DA reaction.

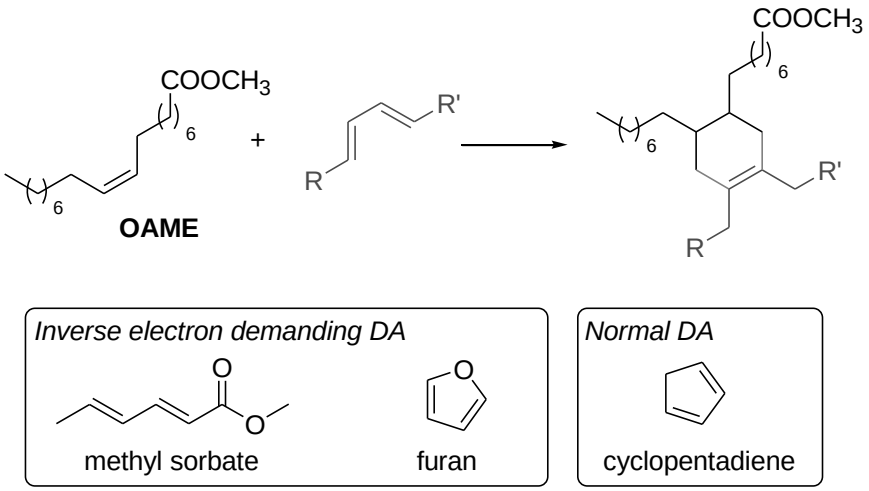


Figure 6.4. Proposed Diels-Alder cycloadditions between methyl oleate and some dienes.

In order to establish suitable baseline conditions, the reactions were initially performed using water or toluene as solvents, at various temperatures and with a catalytic amount of p-toluenesulfonic acid (PTSA). All three dienes were tested with methyl oleate under all the conditions listed in Table 6.4.

In a typical experiment the diene (6 mmol) was loaded in a 2:1 molar ratio with respect to methyl oleate (3 mmol, 0.89 g) and xx mL of the indicated solvent (water or toluene). The final reaction mixtures were extracted with ethyl acetate when water was the reaction medium, concentrated and analysed by GC-MS and ^{1}H-NMR.

Table 6.4. Media and temperatures for the reaction between methyl oleate and the chosen dienes.

MEDIUM	CONVERSION[b] (%)		
	Temperature (°C)		
	180	200	220
H_2O	*0*	*0*	*0*
Toluene	*0*	*0*	*0*
Toluene + PTSA	*0*	*0*	*0*

[a]All the reactions were performed in stainless steel autoclaves with an internal volume of 12 ml, arranged in an Amtec SPR16 reactor. Reaction times were 3 and 6 hours. [b]Conversion was determined by GC-MS and ^{1}H-NMR.

None of the experiments gave any conversion. When water was used as a reaction medium at high temperatures, small percentages of the hydrolysis product (the corresponding fatty acid) were observed. It was concluded that the unsaturated moiety of methyl oleate is not activated enough towards this kind of cycloaddition. It was then decided to move on to linoleic acid methyl ester, to be used as diene rather than dienophile and therefore possibly more prone to cycloaddition once in its conjugated form.

6.2.2. Linoleic acid methyl ester

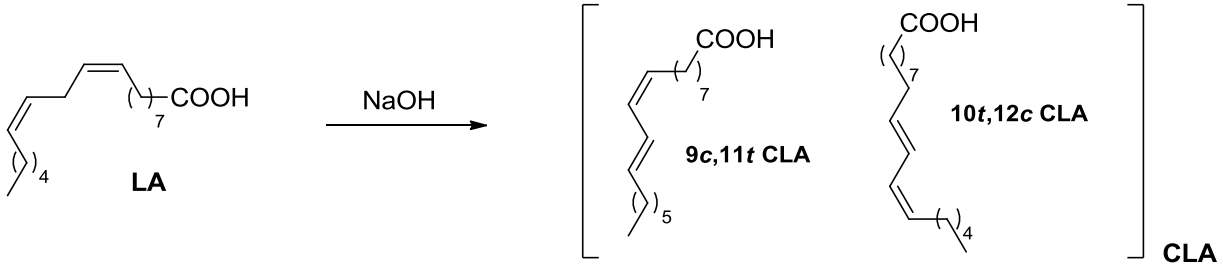
Linoleic acid methyl ester, that contains a double unsaturation on the aliphatic chain and can therefore act as the diene moiety in a DA reaction, was then investigated for derivatisation by cycloaddition with a suitable dienophile. This part of the study involved first the isomerisation of linoleic acid (LA) to conjugated linoleic acid (CLA), followed by Fischer esterification, and then the DA reaction of the CLA methyl ester (CLAME) with dimethyl fumarate.

6.2.2.1. Linoleic acid isomerisation to conjugated linoleic acid.

Since LA contains two unconjugated double bonds in the C9 and C12 positions, these had to be isomerised first to obtain conjugated linoleic acid (CLA), in order for it to act as the diene moiety in the DA reaction. The process for linoleic acid conjugation is known, being CLA a valuable compound (it is used as a dietary supplement, on the basis of its health benefits,[16-18] and as a drying oil in the formulation of oil paint and some varnishes). Typically it involves the use of excess base (generally NaOH), in ethylene glycol (EG), or one of its higher homologues, as a reaction medium. On the other hand water received

little attention as an alternative to glycols, which are still the most commonly used solvents. However in our study, where the use of water is already planned, the possibility to replace glycols was preferable (also in a view of a possible one-pot process involving both the conjugation step and the DA reaction). For this reason we performed an initial study on LA conjugation using water as a reaction medium.

CLA is formed as mixture of isomers, the great majority of which are *cis*-9,*trans*-11-CLA (generated by the isomerisation of the C12-C13 double bond) and *trans*-10,*cis*-12-CLA (generated by the isomerisation of the C9-C10 double bond; see Scheme 6.2).



Scheme 6.2. Major isomers generated from CLA isomerization.

EG was employed for the first conjugation experiments, and then replaced by water. The reactions were performed in an SPR16 reactor using stainless steel autoclaves; a typical loading used 0.25 g of LA with NaOH (14:1 mol/mol LA) in 4 ml of the desired solvent. Results are summarised in Table 6.5.

Table 6.5. Yield of CLA obtained by isomerisation of LA with NaOH in two different solvents at various temperatures.

Entry[a]	Solvent	Temperature (°C)	Time (min)	Conjugation[b] (%)
1	Ethylene Glycol	160	30	80
2		200		93
3	Water	160		5
4		200		45
5		220		76
6		180	60	17
7		200		60
8		220		96
9			90	99

[a]All the reactions were performed in an SPR16 reactor using stainless steel autoclaves , with a ratio LA:NaOH = 1:14 and 0.25 g of LA. [b] The yield of CLA was determined by ^{1}H-NMR.

As expected, the isomerisation occurred faster in EG than in water, where higher temperatures were needed to obtain high conversions. At 160 °C after 30 minutes a conversion of 80% was obtained in glycol (entry 1, Table 6.4), while at the same temperature and time water gave only a 5% conversion. The difference was less pronounced at 200 °C, but glycol gave again a more than double conversion after 30 min (93% against 45% in water, Table 6.4, entries 2 and 4 respectively). However, since the reaction in water showed an increase in conversion with temperature, a set of experiments to maximize isomerisation in this solvent were carried out. After 30 min a conversion of 76% of CLA was obtained increasing the temperature to 220 °C. At the same temperature the conversion could be maximised by increasing the reaction time: 96% conversion was obtained with 60 minutes, and almost quantitative CLA formation was observed after 90 minutes.

The next goal was to reduce the base amount. As described above, a molar ratio base/LA of 14 was initially used, according to a reported procedure.[19] Next, we progressively reduced the base amount, passing to ratios of 7, 3 and 1 (Table 6.5).

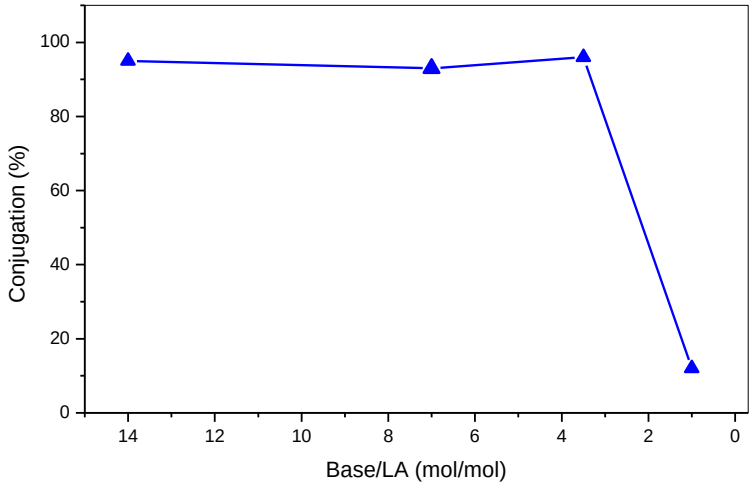
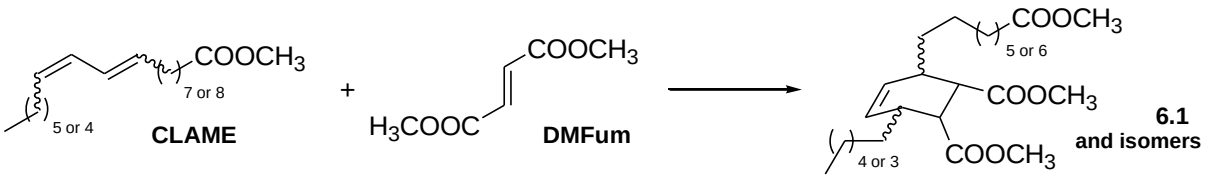


Figure 6.5. Effect of base/LA molar ratio on the final degree of conjugation.

As expected, a molar ratio NaOH/LA = 1 is only sufficient to saponify the fatty acid. On the other hand, we did not observe significant differences with molar ratios of 3, 7 or 14. In the present study, the lower limit to obtain complete conjugation was a ratio NaOH/LA = 3. We did not extend the research further, not being this our main objective. Isomerised CLA was then converted in the corresponding methyl ester (CLAME) via simple Fischer esterification and used in the following steps.

6.2.2.2. Diels-Alder reaction of conjugated linoleic acid methyl ester with dimethyl fumarate

For the Diels-Alder cycloaddition reaction with CLAME we chose as a suitable anactivated (electron poor) dienophile, i.e. alkenes bearing electron withdrawing groups. The choice fell on dimethyl fumarate (DMFum), already used by Beattie *et al.* in their study of the on-water catalysis mechanism.[20] The reaction studied is shown in Scheme 6.3. It occurs between the mixture of conjugated linoleic acid methyl esters (CLAMEs) and DMFum, to give the corresponding Diels-Alder cycloadduct. The results of the first set of reactions are presented in table 6.6.



Scheme 6.3. Diels-Alder cycloaddition between CLAME and dimethyl fumarate.

Table 6.6. Reaction between CLAME and dimethyl fumarate in different solvents.

Entry[a]	Medium	T (°C)	time (h)	Conv. (%)	6.1 Yield (%)	Isolated Yield (%)
1	Et acetate[b]	80	6	>3	>3	-
2	On-water[c]	80	6	4	4	-
3	Et acetate[b]	160	3	16	16	-
4	On-water[c]	160	3	23	23	19
5	neat	160	3	24	24	-

[a] The reaction of entry 1 and 2 were performed in a r.b. flask, charging 0.25 g of *t,t*-CLAME and with a molar ratio *t,t*-CLAME:DMFum = 1:1.1. The reactions from lines 3 to 5 were performed in an SPR16 reactor using stainless steel autoclaves, using the same amounts of above. [b] 2 ml of ethyl acetate were used. [c] 4 ml of water were used. [d]Conversions and yields of **6.1** were determined by GC-MS.

After this first set of reactions it appeared clear that CLAME was not an active enough diene. The behaviour was explained by considering the geometry needed for the Diels-Alder reaction (Figure 6.6, left) and the stereochemistry of the rotamers corresponding to the two isomers obtained from the LA conjugation step (Figure 6.6, right).

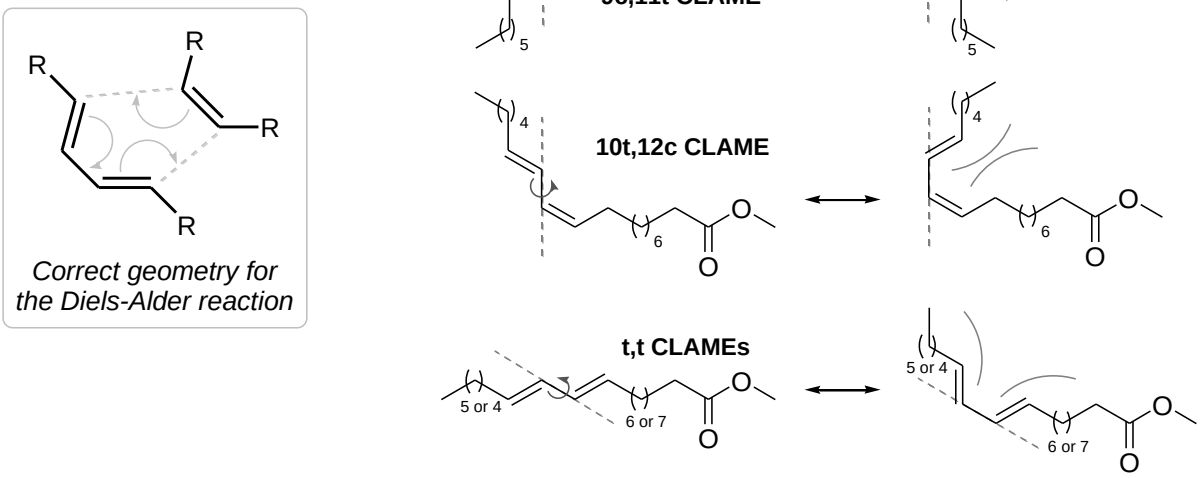
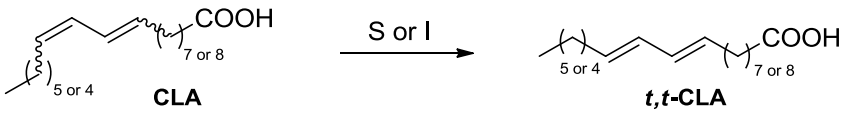


Figure 6.6. Configuration needed for the Diels-Alder reaction to occur (left) and rotamers of CLA components (right)

The Diels-Alder reaction requires that the double bonds of the diene face each other in order to be in the correct configuration to react with the dienophile. However, when this situation is verified for the two CLAME isomers by the free rotation around the bond between the two unsaturations, the repulsion between the two cis chain fragments is maximized, making this conformation unfavoured. On the contrary the *trans*,*trans* isomer would have lower energy and would be correctly configured for the cycloaddition reaction. Thus, we started considering the possible ways to obtain the *trans*,*trans*-CLAME. This kind of isomerisation has been known for decades and it is often referred as "elaidinisation" (mainly known for improving fatty acids resistance to oxidation).[21-22] It can be performed by using elemental sulfur or iodine as catalysts (see Scheme 6.4).



Scheme 6.4. Isomerisation of CLA to *t,t*-CLA can be achieved by using elemental S or I.

No excessive time was devoted energy to the optimization of this step; anyhow both the methodologies were tested, as described below.

Isomerisation of CLA to t,t-CLA – Iodine

The use of elemental iodine in organic solvent (e.g. hexane) is one of the oldest and easiest methods to isomerise olefins,[23-24] which can be efficiently applied to fatty acids.[25] We tested this catalyst for obtaining *t,t-CLA*. In a typical example CLA was dissolved in

hexane, a crystal of iodine was added, and the mixture was exposed to the sunlight under stirring for 5 hours. Results are summarised in Table 6.7.

Table 6.7. Iodine mediated Isomerisation of CLA to *t,t*-CLA.

Entry	Mass recovery	Conversion (%)	Yield *t,t*-CLA (%)	Others (%)
1	95%	70	70	-
2	97%	68	68	-

[a]All the reactions were performed in a r.b. flask, at r.t. for 5 hours, exposed to sunlight. Iodine and CLA were dissolved in hexane. [b] The yield of *t,t*-CLA was determined by GC-MS after esterification of the mixture.

Isomerisation of CLAME to t,t-CLAME – Sulfur

Sulfur is another catalyst known to isomerise double bonds; some references describe its applicability to the isomerisation of unsaturated fatty acids.[26-27] We carried out a few experiments to verify the suitability of sulfur for our purposes. A typical experiment was run using a mixture of CLA in ethyl acetate and sulfur in a 4% m/m amount over CLA. The reaction was carried out at 200 °C for 3 hours; the mixture was then concentrated, esterified and then analysed. Results are summarised in Table 6.8.

Table 6.8. Sulfur mediated Isomerisation of CLA to *t,t*-CLA.

Entry	Mass recovery	Conversion (%)	Yield *t,t*-CLA (%)	Others (%)
1	85%	77	53	24
2	86%	81	56	25

[a]All the reactions were performed in an SPR16 reactor using stainless steel autoclaves at the temperature of 200 °C for 3 hours, using 2.0 g of CLA dissolved in 4 ml of ethyl acetate and S in 4% m/m over CLA. [b] The yield of *t,t*-CLA was determined by GC-MS after esterification of the mixture.

Diels-Alder reaction of CLAME with DMFum in the presence of sulphur as isomerising agent

Once proven that elemental sulfur is able to isomerise CLA to the *trans,trans* geometry, it was checked if that step could have been combined directly with the Diels-Alder reaction. It is already known from the literature that this approach is successful when using organic solvents at high temperature,[18] but no data are available in water. Table 6.9 summarises two experiments in which sulfur was added to the same reaction mixture previously described (see paragraph 6.2.2.2).

Table 6.9. Reaction between CLAME and DMFum in the presence of sulfur.

Entry[a]	Medium	T (°C)	Time (hours)	Conv[d] (%)	6.1 Yield[d] (%)	Isolated Yield (%)
1	On-water	80	3	3	3	-
2	On-water	120		22	22	17

[a]The reactions were performed in a r.b. flask, loading 0.25 g of CLAME and using a molar ratio CLAME:DMFum = 1:1.1. S was added in 4% m/m over CLAME. 4 ml of water were used. [d]Conversion and yields of **6.1** were determined by GC-MS.

While at 80 °C (Entry 1, Table 6.10) the conversion was about the same observed without using sulfur (see entry 2, Table 6.6), at 120 °C we observed the same conversion previously achieved at 160 °C (see entry 4, Table 6.6). The latter result seems to indicate that sulfur can be directly used in on-water conditions. This test was not carried out with iodine because it reacts with water to form iodide and hypoiodite anions, which do not isomerise CLAME.

Diels-Alder reaction using t,t-CLAME

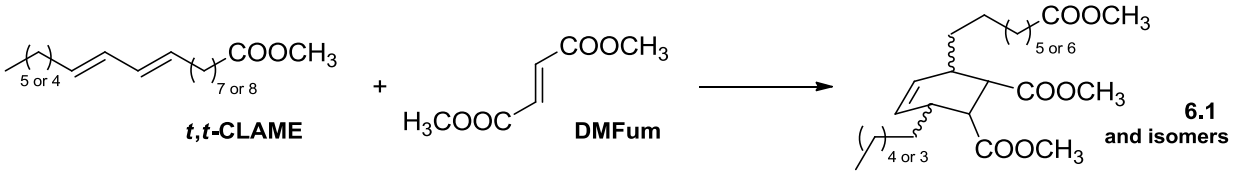
The *t,t*-CLAME obtained from the iodine mediated isomerisation was used to run several tests of the Diels-Alder reaction with dimethyl fumarate. The reaction was performed under three different conditions: with an organic solvent (ethyl acetate), on-water and neat; and at two different temperatures and two reaction times. The results are summarised in Table 6.10.

Table 6.10. Reaction between *t,t*-CLAME and dimethyl fumarate.

Entry[a]	Medium	T (°C)	Time (h)	Conv.[d] (%)	Yield[d] (%)	Isolated Yield (%)
1	EtOAc[b]	150	6	95	55	-
2	On-water[c]			100	60	-
3	EtOAc[b]	120		67	50	-
4	On-water[c]			100	59	-
5	EtOAc[b]		3	50	50	-
6	On-water[c]			95	70	60
7	Neat			97	80	72

[a]The reactions from entries 1 to 6 were performed in an SPR16 reactor using stainless steel autoclaves, charging 0.25 g of *t,t*-CLAME and with a molar ratio *t,t*-CLAME:DMFum = 1:1.1. The reaction of entry 7 was performed in a r.b. flask using the same amounts. [b]2 ml of ethyl acetate were used. [c]4 ml of water were used. [d]Conversion and yields of were determined by GC-MS.

The reaction was initially performed at 150 °C for 6 hours. The on-water reaction (entry 2) was apparently slightly faster than in ethyl acetate (100% against 95%). However, being the on-water reaction already complete we had no indications on when it had ended. The temperature was hence lowered to 120 °C and the reaction run for the same time. Again water gave complete conversion, while ethyl acetate gave a lower conversion in these conditions (67%). Reducing the reaction time to 3 hours the reaction on-water gave almost complete conversion (95%), and ethyl acetate reached only 50% conversion. Under such conditions the neat reaction gave almost complete conversion as well. The product **6.1** was isolated through flash column chromatography (see experimental section) from the reactions of entries 6 and 7 of Table 6.10, with a yield of 60 and 72% respectively.



Scheme 6.5. Diels-Alder cycloaddition between *t,t*-CLAME and DMFum.

Melting point tests of biodiesel added with the DA adduct

Compound 6.1 was purified as mentioned above and used as an additive in a biodiesel sample mixture prepared from tallow (all the details are included in the experimental section) at different concentrations. The sample mixture was analysed by DSC, recording the cooling and heating curves twice (cycles were registered starting from r.t., cooling down to -50 °C and heating up to 70 °C). Successively new samples were prepared at increasing concentration of our additive, and then analysed as already described. The recorded melting points are reported in Table 6.11.

Table 6.11. Melting points of a tallow biodiesel mixture with increasing percentage of additive.

% of added 6.1	m.p. (°C)[a]
0 (pure biodiesel)	17.4 – 17.5
5	15.1 – 15.2
10	13.4
15	12.4 – 12.5
20	12.2 – 12.3

[a]m.p. were recorded by DSC.

The same DSC analysis (2 cycles from r.t. to -50 °C, to 60 °C) was performed on the pure compound **6.1**. No phase change was observed in this temperature interval; therefore

the experiment was repeated down to a temperature of -100 °C. A small peak started to appear during the cooling cycle at -91 °C. However, being so close to the lower temperature limit, the analysis range was too narrow to allow complete solidification of the mixture. A fluctuation in the heat flow was observed at -62 °C during the heating cycle, but it was too small to justify a change of phase. It could be explained as the melting of a partially solidified mixture.

6.3. Discussion

The isomerisation of linoleic acid to conjugated linoleic acid (CLA) was carried out by means of sodium hydroxide. Ethylene glycol was initially used as a reaction solvent, and was then substituted by water. The latter solvent would have been preferable, in view of the possibility of coupling this step with the following one also in water. It is clear from the data summarised in Table 6.5 that the glycol is a more efficient solvent compared to water: after only 30 minutes at 160 °C the mixture already contained 80% of CLA (entry 1), while running the same reaction in water the amount of CLA was only 5% (entry 3). However, it was still possible to obtain complete conversion using water by increasing the temperature to 220 °C and running the reaction for 90 minutes (entry 9). The CLA was then converted to its methyl ester CLAME (Fischer esterification with methanol; see experimental section), to be used in a Diels-Alder (DA) reaction with dimethyl fumarate (DMFum).

Unfortunately we observed that the CLAME mixture (*cis*-9,*trans*-11-octadienoic and *trans*-10,*cis*-12-octadienoic acid) did not react efficiently in a Diels-Alder cycloaddition with DMFum, even though the latter is a very activated dienophile. The lack or reactivity was hypothesized to be due to the conformation of the CLAME, as explained pictorially in Figure 6.6 because the two diene isomers obtained from the previous step lead to an extremely hindered conformation in the molecular geometry needed for the DA reaction. By using CLAME the maximum conversions was 24%, under a variety of reaction conditions (Table 6.6). Thus, a double bond isomerisation step was added to the procedure, in order to obtain the *trans*,*trans*-CLAME geometry. Two isomerisation reagents were tested: sulphur and iodine. Table 6.12 summarises the main advantages and disadvantages of each.

Table 6.12. Comparison between sulfur and iodine in the isomerisation of CLA.

SULFUR	IODINE
Advantages	
Can be used on-water (one-pot isomerisation/cycloaddition)	Can be used at room temperature (sunlight exp.) Easily removable (washing with acq. thiosulfate)
Disadvantages	
Needs high temperatures (120-150 °C) Needs to be carefully removed { - Poisonous for many catalysts - Problematic for fuels	Cannot be used on-water (two steps: isomerisation + cycloaddition)

When *t,t*-CLAME was used to replace CLAME in the DA reaction with dimethyl fumarate, higher conversions were obtained, as clearly represented in Figure 6.7. It is also worth to be underlined that such conversions were obtained at lower temperatures than the one needed to obtain even a small conversion using CLAME.

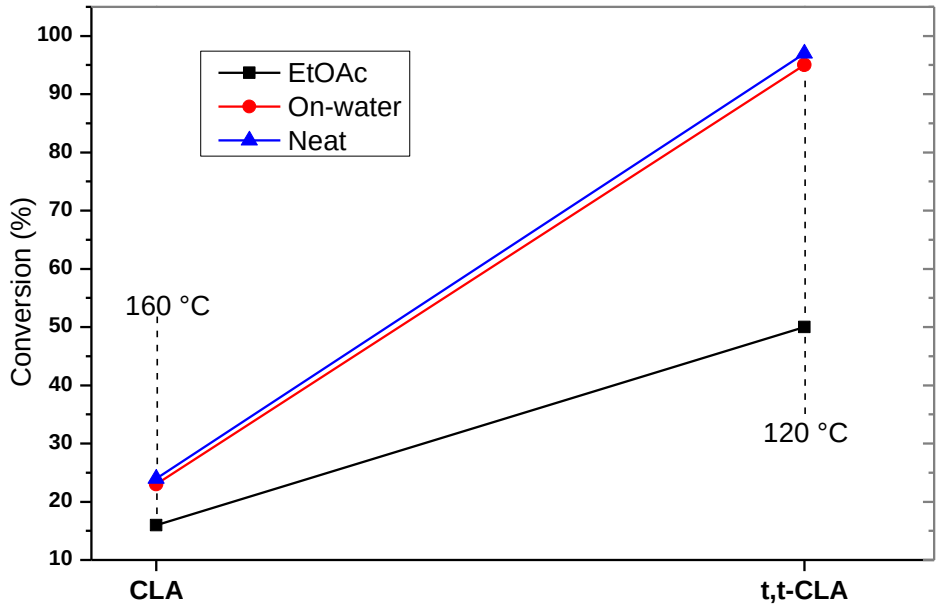


Figure 6.7. Comparison of CLAME and *t,t*-CLAME reactivity towards DMFum in different media.

It was already clear from DA reactions involving CLAME that they were favoured when run on-water rather than in an organic solvent (ethyl acetate; see Table 6.6). Also, by using *t,t*-CLAME the gap between on-water and organic solvent widened, even when carrying out the reactions at lower temperature (120 vs. 160 °C).

Unfortunately, the preliminary experiments did not highlight any significant difference between the on-water and the neat conditions. With *t,t*-CLAME the neat

reaction was again as fast as the on-water one (or even a bit faster). This was in disagreement with the theory of on-water catalysis, which we wanted to apply to our system. In our hypothesis, as already explained in the introductory part, on-water reactions should have been faster than neat ones. The mechanistic explanation given elsewhere (see chapter 1, paragraph 1.3.1.5)[26] for on-water catalysis involved proton exchange between water and dimethyl fumarate at the water/organic interphase (step 1, Figure 6.8). DMFum becomes positively charged, its charge being stabilized by resonance (step 2, Figure 6.8). In the next step, the activated dienophile is proposed to react readily with the diene, giving the corresponding cycloadduct (step 3, Figure 6.8). This proton can then be released to a hydroxyl (again step 3, Figure 6.8) or catalyse another reaction.

Figure 6.8. Initial hypothesis of the reaction between CLAME and DMFum in on-water conditions.

Since we did not observe any rate enhancement due to on-water conditions, we had to reconsider the possible mechanism and try to understand the reason for such a behaviour. Dimethyl fumarate was already efficiently employed in Diels-Alder reactions on-water, so the limiting factor was identified in the FAME. More specifically we hypothesized that the long linoleic chain could be responsible for the reduced/absent on-water effect. In our hypothesis this lack of on-water catalysis could be caused by two major diffusion limiting effects: 1) the long aliphatic chains present hamper diffusion of DMFum to the interphase between water and the oil droplet and consequently its protonation; 2) any DMFum molecules that could get protonated at the interphase could not diffuse back into the organic droplet to react readily with the diene portion of the FAME. We had no previous evidence on similar effects, and the literature did not help from this point of view. Therefore, a study aimed at understanding any effect on on-water catalysis due to the chain lengths on Diels-Alder reactions was carried out. This will be described in the next chapter.

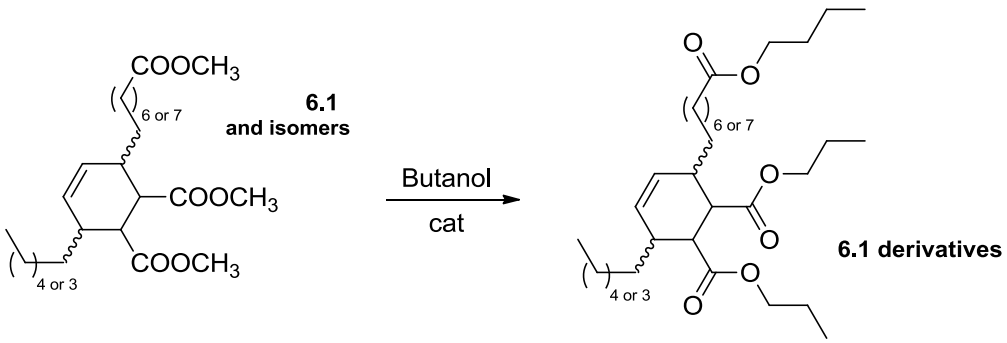
The above study on the functionalization of FAMES by DA reactions was completed by investigating the thermal properties of a biodiesel in mixture with different percentages of the new synthesised molecule **6.1**. The latter is a new compound, not reported in the literature, and was fully characterised. Despite its very low melting point (not observed at a temperature as low as -50 °C) its use as an additive did not significantly alter the melting point of a tallow biodiesel mixture (see Table 6.11), unless it was used in high amounts (commercially available additives for standard petrodiesel lower their melting point by 10 °C when used in about 0.5% v/v).

Even if the synthesised compound is not a powerful modifier of the cloud point, we have here demonstrated that water is a suitable medium to perform this kind of reactions. In our particular case the vigorously stirred water medium allowed to reduce issues connected to the use of dimethyl fumarate. Such compound starts to sublime at temperatures around 80 °C, especially in neat conditions, causing its crystallization in the cold parts of the glassware or of the autoclave and subtracting it from the reacting mixture (the reaction of Table 6.10, entry 7, was carried out by completely dipping a small r.b. flask in an oil bath so as to avoid as much as possible the presence of cold parts. Eventual crystal deposits on the stopper were scratched down in the reaction mixture during its course.). When using water the issue is overcome in virtue of the more efficient mixing. The same effect can be obtained by using an organic solvent, however we have demonstrated that water is much more efficient. On the other hand, molecules such as the one we synthesised can find application in other applications, such as plasticisers and lubricants. Examples of the latter were given in a recent paper.[ref] As future work, compound **6.1** could be tested in other properties (*e.g.* viscosity) to understand its applicability in fields other than just biofuels. Nonetheless it has to be considered that the presence of three carboxylic acid functionalities makes possible the synthesis of many different derivatives.

6.4. Conclusions

In this chapter the experimental work was described that allowed for the development of a derivatisation method for conjugated linoleic acid methyl ester (CLAME), via Diels-Alder cycloaddition, in an aqueous medium (on-water conditions). Water showed to be a more efficient reaction medium than an organic solvent (ethyl

acetate) both in terms of conversion and yield: complete conversion was achieved in three hours at 120 °C, whereas using ethyl acetate at the same temperature conversion was still only 67% after 6 hours. Despite of this interesting result, the reaction could not be classified as catalysed on-water: as a matter of fact the neat reaction reaches complete conversion in the same time of the on-water one. This fact was explained considering the fatty acid methyl ester moiety that was thought to prevent the interface mechanism proper of on-water catalysed reactions. However this observation inspired a dedicated research on this very effect, which will be discussed in the following chapter. The newly synthesised compound was tested as an additive in a biodiesel. The measurement of the melting points of mixtures with increasing percentage of additive showed slight improvements (a mixture with 20% of additive melted 5 °C lower than the pure biodiesel). At any rate, future work will need to assess the suitability of the synthesised molecules for other applications, or consider to further modify the new compound, in order to increase its efficacy in the cloud point reduction. For instance, the transesterification of the carboxylic acid functionalities with long alkyl chains (an example is given in Scheme 6.6) might probably lead to better performance.



Scheme 6.6. Possible transesterification of 6.1 with butanol.

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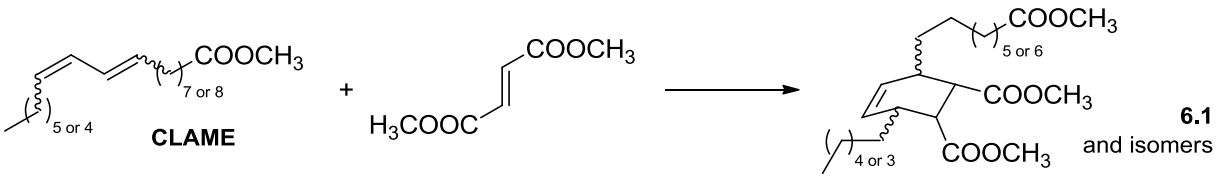
7 | ON-WATER CATALYSIS OF DIELS-ALDER REACTIONS: INFLUENCE OF THE STRUCTURE OF THE REAGENTS

7.1. Introduction

7.1.1. Previous results and initial hypotheses

The previous chapter described the study of the cycloaddition reaction between *t,t*-conjugated linoleic acid methyl ester (*t,t*-CLAME) and dimethyl fumarate (Scheme 7.1). The reaction could be carried out on-water with near quantitative conversion, with a positive rate enhancement compared to that obtained in an organic solvent (ethyl acetate). However, it was not possible to obtain a proper on-water catalysed Diels-Alder reaction, *i.e.* the reaction carried out in on-water conditions (vigorously stirred suspension in water medium) was as fast as the neat one.



Scheme 7.1. Diels-Alder reaction between CLAME and dimethyl fumarate.

Those results were interpreted in terms of the excessive length of the fatty ester moiety disrupting the on-water effect. However, to the best of the author's knowledge, there are no data in the literature that consider an on-water cycloaddition involving such large molecules, thus it is necessary to consider why a long carbonaceous chain would break down or limit the rate enhancement due to the on-water environment. Two possible hypotheses were set forth:

1. the long fatty chains are "masking" dimethyl fumarate in the bulk of the lipophilic droplet, preventing, or limiting, its protonation at the droplet/water interphase (Figure 7.1, left);
2. dimethyl fumarate can still be activated by protonation at the interphase. However the migration of the activated species within the oil droplet cannot occur readily. This decreased mobility of the active species hinders reaction with the dienic part of the CLAME (lower interaction probability; Figure 7.1, right).

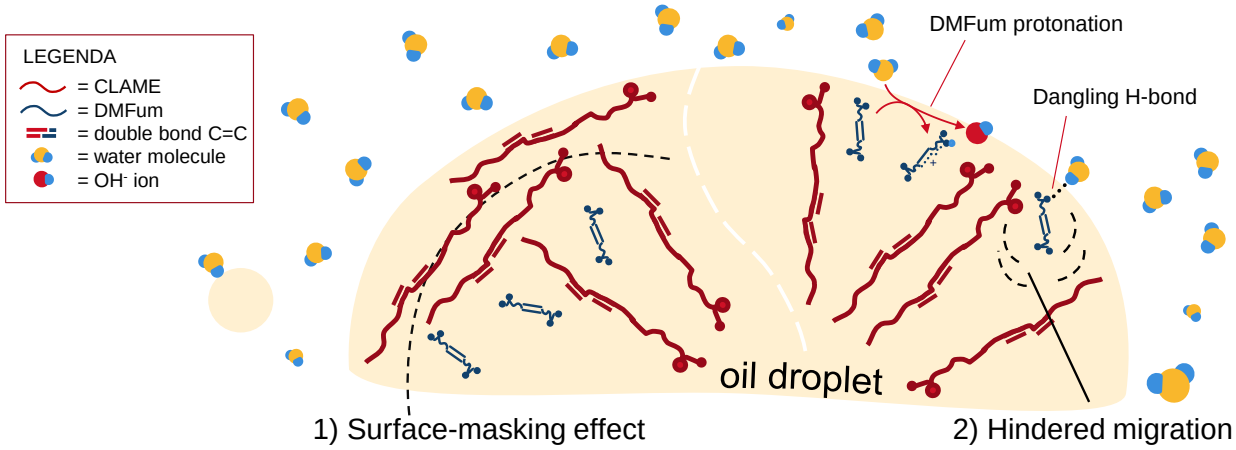


Figure 7.1. Possible effects of CLAME chains on DMFum behaviour within the oil droplet.

Both the hypotheses are plausible; and the observed effect could also be due to a combination of the two.

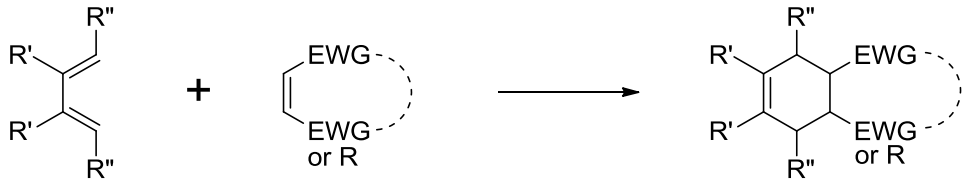
7.1.2. Testing the hypotheses – design of the experiments

Based on the hypothesis that the fatty acid chain length determines reactivity, to better understand the consequences of one of the Diels-Alder reactants, involved in an on-water catalysed reaction, bearing a medium/long chain, a new set of experiments was designed. The general aim was to find an unambiguously on-water catalysed DA reaction, with an easy to study kinetic profile. To comply with these requirements a set of requirements was needed:

- To probe the hypothesis that the shorter aliphatic chain will enhance the reaction (i.e. be on-water catalysed), compounds bearing different aliphatic moieties, were needed.
- The DA reaction should occur in a reasonably short time, but not be too fast (in this latter case any rate-differentiations would be difficult);

- The reagents must not be soluble in water.

These requirements implied a few practical aspects. First of all, in order to obtain a fast kinetic profile the reaction had to be favoured. This could be achieved by using an activated dienophile, i.e. one bearing at least one electron withdrawing group.



Scheme 7.2. Diels-Alder reaction between a generic diene and a generic activated dienophile.

Another aspect which could favour the Diels-Alder reaction was the use of a cyclic dienofile (e.g. maleic anhydride, as seen in the previous chapter). A third important thing that had to be considered was the ease of changing the chain length of one of the two reactants. Also the use of exotic reagents was undesirable because:

1. the new data had to be directly comparable with those obtained using conjugated linoleic acid (see chapter 6);
2. a general rule that could be applied to analogous bio-derived compounds was sought.

7.1.3. Choice of the reactants and aim

Two main reagent choice strategies were followed. In the first the diene structure was modified, in the second the effect of the dienophile chain length was investigated. The dienes were selected from amongst the simplest ones, which chain lengths can be easily modified. Examples of these are sorbyl esters, from sorbyl acetate (SA) onwards (Figure 7.2, top left). Such compounds can be obtained from sorbic acid (another promising bio-based chemical) as explained in the results. The DA reaction of these diene substrates was tested with two maleimides (a liquid and a solid one, N-butylmaleimide (NBM) and N-phenylmaleimide (NPM) respectively), which are strongly activated dienophiles (see Figure 7.2, top right).

For the second set of experiments cyclopentadiene was chosen as a diene, in view of its symmetry and absence of substituents, factors that both avoid complexity of the reaction outcomes. Two classes of compounds were tested as dienophile. Acrylates appeared to be a good option as they are activated by the vicinal carbonyl, the

unsaturation is not hindered and their alkyl chain can be easily modified (also, many different acrylates are in fact commercially available). The second group was f vinyl ketones. As in the previous case they are activated and not hindered, and their synthesis is viable starting from the corresponding aldehydes or alkyl halides.

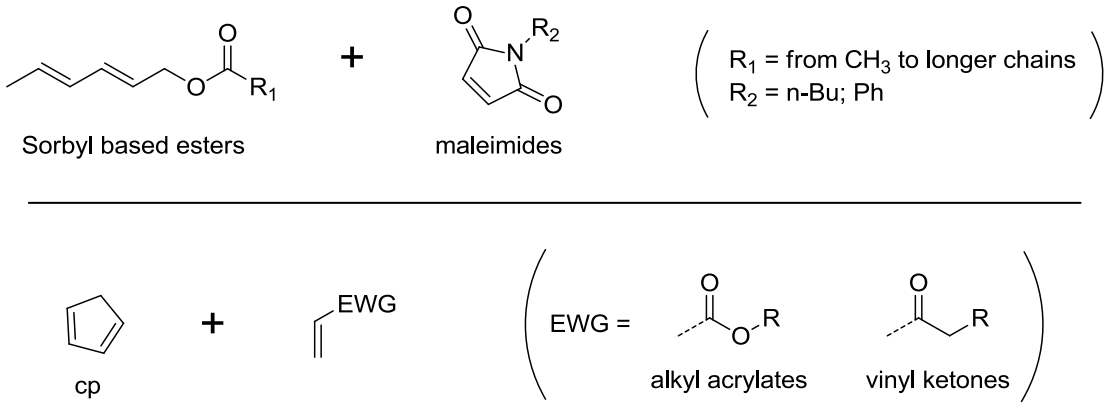


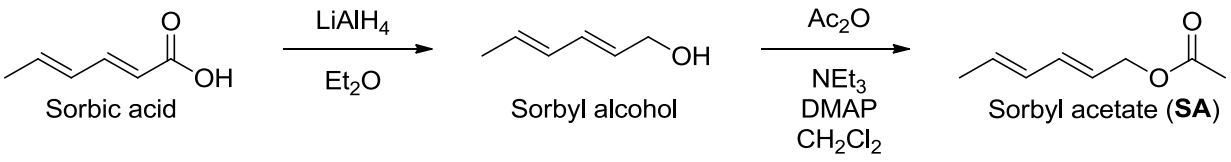
Figure 7.2. Reactant choices for the investigation of the new hypothesis.

The final aim was to correlate the on-water catalytic effect with chain length. Such an effect seems not to have been previously reported. If it indeed operated, this would explain the previous observations on CLAME (see previous chapter), and, moreover, have a significant impact on the whole research on on-water catalysis.

7.2. Results

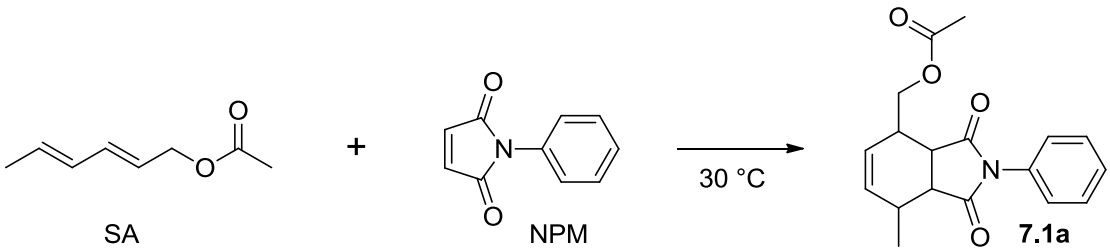
7.2.1. Less lipophilic dienes: sorbyl based esters

The reaction between sorbyl acetate (SA) and *N*-phenylmaleimide was chosen as the model for the on-water studies. Generally *N*-alkylmaleimides are very activated towards Diels-Alder reactions with an electron rich diene, however *N*-phenyl maleimide, a solid, is expected to react more slowly in the present reaction conditions (see below). Sorbyl acetate (SA) was prepared by reduction of sorbic acid to sorbyl alcohol, followed by transesterification with acetic anhydride (Scheme 7.3).



Scheme 7.3. Preparation of sorbyl acetate (SA) from sorbic acid.

The reaction between SA and *N*-phenylmaleimide (NPM) was performed at 30 °C. Four different conditions were applied: on-water (mixture of reagents and water vigorously stirred); on-D_2O; at-water (mixture of reagents and water gently stirred); neat (mixture of the reagents with no added solvent and vigorously stirred).



Scheme 7.4. DA reaction between sorbyl acetate and N-phenylmaleimide.

The results are summarised in Figure 7.3. Every point in the graph corresponds to a single reaction. In a typical example SA (56 mg, 0.40 mmol) was loaded together with NPM (69 mg, 0.40 mmol) in a screw-top vial; when it was used, water was then added as a single aliquot (4.0 ml). After the indicated time, the mixtures were analysed via ^{1}H-NMR; if water was used the mixtures were extracted with deuterated chloroform and directly analysed.

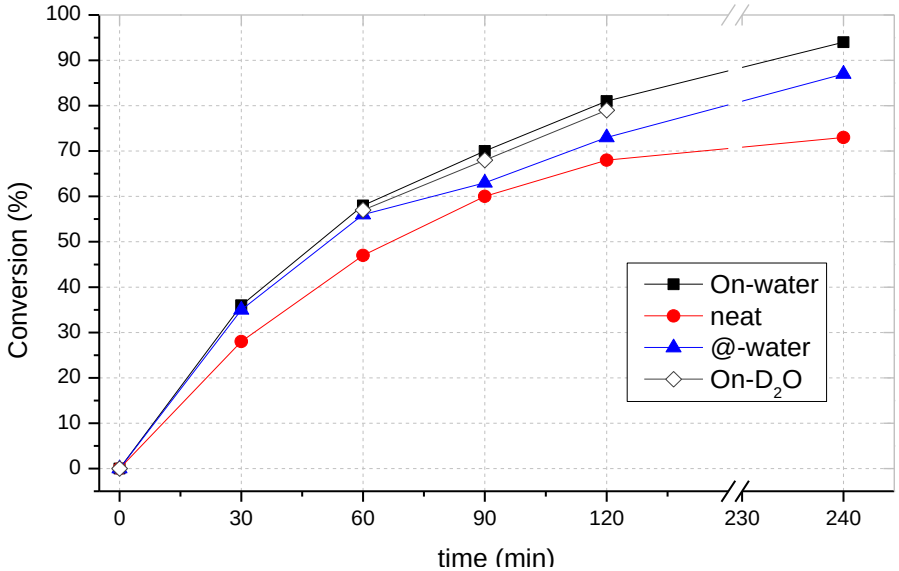
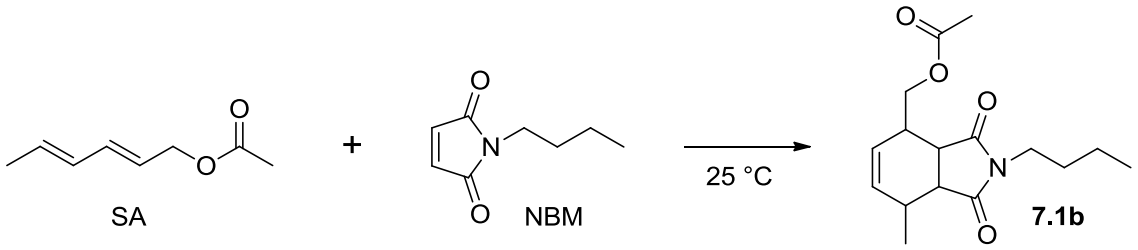


Figure 7.3. Conversion profiles for the reaction between sorbyl acetate (SA) and *N*-phenylmaleimide (NPM) (selectivity was completely towards the desired product).

The rate of the on-water reactions (black line, squares) appeared to be faster than both at-water and neat. In particular the neat reaction (red line, circles) slowed down significantly after 50% conversion. The rate of the at-water reaction (blue line, triangles) initially seemed very close to the on-water one, but was slower as the reaction proceeded.

The reaction carried out on-D_2O (black line, empty rhombus) gave almost identical results to the on-water one.

Next a similar reaction involving liquid reagents was investigated. NPM was substituted by *N*-butylmaleimide (NBM). Preliminary results at 30 °C indicated that this reaction was faster than the previous one; therefore it was carried out at 25 °C. The results are summarised in Figure 7.4.



Scheme 7.5. DA reaction between sorbyl acetate and N-butylmaleimide.

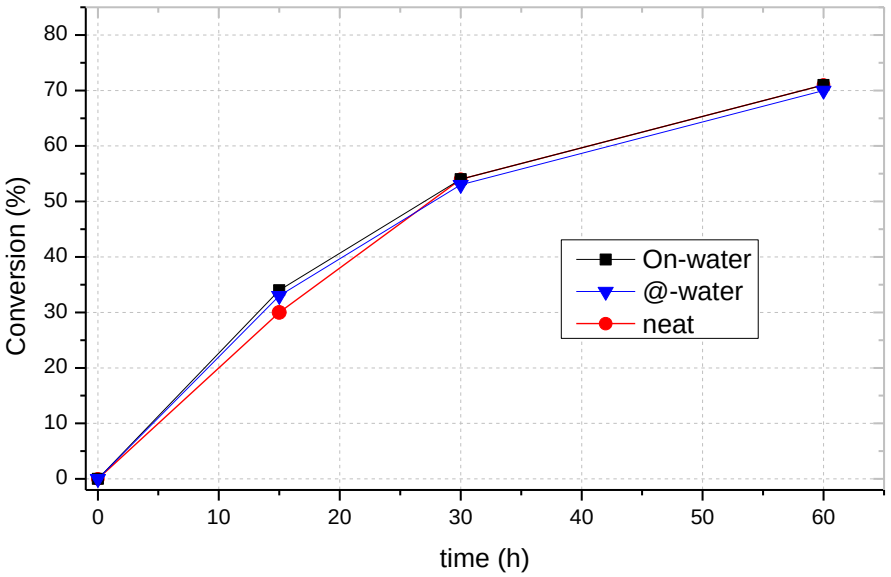


Figure 7.4. Conversion profiles for the reaction between sorbyl acetate (SA) and *N*-butylmaleimide (NBM) (selectivity was completely towards the desired product).

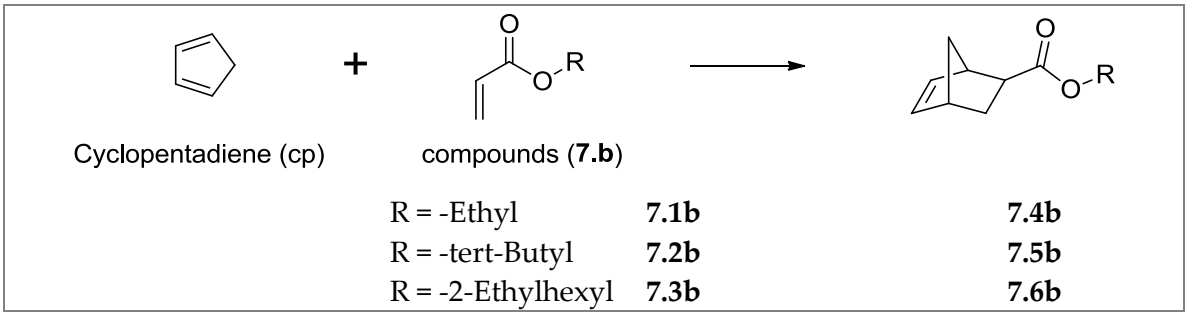
The reaction rates were substantially identical in all the different conditions. This suggested the absence of an on-water catalytic effect, notwithstanding that the reaction between SA and *N*-alkylmaleimides (particularly *N*-propylmaleimide) is often described in the literature as a typical example of an on-water Diels-Alder reaction.[1] The experiments here reported were carried out following a standard methodology, thus the discrepancy is probably not ascribable to experimental conditions. Considering that longer-chain

analogues of sorbyl acetate were predicted to further inhibit the on-water catalytic effect, the experiments on sorbyl-esters were abandoned.

7.2.2. Effect of the dienophile structure

7.2.2.1. Acrylates

As mentioned above, a set of acrylates with different aliphatic substituents was selected as dienophiles to investigate the effect of the chain length on the Diels-Alder reaction with an electron rich diene. Their commercial availability provided easy access to a number of compounds from which to choose. Thus a set of model experiments was designed in which compounds with progressively longer alkyl chains were reacted with cyclopentadiene (see Scheme 7.6).



Scheme 7.6. Reaction between cyclopentadiene and various alkyl acrylates.

A typical reaction was set up similarly to sorbyl acetate ones. Freshly cracked cyclopentadiene (40 mg, 0.6 mmol) and the chosen acrylate were charged in a screw-top vial; when it was used, water was then added as a single aliquot (4.0 ml). After the indicated time, the mixtures were analysed via ^{1}H-NMR; if water was used the mixtures were extracted with deuterated chloroform and directly analysed.

Ethyl acrylate is slightly soluble in water (1.5 g/100 ml). In order to overcome the solubility problem we decided to use the acrylate in a molar ratio of 2:1 over the cp. Such a quantity (1.2 mmol = 120 mg) should have provided at least 1 equivalent of insoluble reactant, in respect to the cp (maximum dissolved quantity under these conditions, 4 ml of H_2O, was 60 mg). *Tert*-butyl acrylate (**7.2b**) is much less soluble in water: 2.0 g/l that means 8 mg in 4 ml. Again the reactant was used in the excess necessary to allow 1 equivalent to not be dissolved. Like in the previous experiments, the reaction was performed on-water, at-water and in neat conditions. Results obtained for the two acrylates are summarised in Figure 7.5, a) and b) respectively.

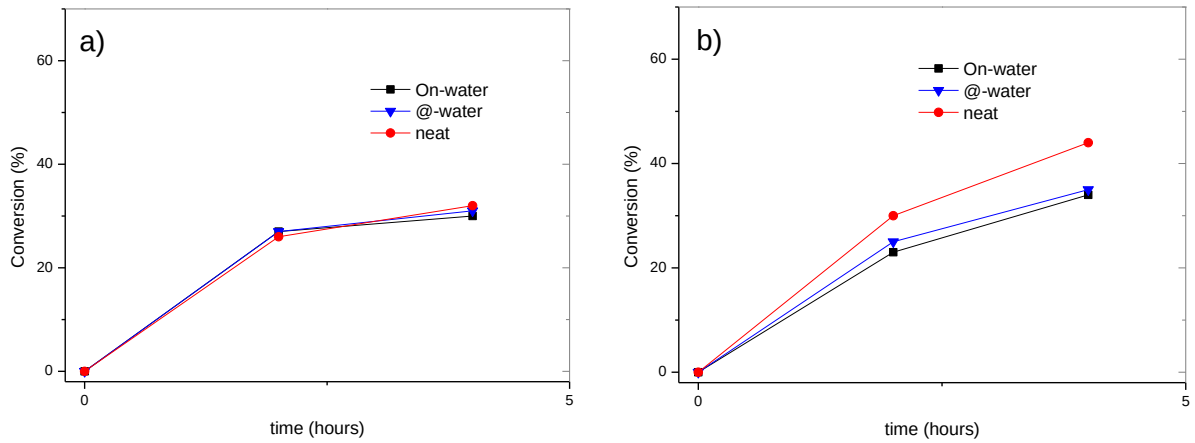
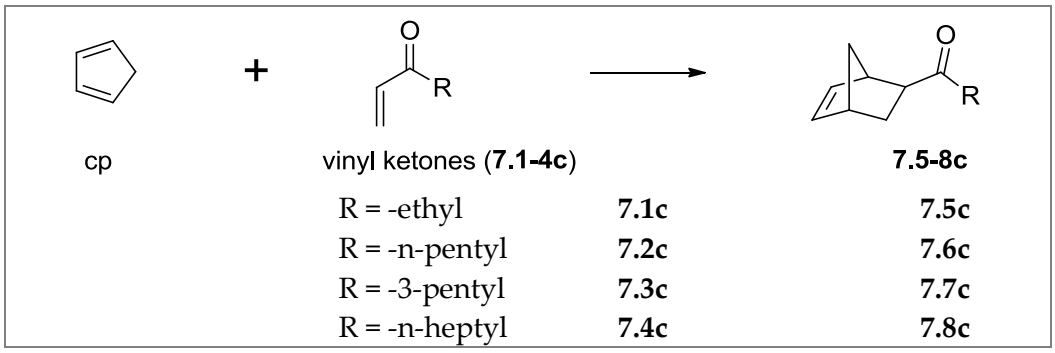


Figure 7.5. a) Conversion rates for the reaction between cp and 7.1b; b) Conversion rates for the reaction between cp and 7.2b (selectivity was complete towards the desired products).

Both the acrylates exhibited similar reaction rates for all the tested conditions. In the case of **7.1b** (Figure 7.5 a) the obtained conversions are almost the same, while in the case of **7.2b** (Figure 7.5 b) the neat reaction was a bit faster than the on-water one. This latter example could be accounted as an inverse on-water effect, *i.e.* the solubility of the reagent in water is slowing down the reaction. In the same conditions the reaction of **7.3b** (used in a 1:1 ratio over the cp), exhibited a similar behaviour: after 2 hours the product was 20% on-water, 19% for the at-water reaction and 21% for the neat one. On the basis of these results, and considering that the acrylates exhibit substantial solubility in water, we decided to test alkyl vinyl ketones with different R aliphatic chains.

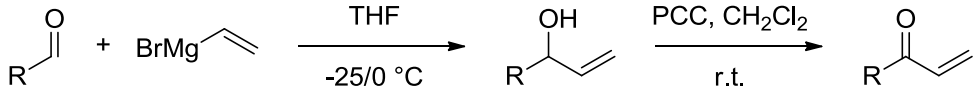
7.2.2.2. Vinyl ketones

Vinyl ketones are a class of potential dienophiles, synthesisable with different chain lengths. They are more active towards Diels-Alder cycloaddition than the corresponding acrylates. In fact, their vinylic protons are more deshielded in a ^{1}H-NMR experiment, in particular the proton in trans to the carbonyl (*e.g.* the proton in trans to the carbonyl of ethyl vinyl ketone has a chemical shift of 6.23 ppm, while the same proton of ethyl acrylate has a chemical shift of 6.11). Based on the results obtained with acrylates the lightest homologue, methyl vinyl ketone, was avoided because of its solubility in water. Fortunately the solubility of vinyl ketones in water is substantially less for longer alkyl chains. Thus, commercially available ethyl vinyl ketone was chosen as starting point. Three other vinyl ketones were synthesised as described in Scheme 7.8. Scheme 7.7 summarised all the vinyl ketones tested in their reaction with cp.



Scheme 7.7. Reaction between cp and various alkyl vinyl ketones.

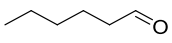
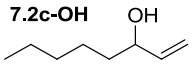
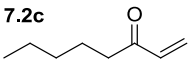
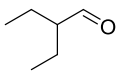
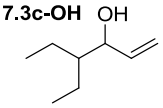
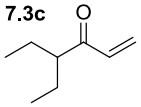
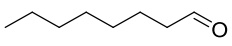
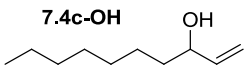
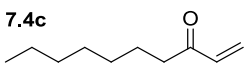
. In the first step the desired aldehyde was reacted with vinyl magnesium bromide. The resulting alcohol was then oxidised with pyridinium chlorochromate (PCC) to the corresponding vinyl ketone.



Scheme 7.8. Preparation of the vinyl ketones.

Table 7.1 summarises the synthesized vinyl ketones, together with their starting aldehydes and alcohol precursors, underlining the increase in carbon atoms of their alkyl chain.

Table 7.1. Starting aldehydes and their products (vinyl alcohols and ketones) with the relative yields.

Aldehyde	Vinyl alcohol		Vinyl ketone		ΔC[a] (vs 7.1c)
		95%		53%	+3
		90%		43%	+1+2(side chain) = +3
		98%		60%	+5

[a]ΔC = the difference in the number of carbons between the vinyl ketone at which ΔC is referred and ethyl vinyl ketone **7.1c**.

Compound **7.2c** has three carbons more than **7.1c**, as does **7.3c**, that is however a branched ketone; while ketone **7.4c** has a much longer alkyl chain than **7.1c** (five carbons more).

The reaction between cp and ethyl vinyl ketone was initially carried out as described previously: on-water, at-water and in neat conditions, followed by other tests as shown in Figure 7.6 and described below.

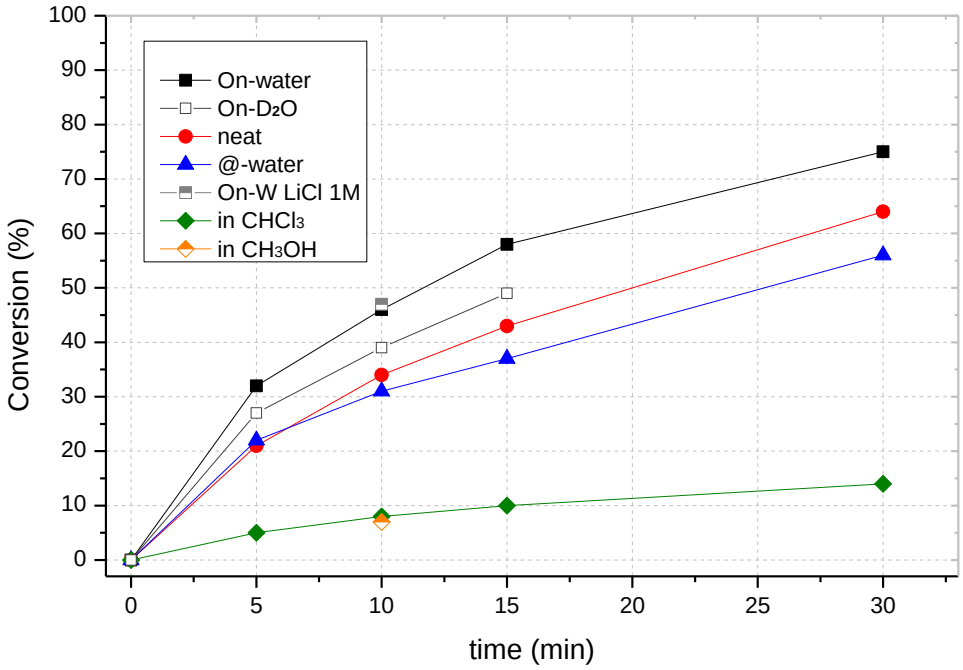
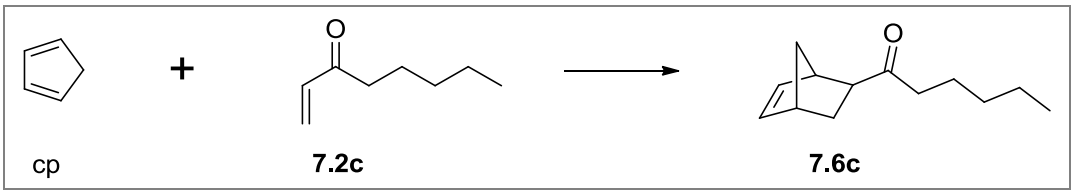


Figure 7.6. Conversion rates for the reaction between cp and 7.1c.

The reaction on-water (black line, squares) was much faster than the neat one (red line, circles): after 5 minutes it gave 50% higher conversion. The conversion gap continued to widen until 15 minutes, and then appeared to stabilise. The rate of the at-water reaction (blue line, triangles) was initially very close to that of the neat one, but decreased as the reaction progressed. The reaction on-D_2O (black line, empty squares) yielded lower conversions than on-water. To have a complete picture of the possible reaction media, the reaction was conducted in chloroform (an aprotic solvent, green line, rhombus) and in methanol (a protic solvent, orange half-filled rhombus). In both the cases the reaction was very slow: less than 8% conversion after 15 minutes, to be compared with 43 and 59% conversions, obtained for the neat and the on-water reactions, respectively. Finally the common test for the hydrophobic effect was conducted, (also called "salting out") by collecting a single data point using 1M LiCl aqueous solution in place of water, . The interest on this reaction will be discussed later, with particular attention on the methodology employed to understand which mechanism is actually responsible for an enhanced rate in on-water conditions.

For all the other vinyl ketones two data points were collected, at 5 and 15 minutes. At these two times the reaction was carried out on-water, on-D_2O and neat. A reaction at-water was carried out only at the longer reaction time. The reaction between cyclopentadiene and pentyl vinyl ketone **7.2c** (Scheme 7.9) is summarized in Figure 7.7 and Table 7.2.



Scheme 7.9. Reaction between cp and pentyl vinyl ketone 7.2c.

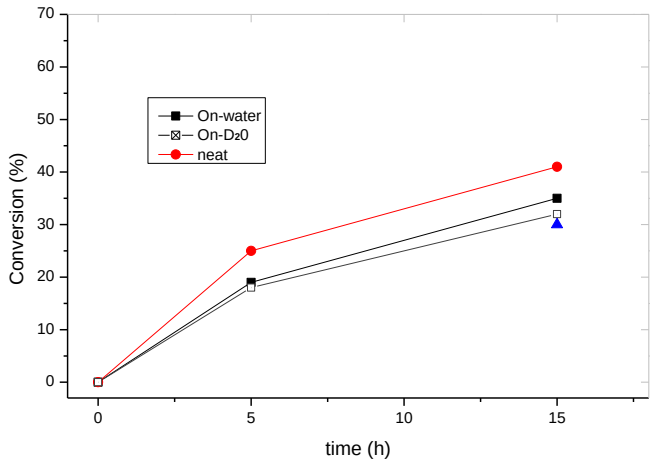


Figure 7.7. Conversion rates for the reaction between cp and 7.2c

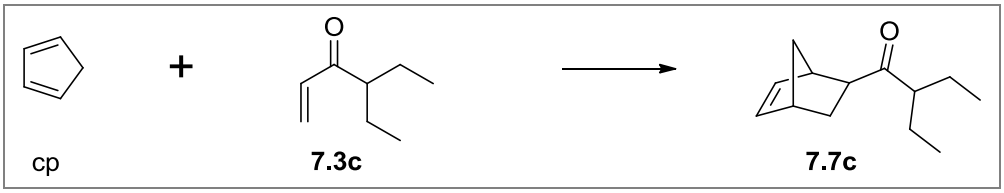
Table 7.2. Reactions of cp with 7.2c.

Entry.[a]	time	Kind	Conv.[b] (%)
1	5′	On-Water	19
		neat	25
		D_2O	18
2	15′	On-Water	35
		at-Water	30
		neat	41
		D_2O	32

[a]All the reactions were performed at 25 °C. [b] Conversions were determined via ^{1}H-NMR analysis (selectivity was complete towards the desired product).

No acceleration was observed under the on-water conditions. The reaction on-water was even slightly slower than the neat one. On the other hand the reaction on-D_2O was slightly slower than that on-water.

The results of the reaction between cp and 2-ethyl-1-hexen-3-one **7.3c** (Scheme 7.10) are summarised in Figure 7.8 and Table 7.3.



Scheme 7.10. Reaction between cyclopentadiene and 2-ethyl-1-hexen-3-one 7.3c.

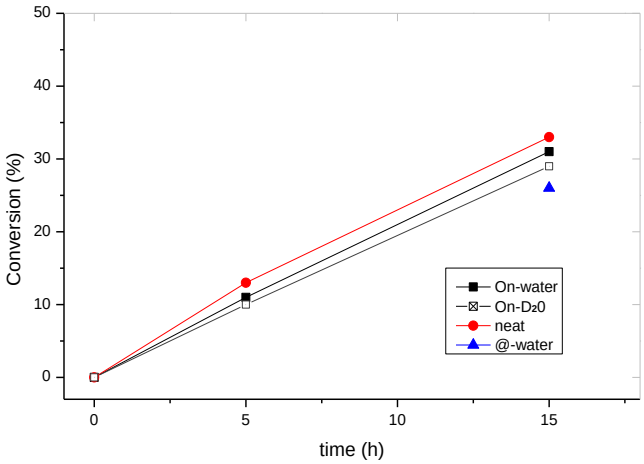


Figure 7.8. Conversion rates for the reaction between cyclopentadiene and 7.3c

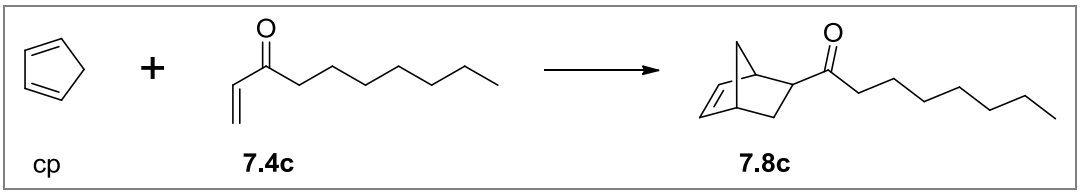
Table 7.3. Reactions of 2 with 7.3c.

Entry[a]	time	Kind	Conv.[b] (%)
1	5′	On-W	11
		neat	13
		D_2O	10
2	15′	On-W	31
		at-W	26
		neat	33
		D_2O	29

[a]All the reactions were performed at 25 °C. [b]Conversions were determined via ^{1}H-NMR analysis (selectivity was complete towards the desired product).

The reaction between cp and **7.3c** gave similar results to that between cp and **7.2c**: no on-water acceleration was observed (Figure 7.8 and Table 7.3), and the at-water reaction appeared to be slower than the on-water one.

Finally, the reaction between cp and 1-decen-3-one **7.4c** was conducted (Scheme 7.11); results are summarized in Figure 7.9 and Table 7.4.



Scheme 7.11. Reaction between cp and 1-decen-3-one 7.4c.

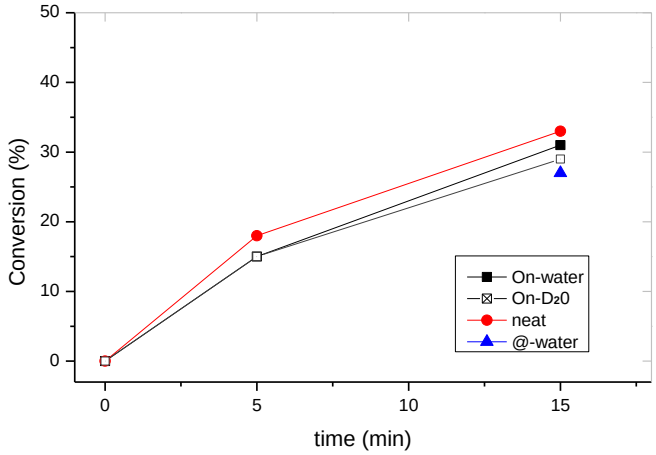


Figure 7.9. Conversion rates for the reaction between cp and 7.4c.

Table 7.4. Reactions of cp with 7.4c.

Entry[a]	time	Kind	Conv.[b] (%)
1	5′	On-W	15
		neat	18
		D_2O	15
2	15′	On-W	31
		at-W	27
		neat	33
		D_2O	29

[a]All the reactions were performed at 25 °C. [b]Conversions were determined via ^{1}H-NMR analysis (selectivity was complete towards the desired product).

The data are completed by the reaction between cp and **7.4c**, which bears a much longer chain than **7.1c** (Figure 7.9 and Table 7.4). Again no on-water acceleration was

observed. Data were distributed similarly to the previous reactions, with the neat reaction slightly faster than the on-water one, to which the rate of the reaction on-D_2O is very close. Finally the reaction at-water is slightly slower than the on-water one.

7.3. Discussion

The aim of these experiments was to understand whether the lipophilicity (determined in the present case by the length of the alkyl chain) of compounds involved in a Diels-Alder cycloaddition, had any effect on the reaction rate when the reaction is conducted under on-water conditions. In the initial hypothesis of this work long alkyl chains were responsible for disrupting the molecular interactions that take place at the interface between water and oil droplets, and are responsible for the rate enhancement (catalysis) observed for some on-water reactions. It seems that the molecular size and lipophilicity have not previously been considered as important factors governing on-water catalysis. The present study aimed to fill this gap and contribute to a better understanding of the on-water effect.

To pursue this objective two kinds of reactions were investigated. In the first one, the Diels-Alder cycloaddition between sorbyl-based esters and maleimides, in which the lipophilicity could have been tuned on the diene was studied. In the second instance, the Diels-Alder reaction of cp with acrylates and vinyl ketones, the lipophilicity was tuned by changing the structure of the dienophile.

7.3.1. Sorbyl acetate

The reaction between sorbyl acetate (SA) and *N*-phenylmaleimide (NPM) proceeds with higher conversions, in a given time, when run on-water compared to both at-water (gentle stirring) and neat. The latter particularly was around 20% slower than the reaction on-water in the early reaction times. Also the neat reaction slowed further after reaching 60% conversion, whereas the on-water tended to reach completion. Thus, as in the conjugated methyl linoleate case (see chapter 6), water showed again to be a suitable medium in which to perform Diels-Alder reactions. On the other hand, further experiments carried out using D_2O did not show any isotope effect compared to the normal water profile. This fact was inconsistent with on-water catalysis in the present case, as Beattie has shown that on-D_2O reactions are slower than on-water (considering

their theory of the interfacial-proton-exchange and the kinetic isotope effect).[2] Some considerations that can account for the appearent on-water catalysis in this case (in fact, considering the graph in Figure 7.3, the reaction on-water is faster than both the at-water and the neat ones) are the following (see figures below for some exemplification of these statements):

- One reactant is a solid (NPM), and the product is a solid too. The maximum conversion achievable for the neat reaction is limited by the fact that the mixture becomes more viscous, approaching a paste, with the proceeding of the reaction. This explains why the conversion of the neat reaction cannot be compared with the on-water one as the conversion in the former plateaus at 60%.
- The at-water reactions suffer from a number of operational drawbacks that affect reproducibility The reagents tend to stick at the bottom of the vials and to the stir bar. This may be the reason why at-water reactions are initially almost as fast as on-water ones. The initial rate enhancements of the latter may be masked by mechanical reasons.
- The vigorous stirring required by on-water conditions keeps the reagents well dispersed; this may account for the similar rates observed for on-water and on-D_2O reactions, apparently excluding catalysis.

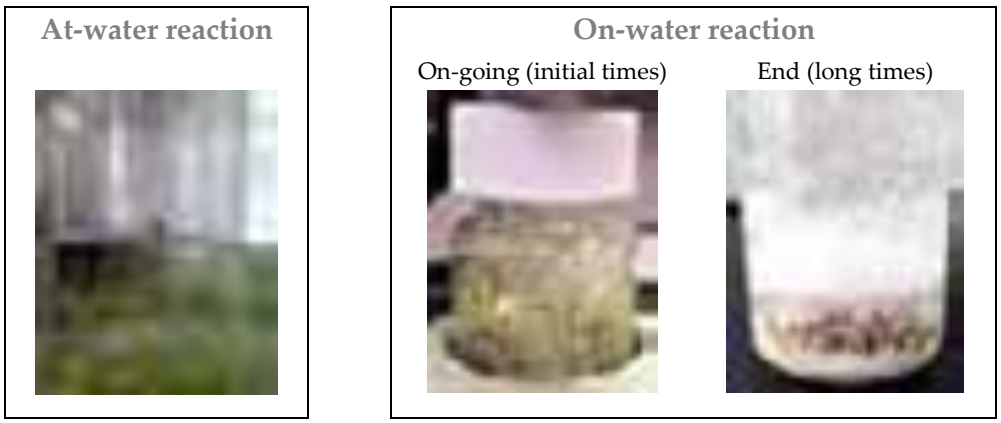


Figure 7.10. Images of at-water (left) and on water (initial times, centre; long times, right) reactions.

It should be highlighted that neat and at-water reactions were carried out under ideal conditions ensuring intimate contact between neat reagents; and gently mixing the reactants in the at-water reactions. Instead, on-water experiments did suffer from the operational problems listed above. Therefore, it may be premature to completely exclude on-water catalysis for this reaction. To overcome the mechanical mixing issues, due in part

to the solid nature of NPM, *N*-butylmaleimide (NBM) which is a liquid was tested as dienophile. In this case the reaction rates on-water, at-water and neat conditions are identical, demonstrating that on-water catalysis is not occurring.

These data not only indicated that the reaction between SA and N-butylmaleimide is not on-water catalysed, but also that it is not accelerated in water emulsion. Surprisingly, the typical example cited for on-water accelerated Diels-Alder cycloadditions is the very similar reaction between sorbyl acetate and N-propylmaleimide (NPrM) originally reported by Sharpless *et al* in their landmark paper, on "on-water" reactions.[1] The original paper does not give many experimental details. It reports that the Sharpless reaction is clearly slower in organic solvents, but it is not clear whether there was a difference in the rates for the neat and the on-water reactions. It is recognised that on-water reactions require vigorous stirring, as opposed to neat reactions that are carried out under gentle, or even the absence of, stirring. Slower agitation can induce a slower reaction, particularly at high conversions when the product concentration gets higher and the mixture viscosity increases. By using water this mixing problem is overcome, as is reported herein in the reaction between sorbyl acetate and N-phenylmaleimide. These considerations seem to indicate that the reaction between sorbyl acetate and N-propylmaleimide reported by Sharpless *et al* might not be on-water catalysed, but simply favoured by mechanical reasons.[1]

7.3.2. Dienophile chain length

7.3.2.1. Acrylates

Three acrylates, with increasing chain length and different levels of branching, were reacted with cp (see Figure 7.11).

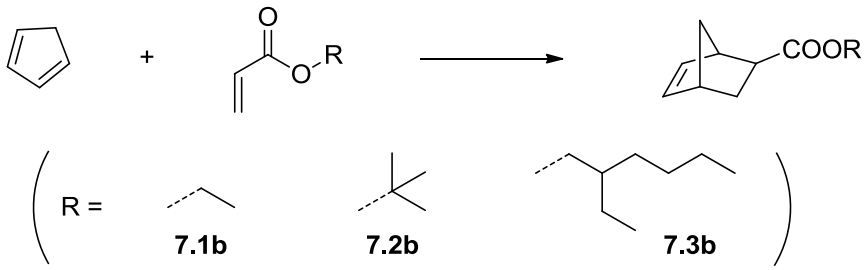


Figure 7.11. Reaction between cyclopentadiene and various alkyl acrylates

The cycloaddition product was selectively obtained for all the substrates, however no rate enhancement was observed for the less lipophilic substrates **7.1b** and **7.2b** compared to the more lipophilic **7.3b**, when using on-water conditions. In the first two cases the non-observance of a rate enhancement was ascribed to the partial solubility of the acrylate **7.1b** in water. Significantly, despite the use of a large excess of acrylates **7.1b** and **7.2b** in an attempt to overcome dissolution, solubility is a dynamic process, *i.e.* there is an equilibrium between the dissolved and non-dissolved fraction. It is therefore likely that such an equilibrium disrupts the catalytic effect at the interphase between water and the organic droplet. This disruption is a realistic hypothesis, considering that the exchange of reactant molecules between the water phase and the droplet is likely to minimise the adsorption there of hydroxide anions, the latter considered to be the driving force of the protonation mechanism. Even though the solubility of **7.2b** is much lower than **7.1b**, nonetheless no catalysis was observed. For **7.3b** the solubility issue is absent therefore, based on the initial hypothesis, no on-water catalysis was expected due to presence of the long alkyl chain. The latter probably exhibit those hindering effects described in the introduction.

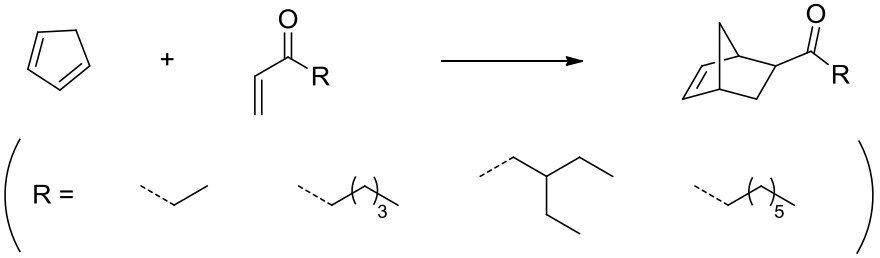
7.3.2.2. Vinyl ketones

The reaction between ethyl vinyl ketone and cyclopentadiene (cp) was studied in a wide range of reaction media. Figure 7.6 summarises all the reaction profiles, and makes evident that the reaction on-water is faster than all the others. The neat reaction gave about 10% less conversion early on, while the reaction at-water was even slower. In the presence of a solvent the conversion was very low even for the longer reaction times. These and the following observations demonstrate on-water catalysis.

- Mechanical issues. The reagents and the product are all liquid, poorly viscous, compounds. Therefore, reaction inhibition due to poor mixing is not an issue .
- The reaction on-D_2O is slower than on-water. This suggests the existence of an isotope effect, already observed from Sharpless and Beattie.[1-2] This is consistent with the mechanism of on-water reactions that involves proton abstraction from water, proposed by Beattie.[2]
- The reaction on-$LiCl_{(aq)}$ 1M is as fast as on-deionized water. This excludes the possibility of hydrophobic acceleration.

The reaction between ethyl vinyl ketone and cyclopentadiene is one of the very few reported Diels-Alder cycloadditions, where on-water catalysis is demonstrated, and represents an important goal achieved during this study.

Having found a truly on-water catalysed reaction, it was then possible to pursue the second part of the project: to probe how the structure of the dienophile (length of the alkyl chain) affected on-water catalysis. For this reason three new vinyl ketones were synthesised, and reacted with cyclopentadiene. In order to establish the existence of on-water catalysis, each dienophile was reacted under on-water, at-water, and neat conditions and the outcomes compared.



Scheme 7.12. Reaction between cyclopentadiene and vinyl ketones.

The results demonstrate that the reaction of all the heavier vinyl ketones with cyclopentadiene was not on-water catalysed. The graphs of Figure 7.7, Figure 7.8 and Figure 7.9 show very consistently that the neat reaction was always slightly faster than on-water, and that the reaction on-water was a bit faster than that at-water. Reactions carried out on-D_2O showed almost equal rates compared to on-water; generally less than 1% conversion difference was observed.

The results obtained with the vinyl ketones open a new scenario on Diels-Alder reactions accelerated in water emulsions. In such conditions ethyl vinyl ketone reacts readily with cyclopentadiene, and much faster than in any other conditions, indicating on-water catalysis. By increasing the alkyl chain length by only three carbons, the same acceleration on-water compared to at-water and neat is not observed. It is unreasonable to assume that this change in the reaction rate could be due to a different mechanism taking place due to the structure of the new substrates. In fact the rates of the neat reactions do not suffer from relevant rate reductions on changing the dienophile, while the on-water reaction of the heavier dienophiles loses a 27% conversion at 15 minutes passing from **7.1c** to **7.2c** (see Figure 7.12). A quite big decrease in the rate of the Diels-Alder reactions of the more lipophilic substrates was observed at 5 minutes as well, where the on-water reaction

passes from a 32% conversion for **7.1c** to a 19% for **7.2c** (difference of 13%). The neat reaction instead remained more or less constant, as it shown clearly in the graph of Figure 7.12: only a small decrease could be observed while increasing the chain length.

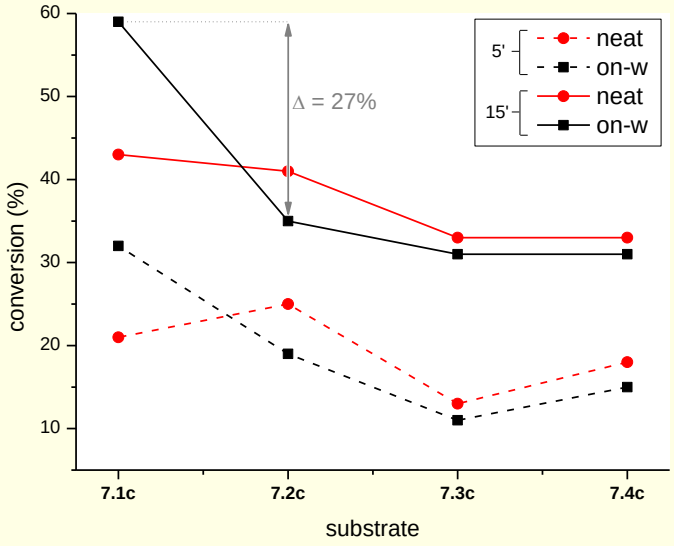


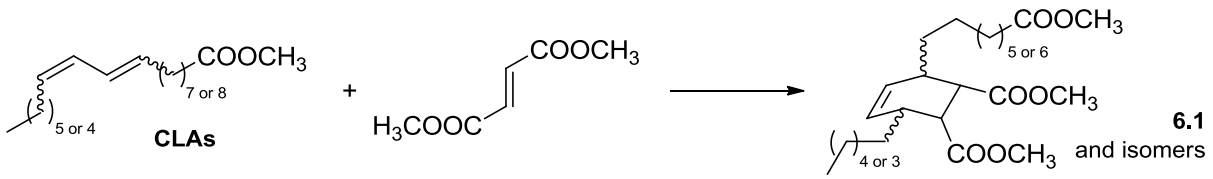
Figure 7.12. Comparison between conversions of on-water and neat reactions of cp with different vinyl ketones after 5 and 15 minutes.

Table 7.5. Comparison between conversions of on-water and neat reactions of cp with different vinyl ketones

Sub	Neat reac.		On-w reac.	
	5′	15′	5′	15′
7.1c	21	43	32	59
7.2c	25	41	19	35
7.3c	13	33	11	31
7.4c	18	33	15	31

[a] All the reactions were performed at 25 °C. [b] Conversions were determined via ^{1}H-NMR analysis (selectivity was complete towards the desired product).

In order to rationalise the observed behaviour the model needed to consider all the collected data relative to the chain length, while retaining consistency with existing literature data. To introduce this new model, it is instructive to consider first the data obtained using conjugated linoleic acid methyl ester (CLAME) and dimethyl fumarate (DMFum) (see previous chapter and introduction of this chapter). The reaction between the two moieties (Scheme 7.13) had similarities with the reactions with cyclopentadiene of the higher molecular weight more lipophilic vinyl ketones described above. That is, the on-water reaction was roughly as fast as the neat reaction, *i.e.* no on-water catalysis was observed.



Scheme 7.13. Reaction between CLA and dimethyl fumarate.

Previously the explanation for the lack of an on-water effect involved the long tails of the fatty ester. In particular it was hypothesized that the tails limited the mobility of

DMFum to and from the water-organic interphase. In light of the new results a different explanation can be given.

The proposed model is consistent both with the theory of the dangling H-bonds at the interphase[3] and the protonation theory.[2] When a substrate such as DMFum is protonated by water at the interphase it is reasonable to assume that the resulting cationic species remains preferentially at the interface, with its charge balanced by the nearby hydroxyl counterions (see Figure 7.13, both right and left: "substrate protonation region"). The energy required to move the charged species within the droplet is too high. This implies that catalysis occurs in, or immediately below, the layer of these protonated species. This is represented in Figure 7.13 on the left. Ethyl vinyl ketone is protonated at the interphase, and it readily reacts with cyclopentadiene immediately below this "protonation region", in what can be dubbed as an "enhanced reaction rate region". Within this, and depending on the droplet size, one can imagine a third region, in which the reaction proceeds as in the neat phase in what can be called a "neat reaction rate region".

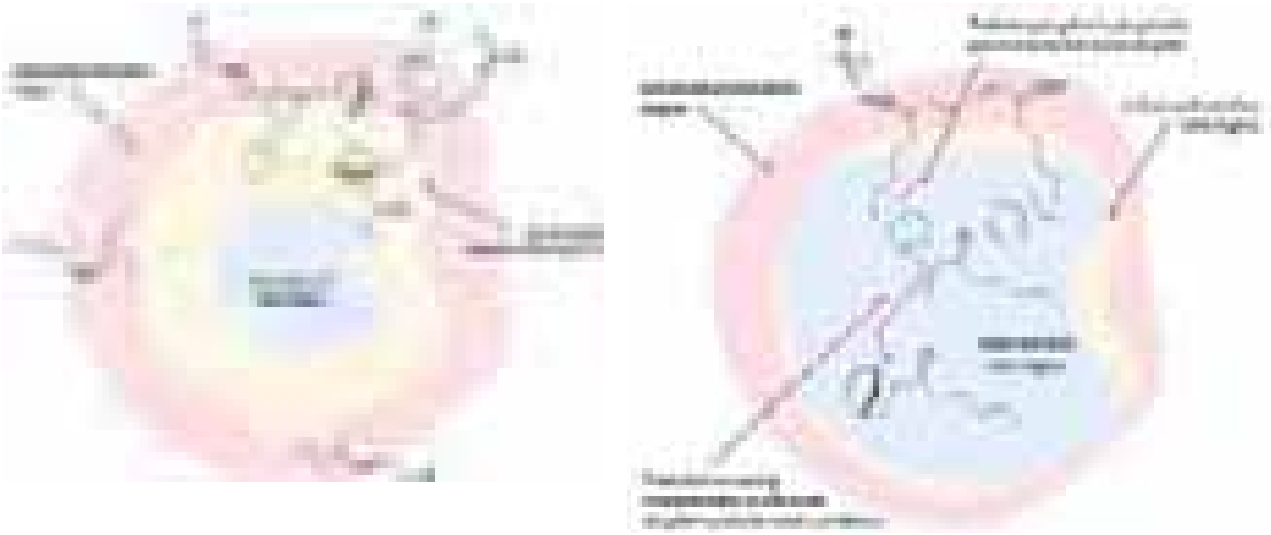


Figure 7.13. Proposed mechanism for the reaction on-water between ethyl vinyl ketone and cp (left) and proposed mechanism for the reaction on-water between pentyl vinyl ketone and cp (right).

When the ketone is the dienophile, and its alkyl chain length increases, the model predicts that it will be similarly protonated. However, the lipophilic alkyl chain will reduce interaction between the dienophile and cp. This will happen because the lipophilic alkyl chain of the vinyl ketone will preferentially dangle towards the inner part of the droplet, which is lipophilic as well (in contrast with the interface that will be charged or at

least polar). The interface, where the reaction can be accelerated, will be thus hindered by the dangling chains of the vinyl ketone, and cp will have lower probability to react with the activated vinylic group. Cyclopentadiene molecules will then react more favourably in the bulk of the droplet in a pseudo-neat environment (Figure 7.13, right). This assumption is also in agreement with the slightly slower reaction rates observed on-water in comparison with the neat conditions.

Therefore, longer alkyl chains probably have two main effects:

- To reduce the probability of interaction between active sites when a compound is protonated at the interphase (hindering effect of the alkyl chains, shown in Figure 7.13, right)
- To reduce the probability of protonation at the interphase (the bigger the molecules, the more the interface is hindered, which implies a reduction of the probability for other molecules to be there activated; see both the linoleic acid case and the pentyl vinyl ketone).

It is proposed that on-water catalysis holds true only for small molecules, *i.e.* those the size of which allows easy migration and faster reaction at the water-organic interface. In support of this hypothesis there appear to be no examples, of on-water catalysed Diels-Alder reactions between large lipophilic molecules.

To conclude, it should be emphasized that this proposed model should hold true also for the interfacial H-bonds theory. Indeed, even considering an H-bond, that has a lower potential than an ion pair, it is still reasonable to assume that a species which is H-bonded at the interphase, does not improve the reaction rate if it cannot react readily with another moiety. And this is again the case of lipophilic molecules with a long alkyl chains.

7.4. Conclusions

The work described in this chapter not only gives an explanation of effects observed previously in the reaction between CLAME and dimethyl fumarate, but explores deeply an effect never previously reported in the literature: the influence of the reagents' structures in their on-water catalysed reactions. More precisely, this work demonstrates that a small increase of the alkyl chain born by vinyl ketones suppresses on-water

catalysis, which can be observed for shorter alkyl chain analogues (ethyl vinyl ketone). This seems to indicate that on-water catalysis on Diels-Alder cycloaddition can be achieved only for small molecules. A mechanism was proposed, which explains such behaviour by considering that:

1. molecules protonated at the interface are most likely to remain there to balance the adsorbed hydroxides;
2. apolar chains of the molecules adsorbed to the interface are most likely to dangle towards the inner part of the molecule (in a comparison with micelles), establishing hindering effects in the region close to the interface.

The two considerations above implies that a second reactant cannot approach easily to the interface, thus it cannot be involved in an accelerated reaction with the activated molecule that is there placed.

A literature search reveals no examples of on-water Diels-Alder reactions between large molecules. Thus, the work represents a further step towards the deep understanding of the mechanism of on-water catalysis, and opens a line of future research. In this sense, interesting tests could be carried out on molecules that give intramolecular Diels-Alder reaction (or another intramolecular reaction that is accelerated on-water), by changing the length their side alkyl chain.

7.5. Bibliography

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8 | CONCLUDING REMARKS

This PhD project, in cotutelle between the Green Organic Synthesis Team (GOST; Università Ca' Foscari, Venice) and the Laboratory of Advanced Catalysis for Sustainabilty (The University of Sydney), was focused on the development of green chemical technologies for the upgrading of platform molecules obtainable from renewable feedstocks through a biorefinery scheme. The starting compounds were chosen among those considered as the most promising for the development a new, sustainable, chemical industry. On the other hand, the transformations were developed based on the wide experience of the two research groups in two important areas of green chemistry: the use of organic carbonates as green reagents and solvents (Venice, chapters 2 to 5), and the use of water as reaction medium (Sydney, chapters 6 and 7). The whole work was thus divided into single studies, each one focused on a particular platform chemical (or class of platform chemicals) and a particular transformation. Below the main results obtained for each part are listed.

- **Chapter 2: Upgrading of levulinic acid with DMC as solvent/reagent**

Levulinic acid (LA) was successfully converted into new derivatives with a higher degree of oxygenation (methyl levulinate and its 4,4-dimethyl ketal, dimethyl succinate and dimethyl 3-methylsuccinate), by using dimehtyl carbonate (DMC), a green reagent and solvent, as a formal oxidant in conditions of basic catalysis (K_2CO_3), at temperatures between 160 and 200 °C. Mechanisms are proposed to account for the observed product selectivity.

This work was published: A. Caretto and A. Perosa *ACS Sust. Chem. Eng. 2013*, **1**, 989-994.

- **Chapter 3: Derivatisation of bio-based lactones**

Bio-derived lactones such as γ-valerolactone, γ-butyrolactone, δ-valerolactone and ε-caprolactone were reacted with three dialkylcarbonates (DMC, diethyl- and

dibenzylcarbonate), again in conditions of basic catalysis and temperatures between 180 and 220 °C. The five-membered ring lactones afforded the corresponding α-alkylated derivatives with high selectivity and yields. On the other hand, the six- and seven-membered ringed lactones afforded highly oxygenated acyclic monomeric derivatives otherwise hardly accessible by previous chemistry.

This work was published: A. Caretto, M. Noè, M. Selva and A. Perosa *ACS Sust. Chem Eng.* 2014, **2**, 2131-2141.

❖ **Chapter 4: Ring opening of bio-based lactones**

γ-Valerolactone was chosen as a model to study acid catalyzed ring-opening reactions. A novel reactivity of the molecule was discovered in the presence of DMC. The 4-methoxy pentanoyl moiety was thus accessible by a green route. A reaction mechanism, supported by experimental and computational data, was proposed. The reaction was then extended to a continuous flow process, with solid acid catalysts. In such conditions, the selectivity towards methyl 4-methoxy pentanoate or methyl pentenoate, monomer for the production of polymers, can be tuned by optimising the operating parameters.

This work is under preparation for publication.

❖ **Chapter 5: Diols as a route to linear and cyclic carbonates**

Bio-derived diols were efficiently upgraded using organic carbonates in tandem with ionic liquids as organocatalysts. The study investigated the parameters that control the selectivity towards cyclic- or linear di-carbonates, which can be obtained with very high yields depending on the molecular structure of the diol. In particular, shorter diols yield the cyclic carbonate while linear dicarbonate monomers are obtained with longer chain diols. This kind of products are generally never obtained from reactions carried out in these conditions and by using conventional organic and inorganic bases as catalysts, being predominant the formation of corresponding polycarbonates. In our case, the observed behaviour finds a plausible explanation in the nature of the organocatalysts used for the transesterification processes.

This work was published: M. Selva, A. Caretto, M. Noè and A. Perosa *Org. Biomol. Chem.* 2014, **12**, 4143-4155.

- **Chapter 6: On-water modification of FAMEs to improve cold flow properties of biodiesel**

The derivatisation of fatty acids methyl ester in conditions of on-water catalysis was investigated whilst at the University of Sydney, with the aim of developing a green strategy to reduce the cloud point of biodiesels. A new branched additive was synthesised by diels-Alder reaction between conjugated linoleic acid methyl ester and an activated dienophile such as dimethyl fumarate. Thermal characteristics of this product were analysed, both pure and blended with biodiesel. If on one side the synthesised additive does not significantly alter the cloud point of a sample biodiesel, on the other one it can still be considered as a starting point for future work. Its synthesis was used to initiate a study on the on-water catalysis mechanism.

This work is under preparation for publication.

- **Chapter 7: On-water catalysis of Diels-Alder reactions: Influence of the structure of the reagents**

The study of on-water catalysis continued by investigating the mechanism and the effect of reagent structure on on-water catalysis. It was demonstrated, by using the model reactions between cyclopentadiene (Cp) and alkyl vinyl ketones, that little changes of the alkyl chain of a reactant have a dramatic influence on the catalytic effect. In particular, the reaction between ethyl vinyl ketone and Cp was demonstrated to be on-water catalysed. When vinyl ketones bearing a longer or bulkier alkyl chain were tested, the catalytic effect was not observed, and the reactions were as fast as in neat conditions. The data have led to propose that on-water catalysis holds true only for "small" and less lipophilic molecules, *i.e.* those the size of which allows easy migration and faster reaction at the water-organic interface. These results represent a milestone for the understanding of the on-water catalysis.

This work is under preparation for publication.

9 | EXPERIMENTAL

9.1. General

All the chemicals were of reagent grade and were used as received, unless otherwise stated.

Analysis for the reactions of chapters 2 to 5 were performed using the following instruments:

- GC-MS analyses were performed with a HP-5890 gas-chromatograph equipped with a HP-5 MS capillary column (30 m x 0.25 mm; coating thickness 0.25μm) and a HP-5970 quadrupole mass detector (EI, 70 eV). Analytical conditions: injector and transfer line temperatures 260 and 280 °C respectively; oven temperature programmed from 100 °C (isothermal condition for three minutes) to 280 °C at 10°C min-1; carrier gas helium at 1 ml/min-1; split ratio 1:20.
- NMR spectrometer Varian Unity, operating at 400 and 100 MHz (^{1}H and ^{13}C respectively). NMR spectra were collected in $CDCl_3$ solution at 25 °C on a Varian Unity at 400 and 100 MHz, respectively.
- IR spectrophotometer Perkin-Elmer Spectrum-One. Analysis were performed by preparing KBr pads of the samples.

Analysis for the reactions of chapters 6 and 7 were performed using the following instruments:

- GC-MS QP2010 Gas chromatograph/mass spectrometer (EI) with an Rtx-5MS column (30 m × 0.25 mm × 0.25 μm). Data were collected and analysed using Shimadzu LabSolutions GCMS solution version 2.72.

- NMR spectrometer Bruker AVANCE DPX200, or Bruker DPX300 spectrometer (^{1}H frequencies 200, 300 MHz; ^{13}C frequencies 50, 75 MHz respectively).
- Finnigan LCQ mass spectrometer equipped with an Electronspray Ionisation Probe (ESI) and a quadrupole ion trap. Data collection and analysis were performed by Dr. Nick Proschogo of the Mass Spectrometry Facility, School of Chemistry, The University of Sydney.
- DSC 2920 Modulated DSC, TA Instruments, Inc. Data were collected at constant atmospheric pressure using samples between 3-10 mg. Samples were placed in closed aluminum pan. An empty closed pan was used as a reference. The DSC was adjusted so that zero heat flow was between 0 and -0.5 mW and the baseline drift was less than 0.1 mW over the temperature range of -150-180°C.

^{1}H chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ 7.26) as internal reference and are reported as chemical shift (δH); relative integral; multiplicity (s = singlet, br = broad, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, q = quartet, m = multiplet); and coupling constants (J) reported in Hz. 13C NMR chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ 77.1) as internal reference and are reported as chemical shift (δC); multiplicity (assigned from DEPT experiments).

9.2. Levulinic acid

All the reactions involving levulinic acid were performed in stainless steel autoclaves of 120 or 220 ml volume, equipped with pressure gauge and thermocouple (see appendix for the complete scheme). Heating was provided by means of an electric oven, powered and controlled by a thermoregulator "ASCON" (model C1-3000), which was connected to the thermocouple of the autoclave. The autoclave was flushed with nitrogen before every reaction, after the loading of the reagents. Stirring was provided by a stirrer hot plate, set at 600 rpm. The reactions were sampled, diluted in diethyl ether, washed with ph 4 water, and analysed at the GC-MS.

Methyl levulinate (2.1)

Levulinic acid (1.0 g, 8.6 mmol), DMC (14.5 ml, 172.2 mmol) and K_2CO_3 (2.4 g, 17.2 mmol) were loaded in a stainless steel autoclave. After washing with nitrogen the mixture was heated to 160 °C under stirring for 6 hours. The reaction was allowed to cool to room temperature and the mixture was dried under vacuum, than diluted in diethyl ether and filtered to remove K_2CO_3. The resulting solution was concentrated and a brown oil was obtained. Distillation under reduced pressure yielded **2.1** (90%).

^{1}H NMR (400 MHz, CDCl3) δ 3.67 (s, 3H), 2.75 (t, *J* = 6.6 Hz, 2H), 2.57 (t, *J* = 6.6 Hz, 2H), 2.18 (s, 3H). Mass spectrum, m/z (I_{rel}, %): 130 (M^+, <1%), 115 (10), 99 (14), 98 (5), 88 (5), 87 (4), 71 (4), 59 (10), 57 (9), 56 (4), 55 (16), 43 (100), 32 (4).

Dimethyl succinate (2.2)

The same mixture used to synthesize **2.1** was heated to 200 °C instead of 180 °C. After the same workup a brown oil was obtained. A distillation under reduced pressure yielded **3** (18%).

^{1}H NMR (400 MHz, CDCl3) δ 3.68 (s, 6H), 2.62 (s, 4H). Mass spectrum, m/z (I_{rel}, %): 146 (M^+, <1%), 116 (5), 115 (84), 114 (28), 87 (20), 59 (72), 57 (10), 56 (10), 55 (100), 53 (18).

Dimethyl 2-methylsuccinate (2.3)

The compound was identified by comparison of its GC-MS with a commercial sample.

Mass spectrum, m/z (I_{rel}, %): 160 (M^+, <1%), 129 (16), 128 (10), 101 (11), 100 (11), 69 (12), 59 (100), 55 (8).

Methyl 4,4-dimethoxypentanoate (2.4)

The same mixture used to synthesize **2.1**, with methanol (7.0 mL, 172.2 mmol), was heated to 200 °C. After the same workup a brown oil was obtained. The mixture was purified by flash chromatography on silica gel by eluting with a mixture of 1% of triethylamine, petroleum ether and diethyl ether (gradient elution: 1:0, 4:1, 2:1). The amine was added to neutralize the acidic centers of silica. The resulting fraction was than distilled under reduced pressure, leading to a yield of **2.4** of 20%, with a purity ≥ 95%.

^{1}H NMR (400 MHz, CDCl3) δ 3.67 (s, 3H), 3.17 (s, 6H), 2.35 (m, 2H), 1.95 (m, 2H), 1.24 (s, 3H).Mass spectrum, m/z (I_{rel}, %): 176 (M^+, <1%), 161 (6), 146 (3), 145 (32), 113 (20), 101 (11), 89 (100), 85 (97), 71 (10), 55 (34).

9.3. Upgrading of bio-based lactones

GBL, GVL, DVL, ECL, dimethylcarbonate and diethylcarbonate were ACS grade and were employed without any further purification. Dibenzylcarbonate was prepared according to a recently reported method. K_2CO_3 was stored under vacuum at 60 °C prior to use.

All reactions involving DMC and DEC were performed in stainless steel autoclaves with an internal volume of 120 or 220 mL, equipped with a pressure gauge, a thermocouple and a magnetic stir bar. Heating was provided by means of an electric oven powered by a thermoregulator connected to the thermocouple. All the reported reactions generate endogenous pressure due to the formation of gaseous mixtures. The final maximum observed pressure (syntheses of **3.1c** and **3.4c**) at 200 °C was 60 atm (10 atm observed once cooled to room temperature).

α,α-carboxymethyl,methyl-γ-butyrolactone (3.1b)

GBL (2.00 g, 23.23 mmol) was loaded into an autoclave, together with DMC (29.4 ml, 348.47 mmol) as reagent/solvent and K_2CO_3 (3.21 g, 23.23 mmol). Once the autoclave was closed, air was purged by fluxing nitrogen through needle valves placed on the autoclave head. The mixture was then heated to reaction temperature (180 °C) and maintained under stirring (600 rpm) for the desired reaction time. After that the stirring was stopped while the autoclave was cooled down to room temperature and successively vented. DMC was removed under vacuum and K_2CO_3 was filtered. The compound **3.1b** was isolated through flash column chromatography on silica gel (gradient elution of petroleum ether and diethyl ether).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.35 (m, 2H), 3.77 (s, 3H), 2,75 (ddd, 1H, J_1= 4.4 Hz, J_2= 7.0 Hz, J_3= 13.0 Hz), 2.18 (dt, 1H, J_1 = 8.4, J_2 = 13.2 Hz), 1.52 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ(ppm): 175.7, 170.9, 65.8, 53.1, 49.8, 34.9, 20.2. Mass spectrum, m/z:158 ([M]$^+$, <1%), 127 (5), 114 (13), 99 (33), 83 (42), 82 (36), 71 (13), 69 (20), 59 (32), 55 (100), 43 (30), 41 (64), 39 (67), 31(6).

α-methyl-γ-butyrolactone (3.1c)

The reaction was set up and worked up as described for **3.1b**. After 24 hours of reaction time at a temperature of 200 °C, **3.1c** was isolated through distillation under reduced pressure (b.p. 116-118 °C, 8 mmHg) with a yield of 45%.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.34 (td, 1H, J_1= 2.7 Hz, J_2= 8.7 Hz), 4.18 (td, 1H, J_1= 6.6 Hz, J_2= 9.3 Hz), 2.60 (m, 1H), 2.43 (m, 1H), 1.92 (m, 1H), 1.29 (d, 3H, J = 7.1 Hz).^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 180.2, 66.3, 34.2, 30.7, 15.2.Mass spectrum, m/z:100 ([M]$^+$, 2%), 56 (38), 55(14), 42 (34), 41 (100), 39 (29).

α-carboxyethyl-γ-butyrolactone (3.2a)

The title compound was not isolated. Its spectroscopic data match those reported in the literature.

α,α-carboxyethyl,ethyl γ-butyrolactone (3.2b)

The reaction was set up and worked up as described. After 24 hours of reaction time at a temperature of 200 °C, **3.2b** was isolated through flash column chromatography on silica gel (petroleum ether : diethyl ether = 1 : 1 as eluant).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.32 (dd, J_1= 5.4 Hz, J_2= 8.9 Hz, 2H), 4.22 (ttd, J_1= 3.6 Hz, J_2= 7.4 Hz, J_3= 10.8 Hz, 2H), 2.71 (m, 1H), 2.22 (td, J_1= 8.8 Hz, J_2= 13.1Hz, 1H), 2.12 (qd, J_1= 7.4 Hz, J_2= 14.9 Hz, 1H),1.84 (qd, J_1= 7.4 Hz, J_2= 14.8 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H).^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 174.9, 169.6, 66.1, 62.1, 54.7, 31.2, 27.2, 14.0, 9.0.Mass spectrum, m/z:186 ([M+1]$^+$, 3), 158 (22), 141 (7), 130 (10), 127 (9), 114 (32), 113 (11), 112 (13), 99 (59), 97 (9), 96 (10), 95 (6), 85 (6), 83 (11), 81 (13), 69 (54), 68 (11), 67 (15), 55 (28), 54 (10), 53 (19), 45 (11), 43 (14), 42 (8), 41 (100), 39 (42), 30 (6).

α-ethyl-γ-butyrolactone (3.2c)

GBL (2.00 g, 23.23 mmol) was loaded into an autoclave, together with DEC (33.80 ml, 278.97 mmol) as reagent/solvent and K_2CO_3 (3.21 g, 23.23 mmol). The reaction was then set up and worked up as already described. The product **3.2c** was distilled at

reduced pressure together with the product **3.2d**. They were then separated through flash column chromatography on silica gel (diethyl ether:petroleum ether = 3 : 2 as eluant).Yield = 40%.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm):4.33 (td, *J* = 8.8, 3.1 Hz, 1H); 4.19 (td, *J* = 9.2, 6.7 Hz, 1H); 2.51-2.34 (m, 2H); 1.99-1.85 (m, 2H); 1.51 (ddq, *J* = 14.7, 8.6, 7.4 Hz, 1H); 1.00 (t, *J* = 7.5 Hz, 3H).^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 179.1, 66.7, 40.8, 28.2, 23.6, 11.8. Mass spectrum, m/z:114 ([M]$^+$, <1%), 113 (<1), 99 (1), 87 (4), 86 (89), 85 (8), 58 (6), 56 (20), 55 (100), 53 (7), 42 (51), 41 (39), 39 (23).

diethyl cyclopropane-1,1-dicarboxylate (3.2d)

The product **3.2d** was isolated from the same mixture of **3.2c**. After fcc, its yield was 8%.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.19 (q, *J* = 7.1 Hz, 4H), 1.42 (s, *J* = 1.9 Hz, 4H), 1.27 (t, *J* = 7.1 Hz, 6H).^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm):170.0, 61.6, 28.5, 16.5, 14.3.170.0, 61.6, 28.5, 16.5, 14.3.Mass spectrum, m/z:186 ([M]$^+$, 1%), 159 (20), 158 (21), 142 (8), 141 (100), 140 (6), 131 (6), 130 (41), 114 (21), 113 (63), 112 (56), 95 (12), 86 (22), 85 (14), 84 (7), 69 (10), 68 (12), 45 (8), 41 (17), 40 (21), 39 (20).

α-benzyl-γ-butyrolactone (3.3c)

GBL (1.0 ml, 13.1 mmol), DBnC (3.5 g, 14.4 mmol) and K_2CO_3 (1.8 g, 13.1 mmol) were introduced in a round-bottomed flask equipped with a condenser. The stirred mixture was heated to 200°C by an oil bath; after 12 hours, the reaction was stopped and the mixture was cooled down to room temperature. K_2CO_3 was filtered off and the crude was concentrated by rotary evaporator. Benzyl alcohol was then distilled at reduced pressure, and the oily residue was purified by flash column chromatography on silica gel (petroleum ether:diethyl ether:ethyl acetate = 4:1:1 as eluent). Compound **3.8a** was obtained in a 50% yield.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39-7.15 (m, 5H), 4.23 (td, *J* = 8.8, 3.1 Hz, 1H), 4.14 (td, *J* = 9.3, 6.7 Hz, 1H), 3.25 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.91-2.80 (m, 1H), 2.75 (dd, *J* = 13.6, 9.5 Hz, 1H), 2.30-2.20 (m, 1H), 1.99 (dtd, *J* = 12.8, 9.7, 8.6 Hz, 1H).Mass spectrum,

m/z:177 ([M+1]$^+$, 7%), 176 ([M]$^+$, 59%), 149 (7), 148 (73), 147 (89), 131 (17), 130 (13), 117 (16), 115 (15), 104 (29), 103 (7), 92 (10), 91 (100), 78 (7), 77 (7), 65 (13), 51 (6).

α-carboxymethyl-γ-valerolactone (3.4a)

The title compound was not isolated; its structure was confirmed by comparison with an authentic commercial sample.

α,α-carboxymethyl,methyl-γ-valerolactone (3.4b)

The title compound was not isolated. Its spectroscopic data match those reported in the literature.

α-methyl-γ-valerolactone (3.4c)

A mixture of GVL (2.00 g, 19.98 mmol), DMC (25.25 ml, 299.64 mmol) and K_2CO_3 (2.76 g, 19.98 mmol) was charged in a stainless-steel autoclave. The reaction was then set up and worked up as already described for **3.1b**. After 24 hours 220 °C, **3.4b** was isolated by distillation at reduced pressure (b.p. 102-103 °C, 70 mmHg). A mixture of diasteroisomers was obtained in a 82% yield.

^{1}HNMR (400 MHz, CDCl3) δ (ppm): 4.64 (m, 1H), 4.44 (m, 1H), 2,66 (m, 2H), 2.48 (m, 2H), 2.02 (m, 2H), 1.47 (td, 1H, J_1= 10.4 Hz, J_2= 12.2 Hz), 2.18 (td, 1H, J_1 = 8.4, J_2 = 13.2 Hz), 1.37 (d, 3H, J = 6.1 Hz), 1.33 (d, 3H, J = 6.4 Hz), 1.23 (d, 3H, J = 7.3 Hz), 1.22 (d, 3H, J = 7.0 Hz).^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm):180.0, 179.6, 74.9, 74.6, 39.1, 37.0, 36.3, 34.0, 21.0, 20.9, 15.7, 15.1.Mass spectrum, m/z:114 (M$^+$, <1%), 99 (6), 71 (10), 70 (38), 55 (92), 43 (58), 42 (100), 41 (50), 39 (46).

α-ethyl-γ-valerolactone (3.5c)

A mixture of GVL (2.00 g, 19.98mmol), DEC (29.05 ml, 239.77 mmol) as reagent/solvent and K_2CO_3 (2.76 g, 19.98 mmol)was charged in a stainless-steel autoclave.The reaction was set up as and worked up as already described. After 72 hours at 220 °C, **5c** was isolated by distillation at reduced pressure (b.p. 52-54 °C, 1.5 mmHg). A mixture of diasteroisomerswas obtained in a 50% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.69-4.60 (m, 1H), 4.52-4.42 (m, 1H), 2.62-2.51 (m, 1H), 2.49-2.42 (m, 1H), 2.13 – 1.79 (m, 4H), 1.58-1.42 (m, 4H), 1.38 (dd, *J* = 18.3, 6.3 Hz, 6H), 0.99 (dt, *J* = 9.1, 7.5 Hz, 6H).^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 179.1, 178.8, 75.0, 74.9, 42.9, 40.7, 36.4, 34.6, 23.8, 23.3, 21.3, 21.0, 11.7, 11.6. Mass spectrum, m/z: 128 ([M]$^+$<1%), 127 (1), 113 (14), 101 (6), 100 (100), 87 (3), 85 (4), 84 (5), 69 (25), 67 (8), 57 (8), 56 (51), 55 (62), 54 (5), 53 (5).

α-benzyl-γ-valerolactone (3.6c)

A mixture of GVL (1.00 g, 9.99 mmol) DBnC (,mmol) as reagent/solvent and K_2CO_3 (2.76 g, 19.98 mmol)was set to react as already described for **3.3c**. The title compound was purified by flash column chromatography on silica gel (petroleum ether:diethylether:ethyl acetate = 4:1:1 as eluant). A mixture of diasteroisomers was obtained in a 65% yield.

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 7.34-7.17 (m, 5H), 4.53-4.39 (m, 1H), 3.25 (ddd, *J* = 44.2, 13.9, 4.2 Hz, 1H), 3.02-2.85 (m, 1H), 2.74 (ddd, *J* = 28.1, 13.9, 9.6 Hz, 1H), 2.31 (ddd, *J* = 12.7, 8.4, 5.5 Hz, 1H), 2.13 (dt, *J* = 13.0, 7.5 Hz, 1H), 1.89 (ddd, *J* = 13.0, 9.1, 4.9 Hz, 1H), 1.61-1.48 (m, 1H), 1.34 (dd, *J* = 17.2, 6.3 Hz, 3H). Mass spectrum, m/z: 191 ([M+1]$^+$, 3) 190 ([M]$^+$, 19), 149 (10), 148 (100), 147 (84), 131 (6), 118 (7), 117 (16), 115 (10), 91 (50), 77 (4), 65 (7), 55 (3), 51 (3).

methyl 5-((methoxycarbonyl)oxy)pentanoate (3.7a)

A mixture of DVL (2.00 g, 19.98mmol) DMC (25.25 ml, 299.64mmol) as reagent/solvent and K_2CO_3 (2.76 g, 19.98mmol)was charged in a stainless-steel autoclave. The reaction was then set up and worked up as already described for **3.1b**.After 4 hours at 200 °C, **3.7a** was isolated by distillation at reduced pressure (b.p. 70 °C, 1.12 mmHg). Yield = 80%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (m, 2H), 3.74 (s, 3H), 3.64 (s, 3H), 2.32 (m, 2H), 1.69 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 173.4, 155.7, 67.4, 54.5, 51.4, 33.4, 28.0, 21.1.Mass spectrum, m/z: 190 ([M]$^+$, <1%), 159 (5), 115 (12), 114 (67), 113 (10), 101 (7), 99

(16), 83 (33), 82 (53), 77 (7), 74 (8), 73 (43), 72 (26), 71 (15), 59 (82), 58 (9), 57 (5), 56 (8), 55 (100), 54 (30), 45 (25), 43 (19), 42 (18), 41 (24), 39 (12).

Methyl 2-methyl 5-((methoxycarbonyl)oxy)pentanoate (3.7c)

A mixture of DVL (0.27 g, 2.69 mmol) DMC (3.40 ml, 40.35 mmol)as reagent/solvent and K_2CO_3 (0.37 g, 2.69 mmol)was charged in a stainless-steel autoclave. The reaction was then set up and worked up as already described. After 24 hours at 200 °C, **3.7c** was isolated by flash column chromatography on silica gel (gradient elution, petroleum ether and diethyl ether). Yield = 44%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16-4.10 (m, 2H), 3.77 (s, 3H), 3.67 (s, 3H), 2.51-2.42 (m, 1H), 1.78 – 1.63 (m, 3H), 1.51 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):176.6, 155.7, 67.7, 54.6, 51.5, 39.0, 29.8, 26.4, 17.0. Mass spectrum, m/z: 204 ($[M]^+$, <1%),173 (4), 129 (7), 128 (24), 115 (4), 113 (44), 100 (4), 97 (5), 96 (11), 88 (6), 87 (6), 85 (5), 77 (8), 73 (12), 70 (6), 69 (100) 68 (23), 67 (8), 59 (45), 57 (7), 55 (13), 45 (14), 43 (7), 42 (9), 41 (40), 39 (9).

Ethyl 5-((ethoxycarbonyl)oxy)pentanoate (3.8a)

A mixture of DVL (2.00 g, 19.98 mmol), DEC (36.30 ml, 299.64 mmol) as reagent/solvent and K_2CO_3 (2.76 g, 19.98 mmol) was charged in a stainless-steel autoclave. The reaction was then set up and worked up as already described. After 6 hours at 200 °C, **3.8a** was isolated by distillation at reduced pressure (b.p. 81 °C, 0.82 mmHg). Yield = 77%.

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 4.23-4.09 (m, 6H), 2.36-2.29 (m, 2H), 1.76-1.67 (m, 4H), 1.27 (dt, *J* = 21.6, 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):173.1, 155.1, 67.2, 63.8, 60.3, 33.7, 28.1, 21.2, 14.2, 14.2. Mass spectrum, m/z: 218 ($[M]^+$, <1%), 129 (10), 128 (46), 101 (85), 100 (25), 99 (10), 91 (5), 87 (5), 83 (32), 82 (12), 73 (5), 72 (5), 69 (9), 63 (12), 60 (8), 59 (15), 58 (6), 57 (9), 56 (36), 55 (100), 54 (20), 45 (14), 44 (12), 43 (26), 42 (22), 41 (23), 39 (7).

Methyl 6-((methoxycarbonyl)oxy)hexanoate (3.9a)

A mixture of ECL (2.00 g, 17.52 mmol) DMC (22.14 ml, 262.80 mmol) as reagent/solvent and K_2CO_3 (2.42 g, 17.52 mmol) was charged in a stainless-steel

autoclave. The reaction was then set up and worked up as already described for **3.1b**. After 6 hours at 200 °C, **3.9a** was isolated by distillation at reduced pressure (b.p. 84 °C, 1 mmHg). Yield = 82%.

^{1}HNMR (400 MHz, $CDCl_3$) δ4.13 (t, *J* = 6.6 Hz, 2H), 3.76 (s, *J* = 5.4 Hz, 3H), 3.66 (s, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.72 – 1.60 (m, 4H), 1.45 – 1.35 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):173.5, 155.5, 67.5, 54.3, 51.2, 33.5, 28.1, 25.0, 24.2. Mass spectrum, m/z: 190 204 ($[M]^+$, <1%), 173 (7), 131 (8), 128 (39), 113 (22), 100 (14), 99 (9), 97 (39), 96 (27), 87 (36), 85 (6), 77 (20), 74 (92), 69 (86), 68 (100), 67 (18), 59 (72), 57 (8), 56 (8), 55 (83), 54 (8), 45 (30), 43 (28), 42 (20), 41 (57), 39 (20).

9.4. Ring opening of bio-based lactones

9.4.1. Reactions at low temperature (atmospheric pressure)

9.4.2. Reactions at high temperatures

Batch reactions at high temperature were performed into stainless steel autoclaves with an internal volume of 120 or 220 ml, equipped with a pressure gauge and thermocouple. Heating was provided by means of an electric oven powered by a thermoregulator connected to the thermocouple. The scheme of a 220 ml autoclave is included in the appendix.

GVL (1.0 ml, 10.49 mmol) was loaded into an autoclave, together with PTSA (140 mg, 0.81 mmol). Methanol (MeOH; 6.36 ml, 157.31 mmol) and DMC (8.84 ml, 104.87 mmol) were then added, with various molar ratios over GVL, as summarised in Table 9.1.

Table 9.1.

Entry	1	2	3	4	5	6
MeOH (mol/mol GVL)	30	30	15	10	2	none
DMC (mol/mol GVL)	none	2	10	10	30	30

In the typical example of column 3, MeOH (6.36 ml, 157.31 mmol) and DMC (8.84 ml, 104.87 mmol) were added to the reaction mixture. Once the autoclave was closed, air was purged by fluxing nitrogen through needle valves placed on the autoclave head. The mixture was then heated to reaction temperature (150 °C) and maintained under stirring (600 rpm) for the desired reaction time. After that the stirring was stopped while the autoclave was cooled down to room temperature and successively vented.

Samples for GC-MS analysis were directly taken from the final reaction mixtures and diluted in diethyl ether.

Methyl 4-methoxy-pentanoate (4.2)

The title compound was isolated from a reaction set up as described above. After a reaction time of 30 hours, the final mixture was concentrated at the rotary evaporator,

where MeOH and DMC were removed. **4.2** was isolated via distillation at reduced pressure (), with a final yield of

^{1}H NMR (400 MHz, CDCl3) δ 3.66 (s, 3H), 3.32 (m, 1H), 3.29 (s, 3H), 2.38 (m, 2H), 1.77 (m, 2H), 1.13 (d, 3H, J = 6.2). Mass spectrum, m/z (I_{rel}, %): 146 (M^+, <1%), 131 (M^+-CH_3,), 115 (M^+-OCH_3, 4), 99 ($[C_5H_7O_2]^+$, 4), 83 (4), 73 (14), 71 (18), 59 ($[COOCH_3]^+$, 100), 55 ($[C_3H_3O]^+$, 20), 43 (19), 41 (15), 39 (10), 31 (31).

Methyl 4-hydroxy-pentanoate

^{1}H NMR (400 MHz, CDCl3) δ 3.83 (m, 1H), 3.68 (s, 3H), 2,55 (m, 2H), 1.74 (m, 2H), 1.21 (d, 3H). Mass spectrum, m/z (I_{rel}, %): 132 (M^+, <1%), 117 (M^+-CH3, 3), 101 (10), 88 (75), 85 (53), 83 (14), 74 (12), 59 (40), 57 (88), 56 (46), 55 ([C3H3O]$^+$, 55), 45 (100), 43 (78), 41 (25), 39 (20), 31 (42).

9.4.3. Reactions carried out in continuous flow conditions

Continuous flow reactions were performed in stainless steel tubular reactors (PFR) using the apparatus schematised in **Errore. L'origine riferimento non è stata trovata.**. The following equipment was employed: an HPLC pump Shimadzu LC-10AS; a GC oven HP 5890; a back pressure regulator (BPR) BP-2080 Plus. A scheme of the apparatus is shown in Figure 8.1.

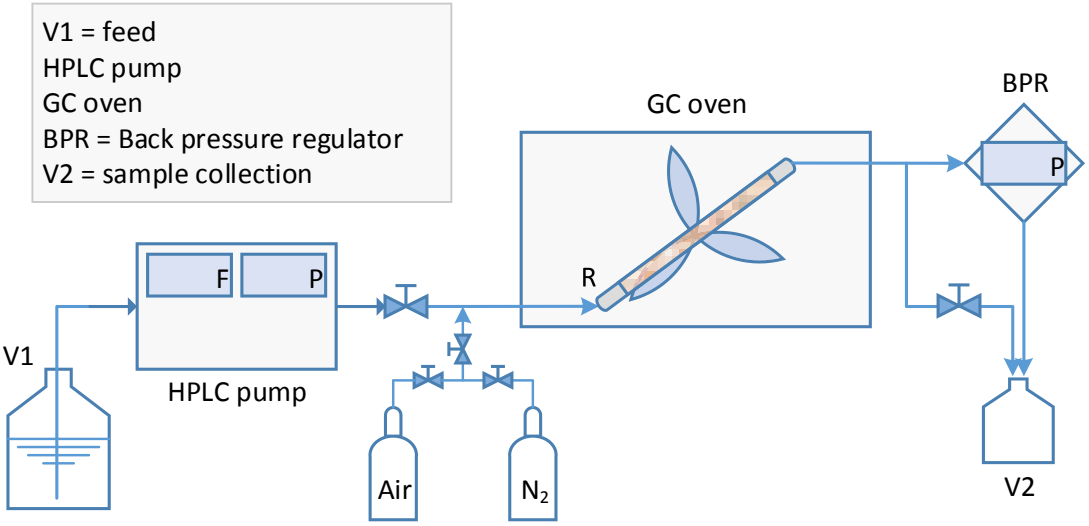


Figure 9.1. Apparatus for performing continuous flow reactions.

All the connections between the apparatus components were realised with stainless steel tubes (internal diameter 1/16″, unless otherwise stated).

Reactors were realised with Swagelok stainless steel tubes of 1/4″ or 1/8″ diameter. The various reactors assembled are listed in Table 9.2. Both the reactor ends were fitted with Swagelok reducing unions (1/4-1/16″ or 3/8-1/16″), together with two frits (Supelco; porosity = 2 μm, ø = 1/4″ or 3/8″), which allowed to connect the reactor to the pipeline.

Table 9.2. Reactors assembled for the continuous flow study.

Entry[a]	$ø_{ext}$		$ø_{int}$		length	volume
	inch	cm	inch	cm	cm	cm^3
1	1/4	0.635	0.15	0.385	12	1.40
2	3/8	0.953	0.25	0.623	12	3.65
3	3/8	0.953	0.30	0.775	42	20

9.4.3.1. Preparation of the catalysts

Acidic alumina

Acidic alumina was dried before use as following described. The solid powder was loaded into the chosen reactor for the maximum capability of the latter. The reactor was then assembled in the apparatus described above, a flow of nitrogen was applied (15 ml min^{-1}) and the temperature was first raised to 100 °C (2 hours), then to 250 °C (6 hours). The so prepared alumina was either used fresh or stored at 70 °C under vacuum.

HY zeolites

HY zeolites were prepared by calcination of NH_4Y zeolites. 8 g of the latter were placed in a quartz tube, placed in a vertical oven. A flow of dry air (25 ml min^{-1}) was applied from the top of the tube, which was then heated up to 500 °C for 5 hours. The so prepared HY zeolites were either used fresh or stored at 70 °C under vacuum.

9.4.3.2. Start-up procedure

i. The HPLC pump was set to the desired flow rate (ml min^{-1}), while the BPR was set on atmospheric pressure.

ii. When collection started at the outlet, the desired pressure was set on the BPR.

iii. Once the system reached the equilibrium (constant pressure both at the pump and at the BPR), the temperature in the oven was increased by programming a temperature ramp (5 °C min^{-1} up to the desired temperature).

iv. Once the desired temperature was reached, and the system reached the new equilibrium (constant pressures and temperature), the apparatus was kept operating for a certain time (equilibration time), the latter calculated by considering an estimated contact time into the reactor and an estimated total time for the mixture to flow across all the pipeline.

v. After the equilibration time, the sampling of the mixture at the outlet was started. Single samples were collected for 30 minutes and analysed at the GC-MS. At least 3 samples (total sampling time of 90 minutes) were collected for every set of conditions. When little discrepancy in the product distribution between the samples was observed, a fourth and a fifth fractions were collected. All the data reported in chapter 4 are an average of the samples collected for that single set of conditions.

vi. When a single parameter was changed, point iv (equilibration time) and v (sampling) were repeated as described.

9.4.3.3. Shut down procedure

Steps followed to stop the apparatus at the end of a reaction.

i. The temperature was decreased to r.t. by applying a temperature ramp of -3 °C min^{-1}.

ii. Once the GC oven reached a temperature of 35-40 °C, the BPR was set to atmospheric pressure.

iii. The feed mixture was replaced by methanol, fed at a flow rate of 2 ml min^{-1} and the whole line was purged for 1 hour. After this time the outlet mixture was sampled and analysed at the GC-MS. When traces of reactant/products were detected, purging was continued for intervals of 30 minutes and systematically sampled, until when the outlet mixture became clean.

iv. The pump was switched off and the valves were closed.

9.5. Diols as a resource for linear and cyclic carbonates

1,2-propanediol (**5.2**), 1,2-ethanediol (**5.3**), 1,3-butanediol (**5.4**), 2-methyl-1,3-propanediol (**5.5**), 1,3-propanediol (**5.6**), 2,2-dimethyl-1,3-propanediol (**5.7**), and 2-methyl-2,4-pentandiol (**5.8**), 1,4-butanediol (**5.9**) and 1,6-hexanediol (**5.10**), dimethyl carbonate (DMC), methanol, propylene and ethylene carbonate were ACS grade and were employed without any further purification. Phosphonium salts **5.1a** and **5.1b** were prepared accordingly to a method recently reported by us.

GC/MS (EI, 70 eV) analyses were run using a HP5-MS capillary column (30 m). ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra at 101 MHz. Chemical shifts were reported in δ values downfield from TMS; $CDCl_3$was used as solvent. IR spectra were recorded using NaCl windows. Combustion analysis data were obtained by an organic (CHN) elemental analyzer.

Structures of final products, both cyclic and linear dicarbonates, as well as those of reaction intermediates were analyzed by GC-MS and NMR techniques. Whenever characterization data were available in the literature, they were in agreement with our spectroscopic results and confirmed the assigned structures. In the case of propylene and ethylene carbonate (**5.2a** and **5.3a**), structures were proved also by comparison to authentic commercial samples.

9.5.1. Transesterification reactions

1,2-propanediol. A typical procedure is described for the model case of 1,2-propanediol (**2**). A round-bottomed 25-mL flask equipped with a condenser and a screw-capped adapter for the withdrawal of samples, was charged with a mixture of 1,2-propanediol (0.84 g,11 mmol), dimethyl carbonate (DMC) (19.8 g, 220 mmol) and $[P_{8,8,8,1}][MeOCOO^-]$ **5.1a** (0.056 g,0.11 mmol). The flask was heated at the reflux temperature (90°C) in an oil bath, and the mixture was allowed to react under magnetical stirring, for 4 hours. The progress of the reaction was monitored by sampling the mixture at chosen time intervals, and by analysing samples *via* NMR.

The above described procedure was used also to investigate the effect of the reaction temperature, of the catalyst loading, and of the DMC amount In particular: i) two experiments were carried out at 70 and 50 °C, respectively; ii) two experiments were carried out at 90 °C, for 2 hours, in the presence of variable amounts of the catalysts **5.1a** (0.11 mmol and 0.055 mmol: 0.056 and 0.027 g, respectively). An additional test was also performed in the absence of the catalyst; iii)four experiments were carried out at 90 °C, for 2 hours, in the presence of variable amounts of DMC (220, 110, 55 and 22 mmol; 18.54, 9.27, 4.63 and 1.85 mL, respectively).

The above described procedure was used also to investigate the recycle of the catalyst. Two recycling tests were performed. A first experiment was carried out at 90 °C, using a mixture of 1,2-propanediol (0.84 g,11 mmol), dimethyl carbonate (DMC) (4.75 g, 55mmol) and fresh [$P_{8,8,8,1}$][$MeOCOO^-$] (**5.1a**: 0.027 g,0.055mmol). Once the reaction was complete (2 hours), the excess of DMC and the co-product MeOH were removed by rotary evaporation. Then, propylene carbonate was distilled under vacuum (65 °C@200 Pa). To the residual catalyst **5.1a** was added a fresh aliquot of DMC (4.75 g) and **5.2a** (0.84 g). The mixture was then set to react at 90 °C for 2 hours. After the completion of the second reaction, and the subsequent removal of the DMC, MeOH and propylene carbonate, the procedure was repeated once again.

The above described procedure was used also to investigate transesterification reactions with diethyl carbonate (DEC)and with [$P_{8,8,8,1}$][HOCOO] (**5.1b**) as the catalyst. In particular: i) diethylcarbonate (DEC) (26 g, 220 mmol)was used in place of DMC; ii) [$P_{8,8,8,1}$][HOCOO] (**5.1b**: 0.025 g,0.055 mmol)was used in place of [$P_{8,8,8,1}$][$MeOCOO^-$] (**5.1a**). All the other conditions were kept unaltered.

The transesterification of DMC with 1,2-propanediolwas scaled up according to the following procedure. A 1L-jacketed reactor equipped with a mechanical stirrer and a reflux condenser, was charged with 1,2-propanediol **5.2** (200 g, 2.63 moles), DMC (475 g, 5.28 moles), and [$P_{8,8,8,1}$][$MeOCOO^-$] (**5.1a**: 6.47 g 13.2 mmoles). The mixture was stirred and heated at the reflux temperature for 1 hour. A methanol/DMC azeotropic mixture (130 mL) was then distilled and the resulting pale yellow liquid was

concentrated by rotary evaporation in order to remove the excess of DMC. The crude propylene carbonate **5.2a** was finally distilled at reduced pressure yielding 258 g of colourless liquid (96 %).

Ethanediol (**5.*3***). The procedure above described for 1,2-propanediolwas used also to investigate the transesterification of DMC with ethanediol (**5.3**).A mixture of ethanediol (11 mmol, 0.68 g), DMC (22 mmol or 55 mmol: 1.85 or 4.63 mL, respectively) and **5.1a** (0.055 mmol, 0.027 g) was set to react at 90 °C, under magnetical stirring, for 4 hours. An additional experiments was carried out by continuously removing the co-product methanol from the reactant mixture: this was done by heating the condenser (on top of the flask) at a constant temperature of 70 °C.

The reaction of DMC and ethanediol was also examined at a higher temperature of 120 °C. In this case, a mixture of **5.3** (11 mmol, 0.68 g), DMC (22 mmol, 1.85 mL) and **5.1a** (0.055 mmol, 0.027 g) was charged in a stainless steel autoclave (internal volume = 12 mL) equipped with a pressure gauge, a thermocouple for the temperature control, and a magnetic stirring bar. The autoclave was initially purged with nitrogen, closed, and finally heated electrically at the desired temperature for 4 hours.

1,3-Butanediol (**5.*4***). Procedures above-described for reactions at both the reflux temperature and at 120 °C (autoclave) were used to investigate the transesterification of DMC with 1,3-Butanediol (**5.4**). A mixture of 1,3-butanediol **5.4** (11 mmol, 0.99 g), DMC (55 or 220 mmol: 4.63 or 18.5 mL, respectively) and **5.1a** (0.055 mmol, 0.027 g) was used.

Other 1,3-diols (**5.*5*-5.*8***) *and 1,n-diols* (**5.*9***, **5.*10***). The procedure above described for 1,2-propanediolwas used to investigate also the transesterification of DMC with diols **5.5-5.10**. A mixture of the chosen diol (11 mmol), DMC (220 mmol, 19.8 g), and **5.1a** (0.055 mmol, 0.027 g) was set to react at 90°C in all cases.

Isolation and characterization of the products

The most abundant products of the investigated transesterification reactions, in particular cyclic carbonates **5.2a**, **5.3a**, and **5.8a**, and linear dicarbonates **5.4c**, **5.5c**, **5.6c**, **5.7c**, **5.9c**, and **5.10c**, were isolated and fully characterized by MS and NMR. Also, two

model mono-carbonate derivatives such as **5.5b** and **5.8b**, were isolated and characterized by NMR.

4-Methyl-1,3-dioxolan-2-one

Propylene carbonate (**5.2a**) was purified by distillation (65 °C @ 200 Pa) after reactions carried out under the conditions of entries 1 and 3 in Table 1. The corresponding yield were 92 and 86%, respectively. GC-purity was > 99% (colourless liquid). Mass spectrum (70 eV), m/z: 102 (M^+, 8%), 87 (30), 58 (16), 57 (100). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.90-4.80 (m, 1H); 4.55 (dd, J_1 = 8.3, J_2 = 7.8 Hz, 1H); 4.02 (dd, , J_1 = 8.4,J_2 7.2 Hz, 1H); 1.49 (d, J = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm): 154.9, 73.4, 70.7, 19.5.

1,3-Dioxolan-2-one

Ethylene carbonate (**5.3a**) was purified by distillation at reduced pressure (78 °C@200 Pa)after the reaction carried out under the conditions of entry 3 in Table 2. The isolated yield was 85%. GC-purity was > 99% (colourless liquid, solidified on standing at rt). Mass spectrum (70 eV), m/z: 88 (M^+, 100%), 73(2), 58 (10). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.5 (s, 4H).

Butane-1,3-diyl dimethyl dicarbonate

The product (**5.4c**) was purified by distillation at reduced pressure isolated (70 °C @ 120 Pa) after the reaction carried out under the conditions of Figure 4 (top). The isolated yield was72%. GC-purity was > 99% (colourless liquid). Mass spectrum(70 eV), m/z: 206 (M^+<1%), 162 (15), 135 (7), 131 (8), 130 (11), 115 (21), 104 (32), 103 (29), 98 (5), 91 (80), 87 (7), 85 (6), 77 (50), 72 (5), 71 (68), 59 (100), 57 (7), 56 (7), 55 (66), 54 (17). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.94-4.84 (m, 1H), 4.21 (t, J = 6.3 Hz, 2H), 3.78 (s+s, 6H), 2.05-1.87 (m, 2H), 1.32 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm): 150.6, 150.1, 67.0, 59.2, 49.6, 49.4, 30.0, 14.9.

2-Methyl propane-1,3-diyl dimethyl dicarbonate

The product (**5.5c**) was purified by distillation at reduced pressure isolated (70 °C@ 100 Pa) after the reaction carried out under the conditions of Figure 4 (bottom). The

isolated yield was75%. GC-purity was > 99% (colourless liquid). Mass spectrum (70 eV), m/z: 206 (M^+<1%), 135 (3), 130 (8), 117 (5), 102 (1), 98 (4), 91 (23), 87 (5), 86 (4), 85 (3), 77 (19), 73 (3), 72 (6), 71 (100), 59 (60), 57 (4), 56 (4), 55 (35), 54 (14), 47 (11), 45 (47), 43 (11), 42 (20), 41 (29), 39 (13). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.11-4.08 (m, 4H), 3.78 (s, 6H), 2.31-2.16 (m, 1H), 1.02 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.5, 68.8, 54.5, 32.4, 13.2. Anal. Calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.55; H, 6.87.

3-Hydroxy-2-methylpropyl methyl carbonate

The product (**5.5b**) was obtained by the following procedure. A mixture of **5.5** (991 mg, 11 mmol), DMC (18.5 mL), and $[P_{8,8,8,1}][OCO_2Me]$ in a 1:20:0.005 molar ratio, respectively, was set to react at 90 °C, for 10 min. Then, aq. HCl(5%, 1 mL) was added. DMC and methanol were removed at reduced pressure. The resulting oily mixture was subjected to FCC on silica gel (eluant: diethyl ether). The title compound (**5.5b**) was so isolated as a colorless liquid (12%). Mass spectrum(70 eV), m/z: 148 (M^+<1%) 77 (100%), 73 (4), 72 (8), 71 (13), 59 (21), 57 (24), 55 (17), 45 (19), 43 (19), 42 (35), 41 (31), 40 (4), 39 (16). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.22-4.06 (m, 2H), 3.78 (s, 3H), 3.63-3.48 (m, 2H), 2.10-1.97 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 156.1, 69.8, 64.1, 54.7, 35.4, 13.4. Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.59; H, 8.20.

Propane-1,3-diyl dimethyl dicarbonate

The product (**5.6c**) was purified by distillation at reduced pressure (80 °C@200 Pa) after the reaction carried out under the conditions of entry 2 in Table 3. The isolated yield was 85%. GC-purity was > 99% (colourless liquid). Mass spectrum(70 eV),m/z: 192 (M^+<1%) 135 (3), 117 (11), 116 (14), 103 (6), 91 (51), 77 (21), 73 (16), 72 (50), 71 (34), 59 (100), 58 (4), 57 (46),55 (3), 47 (15), 45 (86), 44 (4), 43 (12), 42 (21), 41 (47), 39 (10). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.24 (t, *J* = 6.2 Hz, 4H), 3.78 (s, 6H), 2.04 (p, *J* = 6.2 Hz, 2H).^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.4, 64.0, 54.5, 27.8.

2,2-Dimethyl propane-1,3-diyl dimethyl dicarbonate

The product (**5.7c**) was purified by distillation at reduced pressure (68 °C@200 Pa) after the reaction carried out under the conditions of entry 4 in Table 3. The isolated yield was 70%. GC-purity was > 99% (colourless liquid). Mass spectrum(70 eV), m/z: 220 (M^+<1%), 135 (3), 132 (6), 131 (84), 91 (9), 87 (44), 85 (25), 77 (14), 74 (4), 71 (11), 69 (51), 68 (64), 67 (6), 59 (68), 57 (6), 56 (22), 55 (100), 53 (5), 45 (38), 43 (10), 41 (35), 39 (12). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.97 (s, 4H), 3.78 (s, 6H), 1.00 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.5, 72.3, 54.6, 34.8, 21.2. Anal. Calcd. for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 49.15; H, 7.27.

4,4,6-Trimethyl-1,3-dioxan-2-one

The product (**5.8a**) was purified by sublimation at reduced pressure (~100 °C@200 Pa) after the reaction carried out under the conditions of entry 6 in Table 3. The isolated yield was 95%. GC-purity was > 99% (white solid). Mass spectrum(70 eV), m/z: 144 (M^+<1%), 87 (2), 86 (2), 85 (37), 83 (4), 69 (3), 67 (6), 59 (35), 58 (9), 57 (28), 56 (100), 55 (12), 53 (4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.63 (dqd, J_1 = 12.4, J_2 = 6.2, J_3= 3.2 Hz, 1H), 1.85 (ddd, J_1 = 26.1, J_2 = 14.2, J_3 = 7.6 Hz, 2H); 1.46 (s, 6H); 1.41 (d, J = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 149.5, 80.9, 72.3, 40.5, 29.9, 26.5, 21.1.Anal. Calcd. for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.38; H, 8.44.

4-Hydroxy-4-methylpentan-2-yl methyl carbonate

The product (**5.8b**) was obtained by the following procedure. A mixture of **5.8** (11 mmol), DMC (18.5 mL), and [$P_{8,8,8,1}$][OCO_2Me] in a 1:20:0.005 molar ratio, respectively, was set to react at 90 °C, for 10 min. Then, aq. HCl(5%, 1 mL) was added. DMC and methanol were removed at reduced pressure. The resulting oily mixture was subjected to FCC on silica gel (eluant: diethyl ether). The title compound (**5.8b**) was so isolated as a colourless liquid (10%).Mass spectrum (70 eV), m/z: 176 (M^+<1%), 119 (4), 85 (23), 83 (5), 77 (25), 67 (4), 59 (100), 58 (5), 57 (6), 55 (5), 45 (8), 43 (69), 42 (12), 41 (15). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 5.07-4.98 (m, 1H), 3.77 (s, 3H), 1.92 (dd, J = 15.0, 8.6 Hz, 1H), 1.65 (dd, J = 15.0, 3.4 Hz, 1H), 1.32 (d, J = 6.3 Hz, 3H), 1.25 (s, 3H), 1.24 (s, 3H). ^{13}C NMR

($CDCl_3$, 100 MHz) δ (ppm): 155.3, 73.0, 69.8, 54.5, 48.8, 29.8, 29.7, 21.6. Anal. Calcd. for$C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.58; H, 9.19.

Butane-1,4-diyl dimethyl dicarbonate

The product (**5.9c**) was isolated at the end of a reaction carried out by using a mixture of **5.9** (11 mmol, 1.00 g), DMC (220 mmol, 18.5 mL) and **5.1a** (0.05 mmol, 0.027 g). Once the transesterification was complete (90 °C, 4 hours), the excess of DMC and the co-product methanol removed by rotary evaporation. The final product was then distilled at reduced pressure (65 °C@80 Pa). To avoid the solidification of the distillate, the condenser was kept at 50 °C throughout the distillation. The title compound **5.9c** quickly solidified on standing at rt. (72%, white solid; mp: 59-60°C). GC-purity was > 99%. Mass spectrum (70 eV), m/z: 206 (M^+<1%), 135 (14), 131 (5), 130 (8), 117 (19), 103 (4), 102 (66), 91 (42), 77 (41), 71 (31), 59 (73), 58 (28), 57 (4), 59 (73), 58 (28), 57 (4), 56 (4), 55 (63), 54 (100). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.20-4.13 (m, 4H), 3.77 (s, 6H), 1.79-1.74 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.7, 67.3, 54.7, 25.1.

Hexane-1,6-diyl dimethyl dicarbonate

The product(**10c**)was isolated at the end of a reaction carried out by using a mixture of **10** (11 mmol, 1.30 g), DMC (220 mmol, 18.5 mL) and **1a** (0.05 mmol, 0.027 g). Once the transesterification was complete (90 °C, 4 hours), the excess of DMC and the co-product methanol removed by rotary evaporation. The final product was then distilled at reduced pressure (66 °C@80 Pa). To avoid the solidification of the distillate, the condenser was kept at 50 °C throughout the distillation. The title compound **10c** quickly solidified on standing at rt. (78%, white solid; mp: 50-51 °C). GC-purity was > 99%. Mass spectrum (70 eV), m/z: 234 (M^+<1%)130 (2), 117 (5), 99 (4), 91 (9), 83 (35), 82 (100), 81 (11), 79 (3), 77 (34), 71 (11), 69 (5), 68 (6), 67 (82), 59 (32), 58 (4), 56 (4), 55 (45), 54 (67), 53 (4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.13 (t, J = 6.6 Hz, 4H), 3.77 (s, 6H), 1.72-1.62 (m, 4H), 1.45-1.36 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.8, 67.9, 54.6, 28.5, 25.3.Anal. Calcd. for$C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.31; H, 7.71.

9.6. On-water modification of FAMEs to improve cold flow properties of biodiesel

Experiments at high temperature, unless otherwise stated, were performed in a semi-automated autoclave system (AMTEC-Slurry Phase Reactor-SPR16), equipped with sixteen stainless steel 15 mL reactors and automated sampling under reaction conditions. All reactors were connected via a valve system with gas and liquid supply and equipped with individually adjustable stirring (magnetic stirring bars – 500 to 2000 rpm) and heating (external electrical heating jacket – up to 220 ºC)

9.6.1. Diels-Alder reactions of oleic acid methyl ester (OAME)

9.6.1.1. Reactions between OAME and methyl sorbate

Oleic acid methyl ester (OAME; 1.02 ml, 3.00 mmol) and methyl sorbate (0.78 ml, 6.00 mmol) were loaded into an autoclave, and the chosen solvent was added (toluene, 2.0 ml, or water, 4.0 ml). When an acidic catalysis was tested, PTSA was added to the mixture (44 mg, 0.26 mmol). The mixture was then heated to the desired reaction temperature (180 °C) and maintained under stirring (800 rpm) for the desired reaction time. After that the stirring was stopped while the autoclave was cooled down to room temperature and successively vented. When the reactions were performed in organic solvent, a sample was directly taken from the mixture and analysed at the NMR and at the GC-MS. When the reactions were performed in water, the mixture was extracted with ethyl acetate, concentrated at the rotary evaporator, and then sampled.

9.6.1.2. Reactions between OAME and cyclopentadiene

Oleic acid methyl ester (OAME; 1.02 ml, 3.00 mmol) and cyclopentadiene (cp; 1.01 ml, 12.00 mmol) were loaded into an autoclave, and the chosen solvent was added (toluene, 2.0 ml, or water, 4.0 ml). When an acidic catalysis was tested, PTSA was added to the mixture (44 mg, 0.26 mmol). The reaction was then performed and sampled as already described above.

9.6.1.3. Reactions between OAME and furane

Oleic acid methyl ester (OAME; 1.02 ml, 3.00 mmol) and furane (ml, 6.00 mmol) were loaded into an autoclave, and the chosen solvent was added (toluene, 2.0 ml, or water, 4.0 ml). When an acidic catalysis was tested, PTSA was added to the mixture (44 mg, 0.26 mmol). The reaction was then performed and sampled as already described above.

9.6.2. Linoleic acid conjugation

9.6.2.1. Reactions carried out in ethylene glycol

Linoleic acid (0.25 g, 0.87 mmol), sodium hydroxide (0.48 g, 12 mmol) and ethylene glycol (4.0 ml) were loaded into an autoclave, successively assembled into the SPR16 apparatus. The mixture was then heated to the desired temperature (160 or 200 °C) and maintained under stirring (600 rpm) for 30 minutes. After that the stirring was stopped while the autoclave was cooled down to room temperature and successively vented. The mixture was recovered, dissolved in water (30 ml) and neutralised with H_2SO_4 1M. It was then extracted three times with hexane; the hydrocarburic layer was collected and concentrated. A sample was taken from the mixture and analysed at the NMR. The mixture was then esterified in methanol (using PTSA as a catalyst) by heating at reflux for 4 hours, and analysed at the GC-MS.

9.6.2.2. Reactions carried out in water

In a typical example, linoleic acid (0.25 g, 0.87 mmol), sodium hydroxide (0.48 g, 12 mmol) and water (4.0 ml) were loaded into an autoclave, successively assembled into the SPR16 apparatus. The mixture was then heated to the desired temperature (160, 180, 200 and 220 °C) and maintained under stirring (600 rpm) for the desired reaction time (30, 60 or 90 minutes). After that the stirring was stopped while the autoclave was cooled down to room temperature and successively vented. The mixture was recovered, neutralised with H_2SO_4 1M and extracted three times with hexane (3x15 ml). The hydrocarburic layer was collected and concentrated. A sample was taken from the mixture and analysed at the NMR. The mixture was then esterified in methanol (using PTSA as a catalyst) by heating at reflux for 4 hours. It was then washed with saturated

aqueous sodium bicarbonate, brine and water. The organic layer was concentrated and analysed at the GC-MS.

Effect of the base amount

A series of experiments were carried out reducing progressively the amount of sodium hydroxide. The procedure above was modified by using NaOH in the following amounts: 6.09 mmol (0.24 g), 2.61 mmol (0.10 g) and 0.87 mmol (35 mg). Water was added (4.0 ml), the mixture was heated to 220 °C and maintained under stirring (600 rpm) for 90 minutes. The work-up and the analyses were done as already described.

Small scale-up

Linoleic acid (0.75 g, 2.67 mmol), sodium hydroxide (0.32 g, 8.01 mmol) and water (4.0 ml) were loaded into an autoclave. The mixture was then heated to 220 °C and maintained under stirring (600 rpm) for 90 minutes. The work-up and the analyses were done as already described.

9.6.3. CLAME isomerisation to *t,t*-CLAME

9.6.3.1. Isomerisation mediated by iodine

CLA (1.0 g, 3.57 mmol) was dissolved in hexane (50 ml), a crystal of iodine (8 mg) was added and the stirred mixture was exposed to sunlight for 6 hours. The mixture was then recovered, washed with aqueous sodium thiosulfate 0.1 M and water. The organic layer was concentrated; a sample was taken and analysed at the NMR. The mixture was then esterified in methanol (using PTSA as a catalyst) by heating at reflux for 4 hours. It was then washed with saturated aqueous sodium bicarbonate, brine and water. The organic layer was concentrated and analysed at the GC-MS.

9.6.3.2. Isomerisation mediated by sulfur

CLA was esterified to its methyl ester (CLAME) by heating at reflux in methanol for 4 hours, using PTSA as a catalyst. The mixture was then washed with saturated aqueous sodium bicarbonate, brine and water. The organic layer was concentrated and analysed at the GC-MS. CLAME (0.5 g, 1.70 mmol), ethyl acetate (4 ml) and sulphur powder (20 mg) were loaded into an autoclave. The mixture was then heated to 200 °C

and maintained under stirring (600 rpm) for 3 hours. The mixture was recovered and concentrated, then analysed both at the GC-MS and at the NMR.

9.6.4. Diels-Alder reactions between CLAME and dimethyl fumarate in presence of sulphur as isomerising agent.

CLAME (250 mg, 0.85 mmol), dimethyl fumarate (135 mg, 0.94 mmol) and water (4.0 ml) were loaded into a glass reactor (max pressure = 10 bar). The latter was heated, by dipping in an oil bath, to the desired temperature (80 or 120 °C) and maintained under stirring (800 rpm) for 3 hours. The mixture was extracted with ethyl acetate (3x5 ml) concentrated, and analysed both at the GC-MS and at the NMR.

9.6.5. Diels-Alder reactions between *t,t*-CLAME and dimethyl fumarate

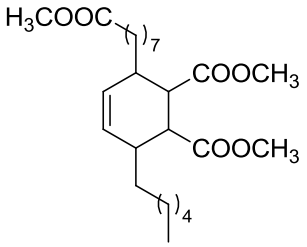
9.6.5.1. Reactions carried out in solvent

t,t-CLAME (250 mg, 0.85 mmol), dimethyl fumarate (135 mg, 0.94 mmol) and the chosen solvent (water or ethyl acetate, 4.0 or 2.0 ml respectively) were loaded into an autoclave, successively assembled into the SPR16 apparatus. The mixture was then heated to the desired temperature (120 or 150 °C) and maintained under stirring (800 rpm) for the desired reaction time (3 or 6 hours).

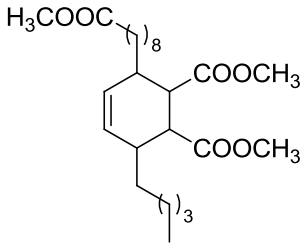
9.6.5.2. Reactions carried out in neat conditions

t,t-CLAME (250 mg, 0.85 mmol) and dimethyl fumarate (135 mg, 0.94 mmol) were charged into a r.b. flask. The mixture was then heated to the desired temperature (120 or 150 °C) and maintained under stirring (800 rpm) for the desired reaction time (3 or 6 hours).

Dimethyl 3-hexyl-6-(8-methoxy-8-oxooctyl)cyclohex-4-ene-1,2-dicarboxylate and dimethyl 3-(9-methoxy-9-oxononyl)-6-pentylcyclohex-4-ene-1,2-dicarboxylate (6.1)



dimethyl 3-hexyl-6-(8-methoxy-8-oxooctyl) cyclohex-4-ene-1,2-dicarboxylate



dimethyl 3-(9-methoxy-9-oxononyl)- 6-pentylcyclohex-4-ene-1,2-dicarboxylate

The mixture of the title compounds was isolated from a reaction set up as follows. t,t-CLAME (250 mg, 0.85 mmol), dimethyl fumarate (135 mg, 0.94 mmol) and water (4.0 ml) were loaded into an autoclave, successively assembled into the SPR16 apparatus. The mixture was then heated to 120 °C and maintained under stirring (800 rpm) for 3 hours. Successively it was recovered, diluted in water (10 ml) and extracted three times with diethyl ether (3x10 ml). The organic layer was concentrated at the rotary evaporator. The compounds **6.1** were isolated through flash column chromatography on silica gel (eluent: hexane:ethyl acetate = 6:1) as a pale yellow liquid. Yield 60%.

The title compounds were isolated also by the following reaction. t,t-CLAME (250 mg, 0.85 mmol) and dimethyl fumarate (135 mg, 0.94 mmol) were charged into a r.b. flask, closed by a glass stopper. The flask was dip, up to the edge of the neck, in an oil bath at the temperature of 120 °C, for a reaction time of 3 hours. Eventual crystals of dimethyl fumarate formed on the stopper were scratched down in the reaction mixture during its course. The compounds 6.1 were isolated through f.c.c. as already described. Yield 70%.

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm):

9.6.6. DSC experiments

DSC experiments were carried out in a TA 2920 Modulated DSC. Samples (8 to 10 mg) were weighed into an aluminium pan and the container hermetically sealed. Each sample was measured for two cycles of heating to 70 °C and cooling to −50 °C at 5 °C min^{-1}, with the sample held isothermally for 10 minutes in between heating and cooling runs and purge gas set at 40 ml min^{-1} nitrogen. The acquired diagrams are shown in the appendix.

9.7. On-water catalysis of Diels-Alder reactions: influence of the structure of the reagents

All reactions were conducted under air in 20 mL screw-top vials that had been washed in distilled water and air dried. Water was triply distilled and stored under air. D_2O (99.9%) was purchased from Aldrich chemical company and used without further purification. All other chemicals, the synthesis of which is not reported, were purchased from commercial sources and used as received. On-water, on-D_2O, and in solvent reactions were performed with vigorous stirring (1100 rpm) on a hotplate stirrer, with replicate reactions being stirred concurrently on the same instrument. At-water and neat reactions were performed with gentle (150 rpm) stirring. Reactions involving water were directly extracted with deuterated chloroform ($CDCl_3$) and analysed at the NMR, whereas neat reactions and reactions in solvents were sampled, diluted in $CDCl_3$ and then analysed.

9.7.1. Diels-Alder reactions between sorbyl acetate and maleimides

9.7.1.1. Synthesis of the starting materials

Sorbyl alcohol (trans,trans-2,4-hexadien-1-ol)

Lithium aluminium hydride (2.00 g, 52.64 mol) was suspended in 60 mL of dry diethyl ether at 0 °C while methyl sorbate (4.0 g, 31.71 mol) in 20 mL of ether was added dropwise. After 3 h 10% ammonium sulfate solution (20 mL) was added, and the solution was filtered and concentrated. The crude sorbyl alcohol was pure enough to be used in the next step without further purification. Yield of the crude = 96%.

Sorbyl acetate (trans,trans-hexa-2,4-dien-1-yl acetate)

Sorbyl alcohol (1.20 g, 12.23 mmol) was dissolved in dichloromethane (35 ml), together with triethylamine (2.22 ml, 15.90 mmol). Acetyl chloride (0.96 ml, 13.45 mmol) was added dropwise to the stirred mixture. The final mixture was recovered and washed with a saturated aqueous bicarbonate, brine and water. The organic layer was

then concentrated at the rotary evaporator. Sorbyl acetate was purified via f.c.c. on silica gel (eluent: hexane:ethyl acetate = 6:1). Final yield = 90%.

9.7.1.2. Diels-Alder reactions between sorbyl acetate and N-phenylmaleimide

Sorbyl acetate (SA; 56 mg, 0.4 mmol) and *N*-phenylmaleimide (NPM; 69 mg, 0.4 mmol) were charged into a screw-top vial. Water (or in alternative D_2O), when it was used, was then added (4.0 ml). All the reactions were performed at 30 °C, and stirred as described in the general part. Set of reactions were stopped at different reaction times, in order to build the kinetic profiles corresponding to the different reaction media.

9.7.1.3. Diels-Alder reactions between sorbyl acetate and N-butylmaleimide

Sorbyl acetate (SA; 56 mg, 0.40 mmol) and *N*-butylmaleimide (NPM; 61 mg, 0.40 mmol) were charged into a screw-top vial. Water (or in alternative D_2O), when it was used, was then added (4.0 ml). All the reactions were performed at 25 °C, and stirred as described in the general part. Set of reactions were stopped at different reaction times, in order to build the kinetic profiles corresponding to the different reaction media.

9.7.2. Diels-Alder reactions between cyclopentadiene and alkyl acrylates

Fresh distilled cp (40 mg, 0.60 mmol) and the chosen acrylate (ethyl acrylate, 120 mg, 1.20 mmol; tert-butyl acrylate 85 mg, 66 mmol; 2-Ethylhexyl acrylate, 111 mg, 0.6 mmol) were charged into a screw-top vial. Water (or in alternative D_2O), when it was used, was then added (4.0 ml). All the reactions were performed at 25 °C, and stirred as described in the general part. Set of reactions were stopped at different reaction times, in order to build the kinetic profiles corresponding to the different reaction media.

9.7.3. Diels-Alder reactions between cyclopentadiene and alkyl vinyl ketones

9.7.3.1. Synthesis of the starting materials

1-octene-3-ol (7.2c-OH)

1-Hexanal (1.0 g, 19.98 mmol) was dissolved in THF (50 ml). A solution of vinyl magnesium bromide in THF (16.98 ml) was added dropwise at 25 °C. Once the adding

was finished, the mixture was kept at 0 °C for 1 hour, then quenched with saturated aqueous ammonium chloride. After further washing with brine and water, the organic layer was collected and concentrated. The crude 1-octene-3-ol was pure enough to be used in the next step without further purification. Yield of the crude = 95%.

2-ethyl-1-hexen-3-ol (7.3c-OH)

The title compound was synthesised, starting from 2-ethyl butanal (1.50 g, 19.98 mmol), as already described for **7.2c-OH**. The crude 2-ethyl-1-hexen-3-ol was pure enough to be used in the next step without further purification. Yield of the crude = 90%.

1-decene-3-ol (7.4c-OH)

The title compound was synthesised, starting from octanal (2.56 g, 19.98 mmol), as already described for **7.2c-OH**. The crude 1-decene-3-ol was pure enough to be used in the next step without further purification. Yield of the crude = 90%.

Pentyl vinyl ketone (1-octene-3-one) (7.2c)

A mixture of PCC (0.84 g, 39.06 mmol) and silica gel (2.00 g) was added to a r.b. flask (250 mL) and 30 mL of methylene chloride was added. **7.2c-OH** (0.50 g, 39.06 mmol) were added to the stirred the orange suspension, which slowly turned dark brown. Stirring was maintained for 1 hour, then the mixture was filtered on a celite pad. The filtrate was concentrated under vacuum and the resulting oil was diluted with ether (15 mL), washed with water (2x10 ml), and finally washed with saturated aqueous sodium chloride (15 mL). The organic layer was then dried over anhydrous sodium sulfate. Concentration of the ether solution afforded **7.2c** which was pure enough to be used without further purification. Yield of the crude = 53%.

2-ethyl-1-hexen-3-one (7.3c)

The title compound was synthesised, starting from **7.3c-OH** (0.50 g, 39.06 mmol), as already described for **7.2c**. The crude 2-ethyl-1-hexen-3-one (**7.3c**) was pure enough to be used in the next step without further purification. Yield of the crude = 43%.

1-decene-3-one (7.4c)

The title compound was synthesised, starting from **7.4c-OH** (0.61 g, 19.98 mmol), as already described for **7.2c**. The crude 1-decene-3-one (**7.4c**) pure enough to be used in the next step without further purification. Yield of the crude = 60%.

9.7.3.2. Diels-Alder reactions between cyclopentadiene and ethyl vinyl ketone

Fresh distilled cp (40 mg, 0.60 mmol) and ethyl vinyl ketone (51 mg, 0.60 mmol) were charged into a screw-top vial. All the reactions were performed at 25 °C, and stirred as described in the general part. Various reaction media were tested: water (4.0 ml), saturated LiCl aqueous solution (4.0 ml), D_2O (4.0 ml), at-water (4.0 ml), $CHCl_3$ (2.0 ml), CH_3OH (2.0 ml), as well as neat conditions. Set of reactions were stopped at different reaction times, in order to build the kinetic profiles corresponding to the different reaction media.

9.7.3.3. Diels-Alder reactions between cyclopentadiene and other vinyl ketones

Fresh distilled cp (40 mg, 0.60 mmol) and the chosen vinyl ketone (51 mg, 0.60 mmol) were charged into a screw-top vial. All the reactions were performed at 25 °C, and stirred as described in the general part. Various reaction media were tested: water (4.0 ml), D_2O (4.0 ml), at-water (4.0 ml), as well as neat conditions. Set of reactions were stopped at different reaction times, in order to build the kinetic profiles corresponding to the different reaction media.