

Kinetic Parameter Estimation of Solvent-Free Reactions Monitored by ^{13}C NMR Spectroscopy, A Case Study: Mono- and Di-(hydroxy)ethylation of Aniline with Ethylene Carbonate

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ABSTRACT: The kinetics of solvent-free reactions can be followed in situ by ^{13}C nuclear magnetic resonance (NMR) spectroscopy, provided that the reaction mixture can be maintained liquid at the monitoring temperature. The pros and cons of the technique and the correct translation of the signal intensities into concentrations are discussed. A good model for this investigation is the reaction of ethylene carbonate (**1**) with aniline (**2**) at 140°C , two alkylation products of N-mono- and N, N-bis-(2-hydroxy)ethylation of aniline form (compounds **3** and **4**, respectively). The overall reaction occurs with heavy volume shrinking, so that the physical as well as the chemical features evolve during the course of the process. The chemical evolution is described by the kinetic constants k_1 and k_2 of the two N-alkylation steps, the physical evolution by the time-dependent activity coefficients $\alpha(t)$. Two complementary procedures are utilized for the determination of these parameters. © 2011 Wiley Periodicals, Inc. *Int J Chem Kinet* 43: 154–160, 2011

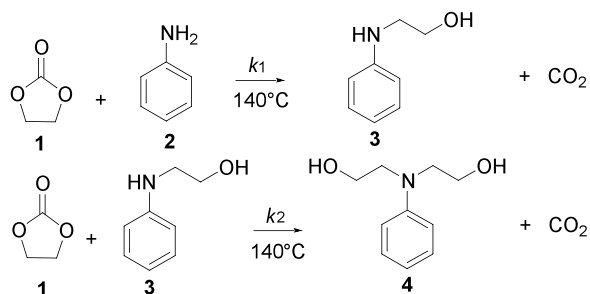
INTRODUCTION

The greenest way to confront the problem of reaction solvents is their elimination altogether. When one or both reagents are liquid, or mutually soluble, at the reaction and the monitoring temperature, the reaction

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Scheme 1

course can be adequately followed by ^{13}C nuclear magnetic resonance (NMR) spectroscopy. The advantages are clear: The highest possible concentrations ensure a swift acquisition of the signals, which are also usually well separated. Also the disadvantages are clear: quantitative estimation of the signal intensities is not very precise (the integration of the NMR signals is, among the NMR parameters, the one measured with the lowest accuracy), and the correspondence between the intensity of the signal and the relative number of nuclei that originate the signal is not strictly proportional (the rule of unitary molar extinction coefficient for NMR spectroscopy is not rigorously observed).

To these problems, an exquisitely physical problem must be added: in reactions performed in solution, the volume is buffered by the overwhelming presence of the solvent, whereas in solvent-free reactions the volume, and the associated properties, may drastically vary. Thus both chemical and physical features evolve during the reaction time. There follows the necessity of discriminating between the two contributions and to anchor the chemical parameters to a standard physical state. This necessity has been already recognized [1].

We have used the alkylation of aniline **2** by ethylene carbonate (EC) **1** (Scheme 1) as a model reaction to address these problems. In this reaction, CO_2 develops in both steps, a fact that should lead to a heavy volume variation. Contrary to a statement in the literature [2], we report here that this reaction occurs, also in the absence of solvent and of any catalyst, at an accessible temperature and within a reasonable time, first to yield *N*-2-hydroxyethylaniline **3** and then, with a 2:1 excess of **1**, *N,N*-bis(2-hydroxyethyl)aniline **4**.

RESULTS AND DISCUSSION

Reaction Conditions

Quantities of EC and of aniline that reproduce the 2:1 molar ratio are weighed at room temperature in a volumetric flask, resulting in EC and aniline concentrations of 9.13 and 4.61 mol L^{-1} . The correct volume

is transferred to a screw-cap NMR tube. The tube is then equipped with a sealed capillary, containing pure $[\text{D}_6]\text{DMSO}$, and blocked in a coaxial position by means of a Teflon spacer, for locking and homogeneity purposes. In our hands, and contrary to what stated [3], the quantity of deuterated substance, in a capillary with an inner diameter of 1.0 mm is sufficient for an acceptable lock level and for easy homogeneity shimming.

Scheme 1 shows that CO_2 develops in both reaction steps, a situation that is evinced from the bubbling observed in the NMR tubes when heated in the thermostated bath and that obliges to a periodic release of the tube pressure. As a consequence, and also because the reactions are of the condensation type, the volume of the reaction mixture shrinks during the reaction course.

To evaluate the volume changes, an auxiliary screw-cap NMR tube is charged with the same reacting mixture, but without capillary; both tubes are then subjected to the same reaction conditions.

The NMR measurements are run at 25°C in a Varian Unity 400-MHz spectrometer equipped with a reverse insert, not optimized for ^{13}C spectroscopy. Nevertheless, spectra with a good signal to noise ratio are collected with 32 scans and a relaxation time of 16 s, under the regime of an inverse-gated ^1H decoupling, to minimize nuclear Overhauser enhancement (NOE) effects.

The kinetics is run at 140°C in a thermostated silicon oil bath, hosting both tubes. In the first run, a volume expansion factor of 1.10 is observed on going from room temperature to 140°C, as directly measured with a gauge in the auxiliary NMR tube, and the concentrations of EC and aniline are then corrected to 8.30 and 4.19 mol L^{-1} , respectively. The reaction times are calculated from the moment when the tubes are dipped into the bath to the moment when they are lifted for the measurements, thus reasonably assuming that the heating time and the cooling time are similar, and that a negligible reaction advancement occurs at room temperature. The capillary-equipped tube is subjected to the NMR analysis; the volume change in the auxiliary tube is measured with a gauge. The volume change is shown later in Fig. 2.

The reaction is followed for 80 h of effective bath heating. The initial insurgence of *N*-2-hydroxyethylaniline **3** is observed, which is then almost totally replaced by *N,N*-bis(2-hydroxyethyl)aniline **4** (Scheme 1). The compounds are identified by the GC-MS analysis of the final reaction mixture, and the corresponding ^{13}C signals easily attributed.

It should be noted that the additions are chemospecific, as the nucleophilic attacks of aniline **2** or secondary aniline **3** occur exclusively at the β -carbon of

EC. Other noncatalyzed additions of aniline to EC or to other dialkyl carbonates (dimethyl and dibenzyl carbonates, respectively) have been reported [2,4], where the nucleophilic attacks at both the alkyl and carboxylic carbons are observed.

The Quantitative Evaluation of the ^{13}C Resonances

As already stated, the ^{13}C spectra are collected under the regime of ^1H inverse gated decoupling, with the aim of minimizing NOE effects. To overcome the limits of the numerical integration procedure of the spectrometer, we adopted the strategy of fitting the peaks into a combination of Gaussian and Lorentzian functions and to evaluate the analytical integration of this combination. The procedure requires a correct definition of the peaks, which is attained by registering the free induction decays (FIDs) with 32 K of memory, and transforming them under zero filling to 262 K and multiplication with the proper window function (the unshifted Gaussian function); proper phase and baseline corrections also must be performed. The fitting is computationally accomplished with the Levenberg–Marquardt method [5]. This procedure allows the correct estimation of the integrated value also of peaks, which are scantily over the spectrum noise. One example of this evaluation is shown in the Supporting Information.

The fit is most accurate when performed on a signal represented by an isolated singlet. It is always possible to detect isolated signals in ^{13}C spectra; they are, how-

ever, rare in ^1H spectra (in our case, only one substance is represented by an isolated singlet), where multiplets and signal overlaps are the rule.

The comparison within the series of subsequent spectra requires the individuation of an internal integration standard. This standard is recognized in the sum of the integrated signals of a moiety, which is present in a constant amount during the reaction course: the ortho carbons of the aniline ring of **2**, **3**, and **4**. Thus the integration of every peak in the spectrum set is multiplied by 4.19/sum, thereby returning the correct time-dependent peak intensities of reagents and products.

The NOE perturbation is reduced by the technique of inverse-gated decoupling, but not totally eliminated, a fact that is recognized in the first control spectrum (zero time spectrum), where the integration of the ethylenic carbons of EC **1** is slightly overestimated with respect to that of the ortho carbons of the aniline **2**. Thus this signal of EC in the control and subsequent spectra is correspondingly amended. The corrected integrated signals of the ortho carbons of **2**, **3**, and **4** and that of the ethylenic carbons of **1**, are then assumed to faithfully represent the variations of concentration of the involved species. The assumption proved correct, as demonstrated by the fact that the weighted sum of a *different* set of signals, those due to an ethylenic group [**1**, **3**, and **4** (twice)], remains constant for the whole reaction time (as shown in the Supporting Information). The time-dependent concentrations are graphically represented in Fig. 1.

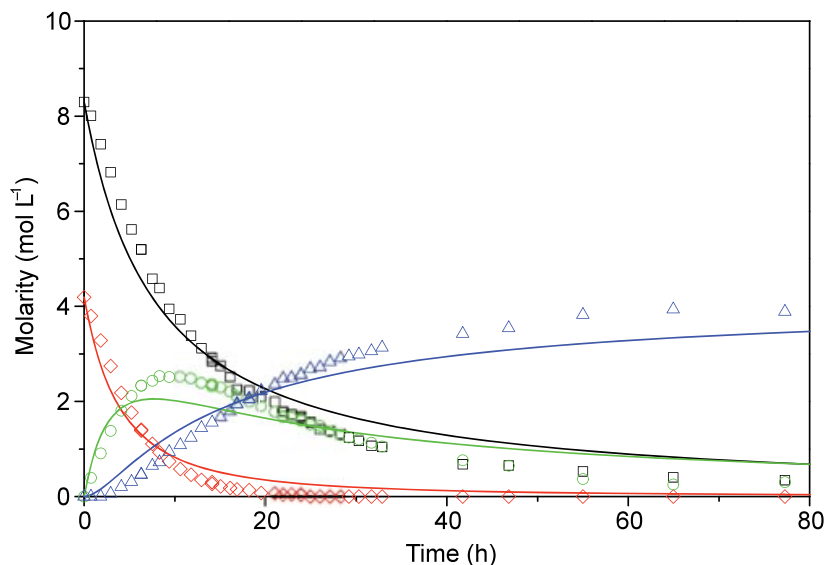


Figure 1 Time dependence of the molarities of EC **1** (\square), aniline **2** (\diamond), *N*-2-hydroxyethyl-aniline **3** (\circ), and *N,N*-bis(2-hydroxyethyl)-aniline **4** (Δ), normalized to the initial concentration of aniline **2**. The best fit of the differential equation system (1), obtained by the numerical Runge–Kutta integration and the Simplex search, is shown. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

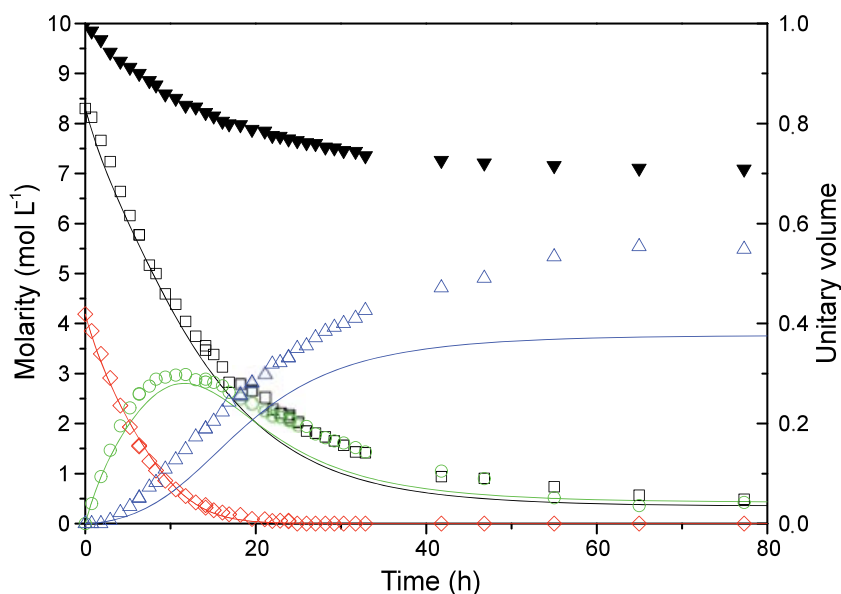


Figure 2 Symbols for compounds **1–4** as in Fig. 1 (left ordinate). The volume shrinking is represented by ▼ (right ordinate). The molarities are normalized according to the reaction volume. The best fit (obtained by the numerical Runge–Kutta integration and the Simplex search) of the differential equation system (1), with concentrations prefixed by the volume factor (2), is shown. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

This procedure assumes implicitly that the total amount of a reference carbon (the ortho carbons of the aniline rings) remains unchanged. On the other hand, the volume change implies an increment of the total amount, as detected by the measuring coil of the instrument probe. Consideration of the volume shrinkage brings about the time-dependent concentrations shown in Fig. 2. As shown in the following paragraph, this correction is not compatible with the system (1) of differential equations describing the reactions of Scheme 1.

The Evaluation of the Kinetic Parameters

The system of consecutive reactions shown in Scheme 1 is kinetically described by the system of differential equations (1).

$$\begin{aligned} d[\mathbf{1}]/dt &= -k_1[\mathbf{1}][\mathbf{2}] - k_2[\mathbf{1}][\mathbf{3}] \\ d[\mathbf{2}]/dt &= -k_1[\mathbf{1}][\mathbf{2}] \\ d[\mathbf{3}]/dt &= k_1[\mathbf{1}][\mathbf{2}] - k_2[\mathbf{1}][\mathbf{3}] \\ d[\mathbf{4}]/dt &= k_2[\mathbf{1}][\mathbf{3}] \end{aligned} \quad (1)$$

The analytical integration of this system is awkward. Actually, although this set is described in an exhaustive list of kinetic systems [6], no analytical integration is offered, but rather a treatment based on the stationary state approximation of **3** is described. This approxima-

tion is clearly not suited for our reaction system; therefore, we resorted to a numerical method, the Runge–Kutta integration of a system of ordinary differential equations [7]. This method gives the calculated concentrations of reagents and products at any measurement time, based on the equations and the parameters in (1), the initial concentrations, and the kinetic constants k_1 and k_2 . The sum of the squares of the residuals (the differences between experimental and calculated concentrations) is minimized with the Nelder–Mead Simplex search [8], by varying a selected set of parameters. In our case, the initial concentrations are precisely known and therefore kept unchanged, while the variation is applied to the kinetic constants.

The Fitting Trial of the Volume-Corrected Concentrations. Because of the volume shrinking, the monitoring solenoid of the NMR probe is sensing an increasing amount of matter (i.e., progressively higher concentrations). This apparent “creation” of matter cannot be accounted for by system (1) of differential equations that describes the chemistry. To include the component due to volume shrinking, all concentration terms in system (1) were divided by the factor V_t/V_0 ($V_0 = 1$). The Runge–Kutta procedure requires the knowledge of the volume shrinking at the experimental monitoring times but also at a number of intermediate times. We utilized the following equation:

$$V_t/V_0 = 0.7088 + [1 - 0.7088 \exp(-0.06711t)] \quad (2)$$

obtained from fitting of the experimental volume change represented by \blacktriangledown in Fig. 2.

No acceptable fit is achieved. We will show in the next section (where the volume correction is neglected) that the introduction of optimized time-dependent activity coefficients allows to reach a good fit. In the present case, this procedure is of no help. In fact, the results, shown in Fig. 2, indicate that the Runge–Kutta integration procedure refuses to calculate a cumulated concentration of aniline **2** and substituted anilines **3** and **4** greater than the initial concentration of **2**

The Fitting of the Volume Uncorrected Concentrations.

One alternative option is to calculate the concentrations with the Runge–Kutta integration procedure on the basis of the unamended system (1) and then correct the values by the measured volumes. A second alternative is to perform no correction and to assume no volume change (the concentration are normalized to a constant value). The two choices are logically and mathematically equivalent. We adopted the second one.

The result of the fitting is presented in Fig. 1. The inability of the best set of k_1 and k_2 to fit the experimental concentrations is evident. Because no other reactions than those illustrated in Scheme 1 can be conceived, we attribute the discrepancy to a heavy change of the physical environment during the reaction course, which depends on the volume change.

Thus, a time-dependent activity coefficient α must be applied to the concentrations, and while the concentrations will change because of the reaction kinetics, α will be a function of the reaction volume and of some property thereof, and, in the last instance, of time. An acceptable treatment would dictate that the coefficient be the same for all species. The functional form of this coefficient is unknown, but can, in any case, be expanded as a McLaurin series:

$$\alpha(t) = \alpha(0) + \alpha'(0)t + (\alpha''(0)/2!)t^2 + (\alpha'''(0)/3!)t^3 + \dots \quad (3)$$

For the reasons outlined below, the zero time coefficient can be put to 1 ($\alpha(0) = 1$), thus selecting the initial state as the standard physical state.

The expansion can be inserted into system (1), utilized in the Runge–Kutta numerical integration, and the parameters (k_1 , k_2 , $\alpha'(0)$, $\alpha(0)''$, etc.) optimized by the Simplex search. It turned out that, having put $\alpha(0) = 1$, only the first-order ($\alpha'(0)$) coefficient is necessary and sufficient for a quite good fit (Fig. 3). The results are $k_1 = 1.80 \times 10^{-2} \text{ L mol}^{-1} \text{ h}^{-1}$, $k_2 = 5.22 \times 10^{-3} \text{ L mol}^{-1} \text{ h}^{-1}$, $\alpha'(0) = 6.46 \times 10^{-2} \text{ h}^{-1}$, $\alpha''(0)/2$, and subsequent coefficients, negligible.

This result may, however, be misleading: covariance of the optimized parameters is not rigorously ruled out, so that different combinations of them may give equally acceptable fits. Thus no physical or chemical meaning can be associated with the optimized

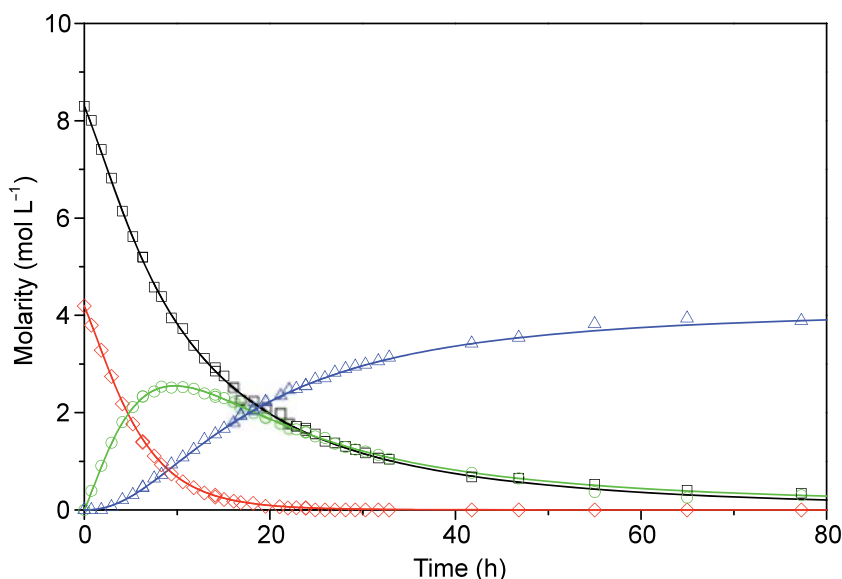


Figure 3 Symbols for compounds **1–4** as in Fig. 1. The numerical Runge–Kutta integration and the Simplex search are applied to differential equation system (1), although with concentrations prefixed by the unique time-dependent activity coefficient $\alpha(t)$, in the functional form (3). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

parameters, and an independent method for the evaluation of k_1 and k_2 must be looked for. It can be anticipated that one important finding of the Simplex search, the uniqueness of the activity coefficient $\alpha(t)$, valid for all involved species, will confer reliability to this method.

The k_1 parameter can be derived from the evaluation of the initial rates for the conversion of EC **1** and aniline **2**, which are equal:

$$d[\mathbf{1}] / dt = d[\mathbf{2}] / dt = -k_1[\mathbf{1}]_0[\mathbf{2}]_0 \quad (4)$$

These rates are usually determined by the slope of the straight line passing through the first experimental concentrations. In our case, an insufficient number of concentrations can be monitored, which are also biased by the time-dependent activity coefficient; therefore, we devised to take advantage of the procedure based on the Newton polynomial interpolation of the experimental data [9]. We selected an eighth-degree interpolation. The zero-order coefficient of the derivative is the first-order coefficient of the interpolation and is the only surviving coefficient at zero time, thus supplying the estimation of the initial rate. The procedure gives -0.58 and $-0.61 \text{ mol L}^{-1} \text{ h}^{-1}$ for the initial disappearance rates of **1** and **2**. The degree of similarity of the two values is a test for the reliability of the procedure. The average value divided by the initial concentrations $[\mathbf{1}]_0$ and $[\mathbf{2}]_0$ gives $k_1 = 1.71 \times 10^{-2} \text{ L mol}^{-1} \text{ h}^{-1}$. Because of the covariance biasing the Simplex search, the k_1 values obtained with the two methods can agree as for the order of magnitude only.

The evaluation of k_2 by this procedure is impossible. We can, however, evaluate the ratio k_2/k_1 at a singular time: when the concentration of **3** reaches a maximum. At this time

$$d[\mathbf{3}] / dt = k_1\alpha(t)^2[\mathbf{1}][\mathbf{2}] - k_2\alpha(t)^2[\mathbf{1}][\mathbf{3}] = 0$$

$$\text{and } k_2/k_1 = [\mathbf{2}] / [\mathbf{3}] \quad (5)$$

This singular time is recognized by fitting the points of **3** in an eighth-degree polynomial and calculating the concentrations of **3** from this polynomial, starting from time zero and for small time increments, until the calculated value starts to decrease. At this time (10.00 h) $k_2/k_1 = 0.25$. From the above-reported value of k_1 , $k_2 = 4.28 \times 10^{-3} \text{ L mol}^{-1} \text{ h}^{-1}$. Also the comparison between the k_2 values obtained by the two methods is poor, but the trend and the order of magnitude can at least be reproduced.

It is gratifying that similar rate constants are obtained when the methods are applied to the kinetics with volume-corrected concentrations. The fitting of

the concentrations of **1** and **2** to an eighth-degree polynomials gives -0.56 and $-0.57 \text{ mol L}^{-1} \text{ h}^{-1}$ for the respective initial disappearance rates, whence $k_1 = 1.62 \times 10^{-2} \text{ L mol}^{-1} \text{ h}^{-1}$. At the time when the concentration of **3** reaches a maximum, equation (5) is still valid, referring to a situation where the volume shrinking is the same for all species. The value of $k_2 = 3.56 \times 10^{-3} \text{ L mol}^{-1} \text{ h}^{-1}$ can be derived.

CONCLUSIONS

Under solvent-free conditions, both chemical and physical reasons may affect the reaction outcome. We have purposely chosen a reaction model where the physical changes are most relevant. Quite clearly, chemical parameters, as the kinetic constants, must refer to a standard physical state. And quite reasonably, the best choice for this state is the initial state.

Two different computational methodologies have been adopted, to recover these standard state kinetic constants. (a) The fitting of the experimental points into the integrated expression (either analytical or, as in our case, numerical) of the system of differential equations (1). An acceptable fit requires the inclusion of a time-dependent concentration coefficient, which is adequately chosen as having a unitary value at the standard state. The fact that the coefficient is unique and applicable to all involved species will validate the following alternative methodology. (b) The rate constant k_1 , which is "operative" at the standard state, can be deduced from the evaluation of the initial rate (by differentiations of the correct polynomial fittings of the reaction progress). The rate constant k_2 is given from the ratio k_2/k_1 measured at a singular state (when **3** is highest) different from the standard state.

The comparison of the kinetic constants obtained by the two methodologies is strongly biased by the covariance problem innate in the Simplex search. Thus procedure (b) should be adopted when trustworthy kinetic parameters are required for meaningful comparisons within a coherent panel of solvent-free reactions [10].

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