



Catalytic peptides in water: Bridging organocatalysis and enzyme catalysis

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Aqueous media offer a sustainable framework for catalysis, spanning the continuum from single amino acid-based organocatalysis to complex enzymatic systems. Within this landscape, catalytic peptides have emerged as a pivotal intermediary class. This field is rapidly expanding, driven by the inherent modularity of peptide sequences and advancements in synthetic methodology. Notably, the catalytic efficacy of these systems is inextricably linked to their folding and aggregation behavior in water. Investigating these peptide-based architectures provides critical insights into noncovalent catalytic networks, ultimately refining our understanding of enzymatic mechanisms and facilitating the design of biomimetic catalysts.

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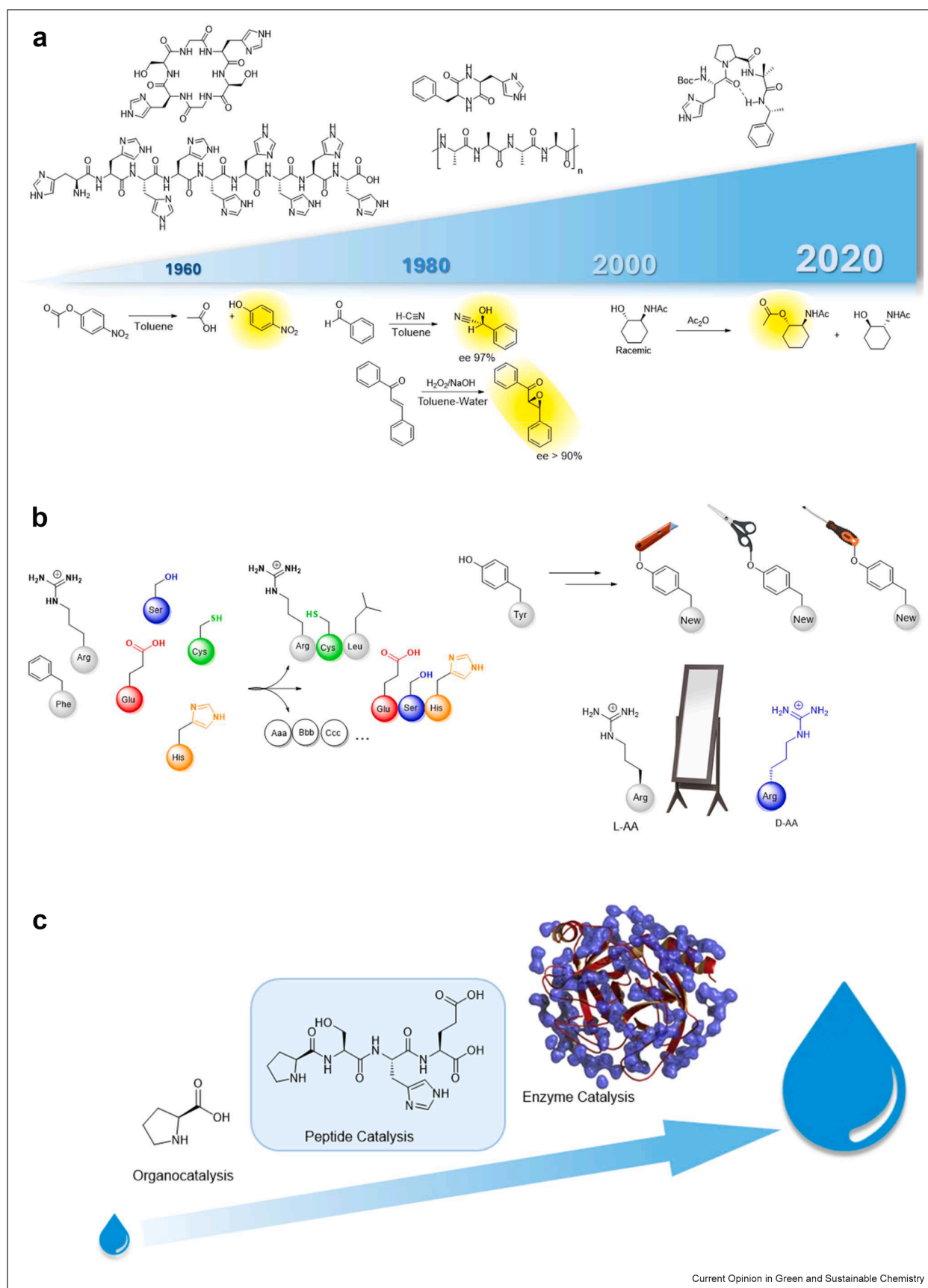
Introduction

Enzymes are catalysts *par excellence*, with orotidine 5'-phosphate decarboxylase as one of the most proficient catalysts known to date able to perform the corresponding reaction within 18 ms, while without enzyme, it requires 78 million years, corresponding to a $k_{\text{cat}}/k_{\text{uncat}}$ of approximately 10^{17} [1]. Enzymes exhibit exquisite substrate specificity and chemoselectivity, regioselectivity, and enantioselectivity, inspiring the design of biomimetic artificial enzymes. Enzymes are also characterized by inherent fragility, high production costs, and demanding storage requirements. To address these

limitations, researchers have explored the potential of short peptides as biocatalytic alternatives since they maintain stability at elevated temperatures and exhibit high functionality within organic solvents. Furthermore, their scaffolds allow for precise, quantitative modifications—such as the incorporation of nonproteinogenic amino acids at multiple sites—to fine-tune catalytic activity. Ultimately, their reduced molecular weight ensures they are more cost-effective to synthesize at scale and significantly easier to store than complex proteins. Earliest examples of synthetic peptide catalysis date back to 1960s with the contributions of Katchalski [2] and Sheehan [3] who reported efficient hydrolysis of *p*-nitrophenyl acetate as a peptide model substrate using poly-L-histidine and a cyclic hexapeptide, respectively (Figure 1a). However, the extension of peptide catalysis to stereoselective transformations required several decades to mature. Key milestones include the reports by Inoue on the asymmetric hydrocyanation of benzaldehyde using cyclic dipeptides [4] and the Juliá-Colonna asymmetric epoxidation of electron-deficient alkenes catalyzed by poly-Ala [5,6]. These contributions effectively inaugurated the field of peptide-based asymmetric organocatalysis. The field underwent a significant expansion during the 2000s, driven by the implementation of short, well-defined peptide sequences bearing constrained structures with reduced conformational flexibility. This enhances directed steric interactions and provides noncovalent interactions like hydrogen bonding to ensure high enantioselectivities [7]. Over the past two decades, peptide catalysis has emerged as a premier strategy for stereoselective synthesis, offering several modular advantages over traditional catalyst classes (Figure 1b). The field of research has been reviewed several times until recently [8–11], documenting its application across a diverse repertoire of chemical transformations.

Despite these advances, the field has predominantly relied on organic media. This historical reliance stems from a nascent focus on green chemistry during the field's inception, coupled with the inherent solubility challenges of peptide catalysts and hydrophobic substrates in aqueous systems. More recently, the integration of green chemistry metrics has redefined catalytic research; since solvents constitute the primary source of waste, transitioning to aqueous media is now a priority. Specifically, micellar catalysis [12,*13] utilizing

Figure 1



designer surfactants [14] has emerged as a robust alternative to conventional organic solvents, bridging the gap between fundamental academic research and the industrial synthesis of active pharmaceutical ingredients [15,16].

Elucidating the fundamental features of peptide catalysis in aqueous media is essential for advancing our understanding of enzymatic mechanisms. In water, traditional noncovalent interactions—such as hydrogen bonding and electrostatic forces, which predominate in organic solvents—are significantly attenuated. Consequently, the exploitation of both classical and nonclassical hydrophobic effects emerges as a primary strategy for driving molecular recognition and catalytic activation.

This perspective highlights recent advancements in peptide-based catalysis within aqueous media, elucidating the strategic objectives, innovative methodologies, and the transformative potential of these systems. This work establishes a conceptual bridge between small-molecule organocatalysis [17,*18]—traditionally centered on individual amino acids [19]—and the sophisticated architectural efficiency of enzymatic catalysis (Figure 1c) inspiring future integration of biomimetic scaffolds catalysis in water.

Results and discussion

The earliest examples of peptide catalysis in water date back to 2000's exploiting the use of cosolvents [20], micellar media [21], or later endowing peptides with hydrophobic side chains to promote self-assembly [22]. Since then, the field has evolved through several sophisticated strategies like (i) the biomimetic replication of enzymatic active sites, (ii) rational [23] and combinatorial approaches [24] such as yeast and phage display [25,26] for high-throughput library screening, and (iii) the utilization of supramolecular self-assembly to impose conformational rigidity and mitigate solubility constraints. All these approaches have been recently reviewed [27–*31]. In particular, self-assembly of peptides turned out to be highly beneficial favoring rate acceleration of hundreds of times, thanks to localized concentration effects and unique nanoenvironments [32,33]. A prominent example is the tripeptide **H-DPro-Pro-Glu-NHC₁₂H₂₅** which catalyzes stereoselective aldol condensations with high efficacy across diverse aqueous matrices, ranging from environmental water samples to complex cell lysates [*34], preserving

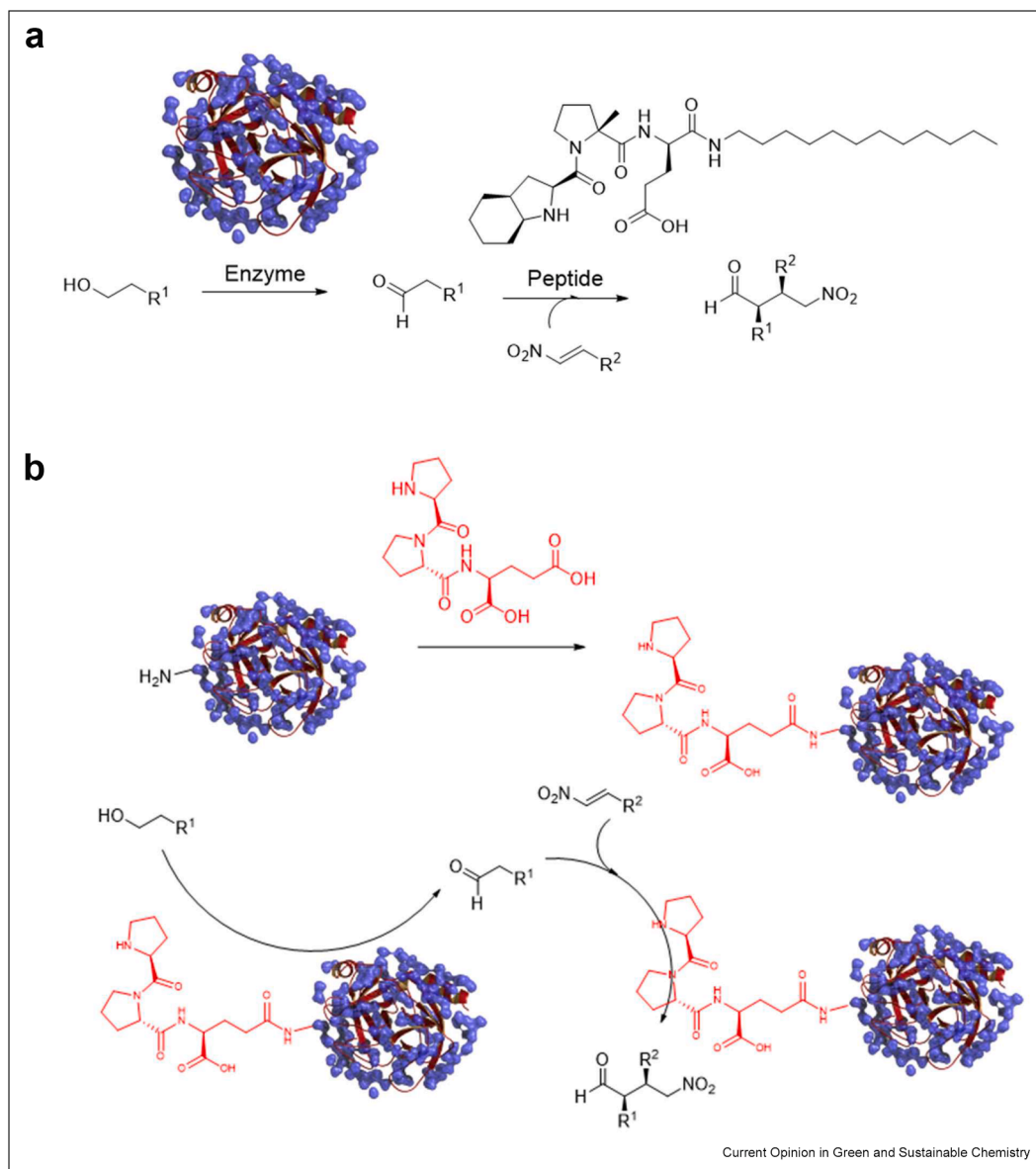
the activity in the presence of competing biomolecular classes, including lipids, carbohydrates, vitamins, and antioxidants. Short catalytic peptides typically necessitate conjugation with auxiliary motifs to modulate their self-assembly and enhance aqueous solubility. In a representative approach, the dipeptide **H-Pro-Ala** was conjugated at the C terminal to poly(poly(ethylene glycol) methyl ether methacrylate) and hydrophobic poly(methyl methacrylate) (PMMA) macrochain transfer agents. The resulting amphiphilic polymers displayed robust aldolase-mimetic activity in the condensation of cyclohexanone with 4-nitrobenzaldehyde. These biocatalytic assemblies achieved high conversions and excellent enantioselectivities up to 94% *ee* in monophasic aqueous–organic media enabling also catalyst recycling [35]. The tripeptide scaffold pioneered by Wennemers et al., originally optimized for organic media [36,37], has been strategically adapted for aqueous environments. The Pro-Pro-Glu catalytic motif was functionalized at the C-terminus, with spacers bearing complementary nucleobases, such as thymine and adenine [38]. The resulting nucleobase-driven self-assembly promotes the formation of supramolecular fibrils, which serve as a structured platform for enhanced catalytic performance. These fibrillar architectures provide a privileged microenvironment that significantly boosts both chemical yields and diastereoselectivity for transformations conducted in water.

Recent advances in chemoenzymatic tandem catalysis have demonstrated the efficacy of tripeptide–enzyme cooperatives in aqueous media. For instance, a tripeptide catalyst was integrated with an oxidase from *Arthrobacter chlorophenolicus* (AcCO6) to facilitate the one-pot oxidation of primary alcohols followed by an enantioselective aldol condensation with nitroolefins, achieving high yields and stereocontrol [*39]. The success of this chemobiocatalytic relay was attributed to the amphiphilic architecture of the peptide **H-Oic-D^αMep-DGlu-NHC₁₂H₂₅**, which enables catalytic turnover at low concentrations compatible with enzymatic stability (Figure 2a).

Expanding upon this modular approach, recent efforts by the same research group have focused on the covalent integration of the catalytic tripeptide **H-Pro-Pro-Glu** directly onto the N-terminus of an alcohol dehydrogenase within a single protein domain (Figure 2b) [40].

Evolution, advantages, and future perspectives of peptide catalysis. (a) Chronological development of peptide-based catalysis: from 20th-century pioneering reports on accelerated hydrolysis to the first asymmetric hydrocyanation and epoxidation reactions in the 1980s. The 2000s saw the emergence of short, folded sequences (e.g. Miller-type catalysts) for stereoselective transformations in organic media. (b) Key architectural benefits of peptide scaffolds: (i) high modularity via straightforward synthetic assembly; (ii) expanded reactivity through the incorporation of nonproteinogenic amino acids; and (iii) precise stereocontrol afforded by the availability of both enantiomeric series. (c) Current paradigm shift toward aqueous media, driven by sustainability, positioning peptide catalysis at the interface of small-molecule organocatalysis and enzymatic biocatalysis.

Figure 2

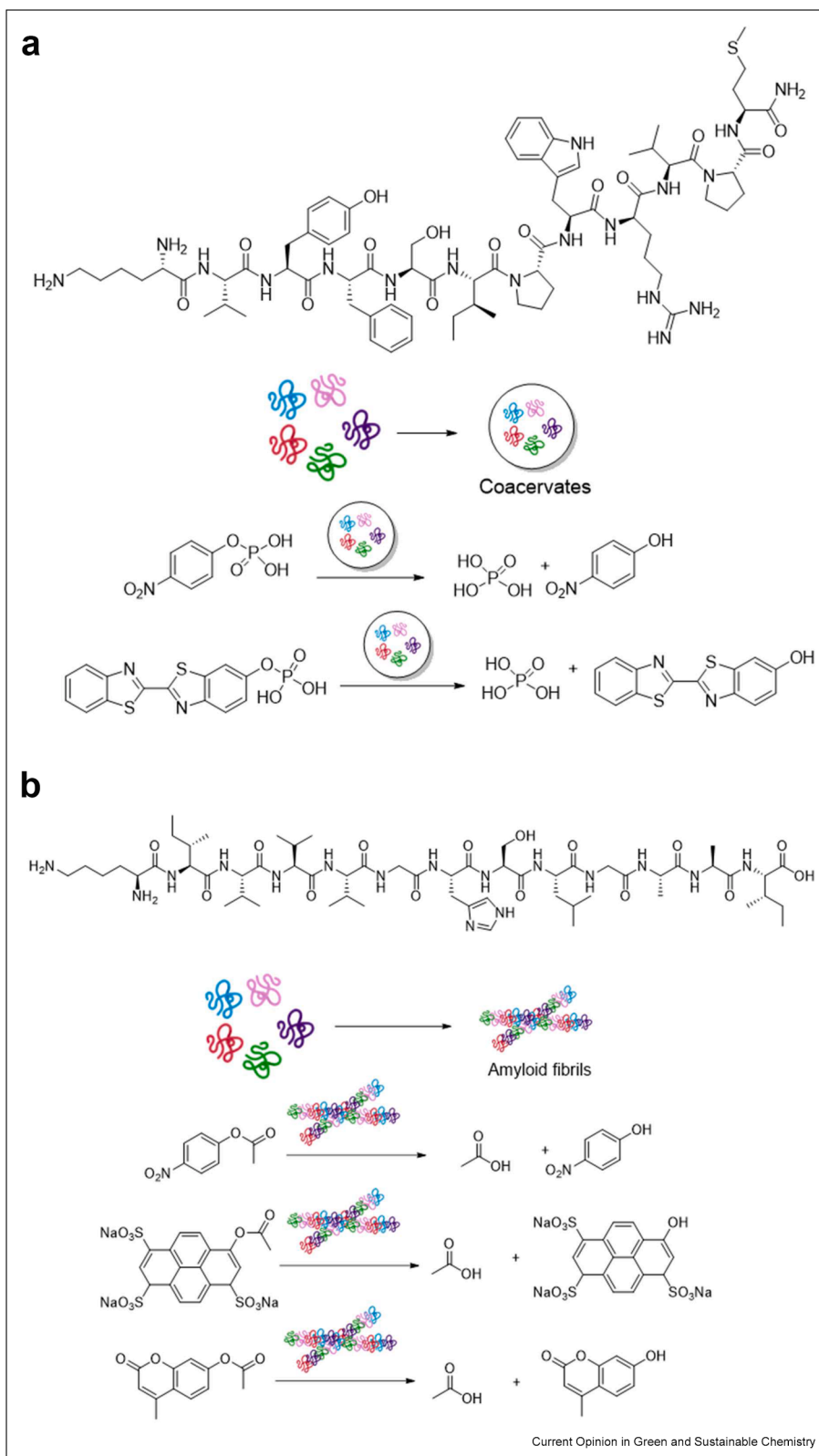


(a) Combination of enzyme and peptide catalysis in water for the oxidation of butanol into the corresponding aldehyde and the aldol condensation of the latter with a nitroolefin substrate providing a chiral product with high stereoselectivity and enantioselectivity; **(b)** direct conjugation of a catalytic tripeptide on the N terminal of an alcohol dehydrogenase enzyme provides a single-protein system endowed with two catalytic sites to promote the cascade reaction between a linear alcohol and a nitroolefin substrate.

To achieve a reliable proof-of-concept it was necessary to overcome several issues like the presence of interference in the aldol condensation caused by the exposed lysine residues of the enzyme that promote the reaction in a nonstereoselective way diminishing the enantioselectivity. This demonstrates the precise tailoring of experimental conditions requested to combine within the same protein unit two separated chemocatalytic and biocatalytic sites.

Drawing inspiration from natural membraneless compartmentalization, liquid–liquid phase separation (LLPS) was used by Pina et al. to drive the concentration-dependent assembly of catalytic peptides. The hairpin-like peptide **P7** (**H-KVYF-SIPWRVPM-NH₂**) facilitated phosphate ester hydrolysis within coacervates (Figure 3a), whose formation was mediated by optimization of ionic strength and peptide stoichiometry [41]. The sequestered

Figure 3



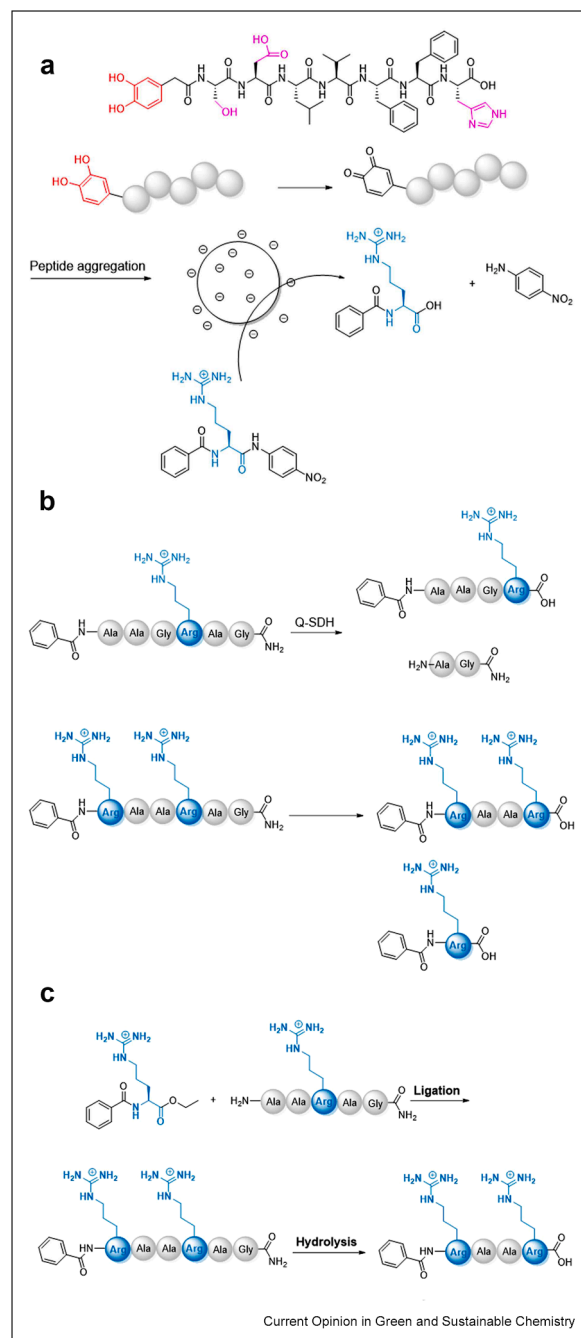
(a) Coacervate formation from a catalytic amphiphilic peptide **P7** triggers its activity as esterase mimic promoting the hydrolysis of different phosphate ester substrates; **(b)** the aggregation of a tridecapeptide forming amyloid fibrils promotes the catalytic activity towards a series of acetate ester substrates.

environment within the LLPS significantly restricted polypeptide flexibility, providing a remarkable 15,000-fold enhancement in phosphodiesterase-like activity compared to the disordered peptide in bulk solution. This substantial rate acceleration stems from a drastic conformational transition: the nanoenvironment of the coacervate droplets induces the folding of a flexible, hairpin-like monomer into a well-defined β -hairpin architecture. Kinetic profiling at 25 °C revealed Michaelis–Menten behavior, characterized by a 20-fold reduction in K_M and a 500-fold increase in k_{cat} , culminating in a total catalytic efficiency enhancement of four orders of magnitude (1.5×10^4).

The significance of peptide self-assembly is further exemplified by the tridecapeptide **H-KIVVVGHSL-GAAI-OH**, derived from *Aspergillus flavus* lipase, which undergoes spontaneous amyloid fibrillation in aqueous media at millimolar concentrations [42]. The supramolecular assemblies catalyzed the hydrolysis of 1-propyl pyrene-3,6,8-trisulfonate (PrPTS), yielding a fluorescent moiety through the site-specific activity of the His side chains. Similarly, the peptide demonstrated high catalytic efficiency toward *p*-nitrophenyl acetate exclusively in its helical fibrillar state (Figure 3b), while nonaggregated species exhibited significantly attenuated activity. These fibrils were further utilized to stabilize chloroform-in-water Pickering emulsions, where the formation of a robust peptide shell at the interface facilitated stability in conjunction with silica and surfactants. The integrity of the Pickering emulsion was reversibly modulated by pH-induced changes in the protonation state of the His residues.

A significant advancement in biomimetic supramolecular chemistry involves the designer peptide **Q-SDH**, which undergoes self-assembly at pH 8.0 to yield spherical morphologies with diameters ranging from 600 nm to 1 μ m. The peptide sequence **Q-SDLVFFH-OH**, incorporates the conserved Ser-Asp-His catalytic triad characteristic of extant serine proteases. Furthermore, N-terminal functionalization with 3,4-dihydroxyphenylacetic acid (**Q**) in the catalytic peptide provides a strategic moiety for the molecular recognition of substrate peptides bearing cationic Arg side chains (Figure 4a) [43]. Oxidation of the catechol aromatic moiety triggered the self-assembly of the peptide into ordered, twisted β -sheet-like supramolecular architectures in aqueous media. These assemblies exhibited potent catalytic activity toward the hydrolysis of N- α -benzoyl-L-arginine-4-nitroanilide (L-BAPA), mediated by a specific quinone-guanidinium recognition motif and ion pairing between the positive substrate and the negatively charged spherical peptide assemblies. The essential role of the supramolecular scaffold was confirmed by the loss of catalytic efficiency upon

Figure 4



(a) Oxidation of the catechol moiety of **Q-SDH** triggers its aggregation in water forming negatively charged nanoparticles. Through ion pairing, arginine-based substrate L-BAPA is recognized by the catalytic peptide assembly promoting the hydrolysis of the amide bond. (b) **Q-SDH** showed site selective hydrolysis of Arg-containing peptides cleaving selectively the C-terminal amide bond of this amino acid; (c) **Q-SDH** promoted the ligation reaction between an Arg amino acid with activated ester on the carboxylic unit and the free N terminal of a pentapeptide containing Arg as recognition site. The obtained peptide subsequently underwent preferential site selective hydrolysis forming preferentially a tetrapeptide containing two Arg residues.

disassembly in hexafluoro-2-propanol. Furthermore, the peptide demonstrated biomimetic site-selectivity, promoting the regioselective hydrolysis of several peptides at the C-terminal bond of Arg residues (Figure 4b). Beyond hydrolysis, the peptide demonstrated biomimetic proficiency in catalyzing amide bond formation, facilitating both directions of the reaction coordinate. The ligation between N- α -benzoyl-L-arginine ethyl ester hydrochloride (L-BAEE) and a pentapeptide bearing Arg was achieved with significant yields operating at subambient temperatures to direct the chemoselectivity toward synthesis over hydrolysis (Figure 4c). The versatility of the Q-SDH catalyst was further exemplified through a programmed cascade of ligation and site-selective hydrolysis in water. Such findings represent a cutting-edge example of the emergent potential of short, synthetic peptides for replicating natural enzymes.

Conclusions

In summary, this work highlights the synergistic potential of peptide catalysis within aqueous media, where the structural versatility of amino acid sequences meets the sustainability requirements of modern organic synthesis. Further investigations in this area will spur better understanding and future exploitations of weak intermolecular activations for selective noncovalent catalysis [44]. The development of sophisticated methodologies for the site-selective modification of amino acid side chains will be crucial for installing nonproteinogenic catalytic handles [45]. Future advancements potentially yielding hybrid biomimetic platforms are expected to arise from the integration of peptide-based frameworks with other classes of bio-based catalysts, like for instance recently disclosed bio-based glycan catalysis [46]. A better understanding of self-assembling features of peptides [47] will enable the construction of discrete supramolecular enzyme mimics, and machine learning will spur the achievement of efficient peptide catalysts [48,49]. Further opportunities are also possible considering catalytic peptides synthesized through solid-phase peptide synthesis still bound to the resin as heterogeneous support, enabling efficient catalyst recycling and scale-up in water [50]. All these strategies will refine our ability to engineer highly efficient, water-compatible catalysts that mimic the complexity and efficiency of natural biological machinery, providing insights into the role of peptides in prebiotic to biotic catalysis [51–53]. The frontier of aqueous peptide catalysis represents a burgeoning intersection of supramolecular chemistry and green synthesis. This field, driven by the synergistic integration of organic synthesis and biochemistry, will soon comprise an increasing number of chemical reactions in water—the quintessential green solvent.

Author contribution credit

Conceptualization: A.S., supervision: A.A., F.F., and A.S., data curation: M.S. and A.A., visualization: M.S. and A.A., writing original draft: A.A. and A.S., and writing, reviewing, and editing: M.S., F.F., A.A., and A.S.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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- * of special interest
- ** of outstanding interest

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