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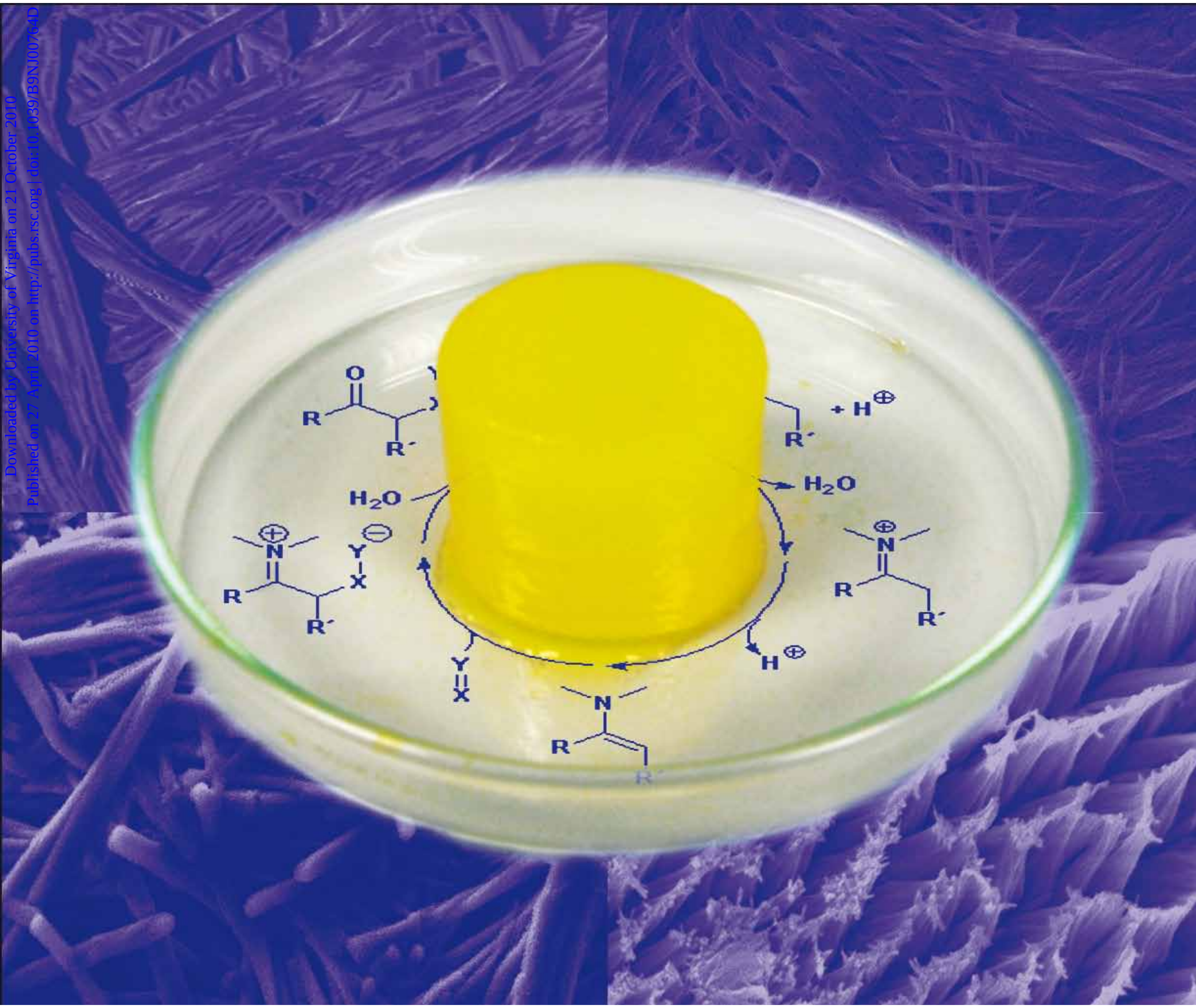

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PERSPECTIVE
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Supramolecular gels as active media for organic reactions and catalysis

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Supramolecular gels have attracted an enormous amount of interest from scientists in the last decade because of their potential applications proposed up to now in fields of great social impact like biomedicine or materials science. However, their potential in organic transformations and catalysis has been only scarcely explored. In this review we describe the state-of-the-art as well as the contribution of our group to the field of reactive and catalytic supramolecular gels.

1. Introduction

Supramolecular gels are nanostructured soft materials formed by low-molecular-weight organic compounds by the sole action of non-covalent intermolecular interactions (solvophobic, ionic, H-bonding, π–π stacking, van der Waals, metal coordination, *etc.*).[1,2] Amazingly, very simple and easy to synthesize molecules are capable of self-assembly into nanoscopic aggregates that form a 3D network that immobilises a large amount of solvent. Unlike their polymeric counterparts, polymer physical gels, their study and application has been only recently explored. However, the number of reports on their applications is growing fast, especially in fields of great social impact such as biomedicine or materials science. Excellent reviews have been published in recent years reporting the diverse applications of supramolecular gels developed in different fields.[3] As the main topic of the present perspective is focused in catalysis, many other amazing applications will not be discussed in depth. Nevertheless, the broad practical possibilities shown by supramolecular gels are summarized in Table 1.

Supramolecular gels are hierarchically built-up from the molecular into supramolecular level (Fig. 1). All the information required for self-assembly and function is programmed by design at the molecular level and is transferred in a self-instructed manner. Simple low-molecular-weight molecules are prepared by conventional solution synthesis and provided with assembling and functional groups. These molecules will be organised into 1D objects that will further assemble into fibrillar architectures that after physical cross-linking will form a spanned network that percolates the solvent. The network will be formed by a highly organized material. Indeed, in many cases, gels and xerogels obtained after solvent removal, are microcrystalline and it has been proposed by Menger that supramolecular gelation can be considered as an uncompleted crystallization process.[4] In general, relevant features such as conformational preferences, orientation of functional groups and molecular or supramolecular chirality are well defined.

Moreover, the weak nature of non-covalent interactions allows for thermal- and lyo reversibility. The gel phase can be regarded as a high aspect ratio solid phase that is involved in a solubility equilibrium. The gel is formed in a supersaturated solution and, depending on the solubility constant and the mechanism of self-assembly, a given amount of free gelator could remain in solution.[5] Interestingly, in some cases this solubility equilibrium leads to self-correction of assembly

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Beatriu Escuder

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Francisco Rodríguez-Llansola

Francisco Rodríguez-Llansola graduated in chemistry at the University Jaume I, Castelló (Spain) in 2006. Currently he is doing his PhD working on proline-based supramolecular gels and their application in organocatalysis.

Table 1 Applications of supramolecular gels

Concept	Application
Biomaterials	Regenerative medicine and tissue engineering
	Enzyme-responsive hydrogels
	Enzyme–hydrogel hybrid materials
	Biomineralization
	Drug delivery and therapeutic agents
Smart materials	Optoelectronic applications
	Responsive gels ($h\nu$, pH, ions, *etc.*)
	Light harvesting systems
	Catalysis
Templates for nanostructured materials	Nanoporous inorganic materials
	Gel–nanoparticle hybrid materials
	Imprinted organic polymers

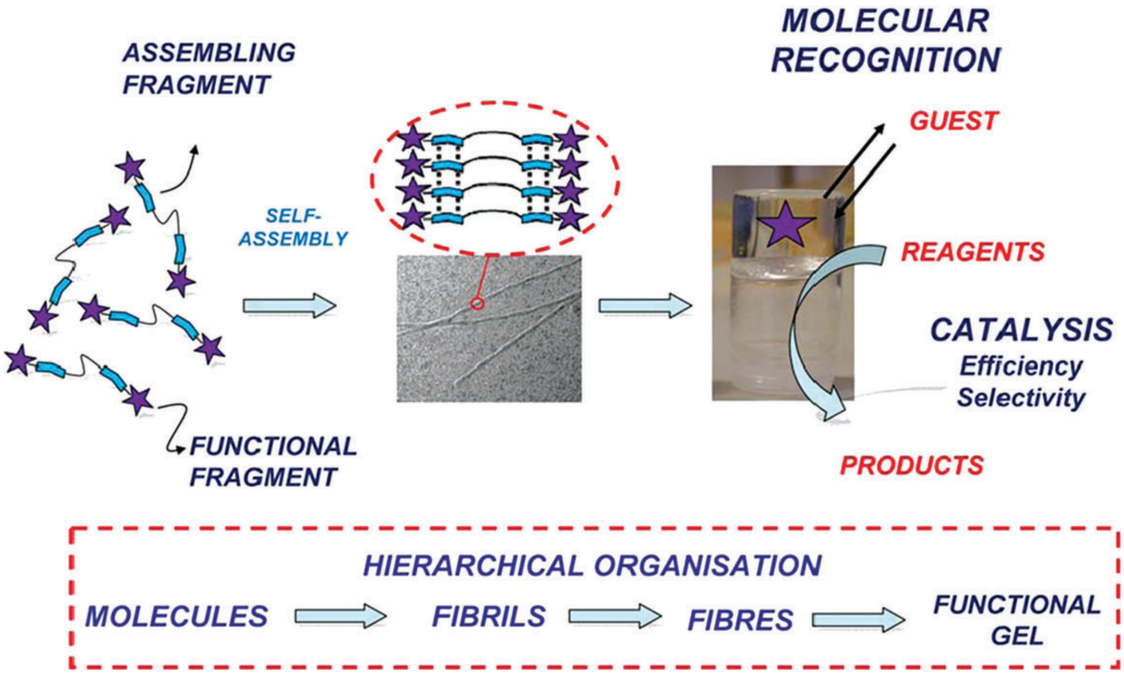


Fig. 1 Strategy for the bottom-up construction of functional gels.

mistakes. In many cases gels are formed by dissolution of gelator in hot solvent and subsequent cooling to a given temperature. In this process, depending on cooling rate, poorly organized metastable aggregates can be formed that, if the energy barrier is not too high, can be corrected into thermodynamically more stable and highly organized gels or even into crystals in some cases.[6] Aside from temperature and concentration, gelation can be modulated by chemical or physical stimuli if sensitive groups are introduced in the structure. For instance, pH, light or different chemical species can be used to switch from gel to sol and *vice versa*.[7] Their thermoreversibility and sensitivity for stimuli make them very appealing for functional applications as their activity may be conveniently tuned by temperature and those stimuli.

Juan F. Miravet

Juan F. Miravet graduated in chemistry at the University of Valencia (Spain) in 1991 and obtained his PhD at the University Jaume I, Castelló (Spain) in 1994. From 1996 to 1997 he was a postdoctoral fellow with Prof. J. M. J. Fréchet at Cornell University and at the University of California, Berkeley. He is currently an Associate Professor at University Jaume I. His research activities deal with supramolecular chemistry and in particular with the study of supramolecular gels.

On the other hand, at the microscopic level, gels are heterogeneous systems formed by a solid network with a microporous structure filled by pools of solvent. This network presents a large surface area in contact with solution and it can be envisaged that if the fibres are provided with active groups they can effectively perform any task (*e.g.* recognition, catalysis). Additionally, these solid-like properties allow for easy recovery of the gelator once this task has been done by simple filtration.

2. Supramolecular gels as media for organic reactions and molecular recognition

Can supramolecular gels be used as media for reactions? To answer this question we have to consider not only the macroscopic but the microscopic and molecular features of the gel network and the potential interactions between reagents and the different domains of the gel. According to these features, physicochemical processes may take place in solution (i), within the solid-like network (ii) or at the liquid/solid network boundary (iii).

(i) Processes in solution

The porous network of a gel allows for diffusion of solutions, although slower than in homogeneous systems. It can be easily observed by addition of supernatant coloured solutions on top of a gel (for instance, see the gels in Fig. 11). Thus, gels can be loaded with solutions containing different components. Additionally, other molecules can be entrapped in the voids of the gel during the gelation process (*in situ* loading) only if they do not interfere with gelator self-assembly mechanism.

It has been shown that solvent pools held by the gel network behave as true independent solutions. For instance, photochemical quenching rates, which measure diffusion rates in the range of nanometres, showed that molecules trapped in solvent pools of a hyaluronan gel diffuse as fast as in solution.[8] A similar behavior has been described by Galindo *et al.* in a supramolecular gel.[9] On the other hand, Hanabusa *et al.* have studied organogel electrolytes and have found that the ionic conductivity is only slightly affected by the presence of the gel network.[10] Furthermore, Duncan and Whitten have studied supramolecular gels by NMR and have reported that the line width of NMR solvent signals in supramolecular gels is not affected by gel formation, revealing that the macroscopic viscosity increase does not affect the tumbling rates of the solvent molecules.[11] Furthermore, we have used NMR in order to study interaction and molecular recognition of small molecules in supramolecular gels and we have observed that *molecules that are not interacting with the gel network remain unaffected as if they were in pure solvent*.[12] Thus, we studied the NMR of compounds **2**, an apolar molecule, and **3**, bearing two H-bonding groups, in the presence of a gel formed by **1** in C_6D_6 (Fig. 2). We could observe that compound **3**, capable of H-bonding interaction with the gel phase shows a decrease of T_2 values meaning a slower tumbling rate than the corresponding solution in the absence of the gel ($T_{2\mathrm{sol}}$ = 1.77 s, $T_{2\mathrm{gel}}$ = 1.20 s). On the contrary, T_2 values for compound **2**, non-interacting with the gel phase and well solvated by C_6D_6 were unaffected by the presence of the gel ($T_{2\mathrm{sol}} = T_{2\mathrm{gel}}$ = 4.95).

(ii) Processes within the solid-like network

As mentioned before, the fibrillar network is a solid-like microcrystalline phase in which molecules are anisotropically packed in one dimension. Therefore, fibres are not 3D crystals but dynamic aggregates. Indeed, it has been demonstrated that different reagents can reach reactive groups within the gel phase. We have prepared reactive gels formed by compound **4** that can be converted in a stronger gel phase after diffusion of an amine and reaction into the gel network (Fig. 3).[13] Additionally, other groups have shown that functional nanostructures provided with reactive fragments can be covalently captured. Photopolymerization of alkene or alkyne groups has been widely used to obtain more robust nanostructures.[14] Besides, Díaz-Díaz *et al.* have reported the use of Cu(I)-catalyzed azide-alkyne [3 + 2] cycloaddition for the *in situ* cross-linking of preformed organogels and Mésini *et al.* have used the same reaction for the effective post-modification of self-assembled nanotubes.[15] On the other hand, Smith *et al.* have recently reported on the use of alkene metathesis for the covalent capture of different nanoscale morphologies.[16]

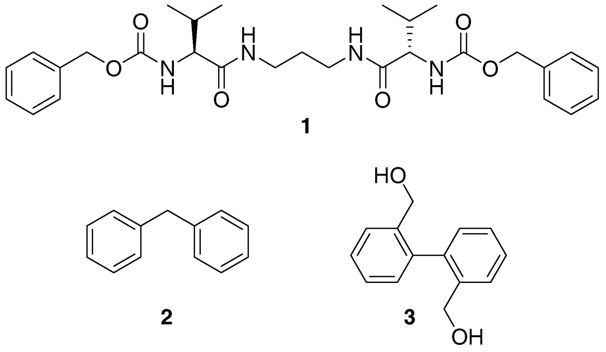


Fig. 2

(iii) Processes at the liquid/solid network boundary

The boundary region between solution and the solid-like network is highly dynamic and difficult to understand. Owing to the weak nature of non-covalent interactions, free gelator molecules are in equilibrium with aggregates (oligomers or large aggregates depending on the cooperativity of the self-assembly process) and it can be observed by NMR that free molecules are exchanging between solution and gel phase. Therefore, many interesting processes such as the interaction with substrates, phase-transfer catalysis and the templating of chemical processes may take place at this diffuse and dynamic region. For instance, as commented before for the interaction of compound **3** with the gel formed by compound **1**, small

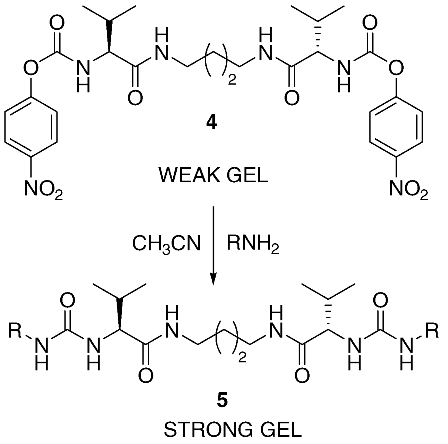


Fig. 3 Reaction of compound **4** and amines within the solid-like phase.

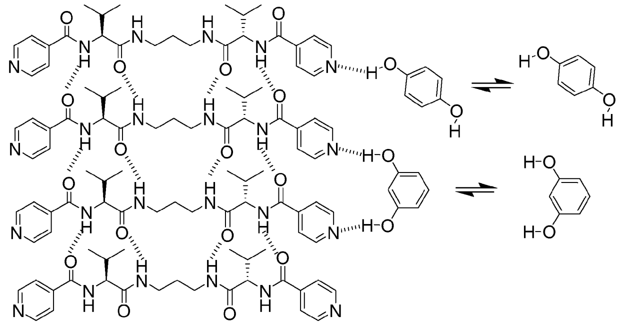


Fig. 4 Selective recognition of phenol derivatives by functional gel fibres.

molecules can interact with the gel phase and their properties can be analysed in solution after rapid exchange by NMR (in the appropriate time scale).[12] In this sense, we have also studied the selective interaction between substrates dissolved in solution and functional groups present in the gel fibres. We have shown that arrays of pyridine H-bond acceptor groups organized in the fibres are able to participate in a multivalent selective interaction with phenolic substrates (Fig. 4).[17]

Moreover, Shinkai *et al.* have reported a supramolecular organogel formed by a perylenediimide derivative that was able to selectively signal the presence of 2,6-dihydroxynaphthalene by a change in colour associated with charge-tranfer interactions between this substrate and the molecules in the gel fibres.[18] Dötz *et al.* have reported the use of organogels formed by pyridine-bridged benzimidazolium salts as phase-transfer catalysts for the N-alkylation of benzimidazole, benzotriazole and imidazole in acetonitrile/NaOH.[19]

We have also shown an example of such dynamic processes at the boundary in which a cyclization reaction leading to compound **6** in solution pulls the sol–gel equilibrium of self-assembled reagent **4** towards solution (Fig. 5).[20]

Furthermore, interactions at the interphase have been used in the templated synthesis of inorganic[21] and organic[22] nanostructured polymeric materials and for the topotactic reaction of simple organic molecules.[23]

The effect of interaction between the gel network and proteins in solution also has been studied. For instance, Xu *et al.* have reported examples of enhanced activity and stability of an acid phosphatase and increased bioluminescence after luminol oxidation catalyzed by heme proteins by confinement in a hydrogel matrix.[24]

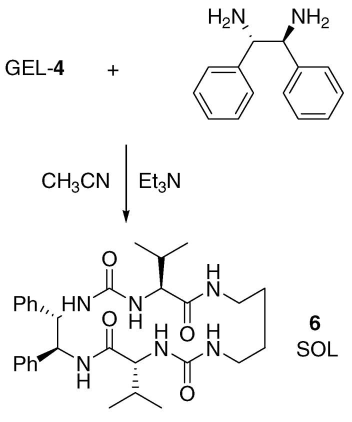


Fig. 5 Gel to sol disassembly driven by an organic reaction.

In summary, different reactions can take place within the gel phase, on the surface of the fibrillar network and in solution, depending on the relative affinity between reagents, solvent and gelator.

3. Catalytic supramolecular gels

3.1 Supramolecular chemistry and catalysis

Catalysis is one of the main goals of supramolecular chemistry that started 30–40 years ago with the pioneering work of Pedersen, Cram and Lehn in that field. Indeed, it appeared as one of the most important applications of supramolecular complexes or supramolecules in their seminal publications and books.[25] Since then the supramolecular approach to the field of catalysis has attracted the attention of many researchers in the most prestigious groups. An excellent revision of the state-of-the-art in that field has been recently collected by van Leeuwen in a book in which the most active researchers in the field present different strategies towards the objective of emulate the magnificent efficiency and selectivity of natural catalysts, the enzymes.[26a]

In the introductory chapter, Ballester and Vidal-Ferran classify supramolecular approaches to catalysis into three categories:[26b] (1) molecular receptors that place a binding site close to a catalytic centre, (2) molecular receptors that simultaneously bind two reactants and promote their reaction, and (3) systems in which supramolecular interactions are used to construct a catalytic centre (Fig. 6).

In the case of catalytic supramolecular gels, non-covalent interactions are used for the construction of a multitopic catalyst. In this sense, they represent an extended and more complex version of the third family in that classification. For instance, gelators can be designed in a modular approach by combining an assembling fragment with a functional fragment (catalytic or pre-catalytic) (Fig. 7). After self-assembly, an extended supramolecular object with built-in catalytic sites will be obtained. The functional fragment could be either a known catalyst or a pre-catalyst that will be activated after aggregation. Besides the single site catalysis, the organization of multiple catalytic sites in the fibre surface could generate additional catalytic features such as multivalent interactions, neighbouring effects and cooperativity. On the other hand, differences in polarity between solvent pools and inner regions

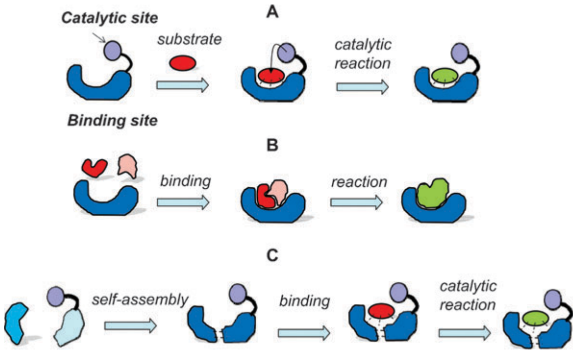


Fig. 6 Supramolecular approaches to catalysis.

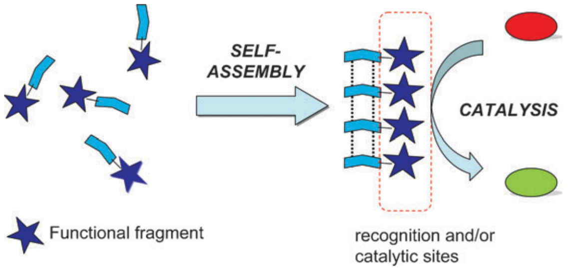


Fig. 7 Design of a catalytic gel.

of the fibres may lead to substrate selectivity. Additionally, the high degree of molecular order may ultimately induce regio and stereoselective transformations.

Catalytic centres can be metals coordinated to the gel fibres (metallocatalysts) and catalytic organic fragments (organocatalysts). Further discussion will follow this fundamental distinction.

3.2 Supramolecular gels in metallocatalysis

Coordination of metals has been used quite often to obtain metallogels with interesting physical properties and applications.[27] However, its use for the construction of gel-supported catalytic systems is still in its infancy and it is a promising field of development in the gel materials research.

Among the so-far limited examples found in literature three different types of catalytic metallogels could be considered (Fig. 8):

(a) Self-supported metallogels. In those systems metal coordination is responsible for the formation of a cross-linked coordination polymer that entraps the solvent and in consequence forms a gel. Additionally, this supramolecular material may present catalytic activity.

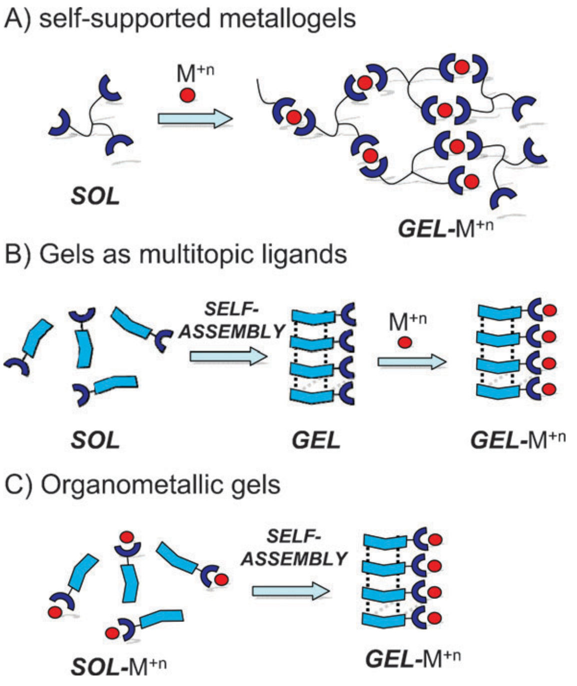


Fig. 8 Classification of catalytic metallogels.

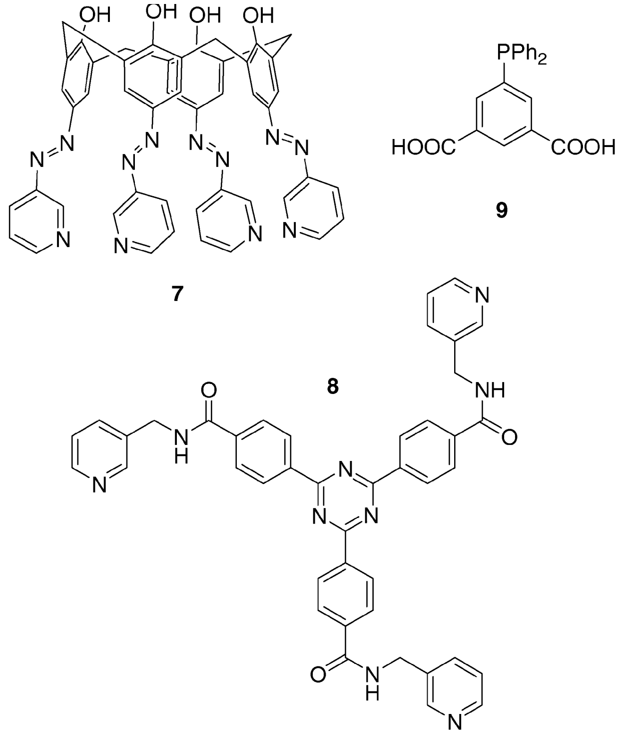


Fig. 9 Ligands employed for the preparation of self-supported catalytic metallogels.

One of the first examples of this class was described by Xu *et al.* in which pyridine based ligands such as **7** (Fig. 9) were used to construct Pd-metallogel networks in DMSO that were active catalysts for the aerobic oxidation of benzyl alcohol to benzaldehyde.[28] Catalytic reactions were analyzed after 2 h with turnover number values twice that those obtained using $Pd(OAc)_2$ as the catalyst, as a consequence of the superior stability of the catalytic gels.

More recently Zhang *et al.* have prepared pyridine-based tripodal ligands for Pd(II) (**8**) that are able to form metallogels in methanol–chloroform mixtures and can be used as catalysts for the Suzuki-Miyaura C–C cross-coupling between 4-bromopyridine and phenylboronic acid in high yield after few hours.[29a] This gel-phase catalyst was also used for the cross coupling of other aryl halides such as iodobenzene being reused up to three times, with progressive inactivation. However when the metallogel was dried and used directly as a xerogel, catalytic activity was comparable to the gel in the first run and maintained for at least five consecutive runs. More recently the same authors have reported the study of Fe-metallogels based on 1,3,5-substituted benzene as ligand (**9**), their post-modification by diffusion of a $Pd(COD)Cl_2$ solution, and their use as catalysts for the same organic reactions.[29b] In that case, the catalyst was packed in a paper bag to avoid mechanical degradation and easy separation from reaction medium. The products were obtained in high yield and recycled for several runs.

(b) Supramolecular multitopic ligands. A fibrillar network is constructed with free ligand sites for *a posteriori* metal binding.

Some years ago we reported compounds **10** and **11** as ambidextrous gelators for both organic solvents and aqueous media (Fig. 10).[30] These compounds are armed with arrays of pyridyl fragments and, after their self-assembly in toluene, the gels could be loaded with Pd(II) and tested for the aerobic oxidation of benzyl alcohol (Fig. 11). The first results indicated that the catalysts were active in that reaction with low turnover numbers, however it could be observed later that leaching of Pd species was most likely responsible for the observed catalityc behaviour.

(c) Low-molecular-mass organometallic gelators. Metallogels can be built-up from gelators that already contain a metal in their structure. This approach has been particularly explored by Dötz *et al.* They described the first example of a chromium metal-carbene based low-molecular-mass organometallic gelator and more recently they have reported the use of palladium-CNC pincer biscarbene **12** (Fig. 12) as an air stable organometallic low-molecular-mass gelator able to catalyse C–C bond formation reactions in the gel state, for example as a double Michael addition.[31]

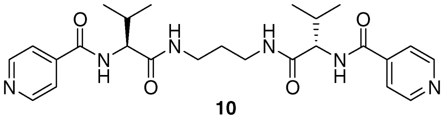
Problems usually associated with heterogeneous metallocatalysis are also present in gels (leaching, catalyst inactivation, toxicity of metals for some applications, *etc.*) together with additional problems relative to the supramolecular nature of gel materials (disassembly of catalytic fragments in solution, slow diffusion, *etc.*)

3.3 Supramolecular gels in organocatalysis

In the last ten years organocatalysis, and in particular aminocatalysis, has experienced a ‘gold rush’ as termed by Melchiorre *et al.*[32] Structurally diverse examples of homogeneous phase organocatalysis have been reported.[33] Polymer-supported organocatalysts have been also widely studied.[34] Moreover, supramolecular organocatalysis has become a potent approach. In this sense different organized systems formed by low-molecular weight compounds have been studied in catalysis such as discrete self-assemblies (capsules, cages, self-complementary catalytic dimers, *etc*),[35] micelles,[36] vesicles[37] or emulsions.[38] However, the study of supramolecular gels in organocatalysis is barely reported.

The first mention of the presence of a supramolecular gel in an organocatalytic system was made by Inoue *et al.* by 1990 in their studies on the asymmetric addition of hydrogen cyanide to *m*-phenoxybenzaldehyde catalyzed by cyclodipeptide **13** (Fig. 13).[39a] They observed that low temperatures (and formation of a gel) was accompanied by an increase in stereoselectivity. Following this work, Danda reported that depending on the purification procedure of the catalyst either transparent or opaque gels or even solid suspensions were obtained in toluene.[39b] It was observed that those gels were thixotropic—namely, viscosity decreased on increasing stirring rate—and that faster stirring rates gave increasing enantioselectivities. Other groups dedicated some attention to the study of the mechanism of catalysis employing kinetic, NMR and computational studies.[39c] It was proposed that the process was second order with respect to the catalyst, with two imidazole residues necessary for the catalytic action. However, not much attention was paid to the supramolecular structure of the gel and the heterogeneous nature of the system was regarded as ‘*A significant obstacle … which makes the interpretation and comparison of experimental data difficult*’. Indeed, prevention of catalyst aggregation is a major issue in many examples in which the catalyst presents groups suitable for intermolecular interactions.[40]

It has been only recently that Stupp *et al.* have described His-containing peptide **14** that forms a hydrogel at pH above



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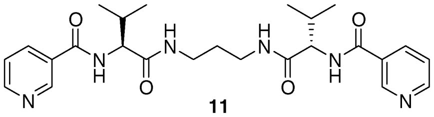

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Fig. 10 Pyridine-derived gelators used in the study of gels as multitopic ligands.

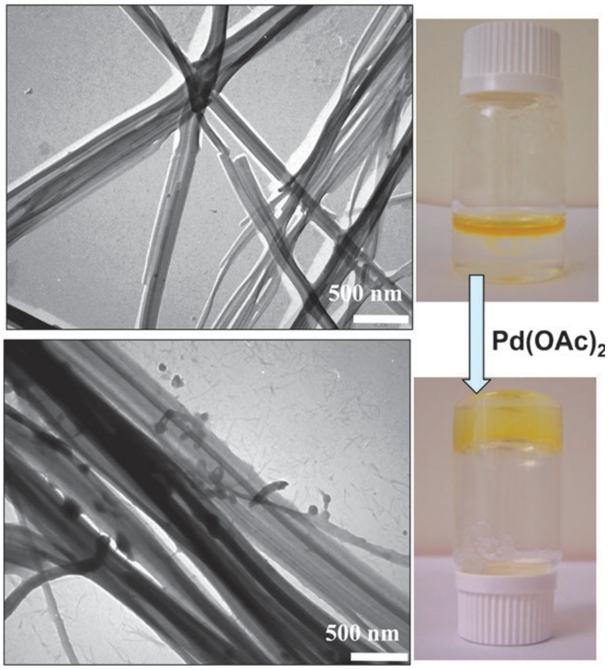

Fig. 11 TEM and macroscopic images of toluene gels formed by compound **10** before (*top*, Pt-shadowing) and after (*bottom*, no shadowing) post-diffusion of Pd(OAc)$_2$.

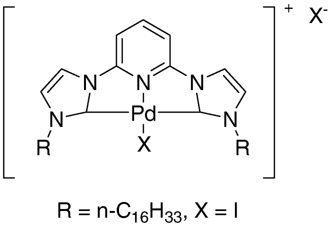

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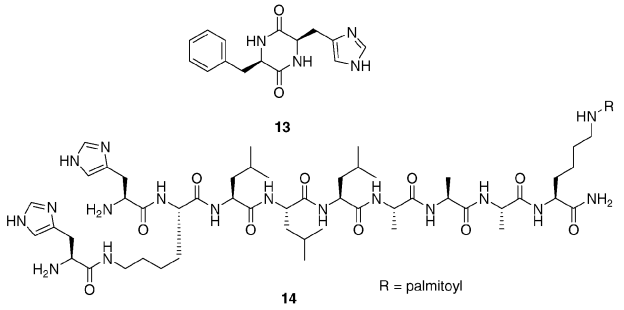
Fig. 12 Organometallic gelator.



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14

Fig. 13 Organocatalytic self-assembling peptides.

6.5 and at concentrations above 0.1 wt% capable of catalyse ester hydrolysis.[41] They showed that the nanofibres were better catalysts than other aggregates due to the high density of catalytic sites on their surface.

Our research group has focused on this topic in the last five years. Our main interest has been to design supramolecular gelators provided with catalytic groups, to study their catalytic activity and to analyse the role of the gel matrix in catalysis and the influence of all experimental variables in the outcome of the process. Solvent, temperature, polymorphism, chirality, stereoelectronic effects and any parameter that may affect the catalytic process has been considered in detail with the main goal of controlling the reaction performance by tuning the molecular and supramolecular gel structure. Moreover, we have not considered the heterogeneous nature of the gel as a drawback but as an additional advantageous feature that allows, for instance, easy recovery and recycling of the catalyst at a low synthetic cost. Moreover, the dynamic nature of supramolecular gels allows for an adaptable substrate–catalyst interaction reminiscent of the currently accepted enzyme–substrate induced-fit mechanism.[42]

Among the most popular organocatalysts that are studied in this burgeoning field a prominent position is reserved for L-proline.[43] This amino acid has been extensively used as an active and stereoselective catalyst for C–C bond forming reactions such as aldol reaction or Michael addition reactions and its mechanism of action is well known. It is well accepted that these reactions follow mechanisms resembling that of natural Aldolase I enzymes in which an amine—L-lysine residue in enzymes, L-proline in the current case—forms an enamine intermediate with a ketone substrate that further attacks to the electrophylic reagent (aldehyde, α,β-unsaturated carbonyl, nitroalkene, *etc.*) (see Fig. 14).[44]

We have chosen this fascinating catalyst as a model and have designed gelators containing L-proline fragments in order to test their gels in enamine-based catalytic organic transformations such as those commented before (Fig. 15). We have used as a reliable assembling backbone a general bolaamphiphilic structure well known in our group in recent years.[13,30,45] We have introduced L-prolyl fragments as end groups believing that in those positions they would be more accessible to substrates.[46]

Compounds **15a–c** have been prepared and they have been shown to aggregate in organic solvents such as acetonitrile, ethyl acetate or toluene forming fibrillar networks. They have been shown to form gels under different conditions mainly by the formation of a 1D array of H-bonds between amide NH donors and carbonyl acceptors as depicted in Fig. 16. Structural analysis has demonstrated that compounds **15a–c** have a tendency to fold in solution (in both acetonitrile and toluene) by forming several intramolecular H-bonds (Fig. 16). However, above the minimum gel concentration and after heating for dissolution and spontaneous cooling to room temperature, unfolded conformations are captured into metastable gels. In some cases, such as compound **15a** in acetonitrile, a slow correction process converted the initial kinetically trapped gel into a thermodynamically more stable polymorphic structure.

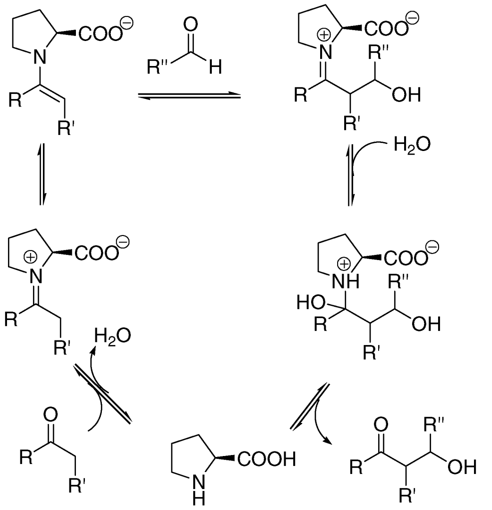
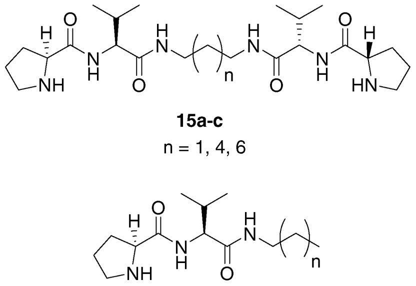


Fig. 14 Catalytic cycle of L-proline in a direct aldol reaction between a ketone and an aldehyde.



15a-c
n = 1, 4, 6

n = 1, 10
16a-b

Fig. 15 L-Proline derivatives.

These compounds were initially tested for the aldol reaction between acetone and 4-nitrobenzaldehyde.[47] Reactions were performed at -20 °C in acetonitrile gels and in blank solutions in which the concentration was similar to that of catalyst that remains in the sol phase in equilibrium with the gel. Unfortunately, it was observed that the catalytic activity was similar in both systems indicating that the reaction was not taking place in the gel phase but only in solution. Apparently, catalytic activity was inhibited by aggregation. A closer analysis of the data brought our attention to the fact that if the gel reactions were left for several days under reaction conditions the product, initially obtained with a 1 : 5 enantiomer ratio, was racemized, whereas in pure diluted solutions it

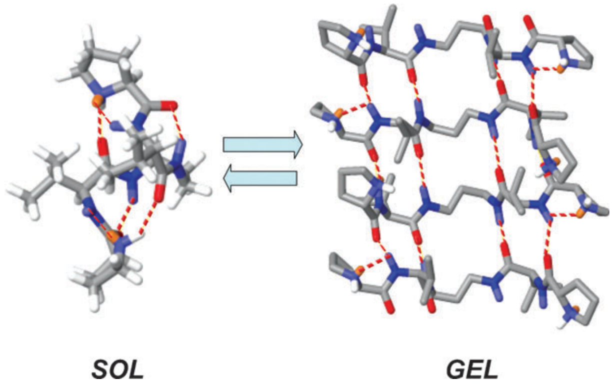


Fig. 16 Molecular models of the structure of compound **15a** in solution (left) and in the fibrillar network of the gel (right). (MACROMODEL, AMBER*)

remained unaffected. Several tests were performed and it was concluded that the gels were acting as a base as confirmed by the use of a pH indicator, Bromothymol blue, that turned to its basic colour (blue) only in the presence of the gels (Fig. 17). Additionally, basicity of the gels was compared to the same compounds under non-assembling conditions (diluted or at high temperature) and it could be assigned a difference of 3 units in the pK_a values of the respective conjugated acids. Remarkably, self-assembly produced an enhancement of basicity most probably due to a cooperation of neighbouring proline moieties organised as a charge relay system (Fig. 18).

This fully new property that arose from catalyst organization at the supramolecular level into the nanofibres could be exploited for a base-catalysed transformation in which the gel phase was participating for the first time as the active phase.[48]

The selected benchmark reaction was the Henry nitroaldol reaction in which a basic catalyst has to deprotonate a nitroalkane that afterwards attacks the carbonyl of an aldehyde (Fig. 19A). Basic catalytic gels could be formed in a very convenient way in neat nitroalkanes (nitromethane and nitroethane) (Fig. 19B) and gave excellent yields of the nitroaldol product after addition of aromatic aldehydes in contrast with non-aggregated samples of compound **16a** (Fig. 19C). Moreover, that system showed a switchable catalytic performance controlled by temperature. Thus, cooling below T_{gel} yielded an active basic system, whereas heating above that temperature switched-off the catalytic activity after disassembly into inactive free molecules.

Why were gels formed by compounds **15a–c** in acetonitrile active as basic catalysts but inactive in the direct aldol reaction? It has been shown in the application to the Henry reaction that catalytic sites in the gel phase were accessible for nitroalkane substrates. On the contrary, it seems that enamine intermediates cannot be formed within the gel phase. We have observed in the structural study of the gels that a strong intramolecular H-bond involves the proline amine lone pair and an amide NH as depicted in Fig. 16. Accordingly, this lone pair could not be fully available for the enamine formation.[46]

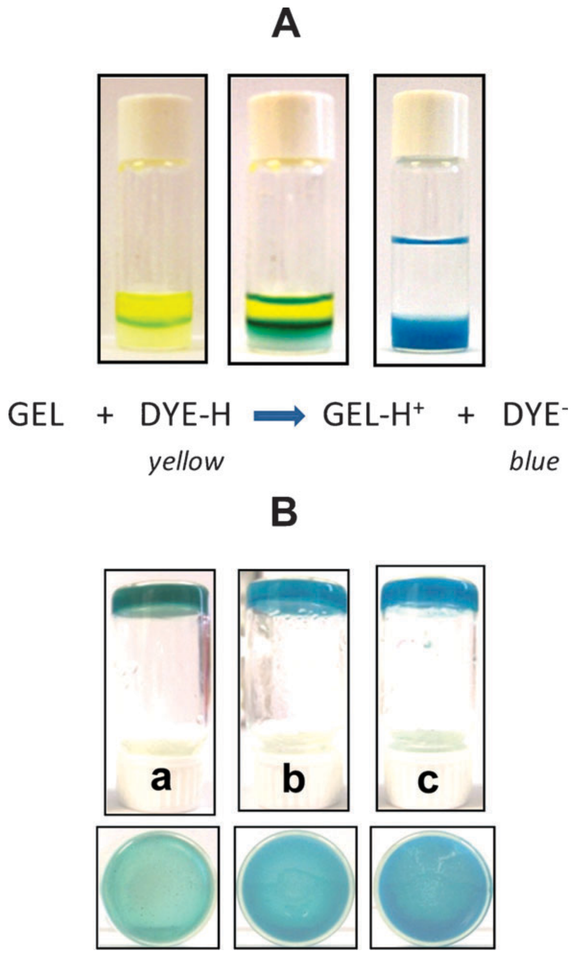


Fig. 17 (A) Post-diffusion of a solution of Bromothymol Blue (yellow) through a gel of compound **15c** in acetonitrile. (B) Gels of compounds **15a–c** in acetonitrile in the presence of Bromothymol Blue.

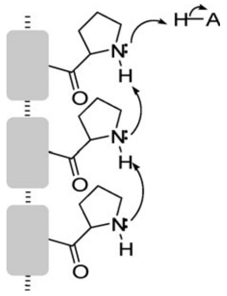


Fig. 18 Cooperation of neighbouring proline moieties in basic catalysis.

Solvent could also play a relevant role in catalytic performance. Firstly, the solvent has an important influence on the structure of the catalytic centres. In particular, working with molecules such as those presented here with a relative flexibility, solvent is determinant for the crystalline packing of gelator. We have reported that closely related molecules bearing the same assembling fragment showed a high degree of polymorphism depending on solvent polarity.[49] Secondly, solvent polarity and solvophobic interactions will determine the solubility of gelator, namely concentration of free gelator molecules in solution in equilibrium with the gel phase. And finally, solvophobic interactions may be very important for the

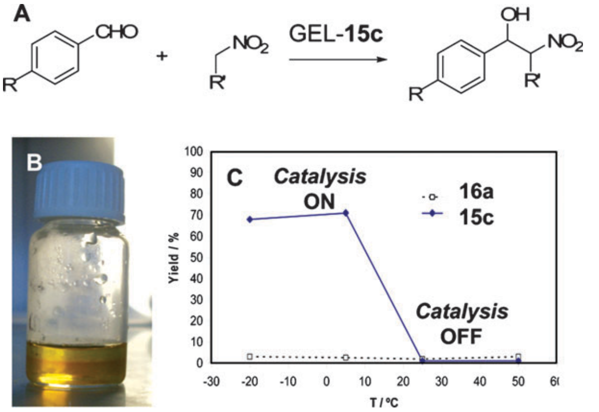


Fig. 19 (A) Henry nitroaldol reaction. (B) Reaction mixture formed by a nitroethane gel of **15c** (bottom layer) and a solution of 4-chlorobenzaldehyde (top layer). (C) Catalytic activity of **15c** and **16a** *vs.* temperature.

distribution of substrates between solution and the gel phase and consequently for the access of them to the catalytic sites within the gel network. In this sense, our very recent results indicate that replacing acetonitrile by toluene as solvent has an enormous effect on the accessibility of the proline moiety to enamine formation as well as on the solubility of these gelators. Namely, decreasing solvent polarity produces changes on the catalyst structure. Relevant results on their application on enamine addition reactions will be communicated shortly.

On the other hand, replacement of organic solvents by water is highly convenient both from an environmental as well as an economic point of view.[50] It is also remarkably important that water is the biological solvent, with the hydrophobic effect the most important non-covalent interaction in biocatalysis. In this sense, the study of L-proline and related catalysts in water is receiving increasing attention.[51] There have been reported examples of catalysis in pure water and also in surfactant systems.[52] Moreover, Barbas *et al.* have described an amphiphilic proline derivative that formed an emulsion in water and behaved as an efficient catalyst for the direct aldol reaction.[53] Recently, we designed an amphiphilic hydrogelator derived from L-proline (**16b**).[54] This compound self-assembled in water forming an almost transparent hydrogel (Fig. 20) that was tested for the direct aldol reaction between cyclohexanone and 4-nitrobenzaldehyde (Fig. 21).

Reagents were easily added on top of the gel dissolved in toluene and the reaction was quantitatively completed after 24 h at 5 °C with high stereoselectivity (*anti* : *syn* 92 : 8, 88% ee). Moreover, the catalytic hydrogel could be reused after decantation of the toluene phase for at least three times with the same efficiency and stereoselectivity (Table 2).

Very interestingly, in this system the hydrophobic effect plays a dual role: first as the driving force for gelator self-assembly and, secondly, conducting reagents to the hydrophobic pockets inside the gel fibres. Current work is in progress in order to understand the role of the organic phase in substrate transport into the catalytic sites and to explore the possibilities of achieving substrate selectivity in the path for ultimate enzyme mimicry.

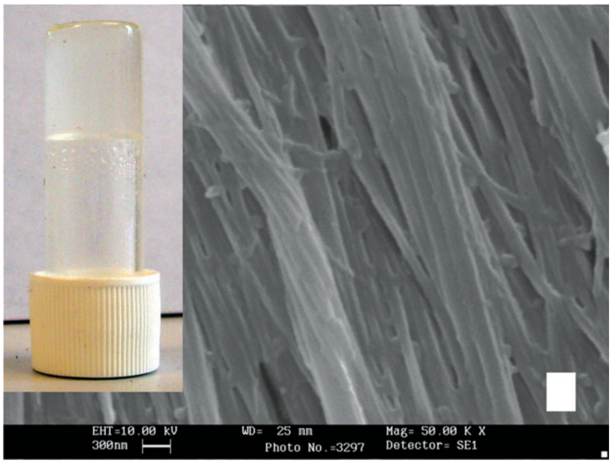


Fig. 20 Macroscopic (left) and microscopic (right) aspect of hydrogel-**16b** (bar: 300 nm).

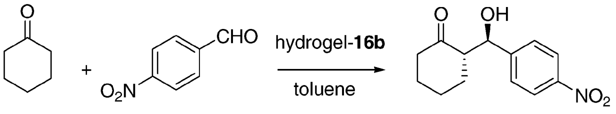


Fig. 21 Hydrogel-catalysed direct aldol reaction.

Table 2 Catalytic performance of hydrogel-**16b**[a]

Entry	*t*/°C	*T*/h	Yield[c] (%)	*anti* : *syn*[c]	EE[d] (%)
1[b]	25	36	> 99	75 : 25	12
2	25	16	> 99	91 : 9	18
3	5	24	98	92 : 8	88
4[e]	5	24	> 99	93 : 7	87
5[f]	5	24	> 99	92 : 8	90

[a] Hydrogel: 0.026 mmol of **1** (0.2 eq) in water (4 mL); reagents: 4-nitrobenzaldehyde (1 eq.), cyclohexanone (20 eq.) in toluene (1 mL). [b] Without toluene. [c] Determined by NMR. [d] Determined by chiral-phase HPLC of the *anti*-product. [e] Entry 3, second run. [f] Entry 3, third run.

4. Conclusions and future

In summary, the intention of this perspective article was to highlight the range of possibilities that supramolecular gels offer in the field of catalysis. Several of the features of these materials result very convenient from a practical point of view: reversibility and sensitivity to external stimuli allows control of catalytic events, straightforward molecular synthesis and possibilities for valuable catalysts recovery and regeneration, *etc.* After selecting a convenient self-assembling fragment, whose aggregation behaviour should be known, any catalytic moiety could be easily attached. On the other hand, unlike conventional polymer-supported heterogeneous catalysts, in supramolecular gels the structure of the catalytic sites can be controlled at a molecular level and, once the structure of the gel phase is well understood a fine tuning of catalytic performance can be achieved by subtle changes (solvent, structure modification, temperature, *etc.*).

As has been shown, both metallic or organic catalysis are feasible although the use of metals introduces additional variables such as complex stability, leaching, precipitation of metallic aggregates, *etc*. Regarding organocatalysis, supramolecular gels can be explored as enzyme mimetics. Combination of catalytic sites with selective binding pockets should be one of the future goals in that field as it may render efficient and selective catalysis.

Furthermore, we have shown that self-assembly processes can have different levels of action: (i) self-construction of the catalytic system after simple input from a small molecule design and (ii) generation of new catalytic properties associated with multimolecular aggregates (cooperativity, multivalency, *etc*.). Moreover, it has been reported that self-assembly could play an important role in chemical evolution in the prebiotic environment in earth.[55] It has been proposed that small organic molecules, under appropriate concentration conditions in water, with the help of some sources of chemical energy and maybe mineral interfaces, could form membrane-bound compartments that encapsulate subsets of components capable of react and produce new molecules, *i.e.* polymers. Posterior development of additional self-catalytic properties could lead to the beginning of replication and cellular life. In this context, supramolecular gels can be regarded as compartmentalised self-supported materials that, as has been shown above, can develop new catalytic features after self-assembly, *i.e.* basic catalysis. It can be envisaged that the formation of hydrogels capable of developing self-catalysis could represent a suitable model for understanding of emergence of life. Furthermore, van Esch *et al.* have recently reported that different compartmentalised structures (vesicles, micelles, interpenetrating networks) can coexist with a hydrogel matrix.[56] Combination of multi-compartmentalisation and new catalytic features in supramolecular hydrogels could be a step forward toward the construction of cell mimetics.[57]

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