CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000654

Supramolecular Catalysis with Extended Aggregates and Gels: Inversion of Stereoselectivity Caused by Self-Assembly

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Abstract: L-Proline-L-valine dipeptide derivatives, which self-assemble in toluene, have been studied as stereoselective catalysts in the conjugate addition of cyclohexanone to *trans*-β-nitrostyrene. Remarkable effects on the stereoselectivity are observed associated to the aggregation of the catalyst. Outstanding differences were observed between the catalytic activity of compound **1**, which forms supramolecular gels in toluene, and compound **2**, which is not a gelator. In the former case, the enantioselectivity of the reaction was almost insensitive to changes in catalyst concentration and temperature, but in the case of compound **2**, the catalytic activity was very much affected by those variables. Structural studies indicate that the results can be rationalized by taking into account significant conformational changes experienced by the catalytic L-proline derivatives associated with the aggregation process. The results highlight that catalyst self-assembly is a very important issue to consider in the stereoselective outcome of organocatalytic reactions. Especially relevant is the fact that the use of supramolecular gels as organocatalyts emerges as a technique that affords reliable and constant stereoselectivity in different conditions with the added value of easy catalyst recovery.

Keywords: gels · organocatalysis · proline · self-assembly · supramolecular chemistry

Introduction

Supramolecular catalysis is a highly active field of research on the frontier of organic chemistry, supramolecular chemistry, catalysis, and biochemistry.[1] Catalysts have been finely designed that use noncovalent interactions either for interactions with substrates or for the construction of the active center itself with the goal of emulating the efficiency and selectivity achieved by enzymes.[2] However, the use of extended aggregates in catalysis has been barely reported.[3] Moreover, quite often aggregation of the catalyst has been considered as a problem to be avoided.[4]

On the contrary, we have been recently interested in the study of catalysis in aggregated systems and, in particular, on the design of catalytic supramolecular gels.[5] Gels formed by low-molecular-weight compounds may combine properties of homogeneous catalysts (easy synthesis and characterization) with heterogeneous ones (phase separation and easy recycling) with an added value: their bottom-up self-programmed construction. Furthermore, gelation can be regarded as a partial crystallization process in which the fast growth of one-dimensional objects frustrates the three-dimensional crystallization.[6] Nevertheless, the internal structure of those objects (fibers in many cases) remains highly ordered. Overall these features may be attractive for their use in catalytic transformations.

Herein, we present an unprecedented detailed study of the influence of molecular self-assembly into fibrillar nanostructures on the organocatalytic activity based on an exhaustive structural understanding of the aggregated catalytic species as well as their self-assembly mechanism.

Very recently we have reported supramolecular gels incorporating L-proline residues;[5b,c] a widely studied catalytic fragment in the field of organocatalysis.[7] Herein, we have studied the 1,4-conjugate addition of cyclohexanone to *trans*-β-nitrostyrene (Scheme 1) as a well-known, benchmark, L-proline-catalyzed reaction[7b,f,8] with the aim of understanding the role of each segment of the structure of the catalysts, as well as the assembly process on the catalytic efficiency and stereoselectivity. Three catalytic model systems have been studied: 1) bolaamphiphilic supramolecular gela-

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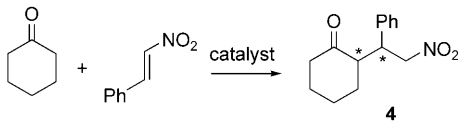
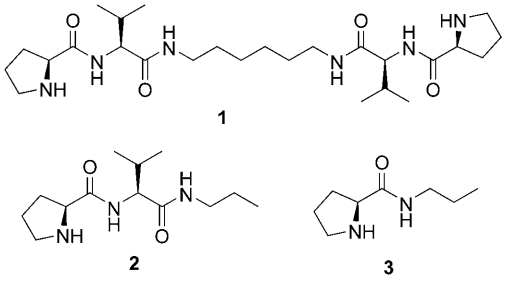
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000654.



Scheme 1. The 1,4-conjugate addition of cyclohexanone to *trans*-β-nitrostyrene.

tor **1**, 2) simplified dipeptide **2**, and 3) prolinamide analogue **3**.



Results and Discussion

Compounds **1**–**3** have been prepared as previously reported,[9] and their aggregation behavior in toluene has been studied. Compound **1** forms rapidly transparent gels after cooling a hot solution of this compound in toluene to room temperature. The measured minimum concentration for gel formation was 7 mM. Addition of 10% hexane decreases this value to 5 mM, affording more stable gels convenient for the catalytic studies. Compound **2** has been designed as half of compound **1** and only forms unstable gels at concentrations above 150 mM. Below this value, a concentration-dependent aggregation process takes place, but the size of the aggregates is not sufficient to immobilize the solvent because it is below the network spanning threshold. Compound **3** was studied to assess the importance of the second amino acid in both self-assembly and catalysis.

As mentioned before, in the present work, the 1,4-conjugate addition of cyclohexanone to *trans*-β-nitrostyrene has been studied in different systems, including gels of compound **1** and analogous aggregated and nonaggregated solutions of compounds **2** and **3**. Three different catalysts were employed at a concentration of 20% relative to the substrate: compound **1** (gel), compound **2** (solution) and compound **3** (solution). Results after three days of reaction at room temperature are collected in Table 1.[10]

First, it can be observed that all of the catalysts except compound **3** gave quantitative yields of product **4** after 3 d; the *syn* diastereoisomer was favored in all cases. Remarkably, the highest diastereoselectivity was observed for the catalytic gel-**1** (Table 1, entry 1). On the other hand, an effect on the enantioselectivity was also observed. Compound **3** gave a low *ee* value (12%) of the enantiomer *syn*-(2*S*,1′*R*)-**4**, which behaved in a similar way as other homogeneous

Table 1. 1,4-Conjugate addition of cyclohexanone to *trans*-β-nitrostyrene catalyzed by compounds **1**–**3**.[a]

Entry	Catalyst	Yield [%][b]	d.r.[b] *syn*/*anti*	*ee* [%][c]
1	gel-**1**	99	98:2	34 (2*R*,1′*S*)
2	**2**	99	93:7	15 (2*R*,1′*S*)
3	**3**	71	90:10	12 (2*S*,1′*R*)

[a] Gel-**1** (0.019 mmol) or **2**–**3** (0.038 mmol) in toluene/hexane 9:1 (1 mL); Reagents: *trans*-β-nitrostyrene (0.19 mmol), cyclohexanone (20 equiv) in toluene/hexane 9:1, $t=72$ h, $T=25$ °C. [b] Determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excess (*ee*) was determined by chiral-phase HPLC of the *syn* product.

phase catalysts derived from L-proline described in literature.[8] However, catalysts **1** and **2** yielded the opposite enantiomer, *syn*-(2*R*,1′*S*)-**4**, and once again the best enantioselectivity was observed for the gel system. These results prompted to study the influence of other variables, such as temperature (−20, 5, 25, and 50 °C) and concentration (6.5 to 19.5 mM for **2** and **3**, 3.2 mM to 9.8 mM for **1**), more deeply (see the Supporting Information for details).

Figure 1 collects the effect of concentration on enantioselectivity at 25 °C. It can be observed that compound **1**, which forms a gel in the concentration range, does not show

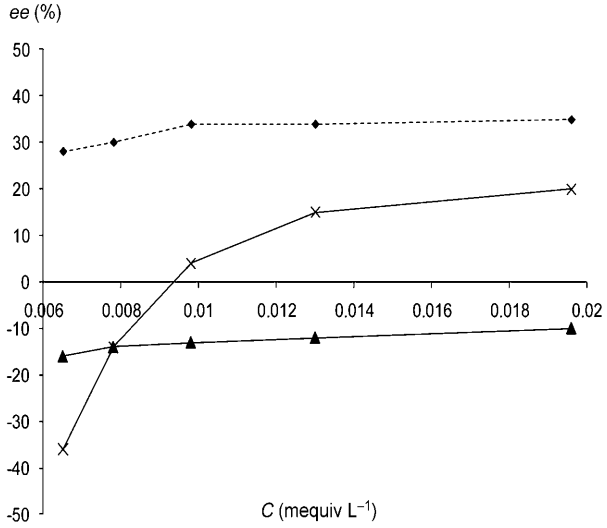


Figure 1. Effect of the concentration of catalyst (milliequivalents (mequiv) of proline per L) on the enantiomeric excess of *syn*-(2*R*,1′*S*)-**4** at 25 °C. ◆: **1**, ×: **2**, and ▲: **3**.

a significant variation in *ee* value and is only slightly affected at lower concentrations. In addition, compound **3** does not show changes in *ee* value with concentration either. However, in the case of compound **2**, a clear shift in *ee* value is observed on going from a maximum *ee* value of −35% at 6.5 mM to an opposite sign value of 20% at 19.5 mM.

The effect of temperature on catalysis at low concentration is shown in Figure 2. It can be seen that for compound **1** there is only a slight variation in *ee* value. Temperature is more important for compound **3**, and shows remarkable re-

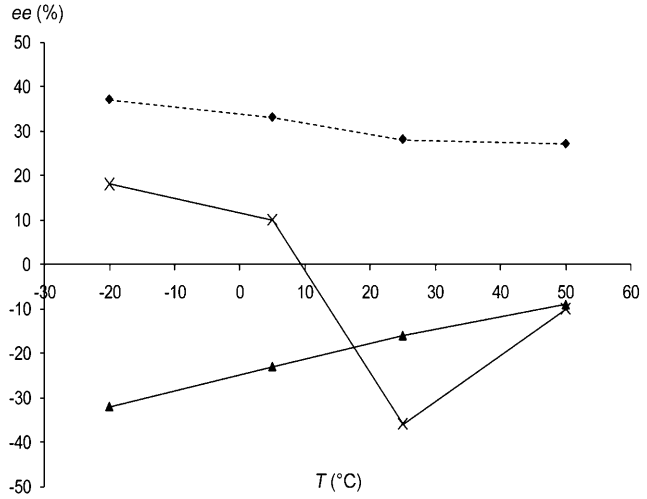


Figure 2. Effect of temperature on the enantiomeric excess of *syn*-(2*R*,1′*S*)-**4**. [**1**] = 3.2 mM, [**2**] = [**3**] = 6.5 mM. ◆: **1**, ×: **2**, and ▲: **3**.

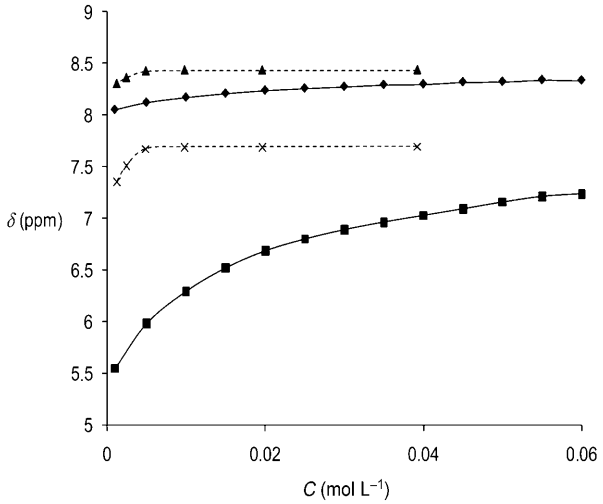


Figure 4. Concentration-dependent chemical shift of amide NHs for compounds **1** and **2** (see Figure 3 for numbering). ▲: **1** (H1), ×: **1** (H2), ◆: **2** (H1), and ■: **2** (H2).

sults for compound **2**, in particular. In the latter, at low temperatures, enantiomer *syn*-(2*R*,1′*S*) is formed similar to compound **1**; however, at higher temperatures, the opposite enantiomer *syn*-(2*S*,1′*R*) is the major one. All of these results point out to a scenario in which aggregation seems to play a fundamental role in the outcome of the reaction.

To understand these results, it was considered necessary to investigate the structure of catalytic centers both at the molecular and at the supramolecular level. For this purpose, solution NMR spectroscopy and X-ray diffraction techniques were employed. 1D and 2D ^{1}H NMR spectroscopy experiments of a solution of compound **2** (6.5 mM) in [D_8]toluene allowed the assignment of signals in a nonaggregated state (see the Supporting Information). Remarkably, the two amide signals *1* and *2*, which are apparently in quite a similar magnetic environment, appear separated by about $\Delta\delta = 2$ ppm (see Figure 3A for numbering). This difference, observed previously when using acetonitrile as the solvent,[8a] is caused by the formation of an intramolecular hydrogen bond between amide NH *1* and the proline residue amine lone pair, as shown in Figure 3B. Next, the variation of chemical shift with concentration was studied. The most informative signals were those corresponding to the amide signals, which are commonly very sensitive to aggregation by hydrogen bonding (Figure 4). Amide hydrogen *1* has a moderate downfield shift with increasing concentration

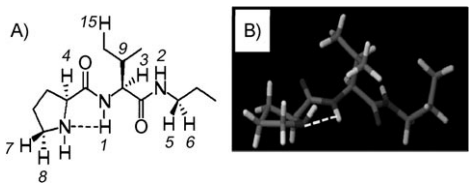


Figure 3. A) Numbering scheme for the dipeptidic fragment in compounds **1** and **2**. B) Molecular model of the proposed structure of compound **2** in solution.

($\Delta\delta = 0.3$ ppm). This is probably due to the fact that a strong intramolecular hydrogen bond is progressively replaced by an effective intermolecular one upon aggregation. The shift with concentration is much more evident for amide hydrogen *2*, which is clearly involved in aggregation ($\Delta\delta = 1.5$ ppm). Slight shifts in some of the aliphatic signals (i.e., *3* and *5*) suggest that a conformational change is happening to accompany the aggregation process for compound **2**.

Needlelike crystals of compound **2** suitable for single-crystal X-ray analysis were obtained for concentrated solutions (100 mM) in the matrix of jelly aggregates in toluene (Figure 5). Compound **2** crystallized in the monoclinic crystal system and *C*2 space group. The molecule appears in a fully extended conformation without any intramolecular hydrogen bonds. Molecules are assembled in columns by two intermolecular hydrogen bonds between Pro C=O and Val N_α (2.109 Å, 162.21°) and between Val C=O and propylamide NH (2.0 Å, 171.38°). Moreover, columns are interconnected by an intercalated array of head-to-head hydrogen bonds between the Pro N_α lone pair and Pro N_αH of adjacent column residues (2.120 Å, 157.86°). Altogether, these experiments proved the presence of a relevant conformational change upon aggregation of compound **2** associated with the breaking of the intramolecular hydrogen bond mentioned above.

Similar studies were performed for compound **1**, in that case for concentrations below the minimum gel concentration, since above this value the large aggregates that form the gel are not detectable by NMR spectroscopy. The variation in chemical shift of the amide ^{1}H NMR spectroscopy signals of compound **1** with concentration is shown in Figure 4. As already mentioned for compound **2**, amide signals shifting downfield with increasing concentration is indicative of the formation of intermolecular hydrogen bonds. These shifts reach a plateau after 7 mM, the concentration at

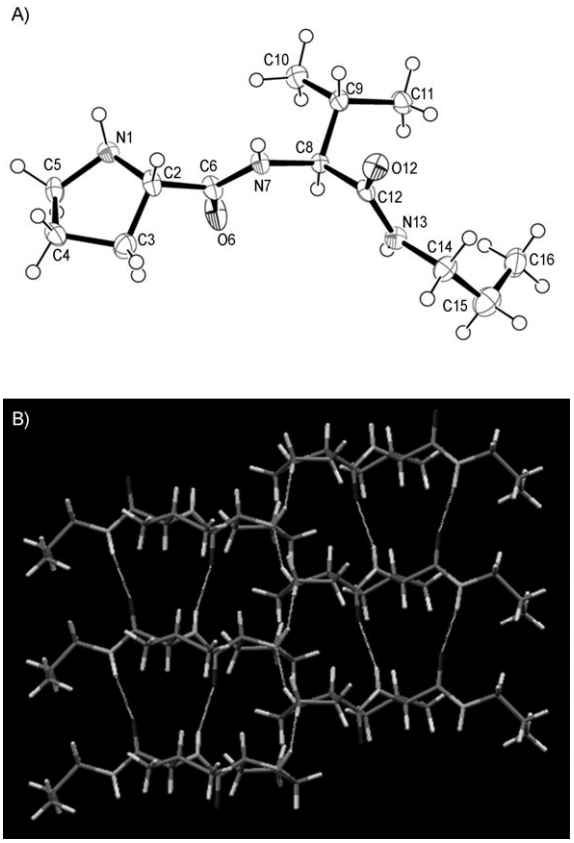


Figure 5. Single-crystal X-ray structure of compound **2**: A) ORTEP diagram, B) extended molecular view (Mercury 2.2).[14]

which the gel is formed, and thereafter all added material becomes undetectable. A detailed analysis indicated that a conformational change is also taking place upon aggregation of compound **1**. NOESY-1D experiments confirmed the presence of folded conformations in dilute solutions of compound **1** (see the Supporting Information). Actually, compound **1** and other analogues have been studied before in acetonitrile and it is known that they can be folded by several intramolecular hydrogen bonds in solution.[9] Upon irradiation of Val methyl groups, contacts were only found for amide protons and C–H signals in the same residue (*3* and *9*). However, in the case of concentrated samples, and in particular in gel samples, irradiation of the same signal gave negative NOE contacts with many of the protons of the spacer as well as of the proline residue, indicating an important conformational change and suggesting that molecules could be unfolded in the aggregates. Furthermore, negative NOEs are due to a transfer of NOE from the large aggregates present in the gel, so this information is relevant for the assignment of the real structure that the molecule adopts in the gel fibers.[11] It is worth mentioning that when a highly concentrated sample of compound **2** (107 mM) near to gelation is compared with a sample of compound **1** near gelation (4.9 mM), similar chemical shifts are observed for both amide protons as well as for aliphatic signals *3* (C_α Val), *4* (C_α Pro), *9*, *15* (*i*Pr), and *7*, *8* (Pro CH), suggesting that the rigid dipeptidic fragment is in a highly similar conformation. Additionally, xerogels prepared from compound **2** at 107 mM showed the same powder diffraction pattern as the single crystals (see the Supporting Information). As a consequence, the crystal structure obtained for compound **2** can be taken as an approximation of the structure of the dipeptidic fragment in compound **1** in the gel.

With all of this information, models of the supramolecular packing of compound **1** in the gels can be constructed, as depicted in Figure 6, in which molecules are in an S-shaped conformation with all of the amide groups involved in intermolecular hydrogen bonding and L-Pro residues oriented outwards with free NH ready for catalysis.

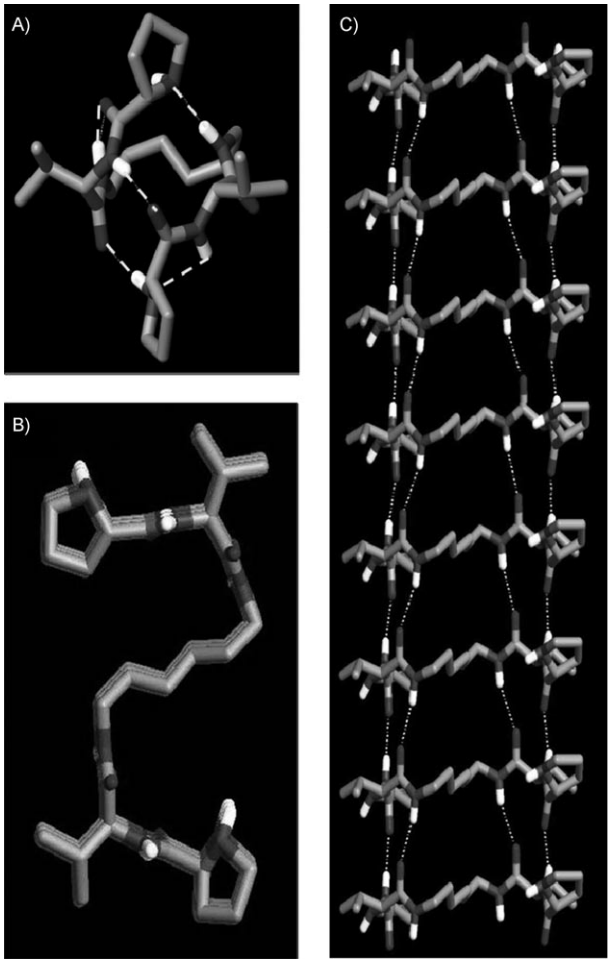


Figure 6. Models proposed for compound **1** in solution (A) and in the gel phase (B, C). The models correspond to energy minima obtained with molecular mechanics calculations using the AMBER* forcefield (MACROMODEL 9.5). Nonpolar hydrogen atoms have been omitted for clarity.

Finally, structural analysis of compound **3** was also performed (see the Supporting Information). The amide NH appears at $\delta = 7.2$ ppm, 1 ppm upfield with respect to previous compounds, revealing the presence of a weaker intramolecular hydrogen bond. Additionally, the two protons of the

methylene connected to the amide NH are equivalent. Altogether these facts suggest that the L-proline region of this molecule is more flexible than in the other compounds, probably related to the absence of the second amino acid, L-Val, in the structure. Besides, concentration-dependent NMR spectroscopy studies (up to 19.5 mM) revealed no variation in chemical shifts, evidencing that this molecule is not aggregating within the interval used for catalysis (see the Supporting Information).

Regarding the self-assembly mechanism, ^{1}H NMR spectroscopy data of the amide *2* proton in compound **2** could be fitted to a cooperative model, which presents a dimerization constant (K_2) of 29 M^{-1} and successive oligomerization constants (K_n) with a value of 100 M^{-1} (see the Supporting Information). According to this model there is a considerable amount of free compound **2** in the range of concentrations used in catalysis, as shown in Figure 7. In the case of compound **1**, this analysis could not be performed at the desired concentration range because above 7 mM all of the added material becomes undetectable. However, when considering a similar self-assembly process as that for compound **2**, the degree of cooperativity should be much higher because the number of intermolecular interactions is larger.

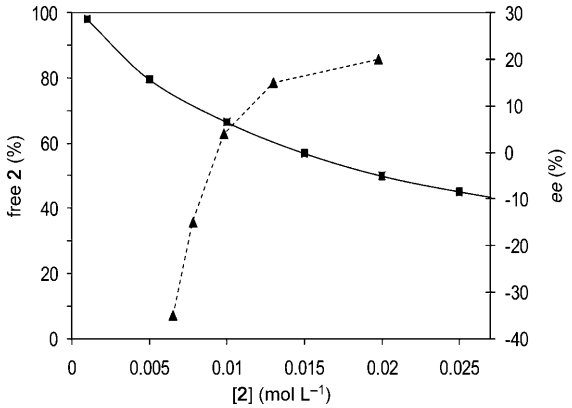
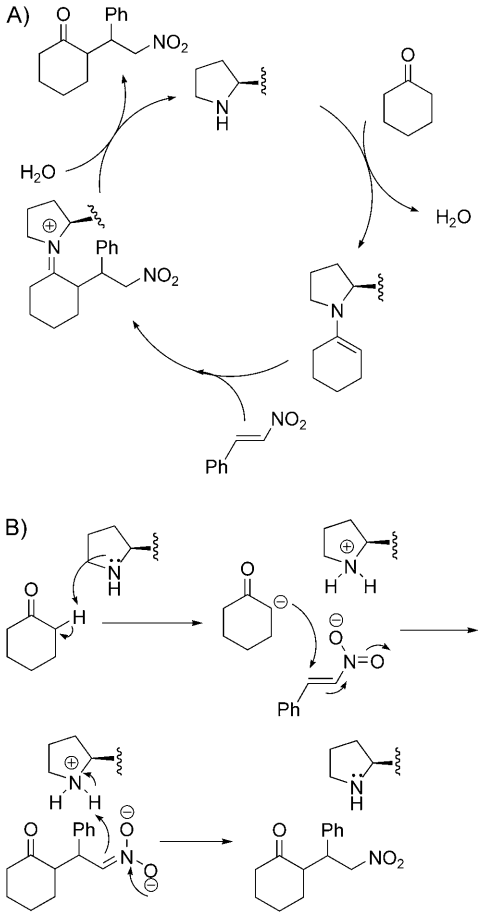


Figure 7. Calculated percentage of free **2** and isolated product enantiomeric excess (*ee*) at different total concentrations of **2**. ■: free **2** and ▲: *ee* syn-(2*R*,1′*S*).

Taking into account all of the information on structure and self-assembly mechanisms, the results of catalysis can be rationalized. Generally, two different mechanisms could account for this reaction : 1) the formation of an enamine intermediate after the reaction of cyclohexanone and catalyst and subsequent addition to nitrostyrene (Scheme 2 A), and 2) the formation of a cyclohexanone enolate by basic catalysis and further addition (Scheme 2 B). In general, it is accepted that most of proline catalysts developed for homogeneous catalysis proceed via enamine intermediates. However, in the current case we cannot ignore the second possibility when taking into account our previous results for similar compounds in acetonitrile. Indeed, we recently reported that gels formed by closely related compounds in acetonitrile were unable to form enamines, but showed a remarkable enhancement of basicity and were capable of catalyzing the Henry nitro aldol reaction.[5c]

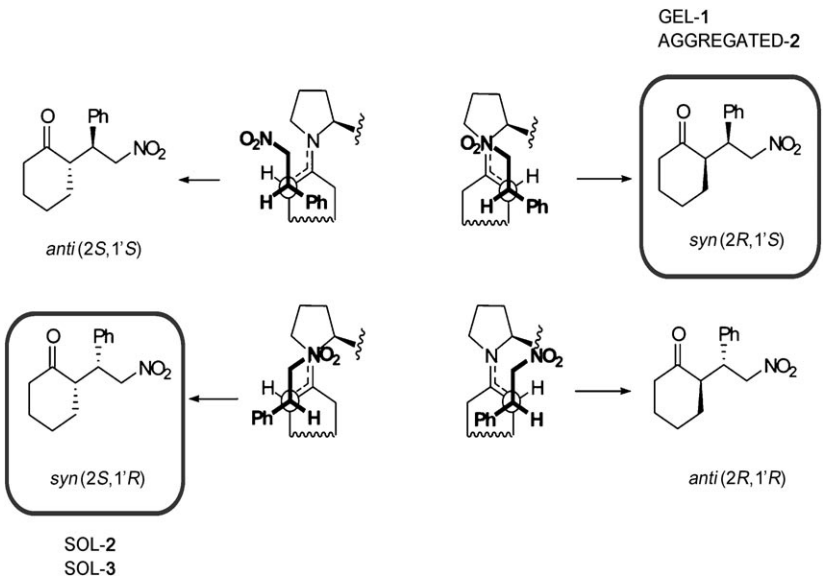


Scheme 2. Enamine- (A) and enolate-based (B) catalytic mechanisms.

To check this possibility, a test of gel formed by compound **1** in a toluene/hexane mixture as a catalyst for the Henry reaction between nitromethane (more acidic than cyclohexanone) and 4-nitrobenzaldehyde was performed (see the Supporting Information for details). It could be observed that after 3 d only 5% of nitroaldol was obtained, revealing that base catalysis was almost insignificant.

These results provide evidence for the remarkable solvent effect on the catalytic performance of the aggregates. This effect is clearly related to the different conformation adopted by compound **1** in the gel phase in both solvents, and highlights the importance of controlling all of the environmental parameters (solvent, polymorphism, cooperativity, etc.) in extended supramolecular catalytic systems.

A second question than needs examination is the stereoselectivity of the reaction. Scheme 3 summarizes the four possible modes of addition of the enamine intermediates to nitrostyrene, the crucial step for the stereoselectivity of the reaction. Probably, in solution, the orientation of the nitro group towards hydrogen-bonding sites of the catalyst leads to the formation of *syn*-(2*S*,1′*R*). In the aggregates, compounds **1** and **2** present a similar structure of the catalytic



Scheme 3. Stereochemical modes of addition of enamine catalyst intermediate to *trans*-β-nitrostyrene. Major enantiomer is highlighted for each case.

center, with all of the hydrogen-bonding sites involved in intermolecular interactions forming aggregates not available for interaction with the nitro group, leading to the observed enantioselectivity *syn*-(2*R*,1′*S*). However, since there is a significant amount of free-**2** in the range of concentration studied in catalysis, the catalytic activity of its aggregates overlaps with that of free molecules. As seen in Figure 7, the variation of *ee* values obtained at different concentrations of the catalyst **2** correlate well with the variation of free, non-aggregated, species. Indeed, at low concentration, most of compound **2** was not aggregated and enantioselectivity was reversed to *syn*-(2*S*,1′*R*), the same as that observed for non-aggregating compound **3**. On the other hand, since in the studied concentration range most of compound **1** is in the gel phase, the *ee* value is only slightly affected by concentration. Besides, the effect of temperature on the *ee* value is not as important as it is for compound **3**, which remains in solution, since molecules of **1** are rigidified within the fibrils even at room temperature.

Conclusion

We have reported an example of the appearance of new catalytic properties caused by self-assembly. There are few reports on the effect of aggregation on enantioselectivity and this is an important issue that has to be taken into account in homogeneous phase catalysis. Moreover, it can be conveniently used for the control of the reaction outcome. In this case, there is a reversal of stereoselectivity associated with a self-assembly-driven conformational change around the catalytic sites going from solution to the aggregated phase. These results can be also interesting in the context of studies of prebiotic chemistry. It has been proposed that self-assembly of small molecules could play an important role in chemical evolution from simple to more sophisticated systems by compartmentalization, but also by the appearance of new catalytic features.[12]

Furthermore, the use of a supramolecular gel for a stereoselective organocatalytic process may be very convenient. Although the enantioselectivity obtained herein is only moderate, it is remarkable that catalytic activity and selectivity in the gel phase is quite insensitive to temperature and concentration changes. The enantioselectivity is exclusively controlled by the steric environment of the catalytic site, which appears rigidified in a highly organized material. Supramolecular gels can be considered as self-supported catalytic heterogeneous phases,[13] and in contrast to classical solid-supported heterogeneous catalysts, the use of low-molecular-weight compounds and noncovalent interactions to build up the catalytic phase allows for simple synthetic procedures and easy access to libraries of potential catalysts. Furthermore, the reversible nature of these systems allows for easy recovery of the catalyst not only by filtration at the end of reaction but by pH or temperature change. Further studies are being carried out to improve stereoselectivity by simple structural changes, by using compound **2** derivatives as model compounds for the gels. We believe that this methodology can be exploited for the immobilization of most of the organocatalysts that are currently being used in homogeneous catalysis.

Acknowledgements

We thank Spanish Ministry of Science and Innovation (Grant CTQ2009-13961) and Universitat Jaume I-Bancaixa (grants P1·1B2007-11 and P1·1B2009-42) for financial support. F.R.L. thanks Generalitat Valenciana for a FPI fellowship.

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[14] CCDC-762391 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: March 15, 2010
Published online: June 10, 2010

