J|A|C|S ARTICLES

Published on Web 05/21/2009

Switchable Perfomance of an L-Proline-Derived Basic Catalyst Controlled by Supramolecular Gelation

Francisco Rodríguez-Llansola, Beatriu Escuder,* and Juan F. Miravet*

Departament de Química Inorgànica i Orgànica, Universitat Jaume I, Avda. Sos Baynat s/n, 12071 Castelló, Spain

Received April 2, 2009; E-mail: escuder@uji.es; miravet@uji.es

Abstract: An L-proline-derived low molecular weight gelator forms gels in nitromethane and nitroethane and acts as a basic catalyst for the Henry nitroaldol reaction of these solvents with 4-nitrobenzaldehyde and 4-chlorobenzaldehyde. The reported catalyst is efficient only upon aggregation into self-assembled fibrillar networks. The formation of the gels is associated to a basicity boost of the L-proline residues. Gel dissociation blocks the catalytic efficiency for the nitroaldol reaction but enhances a reaction pathway leading to alkenes. Because of the reversible nature of supramolecular gels, subtle temperature changes allow for a reversible sol−gel transition associated to an activation of the catalyst. The catalytic gel from nitroethane is significantly more active than the one from nitromethane probably because of its different structure as revealed by X-ray diffraction and thermal stability studies. The results shown indicate that in solution the L-proline moiety catalyzes the reaction of nitroalkanes with aldehydes via iminium intermediates while efficient nitroaldol reactions are promoted in the gel phase through an ionic pair type mechanism. The fact that upon aggregation the amino acid-based molecule used as gelator plays both a structural (gel formation) and catalytic role is interesting for the point of view of life origin studies.

Introduction

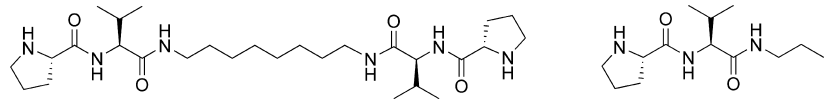
One of the key ideas of supramolecular chemistry is that noncovalent assemblies can present new functions or properties which are absent for the isolated components that comprise a supramolecule.[1] In particular, supramolecular catalysis has become an especially active field in recent years.[2] Different approaches to the development of supramolecular catalysts have been described which include the preparation of supramolecules that act as ligands with the appropriate bite angle for transition metals, and the use of supramolecular assemblies such as nanoreactors or catalytic capsules.[3] Supramolecular aggregation is also claimed to be responsible for interesting catalytic processes associated with chirality amplification.[4] Additionally, reversible covalent self-assembly has been used to develop catalysts.[5] The use of stimulus-controlled catalytic systems represents a challenge for the development of smart materials, and, for example, light has been described recently as a means to activate basicity.[6] In this context, the reversible nature of supramolecular interactions seems ideal for those purposes because functions such as catalysis can be controlled by stimuli that affect noncovalent bonding such as temperature, concentration of species, or solvent polarity among others.

Following our work in the study of supramolecular gels, we are interested in the use of these systems as catalysts. Supramolecular gels are formed in most cases by extended supramolecular aggregates that are built through the anisotropic 1-D assembly of low molecular weight molecules. The self-assembled fibrilar networks formed in this way percolate the solvent and provoke gelation.[7] We believe that these systems are interesting candidates as catalysts because of several reasons: (1) supramolecular gels can behave as self-supported catalyst that can be filtered out of the reaction and present a large active surface; (2) their formation is in most cases reversible (controlled by temperature and concentration) which could result in a tunable catalytic activity; (3) self-assembled fibers commonly present a well ordered arrangement of gelator molecules, which in the case of catalytic groups could result in enhanced efficiency

(1) (a) Lehn, J.-M. *Supramolecular Chemistry*; VCH: New York, 1995. (b) Ariga, K.; Kunitake, T. *Supramolecular Chemistry - Fundamentals and Applications*; Springer: New York, 2006. (c) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley-VCH, New York, 2008.
(2) *Supramolecular Catalysis*; van Leeeuwen, P. W. N. M., Ed.; Wiley-VCH: New York, 2008.
(3) (a) Vriezema, D. M.; Comellas, M.; Elemans, J. A. A. W.; Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105*, 1445–1489. (b) Laungani, A. C.; Slattery, J. M.; Krossing, I.; Breit, B. *Chem.—Eur. J.* **2008**, *14*, 4488–4502. (c) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 11423–11429. (d) de Greef, M.; Breit, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 551–554.
(4) Schiaffino, L.; Ercolani, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6832–6835.
(5) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J. L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652–3711.
(6) Stoll, R. S.; Peters, M. V.; Kuhn, A.; Heiles, S.; Goddard, R.; Bühl, M.; Thiele, C. M.; Hecht, S. *J. Am. Chem. Soc.* **2009**, *131*, 357–367.
(7) (a) *Molecular Gels: Materials with Self-Assembled Fibrillar Networks*; Weiss, R. G.; Terech, P., Eds.; Springer: New York, 2005. (b) *Low Molecular Mass Gelators*; FagesF., Ed.; Springer: New York, 2005. (c) Terech, P.; Weiss, R. G. *Chem. Rev.* **1997**, *97*, 3133–3159. (d) Abdallah, D. J.; Weiss, R. G. *Adv. Mater.* **2000**, *12*, 1237–1247. (e) van Esch, J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 2263–2354. (f) Gronwald, O.; Shinkai, S. *Chem.—Eur. J.* **2001**, *7*, 4328–4334. (g) Estroff, L. A.; Hamilton, A. D. *Chem. Rev.* **2004**, *104*, 1201–1207. (h) Hirst, A. R.; Smith, D. K. *Chem.—Eur. J.* **2005**, *11*, 5496–5508. (i) Sangeetha, N. M.; Maitra, U. *Chem. Soc. Rev.* **2005**, *34*, 821–836. (j) Hirst, A. R.; Escuder, B.; Miravet, J. F.; Smith, D. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 8002–8018.

10.1021/ja902589f CCC: $40.75

Scheme 1



1 2

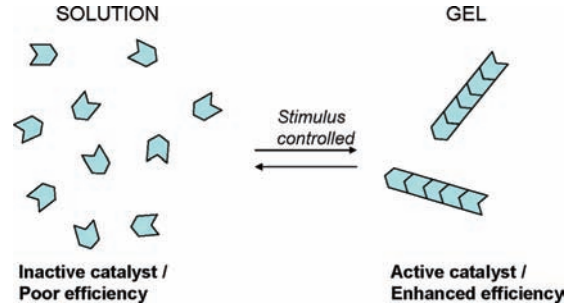
associated with the cooperation among catalytic units or with conformational restrictions. Supramolecular gels can be considered as heterogeneous catalysts that present interesting properties such as self-reparation capabilities, which are absent in conventional heterogeneous catalytic systems.

It has been reported that supramolecular gels with reactive groups can participate in chemical reactions with reagents in solution or in photochemical processes.[8] The use of supramolecular gels in catalysis constitutes an almost unexplored field and only a few examples of catalysis carried out with supramolecular gels or fibrilar aggregates have been reported. The results described in this area include organocatalysis[9] to invoke hydrocyanation or a hydrolysis reaction, metallocatalysis,[10] and the use of supramolecular gels as phase transfer catalysts.[11]

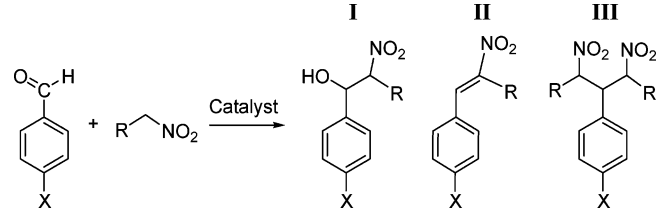
With these ideas in mind, we decided to study gelators containing L-proline moieties as catalysts. The gelator used in this study (**1**, Scheme 1) contains terminal L-proline moieties attached to a L-valine-based gelator scaffold that we have used in previous studies on supramolecular gels.[12] The gelation properties of **1** in acetonitrile have been reported recently.[13] Additionally, we have found that the aggregation of **1** in self-assembled fibrillar networks inhibits the catalytic activity of the L-proline moiety in enamine-based aldol reactions and results in a remarkable increase of its basicity.[14] This property could be ascribed to the cooperation of vicinal L-proline goups in the gel fibers in the proton abstraction process. The aim of this work is to demonstrate how supramolecular gelation can be used to develop systems that present catalytic properties that are absent in solution (see Scheme 2) and, in particular, to explore the use of supramolecular gels as basic catalysts in the nitroaldol Henry reaction.

The nitroaldol Henry reaction was chosen for these purposes because it is advantageous for several reasons. It is an example of a base-catalyzed reaction which has been extensively studied and the mechanisms of the main reaction and of possible side reactions are well understood. Additionally, typical substrates for this reaction such as nitroethane and nitromethane are appropriate solvents for supramolecular gel formation by molecule **1**. A challenge in the development of new promoters

Scheme 2



Scheme 3



for the Henry reaction is to avoid side processes such as dehydration (see Scheme 3) and to achieve enantioselective catalysis.[15] Heterogenous basic catalyst for the Henry reaction have been described in the literature with the use, for example, of alumina, hydrotalcite, silica and with functionalized mesoporous silica materials.[16] It has to be mentioned that L-proline is not found among the wide variety of bases which have been described to promote the Henry reaction because its low basicity.

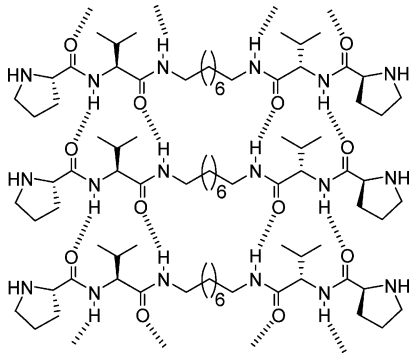
Results and Discussion

Compound **1** has been shown to form gels in acetonitrile.[13] We have found that this compound also forms gels in nitromethane and nitroethane, the solvents used in the catalytic studies that will be discussed later. Gel formation can be explained by the formation of aggregates through multiple H-bonding interactions.[12,17] A schematic model proposed for such interactions, based on those reported for related molecules, is shown in Scheme 4.

The mininum concentration of **1** for gel formation at 20 °C in nitromethane and nitroethane was found to be 3 mM and 18 mM, respectively. The thermal stability of these gels was studied using the vial inversion methodology, and the results are shown in Figure 1. The onset temperature for the gel disassembly (T_{gel}) presents a typical dependence with concentration showing a plateau above certain concentrations (see Figure 1). This can be explained having in mind the exponential relationship

(8) (a) Miravet, J. F.; Escuder, B. *Org. Lett.* **2005**, *7*, 4791–4794. (b) Love, C. S.; Chechik, V.; Smith, D. K.; Ashworth, I.; Brennan, C. *Chem. Commun.* **2005**, 5647–5649. (c) Miravet, J. F.; Escuder, B. *Tetrahedron* **2007**, *63*, 7321–7325. (d) Dawn, A.; Fujita, N.; Haraguchi, S.; Sada, K.; Shinkai, S. *Chem. Commun.* **2009**, 2100–2102.
(9) (a) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181–185. (b) Guler, M. O.; Stupp, S. I. *J. Am. Chem. Soc.* **2007**, *129*, 12082–12083.
(10) (a) Xing, B.; Choi, M.-F.; Xu, B. *Chem.—Eur. J.* **2002**, *8*, 5028–5032. (b) Miravet, J. F.; Escuder, B. *Chem. Commun.* **2005**, 5796–5798. (c) Tu, T.; Assenmacher, W.; Peterlik, H.; Weisbarth, R.; Nieger, M.; Dötz, K. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6368–6371.
(11) Tu, T.; Assenmacher, W.; Peterlik, H.; Schnakenburg, G.; Dötz, K. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7127–7131.
(12) (a) Escuder, B.; Marti, S.; Miravet, J. F. *Langmuir* **2005**, *21*, 6776–6787.
(13) Rodríguez-Llansola, F.; Miravet, J. F.; Escuder, B. *Chem. Commun.* **2009**, 209–211.
(14) Rodríguez-Llansola, F.; Miravet, J. F.; Escuder, B. *Org. Biomol. Chem.* **2009**, DOI: 10.1039/b904523f.
(15) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945.
(16) (a) Akutu, K.; Kabashima, H.; Seki, T.; Hattori, H. *Appl. Catal., A* **2003**, *247*, 65–74. (b) Hoffmann, F.; Cornelius, M.; Morell, J.; Fröba, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3216–3251.
(17) (a) Hanabusa, K.; Tanaka, R.; Suzuki, M.; Kimura, M.; Shirai, H. *Adv. Mater.* **1997**, *9*, 1095–1097. (b) Doi, M.; Asano, A.; Yoshida, H.; Inouguchi, M.; Iwanaga, K.; Sasaki, M.; Katsuya, Y.; Taniguchi, T.; Yamamoto, D. *J. Pept. Res.* **2005**, *66*, 181–189.

Scheme 4



between solubility and temperature.[18] In accordance with the higher concentration required for forming gels in nitroethane as compared to nitromethane, T_{gel} values are significantly lower in the former solvent in the range of concentrations 10−50 mM.

Scanning electron microscopy images of the xerogels formed by **1** in nitromethane and nitroethane revealed a microscopic fibrillar structure which is a common feature in many examples of supramolecular gels (Figure 2). These fibers are microcrystalline as demonstrated by X-ray powder diffraction studies carried out for the xerogels. As seen in Figure 3, different diffraction patterns were obtained for the xerogels prepared from nitromethane and nitroethane, indicating different microcrystalline arrangements. This fact agrees with the rather important differences in gelation efficiency of **1** in nitromethane and nitroethane which could be related to the different polarities of these solvents (dielectric constants at 298 K are, respectively, 35 and 28).

A key issue in the catalytic studies that were planned was the expected basicity boost of L-proline secondary amine upon gel formation. The use of an acid−base indicator dye is very convenient to qualitatively test this property. As can be seen in Figure 4, bromothymol blue is drawn to its blue form in the presence of the gel formed by **1** in nitromethane but remains yellow in the presence of a diluted solution of **1** (concentration lower than 2 mM) or when compound **2**, which is an analogue of **1** that does not form gels (see Scheme 1), is present. As a reference, it is worth noting that the pK_a of bromothymol blue in a solvent of similar polarity such as acetonitrile has been shown to be ca. 18. In this solvent the dye can be drawn to its basic form by bases such as pyrrolidine (the pK_a of its conjugated acid in acetonitrile is 19.5).[14] Interestingly, the basicity enhancement can be monitored with the help of ^{1}H NMR spectroscopy (Figure 5). The ^{1}H NMR spectra of **1** recorded in nitromethane-d_3 for a solution and a gel differ remarkably in the disappearance of the L-valine NH signal. This behavior can be understood on the basis of the higher basicitiy of the L-proline moieties in the gel sample which would provoke deuteration of the L-proline amine as a result of deuterium abstraction from nitromethane-d_3. The deuteration of L-valine NH can be explained because L-valine amide and L-proline amine NHs are in fast chemical exchange due to the intramolecular H-bond present in this compound[13] (see Figure 5).

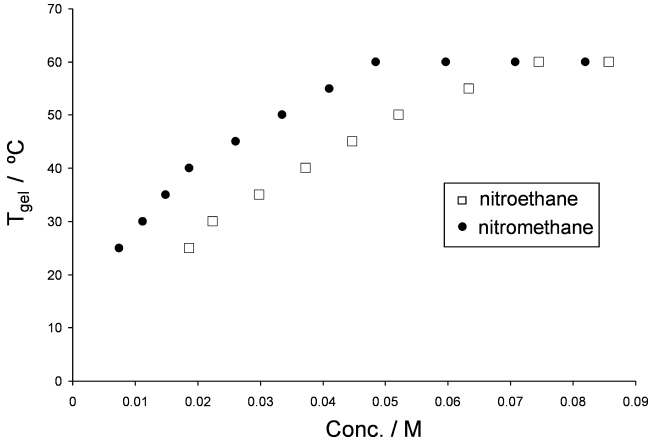


Figure 1. Measured thermal stability of the supramolecular gels formed by compound **1** at different concentrations in nitromethane and nitroethane.

To study the activity of the gels as catalysts for the Henry reaction, 4-nitrobenzaldehyde was used as substrate in the initial studies. In a typical procedure the gel was prepared using as solvent the corresponding nitroalkane, and then a solution of 4-nitrobenzaldehyde was left to diffuse into the gel (see Scheme 5). The diffusion of reactants could be monitored easily because of the yellowish color of nitrobenzaldehyde solution which permeated all the gel after ca. 2 h. After the corresponding reaction time, the gel was disassembled by addition of acidic water and chloroform. In this way the protonated gelator is solubilized in the aqueous phase while the reaction products are isolated from the organic phase. The catalyst can be recovered by basification of the aqueous phase and extraction with chloroform. Alternatively, the solution over the gel can be decanted and the product isolated from there. Although in this way part of the product is retained in the gel phase, the gel could be reused for the transformation of further aldehyde at least three times with similar efficiency.

The studies were carried out both at temperatures above and below gel−sol transition. Additionally, experiments were carried out with compound **2** which, as mentioned above, is a structurally simpler analogue of gelator **1** that does not form gels and is soluble in all the reaction conditions that were studied. The results obtained for the reaction using nitroethane as solvent and reagent are collected in Table 1.

It can be noticed that a quantitative conversion of the aldehyde to the corresponding nitroaldol was obtained only in the case where a gel was present, entry 1 in Table 1, namely using the gel formed by **1** at 5 °C. When the reaction was carried out at 25 °C, the gel formed in nitroethane was converted to a solution and, remarkably, the conversion of aldehyde dropped noticeably and only 15% yield of nitroaldol was isolated (entry 2). In this case, side products corresponding to dehydratation (II in Scheme 3) and conjugated addition to the nitroalkene (III in Scheme 3) were detected. As can be seen in entries 3 and 4 of Table 1, the use of nongelling molecule **2**, which is formally a half of **1**, yielded nitroaldol in poor yields both at 5 and 25 °C accompanied by similar amounts of side products. The similarity of the results obtained in entries 2−4 indicate that the active catalytic species in those systems are similar and correspond basically to free, nonaggregated, L-proline moieties. The use of 4-chlorobenzaldehyde afforded similar results, a sharp change in the perfomance of the catalyst being noticeable upon gel formation. As shown in Figure 6, the reactions carried out with gels at −20 and 5 °C afforded the nitroaldol in ca. 70% yield after 48 h with negligible formation of alkene side product.

(18) Hirst, A. R.; Coates, I. A.; Boucheteau, T. R.; Miravet, J. F.; Escuder, B.; Castelletto, V.; Hamley, I. W.; Smith, D. K. *J. Am. Chem. Soc.* **2008**, *130*, 9113–9121.

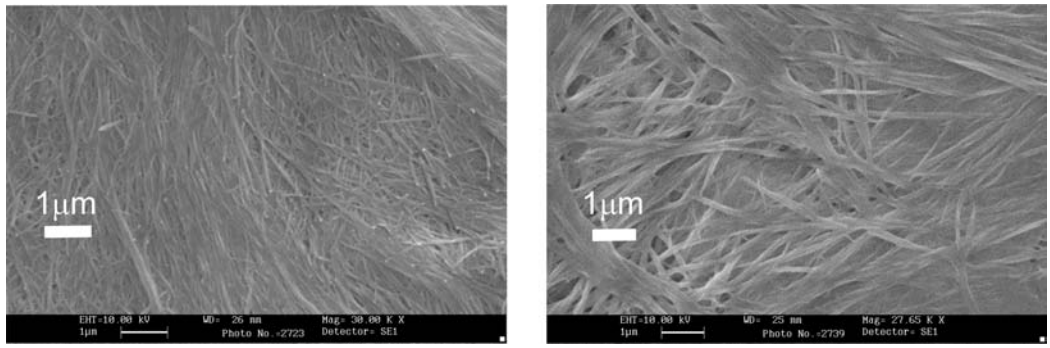


Figure 2. Scanning electron microscopy images of the xerogels of **1** from nitromethane (left) and nitroethane (right).

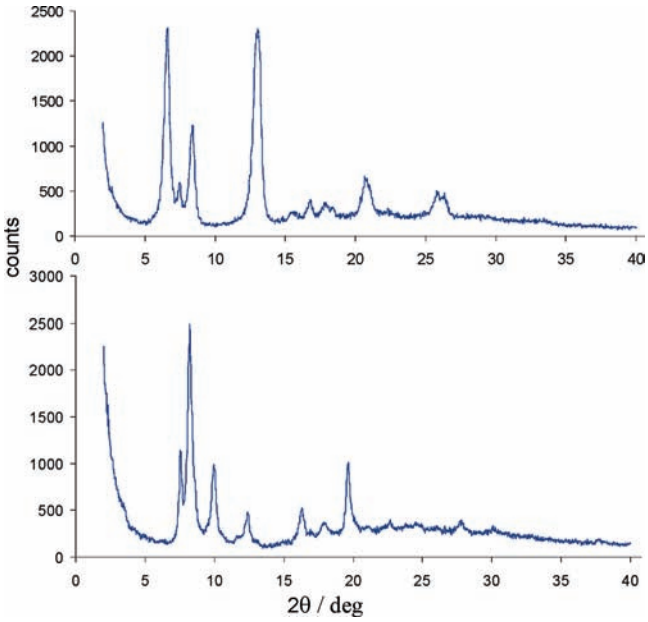


Figure 3. X-ray powder diffractograms obtained for the xerogels of **1** from nitromethane (top) and nitroethane (bottom).

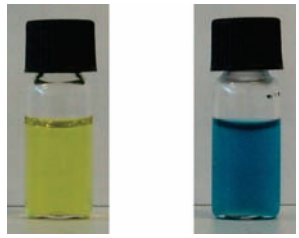


Figure 4. Samples prepared using nitromethane as solvent and containing bromothymol blue as an acid−base indicator. Left: Compound **2** ([**2**] = 33 mM); Right: gel formed by compound **1** ([**1**] = 16.5 mM).

However, the reactions carried out at temperature values where the gel is disassembled (25 and 50 °C) afforded a conversion below 5%, revealing that in this temperature range the basic catalysis is deactivated. It is interesting to note that similar yields are described for the reaction carried out at −20 and 5 °C which is unexpected considering the reactivity increase observed commonly at higher temperatures. This result can be understood having in mind the dynamic nature of supramolecular gels, which can present significant amounts of gelator molecules in solution that are in equilibrium with the solid-like fibers. For example, the solubility at 25 °C of gelator **1** in nitromethane-d_3 was calculated to be 0.8 mM with the use of NMR measurements. Additionally, the solubility of gelator **1** in nitroethane at 25 °C is ca. 15 mM as estimated from the expected relationship between solubility and T_{gel}.[18] Decreasing temperature reduces the amount of molecules in solution and therefore increases the amount of catalytically active molecules in the system, compensating for the temperature reduction. Overall, it is remarkable how easily the reaction outcome can be controlled with the temperature, the impressive activation of the catalyst upon *decreasing* temperature as a result of gel formation being counterintuitive.

These results can be understood if one considers two reaction pathways for the reaction of nitroethane with 4-nitrobenzaldehyde as shown in Scheme 6.[19] In the presence of a gel, the L-proline fragment would act as a basic catalyst promoting the nitroaldol reaction through the so-called ionic pair type mechanism which is initiated by nitroalkane deprotonation. However, in solution an iminium-based mechanism would be operative and responsible for the formation of dehydrated product that could suffer a further conjugated addition of nitroalkane. Interestingly, L-proline units in the gel seem to be inactive for the formation of imines probably due to steric effects. This fact has also been observed when the aldol reaction was assayed in acetonitrile gels.[14] Regarding the stereoselectivity of the nitroaldol reaction, a mixture of anti and syn diastereomers was obtained with a ca. 1:1 ratio (determined by NMR). No enantioselectivity was found by chiral HPLC in the nitroaldol formation in any of the reactions.

The behavior described above for the reaction with nitroethane was also observed in the case of nitromethane (see Table 2). In this solvent the reaction in the gel phase resulted in almost negligible amounts of alkene (entry 1, Table 2) although the reaction was significantly slower than that carried out in nitroethane, and 6 days were required to obtain 84% yield of nitroaldol (entry 2, Table 2). Reactions carried out in a nitromethane solution or with the use of nongelling compound **2** (entries 3−6, Table 2) afforded poor yields of nitroaldol with important amounts of the products associated to the iminium mechanism. The significant decrease of reactivity found upon changing from nitroethane to nitromethane probably cannot be ascribed to the slightly higher acidity reported for nitroethane as compared to nitromethane (pK_a values in DMSO are, respectively, 16.7 and 17.2).[20] Most likely the change in reactivity should be associated with the fact that the gel formed by **1** in nitroethane presents a higher basicity than the one in

(19) Bass, J. D.; Solovyov, A.; Pascall, A. J.; Katz, A. *J. Am. Chem. Soc.* **2006**, *128*, 3737–3747.
(20) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.

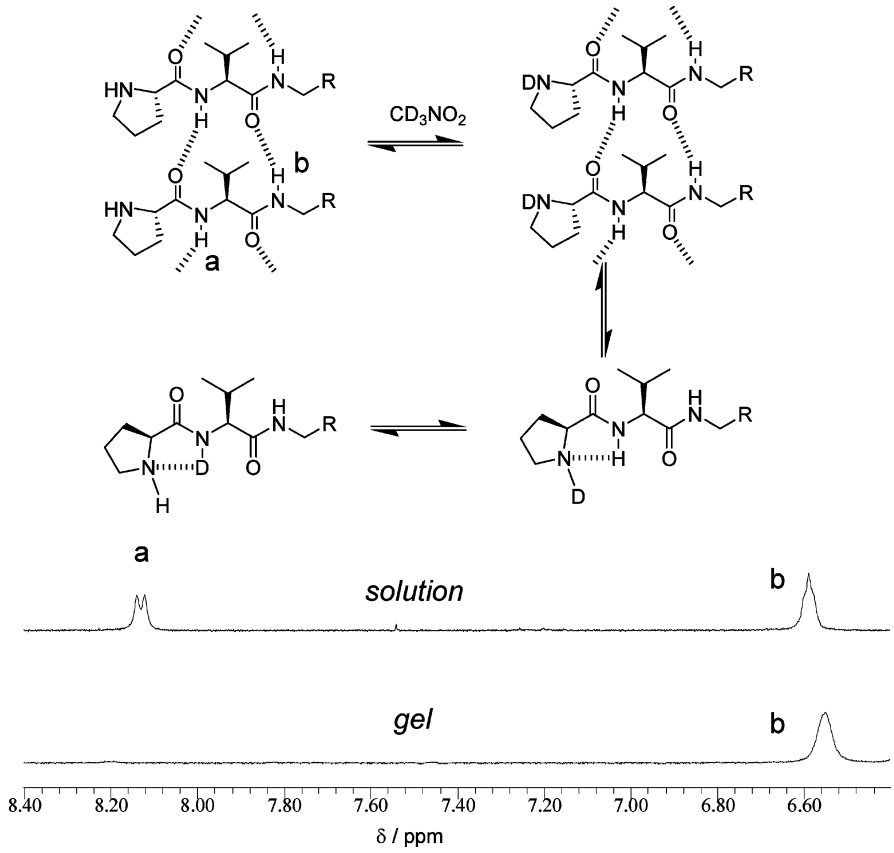


Figure 5. Mechanism proposed for the observed amide deuteration and partial ^{1}H NMR spectra of compound **1** in CD_3NO_2. Solution: [**1**] = 0.5 mM; gel: [**1**] = 5 mM.

Scheme 5

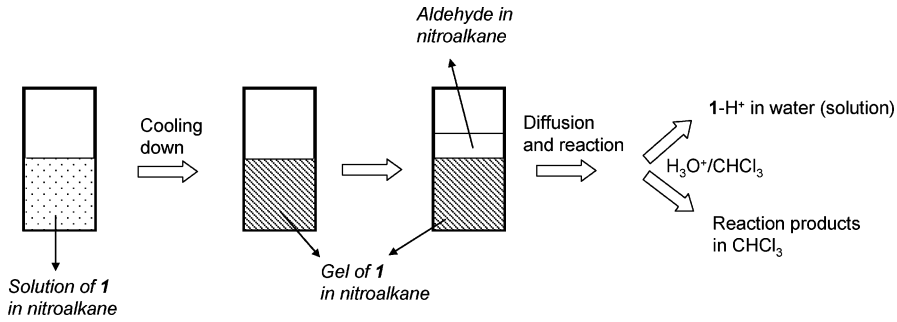


Table 1. Yields of Nitroaldol Obtained for the Reaction of Nitroethane and 4-Nitrobenzaldehyde in the Presence of Catalyst **1** and **2**[a]

entry	catalysts	*T* (°C)	yield of nitroaldol (%)	yield of II + III (%)[b]
1	**1**	5 (gel)	99	-
2	**1**	25 (solution)	15	5
3	**2**	5 (solution)	14	10
4	**2**	25 (solution)	15	16

[a] [**1**] = 13 mM; [**2**] = 26 mM; [aldehyde] = 130 mM; total volume 1.3 mL; reaction time = 48 h. [b] See Scheme 3.

nitromethane. The above-mentioned differences in the microcrystalline structure of the gels supports this hypothesis and suggest that the arrangement of L-proline units in the gel fibers formed in nitroethane results in a stronger basicity (bromothymol blue was not useful to study this issue because it was drawn to its blue form in both gels).

When the gel-promoted reaction in nitromethane was carried out with 4-chlorobenzaldehyde, the conversion was significantly smaller than that observed with 4-nitrobenzaldehyde, reflecting the lower reactivity of 4-chlorobenzaldehyde (see Table 3).

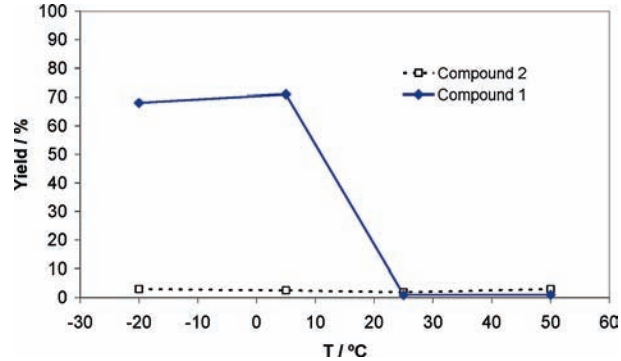


Figure 6. Yield of nitroaldol as a function of temperature for the reaction of 4-chlorobenzaldehyde with nitroethane using compounds **1** (solid line) and **2** (dashed line) as catalysts. ([**1**] = 13 mM; [**2**] = 26 mM; [aldehyde] = 130 mM; total volume 1.3 mL; reaction time = 48 h).

Scheme 6

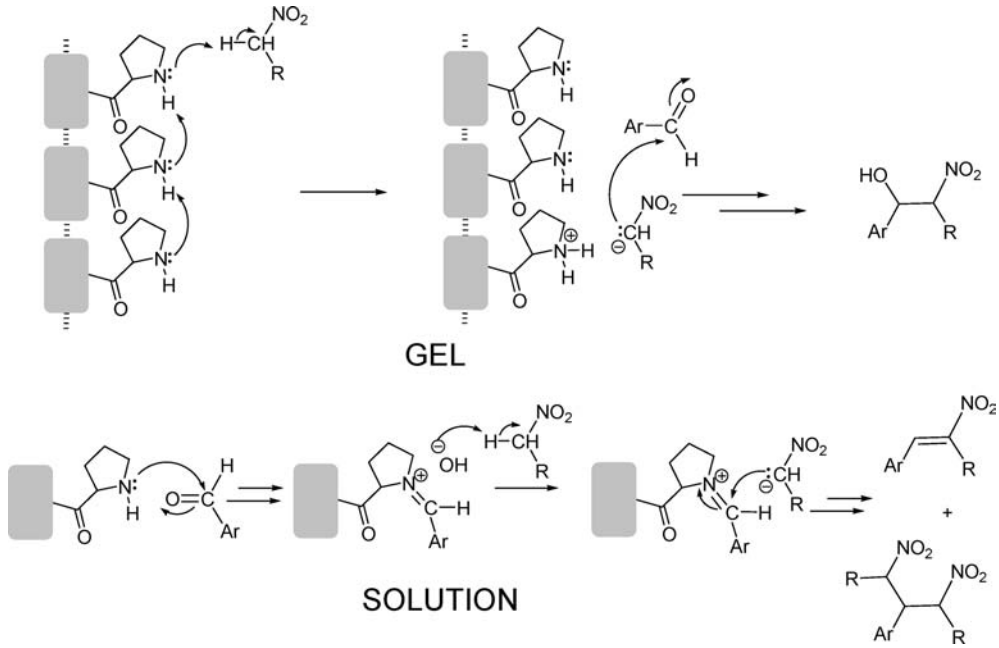


Table 2. Yields of Nitroaldol Obtained for the Reaction of Nitromethane and 4-Nitrobenzaldehyde in the Presence of Catalyst **1** and **2**[a]

entry	catalyst	reaction time, days	*T* (°C)	yield of nitroaldol (%)	yield of II + III (%)[b]
1	**1**	2	5 (gel)	38	2
2	**1**	6	5 (gel)	84	3
3	**1**	2	50 (solution)	46	33
4	**2**	2	5 (solution)	7	7
5	**2**	6	5 (solution)	13	25
6	**2**	2	50 (solution)	24	54

[a] [**1**] = 13 mM; [**2**] = 26 mM; [aldehyde] = 130 mM; total volume 1.3 mL. [b] See Scheme 3.

Table 3. Yields of Nitroaldol Obtained for the Reaction of Nitromethane with Different Aromatic Aldehydes in the Presence of Catalyst **1**[a]

entry	reagent	*T* (°C)	yield of nitroaldol (%)	yield of II + III (%)[b]
1	4-nitrobenzaldehyde	5 (gel)	38	2
2	4-nitrobenzaldehyde	50 (solution)	46	33
3	4-chlorobenzaldehyde	5 (gel)	11	4
4	4-chlorobenzaldehyde	50 (solution)	-	99
5	4-methoxybenzaldehyde	5 (gel)	-	-
6	4-methoxybenzaldehyde	50 (solution)	-	100

[a] [**1**] = 13 mM; [aldehyde] = 130 mM; total volume 1.3 mL; reaction time = 48 h. [b] See Scheme 3.

Despite this, a "gel effect" was also clearly manifested in this case, affording nitroaldol as the prevailing product in the presence of the gel (entry 3, Table 3). Interestingly, the analogue reaction in solution at 50 °C (entry 4) afforded exclusively the products obtained via the iminium mechanism with no nitroaldol detected. This result differs from that found for 4-nitrobenzaldehyde which yielded a significant amount of nitroaldol when the reaction was carried out in solution at 50 °C (entry 2). It can be rationalized that the presence of the chlorine substituent in aromatic aldehyde favors the iminium mechanism over the ion-pair mechanism both by resonance stabilization of the cationic iminium intermediate and by diminishing the reactivity of the aldhehyde toward nucleophiles. The results obtained with 4-methoxybenzaldehyde agree with this reasoning. The use of this deactivated aldehyde produced no reaction at 5 °C in the presence of a gel formed by **1** in nitromethane (entry 5, Table 3). However a quantitative conversion to the nitroalkene and its derivative was obtained at 50 °C for the same system, and no nitroaldol product was detected in this case (entry 5, Table 3). Therefore, 4-methoxybenzaldehyde is found to be completely unreactive toward an ion-pair type mechanism but reacts very efficiently via an iminium mechanism.

It is worth noting that the results described above with the use of supramolecular gels as catalyst for the nitroaldol reaction belong to the area of heterogeneous catalysis because the active species are solid-like microfibers. In particular, heterogeneus amine type catalysts suported on mesoporous silica have been described which produced nitroaldol products with the use of secondary and tertiary amines but yielded alkenes and its derivatives with the use of primary amines.[21] In a related work, nitroaldol product could be prepared efficiently with the use of primary amines supported on silica and controlling the acid−base properties of the material.[19] However, the results presented here are unprecedented in the sense that the same catalyltic moeity shows a dual behavior depending on its aggregation state, which can be regulated easily with minor temperature changes.

Conclusions

For the first time a sharp change in catalytic activity associated with supramolecular gelation is described. The activation of compound **1** as an efficient catalyst for the Henry reaction upon gel formation serves as a proof of principle, showing that catalytic activity may arise as a result of enhanced properties (basicity in this case) associated with aggregation phenomena. The reversible nature of supramolecular gels makes these results especially interesting because the catalytic activity can be regulated by minor temperature changes (for example from 5 to 25 °C in one case) which produce either gel formation or dissociation. It can be envisaged that this type of tunable catalyst

(21) Anan, A.; Vathyam, R.; Sharma, K. K.; Asefa, T. *Catal. Lett.* **2008**, *126*, 142–148.

may have very interesting applications, especially if one considers the different stimuli than can be used, aside from temperature, to regulate gel formation such as concentration or the presence of chemical species among others. In the case reported here molecule **1** behaves as a heterogeneous catalyst for the nitroaldol reaction. An interesting point is that the catalyst can be easily recovered and reused by filtration. Under these conditions, the prevailing reaction mechanism most likely starts with the deprotonation of the nitroalkane by the secondary amine of L-proline. Remarkably, when **1** is in solution, a different mechanism may operate which is based in the formation of iminium intermediates that evolve to nitroalkenes. It has been shown that the gel catalyzes the Henry reaction with both highly and moderately reactive aldehydes such as 4-nitrobenzaldehyde and 4-chlorobenzaldehyde. A deactivated aromatic aldehyde such as 4-methoxybenzaldehyde is not reactive through the ionic pair mechanism but is converted quantitatively to nitroalkenes and their derivatives in solution. This case serves as an example of a soluble catalyst that can be inactivated by gel formation upon decreasing the temperature.

Finally, it can be mentioned that these results may be relevant in the context of life origin studies. The role of self-assembling molecules, particularly surfactants, in the early stages of origin of life has been pointed out.[22] The amino acid-based molecule **1** represents an interesting example of a self-assembling low molecular weight species because it can play a dual role, behaving as a structuring agent (as surfactants do) and, additionally, as a catalyst after aggregation.

Acknowledgment. We gratefully acknowledge financial support from the DGICYT (CTQ2006-14984) and Universitat Jaume I-Bancaixa (P1.1A2006-1). We acknowledge technical support from SCIC (Universitat Jaume I). F.R-L. thanks Generalitat Valenciana for a FPI fellowship.

Supporting Information Available: Experimental section, ^{1}H NMR spectra of reaction crude products, and pictures of the catalytic gels. This material is available free of charge via the Internet at http://pubs.acs.org.

JA902589F

(22) Walde, P. *Origins Life Evol. B* **2006**, *36*, 109–150.