

Remarkable increase in basicity associated with supramolecular gelation†

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L-Proline derivatives which are able to form supramolecular gels show an amazing basicity increase in the aggregated (gel) state as compared to solution. As a result they behave as enantioselective catalysts for the aldol reaction in solution but produce a base-catalyzed aldol racemisation in the gel state.

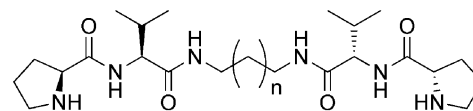
Introduction

Supramolecular catalysis may present several advantageous features when compared with conventional homogeneous and heterogeneous catalysis. Those are, for instance, precise organization of catalytic sites, reversibility and the ability for self-correction among others.¹ In particular, supramolecular gels are soft solid materials formed by the assembly of low molecular weight compounds through noncovalent interactions. In these materials molecular information (structure and function) is precisely translated from the molecular into the supramolecular level. Furthermore, in many cases the fibrillar networks present in a gel are microcrystalline, with functional groups in a precisely organized environment.² These characteristics prompted us to study supramolecular gels as heterogeneous supramolecular catalytic systems by preparing gelators with active groups on its periphery. We have already described catalytic Pd-loaded supramolecular gels designed for use in the aerobic oxidation of alcohols and other Pd catalysed organic processes.³ There we showed that gelator fibres were accessible and capable of interacting with different species—Pd(II) in that case—after diffusion through the gel matrix.

Here, we describe the first example of a designed organocatalytic gel in which a dramatic change in activity is observed upon aggregation into fibrillar gels. To our knowledge there are only two previously reported related examples in literature: the first one was reported by Inoue *et al.*, who serendipitously found that some cyclic dipeptides were able to catalyse the asymmetric addition of HCN to aldehydes in the gel phase; a second example has been recently reported by Stupp *et al.* in which His-containing peptides were able to form self-assembled fibres and catalyse ester hydrolysis.⁴ More recently, Dötz *et al.* described the use of gels formed by benzimidazolium salts as phase transfer catalysts.⁵

Results and discussion

Compounds **1a–c** (Scheme 1) were initially designed as catalysts for the aldol reaction as they are built with an L-proline fragment, one of the most studied organocatalysts.⁶ The bolaamphiphilic backbone based on L-valine has been used by us and others as a robust assembling fragment that renders fibrillar aggregates.⁷ The



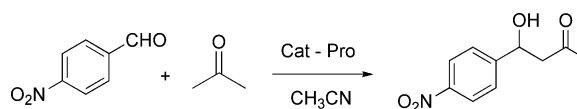
1a–c, n = 1, 4, 6

Scheme 1

synthesis and detailed aggregation behaviour of compounds **1a–c** has been recently described by us.⁸ These compounds form gels in several organic solvents, with the main driving force being the formation of an array of intermolecular H-bonds between amide groups.

Before starting any catalytic study in a gel some experimental variables have to be established. First, it has to be considered that a supramolecular gel is a dynamic system in which a fraction of the molecules remain in solution in equilibrium with the phase separated fibrillar material. This fraction of molecules stays either as free molecules or as small oligomers, depending on the degree of cooperativity of the aggregation process⁹ and can be easily quantified by ¹H NMR with the use of an internal standard.¹⁰ Secondly, and in consequence, in any reaction performed in a gel it has to be determined whether the reaction is taking place in solution or in the gel fibres as the results may differ considerably.¹¹

Keeping all these considerations in mind, we started the study of the catalytic activity of compounds **1a–c** in the aldol reaction between acetone and 4-nitrobenzaldehyde as a benchmark reaction (Scheme 2). The aldol reaction catalysed by L-Pro and derivatives is one of the most widely studied organic transformations. The mainly accepted mechanism implies the formation of an enamine by reaction of the heterocyclic secondary amino group with a ketone and further attack on the aldehyde *via* a six-membered transition state stabilised by some H-bonds between the aldehyde O and Pro OH or amide NH. Steric interactions around this transition state are responsible for the observed stereoselectivity.⁶ In our study, gel samples were prepared by dissolving the required amount of compound in hot acetonitrile and, after quick addition of acetone, being cooled down to –20 °C in order to form a kinetically trapped gel. Afterwards, the aldehyde was diffused through the gel and the reaction was kept at this temperature.



Scheme 2

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Under these experimental conditions the concentration of free gelator in solution was determined to be 6.5 mM for **1a** and 2.4 mM for **1b** and **1c**. For that reason, blank experiments with non-aggregated solutions at the same concentration as the solution coexisting with the gel were studied for comparison.

Results are collected in Fig. 1. As can be seen, yields of the aldol in the presence and in the absence of gel were quite similar indicating that most likely the aldol reaction was taking place in solution. This suggests that the reaction in solution is much faster than in the fibres or that even it is not taking place there.

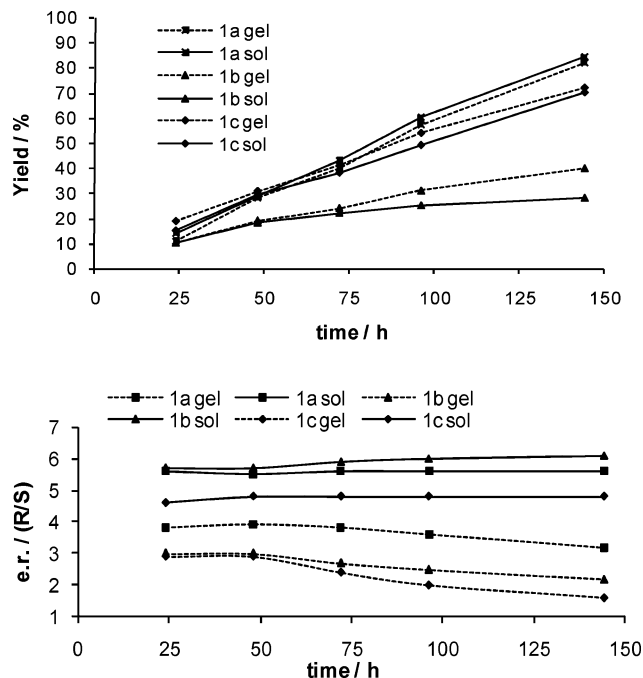


Fig. 1 Results of the aldol reaction between acetone (1.2 M) and 4-nitrobenzaldehyde (60 mM) in acetonitrile catalyzed by **1a–c** in solution and in gel; (top) aldol yield; (bottom) enantiomeric ratio (e.r., *R/S*).

Intriguing results were found for the enantiomeric ratios (e.r.) of both systems. In the case of the solutions, e.r. were determined to be about 1 : 5 to 1 : 7 and remained constant over long reaction times. However, when gels were present a tendency to racemisation was observed with time, being more pronounced in the case of compound **1c**. This different behaviour suggested that the presence of the gel phase was responsible for the racemisation.

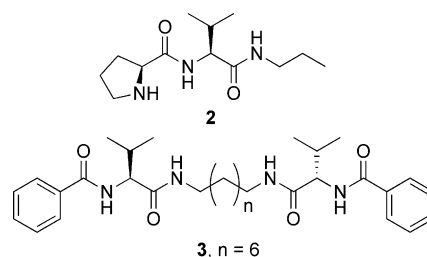
In order to investigate this possibility, additional experiments were performed in which a solution of aldol of a given optical purity was diffused through samples of the gels in acetonitrile. Results revealed that after 2 weeks the e.r. was reduced considerably in the gel samples whereas it remained unchanged for the corresponding solutions (Table 1).

Especially revealing is the comparison of the results obtained with the gel formed by **1c** and with compound **2** (Scheme 3) which is an analogue of **1c** that does not form gels. It can be observed that, although the gel of **1c** and the solution of **2** present the same equivalents of L-proline units, racemisation is only observed in the case of the gel sample. These experiments confirmed that the gel was responsible for the racemisation of the product, most likely through a base catalysed process. A base catalysed racemisation through a retro-aldol reaction was discarded because

Table 1 Results of racemisation of 4-hydroxy-4-(*p*-nitrophenyl)-2-butanone^a

Catalyst	[Catalyst] sol/mM	[Catalyst] gel/mM	e.r. (<i>S</i> : <i>R</i>) ^c
Blank ^b	—	—	1 : 4.1
1a sol	6.5	—	1 : 4.0
1a gel	6.5	5.5	1 : 2.9
1b sol	2.4	—	1 : 4.0
1b gel	2.4	9.6	1 : 1.3
1c sol	2.4	—	1 : 4.0
1c gel	2.4	9.6	1 : 1.2
2 sol	24	—	1 : 4.0

^a –20 °C, CH₃CN; [aldol] = 60 mM; reaction time = 2 weeks. ^b Scalemic aldol mixture prepared as described in ref. 6a. ^c e.r.: enantiomeric ratio.



Scheme 3

the use of acetone-*d*₆ as reagent did not result in the formation of deuterated aldol. Additionally, racemisation through water elimination followed by non-stereospecific Michael addition was also discarded due to the fact that the α,β -unsaturated product was never detected neither in the aldol reaction nor in the racemisation experiments. It is important to note that the most acidic centre in this molecule in acetonitrile corresponds most likely to the benzylic chiral carbon atom due to the electron-withdrawing effect of the 4-nitrophenyl group. As a matter of fact, it has been described that this type of carbon atom is much more easy to deprotonate than ketone α -methylenes and alcohols in DMSO (pK_a ca. 20, 26 and 30 respectively).¹²

Therefore, the most plausible mechanism seems to be the base-catalysed deprotonation of the chiral carbon that renders a stabilized carbanion (Fig. 2). Indeed, when the aldol derived from benzaldehyde was studied instead of 4-nitrobenzaldehyde, racemisation was not detected.

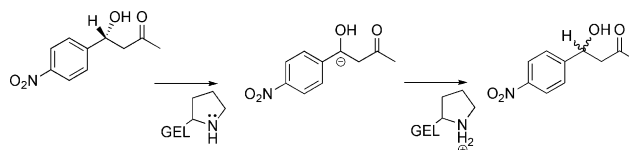


Fig. 2 Suggested mechanism of racemisation.

Furthermore, in order to determine the relative basicity of compounds **1a–c** in solution and in the gel phase they were compared with several bases whose conjugate acid pK_a values in CH₃CN are known.¹³ For a semiquantitative naked-eye analysis, different pH-indicator dyes were employed (Fig. 3A). As can be seen, the gel formed by **1c** in acetonitrile is slightly more basic than pyrrolidine. The latter produces only a partial change in the colour of Phenol Red (**I**₄) while the gel sample shows a net reddish colour. Additionally, the gel formed by **1c** is clearly more basic

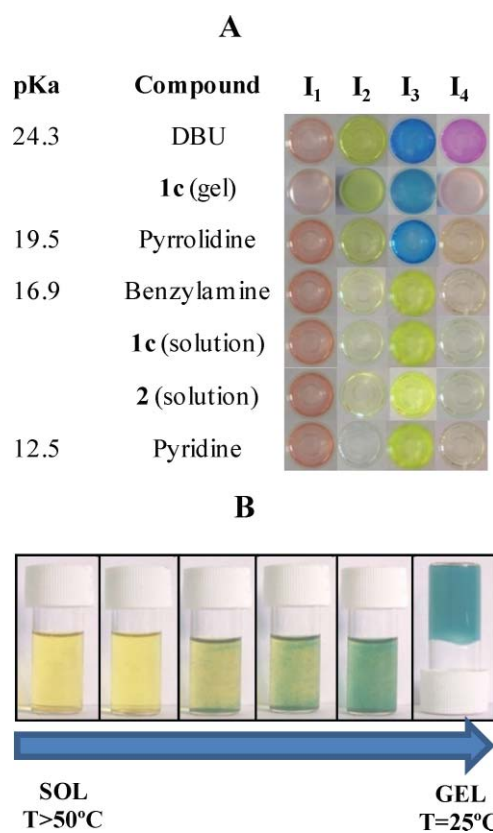


Fig. 3 (A) pK_a scale for **1c** and other common organic bases in CH₃CN and their solutions with dyes (I₁: Congo Red; I₂: 4-nitrophenol; I₃: Bromothymol Blue; I₄: Phenol Red; [I_n] = 3 × 10⁻⁴ mM; [base] = 18 mM in all the cases but **1c** gel (9 mM) and **1c** sol (1.8 mM); for other concentrations of base, see ESI†. (B) Evolution of I₃ colour during gelation of compound **1c** in CH₃CN.

than the corresponding compound in solution as evidenced with the use of Bromothymol Blue (I₃) as the indicator. Using this approach, it can be estimated that **1c** in solution is less basic than benzylamine (pK_a = 16.9) and that the gel formed by **1c** is more basic than pyrrolidine (pK_a = 19.5). Therefore, it can be concluded that gelation of **1c** in acetonitrile provokes approximately a three-order of magnitude difference in the pK_a of the conjugate acids. It is interesting to compare the basicity of compound **1c** with soluble analogue **2**. It can be noticed that for the same concentration of L-proline units, the gel formed by **1c** is clearly more basic than **2** as revealed by the change experienced by indicator I₃.

Furthermore, experiments were performed in which I₃ was added to a hot solution of compound **1c** in acetonitrile and colour evolution was followed during spontaneous cooling until room temperature and in parallel with aggregation and gelation. As can be seen in Fig. 3B, after several minutes the starting yellow (not basic) solution turned into a blue (basic) gel. Similar results were obtained with compounds **1a** and **1b**, although the basicity was slightly lower, in agreement with the observed slower racemisation (Fig. 4).

These facts clearly confirm that there is a supramolecular enhancement of basicity probably due to the close proximity of pyrrolidinic residues on the surface of the gel fibres that could provoke the cooperative assistance of several basic groups (proton relay system). In order to demonstrate the existence of proximity

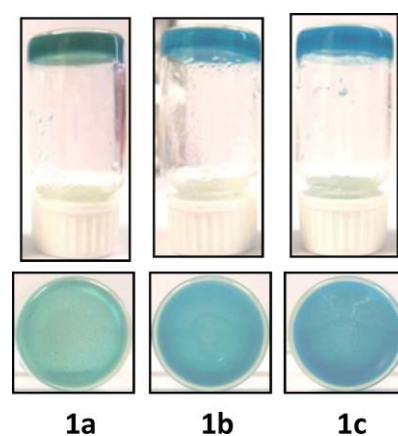


Fig. 4 Gels of compounds **1a–c** in acetonitrile in the presence of Bromothymol Blue (I₃, conc = 3 × 10⁻⁴ mM). Blue colour appears more intense for gels of compounds **1b** and **1c** than for the less basic gel of **1a**.

effects between L-Pro residues, several gels were prepared in which compound **1c** was mixed with gelator **3**, which lacks the catalytic moiety, at different ratios.^{7b} Co-aggregation of **1c** and **3** would provoke a random distribution of L-Pro sites and prevent the supramolecular enhancement of basicity. For this purpose we prepared two-component gels in the presence of indicator I₃ and we could clearly observe that upon gradual increase in the molar fraction of **3** in the mixture the intense blue colour turned greenish for an equimolar gel and yellow as the L-Pro residues were diluted with **3** (Fig. 5 and ESI†).¹⁴

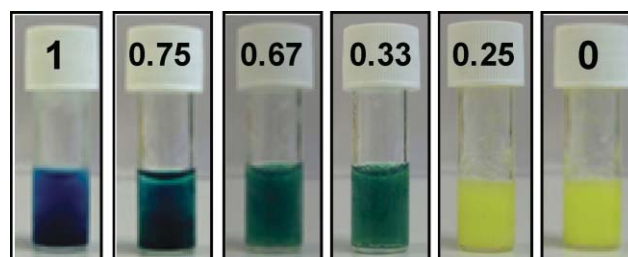


Fig. 5 Two-component gels of **1c** and **3** in CH₃CN in the presence of I₃. Molar fraction of **1c** is indicated. Total concentration of gelators: 15 mM. [I₃] = 3 × 10⁻⁴ mM.

Conclusions

In summary, compounds **1a–c** showed a dual catalytic behaviour as free molecules and as aggregates. Thus, in solution they behave as moderately active and stereoselective L-Pro-based organocatalysts participating in the aldol reaction, whereas in the gel phase they turned into basic catalytic residues inactive in the aldol reaction but active in the non-stereospecific deprotonation of the aldol product, although at longer reaction times (racemase activity). Furthermore, a remarkable supramolecular enhancement of basicity related to proximity effects could be detected. These results are especially interesting if one considers the reversible nature of supramolecular gels and the possibility of controlling the aggregation state by external stimuli. This may allow, for instance, the on–off switching of catalytic activity or even the linkage of sol–gel cascade catalytic events. Currently, we are exploring in

detail basic organocatalysis within supramolecular gels as well as modifying the original design to achieve the aldol reaction in the gel phase.

Experimental

General procedure for the preparation of catalytic systems for the aldol reaction

Catalytic system in gel phase. Typically, 0.066 mmol of the gelator in CH₃CN (2 mL) were heated in a screw-capped vial until it was completely dissolved and, afterwards, 0.5 mL of acetone (6.8 mmol) were added. Then, the mixture was left to cool at -20 °C for 120 minutes to yield a gel.

Catalytic system in solution. A suspension of gelator (0.0364 mmol for **1a**, 0.0132 mmol for **1b–c** and 0.132 mmol for **2**) in CH₃CN (2 mL) was heated in a screw-capped vial until it was completely dissolved and, afterwards, 0.5 mL of acetone (6.8 mmol) were added. The mixture was left to cool at -20 °C for 120 minutes to yield the homogeneous catalytic system.

General procedure for the aldol reactions

A solution of 4-nitrobenzaldehyde (0.33 mmol) in CH₃CN (3 mL) was cooled at -20 °C during 4 h and then it was added to the corresponding catalytic system. To stop the reaction the solvent was evaporated under a N₂ stream and the resulting yellow solid was analyzed by ¹H-NMR in CDCl₃ in order to determine the yield (see ESI†). Afterwards, the crude product was purified by column chromatography on silica gel (hexane : ethyl acetate, 1 : 1) to afford the aldol product. The enantiomeric excess of the corresponding aldol was determined by HPLC using a Chiralpak IA column, λ = 250 nm, hexane–THF (v/v: 75 : 25), flow rate = 1 mL min⁻¹; t_r = 9.3 min (minor), 11.5 min (major). The racemic product was prepared by using diethylamine (20%) in acetonitrile and the product enriched in the *S* enantiomer was obtained as described by ref. 6a (see ESI†).

Acknowledgements

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