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Reactive Organogels: Self-Assembled Support for Functional Materials

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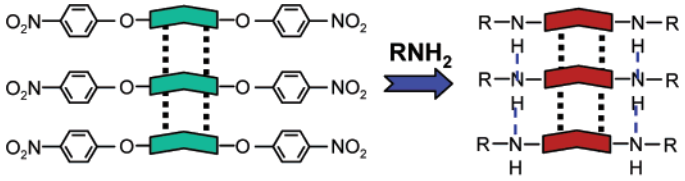
ABSTRACT



An organogel bearing reactive groups has been used as a platform for the gel-phase synthesis of more sophisticated materials. The results show that reactions take place on the gel fibers and that supramolecular aggregation modifies the product distribution in cases where several compounds can be obtained.

The design of functional supramolecular materials has received increasing attention in the past few years, and applications have been reported in many different technological and biomedical fields, for example, catalysis, drug delivery, and nanoscience.[1,2] Among them, one of the most emerging groups are supramolecular physical gels.[3] These soft materials are commonly made by the assembly of low molecular weight molecules with concurrence of weak noncovalent intermolecular interactions and, therefore, they are thermo- and lyoreversible. On the other hand, they present soft solidlike macroscopic properties being less mechanically strong than covalent polymeric gels.

Many gels are still being found serendipitously, and the rational design of gelators with functionalities required for valuable applications is a demanding task. Several examples of functional materials based on supramolecular gels have been reported, but those are still limited when compared with the polymeric ones.[4] A basic strategy for the preparation of functional organogels is the introduction of functional groups into an already studied gelator skeleton. A possible inconvenience of this methodology is that the aggregation properties could be significantly changed since the new functionalities could, for example, compete for H-bonding, alter the solubility of the molecule, change the conformation in solution, etc. For instance, in some cases the new compounds could present improved aggregation efficiency and, as a result, very low solubility in the solvents of interest. This can be a serious drawback from a practical point of view for most of the envisaged applications because the preparation of the desired gel may either not be possible or require a prolonged heating process up to the boiling point of the solvent in order to dissolve the gelator. One way to overcome this problem is, as recently reported by Suzuki et al., by in situ synthesis of the gelator in the solvent that is going to be jellified.[5] Other approaches are the generation of gelating species in response to a simple stimulus (i.e., pH, redox, light, etc.) or the use of mixtures of solvents.[6]

In this paper we address a different approach. As a proof of concept, we use a gel made by compound **2**, a low molecular weight organogelator (LMOG) with reactive

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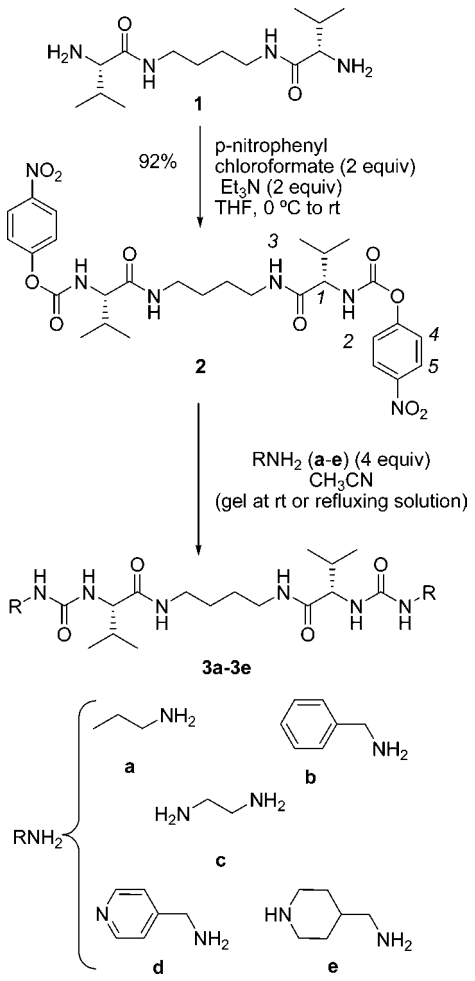
groups, namely, a reactive gel, that can be easily reacted with other functional moieties to obtain new gels with properties different from those shown by the initial gel. In this system, the gel is assembled before the reaction takes place, acting as a scaffold for the construction of the new material. Amino acid derived compound **2** presents reactive *p*-nitrophenyl carbamoyl groups able to react with nucleophiles such as amines to yield amino acyl bisureas **3a**−**e**. Urea functions are present in many good gelators reported in the literature,[3] and for example, a bisurea related to **3a**−**e** has been recently used by Hanabusa et al. for the formation of helical hybrid silica bundles.[7]

Compound **2** has been prepared in good yield by reaction of bis-amine **1**[8] with *p*-nitrophenyl chloroformate in THF at room temperature in the presence of 2 equiv of Et_3N (Scheme 1). Compound **2** forms transparent gels in acetonitrile with

Scheme 1



a minimum gelator concentration of 3 mg/mL (4.9 mM) and with thermal stability below 50−55 °C.[9] As previously reported for related compounds, FT-IR of the xerogel reveals H-bonding as the driving force for gelation. Thus, the associated NH stretching band appears at 3290 cm^{-1}, and the carbamate and amide C═O stretching bands appear at 1718 and 1646 cm^{-1}, respectively. ^1H NMR of gel in CD_3CN shows the signals of about 10% of nonaggregated molecules present in solution (TMS as internal standard) (Figure 1A).

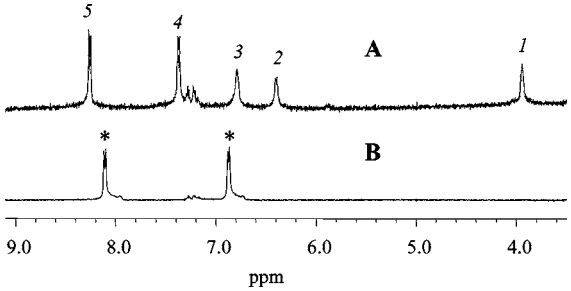


Figure 1. ^1H NMR of compound **2** gel (A) before and (B) after addition of propylamine (300 MHz, CD_3CN). See Scheme 1 for signal labeling. Asterisks denotate signals from *p*-nitrophenolate.

To check the versatility of the approach the reactivity of the organogel formed by compound **2** in acetonitrile was assayed with a variety of primary amines (see Scheme 1) such as propylamine (**a**), benzylamine (**b**), and some amines with additional functional groups such as ethylenediamine (**c**), 4-amino methyl pyridine (**d**), and 4-aminomethyl piperidine (**e**), to give bisurea derivatives **3a**−**e**. In a typical experiment a gel was obtained by dissolving 6 mg of compound **2** in 2 mL of acetonitrile by gentle heating in a screw-capped vial and then cooling at room temperature. Once the gel was formed, 4 equiv of the amine dissolved in 100 μL of acetonitrile was added on top of the gel. The gels were left a few hours at room temperature and filtered. The solid material was characterized by ^1H NMR in DMSO-d_6 and MS (see Supporting Information for details).

The gels obtained after reaction of compound **2** with amines **a**−**d** did not show any sign of deterioration even after several days. The T_g of such gels was determined following the same procedure as for compound **2**, and in all of these cases, they were found to be stable until at least 100 °C. For bisurea gels **3a** and **3b**, a small volume contraction was observed at ca. 80 °C; nevertheless, no weakening of the gel was detected at this point. In the case of urea gel **3c**, constructed using a difunctional amine, the gel was stable until 110 °C and no volume change was observed during the heating process. ESI-MS study of **3c** revealed the presence of three different peaks corresponding to a cyclic tetraurea ($M + H^+$, 797.6 *m*/*z*) and acyclic dimer ($M + H^+$, 857.6 *m*/*z*) and trimer ($M + 2H^+$, 628.4 *m*/*z*) (see

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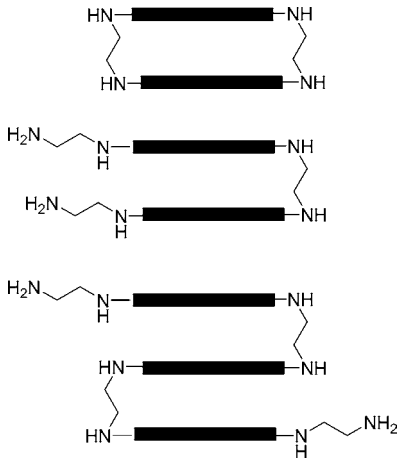
(9) Thermal stabilities were determined by immersion of the vial upside down in a thermocontrolled bath.

Scheme 2. Products Obtained after Reaction of Organogel **2** and Diamine **c**; Rectangles Represent Peptidomimetic Backbone



Scheme 2). Pyridine-functionalized gel **3d** was especially attractive, from a practical point of view, since the free nitrogen atom could be sensitive to pH and metals. As expected, reaction of amine **d** with the organogel **2** gave the bisurea gel **3d**. In these four cases almost quantitative yields were obtained after few hours as checked by NMR and UV−vis spectroscopy (measurement of released *p*-nitrophenolate). Although no starting material was detected by ^{1}H NMR, a slight yellow color was observed after dissolution in DMSO-d_6, and in some cases, signals of residual *p*-nitrophenolate could be detected. UV−vis quantification was affected by many experimental errors and has to be taken as approximate. In most of the cases, yields above 80−90% were calculated. The most conclusive technique was IR spectroscopy. A sample of the reaction mixture was spreaded on top of a NaCl plate and the spectrum was collected. In this case, a residual band at 1720 cm^{-1}, corresponding to the C═O vibration of the carbamate in the starting material, could be observed. However, this band could not be seen when the gel was isolated from the mixture, exhaustively washed, and dried (see Supporting Information). Furthermore, the reaction of compound **2** and propylamine to give **3a** was also carried out in CD_3CN and followed by ^{1}H NMR using TMS as an internal standard (Figure 1B). It could be seen that after 15 min the reaction was complete since no signals of the carbamate were observed and signals corresponding to the release of all of the *p*-nitrophenolate were quantified.[10] These data also reflect a reinforcement of intermolecular interactions in the newly formed gel since, in difference with the starting gel, no free gelator molecules in equilibrium with the gel can be detected upon bisurea formation.

In the case of 4-methylamino piperidine (**e**), reaction also took place in high yield but the gel was progressively disassembled. Analysis of the reaction products by ^{1}H NMR in DMSO-d_6 revealed the presence of signals corresponding to two urea NH groups (see Supporting Information), indicating that the reaction occurred mainly on the primary amine of 4-methylamino piperidine. However, the presence of a small amount of other products resulting from the reaction of the secondary amino group of the piperidine moiety cannot be fully discarded. The observed gel disassembly could be tentatively ascribed to the fact that the basic secondary amino group of the piperidine could also capture the proton released upon reaction by the primary amino group, resulting in charged groups that could make the gel unstable due to electrostatic repulsions.

Bisurea derivatives **3a**−**e** were also prepared by conventional synthesis in refluxing acetonitrile for comparison. For instance, 4 equiv of the amine was added to a refluxing acetonitrile solution of compound **2**. After a few hours the suspension was filtered off and exhaustively washed with acetonitrile to obtain a white solid. The analysis of the compounds by ^{1}H NMR (DMSO-d_6) revealed that they are indentical to those obtained in the reaction upon a gel for the cases of **3a**, **3b**, and **3d**. The obtained compounds were poorly soluble in acetonitrile, and exhaustive heating in a closed vial was required in order to dissolve them. After a few minutes at room temperature, strong gels of compounds **3a** and **3b** were obtained for concentrations in the range of 2 mM. The preparation of gels at a concentration similar to that employed for compound **2** led to the formation of an opaque gel with fragments of solid in suspension. In the case of pyridine-functionalized bisurea **3d**, this compound was not completely soluble even below 1 mM, and the organogel could not be formed. Thus, in situ gel-to-gel reaction is, in general, a milder procedure for the preparation of bisurea gels and, for the case of **3d**, the only way to obtain a gel in acetonitrile.

In the case of the reaction of bifunctional amines **c** and **e** in refluxing acetonitrile, significant differences were found from the reactions carried out at room temperature in the gel. Complex mixtures of oligomeric compounds were obtained after refluxing as revealed by the presence of multiple and broad signals in their ^{1}H NMR spectra and by ESI-MS (see, for example, Figure 2 and Supporting Information). This constitutes an interesting example of how supramolecular organization can modify the outcome of a reaction. For example, in the case of the reaction of **2** with ethylenediamine, the formation of supramolecular aggregates preorganizes the system in such a way that cyclization is favored. Further work is being carried out to better understand this template effect.

FT-IR studies of both xerogels and solids synthesized following conventional procedure suggest that, as already mentioned, the H-bonding interaction is more intense in the bisurea compounds than in the initial biscarbamates, as shown by the shift toward lower frequency numbers experienced by both carbonyl groups (amide and urea) appearing as a single band centered at 1630 cm^{-1} in contrast with the amide C═O in compound **2** that appeared at 1650 cm^{-1} (see Supporting Information). Remarkably, differences between the initial gel and the resulting bisurea could be

(10) The NMR tube was shaken after addition of the amine to avoid diffusion limitations. It is well-known that diffusion processes are slow in the gel medium and that the shape of the container also plays an important role in the strength of the gel. When samples were not shaken, a slow diffusion of the amine could be detected.

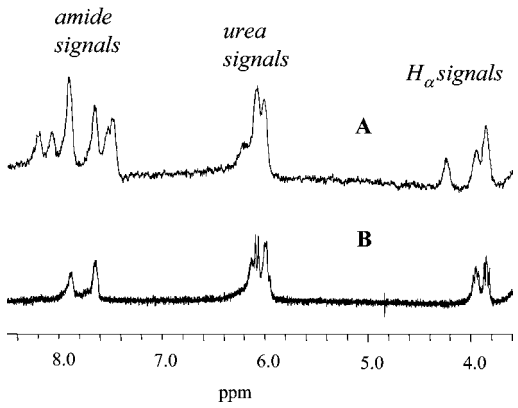


Figure 2. ^{1}H NMR of crude bisurea **3c** obtained (A) in refluxing acetonitrile and (B) through the reactive gel strategy (300 MHz, DMSO-d_6).

also observed at the microscopic level. For example, the scanning electron micrographs of the xerogel of compound **2** shows an entanglement of fibrils of less than 50 nm wide, whereas in the case of bisurea xerogel **3c**, larger fibers and a higher degree of entanglement is found, probably due to the cross-linking introduced upon reaction with the diamine (see Supporting Information). On the other hand, the accessibility of the active functionalities embedded in a gel is of great importance regarding to their application, for example, to catalytic processes or sensing devices.[11] In our case, almost complete reaction was observed within few hours revealing that the nucleophile molecules can diffuse and react relatively quickly within the gel network. This could be explained, considering that a gel is a dynamic system hold by weak interactions, by a disassembly/reassembly process taking place at some of the different hierarchical assembly levels.

In summary, we have reported, to our knowledge, the first example of a reactive supramolecular organogel as a platform for the preparation of new ones. Other examples of gel post-modification have been reported, but in all of them the gel was reinforced by the formation of covalent bonds between polymerizable groups. In the present work, the newly formed material is held only with weak noncovalent interactions.[7,12] This represents an easy way to prepare materials with different properties and functionalities. Furthermore, the relative accessibility of the reactive groups in the gel network has been demonstrated, and it has been shown that supramolecular aggregation preorganizes to some extent the studied compound for the formation of macrocycles. On the other hand, we have avoided the strong heating conditions usually required to dissolve molecules that, as in this case, have a great tendency to aggregate, presenting a considerably low solubility. The materials derived from the reactive-gel strategy can be envisaged as bottom-up programmed soft-solid supports for heterogeneous processes (i.e., catalysis, separation, etc.) but keeping some of the unique features of supramolecular gels. For instance, the degree of functionalization of the gel can be easily monitored by NMR or UV−vis, and the functional materials can be recycled after use since they are reversibly assembled through noncovalent interactions. Current work is in progress to explore the scope of this methodology by the study of different solvents and the attachment of different functional groups to the reactive gel. We believe that this methodology could be of use for many different reactive groups as well as structural gelator scaffolds.

Supporting Information Available: Detailed gelation and reaction procedures, characterization of new compounds, spectroscopic studies, and SEM images and ESI-MS data of **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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