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Insight on the NMR Study of Supramolecular Gels and Its Application to Monitor Molecular Recognition on Self-Assembled Fibers

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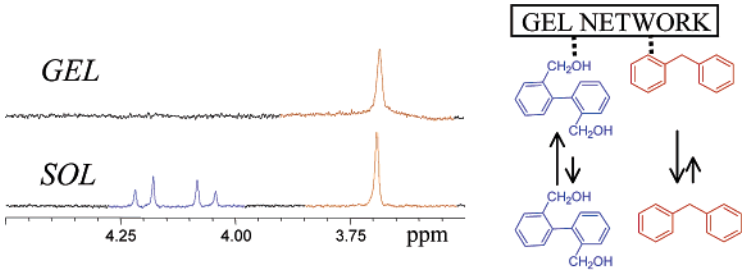

The ^{1}H NMR study of supramolecular gels formed by two organogelators derived from valine is described. The analysis of the variation of chemical shift values and relaxation times in the gel samples reveals that in these systems only discrete species are observed by ^{1}H NMR. The reduced T_2 values and negative NOEs that are measured upon gel formation can be ascribed to an exchange between discrete organogelator species and the gel network. This process is found to be fast in the time scale of ^{1}H NMR relaxation and slow in the NMR observation frequency time scale. It is shown here that other molecules, aside from the gelator itself, can interact with the gel network and this process can be monitored easily by measurement of relaxation times. As a proof of principle, the selective interaction of 2,2′-bis(hydroxymethyl)biphenyl over diphenylmethane with the self-assembled fibers formed by one of the gelators in benzene is described.

Introduction

Physical gels formed by supramolecular association of low molecular weight molecules have received increasing attention in recent years.[1,2] The formation of gels from small molecules requires a hierarchically organized aggregation through noncovalent bonds to yield elongated assemblies that further self-organize into fibers that percolate the solution. Therefore, supramolecular gels are an interesting example of bottom-up construction of nanostructured fibrous materials. Recently, attention is being paid to the development of functional supramolecular gels that can be used, for example, as photonic, stimuli responsive, catalytic, or sensing materials, as well as in drug release.[3]

For the rational design of those materials it is desirable to gain detailed structural information of the molecules in the assemblies, which is a main challenge in most of the studies with low molecular weight gelators. In this context, spectroscopic techniques such as IR, UV−vis, and CD together with X-ray diffraction or scattering are commonly employed with the aim to elucidate the detailed structure of supramolecular gels. Having in mind the enormous potential of NMR for the

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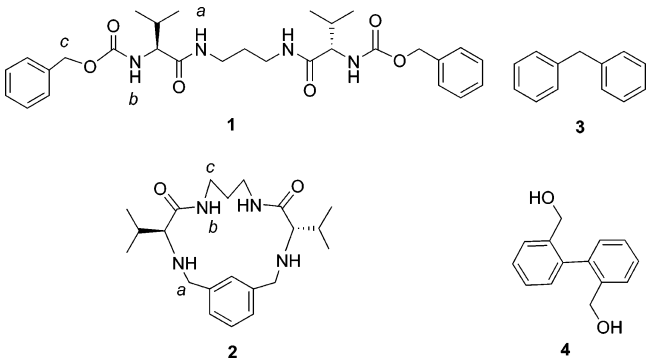
structure elucidation in solution, the study of supramolecular gels by this technique is especially appealing. Actually, NMR has been commonly used as a complementary tool for the investigation of low molecular weight gelators.[4,5] In most cases attention is paid to the analysis of the variation of either chemical shifts,[4] NMR relaxation times,[5b−d,f,g,i] or intensity[5j,r] of the NMR signals with concentration, solvent composition, or temperature. Those data can be used to obtain useful information such as the nature of the intermolecular interactions, the critical concentration values, the change in the motion of the molecules, or thermodynamic parameters associated with gel formation.

However, often those studies do not involve samples where a supramolecular gel is present, but instead the gelator is studied in conditions of concentration, solvent, or temperature that preclude gel formation.[4] A main reason for this could be the fact that in those cases the supramolecular gel yields either almost unobservable or very broad resonance signals of little practical use. On the other hand, in quite some cases ^{1}H NMR signals corresponding to the low molecular weight gelator have been observed when a supramolecular gel has been studied by NMR.[5] However, the intensity of such signals compared to an internal standard indicates that only a percentage of the gelator molecules are observable by NMR. This is ascribed to the fact that the molecules that are part of the gel network are not observable by NMR as a result of the large correlation time of the assemblies, which results in a very short transversal relaxation time, T_2, and very broad (unobservable) signals.

CHART 1



A key issue in the study of supramolecular gels by NMR is to discern if the signals observed correspond to discrete (nonassociated) organogelator molecules or oligomeric assemblies. It seems that no structural information on the gel assembly can be obtained by NMR if the observed signals correspond to free gelator molecules (this assumption is not completely right as shown in the following discussion), and on the contrary, if oligomeric molecular assemblies are being observed, they are prone to a detailed study highly relevant for the elucidation of the gel structure. In the latter case, very valuable information such as intermolecular binding points or the conformation of the molecules in the assemblies could be obtained, for example, by analysis of chemical shift variations and techniques such as NOE, respectively. Most of the studies on supramolecular gels cited above, dealing with the variation of chemical shifts with temperature and solvent polarity, as well as those studying NMR relaxation, implicitly assume that the observed NMR signals correspond to oligomeric molecular assemblies.[5] However, this behavior is not to be taken for granted for all the supramolecular gels. For example, Menger et al.[5e] proposed that only discrete molecules were observable by NMR when a gel of dibenzoyl-L-cystine was studied, but on the other hand, Whitten et al.[5i] studied this issue in detail and concluded that mobile sections of a gel (therefore associated species) were observable in the studied system.

Here we report on the NMR study of two of the molecules used as organogelators in our laboratories with the aim to highlight the information on the structure and dynamics of the supramolecular gels that can be obtained with conventional NMR. Additionally, we are particularly interested on the study of the capabilities of functional self-assembled fibers to interact selectively with guest molecules, namely, to asses the molecular recognition properties of supramolecular gels. This issue has been scarcely explored, and only recently has molecular colorimetric sensing by a supramolecular gel been reported.[3h] The results presented here reveal that selective recognition of chemical species on a supramolecular gel can take place and be easily monitored by NMR.

Results and Discussion

Discerning if the observed NMR signals of a supramolecular gel sample correspond to free or aggregated organogelator molecules can conduce to apparently contradictory results. This can be exemplified by the ^{1}H NMR study of compounds **1** and **2**, which are organogelators prepared in our group recently (Chart 1). These gelators form gels in a variety of solvents, and a model for their assembly through multiple intermolecular

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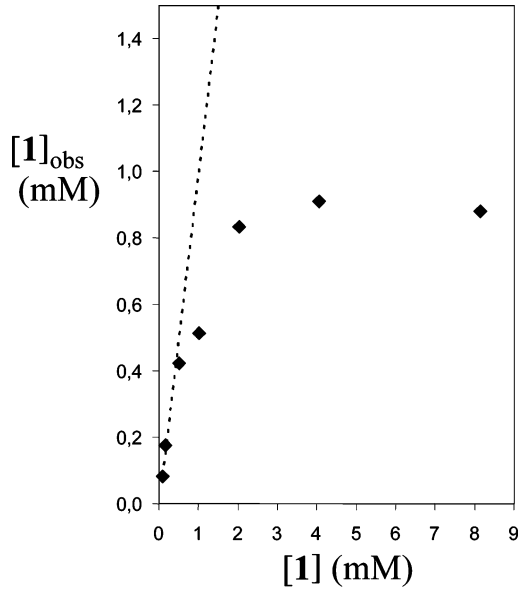

FIGURE 1. Plot of the concentration of **1** in CD_3CN measured by ^1H NMR (30 °C) using diphenylmethane as internal standard ($[\mathbf{1}]_{obs}$) against the total concentration present in the sample ([**1**]).The dotted line indicates the case where the observed concentration would be equal to the total concentration.

H-bonding interactions have been proposed for both **1**[5k] and **2**[5p] and related compounds.[6]

In the NMR analysis of supramolecular gels it is useful to monitor the intensity of the NMR signals of the gelator at different concentrations. As shown in Figure 1, if the observed concentration of **1** in CD_3CN (measured using an internal standard) is plotted against the total concentration of gelator, a saturation curve is obtained. It can be seen that for diluted solutions the total concentration of gelator equals that observed. However, at some point upon increasing the amount of gelator, the ^1H NMR observed concentration is lower than the total. These data clearly indicate that when a given concentration is reached, large assemblies that are NMR-silent are formed. Finally, a plateau is observed (a gel is formed at this point), and thereafter increasing the gelator concentration does not affect the intensity of the observed signals. In these conditions all of the newly added material is incorporated in the NMR-silent aggregates and the observed concentration value corresponds to the solubility of the gelator in the studied solvent and temperature.

Figures 2 and 3 show, respectively, a fragment of the ^1H NMR spectra of compounds **1** and **2** obtained at a concentration where a gel is formed and at a concentration where no aggregation takes place. It can be noticed that all of the signals present almost identical chemical shifts in both spectra. Particularly significant is the fact that the NHs signals do not shift upon gel formation despite the fact that intermolecular H-bonding is a driving force for aggregation of these molecules as shown by IR in previous work.[5k,p] This fact clearly suggests that the observed species within the gel are free organogelator molecules. However, it can be also noticed that the signals corresponding to the gel sample are broader than those in

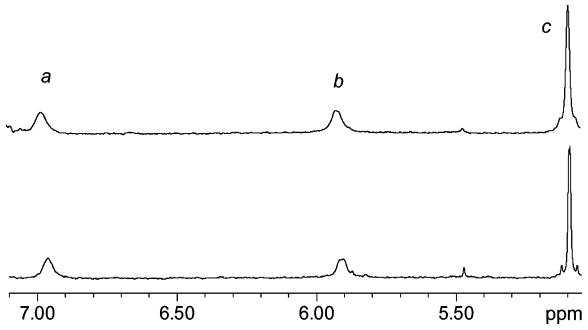

FIGURE 2. Partial ^1H NMR spectra of **1** in CD_3CN (30 °C). Bottom: solution, $[\mathbf{1}] = 0.5 \times 10^{-3}$ M. Top: gel, $[\mathbf{1}] = 8.1 \times 10^{-3}$ M. See Chart 1 for signal labels.

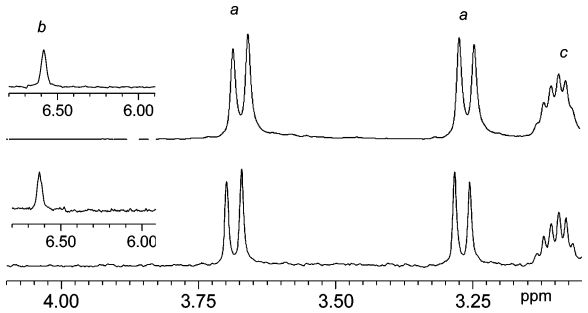

FIGURE 3. Partial ^1H NMR spectra of **2** in D_6-benzene (30 °C). Bottom: solution, $[\mathbf{2}] = 0.7 \times 10^{-3}$ M. Top: gel, $[\mathbf{2}] = 13 \times 10^{-3}$ M. See Chart 1 for signal labels.

TABLE 1. Longitudinal (T_1) and Transversal (T_2) ^1H NMR (300 MHz) Relaxation Times Measured for Organogelators 1 and 2

entry	gelator/ concn (mM)	^1H probe	solvent	T_1 (s)	T_2 (s)
1	**1**/7.9 (gel)	**1** (benzylic CH_2)	CD_3CN	2.29 (0.07)	0.99 (0.06)
2	**1**/0.8 (sol)	**1** (benzylic CH_2)	CD_3CN	2.40 (0.08)	2.20 (0.14)
3	**2**/24.9 (gel)	**2** (benzylic CH_2)	C_6D_6	0.87 (0.05)	0.25 (0.05)
4	**2**/2.5 (sol)	**2** (benzylic CH_2)	C_6D_6	0.84 (0.1)	1.0 (0.1)

solution, indicating shorter T_2 relaxation times and, therefore, higher correlation times and slower tumbling rates.

As a matter of fact, the T_2 values of the organogelator signals in the gel are considerably reduced when compared to the solution state. As can be seen in Table 1, the T_2 relaxation time of protons of organogelator **1** was significantly decreased when a gel is formed in CD_3CN (entries 1 and 2). The same study in benzene could not be carried out for compound **1** because of the very low intensity of the signals of the gelator when a gel was formed in this solvent. An analogous behavior regarding T_2 values was observed for organogelator **2** in C_6D_6 (Table 1, entries 3 and 4) (this gelator does not form gels in acetonitrile). It has to be mentioned here that T_2 values are more reliable than T_1 values for the analysis of changes in tumbling rates. The former shows an almost linear dependence on correlation times, whereas T_1 values have a quadratic-type dependence with correlation times.[7] This behavior can result in cases such as that shown in entries 1−4 of Table 1. There it can be seen that gel formation produces the above-mentioned very significant reduction of T_2 values while T_1 remains almost unaltered.

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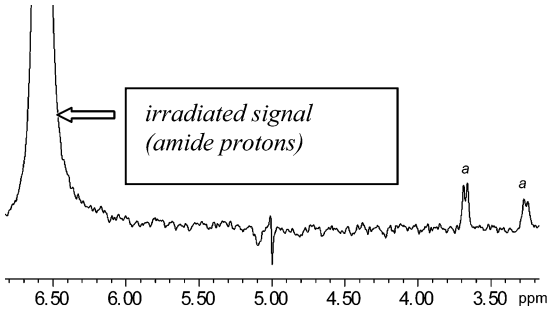

FIGURE 4. Partial ^{1}H NMR NOE spectrum recorded for **2** (25×10^{-3} M, gel) in D_6-benzene at 30 °C. See Chart 1 for signal labels.

TABLE 2. Longitudinal (T_1) and Transversal (T_2) ^{1}H NMR Relaxation Times (300 MHz) Measured for Diphenylmethane (3) and 2,2′-Bis(hydroxymethyl)biphenyl (4) in the Presence of Organogelator 1

entry	[**1**] (mM)	^{1}H probe/ concn (mM)	solvent	T_1 (s)	T_2 (s)
1	7.9 (gel)	**3** (CH_2)/9	CD_3CN	8.53 (0.06)	3.35 (0.04)
2	0.8 (sol)	**3** (CH_2)/9	CD_3CN	6.55 (0.27)	5.95 (0.11)
3	7.9 (gel)	**4** (CH_2)/9	CD_3CN	4.7 (0.07)	1.07 (0.07)
4	0.8 (sol)	**4** (CH_2)/9	CD_3CN	4.07 (0.11)	2.91 (0.07)
5	6.3 (gel)	**3** (CH_2)/10	C_6D_6	7.19 (0.08)	4.94 (0.19)
6	0.6 (sol)	**3** (CH_2)/10	C_6D_6	7.01 (0.09)	4.95 (0.14)
7	6.3 (gel)	**4** (CH_2)/10	C_6D_6	2.78 (0.07)	1.20 (0.05)
8	0.6 (sol)	**4** (CH_2)/10	C_6D_6	3.31 (0.11)	1.77 (0.02)

The reduction in T_2 values upon gel formation is the result of an increase in the correlation time of the observed species, which can even give place to negative NOEs (see Figure 4). Indeed, negative NOEs measured in gel samples have been ascribed to the observation of oligomeric species (which would present reduced tumbling rates compared to those of discrete species) by us and other groups.[4i,5k,p]

Summarizing, a puzzling contradiction may appear upon analysis of the NMR data. The chemical shift variation clearly indicates that discrete molecules are observed, and the reduced tumbling rates detected by relaxation measurements and NOE experiments suggest the presence of oligomeric assemblies. The possibility that an increase in viscosity would result in the variation of the described T_2 values can be excluded since some species such as, for example, diphenylmethane (**3**) do not change their relaxation times upon gel formation (see Table 2, entries 5 and 6). It has also been shown previously 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 in accordance with the presence of large pools of solvent within the gel.[5c,i] The invariance of chemical shifts and modification of tumbling rates (T_2 values) upon gel formation is not unique for organogelators **1** and **2**, and this issue has been addressed previously by Duncan and Whitten for an organogelator containing cholesterol and stilbene moieties.[5i] These authors found the above-mentioned contradictory facts and concluded that in their system there is a fast exchange between "mobile" gel regions (that are observable by ^{1}H NMR) and free organogelator that would explain the observed change in T_2 values. The disturbing observation that no chemical shift variation is observed upon gel formation is explained on the basis of the fact that for gel regions accessible to solvent (mobile gel regions) smaller shifts would be anticipated.

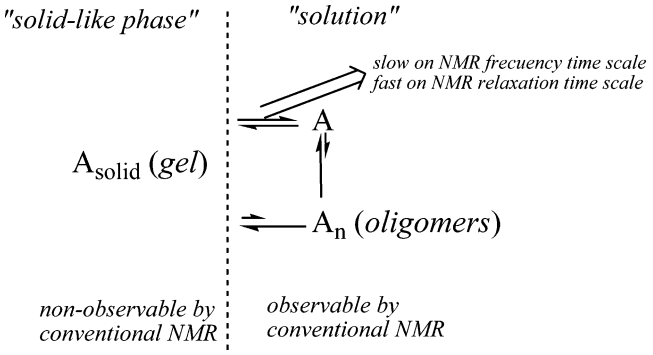

FIGURE 5. Schematic representation of the equilibria present in the gel samples of **1** and **2**. Discrete organogelator molecules are represented by "A".

Here we propose a refinement of that explanation for the reported data. We believe that in these systems there is an exchange of the discrete organogelator molecules between the solution (nonaggregated state, observable by NMR) and the gel (aggregated state, NMR-silent) that is *fast* in the NMR time scale of relaxation (seconds) and *slow* on the commonly known NMR time scale (related to the frequency of observation, i.e., milliseconds for high field instruments).[8] Such type of exchange would result in reduced tumbling rates (and also reduced relaxation times and negative NOEs). In this case, the chemical shift of the gelator signals would be unchanged on going from diluted solutions to gels because free and aggregated species should give separated signals (slow exchange on NMR-frecuency time scale), those of the aggregates being nonobservable.

As a matter of fact it turns out that this behavior is related to that observed in the NMR study of small molecules in the presence of macromolecules such as proteins and polynucleotides and is exploited in the so-called transfer experiments.[9] For example, in a transfer-NOE experiment small molecules that interact with a macromolecule experience a fast exchange between bound and free states that results in a considerable reduction of the measured T_2 values and negative NOEs. It is worth mentioning that the negative NOE enhancements correspond to the conformation of the molecule when bound to the macromolecule. For that reason, such information could be of interest to analyze the conformations of the organogelator molecules in the gel aggregates.

Therefore, we believe that it can be concluded that, in the described experiments for **1** and **2**, the detected NMR signals of the gel samples would correspond to free organogelator molecules that present reduced T_2 values due to an exchange with the unobservable gel aggregates. Additionally the observed negative NOEs should be ascribed to a transfer-NOE mechanism taking place.

As mentioned above, the study of aggregation by changes in NMR chemical shifts with concentration has been described to

(8) For example, it can be calculated that in a 500 MHz (^{1}H) instrument two species involved in chemical exchange with signals separated by 1 ppm would experiment a fast exchange in the NMR frequency time scale (signal coalescence) for a process that requires less than 2 ms per cycle.

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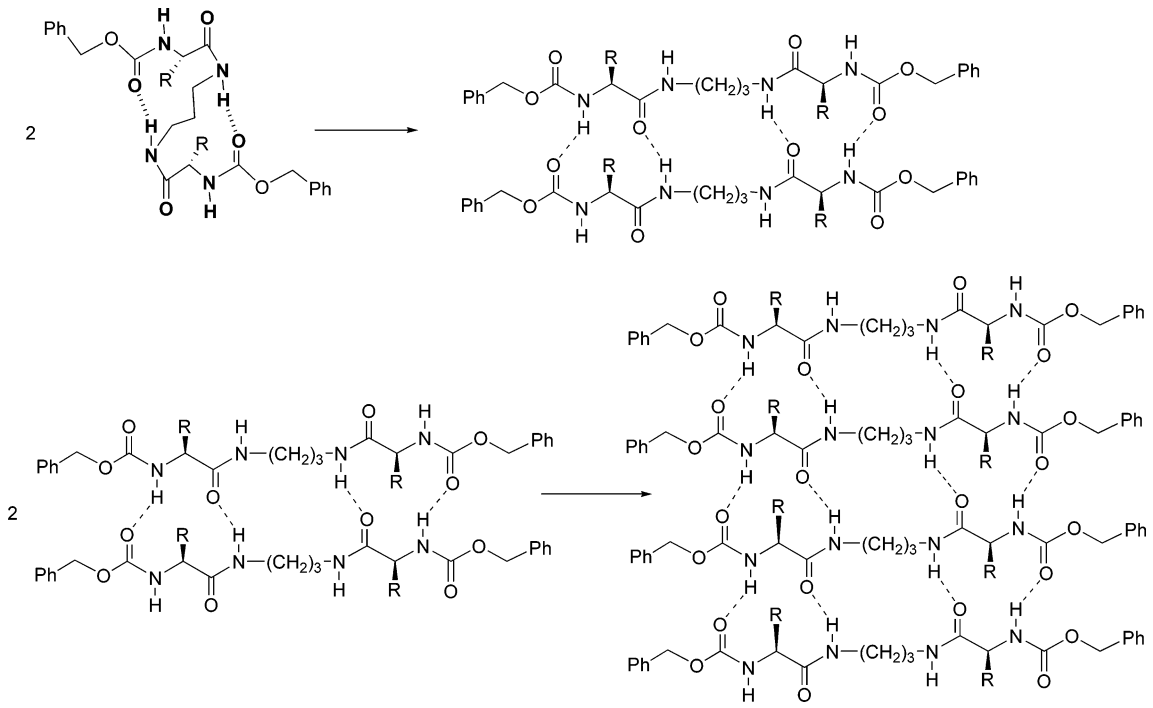

FIGURE 6. Proposed aggregation mode of **2**.[5p]

be useful in the study of the aggregation of low molecular weight gelators in conditions where gel formation is precluded.[4] However, in the presence of a gel phase the studies reported mainly deal with the variation of chemical shifts with temperature and the interpretation of these studies should be examined critically since the observed signals may correspond to isolated gelator molecules and, therefore, no information on the aggregation modes would be obtained by this means.[5]

It seems that in the case of **1** and **2** the equilibria involving discrete species, oligomers, and fibers must present thermodynamic parameters that avoid the existence of oligomeric, NMR-observable species in solution (at least in a concentration range amenable for NMR measurements) (see Figure 5). This would be in accordance with an aggregation model where a cooperative behavior is observed, like that reported for other gelators by Feringa et al.[4d] This cooperative association would result, for example, in a more efficient self-aggregation of dimers compared to that of monomers and can be rationalized if one considers that dimers are more efficiently preorganized for aggregation than monomers. For example, in the case of organogelator **2** in a previous study it was concluded that the organogelator is folded in solution and extended in the aggregated state (see Figure 6). In that type of system it is expected that the self-aggregation of dimers or higher oligomers would be more favorable that dimer formation. For such a system, in the presence of a gel phase the solubility of isolated organogelator would be higher than that of oligomers, as observed in our case. In the case of organogelator **1**, the detailed study of the gel formation of this type of molecules revealed that the isolated species present high conformational mobility that is decreased in the formation of dimers that are properly preorganized for efficient aggregation.[5k]

It has to be noted that, in contrast with the behavior described here, in some systems a variation of chemical shift of the gelator molecules with concentration in the presence of a gel phase has been observed.[5s,u] The fact that species corresponding to molecular assemblies are detected by NMR in other systems in the presence of a gel phase reveals that the thermodynamics of the multiple possible equilibria must be different from that of **1** and **2**, and ultimately this fact must be related with the structural characteristics and intermolecular binding modes of the gelator of study.

Having in mind the previous considerations, if we see a supramolecular gel as material with a high aspect ratio, it is expected that the described exchange process could also take place for other molecules, aside from the organogelator itself, which present functional groups capable of interacting with the organogel fibers. A priori, for molecules with the appropriate structure a sorption−desorption process on the gel fibers may take place that could be exploited advantageously, for example, in sensing or mixture analysis by NMR. The study of the interaction of organic substrates with porous adsorbent materials such as active carbon or polymers has been studied by NMR relaxation studies.[10]

As a proof of principle, we have studied the NMR of diphenylmethane (**3**), an apolar molecule, and 2,2′-bis(hydroxymethyl)biphenyl (**4**), which presents two H-bonding groups, in the presence and absence of physical gels derived from **1** in CD_3CN and C_6D_6 (see Table 2). It can be noticed that in CD_3CN the T_2 values of both 2,2′-bis(hydroxymethyl)biphenyl and diphenylmethane decrease considerably upon gel formation (Table 2, entries 1−4). These data indicate that both molecules interact with the gel phase significantly. In the case of 2,2′-bis(hydroxymethyl)biphenyl presumably H-bonding interactions with the polar moieties of the organogelator can take place and for diphenylmethane solvophobic interactions may drive this apolar molecule toward the apolar domains of the gel fibers.

The study of the gels formed by **1** in C_6D_6 showed, interestingly, that whereas the relaxation times of 2,2′-bis-

(10) See for example: Vartapetyan, R. Sh.; Khosina, E. V. *Colloid Journal* **2006**, *68*, 1−19.

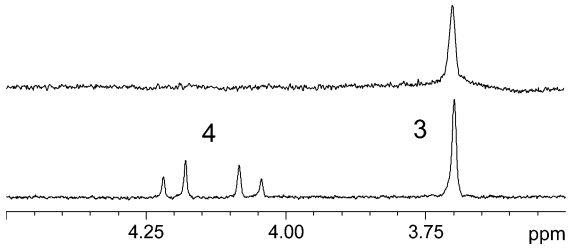

FIGURE 7. Section of the T_2 filtered (CPMG pulse sequence; total time for echoes = 3 s) ^{1}H NMR spectra of mixtures of organogelator **1**, diphenylmethane (**3**), and 2,2′-bishydroxymethylbiphenyl (**4**) in C_6D_6. Top spectrum corresponds to a gel ([**1**] = 6.3 mM, [**3**] = [**4**] =10 mM). Bottom spectrum corresponds to a solution ([**1**] = 0.6 mM, [**3**] = [**4**] =10 mM).

(hydroxymethyl)biphenyl were modified by gel formation, those of diphenylmethane were not (Table 2, entries 5−8). In this case the good solvation of diphenylmethane in benzene seems to prevent the interaction of this molecule with the gel fibers and 2,2′-bis(hydroxymethyl)biphenyl would, as in CD_3CN, interact through H-bonding with the organogel.

The selective interaction of chemical species with a supramolecular gel may be advantageous for a number of applications. In this case a direct use is the selective suppression of ^{1}H NMR signals or the selective inversion of the NOE enhancements of one of the species studied upon gel formation, which can be useful for analysis of mixtures. For example, a mixture of 2,2′-bis(hydroxymethyl)biphenyl and diphenylmethane in C_6D_6 was analyzed by ^{1}H NMR in the presence of organogelator **1**, using the CPMG pulse sequence for T_2 filtering. As can be seen in Figure 7, for a diluted solution the benzylic signals of both the alcohol and diphenylmethane are observed (bottom spectrum), but upon gel formation (top spectrum) the experiment recorded with the same parameters shows only the signal corresponding to diphenylmethane and the benzylic signals of the alcohol disappear as a result of the interaction of the alcohol with the gel.

In another experiment with the same systems, upon irradiation of the benzylic signals positive NOEs were obtained for diphenylmethane and negative NOEs were detected for the dihydroxy compound, reflecting the interaction of the latter with the gel network (see Figure 8).

Conclusions

The results described here have revealed that the observation of NMR signals when a supramolecular gel is studied by this technique should not always be ascribed to the detection of oligomeric assemblies. In the cases reported here only discrete species are detected and therefore the conclusions that could be obtained regarding the variation of those signals upon, for example, polarity or temperature variations should not be ascribed to the aggregation process that explains the formation of a gel. Interestingly, the presence of a gel modifies the motion of the discrete molecules in solution in such a way that negative NOEs can be detected as a result of a transfer-NOE process. The fact that the NOEs obtained by this technique reflect the conformation of the molecule when it is associated could be of potential great interest for the analysis of the supramolecular assemblies responsible of gel formation and probably deserves to be explored in more detail.

Additionally, the interaction of different chemical species with the supramolecular gel can be monitored by the changes in T_2 relaxation time (tumbling rate) that the studied molecules experience in the gel. We have shown that the interaction of the gel fibers with solutes can be selective, and this property is of potential use in the analysis of complex mixtures because signals of the molecules interacting with the gel can be removed or inverted selectively with different NMR pulse sequences.

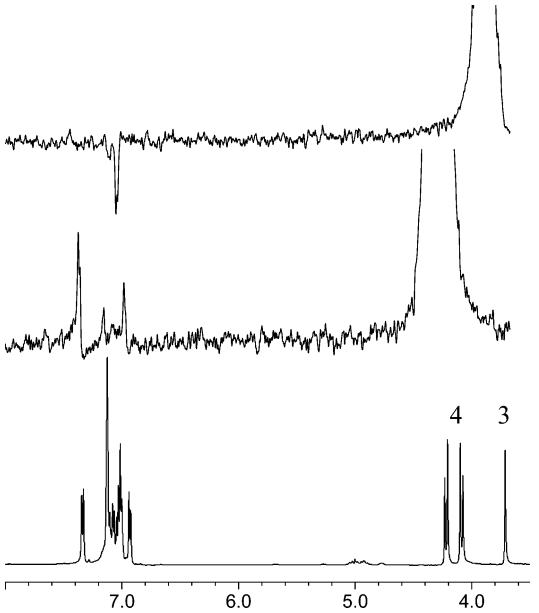

FIGURE 8. Section of the ^{1}H NMR spectra of a gel formed by organogelator **1**, containing diphenylmethane (**3**) and 2,2′-bishydroxymethylbiphenyl (**4**) in C_6D_6. ([**1**] = 6.3 mM, [**3**] = [**4**] =10 mM). Bottom: ^{1}H NMR spectrum, Middle: NOESY-1D obtained by selective excitation of benzylic signals of 4. Top: NOESY-1D obtained by selective excitation of benzylic signals of **3**.

We believe that the described behavior can be useful for the study of molecular recognition on gel networks of more sophisticated species such as bioanalytes or drugs, and we intend to explore this possibility in future work.

Experimental Section

The preparation and characterization of gelators **1** and **2** has been described previously.[5k,p]

The NMR organogel samples were prepared by transfer of a hot solution of the organogelator (containing measured quantities of diphenylmethane and 2,2′-bishydroxymethylbiphenyl in the corresponding cases) to a 5 mm NMR tube. A gel was formed upon cooling to room temperature in a few minutes. For the relaxation experiments the samples were deoxygenated by four freeze−pump−thaw cycles. After deoxygenation the samples corresponding to gel samples were heated in the septum-sealed tube until a dissolution was formed, and then upon cooling to room temperature a gel was obtained.

NMR spectra corresponding to the relaxation experiments were recorded in a 300 MHz instrument at 30 °C. T_1 measurements were carried out with the inversion recovery pulse sequence. T_2 measurements were performed using the Carr−Purcell−Meiboom−Gill (CPMG) sequence with dephasing times of 0.4 ms. A minimum of eight points was obtained for each of the relaxation experiments, and a good fit of the data to an exponential decay was obtained in all reported data.

NOESY-1D experiments were carried out in a 500 MHz instrument equipped with a PFG module.

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