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The triazine ring as a scaffold for the synthesis of new organogelators

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Abstract

The synthesis of new organogelators based on a triazine nucleus is described together with the analysis of the properties of the main compound **15**. This compound revealed an efficient organogelator in both polar and apolar solvents and represents a promising precursor of other functionalized organogelators.
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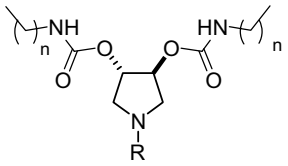
Organogels, gels formed by low molecular weight organic molecules, are attracting interest due to their peculiar behavior as supramolecular systems[1] and for the applications that they promise.[2] Their properties and the mechanisms, which are responsible for their formation, have been long studied although far from being fully described.[3] Particular attention is now posed on the application of these materials. The main goal is the development of gels, which are responsive to external stimuli such as light, temperature, pH variations, or the presence of pollutants. To exploit the potential applications it is necessary to produce organogelators, which are able to form stable gels in several different conditions and which can be appended with large molecular fragments maintaining the gelation ability. This approach will allow the obtainment of many different gels starting from the same organogelator, each of them showing peculiar properties. Examples of gelators are known and the synthetic effort is directed toward their modification introducing reacting centers at the periphery[4] or at the core.[5,2a–d] In this work, we describe our recent efforts toward the synthesis of an efficient gelating scaffold, able to form stable gels supporting a variety of molecular fragments. We have recently introduced a new organogelator, compound **2**,[6] based on a pyrrolidine nucleus substituted with two carbamate groups bearing C_{12} chains (Fig. 1). Some preliminary studies showed that the intertwining fibers forming the gels, obtained with **2** in cyclohexane, are based on the formation of hydrogen bond chains between the carbamate groups.[6a] This was suggested by a temperature dependent FT-IR study as well as by an X-ray analysis.[6b] The length of the aliphatic chains is an important parameter, since compound **1** ($n = 7$) does not show any gelating ability.



1 R = Bn, n = 7
2 R = Bn, n = 11
3 R = H, n = 7
4 R = H, n = 11

Fig. 1.

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The main feature of compound **2** is represented by the chance to remove, by catalyzed hydrogenation, the benzyl group affording the secondary amine **4**, a useful functionality for grafting molecular fragments (Fig. 1). The insertion of a variety of substituents onto the nitrogen atom represented, beside the possible application, a good test for the efficiency of the organogelator and we started the synthesis of a series of derivatives whose structure is reported in Figure 2. As can be seen from Table 1, the substitution of the benzyl moiety with other groups not always preserved the ability to form organogels. The simple substitution of the benzyl group with an allyl moiety, like in compound **5**, removes the gelation ability suggesting the role of the π-stacking interactions in the columnar disposition of **2**. Nevertheless, the simple presence of an aromatic substituent is not a guarantee for the gelation ability as demonstrated by compounds **7** and **9**.

Table 1
Gelating ability

Comp.	Gel formation[a]
1	—
2	Acetonitrile (0.3) Cyclohexane (0.2)
5	—
6	Acetonitrile (0.3) Cyclohexane (0.2)
7	—
8	Cyclohexane (1.0)
9	—
14	Acetonitrile (1.0) Cyclohexane (0.1) Xylene (0.2) Diisopropylether (0.4)
15	Acetonitrile (0.3) Cyclohexane (0.1) Xylene (0.3) Diisopropylether (0.4) Hexane (0.4)
16	Cyclohexane (0.1) Xylene (0.3)
17	Acetonitrile (0.4) Cyclohexane (0.1) Toluene (1.0) Isopropanol (0.4)

[a] Solvent (critical concentration w/v %).

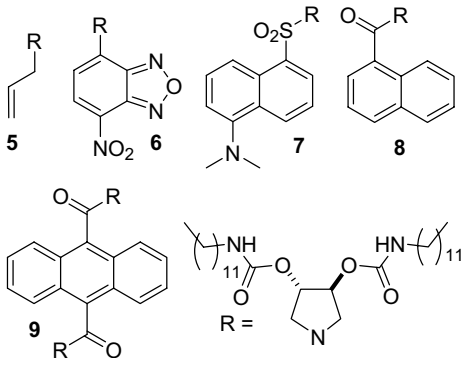


Fig. 2.

Among the five derivatives listed in Figure 2, only compound **6** revealed a good gelator even better than compound **2** itself. As shown in Figure 3, the differential scanning calorimetry (DSC) measurements showed an high gel–sol transition temperature (61.5 °C for **6** vs 36 °C for **2**); this transition is first-order, characterized by a finite ΔH ($\Delta H = 1.17$ Kcal/mol).

The simple gelator **2** revealed to be extremely sensitive to the nature of the molecular fragments grafted onto the nitrogen atom. We reasoned that assembling more than one gelating unit around a central scaffold could afford more efficient and versatile organogelators. The scaffold should also carry a suitable side arm for easily grafting other different molecular fragments. A suitable candidate was identified in cyanuric chloride since its well-known reactivity allows the insertion of up to three different substituents on the heteroaromatic ring.[7] This approach might, in principle, afford a large variety of different gelators varying the nature and number of gelating units and the nature and length of side arms as long as they possess a nucleophilic center to react with the triazine ring.

To start this study, we chose to assemble two units of pyrrolidine **3** around the triazine ring and used the third reacting center of the heteroaromatic ring for the insertion of an ethylene glycol unit as a side arm. The synthesis of the new triazine derivatives **14** and **15** is described in Scheme 1. Practically, it resulted more conveniently to insert the oxygenated moiety initially. The ethylenglycol monobenzyl ether (**12**), obtained through the reaction of benzylchloride with ethyleneglycol catalyzed by Cu(AcAc)$_2$,[8] was reacted with cyanuric chloride (**10**) to afford derivative **13** (Scheme 1). Finally **13** was reacted with pyrrolidine **3** to afford in a moderate yield gelator **14**.

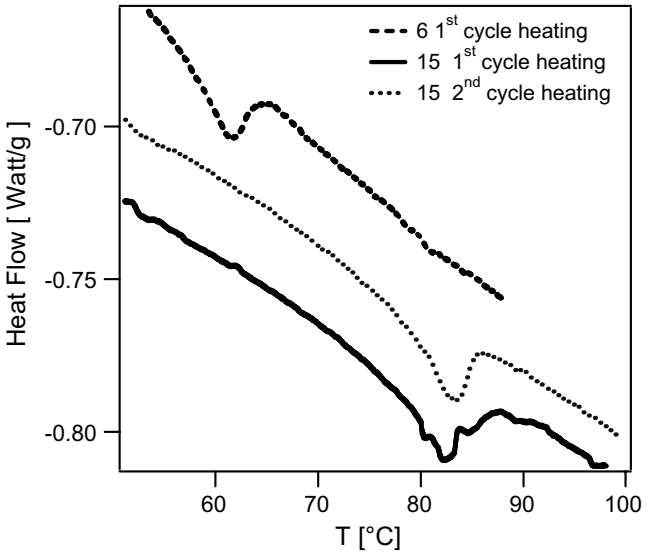
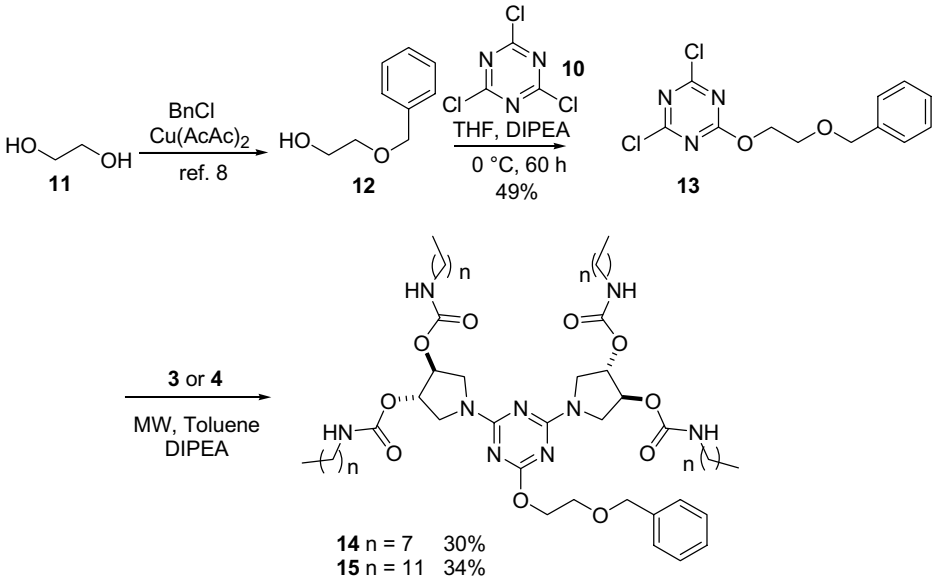


Fig. 3. DSC thermograms of compounds **6** and **15**. The baseline DSC trace corresponding to **6** has been offset for graphical purpose.

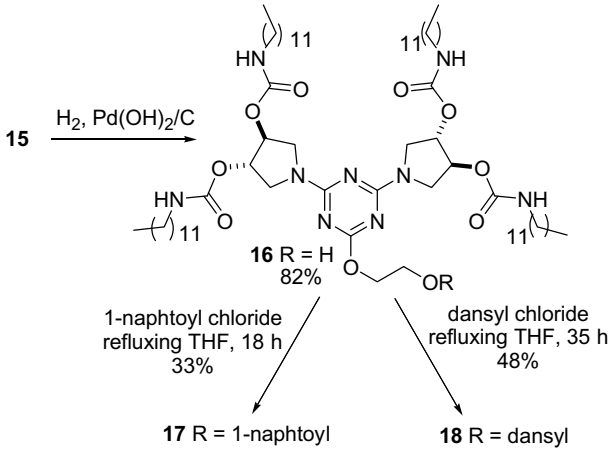


Scheme 1.

The use of microwaves for this step (100 W, Toluene, 15 m) revealed more efficient respect to conventional heating (refluxing toluene, 5 h, 10% yield). The gelating properties of **14** were studied in several solvents. As can be seen from Table 1, compound **14** can gel different solvents and in the case of cyclohexane, the critical concentration is very low. Gels obtained in cyclohexane and xylene are very stable and transparent.

From a comparison between the gelating ability of compounds **1** and **2**, it was obvious that the length of the alkyl chains plays a role in the formation and stability of the gel. For this reason compound **13** was reacted with pyrrolidine **4** to afford compound **15**.[9] Compound **15** revealed an excellent gelator in several solvents although the difference with **14** is not dramatic. The most important improvement was the new value for the critical concentration in acetonitrile (1% for **14** vs 0.33% for **15**) and the ability to form gel also in hexane. The critical concentration of **15** in the tested solvents ranged from 0.78 to 3.12 mM, values that indicate compound **15** as a 'supergelator'.[10] Compound **15** was chosen as the lead compound and some of its properties were analyzed. As already observed for compound **2**,[6a] also the FT-IR spectra of **15** showed significant variations changing from CH_2Cl_2 solution to the cyclohexane gel. The main differences involve the N–H stretching [3447 (CH_2Cl_2) vs 3330 cm^{-1} (cyclohexane gel)] and the C=O stretching of the carbamate groups [1727 (CH_2Cl_2) vs 1697 cm^{-1} (cyclohexane gel)]. The DSC measurements were performed in sealed aluminum pans. The high gel–sol transition temperature ($T_{gel-sol} = 82.2$ °C, slightly above the boiling point of cyclohexane), corresponding to the maximum of the endothermic peak (Fig. 3, solid line), indicates a remarkable strength of the gel structure, while the irregular, broad and multicomponent profile of the peak might indicate that we are observing a second order transition.[11] However, the calorimetric peak becomes more symmetric and narrow upon annealing (cooling and subsequent heating at 1 °C/min) of the sample (Fig. 3, dotted line), while the maximum of the endothermic transition is practically unaffected, ruling out the evaporation of the solvent during the measurement or sample damage. We have attributed the irregular shape observed during the first scan, to the possible presence of inhomogeneities, probably due to the transfer of the highly viscous gel into the measurement pan. The steeper shape of the endothermic peak has been interpreted as a first-order transition.[12]

To fulfill the original aim, to produce a gelating scaffold that can be substituted with different molecular fragments, the benzyl protecting group had to be removed. A simple $Pd(OH)_2/C$ catalyzed hydrogenolysis of **15** afforded alcohol **16** in good yield (Scheme 2). Alcohol **16** maintained



Scheme 2.

some of the gelating properties of **15** and possesses a free hydroxyl functionality that can be used as a versatile linker for attaching new molecular fragments. To demonstrate this possibility we synthesized the two esters **17**[13] and **18** (Scheme 2).

Unexpectedly, the synthesis of compounds **17** and **18** required refluxing THF for several hours for completion and the yields resulted were affected by this reaction conditions.

Compound **18** revealed that it was unable to form gel in any solvent tested while compound **17** revealed that it was an efficient gelator able to gel cyclohexane down to a critical concentration of 1 mg/mL (Table 1). A clear demonstration of the stability of the cyclohexane gel of **17** was offered by the circular dichroism (CD) spectra registered at different temperatures that revealed the persistence of the Cotton effect up to 55 °C (Fig. 4). The presence of CD effect is peculiar of the gel state,[14] since in solution compound **17** is CD silent, in analogy with what already observed for compound **2**.[6a]

Although it cannot be a quantitative observation it is worthwhile to note the remarkable difference of the specific rotatory power ($[\alpha]_D^{25}$) in solution and in the gel state (Table 2). The time required to obtain the formation of a stable, completely transparent, gel in cyclohexane (around 30 min) also allowed for the measurement of the specific rotatory power in cyclohexane solution. These data suggest that during the formation of the self-assembled fibrillar networks new chiral aggregates are formed, which are responsible of the specific rotatory power variations.

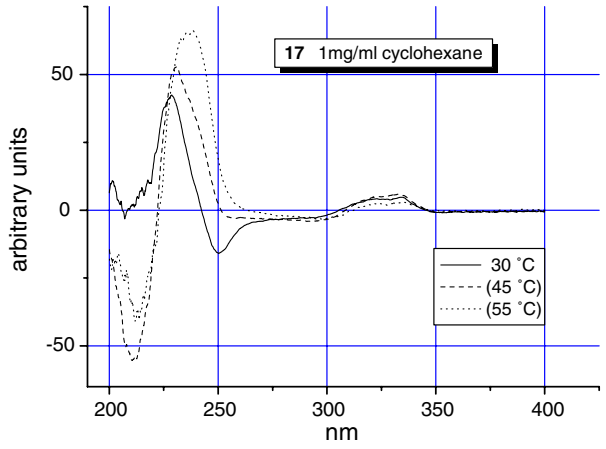


Fig. 4. CD spectra of compound **17** at different temperatures.

Table 2
Specific rotator power values for **15** and **17**

Condition	$[\alpha]_D^{25}$ **15**	$[\alpha]_D^{25}$ **17**
CH_2Cl_2 solution, *c* 0.1	−3.2	−6
Cyclohexane solution, *c* 0.1	+67	+235
Cyclohexane gel, *c* 0.1	+113	+576

The arrangement of substituted pyrrolidine units around a central scaffold revealed a useful approach to the synthesis of an efficient organogelator. This result was not predictable as demonstrated by the failure represented by the antracendicarboxylic acid derivative **9**. Compound **15** revealed to gel several different apolar and polar solvents with a remarkable value of critical concentration and $T_{gel-sol}$. The main goal of this work was the production of a versatile scaffold for further substitution with other molecular fragments. On this aspect compound **16** gave some contradictory results: the derivatization with a simple ester to afford compound **17** gave a good gelator while the correspondent sulphonate **18** failed to form any gel. Our actual effort is aimed to the development of this synthetic approach varying the nature and the length of the side arm while preserving the two gelating pyrrolidine units. Nevertheless we also plan to verify the versatility of this methodology using other gelating units described in the literature.

Acknowledgments

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9. Compound **15**: $[\alpha]_D^{25}$ −3.2 (*c* 0.1, CH_2Cl_2). ^1H NMR (200 MHz; $CDCl_3$) $\delta = 0.97–0.78$ (12H, t, CH_3), 1.40–1.10 (68H, m, aliphatic chains), 1.60–1.40 (12H, m, aliphatic chains), 3.23–3.00 (8H, m, $CH_2NC(O)O$), 3.90–3.65 (10H, m, CH_2 pyrrolidine ring, CH_2O ethyl), 4.52–4.41 (2H, m, CH_2O ethyl), 4.56 (2H, s, OCH_2Ph), 4.86–4.69 (4H, m, NH), 5.20–5.08 (4H, br s, HCO pyrrolidine), 7.40–7.28 (5H, br s, Ph). ^{13}C NMR (50 MHz; $CDCl_3$) $\delta = 169.8$ (2C,s, triazine), 164.3 (s, triazine), 154.8 (4C, s, C═O), 138.0 (s), 128.2 (d), 127.6 (d), 127.5 (d), 75.0 (4C, d, CHO pyrrolidine), 73.1 (t, OCH_2Ph), 68.1 (t, CH_2O ethyl), 65.5 (t, CH_2O ethyl), 50.5 (2C, t, CH_2N pyrrolidine), 50.3 (2C, CH_2N pyrrolidine), 41.1 (4C, t, CH_2N aliphatic chains), 31.9, 29.8, 29.6, 29.3, 29.2, 26.7, 22.7, 14.1; MS (ESI) *m*/*z* 1301 ($M+Na^+$, 100%), 1279.09 (M^++1, 58). Elem. Anal. Calcd for $C_{72}H_{127}N_9O_{10}$: C, 67.62; H, 10.01; N, 9.86. Found C, 67.53; H, 10.22; N, 9.65.
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13. Compound **17**: mp = 153–155 °C; $[\alpha]_D^{25}$ −6 (*c* 0.1, CH_2Cl_2), $\lambda_{abs\,max}$ (THF) = 295 nm; $\lambda_{em\,max}$ (THF, ex 295 nm) = 357 nm; $\lambda_{abs\,max}$ (cyclohexane gel fase) = 313 nm; $\lambda_{em\,max}$ (cyclohexane gel fase, ex 295 nm) = 368 nm. ^1H NMR (200 MHz; $CDCl_3$) $\delta = 0.87$ (12H, t, CH_3), 1.39–1.10 (65H, m, aliphatic chains), 1.60–1.39 (15H, m, aliphatic chains), 3.23–3.00 (8H, m, CH_2NCOO), 3.90–3.64 (8H, br s, CH_2N pyrrolidine), 4.78–4.61 (4H, br s, CH_2O ethyle), 4.88–4.78 (4H, m, NH), 5.23–5.08 (4H, br s, HCO pyrrolidine), 7.62–7.40 (3H, m, naphthyl), 7.86 (1H, d, $J = 7.2$ Hz, naphthyl), 8.02 (1H, d, $J = 8.0$ Hz, naphthyl), 8.21 (1H, d, $J = 7.2$ Hz, naphthyl), 8.92 (1H, d, $J = 8.4$, naphthyl). ^{13}C NMR (50 MHz; $CDCl_3$) $\delta = 169.8$ (2C, s, triazine), 167.2 (s, C═O naphthyl), 164.4 (s, triazine), 154.8 (4C, s, C═O), 133.7 (s), 133.3 (d), 131.3 (d), 130.6 (d), 128.4 (d), 127.7 (d), 126.7 (d), 126.1 (d), 125.8 (s), 124.4 (s), 75.0 (4C, d, HCO pyrrolidine), 64.3 (t, CH_2O ethyl), 63.2 (t, CH_2O ethyl), 50.5 (t, CH_2N pyrrolidine), 50.3 (CH_2N pyrrolidine), 41.2 (CH_2N chains), 31.9, 30.3, 29.8, 29.6, 29.5, 29.3, 26.8, 22.7, 14.1; MS(ESI): *m*/*z* 1365.0 ($M+Na^+$, 100%), 1342.9 (M^++1, 36), 1171.9 (78). Elem. Anal. Calcd for $C_{76}H_{127}N_9O_{11}$: C, 67.97; H, 9.53; N, 9.39. Found C, 67.70; H, 9.32; N, 9.28.
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