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Stable organogels derived from triazines functionalized with chiral α-amino acid derivatives

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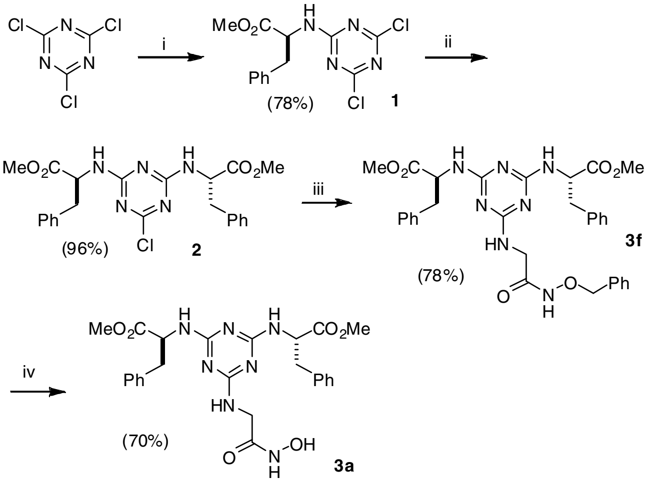
Triazines functionalized with three stereogenic α-amino-acidic appendages having at least one amide or hydroxamate function give highly stable organogels in haloalkanes and aromatic solvents, and their gelating ability depends on both structural and stereochemical properties.

Molecular organogels are one type of soft matter composed of low-molecular-weight organic molecules (the gelators) forming three-dimensional networks held together by multiple noncovalent interactions, in which organic liquids are immobilized.[1] Gelation is a reversible process, and efficient gelators can immobilize solvent at concentrations less than 1 wt%.

These semisolid materials have generated remarkable interests both for basic scientific reasons and for technological applications. Among them, new soft organic materials for special applications, separations, drug delivery and template synthesis. Although new gelators are often found more by serendipity rather than by rational design,[2] it is known that derivatives of fatty acids, cholesterol, urea, amino acids and carbohydrates have a special proclivity to form organogels.[3]

Triaminotriazines (melamines) have a compact and rigid structure endowed with high symmetry that can give rise to multiple non-bonding interactions (Van der Waals interactions and hydrogen bonds)[4] in well-defined directional preferences.[5] We were therefore surprised to find that no melamine-like gelators are described in the literature (except for an example of a binary melamine-barbiturate/cyanurate gelator),[6] the only related example being a family of diaminotriazinecarboxylic acids recently reported by Wuest and co-workers.[7] In this Letter we report the potent organogel-forming ability of triazines functionalized with three α-amino acid substituents, and a study on the influence of structural and stereochemical factors on the formation of the organogels.[8]

The triazine-based organogel-forming molecules were prepared by means of subsequent nucleophilic dechloraminations of the starting trichlorotriazine by different α-amino acid esters, amides or hydroxamates as exemplified by the synthesis of **3a** (Scheme 1).[9]



Scheme 1. Synthesis of the organogel-forming triazines. Reagents and conditions: (i) L-Phe-OMe (1 equiv), NaHCO$_3$, acetone/H$_2$O, 0 °C, 1 h; (ii) L-Phe-OMe (1 equiv), NaHCO$_3$, acetone/H$_2$O, rt, overnight; (iii) Gly-NHOBn (1 equiv), DMSO, DIPEA, 120 °C, 2 h; (iv) H$_2$/Pd, MeOH, rt, 2 h.

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A number of solvents were screened in order to investigate the gelating properties of triazines **3**–**8** (Scheme 2). None of them was found to be able to gelate alcohols (methanol, ethanol and isopropanol gave always solutions), ethers (diethyl ether and diisopropyl ether were poorly solubilizing, whereas THF and dioxane gave solutions), alkanes (these triazines are poorly soluble in hexane and cyclohexane), acetone and acetonitrile (they mostly gave solutions), triethylamine and water (very poor solubility).

Formation of organogel was observed in ethyl acetate for the compounds **3b,c** at a rather high concentration of 3% w/w. Formation of stable gels was observed with haloalkanes and aromatic solvents, in particular toluene, for most triazines **3**–**8** (Table 1).[10] As it can be seen in Figure 1, the gel formed by **3a** in $CHCl_3$ is very clear at a concentration of 1 wt%, and becomes progressively more turbid at higher concentrations.

Table 1 shows that most triazines having an amide or hydroxamate function form gels in toluene, with the exception of the *tert*-butyl ester derivative **3d** and the bis-glycine derivative **5**, which are substantially unable to gelate. Compounds missing the amide or the hydroxamate function, such as the triester derivatives **7** and **8**, are also unable to gelate. Interestingly, also the chlorotriazine **6** can form gels in CH_2Cl_2 and toluene at a concentration of 2 wt%, but the gel is rather unstable and the compound tends to form a precipitate. Chiral bis-phenylalanine triazines methyl or ethyl esters, which bear a glycine functionalized as hydroxamate (**3a**) or amide (**3b,c**), have the strongest capacity to give gels in chloroalkanes, in aromatic solvents and even in ethyl acetate. In contrast, the corresponding achiral meso-structures **4a,b** have lower gelating capacity in chloroalkanes, but they give very strong gels in toluene.

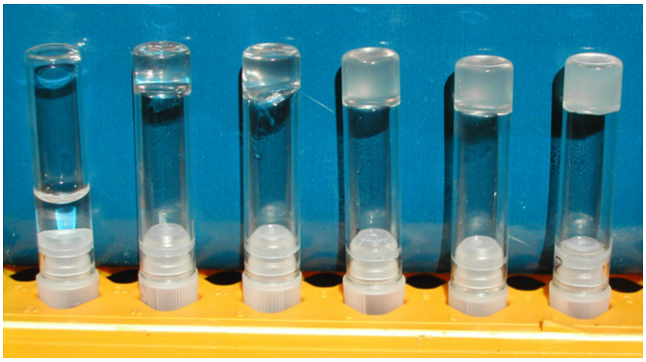
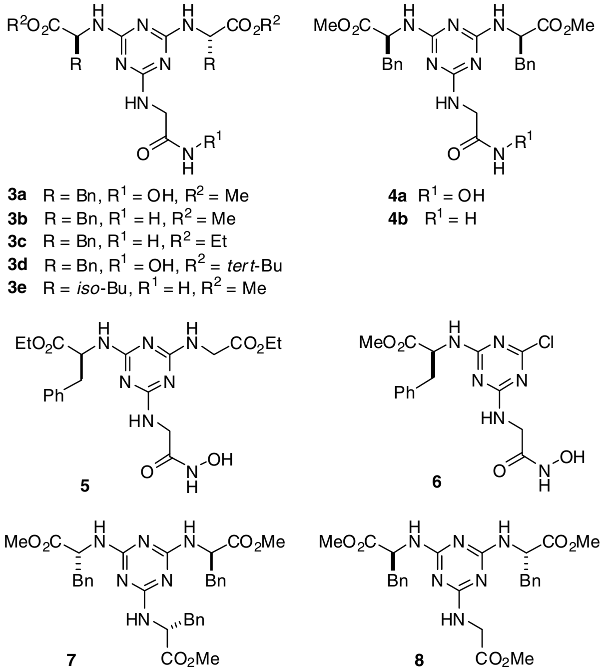


Figure 1. Gels formed by **3a** in $CHCl_3$ at different concentrations at rt. From left: $CHCl_3$ only, 1.0, 1.5, 2.0, 2.5 and 3.0 wt%.

The stability and gel–sol transition temperatures of the organogels formed by chiral **3a,b** and meso **4b** in different solvents were studied in detail by means of the 'falling-ball' method,[11] namely by positioning a steel sphere having 2 mm of diameter and 130 mg of weight on the surface of the organogel, and by monitoring its penetration until the bottom of the gel sample upon increasing the temperature. It is worth noting that the meso-compound **4b** in toluene gives organogels having high thermal resistance with mp above 100 °C. The trends for the gel–sol transitions of **3b** and **4b** in toluene at different temperatures are reported in Figure 2.

To evaluate the influence of the stereochemical purity on the gel-forming capacity of these triazines, we checked the behaviour of racemic compounds **3a** and **3b** in toluene, which showed surprising differences with respect to the enantiomerically pure compounds. Racemic **3a** in toluene at 2 wt% concentration formed a more transparent gel having lower gel–sol transition temperature with respect to enantiopure **3a**, namely 52 ± 2 °C versus 57 ± 2 °C (see Table 2). In contrast, racemic **3b** under the same conditions formed a more turbid gel having higher gel–sol transition temperature with respect to enantiopure **3b**, namely 84 ± 1 °C versus 77 ± 1 °C (see Table 2).[12] Clearly, the strikingly different behaviour of these molecules depends on the presence of either the hydroxa-



Scheme 2. Set of triazine-based structures investigated for their organogel-forming ability.

Table 1

Gel forming capacity of triazines **3**–**8** in different solvents at 3 wt % and rt

Triazine	CH_2Cl_2	$CHCl_3$	$(ClCH_2)_2$	Toluene	EtOAc
3a	Gel	Gel	Gel	Gel	Sol
3b	Gel	Sol	Gel	Gel	Gel
3c	Gel	Gel	Gel	Gel	Gel
3d	Sol	Sol	Sol	Sol	Sol
3e	Sol	Sol	Sol	Gel	Sol
4a	Sol	Sol	Sol	Gel	Sol
4b	Sol	Sol	Sol	Gel	Sol
5	Sol	Sol	Sol	Wgel	Sol
6	Gel[a]	Prec	Prec	Gel[a]	Prec
7	Sol	Sol	Sol	Sol	Sol
8	Sol	Sol	Sol	Sol	Sol

[a] Key: g = gel; sol = solution; wgel = weak gel that is unable to sustain the steel ball on the surface. A precipitate tends to form at a concentration of 2 wt%.

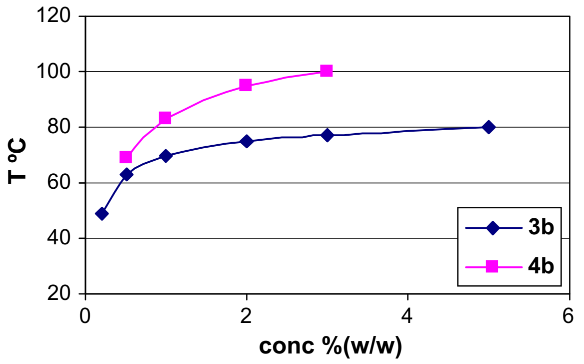


Figure 2. Gel–sol transitions of **3b** and **4b** in toluene at variable temperatures.

Table 2
Gel–sol transition temperatures (°C) of gels formed from some triazines in different solvents

Triazine (wt%)		CH_2Cl_2	$CHCl_3$	$(ClCH_2)_2$	Toluene	EtOAc
3a	2.0	41 ± 1	30 ± 1	35 ± 1	57 ± 2	Sol
	3.0	43 ± 1	33 ± 1	36 ± 1	58 ± 1	Sol
	5.0	44 ± 1	35 ± 1	38 ± 1	61 ± 1	Sol
3b	0.05	Sol	Sol	Sol	Wgel	Sol
	0.2	Sol	Sol	Sol	51 ± 1	Sol
	0.5	Sol	Sol	Sol	64 ± 1	Sol
	1.0	Sol	Sol	Sol	70 ± 1	Sol
	2.0	Wgel	Sol	Sol	77 ± 1	Sol
	3.0	Wgel	Sol	Wgel	78 ± 1	Wgel
	5.0	35 ± 2	Wgel	Wgel	81 ± 2	41 ± 2
4b	0.2	Sol	Sol	Sol	Wgel	Sol
	0.5	Sol	Sol	Sol	72 ± 2	Sol
	1.0	Sol	Sol	Sol	86 ± 2	Sol
	2.0	Sol	Sol	Sol	96 ± 1	Sol
	3.0	Sol	Sol	Sol	103 ± 2	Sol

Key: sol = solution; wgel = weak gel that is unable to sustain the steel ball on the surface.

mic acid or the amide function of **3a** and **3b**, respectively, which probably give rise to different supramolecular structures of these triazines, depending on their enantiomeric purities.

Since triesters **7** and **8** are unable to gelate, it clearly appears that the amide and hydroxamic acid functions of **3–6** are essential for the supramolecular assembly of the triazine molecules, probably contributing to a network of intermolecular hydrogen-bonds.[13] The C_2-symmetry of the organogel-forming triazines **3** might be another important factor, as shown by the fact that low-symmetry molecules like **5** and **6** have lower organogelating power, as well as C_s-symmetrical meso-structures **4a, b**. π-Stacking interactions involving the phenyl groups might be as well important, since Leu-derived **3e** has lower organogelating properties. Finally, the steric bulk of the ester function seems to hinder the organogel formation, as shown by the fact that *tert*-Bu ester **3d** is unable to gelate.

SEM morphologic analysis of the xerogel obtained from **4b** (0.5 wt% in toluene) showed a dense network of fibres having a diameter of about 100 nM (Fig. 3), which is clearly responsible for the encapsulation of the molecules of solvent, and therefore for the formation of the organogel.

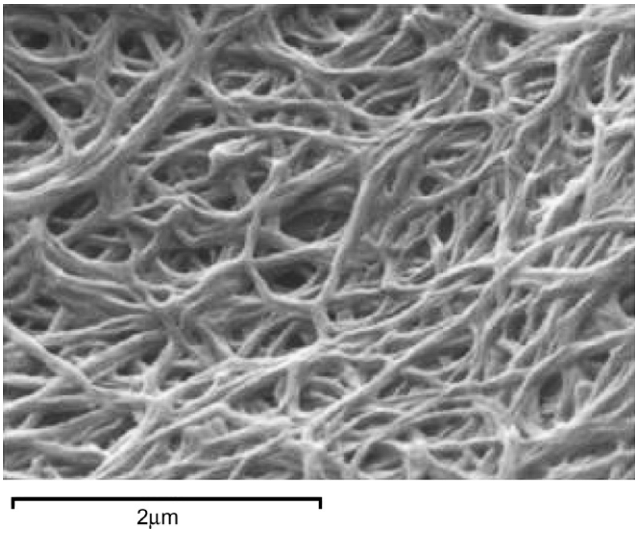


Figure 3. SEM image of the xerogel obtained from **4b** (0.5% w/w in toluene).

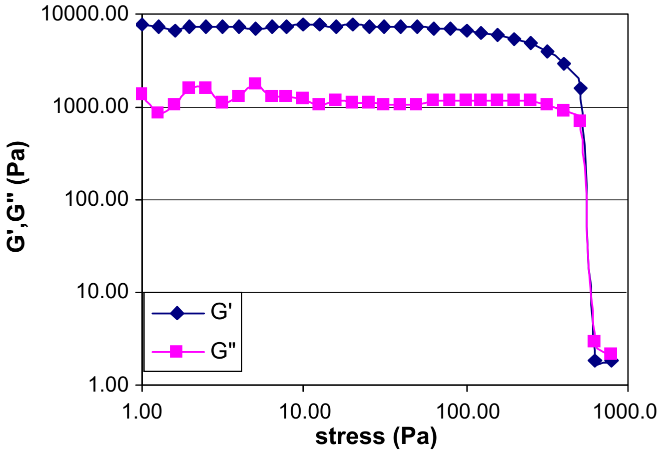


Figure 4. Viscoelastic behaviour of the organogel formed from compound **3b** in toluene (1 wt%) at 20 °C.

To measure the organogel rigidity and its response to stress, a rheological analysis of the gel formed from compound **3b** in toluene (1 wt%) at 20 °C was conducted using a rotational stress-controlled rheometer (constant oscillation frequence = 1 Hz).[14] As shown in Figure 4, the storage (elastic) modulus (G') is greater than the loss (viscous) modulus (G'') showing that this is a well-structured system, having the dominant elastic behaviour typical of a gel. The G' and G'' values remain constant in a wide range of strain below the critical value of 560 Pa. The equilibrium value for $G'_{eq} =$ ca. 10^4 Pa is one order of magnitude greater than that for $G''_{eq} =$ ca.1100 Pa.

In summary, we have identified the first family of melamine-based chiral molecules having very good organogelating properties. The modular structure and smooth synthesis of these triazines substituted by three amino-acidic appendages make these organogelators a promising class of biomimetic, peptide-like compounds having potential applications in biomedicinal field.

Acknowledgements

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