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A family of strong low-molecular-weight organogelators based on aminoacid derivatives

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Abstract—A new family of potent aminoacid-type organogelators obtained via an easy and unexpensive way is described. We demonstrated that structural variations onto the side chains of the aminoacid derivatives allowed modulations of the gelation properties. The organogelators bearing a benzyl or an isopropyl group (compounds **1e**, **2a**, and **2c**) are able to provide gelation of apolar solvents at very low concentration ($\leqslant$0.2 wt%) and to form thermostable gels.

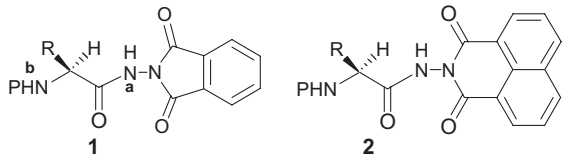
1. Introduction

The organogelation phenomenon exhibited by low-molecular-weight molecules is the subject of increasing attention.[1] Thermoreversible physical gels are generally formed by a self-aggregation leading to the formation of fibrous network imprisoning the solvent, noncovalent cross-links among the nanofibers creating the three-dimensional network. The supramolecular nature of this phenomenon has been demonstrated: gelator molecules are assembled through noncovalent interactions (hydrogen bonding, van der Waal's, π-stacking...).[1,2] However, the relationship between the chemical structure of an organogelator and its gelation properties in a given solvent is not clearly established; discovery of new gelators remains mainly fortuitous and the design of a define gelator is not yet feasible. Furthermore, gels have numerous industrial applications in areas such as cosmetic, lubrification, paper, and health care.[1a] For these applications, the development of unexpensive but efficient organogelators is of great interest.

During investigations dealing with the synthesis of new families of pseudopeptides, we have demonstrated that *N*-protected phthaloylhydrazide aminoacids **1** can be used as acidic partners in the Mitsunobu protocol.[3] Unexpectedly, we observed that the phenylalanine derivative (**1a**, R = CH_2Ph, P = Z) exhibited the property to gelate at low concentration the solvent used for its preparation (1% weight in toluene). Several examples of aminoacid-type organogelators have been reported in the literature such as small peptides or pseudopeptides,[1e–i] cyclopeptides,[1j] and bis-urea.[1k,l] Taking into account data concerning these compounds and the chemical structure of **1a**, network of intermolecular hydrogen bonds as well as π–π stacking and hydrophobic interactions could be important contributors to the aggregation process.

2. Results and discussion

To help understand the organogelation phenomenon and to define a new group of structurally related gelators, a series of aminoacid derivatives **1** and **2** (Scheme 1) was prepared in order to try to establish a



Scheme 1.

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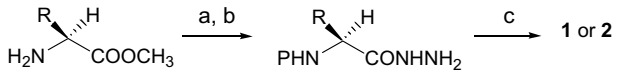

Scheme 2. Reagents and conditions: (a) ZCl or AllocOSu, 1 equiv; (b) NH_2NH_2, 3 equiv, MeOH, rt, 18 h; (c) phthalic or naphthalic anhydride, 1 equiv, toluene, reflux.

structure–physical properties relationship. This new kind of gelling agents possesses the advantage to be very easy to prepare starting from unexpensive starting materials and that many structural variations can be introduced as P and R.

Compounds **1** and **2** were prepared in three steps from (*S*)-aminoacid methyl esters according to the general procedure described in the Scheme 2.[3a] The gels were obtained by heating together the solvent and the organogelator (0.18–2.5 wt%) in a flask fitted with a reflux condenser until the dissolution of the solid was complete. The solution was transferred into a closed vial and cooled to 0 °C. Mainly, the formation of the gel occurred within several minutes, if any.

The organogelation ability of compounds **1** and **2** in apolar solvents is described in the Table 1. The thermostability of the gels has been evaluated considering two factors:

- the critical gelation concentration (CGC in wt%) where the sol-phase changes into gel-phase (stable at room temperature),
- the sol–gel phase transfer temperature (T_m in °C) where the gel (at a concentration of 0.5 wt%) melts into solution. These data were established by rheology, which is described as the more accurate and convenient method.[4]

It appears from this study that modifications of the hydrophobic parts of the compounds do not affect their organogelation ability, which seems to be mainly governed by the polar part of the amphiphilic molecules. We performed some ^1H NMR studies on **1d** in CCl_4/C_6D_6 (4/1) at different temperatures between 25 °C (gel) and 70 °C (solution) (see Electronic Supplementary Information) in order to follow the temperature-dependent chemical shifts of the two NH protons (H^a and H^b, see Scheme 1). Very interestingly, we observed (see Fig. 1) that the chemical shift of H^a is quite invariant up to the sol-to-gel transfer temperature (50 °C) suggesting its implication in a strong hydrogen bond and is shifted upfield at higher temperature. On the contrary, a downfield shift in 25–50 °C range and upfield shift at higher temperature was observed for H^b. As previously reported,[5] these latter chemical shift trends could correspond to a weaker hydrogen bond network. Considering these results, it is possible to postulate that the formation of the aggregates probably occurs through the build up of a strong hydrogen bonds network (involving the more acidic NH^a proton[3a]) but also of weaker hydrogen bonds one involving the NH^b proton.

Compounds **1** or **2** bearing aromatic or aliphatic hydrophobic side chain R can equally cause gelation

Table 1. Organogelation ability of compounds **1** and **2**

Compound	R	P	Toluene			Toluene/cyclohexane 1/1			CCl_4		
			State[a]	CGC[b]	T_m (°C)[c]	Phase[a]	CGC[b]	T_m (°C)[c]	State[a]	CGC[b]	T_m (°C)[c]
1a	CH_2Ph	Z	CG	1	NV[d]	I			I		
1b	Ph	Z	WG	0.5	80	I			I		
1c	$CH_2CH(CH_3)_2$	Z	CG	2.5	NV	CG	0.5	55	I		
1d	CH_2Ph	Alloc	WG	0.5	54	CG	0.35	68	CG	0.25	57
1e	$CH(CH_3)_2$	Z	P			I			I		
2a	CH_2Ph	Z	CG	0.18	80	I			I		
2b	Ph	Z	P			I			I		
2c	$CH_2CH(CH_3)_2$	Z	CG	0.5	45	CG	0.2	92	WG	0.2	78
2d	CH_2Ph	Alloc	CG	0.35	66	I			I		

[a] CG = clear gel, WG = white gel, P = solution upon heating, precipitate at room temperature; I = insoluble.
[b] Critical gelation concentration in wt%.
[c] Determined by rheology[4] for a concentration of 0.5 wt%.
[d] No value (CGC > 0.5%).

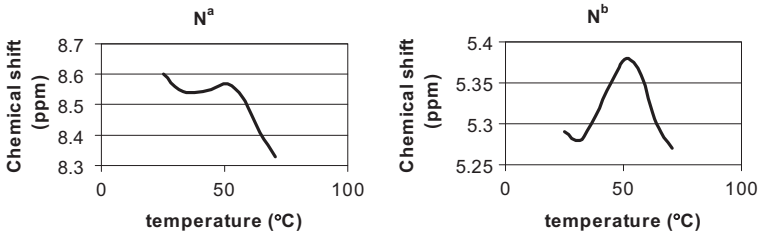

Figure 1. Variation of the chemical shift of NH^a and NH^b protons of **1d** in CCl_4/C_6H_6 recorded between 25 °C (gel) and 70 °C (solution).

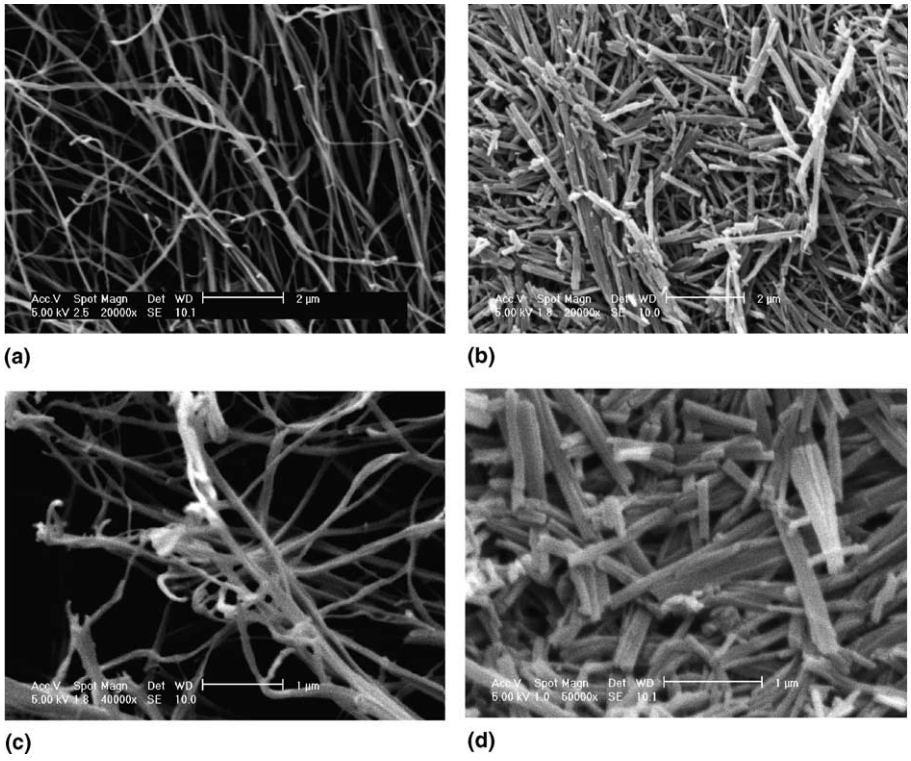

Figure 2. SEM pictures of the dried toluene–gels: × 20,000 (a) **2a**, (b) **1b** (scale bar is 2 μm); × 40,000, (c) **2a**, (d) **1b** (scale bar is 1 μm).

of toluene. On the contrary, a relative small constitutional change occurred onto the lateral chains resulted in a dramatic change of the gelation properties: compounds **1e** and **2b** lacked any gelation abilities because of a tendency to crystallize whereas homologous compounds **1c** and **2a** were able to gelify efficiently the toluene.

The area of the conjugated systems at the *C*- and *N*-terminal parts of the compounds was analyzed in term of gelation ability (CGC and T_m): compound **2a** bearing a benzyl group at the *N*-terminal part has better gelation ability than **2d** bearing an allyl group (Z → Alloc). In the same way, the organogelation behavior of compounds **2** possessing a naphthalimide group in the *C*-terminal part was higher than those of the phthalimide derivatives **1**. This observation could underline the importance of the π stacking in the gelation process of compounds **1** and **2**.

Interestingly, properties of the gels can be altered by a small change of the solvent composition and polarity: for compounds **1c**,**d**, and **2c** possessing only two aromatic moieties, the best gelling ability was observed in a mixture cyclohexane/toluene (1/1) or in CCl_4 whereas the other compounds (bearing three aromatic groups) were not soluble in these solvents. This observation shows that the presence of the aliphatic moiety seems to enhance the gelation of aliphatic solvent, the solvent–gelator affinity affecting the solubility and the morphology of the fibers. Thus, it appears that the CGC for **2a** in toluene and for **2c** in a mixture cyclohexane/toluene or in CCl_4 are very low (respectively, 0.18 and 0.20 wt%); moreover, the sol–gel phase transfer temperature (T_m) of the corresponding gels are high: impressively, for a concentration of only 0.2 wt%, gel from **2c** in CCl_4 can be heated to the boiling point of the solvent without sol-to-gel transition; in the same way, at a concentration of 2 wt%, the compound **2a** forms a gel in toluene which can be heated up to 116 °C (bp of the solvent).

In the table is reported a visual examination of the gels: clear gels (which were mainly transparent) and white gels (for which a white opacity was observed) were distinguished. It appears that both the structure of the organogelator and the nature of the solvent can affect the turbidity of the gel. According to previous works,[6] it is assumed that the optical aspect is related to the crystallinity of the gels. Thus, the electron micrographs reveal a great difference between a clear gel (from compound **2a** in toluene) and a white gel (from compound **1b** in toluene) in the fiber dimensions and in the network structure. Figure 2 displays pictures of aerogels obtained from toluene gels ($c = 0.5$ wt%) dried under supercritical conditions: **2a** exhibits a fibrous aggregated morphology (with fibers length of several μm, pictures a and c) whereas **1b** exhibits a lamellar aggregation mode for which the fibers length are significantly shorter and the fibers tend to be more aggregated (pictures b and d).

3. Conclusion

To conclude we have defined a new family of potent aminoacid-type organogelators of apolar solvents. We have shown that the polar part of the molecules seems

to govern the aggregation of individual compounds via a hydrogen bonds network while the hydrophobic parts could affect the intrinsic flexibility and the fiber–fiber interactions. In accordance with previous works,[7] structural variations of the side chain of the aminoacid affect the solubility and the efficiency of the intermolecular overlap of the aggregation process and so allowed modulations of the gelation properties. Thus, in an aromatic solvent, the π-stacking appears to be an important contributor to the gelation phenomenon whereas the presence of aliphatic moiety seems to enhance the gelation of aliphatic solvent. Depending on the nature of the gelator used, the structure of the aggregates ranges from a fibrous to a lamellar morphology. Some of the organogelators described in this paper are able to form, even at low concentration, gels with good thermal stabilities.

4. Experimental

4.1. Procedure for the preparation of 2a

Step (a): L-Phenylalanine methylester hydrochloride (10.75 g, 50 mmol.) was dissolved in aqueous saturated $NaHCO_3$ solution (200 mL) and benzylchlorocarbonate (8.5 g, 50 mmol) was added under vigorous stirring. Stirring was continued overnight. The solution was extracted with ether (three times). The combined organic layers were washed with HCl 1 N, dried under $MgSO_4$, and concentrated at reduce pressure. The excess of benzylchlorocarbonate was removed using a short column chromatography (eluent: petroleum ether; the product was chromatographed with 40% EtOAc/petroleum ether) to give 14 g (90%) of pure product. **Step (b)**: Hydrazine hydrate (5 g, 100 mmol) was added to a solution of *N*-benzyloxycarbonyl-L-phenylalanine methyl ester (10 g, 32 mmol) in methanol (100 mL). The mixture was stirred overnight at room temperature and the hydrazide was collected by filtration, washed with methanol, and dried (7.8 g, 78%). **Step (c)**: The hydrazide derivative (2 g, 6.3 mmol) was added to a suspension of naphthalic anhydride (1.26 g, 6.3 mmol) in toluene (200 mL) and the resulting mixture was refluxed, the water formed during the reaction was trapped in a Dean–Stark receiver. After 6 h, the solution was cooled and quickly transformed into a gelatinous mass, which was evaporated in vacuo to dryness. The solid residue was recrystallized in $CHCl_3$. ^1H NMR (300 MHz, $CDCl_3$) of **2a**: δ 8.85 (s, 1H), 8.65–8.45 (m, 2H), 8.20 (d, 2H), 7.80–7.60 (m, 2H), 7.45–7.10 (m, 10H), 5.63 (m, 1H), 5.15–5.00 (m, 2H), 5.00–4.75 (m, 1H), 3.38 (dd, 1H), 3.18 (dd, 1H).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.139. NMR data and experimental procedure for the supercritical drying of the organogels are available in Supporting informations.

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