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Hydrazinoazadipeptides as aromatic solvent gelators

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Abstract—In the presence of a small amount of HCl, hydrazinoazadipeptides form thermoreversible physical gels with aromatic solvents. These gels are stable to 70–90°C, and can be stored for months. Electron microscopy reveals that in these solvents, pseudopeptides self-assemble into elongated and very thin fibers, which in turn form a three-dimensional network that traps solvent molecules. Infrared studies showed that aggregation is accompanied by the formation of a hydrogen-bonded network between NH and CO of the hydrazinopeptides. © 2001 Elsevier Science Ltd. All rights reserved.

Thermoreversible physical gels, whose behavior is governed by van der Waals, hydrophobe/hydrophile interactions or intermolecular hydrogen bonding were the province of macromolecules, surfactants and other compounds containing long alkyl chains.[1] Gelation of organic solvents by low-molecular-weight compounds, such as small peptides,[2] cyclodipeptides,[3] depsipeptides,[4] bis-ureas[5–8] and saccharides[9] is the object of increasing attention not only because of the numerous applications of gels, but in particular because these compounds represent a new class of gelators that exhibit striking properties with respect to self-assembly phenomena.[10] Such compounds are characterized by both good solubility upon heating (as compared to macromolecular gelling agents) and by inducement of smooth gelation of organic solvents at room temperature. Moreover only small amounts of gelling agent and at low concentration afford gelation.

During investigations of the synthesis of hydrazinoazapeptides,[11] we met an unexpected phenomenon. Compounds **1**, ClAc-N$^{\alpha}$(Me)hPhegly-azaGly-OR, were able to gelate aromatic solvents such as toluene, xylene and styrene. The most difficult problem for the development of low-molecular-mass gelling agents was how to stabilize the gel, in other words how to prevent the transformation of the metastable gel to a crystalline state. In this paper, we report that pseudopeptides **1** (Fig. 1) are a new class of gelling agents and we show that a small amount of HCl is necessary to stabilize the gel.

A typical procedure for studying gel formation ability was to prepare the pseudopeptides **1** ($R^1 = p$-MeC_6H_4

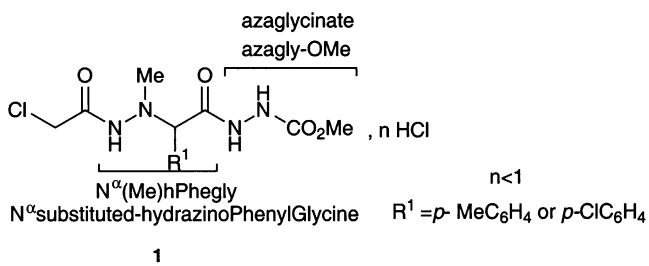
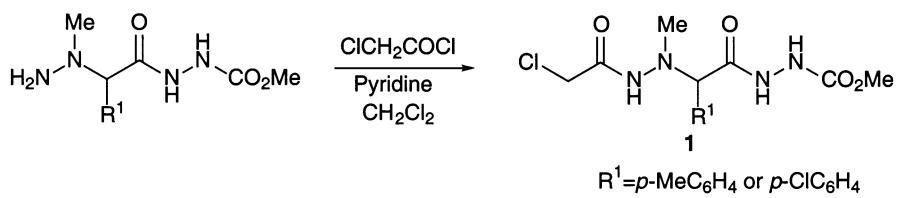


Figure 1.



Scheme 1.

Keywords: hydrazinoazapeptides; gel; electron microscopy; hydrogen bond.

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Table 1. Gelation properties of **1** ($R^1 = p\text{-}MeC_6H_4$) in various solvents

Solvent	Minimum gel concentration g/dm^3 (gelator/solvent)	T_m^g (°C)
Toluene	10	90
Xylene	15	~74
Styrene	15	~80
Dichloromethane	Solution	–
Ethanol	Precipitate	–
Ethyl acetate	Precipitate	–
Acetone	Solution	–
Pentane	Insoluble	–

or $p\text{-}ClC_6H_4$) by reacting chloroacetyl chloride and hydrazinoazapeptide precursors[11] in the presence of pyridine (Scheme 1). Compounds **1** ($R^1 = p\text{-}MeC_6H_4$ or $p\text{-}ClC_6H_4$) were obtained as a precipitate, preparation of the gel was as follows: 10 mg of **1** ($R^1 = p\text{-}MeC_6H_4$ or $p\text{-}ClC_6H_4$) were dissolved in 1 cm^3 of boiling solvent (toluene, xylene or styrene) after filtration on glass-wool the limpid solution was cooled at ~5°C for 12 h to form a very stable gel (months). The test tube could be inverted (for weeks) without alteration of the gel. If **1** ($R^1 = p\text{-}MeC_6H_4$ or $p\text{-}ClC_6H_4$) was first recrystallized in methanol (analytically pure), it was no longer possible to get a gel. Moreover the hydrochloride of **1** ($R^1 = p\text{-}MeC_6H_4$ or $p\text{-}ClC_6H_4$) (**1**, HCl) dissolved in boiling toluene, afforded after cooling a precipitate, no gel was obtained. We went back to a stable gel only if **1** (X = Cl or Me) was partially protonated: for that, recrystallized **1** ($R^1 = p\text{-}MeC_6H_4$ or $p\text{-}ClC_6H_4$) was dissolved in a solution of hot toluene in which HCl_{gaz} was bubbled until the increasing weight was less than the stoichiometry of **1** ($R^1 = p\text{-}MeC_6H_4$ or $p\text{-}ClC_6H_4$) (~0.5 mmol), then the solution was cooled to 5°C and gave a gel. This result shows that a partial protonation of the nitrogen and carbonyl group might lead to multiple interactions between the gelator and the solvent.

The great stability of the gel was reflected in its gel-melting temperature T_m^g. Every gel has a temperature above which it disintegrates and loses all structure. A very simple test for the determination of T_m^g has been developed by Takahashi et al.[12] A small steel ball (100 mg) was placed on top of the gel in a test tube (Ø 10 mm), which was slowly heated in a thermostatted waterbath. At T_m^g the ball falls to the bottom of the test tube. The temperatures determined in this way usually range up to about 55°C. Our hydrazinoazapeptide **1** ($R^1 = p\text{-}MeC_6H_4$) was a good gelator of toluene, xylene and styrene with a gel-melting temperature T_m^g up to 70°C (Table 1). For the gel from **1** ($R^1 = p\text{-}MeC_6H_4$) in xylene a regular increase of the gel-melting temperatures was observed with increasing concentrations (Fig. 2).

The FTIR spectrum of a toluene gel formed by **1** ($R^1 = p\text{-}ClC_6H_4$) is characterized by bands at 3230 (br), 1735, 1676 and 1654 cm^{-1} assigned to N-H and C=O intermolecular hydrogen bonding stretching vibrations, whereas the corresponding homogeneous solution of CCl_4 containing the hydrazinoazapeptide **1** ($R^1 = p\text{-}ClC_6H_4$) (recrystallized in methanol) at less than the minimum gel concentration affords bands at 3422, 3339, 3284, 1759, 1708, 1697 cm^{-1} indicative of non-hydrogen-bonding stretching vibrations. So the formation of the gels probably occurs through the build up of intermolecular hydrogen bonds between N-H and C=O of hydrazide bonds of hydrazinopeptide.

In Fig. 3 are shown transmission electron micrographs (TEM) of a toluene gel formed by **1** ($R^1 = p\text{-}MeC_6H_4$). A two-dimensional network is observed. Numerous juxtaposed fibers with widths of 40–60 nm form cavities. It can be assumed that the fibre-like aggregations

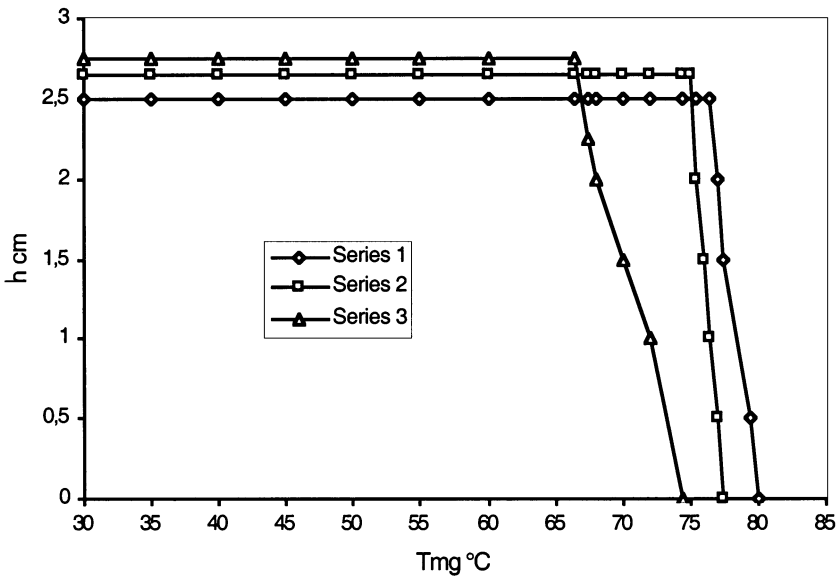

Figure 2. Gel melting temperatures determined by the dropping ball method at different concentrations for **1** ($R^1 = p\text{-}MeC_6H_4$) (Series 1: 30 mg/cm^3; Series 2: 25 mg/cm^3; Series 3: 15 mg/cm^3).

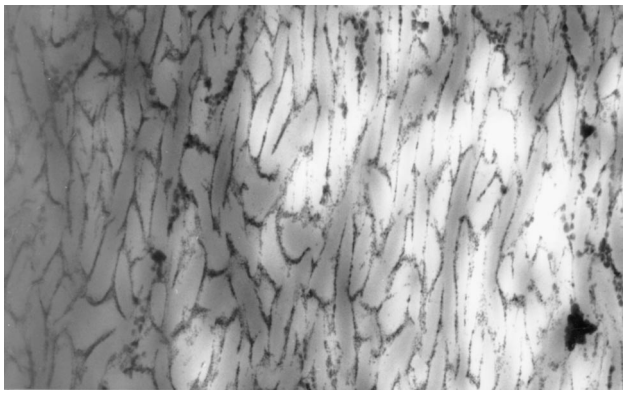

Figure 3. Transmission electron micrograph (TEM) of gel from **1** ($R^1 = p\text{-}MeC_6H_4$).

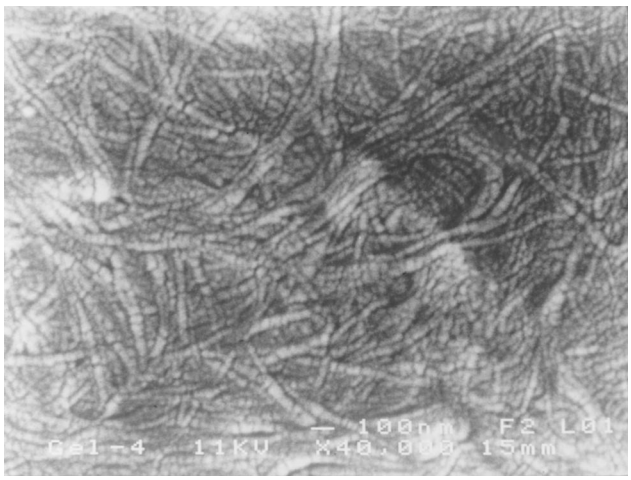

Figure 4. Scanning electron micrograph (SEM) of xerogel from **1** ($R^1 = p\text{-}MeC_6H_4$).

Figure 5. Scanning electron micrograph (SEM) of aerogel from **1** ($R^1 = p\text{-}MeC_6H_4$).

were formed from numerous molecules by intermolecular hydrogen bonding, then they were juxtaposed by van der Waals interactions as has been reported for the thermoreversible gelation of polymers,[1] and finally immobilized the organic liquid in cavities of 250 nm width.

To obtain visual insights into the aggregation mode, we prepared a dry sample for scanning electron microscope (SEM) studies. Fig. 4 shows a typical picture obtained from the xerogel of **1** ($R^1 = p\text{-}MeC_6H_4$). The fibers (30 nm) are stacked and seem to be cracked. To observe a three-dimensional structure of the gel we dry it by the critical point method,[13] and the observation of the aerogel by SEM is shown in Fig. 5. Numerous juxtaposed and intertwined fibers are formed by entanglement of long slender aggregates with widths of 20–50 nm.

In conclusion, the present study has demonstrated that a new class of low-molecular-weight gelators, the hydrazinoazadipeptides, has been developed. These pseudopeptides form thermoreversible physical gels with aromatic solvents in the presence of a small amount of HCl at very low concentration. The gels consist of a network of entangled fibers, presumably stabilized by multiple intermolecular hydrogen bonds between the hydrazinoazapeptide moieties. The overall result is exceptionally long-term thermal stability of these supramolecular structures.

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