

Modular Hydrogelators

Responsive Cyclohexane-Based Low-Molecular-Weight Hydrogelators with Modular Architecture

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Hydrogels have been extensively studied because of their intriguing properties and applications (e.g. foods, cosmetics, biomedical uses), however, most of the systems reported to date are based on polymers.^[1] Hydrogels of low-molecular-weight gelators (LMWGs)^[2–4] are an attractive complement or even alternative for such polymeric systems^[5] as they possess properties unattainable by polymeric gelators, the most important of these being a very rapid response to external stimuli, an inherent thermoreversibility owing to the noncovalent nature of the aggregation process, and the low molecular weight of the gelator, which facilitates a fast clearance from the body after triggering the gel-to-sol transition. As we envisage the use of LMWG systems in pharmaceutical applications, we require responsive and biocompatible systems of which the gel properties can be easily tuned. Low-molecular-weight hydrogelators reported to date,^[3,4] however, have a very limited potential as far as the introduction of functional groups and the regulation of the gel properties are concerned. Furthermore, the use of pH-sensitive groups to bring about the gel-to-sol transition or to effect the surface potential of gel fibers has hitherto been only marginally addressed.^[4] The challenge is to develop novel, biocompatible hydrogelators in which functionalization and tuning of the properties can be easily achieved. Herein we report the rational design and synthesis of a novel family of highly effective hydrogelators with a modular architecture based on a 1,3,5-triamide *cis,cis*-cyclohexane core which functions as a generic gelating scaffold.^[6] To this scaffold various amino acid based substituents were connected, providing additional driving forces for gelation (i.e. hydrogen bonding and hydrophobic interactions), thus allowing us to

influence the stability of the resultant thermoreversible hydrogels. Additionally, the introduction of certain moieties allows us to make these gels highly responsive to pH changes. Remarkably, the degree of pH sensitivity was shown to depend not only on the pK_a of the compound, but also on the strength of the intermolecular interactions. Preliminary in vitro as well as in vivo experiments indicate that these amino acid containing compounds are indeed biocompatible.

To be able to easily synthesize various hydrogelators with properties that can be tuned at the molecular level, we designed a structure possessing a modular architecture (Figure 1). A 1,3,5-triamide *cis,cis*-cyclohexane core was

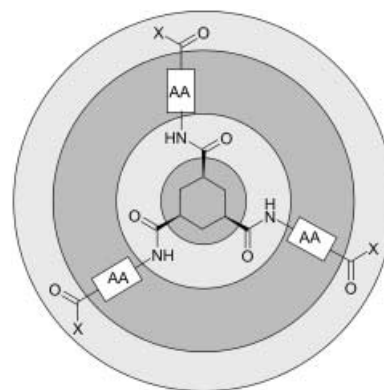


Figure 1. Schematic representation of the hydrogelator design. Light gray regions = hydrophilic; dark gray regions = hydrophobic; AA = amino acid(s); X = hydrophilic substituent.

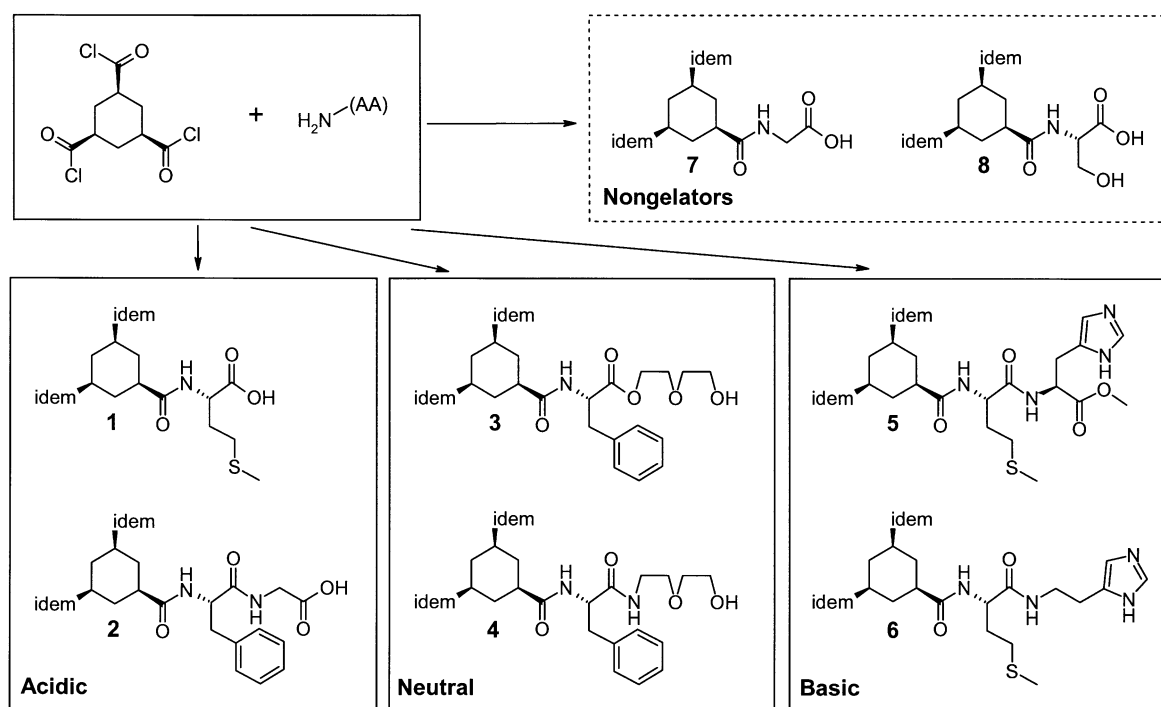
used as a generic gelating scaffold, because the parallel orientation of the three hydrogen-bonding amide moieties provides strong, self-complementary, and uniaxial intermolecular interactions that are necessary to enforce 1D self-assembly and hence allow gelation to occur.^[7] We connected biocompatible building blocks to the cyclohexane core, namely L-amino acid moieties (AA). We selected hydrophobic amino acids for two reasons: first, to introduce hydrophobic interactions as an additional aggregation force, and second to shield the amides from water and thus facilitate the formation of 1D intermolecularly hydrogen-bonded stacks in a solvent that is strongly competitive for hydrogen bonding. A similar combination of hydrophobic interactions and hydrogen bonding is known to stabilize the secondary structures of peptides.^[8] The inherent C_3 symmetry of the resultant molecules allows tuning of the interfacial properties of the gelators (by introducing different functional groups X) without affecting the rudimentary aggregate structure and hence the gelation capability.

Scheme 1 shows examples of new LMWGs (**1–6**) that were prepared according to these design guidelines.^[9] All compounds were synthesized in 2–4 steps starting from commercially available compounds by treating enantiomerically pure amino acids with *cis,cis*-1,3,5-cyclohexanetricarbonyl trichloride^[7] (Scheme 1), followed in some cases by deprotection of the carboxylic acid, or further functionalization. Note that both convergent and divergent synthetic routes could be used, for example, gelator **5** was synthesized

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Supporting information for this article (synthetic and analytical data for compounds **1–8**) is available on the WWW under <http://www.angewandte.org> or from the author.



Scheme 1. Synthesis of the hydrogelators **1–6** and nongelators **7** and **8**; for synthetic details see the Supporting Information. idem: all the compounds **1–8** each have three identical side chains, for simplicity only one is shown for each compound.

in good yields both by reaction of H-Met-His-OMe with the cyclohexane triacid chloride, as well as by reaction of H-His-OMe with compound **1**.

Compounds **1–6** are excellent thermoreversible hydrogelators, and many of them gelate water even at submillimolar concentrations (Table 1). The concentration at which com-

Table 1: Critical gelation concentration CGC,^[a] appearance of the hydrogels, and fiber thickness (TEM).

Gelator	CGC [mM]	wt %	Appearance	Fiber diameter [nm]
1	0.98 ^[b]	0.06	clear	20–300
2	0.97 ^[b]	0.08	clear	20–120
3	0.36	0.033 ^[c]	clear	20–120
4	0.76	0.07 ^[c]	clear	50–350
5	11.75	1.25	turbid	10–500
6	4.72	0.42	turbid	10–500

[a] CGC is the lowest gelator concentration at which gelation is still observed. [b] Determined in 1 N HCl.^[12] [c] Gelation at this concentration took several hours.

pound **3** starts to gelate water (0.36 mM) is, to our knowledge, the lowest concentration reported to date for any hydrogelator.^[3k] In contrast, compounds **7** and **8**, both lacking hydrophobic substituents, are highly water-soluble and thus not able to gelate water. This result clearly shows that hydrophobic interactions, such as those provided by the phenylalanine or methionine residues, are essential for these structures to function as hydrogelators. In addition, intermolecular hydrogen bonding between the amide moieties also contributes to the stability of the gel fibers, as is evident from

the FT-IR spectra of the freeze-dried gels (xerogels) and solid samples of the six gelators.^[10] The NH signals were observed in the range of $\tilde{\nu} = 3320\text{--}3270\text{ cm}^{-1}$, whereas the signals originating from the CO moieties all fell between $\tilde{\nu} = 1680\text{--}1630\text{ cm}^{-1}$, both ranges being characteristic for hydrogen-bonded secondary amides.^[11]

All gels displayed good stability over time, as no changes were observed in over three months.^[13] Investigation of the hydrogels of **1–6** with transmission electron microscopy (TEM, Figure 2) showed that all six compounds form branched or entangled fibrous gel networks with fiber thicknesses of 10–500 nm (Table 1), and fiber lengths of tens of micrometers. The high aspect ratios of the gel fibers clearly indicate that the intermolecular interactions between the gelator molecules are highly anisotropic. Furthermore, the low CGC values imply that the intermolecular interactions are strong and thus most likely the result of the concurrent action of both hydrogen-bonding and hydrophobic interactions.

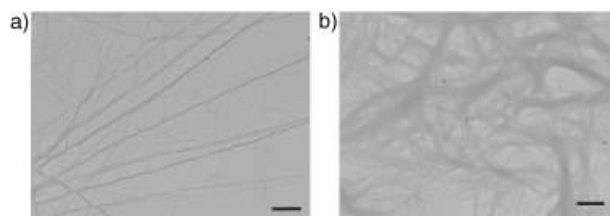


Figure 2. Representative TEM images of hydrogels of LMWGs **1–6**: a) a 0.1 wt% hydrogel of **3** (similar to gels of **1**, **2**, and **4**); b) a 0.8 wt% gel of **6** (similar to a gel of **5**). Scale bars correspond to 500 nm.

Owing to the gelating nature of compounds **1–6**, no crystals suitable for X-ray crystallography could be obtained. Fortunately, it was possible to grow good quality crystals of the tyrosine analogue **9** (Figure 3a) from water. The X-ray crystal structure shows that the molecules stack through the formation of a triple chain of intermolecular hydrogen bonds, with hydrogen-bond lengths ranging from 1.91 to 2.20 Å (Figure 3c). In addition, the molecules all adopt a conformation in which the phenyl moieties fold inward, shielding the amide moieties from the aqueous environment and thus allowing hydrogen-bond formation to occur. The close resemblance of **9** to the tris(amino acid) cyclohexane core of the gelators makes it very likely that the gelators **1–6** adopt a similar arrangement within the gel fibers. The X-ray crystal structure of **9** also shows that the unit cell contains two stacked molecules which are rotated by approximately 6° with respect to each other.^[14] The individual stacks of molecules pack in a hexagonal fashion, giving rise to hydrophobic areas in which the phenyl rings come together (solid circle in Figure 3b), and hydrophilic areas in which the carboxylic acid residues as well as the water and HCl molecules enclosed in the crystal can be found (dashed circle).^[15]

An important feature of low-molecular-weight hydrogelators is the thermoreversible gel–sol phase transition, which can conveniently be characterized by determining the temperature at which the gels turn into solutions (T_{gs}). Figure 4 clearly shows that increasing the concentration of a gelator leads to higher T_{gs} values, a feature generally observed for LMWGs. An interesting aspect of our gelators, however, is the possibility to tune the gel properties at the molecular level. Changing the nature of hydrophobic interactions directly influences the T_{gs} values. Thus a comparison of the Met-based gelators (Figure 4a) and Phe-based gelators (Figure 4b) shows that the latter give higher T_{gs} values at much lower concentrations, with gels of **2** and **4** exceeding the upper experimental limit of 130°C at concentrations just above 2 mM. The occurrence of these high T_{gs} values already at such low gelator concentrations shows the exceptional thermal stability of our gels. Also changing the number of hydrogen-bonding interactions affects the thermal stability of

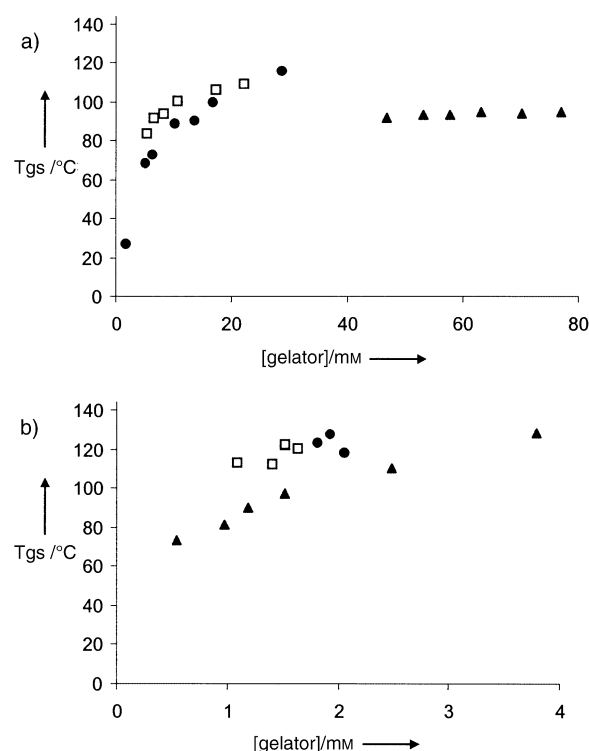


Figure 4. T_{gs} values for hydrogels of different concentrations of: a) Met-based LMWGs **1** (●), **5** (▲), and **6** (□); b) Phe-based LMWGs **2** (●), **3** (▲), and **4** (□). Measurements were stopped at 130°C.^[16]

the gels, as becomes clear by comparing compounds **3** and **4**. The T_{gs} values for gels of **4** are all at least 20°C higher than those for gels of **3** at the same concentration, as in **4** ester groups have replaced the hydrogen-bonding amide moieties that connect the ethylene glycol chains to the phenylalanine residues in **3**. As IR experiments showed that all amides of **4** were fully hydrogen bonded, it is likely that the second set of amides present in **4** forms three additional chains of hydrogen bonds in the molecular stacks present in the gels, resulting in the observed increase in the thermal stability of the gels.

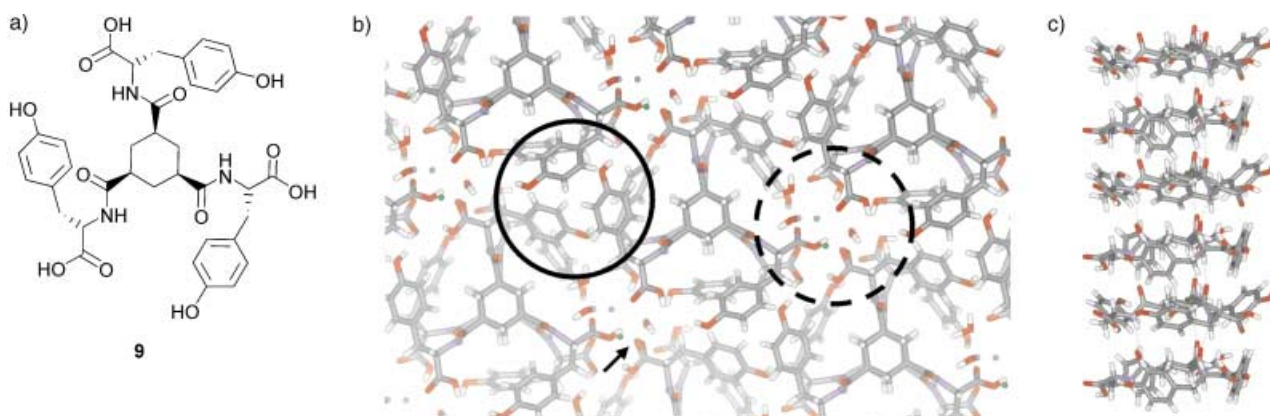


Figure 3. X-ray crystal structure of **9** (crystallized from K_2HPO_4/KH_2PO_4 buffer 0.1 M, pH 5.7); gray C, blue N, red O, white H, green Cl ($HCl_{(aq)}$ was used in the final reaction step (i.e. hydrolysis of the trimethylester of **9**)). a) Tyrosine-based nongelator **9**, b) view along the *a* axis, showing the packing of the individual stacks (arrow: disordered carbonyl, solid circle: hydrophobic area, dashed circle: hydrophilic area), c) side view of a single stack, showing the intermolecular triple hydrogen bonding chain.

The introduction of pH-sensitive groups onto the cyclohexane-based gelating scaffold is another example of how we can tune the gel properties at the molecular level, allowing reversible switching from gel to sol through changes in the pH value. Indeed the addition of base (e.g. 1N NaOH) to a hydrogel of **1** or **2** resulted in the rapid and complete dissolution of the gel, whereas the subsequent addition of acid (e.g. 1N HCl) resulted in instantaneous reformation of the gel. Conversely, hydrogels of **5** or **6** could be turned into solutions and back into gels by the addition of first acid, and then base. Reversible gelation behavior as observed for LMWGs **1**, **2**, **5**, and **6** is far from self-evident,^[4] as several examples exist of inherently pH-sensitive hydrogelators which do not display pH reversible gelation.^[3h,j] Figure 5 shows the pH_{gs} (the pH

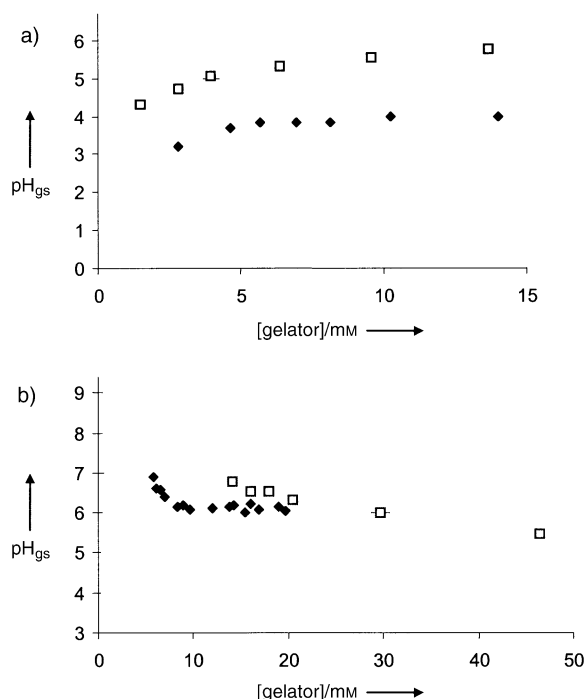


Figure 5. pH_{gs} values for hydrogels of different concentrations of: a) acidic gelators **1** (◆) and **2** (□); b) basic gelators **5** (□) and **6** (◆).

value at which gel-to-sol transition occurs) values that were observed for different gelator concentrations for LMWGs **1** and **2**. Met-containing gelator **1** has pH_{gs} values (3.2 to 4.0) that are significantly lower than those observed for Phe-Gly-containing gelator **2** (3.2–4.0 vs. 4.3–5.8, in the concentration range measured). These differences are remarkable because the carboxylic acid moieties of both gelators are expected to have almost identical pK_a values (3.6–3.7).^[17] Assuming a pK_a value of 3.65 for **1**, the concentrations of the different gelator species g (i.e. gH_3 , $[gH_2]^+$, $[gH]^2+$, and g^{3+}) present at different pH values can be calculated.^[18]

We took each point for gelator **1** in Figure 5a and calculated the corresponding concentration of fully protonated gelator (gH_3). All the points (except for the one at the lowest concentration) corresponded to a gH_3 concentration of 0.9 ± 0.1 mM, a value that corresponds very well to the CGC of 0.98 (see Table 1). Apparently, the onset of gelation of **1**

corresponds with the gH_3 concentration reaching the value of the CGC. Therefore it is concluded that for **1** only neutral species participate significantly in gelation, and a single deprotonation step is enough to cause **1** to dissolve as $[gH_2]^+$. Similar calculations for **2**, using the same assumed pK_a value of 3.65, show that dissolution of the gels takes place at pH values at which the fully deprotonated g^{3-} ion is the dominant species present in solution. Apparently, a significant fraction of the carboxylate moieties in the fibers of **2** is deprotonated and hence the fibers become negatively charged, before dissolution takes place at pH_{gs} . This introduction of negative charges at the fiber surface leads to an increase of the proton concentration in the adjacent layer of counterions and thus to a decrease of the pH value near the surface (pH_s), with respect to the observed (bulk) pH.^[19] Because it is reasonable to assume that in a first approximation the pK_a of **2** in the fibers is similar to that of **1**, with substantial deprotonation taking place at a pH_s value of around 3.65, this means that the gel-to-sol phase transition (pH_{gs}) is shifted to higher (bulk) pH values. Why should this effect occur for gelator **2** and not for **1**? The formation of interfacial charges as a result of the deprotonation of carboxylate moieties introduces strong repulsive electrostatic interactions within the aggregates, which have to be compensated by attractive interactions for the aggregates to survive (Figure 6). Apparently, in **1** these

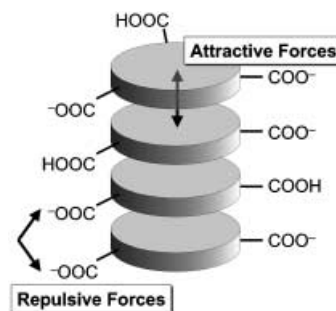


Figure 6. Schematic representation of a stack of gelator molecules.

attractive interactions are weaker than for **2**. This finding agrees very well with higher thermal stabilities observed for gels of **2** with respect to gels of **1**, and can be attributed to the presence of additional amide groups and larger hydrophobic amino acid residues in **2**. Therefore, to tune the pH-sensitivity profile of a gelator it is not necessary to change the ionizable moieties to groups with a different pK_a value, it is possible to adapt the remainder of the structure, leading to different intermolecular interactions, and thereby influencing the pH_{gs} of the gelator. For the basic hydrogelators **5** and **6** we found that, similar to gelator **1**, only the neutral species participate significantly in gelation.^[20]

In conclusion, by adopting a modular design for our hydrogelators we have been able to develop a novel class of cyclohexane-amino acid conjugates that act as excellent gelators for water, and are capable of forming thermoreversible hydrogels at concentrations as low as 0.36 mM. Many of these hydrogels displayed exceptional thermal stability even at very low (< 2 mM) gelator concentrations. The properties of the gels could be easily tuned by changing the nature of the

hydrophobic substituents or the number of hydrogen-bonding moieties. Furthermore, by connecting pH-sensitive moieties to the gelator scaffold, responsive gels were obtained that could be reversibly switched from gel to sol by changes in pH value as well as temperature.^[22] The pH-dependent gelation behavior of our LMWGs can not only be tuned by selecting substituents with different pK_a values, but also by changing the strength of the intermolecular interactions in the gel fibers. Preliminary in vitro experiments in which cells were grown in gelled cell culture medium indicate that these kinds of molecules are noncytotoxic. Initial in vivo tests showed that rats in which gels were implanted subcutaneously, displayed excellent health even after repeated administration.^[21]

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