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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 7285–7301

C_3-Symmetric, amino acid based organogelators and thickeners: a systematic study of structure–property relations

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Received 16 October 2006; revised 25 January 2007; accepted 9 February 2007
Available online 20 February 2007

Abstract—A class of C_3-symmetric amino acid based organogelators and thickeners featuring a rigid core have been developed. Structural variation yielded a number of compounds, the aggregation behaviour and resulting aggregates and gels of which were studied by FTIR spectroscopy, dropping ball measurements, differential scanning calorimetry and transmission electron microscopy. These studies showed that the nature of the core unit, the type of hydrogen-bonding units and the applied amino acids have a strong influence on the interactions, resulting in large differences in aggregation properties, thermal stability and morphology between the various compounds. The results provide a basis for a better understanding of the relation between aggregate/gel properties and molecular structure. The structural variation available for these compounds allows fine-tuning of the gelators with respect to aggregation behaviour and gel properties.

1. Introduction

Low molecular weight gelator compounds (LMWGs) which gel solvents have attracted considerable attention, owing to their striking self-assembling properties, their responsive behaviour and their applicability in, e.g., cosmetics, food or pharmaceutics.[1] The quest for new LMWGs inspired several research groups, including those of Shinkai,[2] Terech,[1a] Weiss,[1c] Hanabusa,[3] Menger[4] and our group,[1b,5] to perform systematic structural studies aimed at the development of criteria for the design of LMWGs. As a result, the field of LMWGs has progressed from a stage in which new LMWGs were discovered by chance, to a point at which the rational design of LMWGs has become feasible.[1] However, whereas the development of new LMWGs has come within reach, the tuning of properties like gel stability (mechanical or thermal), the scope of gelated solvents and morphology of the gels are still less readily achieved. Obviously, these properties depend on the structures of the LMWGs, although the precise relations between various structural parameters and the gel properties under investigation are still not well understood. In an effort to gain a better understanding of these relations, we developed a class of C_3-symmetric amino acid based LMW gelators that allowed a systematic and broad structural variation.[6] LMW hydrogelators belonging to this class of compounds have already been reported.[6] Herein we report the design and synthesis of C_3-symmetric organogelators, their aggregation behaviour and the properties of the aggregates formed, with emphasis on the effect of the interaction strength (determined by the various structural parameters) on the gelation ability.

2. Results and discussion

2.1. Design

A schematic representation of the structure of the C_3-symmetric compounds is shown in Figure 1a. The C_3-symmetric compounds are built up in sections from the centre towards the periphery. The first central section is formed by a C_3-symmetric rigid core. The C_3-symmetry of this core reduces the occurrence of polymorphism and allows a better control over the intermolecular and fiber/solvent interactions. The rigid geometry of the core restricts the conformational freedom of the molecules[1b,5c] and provides an ideal platform to study the influence of the intermolecular interactions on the gelation ability.

The second section consists of hydrogen-bonding units, in general ureas or amides. The application of different types of these units enables variation in the interaction strength. The units have to be connected to the core in an orientation

Keywords: Amino acids; Gel properties; Gels; Self-assembly; Organogelators.
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0040–4020/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tet.2007.02.066

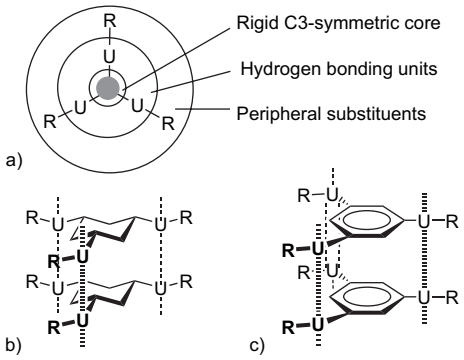


Figure 1. (a) Schematic design of the C_3-symmetric compounds. (b) Representation of the hydrogen-bonded stack formed by cyclohexane-based compounds. (c) Representation of the hydrogen-bonded stack of benzene based compounds.

that enables simultaneous, self-complementary, intermolecular hydrogen bonding of the three units, allowing one-dimensional aggregation and hence gelation to occur. An excellent core and hydrogen-bonding-unit candidate that fulfils these criteria is the *cis*,*cis*-1,3,5-cyclohexanetricarboxamide scaffold.[7,8] In this structure (Fig. 1b), the amide groups are orientated perpendicularly to the mean plane of the molecule and exhibit a parallel alignment with respect to each other.[6–8] This provides the strong uni-axial intermolecular interactions affording one-dimensional columnar self-assembly. A comparable scaffold is the 1,3,5-benzenetricarboxyamide core, which has also been reported to have a hydrogen-bonded columnar type of packing (Fig. 1c).[9–12] The capacity of both scaffolds to form one-dimensional stacks was previously exploited in the preparation of simple alkyl derived LMW gelators or thickeners.[8,10–12] These studies already indicate that some dependence of the gelation ability of the C_3-symmetric 1,3,5-cyclohexane and 1,3,5-benzene based compounds on the strength of the intermolecular interactions (determined by the core, the hydrogen-bonding units and the peripheral substituents) is present. This makes these types of compounds attractive candidates to study the influence of various structural parameters on the gelation ability and as such to acquire a better understanding of their effect and of the balance between the various components in the LMWGs.

To realise this goal, a more extensive and thorough structural variation is required. Therefore, in our design the final peripheral section (Fig. 1a) is based on α-amino acid building blocks. These offer easy access to both urea and amide hydrogen-bonding units via their N-terminus and afford a large structural variety, providing the possibility to tune both the intermolecular and the fibre/solvent interactions. Additionally, derivatisation of the peripheral C-terminus offers further opportunities to influence the fibre/solvent interactions and can determine the solvent compatibility.[1b,f] To achieve the gelation of organic solvents, long alkyl chains are commonly introduced.[1]

2.2. Synthesis

LMW compounds were prepared based both on a benzene core and a cyclohexane core (Fig. 2). For both classes of compounds, two types are envisioned, which differ in the

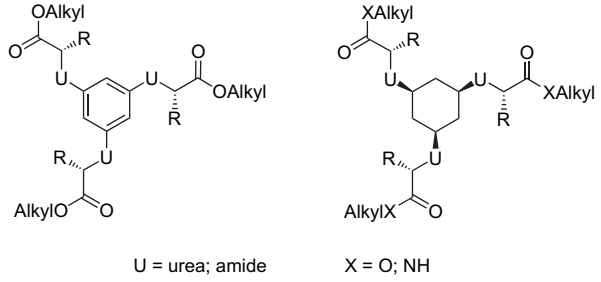
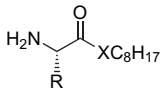


Figure 2. General structures of the different classes of compounds.

number of hydrogen bond donors available for self-assembly: tris-urea and tris-amide derivatives with α-amino acid ester chains. For the cyclohexane core compounds a third type differing in the number of hydrogen bond donors and acceptors was envisioned: tris-amide derivatives with α-amino acid amide chains. All types of compounds have been prepared in a convergent manner by coupling an amino acid derivative at its N-terminus to the core molecule prepared beforehand.

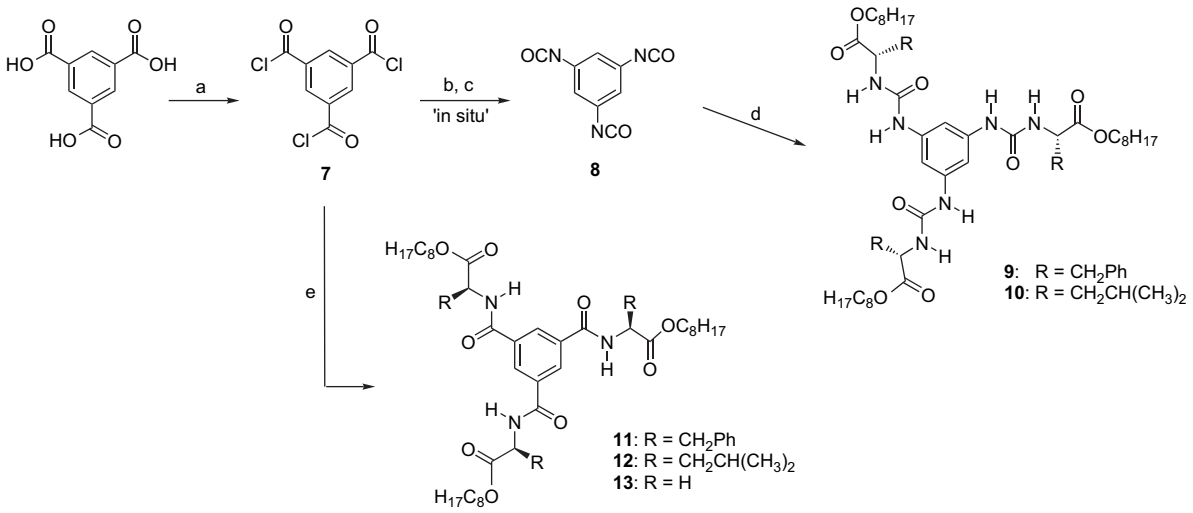
The effect of the peripheral substituents was investigated with the α-amino acid esters and amides presented in Figure 3. Of these compounds, the esters **1**–**3** were prepared under Dean–Stark conditions by reaction of the α-amino acid with 1 equiv of 1-octanol in the presence of 1.1 equiv of *p*-toluenesulfonic acid monohydrate,[13] whereas the amides **4**–**6** were prepared according to standard peptide synthetic methods. All α-amino acid derivatives were obtained in high yields and used without further purification.

The 1,3,5-benzene tris-urea derivatives were prepared following standard procedures by reaction of an amino acid ester with 1,3,5-benzenetriisocyanate **8** (Scheme 1).[14] Compound **8** was prepared from commercially available 1,3,5-benzenetricarboxylic acid via 1,3,5-benzenetricarbonyl trichloride **7**. Compound **7** was obtained as a slightly yellowish oil, which crystallised upon standing at 4 °C and was stable for months. This allowed synthesis of **7** on a large scale made it possible for us to keep it in stock. Reaction of acid chloride **7** with sodium azide afforded 1,3,5-benzenetricarbonyl triazide as a white precipitate. The triazide was not isolated because it easily *detonates*,[15] but was immediately taken up in toluene and separated from the reaction mixture. The toluene solution was gradually heated to 100 °C and stirred till gas evolution ceased, yielding 1,3,5-benzenetriisocyanate **8** in situ via a Curtius rearrangement.[16] Subsequently, **8** was allowed to react with the α-amino acid derivatives **1** and **2** to afford the 1,3,5-benzene tris-urea compounds **9** and **10**. Owing to their good solubility in organic solvents, purification of these compounds could be achieved by column chromatography, yielding **9** and **10** in low yields as analytically pure, sticky solids.



1: X = O; R = CH_2Ph
2: X = O; R = $CH_2CH(CH_3)_2$
3: X = O; R = H
4: X = NH; R = CH_2Ph
5: X = NH; R = $CH_2CH(CH_3)_2$
6: X = NH; R = H

Figure 3. α-Amino acid esters and amides applied in the synthesis of the LMWGs.



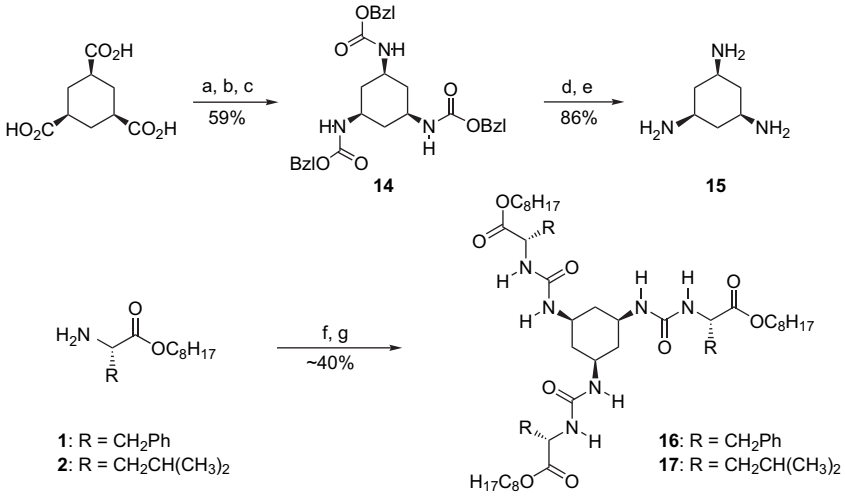
Scheme 1. Synthesis of the 1,3,5-benzene tris-urea and tris-amide derivatives. Reagents and conditions: (a) $SOCl_2$, DMF (cat.), Δ, 3 h, 100% conversion; (b) NaN_3, water/THF, 0 °C, 2 h; (c) toluene, Δ; (d) 3.3 equiv **1** or **2**, toluene, rt, 18 h, 20–40%; (e) 3 equiv **1**, **2** or **3**, Et_3N, CH_2Cl_2, 50–60%.

The 1,3,5-benzene tris-amide derivatives were synthesised following standard amide synthesis procedures from the acid chloride **7** and the α-amino acid derivatives **1**–**3** (Scheme 1). After purification by column chromatography compounds **11**–**13** were obtained as analytically pure, sticky solids. Compared to the tris-urea compounds **9** and **10**, the tris-amide compounds **11**–**13** have the advantage that their synthesis is much more facile and higher yields are obtained in the final coupling step.

Because of the low yields in which the benzene tris-urea derivatives were obtained, the *cis*,*cis*-1,3,5-cyclohexane tris-urea derivatives were synthesised using a different method for the preparation of isocyanates. This method involves the in situ conversion of the amino group of α-amino acid esters into an isocyanate without epimerisation by using $(BOC)_2O$ and DMAP,[17] followed by reaction with *cis*,*cis*-1,3,5-triaminocyclohexane.

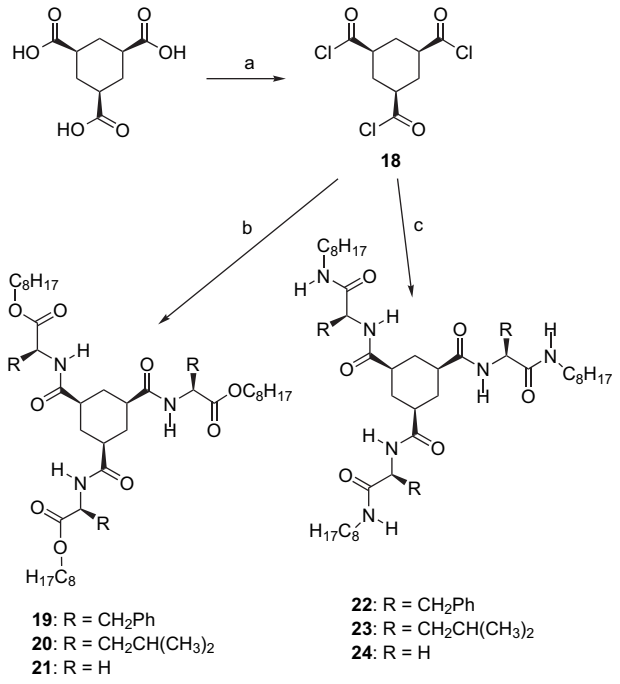
First, *cis*,*cis*-1,3,5-triaminocyclohexane was prepared following the procedure described in Scheme 2. Commercially available *cis*,*cis*-1,3,5-cyclohexane tricarboxylic acid was allowed to react with diphenyl phosphoryl azide (DPPA) to give the acyl azide. Subsequent heating of the mixture led to a in situ Curtius rearrangement and on quenching with benzyl alcohol the tris-benzyl carbamate **14** was obtained as a white powder. Treatment of compound **14** with a strong acid (33% HBr/HOAc) yielded the HBr-salt of *cis*,*cis*-1,3,5-triaminocyclohexane, from which amine **15** was liberated as a pale yellow solid, using alkaline conditions.

Subsequently, the α-amino acid esters **1** and **2** were converted in situ to the isocyanate[17] and allowed to react with 0.33 equiv of **15** (Scheme 2). After evaporation of the solvent, the remaining materials were heated to reflux in ethanol and after cooling the obtained solid or gel was filtered off to yield *cis*,*cis*-1,3,5-cyclohexane tris-urea derivatives **16** and **17**, respectively, as analytically pure white powders. Unfortunately, the yield of the coupling reaction did not improve when compared to the synthesis of the benzene tris-urea compounds, although the purification of the products is much easier.



Scheme 2. Synthesis of the *cis*,*cis*-1,3,5-cyclohexane tris-urea derivatives. Reagents and conditions: (a) DPPA, Et_3N, benzene, rt, 30 min; (b) Δ, 30 min; (c) benzyl alcohol, Δ, 18 h; (d) HBr/HOAc; (e) aq NaOH; (f) $(BOC)_2O$, DMAP, CH_2Cl_2, rt, 30 min; (g) 0.33 equiv **15**, CH_2Cl_2, 40 °C, 48 h.

The *cis*,*cis*-1,3,5-cyclohexane tris-amides derived by reaction with α-amino acid esters or amides were prepared following standard procedures from the α-amino acid derivatives **1–6** and *cis*,*cis*-1,3,5-cyclohexane tricarboxylic acid (Scheme 3). First commercially available *cis*,*cis*-1,3,5-cyclohexane tricarboxylic acid was allowed to react with thionyl chloride to yield the corresponding trichloride **18** as a slightly yellowish oil, which crystallised at 4 °C. In contrast to the synthesis of 1,3,5-benzenetricarbonyl trichloride **7** a catalytic amount of DMF was not added. Analogously to compound **7**, cyclohexanetricarbonyl trichloride **18** could be stored for months at 4 °C.



Scheme 3. Synthesis of the *cis*,*cis*-1,3,5-cyclohexane tris-amide α-amino acid ester and tris-amide α-amino acid amide derivatives. Reagents and conditions: (a) $SOCl_2$, Δ, 20 h, 100% conversion; (b) 3 equiv **1**, **2** or **3**, Et_3N, CH_2Cl_2, 25–88%; (c) 3 equiv **4**, **5** or **6**, Et_3N, CH_2Cl_2, 60–90%.

Reaction of **18** with the amino acid esters **1–3** afforded the *cis*,*cis*-1,3,5-cyclohexane tris-amides **19–21**. These compounds were readily soluble in the reaction medium, thus the $Et_3N{\cdot}HCl$ salts formed upon reaction could be removed by extraction of the reaction mixture. Compounds **19** and **20** were purified by column chromatography and obtained as colourless sticky solids in moderate yields. Compound **21** did not require further purification and was obtained as a white powder in high yield. The compounds were found to be pure within the limits of ^1H NMR and ^{13}C NMR detection and further characterised by elemental analyses. The synthesis of these compounds is simple and straightforward and the desired products are obtained in only three steps starting from the commercially available compounds.

The *cis*,*cis*-1,3,5-cyclohexane tris-amide α-amino acid amide compounds **22–24** were obtained by reaction of the α-amino acid amides **4–6** with compound **18**. In contrast to the synthesis of compounds **19–21**, the products were not readily soluble in the reaction medium and a viscous mixture was formed. Therefore, the solvents were evaporated from the reaction mixture and the remaining materials were stirred in (hot) ethanol to remove the soluble impurities. After purification in this fashion, the desired products were obtained in high yields as analytically pure, white powders.

2.3. Aggregation properties of the benzene core compounds

The aggregation ability of the benzene core compounds **9–13** was investigated in the usual way by first heating a weighed amount of the solid in 0.5 or 1.0 mL solvent followed by cooling to room temperature. The results for several solvents are shown in Table 1; the solvents are ranked in order of increasing polarity according to their $E_T(30)$-values.

In contrast to many bis- and tris-urea or -amide compounds[3a,b,5] it was found that in most solvents, compounds **9–13** are readily soluble, even without heating. Just occasionally a viscous solution is formed, indicative of the formation of higher aggregates. Generally, however, these viscous solutions are formed at higher concentrations and for none of the solid-solvent combinations is the formation of a gel observed. The hydrogen-bonding unit appears to have only a minor influence on the aggregation ability of these compounds. The tris-urea derivatives **9** and **10** exhibit more or less the same aggregation capacities as the tris-amide derivatives **11–13**. Almost the same applies for the influence of the R-group. Only a slight difference is observed between the benzyl (**9** and **11**), the *iso*-butyl (**10** and **12**) and the hydrogen (**13**) compounds, namely somewhat poorer aggregation behaviour for the *iso*-butyl compounds. This can be rationalised by the fact that the benzyl groups are able to form additional intermolecular π–π stacking interactions to favour aggregation. Furthermore, the *iso*-butyl group is sterically more demanding than the benzyl group,[18] which might hinder self-assembly.

Apparently, the C_3-symmetric benzene based compounds exhibit very poor aggregation properties, especially compared to bis- and tris-urea compounds developed in our group.[5] Also compared to trialkyl-1,3,5-benzene tris-urea[12] and -tris-amide[10] derivatives the aggregation properties have diminished. Although comparison with the trialkyl-tris-urea derivatives is difficult due to the limited data available, these compounds were at least able to gelate a solvent.[12] The trialkyl-tris-amide derivatives in turn were able to thicken a

Table 1. Aggregation properties of the benzene core compounds **9–13**[a]

Solvent	Tris-urea		Tris-amide		
	9	**10**	**11**	**12**	**13**
n-Hexane	vs (20)	s	vs (10)	s	c
n-Hexadecane	gp	vs (20)	p	s	p
Cyclohexane	vs (30)	vs (160)	vs (10)	s	s
p-Xylene	s	s	s	s	s
Tetraline	s	s	s	s	s
n-Butyl acetate	s	s	s	s	s
Cyclohexanone	s	s	s	s	s
Olive oil	vs (20)	—	vs (5)	s	s
1,2-Dichloroethane	s	s	s	s	s
1-Octanol	s	s	s	s	s

[a] Abbreviations: vs: viscous solution (digits: minimal concentration at which thickening of the solvent was observed by eye (mg mL^{-1})); gp: gel-like precipitate; s: soluble at room temperature (solubility >20 mg mL^{-1}); p: precipitate; c: crystals.

broad range of solvents.[10] The diminished aggregation behaviour of compounds **9**–**12** is presumably due to the sterically demanding R-groups. The behaviour of the unsubstituted compound **13** (R=H) compared to tridodecyl-1,3,5-benzene tris-amide[10] suggests that the introduced ester groups also have a contribution.

2.4. Aggregation properties of the cyclohexane core compounds

In contrast to the benzene core compounds, the cyclohexane core compounds were sparingly soluble in most of the common organic solvents. Their aggregation properties were investigated in the same way as described above for the benzene core compounds and the results are shown in Table 2. At first glance it can be concluded that, in agreement with results obtained for trialkyl-tricarboxamide derivatives,[8,10,11] replacement of the benzene core by the cyclohexane core resulted in a dramatic increase in the gelation and aggregation abilities of the compounds. All cyclohexane core compounds form a gel with one or more solvents, with minimum gelation concentrations as low as 1 mg mL^{-1}. Remarkably, protic solvents like ethanol were also gelated by several of the compounds. The increased gelation ability compared to the benzene core compounds is presumably related to a more favourable orientation of the hydrogen-bonding units with respect to the mean plane of the core. For the cyclohexane core, published crystal structures show that the amide (or urea groups) is orientated perpendicularly to the core, enabling one-dimensional hydrogen bond formation (Fig. 4A).[6c,7] For the benzene core, however, conjugation causes the hydrogen-bonding units to have a larger

Table 2. Gelation and aggregation properties of the cyclohexane core compounds[a]

Solvent	Tris-urea		Tris-amide			Tris-amide-amide		
	16	**17**	**19**	**20**	**21**	**22**	**23**	**24**
n-Hexane	p	5	2	vvs (5)	i	i	i	i
n-Hexadecane	p	p	10	10	vs (5)	p	i	i
Cyclohexane	p	10	vvs (10)	vvs (5)	pg	i	2	i
p-Xylene	10	vs (5)	vvs (10)	vvs (5)	20	5	5	pg
Tetraline	20	p	10	s	10	10	5	5
n-Butyl acetate	10	5	20	vs (20)	1	p	i	gp
Cyclohexanone	vvs	vs (20)	20	s	5	5	5	2
Olive oil	p	i	vvs (10)	pg	5	p	pg	P
1,2-Dichloroethane	20	gp	20	p	p	gp	p	20
1-Octanol	5	5	2	p	1	p	10	2
Ethanol	i	20	5	s	5	i	i	2

[a] Abbreviations: see Table 1; digits: minimal gelation concentration in mg mL^{-1}; vvs: viscous solution exhibiting almost no flow; pg: partially gelated.

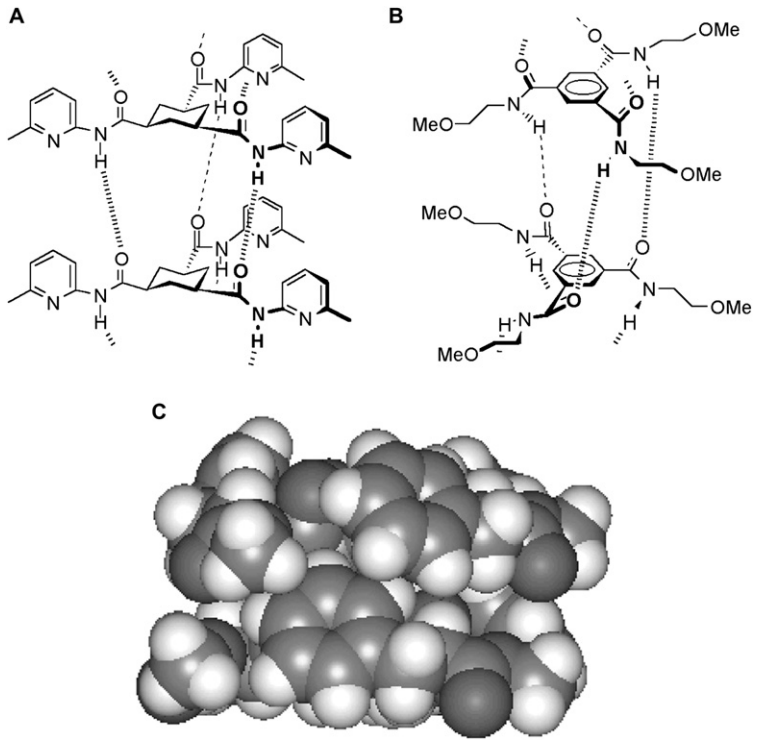


Figure 4. (A) Representation of the translational hydrogen-bonded stack formed by cyclohexane tricarboxamides (from crystal structure).[7] (B) Representation of the triple-helical hydrogen-bonded stack formed by a benzene tricarboxamide derivative (from crystal structure).[9] (C) Model of the stacks formed by the methyl ester derivative of **19**.

preference to be in the plane of the core[9,10] and the units have to be rotated out of this plane to enable hydrogen bond formation. Crystal structures of benzene tricarboxamides show that this is reflected in a partially tilted (Fig. 4B)[9] or parallel[10] conformation of the amides with respect to the benzene core.

The type and number of hydrogen-bonding units and the nature of the R-group have a significant but complicated influence on the gelation and aggregation ability of the compounds. First we will consider the influence of the hydrogen-bonding units by comparing **16** with **19**, **22** (R=CH_2Ph) and **17** with **20** and **23** (R=$CH_2CH(CH_3)_2$) and **21** with **24** (R=H).

For compounds **16**, **19** and **22** (R=CH_2Ph) tris-amide **19** exhibited the best gelation and thickening behaviour and formed clear gels or viscous solutions with all solvents investigated. The minimal gelation concentrations are not very low except for *n*-hexane and the alcohols. Substitution of the amide groups with urea moieties (yielding **16**) increases the number of hydrogen bond donors, and leads to a diminished solubility of the compound. This resulted in a decrease in the range of gelated solvents, especially for the more apolar solvents. Substitution of the ester groups with amides (**22**), thereby increasing the number of both hydrogen bond donor and acceptor groups, also resulted in a decrease of the scope of gelated solvents. Furthermore, this compound is insoluble or precipitates in many solvents. However, for the solvents that were gelated a decrease of the minimal gelation concentrations was observed compared to **19**. Apparently, upon addition of extra amide groups and thus introduction of additional intermolecular interactions, gelation becomes more efficient but at the same time the lower solubility diminishes the scope of solvents gelated.

For the L-leucyl derivatives **17**, **20** and **23** the tris-amide **20** displayed the poorest gelation ability and formed a gel only with *n*-hexadecane. However, a viscous solution was formed with several of the other solvents, indicating that aggregation was still taking place. Substitution of the amides by urea groups (**17**) increased the gelation ability and a gel was formed with several of the solvents tested. Conversion of the ester into an amide (**23**) also increased the gelation scope of the compound and lowered the minimal gelation concentrations. However, the compound was insoluble in half the solvents tested. These differences with the phenylalanyl compounds can most likely be attributed to the loss of π–π stacking and the steric hindrance caused by the *iso*-butyl group,[18] resulting in less efficient stacking of the molecules and subsequent lower gelation abilities for compound **20** compared to **19**. Introduction of additional hydrogen-bonding donors and/or acceptors compensates in these cases for the unfavourable steric effects, resulting in good gelation abilities for compounds **17** and **23**.

For the glycine derivatives (**21** and **24**) the tris-amide **21** showed the best gelation ability. With most solvents investigated a gel was obtained or a viscous solution. The minimal gelation concentrations for the more polar solvents were low. Substitution of the esters by amides (**24**) resulted in a slight decrease in gelation ability, especially for the apolar, aliphatic solvents in which the compound was not soluble.

It can be concluded that in general the tris-amide compounds **19–21** exhibit the best gelation and aggregation abilities. For the leucyl and phenylalanyl derivatives, introduction of additional hydrogen-bonding donors and/or acceptors by substituting the amides with urea moieties (**16** and **17**) or the esters with amides (**22–24**) results in a reduced gelation ability due to a lower solubility. The lowering in solubility is most likely caused by the stronger intermolecular interactions. Together with the reduced gelation ability, the minimal gelation concentrations decreased due to these stronger interactions. Only for the L-leucyl derivatives did the introduction of urea or additional amides result in a positive effect on the gelation ability.

The influence of the R-group on the gelation ability was assessed by comparing **16** with **17** (urea), **19** with **20** and **21** (amide) and **22** with **23** and **24** (amide–amide). From the position of the R-groups in the narrow interior of the stacks, as revealed by a preliminary model of the methyl ester derivative of **19** (Fig. 4C), it can be expected that the steric requirements of the R-groups have a significant influence on the packing and thus gelation ability. In this model, for instance, it seems that the benzyl groups force the stacked molecules to rotate with respect to each other, contrary to the translational aggregate in Figure 4A.

Both the tris-urea compounds **16** and **17** are able to form a gel or viscous solution with several of the solvents tested. Compound **17** (R=$CH_2CH(CH_3)_2$) seems to be slightly more efficient than **16** (R=CH_2Ph), judged from the fact that the minimal gelation concentrations are lower. Furthermore, for compound **17** precipitation is more often observed, especially for the apolar aliphatic solvents. Apparently, for a gelator containing several strong hydrogen bond forming units, introduction of some steric hindrance (*iso*-butyl groups) and thus slightly weakening the intermolecular interactions can have a positive effect on the gelation ability.

For the tris-amides **19–21** the influence of the R-group is much more pronounced. Tris-amide **19** (R=CH_2Ph) was the most efficient gelator and formed a gel or highly viscous solution in all the solvents tested. Introduction of the sterically more demanding *iso*-butyl group[18] (**20**) led to a decrease in the gelation ability of the compound compared to **19**, possibly due to steric hindrance. Apparently, the amide hydrogen bonds are not strong enough to compensate for these unfavourable effects. Furthermore, for compound **19** π–π stacking between the phenyl groups might contribute to the intermolecular interactions and subsequently the gelation ability.[19] The compound with the least steric hindrance (**21**: R=H) was found to gelate a range of solvents comparable to compound **19**. Additionally, the minimal gelation concentrations had decreased. Apparently, the absence of steric hindrance improves the packing in the stacks and thus the intermolecular interactions, resulting in increased gelation abilities.

For the tris-amide-amides **22–24**, the influence of the R-group is rather clear. Comparing **23** (R=$CH_2CH(CH_3)_2$) with **22** (R=CH_2Ph) it seems that as for the tris-urea compounds **16** and **17** the *iso*-butyl group has a positive effect on the gelation ability of the compound, resulting in an increase in the scope of gelated solvents. For the compound

with the least steric demand (**24**: R=H) and thus expected to have the best packing within the stacks, the gelation ability is comparable to **23** (R=$CH_2CH(CH_3)_2$) with a slightly changed solvent scope and decreased minimal gelation concentrations.

Thus, whereas for the benzyl compounds the facile packing together with the additional π–π stacking seem to cause a diminished solubility and thus gelation ability upon introduction of additional hydrogen bonding interactions, for the *iso*-butyl compounds the poorer packing appears to be compensated by the introduction of extra hydrogen bonding interactions resulting in increasing gelation abilities. For the glycine compounds, facile packing can be expected but no additional π–π stacking is present, thus the intermolecular interactions are not too strong and also with additional hydrogen bonding interactions gels are still obtained instead of precipitates.

Apparently for these compounds, a subtle balance between hydrogen bonding strength, steric effects and other interactions, like π–π stacking, are present in order to yield gels, viscous solutions or precipitates. A preliminary model (Fig. 4C) shows that sterically demanding R-groups indeed adopt an important position in the stack, most likely causing deviation from the stacking pattern found for cyclohexane tricarboxamides (Fig. 4A)[7] (presumally twisting of the originally translational aggregate). However, further studies are needed to gain more insight in the precise role of the R-groups.

Comparison of the tris-urea compounds **16** and **17** with known cyclohexane bis-urea organogelators[5] reveals that in general these cyclohexane bis-urea gelators gel a broader scope of solvents and have lower minimal gelation concentrations. Apparently, the additional urea group present in **16** and **17** did not affect these properties positively. However, a fair comparison is difficult, as these bis-urea compounds have substantially different peripheral substituents.

An analogous comparison can be made between the tris-amide compounds and cyclohexane bis-amide organogelators:[3a] a smaller solvent scope is observed for the cyclohexane tris-amides, most likely due to the presence of stereogenic centres with large R-groups. This is consistent with the fact that the poorest gelation behaviour is displayed by the compound exhibiting the sterically most demanding R-group (**20**: R=*iso*-butyl). Compared to the trialkyl-*cis*, *cis*-1,3,5-cyclohexane tricarboxamides reported by Hanabusa[8] the solvent scope had shifted, but, except for the *iso*-butyl derivative, the gelation ability had not significantly decreased for most compounds. The shift in solvent scope might be related to the ester groups present in the compounds **19**–**21**.

2.5. Infrared spectroscopy

FTIR spectroscopy was used to study further the differences in aggregation behaviour observed for the C_3-symmetric compounds. Concentration- and temperature-dependent measurements were performed on cyclohexane solutions or gels of the tris-ureas **9**, **10** and **17** and the tris-amides **12** and **20** and compared to measurements on cast films (see Supplementary data for data and discussion). The results show that aggregation and gelation of the compounds studied is accompanied by hydrogen bond formation. The concentration-dependent measurements and the resulting association constants translate the observed differences in aggregation behaviour to the aggregation ability of the separate components: the core (benzene<cyclohexane), the hydrogen-bonding units (amide<urea) and the R-groups ($CH_2CH(CH_3)_2$<CH_2Ph). For compounds **9**, **17** and **20**, the estimated lower limit for the association constant is already much higher than the association constants observed for the aggregation of cyclohexane bis-urea compounds,[20] demonstrating their strong aggregation and gelation ability. When aggregation (viscous solution or gel) is not visible even up to high concentrations, hydrogen bond formation is not observed by FTIR (**12**). However, if at low concentrations hydrogen bond formation and thus aggregation are present, this will not always lead to thickened or gelated solutions (compare **9** with **10**). This is probably related to the size of the formed aggregates, i.e., a highly thickened solution is only observed when the aggregates are large enough. Preliminary dynamic light scattering measurements indicate that indeed the aggregates formed in a non-thickened cyclohexane solution of **10** (31.6 mM) are smaller than the aggregates formed in a thickened cyclohexane solution of **9** (31.6 mM).

2.6. Thermotropic properties of the gels studied by dropping ball measurements[21]

Dropping ball measurements reveal the temperature at which the gel loses its mechanical stability, the so-called melting temperature (also called gel–sol transition).[21] Falling of the steel ball does not necessarily correspond to loss of (intermolecular) aggregation, but rather to disintegration of the gel network to a point at which the gel is not able to support the steel ball anymore. Measurements were performed on gels formed by cyclohexane-based compounds and the results are shown in Figure 5. Depending on the scope of gelated solvents, gels of 1-octanol (Fig. 5a) or tetraline (Fig. 5b) were studied. The gels were prepared in sealed vials to avoid solvent evaporation and allowed to stabilise for 4–7 days prior to the measurements.

All different gels melted thermoreversibly at temperatures varying from 50 °C to >155 °C, depending on the concentration, the hydrogen bonding unit and the R-group. For most of the gels it was observed that the melting temperature increased with increasing concentration up to a certain level, a behaviour common for low molecular weight gelators. In contrast, the tetraline gels of **22** were found to melt almost independently of concentration. For several of the gels it was observed that after melting a viscous solution (**22** in tetraline) or gel-like precipitate (**16**, **17** and **23** in 1-octanol) remained. For compound **23**, the melting of gels could not be observed for c>17 mM, because the apparatus only allowed measurements up to 155 °C.

The influence of the hydrogen-bonding unit can be discussed by comparing the 1-octanol gels of **16** with **19** (R=CH_2Ph), **21** with **24** (R=H) and **17** with **23** (R=$CH_2CH(CH_3)_2$). Comparison of the 1-octanol gels of **16** (tris-urea) with the gels of **19** (tris-amide) showed considerable higher melting

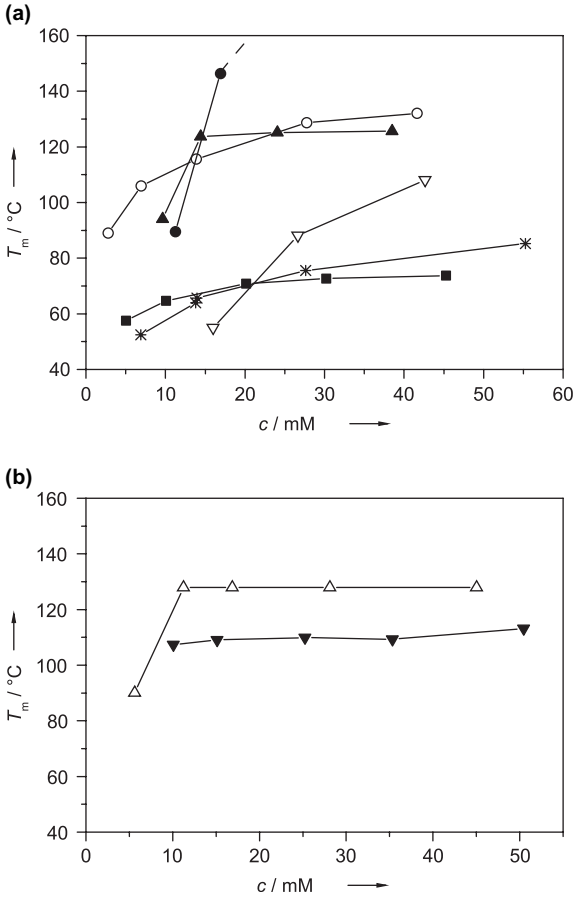


Figure 5. Thermal behaviour of: (a) 1-octanol gels of **16** (-▲-), **17** (-▽-), **19** (-■-), **21** (-∗-), **23** (-●-) and **24** (-○-); (b) tetraline gels of **22** (-▼-) and **23** (-△-).

temperatures for the tris-urea **16**. For compound **16** the intermolecular interactions were so strong that after dropping of the ball a gel-like precipitate was still present, which remained even at temperatures of 150 °C. Thus, as expected the introduction of additional hydrogen bond donors and hydrogen bonds immediately enhanced the thermal stability of the gels. This also corresponds with the higher association constants of the urea compounds (K_{10}) compared to the amide compounds (K_{12}) as found with FTIR (Supplementary data). A similar conclusion can be drawn by comparison of the glycine derivatives **21** (tris-amide) and **24** (tris-amide-amide); substitution of the ester functionality by amides to introduce additional hydrogen bonds also resulted in an increase in melting temperature of 50 °C.

Comparison of **17** (tris-urea) with **23** (tris-amide-amide) reveals a considerably lower melting temperature for the tris-urea **17**. Thus it seems that, at least for R=$CH_2CH(CH_3)_2$, the use of the urea unit produces thermally less stable gels than the combination of two amide groups. A straightforward explanation is not available, however. Perhaps a single amide hydrogen bond is stronger than a single urea hydrogen bond (of the two hydrogen bonds an urea group can form).

The influence of the R-group can be discussed by comparing the 1-octanol gels of the tris-urea **16** with **17**, the tris-amides **19** with **21**, the tris-amide-amides **23** with **24** and the tetraline gels of the tris-amide-amides **22** with **23**. Comparison of the tris-urea **16** (R=CH_2Ph) and **17** (R=$CH_2CH(CH_3)_2$) reveals higher melting temperatures and thus a higher thermal stability for the benzyl derivative **16**, especially at lower concentrations. This can be explained from the additional π–π-stacking interactions and lower steric hindrance for R=CH_2Ph, which will enhance the intermolecular interactions. These results are comparable to the aggregation and FTIR results obtained for the benzene core compounds **9** and **10**, in which the *iso*-butyl group also has a destabilising effect compared to the benzyl derivative.

Comparison of the tris-amides **19** (R=CH_2Ph) with **21** (R=H) shows that these compounds melt in a similar temperature range, depending on concentration. Apparently, removal of the benzyl group does not have a significant influence on the thermal stability of the gels. Most likely the loss of the π–π-stacking interactions is compensated by the diminished steric hindrance, which enables a closer packing and thus increases the intermolecular interactions.

Comparison of the tris-amide-amides **23** (R=$CH_2CH(CH_3)_2$) with **24** (R=H) reveals at low concentrations lower melting points and thus a lower thermal stability for the *iso*-butyl derivative **23**. This is in accordance with the larger steric hindrance of the *iso*-butyl group, which will hinder a close and thus strong packing of the molecules. At high concentrations, however, the melting points and thermal stability of **24** are lower than those of **23**. This is contrary to expectations and difficult to explain.

Comparison of the tetraline gels of the tris-amide-amides **22** (R=CH_2Ph) with **23** (R=$CH_2CH(CH_3)_2$) also reveals thermotropic behaviour, that is, in contrast to expectation, since the benzyl derivative **22** melts at lower temperatures than the *iso*-butyl derivative **23**. However, after melting it is observed that the solution of **22** is still thickened and thus the aggregates are not completely dissociated, whereas for **23** thickening is not observed. Most likely, for compound **22** some structural rearrangement at the transition temperature causes the gel fibres to dissociate into single strands, which thicken the solution. A reason for the thermal instability of the gel of **22** compared to **23** is not obvious, but might be related to the aromatic solvent used.

Summarising, the number of hydrogen bonding interactions has a significant influence on the thermal stability of the gels. Both the tris-urea and the tris-amide-amides form stronger gels than the tris-amides. Between the tris-urea and the tris-amide-amide also a difference is observed, which is related to the nature of the hydrogen-bonding unit. The influence of the R-group is less straightforward. Substitution of the benzyl group with a hydrogen group does not result in a significant difference. This fact might be explained by a compensation of the loss of π–π-stacking interactions with a closer packing due to loss of steric hindrance. However, comparison of these R-groups with the *iso*-butyl group yields peculiar and so far unexplainable results.

Comparison of the melting behaviour of the cyclohexane tris-urea derivatives **16** and **17** with cyclohexane bis-urea gels[5g] reveals higher melting points for the tris-urea. Thus, it can be concluded that the introduction of an additional

urea group and as a consequence of further intermolecular hydrogen bonding has a positive influence on the thermal stability. For the tris-amides **19** and **21** the melting temperatures are comparable with those of cyclohexane bis-amides.[3a] Possibly, the presence of stereogenic centres has a destabilising effect. Unfortunately, no thermotropic data are available for the trialkyl *cis*-1,3,5-cyclohexane tricarboxamides,[8] thus the exact influence of the stereogenic centres cannot be deduced.

2.7. Thermotropic properties of the gels studied by differential scanning calorimetry

Differential scanning calorimetry (DSC) was carried out to gain insight into the phase transitions of the gels. The measurements were performed on 1-octanol gels of **16**, **19**, **23** and **24**, which were prepared inside large volume sample pans by heating in the DSC apparatus. Subsequently, two sets of heating and cooling scans were recorded with an interval of 2–3 h. These subsequent scans revealed identical curves for each compound, indicating that their gelation was fully thermoreversible. Figure 6 presents the heating curves recorded for the different gel samples, showing that large differences between the various gels are present. The cooling scans are not discussed, since clear phase transitions were not observed upon cooling. The common exotherm at T=65 °C is related to the softener present in the Viton O-ring of the sample pans. For compound **19** this peak would coincide with the phase transition of the gel itself, therefore measurements on the gel of **19** were performed without the presence of the Viton O-ring.[22]

The 1-octanol gel of the tris-amide **19** (R=CH_2Ph) displayed a heating curve with a strong endothermic transition at T=72 °C in a rather narrow temperature range, which indicates that this transition is cooperative (Fig. 6).[22] The dropping ball measurements (vide supra) showed that the gel is completely transformed into a homogeneous solution at 73 °C, thus the transition was assigned as the gel–sol transition of the gel. The enthalpy calculated for the gel–sol transition was 19.4 kJ mol^{-1} (Table 3). In apolar aprotic solvents a much higher enthalpy is expected for the breaking up of three hydrogen bonds,[23] thus the low value of the melting enthalpy is most likely caused by the more polar and protic nature of the solvent. This agrees with the finding that for long alkyl bis-urea gelators the gelation process in polar alkanol solvents is primarily driven by solvophobic interactions (entropic) instead of hydrogen bonding interactions.[5g]

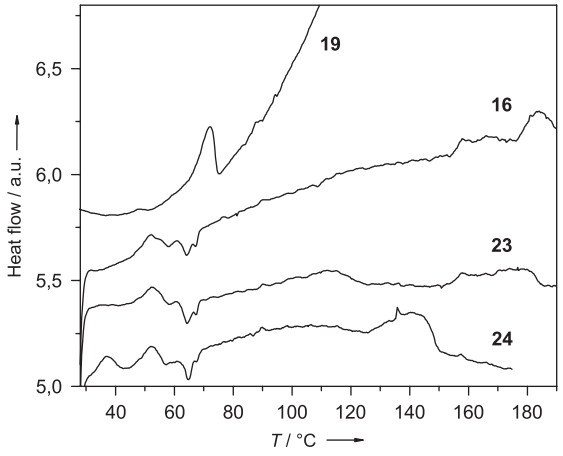


Figure 6. DSC heating curves of 1-octanol gels of **16** (31 mM), **19** (30 mM), **23** (66 mM) and **24** (41 mM).

Table 3. Thermotropic properties of 1-octanol gels of **16**, **19** and **23**–**24**[a]

Gel sample	T_m (°C)	T_1 (°C)	T_2 (°C)	T_3 (°C)
16 (c=31 mM)	125[b]	54 (6.4)	158 (8.1)	183 (8.9)
19 (c=30 mM)	73	72 (19.4)		
23 (c=66 mM)	>154	53 (3.2)	111 (15.8)	176 (9.3)
24 (c=41 mM)	132	37 (3.6)	52 (5.1)	140 (20.9)

[a] T_m is the melting temperature of the gels as deduced by the dropping ball method. T_1, T_2 and T_3 are the temperatures at the maxima of the endotherms observed by DSC. The numbers in parentheses are the associated enthalpies (kJ mol^{-1}).
[b] A gel-like precipitate remained after melting.

Substitution of the amide groups of **19** by ureas to obtain the tris-urea **16** (R=CH_2Ph), led to a completely different DSC heating curve (Fig. 6). Instead of one cooperative transition, three low endothermic transitions are observed at T_1=54 °C, T_2=158 °C and T_3=183 °C, indicating that several processes are taking place (Table 3). None of these can be related to the melting temperature of 125 °C determined by dropping ball measurements (vide supra). Furthermore, the dropping ball measurements showed that after falling of the ball only the mechanical stability of the gel was lost, whereas still a gel-like precipitate was present that remained even at the uppermost temperature (155 °C) of the dropping ball apparatus. The temperatures T_2 and T_3 at which two of the observed transitions occur exceed this limit and thus the macroscopic events at these temperatures were not observed. However, most likely one of these transitions includes the complete dissolution of the compound into the solvent. In addition, the peak at T_3 could be related with decomposition of the urea groups, although this disagrees with the decomposition temperature of the solid ($T_{decomp.}\geq$230 °C). The endotherm at T_1=54 °C is also present in the gels formed by **23** and **24**, suggesting that it is related to a phase transition associated with a common structural reorganisation. The enthalpies calculated for the transitions of **16** are small. However, the total of these enthalpies is larger than the enthalpy associated with the melting of the 1-octanol gel of **19**. Although a direct comparison cannot be made, this does support the high aggregation ability and strength of the urea compounds compared to the amide compounds as found with FTIR and dropping ball measurements.

For the tris-amide-amide **23** (R=$CH_2CH(CH_3)_2$) three endotherms are observed at T_1=53 °C, T_2=111 °C and T_3=176 °C (Fig. 6; Table 3). As discussed above, the relatively small transition at T_1 is also present in the gels of **16** and **24**. The two transitions at higher temperatures are very broad, indicating that the processes related to these transitions are not cooperative. Dropping ball measurements (vide supra) show that melting of the gel does not take place below 154 °C, thus the transition at T_2 cannot be assigned to the melting of the gel. Instead most likely some kind of reorganisation takes place that does not result in a macroscopic event. The phase transition at T_3 is more likely to be due to melting of the gel into a homogeneous solution, although other processes cannot be excluded.

Also for the tris-amide-amide **24** (R=H) three endotherms are observed (Fig. 6; Table 3). The origin of the peak observed at T_1=37 °C is unknown, but might be related to a conformational rearrangement of the peripheral substituents. The transition at T_2=52 °C is comparable to transitions observed for **16** and **23** and is most likely related to a common structural reorganisation. The third transition at T_3=140 °C coincides with the melting point of the gel as deduced by dropping ball measurements (vide supra) and is therefore most likely related to the gel–sol transition of the gel.

The fact that only for the tris-amide **19** a single melting transition is observed, whereas for the thermally more stable tris-urea **16** and tris-amide-amides **23** and **24** multiple peaks are found suggesting that this is related to the increased number of intermolecular hydrogen bonding interactions. Probably the stronger hydrogen bonding interactions are still able to hold the aggregates together after the initial destabilising events have taken place. However, the presence of different hydrogen bonding units could also result in different morphologies involving other transitions. The TEM studies (vide infra), however, do not give a clear and consistent relation between the morphology of the gels and the transitions observed with DSC, since the compounds that show three transitions can form short thin fibres (**16**) as well as elongated sheets (**24**).

2.8. Morphology of the gels

To determine the morphology of the obtained gels, several of them were subjected to transmission electron microscopy (TEM) studies. For this purpose TEM samples were prepared of gels, which were dried and Pt-shadowed prior to investigation. The morphological differences between the gels of the various compounds will be discussed with respect to the differences in R-group and hydrogen-bonding unit. Chirality aspects will not be considered in any detail. Figure 7 represents micrographs of 1-octanol gels of the cyclohexane tris-urea derivatives **16** (R=CH_2Ph) and **17** (R=$CH_2CH(CH_3)_2$). In both gels, fibres are present, however, a clear difference in morphology can be observed. For compound **16** (Fig. 7A) short and thin fibres (diameter of ~13 nm) are present, which cluster into thicker bundles. The presence of large amounts of small fragments indicates that the fibres are brittle. A clear splitting and fusing of the fibres to form the gel network could not be seen. Furthermore, despite the chirality of the molecule, no twisting of the fibres was observed. In *p*-xylene similar fibre morphology was observed. The observed fibre morphology might be related to the fact that **16** precipitates in many of the solvents tested.

In contrast, when the benzyl group is replaced with an *iso*-butyl group (**17**; Fig. 7B) elongated fibres are observed, which exhibit a clear left-handed twisting with a pitch of ~200 nm. The fibres appear to be more flexible and vary in diameter, with an observed minimal size of 18 nm. The twisted fibres join regularly to form thicker fibres of identical handedness (Fig. 7C). Most likely, joining and splitting of the fibres are responsible for the formation of a three-dimensional gel network.

Substitution of the urea groups with amides to obtain the cyclohexane tris-amides **19**–**21**, resulted in a completely different morphology and a different effect of the R-group (Fig. 8). In contrast to the morphology of its tris-urea counterpart (**16**), the benzyl derivative **19** formed is elongated, thin fibres with a monodisperse diameter of 13 nm (Fig. 8A). The fibres exhibited a right-handed helicity with a pitch of 80–100 nm. The fibres neither split nor fuse, but align into thicker bundles. Interestingly, in other solvents like tetraline and 1,2-dichloroethane a similar morphology was observed, which is uncommon for other LMWGs.[5]

Whereas the tris-urea *iso*-butyl derivative **17** formed twisted fibres, the tris-amide *iso*-butyl derivative **20** formed elongated sheet-like fibres, for which nearly no twisting was observed. (Fig. 8B). Their diameter of 40–360 nm was larger than those of the other compounds discussed so far. Occasionally the fibres fuse or split to form the gel network. The observed difference in morphology might be related to the different solvent used,[24] which results from the fact that **20** gels only *n*-hexadecane.

The morphology of **21** (R=H; Fig. 8C), somewhat resembles the morphology observed for the *iso*-butyl derivative **20**. Also elongated sheet-like fibres are observed with a diameter of 10–300 nm, which fuse and split to connect into a three-dimensional gel network. A minor part of these fibres appear

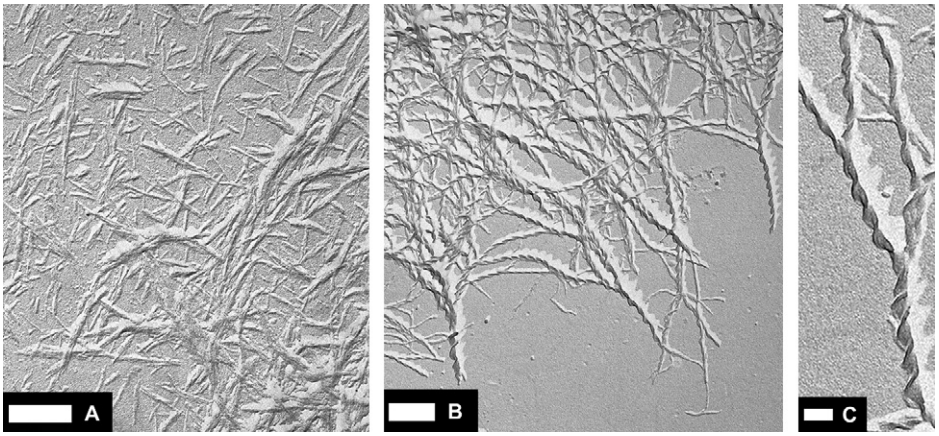


Figure 7. Electron micrographs of 1-octanol gels of the cyclohexane tris-urea: (A) **16** (R=CH_2Ph; c=10 mg mL^{-1}); (B) **17** (R=$CH_2CH(CH_3)_2$; c=5 mg mL^{-1}); bars represent 500 nm and (C) detail of the gel of **17**; bar represents 100 nm.

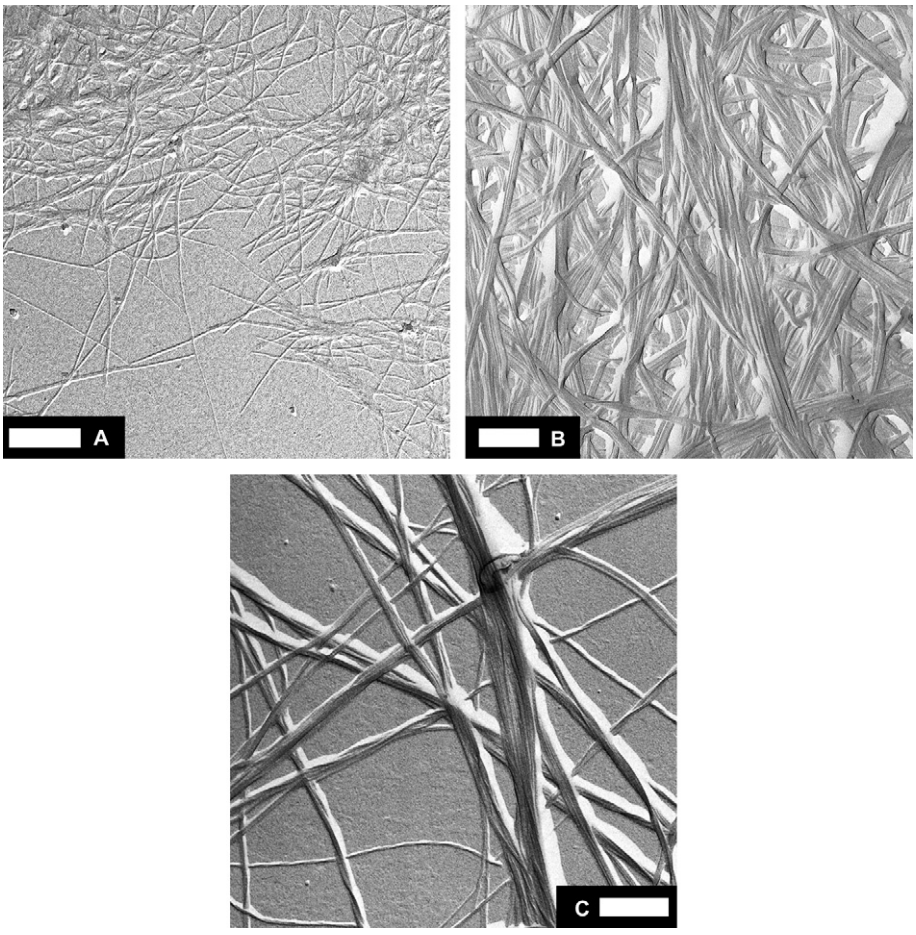


Figure 8. Electron micrographs of gels of the cyclohexane tris-amide derivatives: (A) **19** in 1-octanol (R=CH_2Ph; c=10 mg mL^{-1}); (B) **20** in *n*-hexadecane (R=$CH_2CH(CH_3)_2$; c=10 mg mL^{-1}) and (C) **21** in 1-octanol (R=H; c=10 mg mL^{-1}). Bars represent 500 nm.

to be twisted, equally both left-handed and right-handed. The pitch is mostly irregular and variable. It seems remarkable that the achiral compound **21** forms twisted fibres, whereas for the chiral counterpart **20** nearly no twisting is observed. However, this could well be related to the different solvents used.[24]

For the tris-amide-amide derivatives **22** and **24** differences in morphology are observed, which are comparable to the tris-amide derivatives **19** and **21** (Fig. 9). The benzyl derivative **22** formed short fibres with a diameter of 15–70 nm (Fig. 9A). Similar to its tris-amide counterpart **19**, the fibres exhibited a right-handed twist. In contrast to the regular pitch observed for **19**, the fibres of **22** exhibit an often irregular pitch of about 100–150 nm. Thinner fibres fuse into thicker (bundles of) fibres, which results in the formation of junction zones and consequently a three-dimensional gel network.

Analogously to its tris-amide counterpart **21**, the achiral tris-amide-amide **24** forms sheet-like fibres, which exhibit occasional irregular twisting, both left-handed and right-handed (Fig. 9B). Probably, the sheet-like morphology of the fibres from **21** and **24** is related to the absence of molecular chirality. The diameter of the fibres ranges from 20–250 nm and compared to **21**, the fibres formed by **24** seem to be thinner. The fibres split and fuse to form the gel network. In tetraline it was observed that the fibres were even more sheet-like and exhibited no twist at all.

Comparing all micrographs, it can be observed that almost all compounds form fibres with high aspect ratios, which reflect the high anisotropy of the interactions. Exceptions are the benzyl derivatives **16** and **22**, which form relatively short fibres. Possibly this is related to the fact that these compounds experience the strongest interactions due to the combination of strong hydrogen-bonding units (urea groups or two combined amides, respectively) with π–π-stacking groups. These strong interactions most likely cause the molecules to preferably aggregate fast into new fibres, instead of first diffuse towards existing fibres to co-aggregate with these to form more elongated fibres. This process would lead to a larger number of fibres with a lower fibre aspect ratio. In both cases, decreasing the intermolecular interactions by substitution of the benzyl group with non-aromatic (and sterically demanding) groups or by reducing the number of hydrogen bonds resulted in the formation of elongated, flexible fibres.

Comparison of the morphologies observed for these compounds reveals in general a similar diversity as found for cyclohexane bis-urea[5a,e] or bis-amide[3a] organogelators. The exception is formed by compound **19**, which displays a homogeneous, solvent-independent morphology.

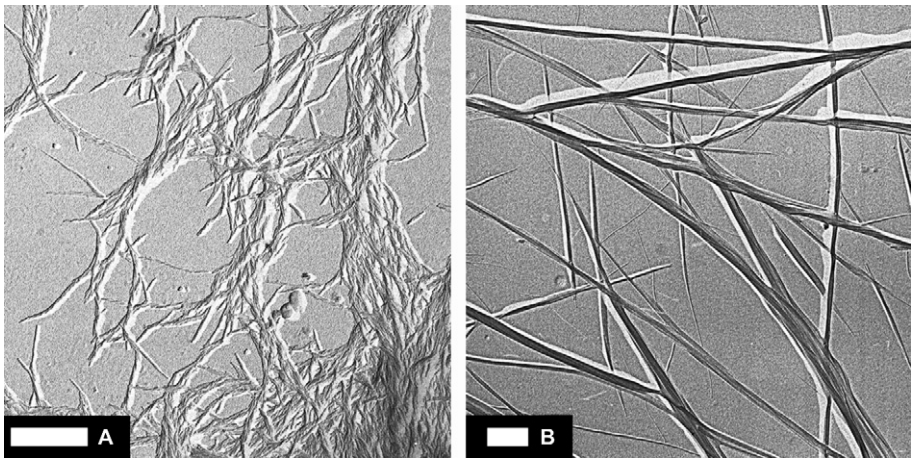


Figure 9. Electron micrographs of gels of cyclohexane tris-amide-amides: (A) **22** in tetraline (R=CH_2Ph; c=10 mg mL^{-1}) and (B) **24** in 1-octanol (R=H; c=5 mg mL^{-1}). Bars represent 500 nm.

3. Conclusions

In conclusion, based on rational considerations a new class of chiral C_3-symmetric α-amino acid based organogelators and thickeners have been developed. Starting from commercially available building blocks, compounds with a large structural diversity are easily accessible in three or four steps. Variation was applied in the central core, the hydrogen bonding units and the amino acids. These modifications have a strong influence on the intermolecular interactions, resulting in large differences in aggregation properties, thermal stability and morphology between the various compounds. This allows fine-tuning of the gelators with respect to aggregation behaviour and gel properties.

The central core unit has a strong influence on the aggregation ability and both gelation studies and FTIR spectroscopy showed that the cyclohexane core was superior to the benzene core. This is consistent with the results obtained for trialkyl-tricarboxamide derivatives.[8,10,11] The type and number of hydrogen-bonding units influenced the number of possible hydrogen bonds and as such the strength of the intermolecular interactions. Generally, stronger hydrogen bonding interactions (urea or amide-amide) resulted in stronger aggregation and higher thermal stabilities. However, this is balanced by the α-amino acids (R-groups) used, which influenced the magnitude of the steric hindrance and the possible presence/absence of π–π stacking. It seems that too strong intermolecular hydrogen bonding interactions (leading to insolubility, crystallisation or precipitation) can be compensated by the introduction of steric hindrance to yield effective gelators. Weaker hydrogen bonding interactions (amides) seem to be strengthened by the presence of π–π-stacking interactions and less steric hindrance.

FTIR spectroscopy showed that for most of the compounds the tendency to aggregate is so strong that even at very low concentrations all molecules are fully hydrogen bonded. This strong aggregation ability is most likely caused by the favourable orientation and cooperativity of the three sets of hydrogen-bonding units, enforced by the rigid cores. The hydrogen bond formation most likely causes the high thermal stabilities of the gels. Indeed, compared to cyclohexane bis-urea 1-octanol gels[5g] the thermal stabilities have increased, indicating that the additional urea positively affects the thermal stability.

The work described here comprises only a limited variation in the peripheral substituents. Further understanding of the influence of steric hindrance, π–π stacking etc. could be obtained by using other natural or unnatural amino acids. Also variation of the stereochemistry of these amino acids offers interesting possibilities. Additional opportunities can be expected from the use of other than alkyl esters. Accordingly we have previously shown that the use of amino acids that are not esterified at the carboxylic acid terminus or esterified with hydrophilic substituents, resulted in a shift of the solvent scope from organic solvents to water and aqueous solutions.[6]

4. Experimental section

4.1. General remarks

Melting points (uncorrected) were determined using a Stuart Scientific SMP1 melting point apparatus; no attempt was made to measure the melting points of sticky solids. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini-200 (200 MHz or 50.32 MHz, respectively) or a Varian VXR-300 (300 MHz or 75.48 MHz, respectively) operating at ambient temperature, unless stated otherwise. Chemical shifts are denoted in δ units (ppm) relative to the residual solvent peaks (^{1}H NMR: $CDCl_3$, δ=7.26; DMSO-d_6, δ=2.49. ^{13}C NMR: $CDCl_3$, δ=76.91; DMSO-d_6, δ=39.5) and converted to the TMS scale. The splitting patterns are designated as follows: s (singlet), br s (broad singlet), d (doublet), br d (broad doublet), dd (double doublet), t (triplet), dt (double triplet), br t (broad triplet), q (quartet), m (multiplet) and br p (broad peak). FTIR spectra were recorded on a Nicolet Nexus FTIR apparatus, $\tilde{\nu}$ values are listed in cm^{-1} units. Elemental analyses and mass spectrometry were performed in the analytical department of this laboratory.

Synthesis of the α-amino acid esters and amides **1**–**6** is described in the Supporting data. *cis*,*cis*-1,3,5-Cyclohexane

tricarboxylic acid was purchased from FLUKA. Diphenyl phophoryl azide (DPPA) and 1,3,5-benzenetricarboxylic acid were purchased from Aldrich. Di-*tert*-butyl dicarbonate was purchased from Acros.

Caution: the synthetic procedures for compounds **9** and **10** involve the preparation of 1,3,5-benzenetricarbonyl triazide, a highly explosive compound in its solid state![15]

4.2. Syntheses

4.2.1. 1,3,5-Benzenetricarbonyl trichloride (7). 1,3,5-Benzenetricarboxylic acid (6.0 g, 28.7 mmol) was placed in a flask together with $SOCl_2$ (12 mL) and a drop of DMF. The suspension was refluxed for 3 h, affording a clear solution. The remaining $SOCl_2$ was evaporated in vacuo, yielding **7** as a pale yellow oil that crystallised upon standing at 4 °C (7.7 g, 28.7 mmol, 100%). ^{1}H NMR ($CDCl_3$): δ=9.08 (s, 3H).

4.2.2. 1,3,5-Benz(U-L-Phe-*O*-octyl)$_3$ (9). To a cooled (0 °C) solution of NaN_3 (1.75 g, 27 mmol) in H_2O (10 mL) was added a cooled (0 °C) solution of 1,3,5-benzenetricarbonyl trichloride **7** (1.0 g, 3.77 mmol) in THF (10 mL). The mixture was stirred for 2 h at 0 °C resulting in the formation of 1,3,5-benzenetricarbonyl triazide as a white precipitate. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.86 (s, 3H). This precipitate can easily be isolated by filtration, however, because of the *explosive nature* of the dry solid this is strongly rejected. Thus, cold toluene (100 mL) was added to the mixture to take up the acyl azide. The toluene layer was separated and washed with water (3×80 mL) and brine and dried over $MgSO_4$. Subsequently, the toluene solution was gradually heated to 100 °C and stirred till gas evolution stopped, yielding in situ the corresponding triisocyanate **8**. The solution was allowed to cool to room temperature and **1** (3.45 g, 12.44 mmol) in toluene (30 mL) was added. The mixture was stirred for one night at room temperature, after which the solvents were evaporated in vacuo yielding a sticky solid. Column chromatography using an eluent gradient (CH_2Cl_2/MeOH; 200:0–200:5) on silica gel yielded **9** slightly contaminated. A second column chromatography (CH_2Cl_2/MeOH; 200:10) on silica gel yielded **9** as a pure colourless sticky solid (0.76 g, 0.74 mmol, 20%). ^{1}H NMR (DMSO-d_6): δ=8.62 (s, 3H), 7.31–7.16 (m, 15H), 7.08 (s, 3H), 6.27 (d, ^3J=7.7 Hz, 3H), 4.48–4.41 (m, 3H), 3.99 (t, ^3J=6.4 Hz, 6H), 3.04–2.91 (m, 6H), 1.48 (s, 6H), 1.20 (s, 30H), 0.83 (t, ^3J=6.6 Hz, 9H); ^{13}C NMR (DMSO-d_6): δ=172.40, 154.66, 140.65, 136.93, 129.34, 128.55, 126.89, 100.55, 64.76, 54.04, 37.66, 31.41, 28.79, 28.20, 25.50, 22.26, 14.13; IR (film, NaCl): $\tilde{\nu}$=3328 (N–H), 1738 (C=O, ester), 1638 (C=O, amide I), 1555 cm^{-1} (N–H, amide II); elemental analysis calcd (%) for $C_{60}H_{84}N_6O_9$ (1033.4): C 69.74, H 8.19, N 8.13; found: C 69.72, H 8.23, N 8.12.

4.2.3. 1,3,5-Benz(U-L-Leu-*O*-octyl)$_3$ (10). Compound **10** was synthesised following the same procedure as described for **9**, using NaN_3 (1.75 g, 27 mmol), **7** (1.0 g, 3.77 mmol) and **2** (2.75 g, 11.3 mmol). After reaction an orange sticky solid was obtained and column chromatography (CH_2Cl_2/MeOH; 200:5) on silica gel yielded **10** as a pure, sticky solid (1.25 g, 1.34 mmol, 36%). ^{1}H NMR (DMSO-d_6): δ=8.49 (s, 3H), 7.09 (s, 3H), 6.30 (d, ^3J=7.7 Hz, 3H), 4.23–4.16 (m, 3H), 4.08–3.98 (m, 6H), 1.68–1.46 (m, 15H), 1.20 (br s, 30H), 0.91–0.80 (m, 27H); ^{13}C NMR (DMSO-d_6): δ=173.30, 154.58, 140.53, 100.19, 64.34, 50.80, 40.86, 31.81, 28.58, 28.54, 28.06, 25.31, 24.34, 22.85, 22.09, 21.62, 13.91; IR (film, NaCl): $\tilde{\nu}$=3347 (N–H), 1740 (C=O, ester), 1645 (C=O, amide I), 1558 cm^{-1} (N–H, amide II); MS (ES): *m/z* 1880.5 [2M+NH$_4^+$]$^+$, 1417.4 [3M+Na$^+$+NH$_4^+$]$^{2+}$, 953.7 [M+Na$^+$]$^+$, 948.8 [M+NH$_4^+$]$^+$, 931.9 [M+H$^+$]$^+$.

4.2.4. 1,3,5-Benz(Am-L-Phe-*O*-octyl)$_3$ (11). To a cooled solution of **1** (2.0 g, 7.2 mmol) and triethylamine (0.73 g, 7.2 mmol) in dry CH_2Cl_2 (50 mL) was added a solution of 1,3,5-benzenetricarbonyl trichloride **7** (0.64 g, 2.4 mmol) in dry CH_2Cl_2 (5 mL). The solution was slowly brought to room temperature and stirred for 20 h. Subsequently $CHCl_3$ (20 mL) was added and the solution was extracted successively with dilute HCl (3×50 mL), water (2×50 mL), 10% aqueous sodium carbonate (3×50 mL), water (2×50 mL) and brine. The solution was dried over $MgSO_4$ and the solvents were evaporated in vacuo, yielding a sticky solid. Column chromatography (CH_2Cl_2/MeOH; 100:1) on silica gel yielded **11** (1.2 g, 1.21 mmol, 50%) as a white sticky solid. ^{1}H NMR (DMSO-d_6): δ=9.12 (d, ^3J=7.3 Hz, 3H), 8.39 (s, 3H), 7.26–7.18 (m, 15H), 4.71–4.63 (m, 3H), 4.01 (t, ^3J=6.4 Hz, 6H), 3.13 (d, ^3J=8.4 Hz, 6H), 1.48 (s, 6H), 1.17 (s, 30H), 0.80 (t, ^3J=6.6 Hz, 9H); ^{13}C NMR (DMSO-d_6): δ=171.55, 165.54, 137.58, 134.16, 129.29, 129.02, 128.26, 126.49, 64.57, 54.62, 36.32, 31.19, 28.58, 28.04, 25.28, 22.07, 13.92; elemental analysis calcd (%) for $C_{60}H_{81}N_3O_9$ (988.3): C 72.92, H 8.26, N 4.25; found: C 72.83, H 8.33, N 4.25.

4.2.5. 1,3,5-Benz(Am-L-Leu-*O*-octyl)$_3$ (12). Compound **12** was synthesised following the same procedure as described for **11**, using **2** (2.0 g, 8.2 mmol), triethylamine (0.83 g, 8.2 mmol) and 1,3,5-benzenetricarbonyl trichloride **7** (0.73 g, 2.73 mmol). Column chromatography (CH_2Cl_2/MeOH; 100:1) on silica gel yielded **12** (1.48 g, 1.67 mmol, 62%) as a white sticky solid. ^{1}H NMR (DMSO-d_6): δ=9.02 (d, ^3J=7.3 Hz, 3H), 8.49 (s, 3H), 4.54–4.47 (m, 3H), 4.10–4.01 (m, 6H), 1.84–1.51 (m, 15H), 1.23–1.19 (m, 30H), 0.93–0.88 (m, 18H), 0.83 (t, ^3J=6.6 Hz, 9H); ^{13}C NMR (DMSO-d_6): δ=172.44, 165.81, 134.30, 129.40, 64.43, 51.25, 39.28, 31.15, 28.55, 28.08, 25.30, 24.42, 22.83, 22.05, 21.21, 13.91; IR (film, NaCl): $\tilde{\nu}$=3226 (N–H), 1753 (C=O, ester), 1640 (C=O, amide I), 1555 cm^{-1} (N–H, amide II); elemental analysis calcd (%) for $C_{51}H_{87}N_3O_9$ (886.3): C 69.12, H 9.89, N 4.74; found: C 69.24, H 9.96, N 4.77.

4.2.6. 1,3,5-Benz(Am-Gly-*O*-octyl)$_3$ (13). Compound **13** was synthesised following the same procedure as described for **11**, using **3** (2.02 g, 10.8 mmol), triethylamine (1.1 g, 10.8 mmol) and 1,3,5-benzenetricarbonyl trichloride **7** (0.93 g, 3.5 mmol). After extraction, compound **13** was obtained as a yellowish sticky solid (1.77 g, 2.44 mmol, 70%). ^{1}H NMR ($CDCl_3$): δ=8.24 (s, 3H), 8.01 (t, ^3J=5.7 Hz, 3H), 4.23–4.14 (m, 12H), 1.72–1.65 (m, 6H), 1.32–1.28 (m, 30H), 0.89 (t, ^3J=6.6 Hz, 9H); ^{13}C NMR ($CDCl_3$): δ=170.59, 166.44, 134.41, 128.49, 65.78, 41.91, 31.70, 29.15, 29.09, 28.45, 25.82, 22.55, 13.97; elemental analysis calcd (%)

for $C_{39}H_{63}N_3O_9$ (724.0): C 65.23, H 8.85, N 5.86; found: C 64.70, H 8.94, N 5.72.

4.2.7. *cis*,*cis*-1,3,5-Tris{[(benzyloxy)carbonyl]amino}cyclohexane (14). A solution of *cis*,*cis*-1,3,5-cyclohexane tricarboxylic acid (4.0 g, 18.5 mmol), diphenyl phophoryl azide (DPPA; 15.4 g, 56 mmol) and triethylamine (8 mL) in benzene (150 mL) was stirred for 30 min at room temperature to obtain *cis*,*cis*-1,3,5-cyclohexane tricarbonyl triazide in solution. Subsequently the solution was refluxed for 30 min till gas evolution stopped. Benzyl alcohol (6.4 mL) was added and the solution was refluxed for 18 h. Subsequently the mixture was cooled to 4 °C and the product was filtered off and washed with cold benzene, yielding **14** as a white powder (5.8 g, 10.9 mmol, 59%). ^{1}H NMR (DMSO-d_6): δ=7.32 (s, 15H), 4.98 (s, 6H), 3.05–3.00 (m, 3H), 1.87 (br p, 3H), 1.07 (br p, 3H); ^{13}C NMR (DMSO-d_6): δ=154.23, 136.16, 127.82, 127.33, 126.78, 64.14, 45.62, 39.74.

4.2.8. *cis*,*cis*-1,3,5-Triaminocyclohexane (15). Compound **14** (2.75 g, 5.2 mmol) was dissolved in 33% HBr/glacial acetic acid (18 mL, 24.9 g). The mixture was allowed to stand for 90 min under occasional stirring. Diethyl ether (100 mL) was added and the product was filtered off and washed with diethyl ether, yielding *cis*,*cis*-1,3,5-triaminocyclohexane·3HBr as a white powder (1.8 g, 4.83 mmol, 93%). ^{1}H NMR (DMSO-d_6): δ=8.16 (br p, 9H), 3.25 (br p, 3H), 2.22 (br p, 3H), 1.42 (br p, 3H); ^{13}C NMR (DMSO-d_6): δ=44.81, 32.80; ES/MS (MeOH) *m*/*z* 130.1 (M·3HBr +H$^+$).

Subsequently, *cis*,*cis*-1,3,5-triaminocyclohexane·3HBr (1.8 g, 4.83 mmol) was dissolved in water (15 mL) and 4 equiv of NaOH (0.8 g, 20.0 mmol) was added. The mixture was stirred for 18 h at room temperature and subsequently heated at reflux for 1 h. After cooling to room temperature, the product was extracted from the aqueous solution by a continuous extraction (48 h) with CH_2Cl_2 (downward displacement). The CH_2Cl_2 solution obtained was filtered and concentrated in vacuo, yielding **15** as a yellowish, crystalline solid (0.58 g, 4.50 mmol, 93%). ^{1}H NMR ($CDCl_3$): δ=2.90–2.59 (m, 3H), 1.98 (br d, ^3J=11.2 Hz, 3H), 0.89–0.92 (m, 3H).

4.2.9. *cis*,*cis*-1,3,5-Chex(U-L-Phe-*O*-octyl)$_3$ (16). To a solution of di-*tert*-butyl dicarbonate (0.83 g, 3.8 mmol) in dry CH_2Cl_2 (10 mL) was added successively a solution of 4-dimethylamino pyridine (44 mg, 0.36 mmol) in dry CH_2Cl_2 (3 mL) and a solution of **1** (1.0 g, 3.6 mmol) in dry CH_2Cl_2 (6 mL). The mixture was stirred for 30 min at room temperature till gas evolution stopped and subsequently *cis*,*cis*-1,3,5-triaminocyclohexane **15** (0.14 g, 1.1 mmol) in CH_2Cl_2 (5 mL) was added. The obtained turbid mixture was first stirred at room temperature for 30 min and then at 40 °C for 48 h. After cooling, the solvent was evaporated in vacuo. The residue was refluxed in ethanol and after cooling the solid was filtered off and washed with ethanol and diethyl ether, yielding **16** as a white powder (0.5 g, 0.48 mmol, 43%). Mp: >230 °C (dec); ^{1}H NMR (DMSO-d_6): δ=7.28–7.13 (m, 15H), 6.03 (br s, 6H), 4.40–4.33 (m, 3H), 3.98–3.94 (m, 6H), 3.35 (br p, 6H), 2.92–2.88 (m, 6H), 1.83 (br d, ^3J=8.8 Hz, 3H), 1.46 (br p, 6H), 1.22 (s, 30H), 0.84 (t, ^3J=6.4 Hz, 9H); ^{13}C NMR (DMSO-d_6, 80 °C): δ=172.01, 156.17, 136.79, 128.67, 127.73, 126.00, 63.91, 53.61, 45.38, 37.60, 30.70, 28.01, 27.65, 24.83, 21.53, 13.32; MS (ES): *m*/*z* 1061.7 [M+Na$^+$]$^+$, 1056.9 [M+NH$_4^+$]$^+$, 1039.8 [M+H$^+$]$^+$.

4.2.10. *cis*,*cis*-1,3,5-Chex(U-L-Leu-*O*-octyl)$_3$ (17). Compound **17** was synthesised following the same procedure as described for **16**, using di-*tert*-butyl dicarbonate (1.66 g, 7.6 mmol) in dry CH_2Cl_2 (10 mL), 4-dimethylamino pyridine (88 mg, 0.72 mmol) in dry CH_2Cl_2 (6 mL), **2** (1.75 g, 7.2 mmol) in dry CH_2Cl_2 (12 mL) and *cis*,*cis*-1,3,5-triaminocyclohexane **15** (0.284 g, 2.2 mmol) in CH_2Cl_2 (10 mL). After cooling, the solvent was evaporated in vacuo. The waxy residue was refluxed in ethanol and after cooling the obtained gel was filtered off and washed with ethanol and diethyl ether, yielding **17** as a white solid (0.94 g, 1.00 mmol, 45%). Mp: >215 °C (dec); ^{1}H NMR ($CDCl_3$+5% TFA): δ=4.46 (br p, 3H), 4.20 (t, ^3J=6.6 Hz, 6H), 3.68 (br p, 3H), 2.26 (br d, ^3J=11.0 Hz, 3H), 1.68–1.52 (m, 15H), 1.27 (s, 33H), 0.96–0.84 (m, 27H); ^{13}C NMR ($CDCl_3$+5% TFA): δ=175.84, 158.18, 67.51, 52.73, 46.55, 40.79, 37.41, 31.62, 28.98, 28.93, 28.04, 25.52, 24.69, 22.49, 22.20, 21.30, 13.85; IR (film, NaCl): $\tilde{\nu}$=3307 (N–H), 1744 (C=O, ester), 1639 (C=O, amide I), 1562 cm^{-1} (N–H, amide II); elemental analysis calcd (%) for $C_{51}H_{96}N_6O_9$ (937.4): C 65.35, H 10.32, N 8.97; found: C 65.05, H 10.44, N 9.33.

4.2.11. *cis*,*cis*-1,3,5-Cyclohexanetricarbonyl trichloride (18). *cis*,*cis*-1,3,5-Cyclohexane tricarboxylic acid (3.0 g, 13.9 mmol) was placed in a flask together with $SOCl_2$ (8 mL). The suspension was refluxed for 20 h, resulting in a clear solution. The remaining $SOCl_2$ was evaporated in vacuo, yielding **18** as a pale yellow oil that formed crystals upon standing at 4 °C (3.77 g, 13.9 mmol, 100%). ^{1}H NMR ($CDCl_3$): δ=2.95–2.64 (m, 6H), 1.80–1.60 (m, 3H); ^{13}C NMR ($CDCl_3$): δ=174.20, 52.06, 30.17.

4.2.12. *cis*,*cis*-1,3,5-Chex(Am-L-Phe-*O*-octyl)$_3$ (19). To a cooled solution of **1** (1.0 g, 3.6 mmol) and triethylamine (0.36 g, 3.6 mmol) in dry CH_2Cl_2 (20 mL) was added a solution of *cis*,*cis*-1,3,5-cyclohexane tricarbonyl trichloride **18** (0.33 g, 1.2 mmol) in dry CH_2Cl_2 (5 mL). The solution was slowly brought to room temperature and stirred for 20 h. Subsequently, the solution was extracted with dilute HCl (3×20 mL), water (2×20 mL), 10% aqueous sodium carbonate (3×20 mL), water (2×20 mL) and brine. The solution was dried over $MgSO_4$ and the solvent was evaporated in vacuo, yielding a sticky solid. Column chromatography (CH_2Cl_2/MeOH; 100:5) on silica gel yielded **19** (0.3 g, 0.3 mmol, 25%) as a white sticky solid. ^{1}H NMR ($CDCl_3$): δ=7.24–7.01 (m, 15H), 5.85 (d, ^3J=7.7 Hz, 3H), 4.84–4.79 (m, 3H), 4.09–4.01 (m, 6H), 3.12–3.04 (m, 6H), 2.09 (t, ^3J=12 Hz, 3H), 1.91 (d, ^3J=12 Hz, 3H), 1.54 (s, 9H), 1.23 (s, 30H), 0.83 (t, ^3J=6.6 Hz, 9H); ^{13}C NMR (DMSO-d_6): δ=174.16, 171.70, 137.30, 128.98, 128.12, 126.44, 64.37, 53.40, 42.09, 36.64, 31.20, 28.53, 27.98, 25.19, 22.05, 13.93; IR (hexane gel, NaCl): $\tilde{\nu}$=3286 (N–H), 1742 (C=O, ester), 1650 (C=O, amide I), 1550 cm^{-1} (N–H, amide II); elemental analysis calcd (%) for $C_{60}H_{87}N_3O_9$ (994.4): C 72.46, H 8.82, N 4.23; found: C 72.47, H 8.98, N 4.26.

4.2.13. *cis*,*cis*-1,3,5-Chex(Am-L-Leu-*O*-octyl)$_3$ (20). Compound **20** was synthesised following the same procedure as described for **19**, using **2** (2.0 g, 8.2 mmol), triethylamine (0.83 g, 8.2 mmol) and *cis*,*cis*-1,3,5-cyclohexane tricarbonyl trichloride **18** (0.74 g, 2.73 mmol). Column chromatography using an eluent gradient (CH_2Cl_2/MeOH; 200:5–200:10) on silica gel yielded **20** (1.06 g, 1.19 mmol, 44%) as a white sticky solid. ^{1}H NMR (DMSO-d_6): δ=8.11 (d, ^3J=7.7 Hz, 3H), 4.26–4.18 (m, 3H), 4.04–3.94 (m, 6H), 2.27 (t, ^3J=12.1 Hz, 3H), 1.69–1.35 (m, 21H), 1.23 (s, 30H), 0.88–0.80 (m, 27H); ^{13}C NMR (DMSO-d_6): δ=174.37, 172.69, 64.27, 50.17, 42.31, 31.19, 28.58, 28.50, 28.04, 25.24, 24.35, 22.73, 22.08, 21.21, 13.97; IR (solid, NaCl): $\tilde{\nu}$=3294 (N–H), 1736 (C=O, ester), 1644 (C=O, amide I), 1539 cm^{-1} (N–H, amide II); elemental analysis calcd (%) for $C_{51}H_{93}N_3O_9$ (892.3): C 68.65, H 10.51, N 4.71; found: C 68.86, H 10.76, N 4.72.

4.2.14. *cis*,*cis*-1,3,5-Chex(Am-Gly-*O*-octyl)$_3$ (21). Compound **21** was synthesised following the same procedure as described for **19**, using **3** (1.53 g, 8.2 mmol), triethylamine (0.83 g, 8.2 mmol) and *cis*,*cis*-1,3,5-cyclohexane tricarbonyl trichloride **18** (0.74 g, 2.73 mmol). After drying of the solution over $MgSO_4$ and evaporation of the solvent in vacuo, **21** was obtained as an analytically pure white solid (1.67 g, 2.4 mmol, 88%). Mp: >210 °C (dec); ^{1}H NMR (DMSO-d_6): δ=8.21 (t, 3H, ^3J=5.7 Hz), 4.00 (t, 6H, ^3J=6.6 Hz), 3.77 (d, 6H, ^3J=5.8 Hz), 2.27 (br t, 3H, ^3J=12.3 Hz), 1.77 (br d, 3H, ^3J=12.8 Hz), 1.53–1.24 (m, 39H), 0.84 (t, 9H, ^3J=6.6 Hz); ^{13}C NMR (DMSO-d_6): δ=174.63, 169.94, 64.28, 42.24, 40.56, 31.22, 28.59, 28.09, 25.29, 22.07, 13.95; IR (1-octanol gel, NaCl): $\tilde{\nu}$=1730 (C=O, ester), 1644 (C=O, amide I), 1548 cm^{-1} (N–H, amide II); elemental analysis calcd (%) for $C_{39}H_{69}N_3O_9$ (724.0): C 64.70, H 9.61, N 5.80; found: C 64.66, H 9.67, N 5.64.

4.2.15. *cis*,*cis*-1,3,5-Chex(Am-L-Phe-*NH*-octyl)$_3$ (22). To a cooled solution of **4** (1.0 g, 3.6 mmol) and triethylamine (0.36 g, 3.6 mmol) in dry CH_2Cl_2 (50 mL) was added a solution of *cis*,*cis*-1,3,5-cyclohexane tricarbonyl trichloride **18** (0.33 g, 1.2 mmol) in dry CH_2Cl_2 (5 mL). A viscous, turbid mixture was formed, which was slowly brought to room temperature and stirred for 20 h. The solvent was evaporated in vacuo, yielding a white solid. Stirring in ethanol to remove the $Et_3N\cdot HCl$ salts followed by filtration afforded **22** as a white powder (1.1 g, 1.11 mmol, 92%). Mp: >215 °C (dec); ^{1}H NMR ($CDCl_3$+5% TFA): δ=7.68 (d, ^3J=8.4 Hz, 3H), 7.24–7.05 (m, 15H), 6.59 (s, 3H), 4.73–4.65 (m, 3H), 3.17–3.11 (m, 3H), 3.00–2.90 (m, 9H), 2.31 (t, ^3J=11.5 Hz, 3H), 1.78 (d, $^2J_{AB}$=12.5 Hz, 3H), 1.45 (dt, $^2J_{AB}$=12.5 Hz, $^3J_{AB}$=11.5 Hz, 3H), 1.22–1.02 (m, 36H), 0.82 (t, ^3J=6.8 Hz, 9H); ^{13}C NMR ($CDCl_3$+5% TFA): δ=176.54, 172.17, 134.43, 128.92, 128.89, 127.69, 55.73, 42.59, 40.68, 38.20, 31.65, 30.12, 28.93, 28.89, 28.21, 26.39, 22.50, 13.83; IR (tetraline gel, NaCl): $\tilde{\nu}$=3285 (N–H), 1640 (C=O, amide I), 1541 cm^{-1} (N–H, amide II); elemental analysis calcd (%) for $C_{60}H_{90}N_6O_6$ (991.4): C 72.68, H 9.16, N 8.48; found: C 72.20, H 9.25, N 8.37.

4.2.16. *cis*,*cis*-1,3,5-Chex(Am-L-Leu-*NH*-octyl)$_3$ (23). Compound **23** was synthesised following the same procedure as described for **22**, using **5** (0.98 g, 4.0 mmol), triethylamine (0.36 g, 3.6 mmol) and *cis*,*cis*-1,3,5-cyclohexane tricarbonyl trichloride **18** (0.33 g, 1.2 mmol). The solvent was evaporated in vacuo, yielding a white waxy solid. Stirring in ethanol to remove the $Et_3N\cdot HCl$ salts followed by filtration afforded **23** as a white powder (0.62 g, 0.70 mmol, 58%). Mp: >230 °C (dec); ^{1}H NMR ($CDCl_3$+5% TFA): δ=7.60 (d, ^3J=8.1 Hz, 3H), 7.19 (s, 3H), 4.65–4.45 (m, 3H), 3.35–3.17 (m, 6H), 2.41 (t, ^3J=11.3 Hz, 3H), 1.98 (d, $^2J_{AB}$=12.1 Hz, 3H), 1.69–1.51 (m, 18H), 1.26 (s, 30H), 0.93–0.85 (m, 27H); ^{13}C NMR ($CDCl_3$+5% TFA): δ=176.13, 173.31, 52.41, 42.71, 40.58, 40.37, 31.58, 30.25, 28.94, 28.86, 28.38, 26.48, 24.64, 22.47, 21.97, 21.81, 13.86; elemental analysis calcd (%) for $C_{51}H_{96}N_6O_6$ (889.4): C 68.86, H 10.89, N 9.45; found: C 68.86, H 11.15, N 9.40.

4.2.17. *cis*,*cis*-1,3,5-Chex(Am-Gly-*NH*-octyl)$_3$ (24). Compound **24** was synthesised following the same procedure as described for **22**, using **6** (1.0 g, 5.37 mmol), triethylamine (0.54 g, 5.37 mmol) and *cis*,*cis*-1,3,5-cyclohexane tricarbonyl trichloride **18** (0.49 g, 1.8 mmol). The solvent was evaporated in vacuo, yielding a white waxy solid. Stirring in hot ethanol to remove the $Et_3N\cdot HCl$ salts followed by filtration afforded **24** as a white powder (0.94 g, 1.3 mmol, 72%). Mp: >210 °C (dec); ^{1}H NMR (DMSO-d_6, 80 °C): δ=7.65 (br t, ^3J=5.5 Hz, 3H), 7.46 (br s, 3H), 3.64 (d, ^3J=5.5 Hz, 6H), 3.09–3.02 (m, 6H), 2.29 (br t, ^3J=12.1 Hz, 3H), 1.88 (br d, ^2J=12.5 Hz, 3H), 1.48–1.19 (m, 39H), 0.86 (t, ^3J=6.4 Hz, 9H); ^{13}C NMR (DMSO-d_6, 80 °C): δ=174.06, 168.25, 42.37, 41.84, 38.23, 31.10, 30.77, 28.67, 28.23, 28.11, 25.95, 21.54, 13.33; elemental analysis calcd (%) for $C_{39}H_{72}N_6O_6$ (721.1): C 64.95, H 10.07, N 11.66; found: C 64.82, H 10.21, N 11.54.

4.3. Gelation experiments

In a typical gelation experiment a weighed amount of the compound under investigation and 0.5 mL or 1.0 mL of the solvent are placed in a closed 1.5 mL vial (∅12 mm). The vial was heated using a heating gun or a heating block until the solid had dissolved, unless the solvent started to reflux prior to dissolution. The solution was allowed to cool to room temperature and subsequently examined. Gelation was considered to have occurred when a homogeneous substance was obtained that exhibited no gravitational flow. The existence of a viscous solution was determined by eye.

4.4. Dropping ball measurements[21]

Gels with a volume of 1.0 mL were prepared as described above. A stainless steel ball (63 mg; ∅2.5 mm) was placed on top of the gel and the vial was closed. A series of these samples were placed in a heating block that was slowly heated (5 °C h^{-1}) while observing the positions of the balls with a video camera and concurrently monitoring the temperature by means of a thermocouple placed in the heating block. The melting temperature of the gel was taken as the temperature at which the steel ball reached the base of the flask. The upper temperature at which the apparatus could run was limited to 155 °C.

4.5. Differential scanning calorimetry (DSC)

For DSC measurements a weighted amount of solid together with a weighted amount of solvent was placed in a large

volume stainless steel DSC pan (for compound **19** a weighted amount of gel was used and the sealing Viton O-ring was not placed in the pan) and heated at 140 °C (**19**) or 175 °C (**16**, **22** and **24**) for 1 h, followed by cooling to 25 °C (cooling rate of 10 °C min^{-1}). After ageing for 5 h, heating and cooling scans were recorded on a Perkin–Elmer DSC 7 instrument from 25 °C up to 140 °C (**19**) or 175 °C (**16**, **22** and **24**) at a scan rate of 5 °C min^{-1}. For each sample two sets of heating and cooling scans were recorded, with an interval of 2–3 h.

4.6. Transmission electron microscopy

Gels were prepared as described above. Collidon- and carbon-coated 400 mesh copper grids were prepared, following standard procedures. A tiny piece of gel was carefully placed on a grid, dried at low pressure (<10–5 Torr) and shadowed with platinum (angle: 30°–40°, distance: ~15 cm). The samples were examined in a JEOL 1200 EX transmission electron microscope operating at 80 kV. First patches of gel were searched for, to be sure that the observed structures originate from the gel. Micrographs were taken from the periphery of the gel patches.

Acknowledgements

P. Oosting is acknowledged for preparing compounds **14**–**15**. Financial support from the Netherlands Organization for Scientific Research (NWO-CW) and BiOMaDe Technology Foundation is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.02.066.

References and notes

1. (a) Terech, P.; Weiss, R. G. *Chem. Rev.* **1997**, *97*, 3133; (b) van Esch, J.; Schoonbeek, F. S.; de Loos, M.; Veen, E. M.; Kellogg, R. M.; Feringa, B. L. *Supramolecular Science: Where It Is and Where It Is Going*; NATO ASI Series C: Mathematical and Physical Sciences; Kluwer Academic: Dordrecht, 1999; Vol. 527, p 233; (c) Abdallah, D. J.; Weiss, R. G. *Adv. Mater.* **2000**, *12*, 1237; (d) van Esch, J. H.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 2263; (e) Estroff, L.; Hamilton, A. D. *Chem. Rev.* **2004**, *104*, 1201; (f) de Loos, M.; Feringa, B. L.; van Esch, J. H. *Eur. J. Org. Chem.* **2005**, *17*, 3615; (g) *Molecular Gels*; Terech, P., Weiss, R. G., Eds.; Springer: New York, NY, 2006.
2. (a) Amanokura, N.; Yoza, K.; Shinmori, H.; Shinkai, S.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2585; (b) Yoza, K.; Amanokura, N.; Ono, Y.; Akao, T.; Shinmori, H.; Takeuchi, M.; Shinkai, S.; Reinhoudt, D. N. *Chem.—Eur. J.* **1999**, *5*, 2722; (c) Amanokura, N.; Kanekiyo, Y.; Shinkai, S.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1995; (d) Luboradzki, R.; Gronwald, O.; Ikeda, M.; Shinkai, S.; Reinhoudt, D. N. *Tetrahedron* **2000**, *56*, 9595; (e) Gronwald, O.; Sakurai, K.; Luboradzki, R.; Kimura, T.; Shinkai, S. *Carbohydr. Res.* **2001**, *331*, 307; (f) Gronwald, O.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1933; (g) Gronwald, O.; Shinkai, S. *Chem.—Eur. J.* **2001**, *7*, 4328; (h) Amaike, M.; Kobayashi, H.; Shinkai, S. *Chem. Lett.* **2001**, 620; (i) Jung, J. H.; Shinkai, S.; Shimizu, T. *Chem.—Eur. J.* **2002**, *8*, 2684; (j) Kobayashi, H.; Friggeri, A.; Koumoto, K.; Amaike, M.; Shinkai, S.; Reinhoudt, D. N. *Org. Lett.* **2002**, *4*, 1423; (k) John, G.; Jung, J. H.; Masuda, M.; Shimizu, T. *Langmuir* **2004**, *20*, 2060; (l) Asai, M.; Sugiyasu, K.; Fujita, N.; Shinkai, S. *Chem. Lett.* **2004**, *33*, 120.
3. (a) Hanabusa, K.; Yamada, M.; Kimura, M.; Shirai, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1949; (b) Hanabusa, K.; Shimura, K.; Hirose, K.; Kimura, M.; Shirai, H. *Chem. Lett.* **1996**, 885; (c) Kato, T.; Kondo, G.; Hanabusa, K. *Chem. Lett.* **1998**, 193; (d) Kato, T.; Kutsuna, T.; Hanabusa, K.; Ukon, M. *Adv. Mater.* **1998**, *10*, 606; (e) Inoue, K.; Ono, Y.; Kanekiyo, Y.; Hanabusa, K.; Shinkai, S. *Chem. Lett.* **1999**, 429; (f) Hanabusa, K.; Maesaka, Y.; Suzuki, M.; Kimura, M.; Shirai, H. *Chem. Lett.* **2000**, 1168; (g) Hanabusa, K.; Nakayama, H.; Kimura, M.; Shirai, H. *Chem. Lett.* **2000**, 1070; (h) Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Chem.—Eur. J.* **2003**, *9*, 348; (i) Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Helv. Chim. Acta* **2004**, *87*, 1; (j) Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Tetrahedron Lett.* **2004**, *45*, 2947.
4. (a) Menger, F. M.; Venkatasubban, K. S. *J. Org. Chem.* **1978**, *43*, 3413; (b) Menger, F. M.; Yamasaki, Y.; Catlin, K. K.; Nishimi, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 585; (c) Menger, F. M.; Caran, K. L. *J. Am. Chem. Soc.* **2000**, *122*, 11679.
5. (a) van Esch, J.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron Lett.* **1997**, *38*, 281; (b) van Esch, J.; De Feyter, S.; Kellogg, R. M.; De Schryver, F.; Feringa, B. L. *Chem.—Eur. J.* **1997**, *3*, 1238; (c) van Esch, J.; Schoonbeek, F.; de Loos, M.; Kooijman, H.; Spek, A. L.; Kellogg, R. M.; Feringa, B. L. *Chem.—Eur. J.* **1999**, *5*, 937; (d) Schoonbeek, F. S.; van Esch, J. H.; Wegewijs, B.; Rep, D. B. A.; de Haas, M. P.; Klapwijk, T. M.; Kellogg, R. M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1393; (e) Schoonbeek, F. S.; van Esch, J. H.; Hulst, R.; Kellogg, R. M.; Feringa, B. L. *Chem.—Eur. J.* **2000**, *6*, 2633; (f) de Loos, M.; Ligtenbarg, A. G. J.; van Esch, J.; Kooijman, H.; Spek, A. L.; Hage, R.; Kellogg, R. M.; Feringa, B. L. *Eur. J. Org. Chem.* **2000**, 3675; (g) Brinksma, J.; Feringa, B. L.; Kellogg, R. M.; Vreeker, R.; van Esch, J. *Langmuir* **2000**, *16*, 9249; (h) de Loos, M.; Friggeri, A.; van Esch, J.; Kellogg, R. M.; Feringa, B. L. *Org. Biomol. Chem.* **2005**, *3*, 1631.
6. (a) van Bommel, K. J. C.; van Esch, J. H.; de Loos, M.; Heeres, A.; Feringa, B. L. Pat. Appl. WO 03/097587, 2002; (b) Heeres, A.; van der Pol, C.; Stuart, M.; Friggeri, A.; Feringa, B. L.; van Esch, J. *J. Am. Chem. Soc.* **2003**, *125*, 14252; (c) van Bommel, K. J. C.; van der Pol, C.; Muizebelt, I.; Friggeri, A.; Heeres, A.; Meetsma, A.; Feringa, B. L.; van Esch, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1663.
7. Fan, E.; Yang, J.; Geib, S. J.; Stoner, T. C.; Hopkins, M. D.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1995**, 1251.
8. (a) Hanabusa, K.; Kawakami, A.; Kimura, M.; Shirai, H. *Chem. Lett.* **1997**, 191; (b) Shikata, T.; Ogata, D.; Hanabusa, K. *J. Soc. Rheol. Jpn.* **2003**, *31*, 229.
9. Lightfood, M. P.; Mair, F. S.; Pritchard, R. G.; Warren, J. E. *Chem. Commun.* **1999**, 1945.
10. (a) Hanabusa, K.; Koto, C.; Kimura, M.; Shirai, H.; Kakehi, A. *Chem. Lett.* **1997**, 429; (b) Ogata, D.; Shikata, T.; Hanabusa, K. *J. Phys. Chem.* **2004**, *108*, 15503.

11. Yasuda, Y.; Iishi, E.; Inada, H.; Shirota, Y. *Chem. Lett.* **1996**, 575.
12. van Gorp, J. J.; Vekemans, J. A. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **2002**, *124*, 14759.
13. Yamada, N.; Okuyama, K.; Serizawa, T.; Kawasaki, M.; Oshima, S. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2707.
14. March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, NY, 1992; p 903.
15. According to personal experience, see also: Curtius, T. *J. Prakt. Chem.* **1916**, *91*, 88.
16. March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, NY, 1992; pp 1091–1092.
17. Knölker, H.-J.; Braxmeier, T. *Synlett* **1997**, 925.
18. Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552.
19. For π–π-stacking effects in related aggregating C_3-symmetric compounds see Refs. 7 and 12.
20. de Loos, M.; van Esch, J.; Kellogg, R. M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 613.
21. Takahashi, A.; Sakai, M.; Kato, T. *Polym. J.* **1980**, *12*, 335.
22. Due to the absence of the O-ring, the DSC pans are less well sealed and thus less able to resist the building up of pressure upon heating the solvent. Because of the resulting slight leakage the base of the curve is not straight.
23. Jadżyn, J.; Stockhausen, M.; Żywucki, B. *J. Phys. Chem.* **1987**, *91*, 754.
24. Fibre morphology is often solvent dependent; see e.g., cyclohexane bis-urea gelators (Ref. 5c).