Self-Inclusion of Proline-Functionalised Calix[4]arene Leads to Hydrogelation

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Solution-phase and solid-state structural studies indicate that the remarkable hydrogelation properties of a proline-functionalised calix[4]arene emerge as a result of extended helical structures formed via inclusion of a proline moiety in a neighbouring calixarene cavity.

The majority of reported examples of gelators involve polymeric systems. More recently, low molecular weight gelators have been of interest, because the supramolecular interactions that cause gelation are reversible, and can respond to specific stimuli, opening up a range of possible applications. 1,3 The relatively simple structure of the molecular gelator, compared to a polymer, also makes design of the system a more tractable, but still a very challenging problem.4 with the aim being to drive the anisotropic aggregation required to form the fibrous structures observed in many gels. 5 The properties of the resulting gels can be readily tuned, particularly when using multi-component systems, 6,9 or by adding or changing additives such as simple ions. 10-14 We have previously described the electrolyte-triggered hydrogelation behaviour of the first calixarene-based hydrogelator, proline-functionalised calix[4]arene 1. 15 While we were unable to propose a detailed mechanism for the anisotropic aggregation of this system, it was shown that the gel formation was controlled by both electrolyte concentration and composition, as well as pH. Zhang et al. very recently reported that 1 will also form hydrogels in the presence of basic amino acids under neutral to acidic conditions. 16 We now report a possible mechanism of assembly that provides the structural information required to refine the properties of this unique hydrogelator. We also demonstrate that the chirality of the molecule has a direct impact on the bulk properties of the hydrogel formed.

calix[4]arene was functionalised with D-proline, following the previously reported synthetic procedure. 15 As expected the gelation properties were found to be identical to those of the L-proline calix[4]arene. Racemic mixtures, in contrast, were found to have lower Tgel values, consistent with observations reported previously for dendritic peptides, 18 and other (but not all 17) racemates, 19 reaching a minimum at the 1:1 ratio of D and L isomers (Figure S1). The reduction in Tgel was found to be ~10 °C for gels formed by the addition of lanthanum nitrate, by both the dropping ball, and flask inversion methods. 7 Atomic force microscopy of the wet gels, on mica, revealed that the fibrous structure of the gels was significantly altered in the racemate, consistent with the changes observed in bulk properties (Figure 1). The racemate appears to form linked spheroidal structures, whereas the pure chiral systems form more elongated fibrous structures.

The impact of chirality upon gelation processes has been reviewed recently. 17 To probe the importance of chirality in 1, calix[4]arene was functionalised with D-proline, following the previously reported synthetic procedure. 15 As expected the gelation properties were found to be identical to those of the L-proline calix[4]arene. Racemic mixtures, in contrast, were found to have lower Tgel values, consistent with observations reported previously for dendritic peptides, 18 and other (but not all 17) racemates, 19 reaching a minimum at the 1:1 ratio of D and L isomers (Figure S1). The reduction in Tgel was found to be ~10 °C for gels formed by the addition of lanthanum nitrate, by both the dropping ball, and flask inversion methods. 7 Atomic force microscopy of the wet gels, on mica, revealed that the fibrous structure of the gels was significantly altered in the racemate, consistent with the changes observed in bulk properties (Figure 1). The racemate appears to form linked spheroidal structures, whereas the pure chiral systems form more elongated fibrous structures.

Fig. 1. Atomic force micrographs of (1 + lanthanum nitrate) hydrogels deposited as thin films on mica and imaged immediately. (a) L-isomer, (b) D-isomer, and (c) DL-racemic mixture.
Racemic mixtures are also reported to crystallise more readily than the pure enantiomers, in some cases not forming gels at all.\(^1\) In the present case, the racemic gels were found to be less stable than the enantiomerically pure systems, tending to collapse and crystallise over a period of days, rather than remaining stable for months as in the case of the enantiomerically pure samples. The crystals that formed in one case were of sufficient quality to carry out an X-ray structure determination.\(^2\)

The resulting X-ray structure provides a fascinating insight into possible structural features of the fibrous network formed by this molecule. The previously reported structure of L-1 showed a typical layered structure, with the calixarene cavity occupied by two 1,3-disposed proline substituents, turning 'inwards' in such a way that the carboxylate O atoms were at a distance (2.47 Å) consistent with a strong intramolecular hydrogen bond.\(^10\) This structure did not, however, provide any indication of how anisotropic assembly might develop. In contrast, the present structure shows intermolecular inclusion of a proline moiety into the cavity of a neighbouring calixarene which results in the formation of a helical structure (Fig. 2). Each helical structure is formed by a single enantiomer, either the D- or L-isomer, indicating that the individual enantiomers could form comparable structures, as the fundamental unit from which larger fibres, and fibre bundles, are formed.

Looking at the structure in more detail, the lanthanum cations bridge two supramolecular helices to form a 2-dimensional coordination polymer. The La atom is bonded to both the carboxylate oxygen atoms of proline 24 and also to both of these atoms of the centrosymmetrically related molecule (Fig. 3). The La atom is also bonded to the carboxylate oxygen O141 of the molecule related by a cell translation along the 6 direction. The polymeric sheets are packed in the unit cell with the proline group (4) of the sheet inserted into the calixarene cavity related by a 2-fold screw axis (Fig. 4). A key feature is that the La ions are bridging two helices, each of which are formed from only one of the isomers, i.e. the La bridges a helix of D-1 with a helix of L-1.

It is notable that the lanthanum atom position appears to be not fully occupied, and that no nitrate anions could be located in the lattice. This causes some difficulty in determining the protonation state of both calixarene and coordinated and free water molecules. It may be that charge balance is achieved by deprotonation at N441\(^+\) and/or water molecules. The presence of a highly disordered nitrate anion that could not be specifically modelled, however, cannot be ruled out.

Proton NMR studies of 1 alone in D\(_2\)O show broadening as a function of concentration, suggesting that the strands observed in the solid-state may be forming spontaneously in solution as the concentration is increased (Figure S2).\(^7\) These structures are thermally reversible, shown through a high temperature VT-NMR study (Figure S3). Introduction of lanthanum nitrate results in peak broadening at lower concentrations, consistent with the electrolyte-triggered hydrogelation reported previously (Figure S4).\(^13\) It is notable that less than an equivalent of La is needed to result in significant broadening of the NMR spectra (Figure S5).

While the nitrate anion could not be located, or was not present, in the lattice, the structure reported here nevertheless...
provides critical information that allows us to propose a gelation mechanism for this system. Our previous work showed a strong relationship with the anion introduced as the electrolyte trigger. Nitrate favoured gelation strongly, for example, whereas sulfate salts did not form a gel under any conditions. This behaviour was suggested to be related to the Hofmeister or Common Ion Effect. The nature of the cation had a moderating influence on the gel formation process. The results reported here lead us to propose a gelation mechanism that commences with spontaneous assembly of I in water as helical strands. Added metal cations may then link these strands together to form more robust fibres. Gels formed in the presence of acids or organic cations may involve similar structures linked by hydrogen bonds. Finally, the anion present plays the dominant role in determining how these fibres aggregate to form extended bundles, and ultimately a network that stabilises a gel.

Conclusions

A possible mechanism of hydrogelation for the unique gelator I has been proposed, based on solution and solid-state studies. The results obtained will enable further structural development and diversification of this class of hydrogelator, and suggests ways to disrupt and/or control the gel formed (by adding hydrophobic guests for example). Further work is underway studying the solution-phase behaviour in more detail, as well as characterisation of the gels using SAXS and cryo-TEM to complement the atomic force microscopy results.

Notes and references

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† Electronic Supplementary Information (ESI) available; X-ray structural data of La(DL-1); CCDC 815038 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. See DOI: 10.1039/b000000x/

‡ Crystal data for La(DL-1): C$_{28}$H$_{57.52}$La$_{0.40}$N$_{0.18}$O$_{38.80}$, $M = 1111.11$, monoclinic, space group $C2/c$, $Z = 8$, $a = 35.5856(13)$, $b = 9.6028(3)$, $c = 35.8812(9)$ $\AA$, $\beta = 99.056(3)^\circ$, $V = 12108.5(7)$ $\AA^3$, $\mu = 0.363$ mm$^{-1}$, $\rho_a = 1.219$ Mg m$^{-3}$, $T = 100(2)$ K. Absorption $T_{	ext{max.min}} = 1.00/0.81$, $\theta_{	ext{max}} = 25.00^\circ$. Total reflections 22605, unique 10435 ($R_{int} = 0.050$), $R_1 = 0.112$ ($I/2I_0$), $wR_2 = 0.374$ (all data). La1 was also modelled as being disordered about an inversion centre with site occupancy refining to 0.385(2) (see also Table S1). Two coordinated water molecules were assigned occupancies constrained to that of the La1 atom. Hydrogen atoms were located on three proline N atoms. Since no hydrogen atom was located on N441 nor did there appear to be an associated water molecule suitable for hydrogen bonding, this hydrogen atom was not included in the model. The program Squeeze$^{21}$ was used to effectively remove electron density which could not be modelled as solvent or anions. See Tables S1 and S2 for more details.


