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A family of simple benzene 1,3,5-tricarboxamide (BTA) aromatic carboxylic acid hydrogels†

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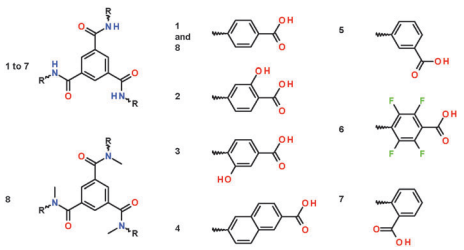
We present the characterisation of a hydrogel forming family of benzene 1,3,5-tricarboxamide (BTA) aromatic carboxylic acid derivatives. The simple, easy to synthesise compounds presented here exhibit consistent gel formation at low concentrations through the use of a pH trigger.

There are an ever increasing number of families of hydrogel forming low molecular weight gelators (LMWGs). Examples include the peptides functionalised with napthyl, FMOC or BOC groups; many varieties of small molecule peptides; the cholesterol family; the sugar-based gelators; and cyclohexyl bisamide-, trisamide- and bisurea-compounds.[1] All of these hydrogelators have proven to be incredibly interesting and applicable, especially as alternatives to conventional biological and synthetic polymers. Applications in drug delivery, cell growth media, crystal growth media, energy capture, and microelectronics are universally recognised as being future technology uses for these materials.[1,2] Even with the large variety in chemical functionality available for material design and applications, there is still a need to increase the chemical and physical variety within the building blocks for these soft materials. When trying to design a new family of hydrogels, the use of a chemically robust principal self-assembly moiety is required that can be easily and systematically modified to vary the properties of the materials.[3] When selecting this moiety we turned to a well-studied supramolecular assembly chemistry in the form of the C_3 symmetric benzene 1,3,5-tricarboxamide (BTA) motif.[4] Not only does it provide a robust supramolecular motif, it can be easily varied chemically in the form of the outer functionality (Scheme 1). This moiety is also structurally similar to the archetypical cyclohexyl triamide gelators that were introduced a decade ago by Feringa and van Esch.[5] Recent work on hydrogels based on N-protected peptides has shown how the carboxylic acid protonation and salt formation can act as a predictable trigger between solvated species, the salt form, and a self-assembled insoluble material, the protonated form. This led us to utilise BTA compounds with peripheral aromatic carboxylic acids. This design strategy for the hydrogel family was confirmed recently as having good potential in a recent publication by Schmidt and Albuquerque.[6] We have thus synthesised a series of compounds, tested their gelation ability and characterised the hydrogels.



Scheme 1 The eight compounds utilised in this study.

The eight compounds, **1–8**, utilised in this study (Scheme 1) were synthesised through the reaction between 1,3,5-benzenetricarbonyl trichloride and the corresponding amino aromatic carboxylic acid in THF and an excess of triethylamine (see ESI† for details). All compounds were synthesised in good yields and as crystalline white solids. They were found to be insoluble in deionised water. However, upon the addition of three equivalents of NaOH the materials dissolved, except for compound **7**, which is insoluble even at pH 12. Addition of small amounts of acid in the form of dilute HCl resulted in gelation of compounds **1–5** (Fig. 1).

Compound **8** formed a precipitate upon the decrease in pH and was therefore not found to form a gel. This implies that the hydrogen bonding between the amides is crucial to gel formation. In the case of compound **6**, no precipitate or gel was observed at any pH. Upon standing for several weeks, crystallisation of trimesic acid occurred. This suggests that the increased hydrolysis potential of the amide bond, due to the electron-withdrawing fluorine groups in compound **6**, has resulted in an unstable compound.

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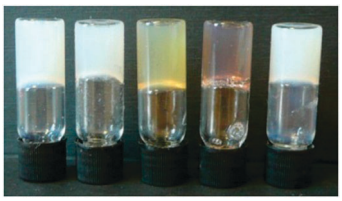

Fig. 1 Photographs of the gels formed by, from left to right, compounds **1** to **5**.

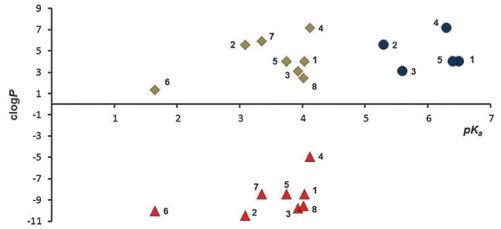

Fig. 2 Graph showing calculated pK_a and *c* log *P* values for the compounds utilised in this study, firstly comparing *c* log *P* values of neutral (green ◇) and tri-anionic species (red △) against calculated pK_a values. Secondly, calculated neutral *c* log *P* values against measured apparent pK_a values (blue ○) for the five gelators.

The gels formed by the addition of HCl were found to be inhomogeneous materials. For this reason, we utilised the gelators as salts, which are easily precipitated from water at high pH, and that are soluble in neutral water. Homogenous gelation followed when the addition of three equivalents of glucono-δ-lactone was used as a substitute for the HCl (see ESI† for details).[7] This method has been successfully utilised in a number of studies of dipeptide gelators and indeed for the gelation by **1** as described in the paper by Schmidt and Albuquerque.[6,7] The pH at which the gelation occurs is an important variable in these materials, especially in terms of the possible biological applications.[7] We thus determined the apparent pK_a of the gelators and compared these to predicted values for the hydrophobicity (*c* log *P*) and pK_a (Fig. 2).[8] Two points of interest can be found from this data. Firstly, upon deprotonation the hydrophobicity of the compounds decreases significantly allowing for the solubilising of the compounds and the desolvation upon protonation. It would be of importance to see if this type of analysis could be utilised to predict other types of chemical triggers for gelation, such as chemical fuels.[9] The second point of interest is that the predicted pK_a are, on average, 2.2 values lower than the measured apparent pK_a values. This has been noted in the dipeptide compounds calculations and measurements, and is due to the assembly process creating hydrophobic character affecting the pK_a's of the compound, a process well known in proteins.[8]

The behaviour of the fibres of the gels when exposed to mechanical stress was investigated using rheometry (Table 1, see ESI† for details, Fig. S9–S23).[10] Frequency sweep rheometry with a small amplitude stress, revealed the solid-like nature of the gels at 20 °C with the storage modulus, G', being typically an order of magnitude greater than the loss modulus, G''. The G' values were consistent over a wide range of frequencies. This viscoelastic behaviour is associated with classical gels and therefore supports the notion that the change in pH of these samples, which caused a change from a clear solution to a solid-like material, indeed resulted in a true gel state. The non-linear rheological response was investigated using stress sweep experiments, during which an oscillatory torque was

Table 1 Rheology characteristics of gels at 1% by weight

Compound	G' (Pa)	G'' (Pa)	Yield stress (μNm)	CGC[a] (by weight%)
1	4000	230	1100	0.2
2	1150	50	2500	0.1
3	9200	390	12 700	0.1
4	13 500	400	1000	0.1
5	470	50	800	0.2

[a] Critical gel concentration.

imposed with a fixed frequency (1 Hz) over a range of shear stress amplitudes. The gels showed a typical G' value, essentially constant below the critical value of oscillatory torque ("*yield stress*"). At this *yield stress* point, the sample starts to flow. From these experiments it is clear that the rheology defined "strengths" of the gels are in the order 3–4 > 1–2 > 5 (Table 1). Kinetic information can be obtained from the rheological data. We utilised the storage modulus temporal changes to follow the kinetics of all five gelators.[11] As it is well known that the formation of the fibrous networks result from nucleation and growth mechanisms, we applied the Avrami equation to the kinetics of gel formation.[11] These analyses resulted in determination of Avrami constants, which can be interpreted in terms of both a nucleation and growth mechanism, and as a fractal dimension.[11]

In this work we have interpreted the data in terms of the Avrami constant. We determined the Avrami constant, with an error of approximately 0.1, for each of the gels to be 1.9, 2.0, 1.7, 1.0 and 1.9 for the gels **1** to **5**, respectively. We can thus suggest the gelation mechanism for compound **1**, **2**, **3** and **5** to be based on *homogeneous spontaneous nucleation*, *interfacial control*, and *one-dimensional growth*. Compound **4**, with an Avrami constant of 1.0, thus shows a gelation mechanism based on *heterogeneous nucleation*, *interfacial control*, and *one-dimensional growth*. Further studies are currently being performed to establish the reasons behind these differences, these are most likely connected to the level of supersaturation.[11b] A concentration study of the rheology of compound **1** shows the relationship between concentration and strength of the gel, in the form of the *yield stress*, to be *yield stress* $\propto$ *concentration*$^{1.82}$. This indicated that the gel conforms to the cellular solid model and not a colloidal gel description.[12] The cellular solid model describes an open-cell cellular material which consists of load bearing struts interconnected *via* crosslinks or junction points which deform by bending. These two rheology-based results, the Avrami constant and the concentration $\propto$ yield stress relationship indicate growth of one-dimensional supramolecular fibres following nucleation, which results in a cellular solid gel matrix. This was confirmed by the cryo-SEM and TEM analysis of the materials, as shown in Fig. 3 (ESI,† Fig. S3–S8). All samples were found to have a fibrous gel matrix with fibre width diameters of approximately 50–200 nm.

Electron diffraction analysis of the samples showed that the fibres are amorphous with no distinct diffraction spots. However, there is a recognisable halo ring in all the samples analysed, which gives *d* spacings (3% error) of 3.39 Å, 3.41 Å, 3.48 Å, 3.41 Å and 3.50 Å for compounds **1** to **5**, respectively. The powder diffraction patterns for the dried gels showed a similar characteristic broad reflection at 3.47 Å, 3.38 Å, 3.44 Å, 3.41 Å and 3.50 Å for compounds **1** to **5**, respectively (ESI,† Fig. S2). A comparison of the recently reported crystal structure of compound **1**, several other BTA crystal structures and with the *d* spacings found from the gel materials gives evidence

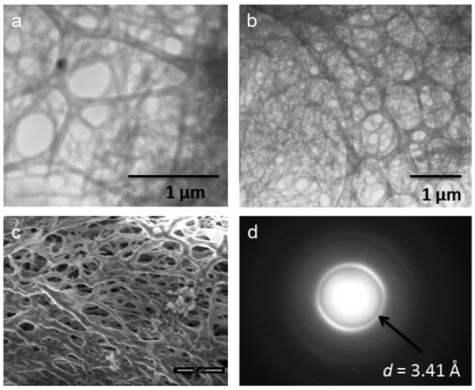

Fig. 3 (a) TEM image showing the fibrous nature of the 1% by weight hydrogel synthesised with compound **2**. Image is slightly out of focus to highlight the gel fibres. (b) TEM image showing the fibrous network of the 1% hydrogel of compound **1**. (a) and (b) The regular darker carbon grid can be seen in both images. (c) Cryo-SEM image showing the fibrous nature of the 1% by weight hydrogel of compound **1**. (d) Electron diffraction of the hydrogel of compound **2** showing the halo ring with a 3.41 Å *d* spacing.

of the packing of molecules in the gel fibres.[13] The *d* spacing distances provided above for the five gelators are similar to the average hydrogen bonding stacking distance 3.64 ± 0.1 Å for the structured examples. The stacking distance of the crystal structure of **1** is considerably shorter at 3.16 Å due to there being no hydrogen bonding between amide groups (ESI,† Fig. S24). The stacking distances found for these gelators, thus indicates that the amide–amide hydrogen bonding is indeed occurring and is complemented by π–π interactions.

In summary, we have shown that there is considerable potential in the hydrogel formation of a family of simple BTA aromatic carboxylic acids. The compounds show *spontaneous nucleation*, *interfacial control*, and *one-dimensional growth* kinetics which results in the molecules stacking into fibres through π–π interactions and amide–amide hydrogen bonding, with these fibres forming a gelatinous network. Further studies currently being done in our laboratory on these materials include researching their potential for drug delivery, cell growth and energy transfer, and analysing their structural characteristics.

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