Structural diversity in 1D hydrogen-bonded chains assembled through bis(triazole) self–association

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We show that simple phenyl-1,3-bis(triazole) groups dimerise in solution. Dimerisation in $CDCl_3$ is too strong to measure by ^1H NMR spectroscopy, and dimerisation in 9:1 $CDCl_3$:d_6-acetone is relatively strong ($K_{dimerisation}$ = 1361 ± 65 M^{-1}). A ditopic compound **1** containing two bis(triazole) groups crystallises to give hydrogen-bonded chains. Four different crystal structures were obtained, all of which are 1D chains, and all of which contain small solvent-filled channels. While the overall structure and packing are similar, diversity in the hydrogen bonding arrangements is observed due to the possibility of the triazole groups adopting either *syn* or *anti* conformations.

Introduction

Self–association, where molecules interact favourably with themselves giving dimeric, oligomeric or polymeric assemblies is critically important in biological systems and in supramolecular chemistry.[1,2] Within synthetic self–assembled systems, self–recognition can give discrete assemblies[3–6] or can be used to form extended structures including one-dimensional polymeric systems,[7–12] or three-dimensional crystalline hydrogen-bonded frameworks.[13–17]

While numerous types of intermolecular interactions have been used to control self–association, hydrogen bonding is particularly prevalent. Unsurprisingly this has tended to focus on hydrogen bonding mediated by N–H and to a lesser extent O–H hydrogen bond donors, as these are synthetically accessible and give relatively strong interactions. C–H hydrogen bond donors typically give relatively weak interactions, although when paired with electronegative groups these can be made significantly stronger, and they have been exploited for anion recognition applications.[18–21] While C–H hydrogen bonding interactions have received less attention in the context of self–association, some work has demonstrated their efficacy.[22–28]

Of relevance to the current work, Byrne and Gunnlaugsson have demonstrated that the 2,6-bis(triazolyl)pyridine (**btp**) motif[29] (Figure 1) can self–recognise through C–H···N interactions, and have used this self–recognition to prepare [2]catenanes.[25,27] In these structures, all triazole groups have an *anti* arrangement relative to the central pyridyl rings (Figure 1 inset), and all four triazole C–H hydrogen groups form hydrogen bonds with the pyridine nitrogen atoms. The related phenylene-1,3-bis(triazole) motif, which contains a central phenyl group in place of the pyridyl group in **btp** is a commonly-used scaffold, and has been demonstrated to interact with both anions and transition metal cations.[18,30–33] However, to the best of our knowledge, it has not been reported to self–associate, and none of the crystal structures containing it show strong evidence of self–association.

In this work, we demonstrate that the phenylene-bis(triazole) motif self–associates relatively strongly in solution. We show that compound **1**, which contains two bis(triazole) motifs persistently self–associates in the solid state to give 1D hydrogen-bonded tape crystal structures.

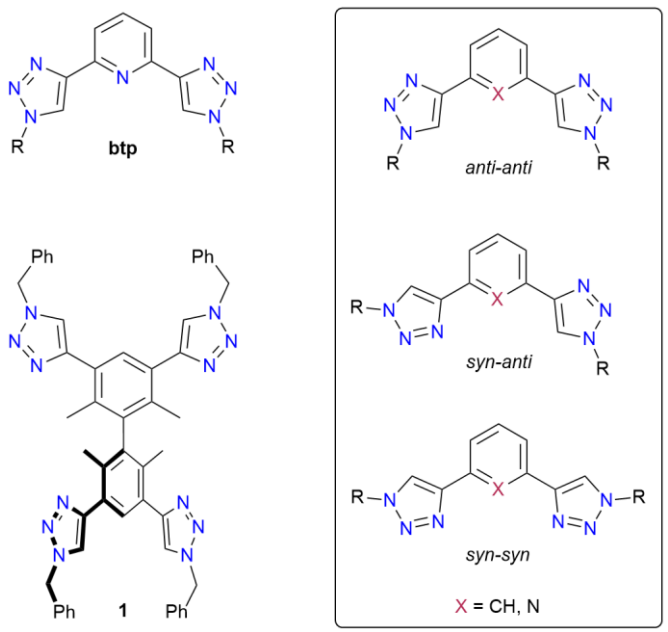


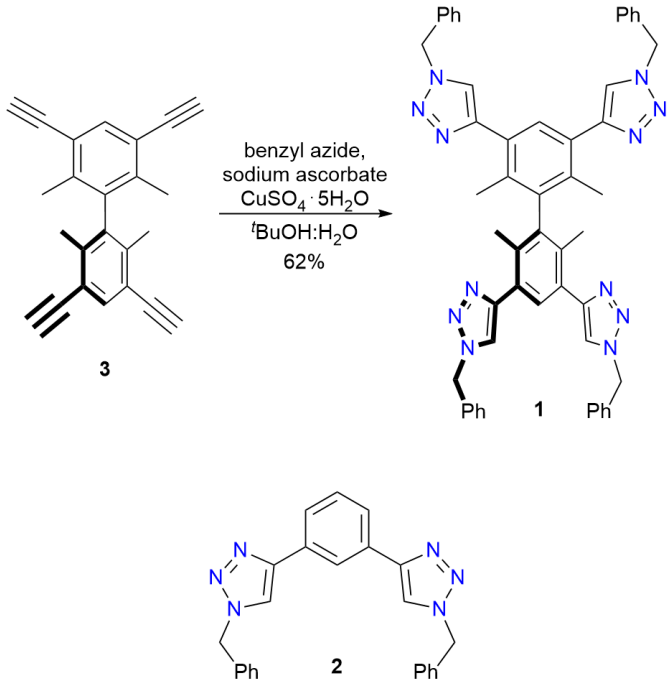
Figure 1 Structure of the bis(triazolyl)pyridine (**btp**) motif and of **1**, which contains two phenylene-bis(triazole) motifs. A representation of the possible conformation of triazole groups in these kinds of compounds is shown inset.

Results and discussion

Design and synthesis of 1

We initially designed **1** to interact with hydrogen bond acceptors such as anions, with the aim of using these interactions to assemble hydrogen-bonded materials. As such, we incorporated methyl groups into the structures to try and preorganise the triazole groups into an *anti-anti* conformation through steric effects. We have previously found that rotation of the triazole groups caused a loss of predictability in crystal engineering studies with related systems,[34] and that this tetramethyl biphenyl scaffold favours the formation of open structures in halogen-bonded systems.[35] In this case, our attempt at preorganisation was largely unsuccessful, as both *syn* and *anti* conformations are observed in X-ray crystal structures (see later).

In order to prepare **1**, known tetra-alkyne **3** was synthesised following literature procedures.[36] A copper(I)-catalysed azide alkyne cycloaddition reaction of this with benzyl azide gave compound **1** containing two bis(triazole) motifs (Scheme 1). This was obtained in 62% yield after purification by column chromatography, and characterised by ^{1}H and ^{13}C NMR spectroscopy and high resolution ESI mass spectrometry. Model bis(triazole) compound **2** was prepared following literature procedures.[31]



Scheme 1 Synthesis of **1** and structure of model compound **2**.

Solution self–association properties of model compound 2

We initially tried to crystallise **1** with guest molecules to form hydrogen-bonded assemblies, however X-ray crystal structures (see later) showed that **1** did not co-crystallise with these intended guests but instead hydrogen bonded with itself. To gain more information about the strength of this interaction, we studied the self–association of the simple bis(triazole) compound **2** in solution using ^{1}H NMR dilution experiments. While **2** is not a perfect model for **1** due to the lack of the methyl groups (which may affect the conformational preference of the triazole groups), this compound is significantly easier to prepare than such a methyl-containing compound. We initially studied association in d_6-acetone, and separately in $CDCl_3$; however, in each case no significant spectral changes were observed across a wide concentration range (Figures S3 and S4). In contrast, when the concentration of **2** in 9:1 v:v $CDCl_3$:d_6-acetone was varied from 0.25 to 25 mM, significant changes were observed for all three resonances on the central phenylene group of **2** as well as the triazole proton resonance (Figure 2). The biggest shifts are seen for the interior phenylene proton resonance 3 and triazole resonance 1 (0.39 and 0.34 ppm change from 0.25 to 25 mM, respectively), while the exterior phenylene proton resonances show smaller shifts (0.13 and 0.06 ppm).

All of these peaks move to higher ppm values at lower concentration. These shifts are consistent with a dimeric form dominating at high concentrations, with the protons at relatively low ppm values due to shielding from aromatic stacking. On dilution this form breaks apart, the stacking interactions are lost, and the peaks move to higher chemical shift values. Global fitting of the movement of the interior phenylene peak and triazole peaks in *Bindfit*[37] gave $K_{dimerisation}$ of 1361 ± 65 M^{-1}.[38] It appears that no significant peak movement is observed in either pure $CDCl_3$ or pure d_6-acetone because association is too strong in $CDCl_3$ and too weak in d_6-acetone to be affected substantially by concentration. That is, as far as can be determined by ^{1}H NMR spectroscopy **2** remains aggregated in $CDCl_3$ even at concentrations as low as 0.25 mM, while in more competitive d_6-acetone no evidence of dimerisation is detected even at 25 mM. While this interaction may not sound particularly strong, we note that it is significantly stronger than the dimerisation of 2-pyridone, which is 63% dissociated at 2.0 mM concentrations in chloroform.[39] Despite this relatively weak interaction, the 2-pyridone self–recognition motif has been used to prepare a range of porous three-dimensional frameworks.[14,40]

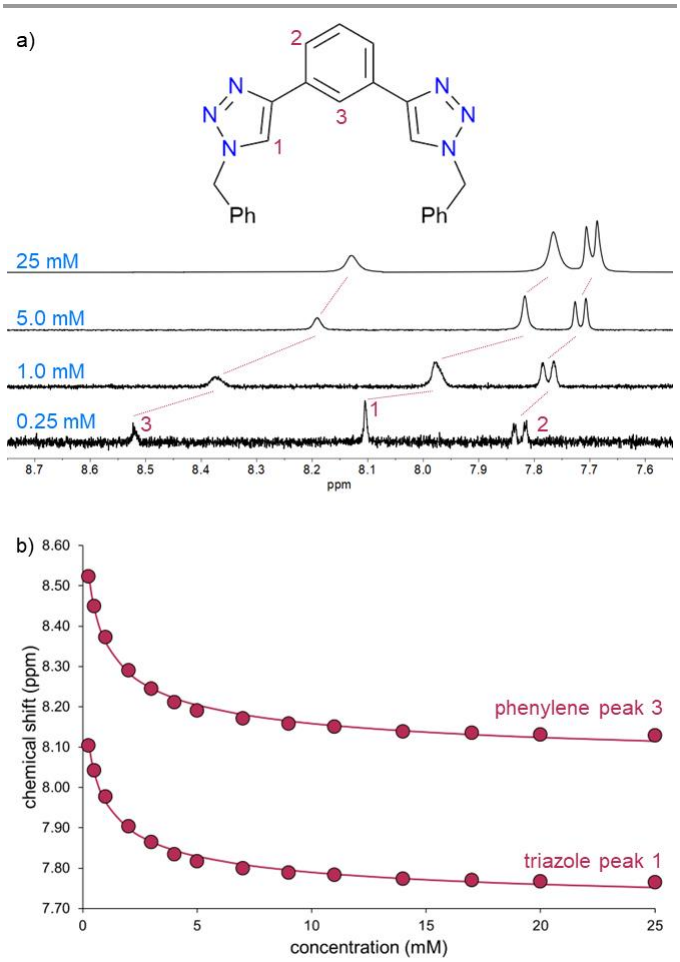


Figure 2 ^{1}H NMR study of self–aggregation of **2** in 9:1 $CDCl_3$:d_6-acetone (298 K): a) partial ^{1}H NMR spectra of **2** at various concentrations; b) chemical shift of interior phenylene and triazole C–H resonances at various concentrations (circles represent data, lines represent dimerization isotherm calculated using *Bindfit*[37]).

X-ray crystal structures

Remarkably, crystallising **1** from chlorinated solvents gave four different crystal structures. In three of the crystallisations, other molecules were added to try and form co-crystals, namely **2,** tetrabutylammonium chloride or the tetrabutylammonium salt of tetrakis(4-carboxyphenyl)methane[41] (see ESI for specific crystallisation conditions). However, no co-crystals were ever observed. Instead, all four structures are one-dimensional hydrogen bonded chains assembled through C–H···N hydrogen bonding interactions. While in many ways these structures are quite similar, there are some surprising differences between them.

Structure of $\mathbf{1}_{\mathbf{DCM/pentane}}$: Crystals of $\mathbf{1}_{\mathbf{DCM/pentane}}$ were obtained by vapour diffusion of pentane into a dichloromethane solution of **1**. The structure contains one-dimensional hydrogen-bonded chains assembled through C–H···N hydrogen bonds between the triazole groups in adjacent bis(triazole) motifs. There is one crystallographically-unique bis(triazole) motif, which has a *syn-anti* geometry, and interacts with itself through a $(s\text{-}a)_2$ hydrogen bonding arrangement (Figure 3). Hydrogen bonds are relatively short (H···N = 2.39 Å, 84% of the sum of the van der Waals' radii, Σ_{vdW}; C···N = 3.331(2) Å, C–H···N = 171°). The two central phenylene rings in each molecule of **1** are almost orthogonal to one another (mean plane angle = 86.8°). The structure contains small one-dimensional channels, which are located between the 1D hydrogen-bonded chains. In the crystal, these contain dichloromethane solvent molecules.

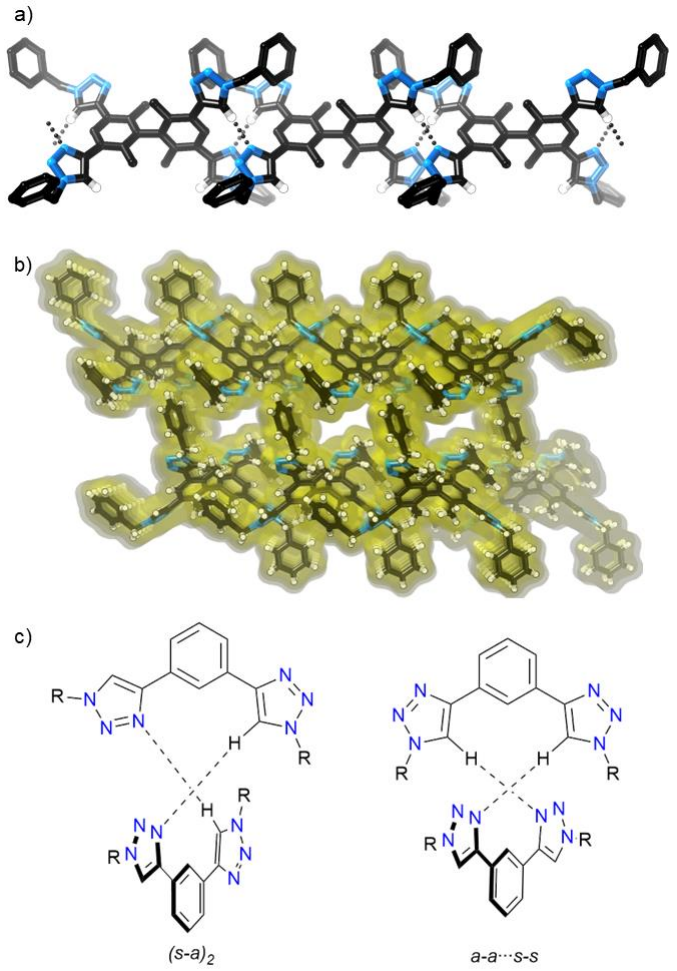


Figure 3 X-ray crystal structure of $\mathbf{1}_{\mathbf{DCM/pentane}}$: a) 1D hydrogen-bonded chain, b) packing diagram showing small 1D channels, c) two possible hydrogen bonding arrangements between phenyl-1,3-bis(triazole) groups. Most hydrogen atoms are omitted in part a), in part b) the van der Waals' radii of the atoms are shown in yellow showing the small channels running through the structure. Solvent molecules are omitted in both parts.

Structure of $\mathbf{1}_{\mathbf{workup}}$: Crystals of $\mathbf{1}_{\mathbf{workup}}$ were obtained from the crude reaction mixture used to prepare **1**. A yellow oil was obtained by concentrating the organic phase after aqueous workup, and this partially crystallised on standing to give crystals of $\mathbf{1}_{\mathbf{workup}}$. These crystals have a structure that is almost identical to those of $\mathbf{1}_{\mathbf{DCM/pentane}}$, and crystallise in the same space group (*C*2/*c*), although with significantly different unit cell parameters (*e.g.* the β angle differs by 3.0°). Both structures contain the same hydrogen bonding arrangement and very similar hydrogen bond distances (H···N in $\mathbf{1}_{\mathbf{workup}}$ = 2.40 Å, 84% of Σ_{vdW}). The main structural difference is a slightly different arrangement of two of the benzyl groups, but this does not

significantly affect the small solvent-filled channels in the structure, which are almost identical to those in $\mathbf{1}_{DCM/pentane}$ (see Figure S8 for an overlay plot of the two structures). The channels contained diffuse electron density, which could not be modelled, and so the OLEX2 mask routine[42] was used to incorporate this electron density into the refinement.

Structure of $\mathbf{1}_{chloroform}$: Crystals of $\mathbf{1}_{chloroform}$ were obtained by evaporation of a solution of **1** in chloroform. In this structure, there are two complete molecules of **1** in the asymmetric unit. One of these has *syn-anti* arrangements of both its bis(triazole) groups, and they interact with their symmetry-generated equivalents *via* a $(s\text{-}a)_2$ hydrogen bonding arrangement to give 1D hydrogen bonded chains (H···N distances = 2.31, 2.49 Å, 81 and 87% Σ_{vdW}). The other crystallographically independent molecule of **1** has a different arrangement, where one bis(triazole) group has an *anti-anti* orientation, while the other has a *syn-syn* orientation. This molecule interacts with itself through an *a-a*···*s-s* hydrogen bonding arrangement, again giving 1D hydrogen bonded chains (H···N distances = 2.35, 2.48 Å, 82 and 87% Σ_{vdW}). Both hydrogen bonding arrangements are shown in Figure 4, as is the 1D hydrogen-bonded chain formed through *a-a*···*s-s* hydrogen bonding, although interestingly the overall structure of the chain is almost identical to that formed from $(s\text{-}a)_2$ hydrogen bonds (both in this molecule and in the other structures of **1**). The structure of $\mathbf{1}_{chloroform}$ again contains 1D channels, which are filled with chloroform molecules in the crystal. These channels are slightly larger than those in $\mathbf{1}_{DCM/pentane}$, presumably to account for the larger size of chloroform compared to dichloromethane (both structures have two solvent molecules for each molecule of **1**).

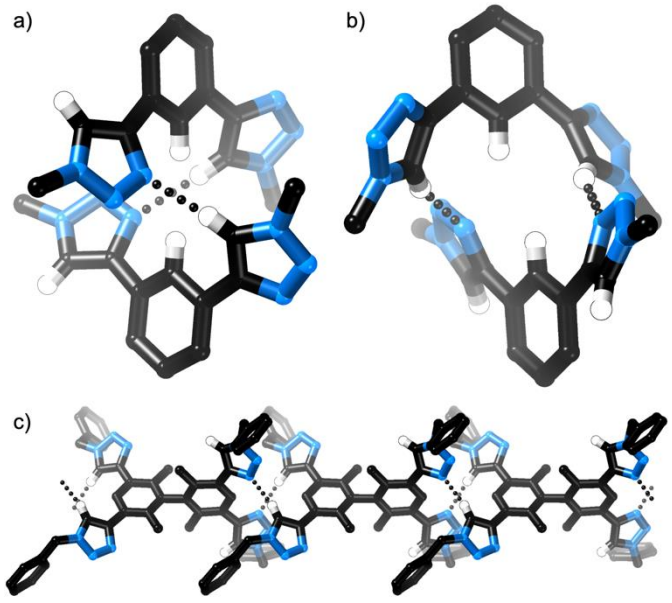


Figure 4 X-ray crystal structure of $\mathbf{1}_{chloroform}$: a) $(s\text{-}a)_2$ hydrogen bonding arrangement, b) *a-a*···*s-s* hydrogen bonding arrangement, c) 1D hydrogen-bonded chain formed from *a-a*···*s-s* hydrogen bonds. Solvent molecules and hydrogen bonds other than those on triazole groups omitted for clarity.

Structure of $\mathbf{1}_{DCM/ether}$: Crystals of $\mathbf{1}_{DCM/ether}$ were obtained by vapour diffusion of diethyl ether into a dichloromethane solution of **1**. There is one complete molecule in the P1 unit cell: this has a *syn-anti* arrangement of both bis(triazole) motifs, and forms a 1D hydrogen-bonded chain through $(s\cdots a)_2$ hydrogen bonding (H···N distances = 2.28, 2.32 Å, 80 and 81% Σ_{vdW}). The structure of these 1D hydrogen-bonded chains (Figure S12) is very similar to that shown in Figure 3a. Solvent molecules could not be resolved crystallographically and so were included in the model using the OLEX2 solvent mask routine.[42] The voids remaining in the structure have a helical shape (Figure S12).

Discussion: The phenyl-1,3-bis(triazole) motif is relatively common, and indeed there are 107 structures containing this motif in the Cambridge Structural Database (CSD).[43] Of these, 56 appear to be set up in such a way that they could contain the hydrogen bonding interactions seen in this work (see ESI for full details of CSD searches). That is, the triazole nitrogen atoms in these 56 structures are not substituted with other groups and do not coordinate to metal ions, so are free to accept hydrogen bonds, and the triazoles contain C–H groups available to donate hydrogen bonds. However, while there are often intermolecular triazole···triazole contacts in these structures, none feature the "double" interaction observed here where all four triazole groups are involved in hydrogen bonding.

It is unclear what the driving force for this interaction is: it is possible that the sterically-demanding methyl groups that favour an orthogonal arrangement of the two rings in the biphenyl group may help preorganise the bis(triazole) groups for such an interaction. However, this is clearly not the only factor as **2** (which does not have these methyl groups) shows significant self–association in solution. The hydrogen bonding interactions are relatively short, but not unusually so. For example, a survey of the CSD shows that while the triazole···triazole H···N hydrogen bonding distances observed in the structures of **1** (2.28 – 2.49 Å) are shorter than the average triazole···triazole hydrogen bonds in the CSD (2.60 Å), they are by no means the shortest (interactions < 2.2 Å have been observed, see Table S2 and Figures S13 – S16 for full analysis).

The hydrogen bonding interactions vary a reasonable amount between the four structures of **1**, both in terms of H···N distance, and in the *syn* or *anti* conformation of the triazole groups and thus $(s\text{-}a)_2$ or *a-a*···*s-s* hydrogen bonding arrangement. Despite this, the overall structures are remarkably similar: as well as all featuring 1D hydrogen-bonded chains, all four structures pack in a similar fashion and all contain small solvent-filled 1D channels, which account for 19 – 23% of the unit cell volumes (values calculated in Mercury[44] using a probe radius of 1.2 Å).

Conclusion

The simple, well-known, and readily-prepared phenyl-1,3-bis(triazole) motif is demonstrated to self–associate in solution and the solid state. ^{1}H NMR titration experiments using the simple model bis(triazole) compound **2** show that self–association is very weak in d_6-acetone, moderately strong in 9:1 $CDCl_3$:d_6-acetone, and strong in $CDCl_3$. Compound **1**, which

contains two bis(triazole) motifs forms 1D hydrogen-bonded chains upon crystallisation from chlorinated solvents. These structures contain small 1D channels running through them. We suggest that in the future the self–association of phenylene bis(triazole) motifs could be used to prepare hydrogen-bonded frameworks where the porosity of the framework could be tuned by varying the substituent attached to the triazole *N*-terminus.

Experimental

Data availability statement

Crystallographic data in CIF format have been deposited with the Cambridge Crystallographic Data Centre (CCDC: 2373363 – 2373366). Other data are provided in the ESI.

General remarks

Model bis(triazole) compound **2**[31] and tetra-alkyne **3**[36] were prepared as previously described, benzyl azide was prepared by the general method described by Smith.[45] Other chemicals were purchased commercially and used as received. Characterisation data and details of X-ray crystallography are provided in the ESI.

Synthesis of 1: Tetra-alkyne **2** (500 mg, 1.63 mmol) was suspended in a 2:1 mixture of *tert*-butanol:water (15 mL) under a nitrogen atmosphere. Benzyl azide (1.30 g, 9.78 mmol), copper(II) sulfate pentahydrate (130 mg, 0.52 mmol) and sodium ascorbate (322 mg, 1.63 mmol) were added and the resulting suspension stirred at room temperature for 18 hours during which time a thick white precipitate formed. The mixture was diluted with dichloromethane (50 mL), and the organic phase was washed with $Na_4EDTA_{(aq)}$ (1.0 M, 50 mL), then brine (50 mL) then dried ($MgSO_4$) and taken to dryness under reduced pressure to yield a yellow oil, that partially solidified to yield crystals on standing. This was purified by column chromatography (85:15 dichloromethane:acetone) to give **1** as a white powder. Yield: 840 mg (1.00 mmol, 62%).

^{1}H NMR ($CDCl_3$): δ 7.90 (s, br, 2H), 7.58 (s, br, 4H), 7.29 – 7.40 (m, 20H), 5.58 (s, 8H), 1.98 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 147.9 (br), 142.4, 134.8, 134.0, 129.5 (br), 129.3, 128.9, 128.8 (br), 128.2, 122.2 (br), 54.4, 18.1. HR ESI-MS (pos.) m/z: 861.3858, calc. for $[C_{52}H_{46}N_{12}{\cdot}Na]^+$, *i.e.* $[\mathbf{1}{\cdot}Na]^+$ = 861.3861.

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