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Bis(amidopyridine)-linked calix[4]arenes: a novel type of receptor for dicarboxylic acids

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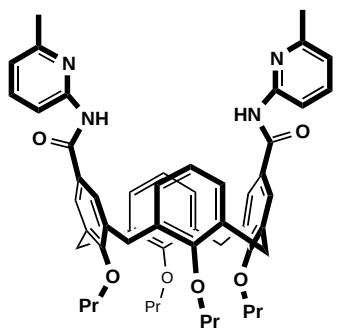
Abstract—Calix[4]arenes **1** and **2**, functionalised on their upper rim with amidopyridine groups, have been synthesised. In the case of **1**, a detailed binding study with a range of aliphatic and aromatic dicarboxylic acids has been carried out using ^{1}H NMR spectroscopy. The binding affinities are largely dependent upon the length of the alkyl spacer group, with the highest binding constant observed for dodecanedioic acid. The X-ray crystal structures of **1** and **2** reveal chain structures formed through intermolecular hydrogen bonds between amidopyridine moieties.

In the last decade, considerable effort has been devoted to molecular recognition and/or self-organisation within the field of supramolecular chemistry.[1] As part of this area of research, we have focused on the recognition and sensing of organic molecules through hydrogen bonding[2–4] and covalent bonding[5] interactions. Previously, we reported the binding of the dicarboxylic acid, glutaric acid, by two amidopyridine groups connected by a ferrocene spacer group, which has enabled us to read-out and control binding using electrochemical methods.[2,4] By changing the type of spacer group, selectivity for a particular target molecule should also change due to distance and orientation effects. In the past, calixarenes have been attractive choices as spacer groups or scaffolds for ditopic molecular recognition.[6–8] However, although a number of receptors with a range of spacer groups for neutral dicarboxylic acids have been reported,[9] calixarenes have not been used in this capacity until now, although related receptors for carboxylate anions are known.[10] Here we report the synthesis of bis-amidopyridine calix[4]arenes **1** and **2** and the binding properties of **1** toward various dicarboxylic acids in solution (0.5–3% DMSO-d_6 in $CDCl_3$). We also report a new type of intermolecular hydrogen bonding motif in the solid-state involving amidopyridine moieties.



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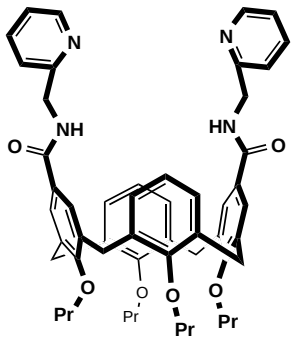

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Keywords: calix[4]arene; hydrogen bonding; host–guest chemistry; self-organization.
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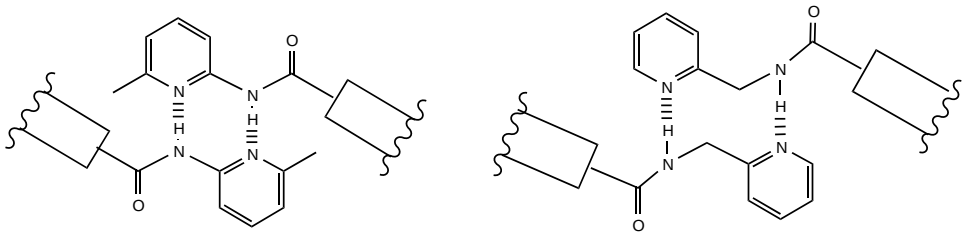


Figure 1. Intermolecular hydrogen bonding of amidopyridines through double N–H···N linkages.

Compounds **1** and **2** were synthesised by amidation of a calix[4]arene dicarboxylic acid with aminopyridines. Specifically, 25,26,27,28-tetrakis(1-propoxy)calix[4]-arene-5,17-dicarboxylic acid[11] was dissolved in dry CH_2Cl_2 and treated with oxalyl chloride. The reaction mixture was refluxed for 3 h. The solvent was then distilled off and the residue was dried in vacuo. The obtained acyl chloride was reacted with 2-amino-6-methylpyridine (for **1**) or 2-aminomethylpyridine (for **2**) in dry THF in the presence of Et_3N. The reaction mixture was stirred at room temperature for 1 h. After removal of THF, the residue was dissolved in $CHCl_3$ and washed with water. The water layer was extracted with $CHCl_3$. The combined $CHCl_3$ layers were dried with $MgSO_4$, and the solvent was evaporated. Purification by column chromatography on silica gel using hexane–ethyl acetate (3:1) as eluent afforded compound **1** in 71% yield (mp = 268–269°C), and on alumina using chloroform–hexane (4:1) as eluent gave compound **2** in 89% yield (mp = 245–246°C). These compounds were fully characterised by ^1H and ^{13}C NMR spectroscopies, mass spectroscopy and elemental analysis.[†]

The X-ray crystal structures[‡] of **1** and **2** reveal intermolecular hydrogen bonded chain structures formed through double N–H···N linkages between neighbouring amidopyridines, as shown in Fig. 1. In the case of **2**, a similar motif has been observed previously through intramolecular hydrogen bonds.[12] Fig. 2 depicts the crystal structure of compound **1**; one and two half molecules are found in the asymmetric unit, making a total of three conformers (**1a**, **1b** and **1c**) overall that form a […(**1a**)(**1b**)(**1c**)(**1b**)…] hydrogen bonded chain. Compound **2** crystallises with two conformers (**2a** and **2b**) in the asymmetric unit, forming independent […(**2a**)(**2a**)(**2a**)…] and […(**2b**)(**2b**)(**2b**)…] hydrogen bonded chains (Fig. 3).

A ^1H NMR spectroscopy study revealed that at millimolar concentrations in mixed solvents (0.5–3% DMSO-d_6 in $CDCl_3$), no aggregation of **1** through intermolecular hydrogen bonding was observed. However, upon addition of dicarboxylic acids to a solution of **1** in 0.5% DMSO-d_6 in $CDCl_3$, downfield shifts in the resonance corresponding to the two amido NH protons of **1** were observed (e.g. 8.45 ppm–10.60 ppm for dodecanedioic acid), consistent with the formation of amidopyridine-carboxylic acid hydrogen bonds. Dicarboxylic acids used in this study up to $n = 8$ showed 1:1 (host:guest) binding stoichiometries as determined by Job plots (maxima at mole fractions of 0.5), as shown in Fig. 4(a) for sebacic acid.[13] For dodecanedioic acid ($n = 10$), a small amount of 1:2 (host:guest) complex was observed whereas for $n = 12$, a 1:2 stoichiometry (0.33 as a maximum) predominated. Binding constants (K_a, Table 1) for the 1:1 stoichiometry were determined from standard non-linear curve fits[§] made

[†] Compound **1**; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.94 (t, $J = 7.4$ Hz, 6H, $OCH_2CH_2\underline{CH_3}$), 1.10 (t, $J = 7.5$ Hz, 6H, $OCH_2CH_2\underline{CH_3}$), 1.97 (m, 8H, $OCH_2\underline{CH_2}CH_3$), 2.49 (s, 6H, NHpy$\underline{CH_3}$), 3.25 (d, $J = 13.6$ Hz, 4H, Ar$\underline{CH_2}$Ar), 3.74 (t, $J = 7.0$ Hz, 4H, $O\underline{CH_2}CH_2CH_3$), 4.08 (t, $J = 8.0$ Hz, 4H, $O\underline{CH_2}CH_2CH_3$), 4.49 (d, $J = 13.5$ Hz, 4H, Ar$\underline{CH_2}$Ar), 6.24 (d, $J = 7.4$ Hz, 4H,ArH), 6.32 (m, 2H, ArH), 6.91 (d, $J = 7.5$ Hz, 2H, ArpyH), 7.61 (t, $J = 7.8$ Hz, 2H, ArpyH), 7.62 (s, 4H, ArH), 8.41 (s, 2H, ArCO$\underline{NH}$). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 10.00, 10.67, 23.20, 23.46, 23.99, 31.01, 76.79, 111.00, 119.07, 122.49, 127.95, 127.99, 132.91, 136.96, 138.75, 149.48, 151.14, 155.40, 156.62, 161.35, 165.65, 221.78. MS (EI) m/e 860.45 (M^+). Elemental analysis found: C, 74.79; H, 7.02; N, 6.27%. Calcd for ($C_{54}H_{60}O_6N_4$): C, 75.32; H, 7.02; N, 6.51%. Compound **2**; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.94 (t, $J = 7.5$ Hz, 6H, $OCH_2CH_2\underline{CH_3}$), 1.06 (t, $J = 7.5$ Hz, 6H, $OCH_2CH_2\underline{CH_3}$), 1.90 (m, 8H, $OCH_2\underline{CH_2}CH_3$), 3.23 (d, $J = 13.6$ Hz, 4H, Ar$\underline{CH_2}$Ar), 3.76 (t, $J = 7.3$ Hz, 4H, $O\underline{CH_2}CH_2CH_3$), 3.99 (t, $J = 7.9$ Hz, 4H $O\underline{CH_2}CH_2CH_3$), 4.47 (d, $J = 13.3$, 4H, Ar$\underline{CH_2}$Ar), 4.73 (d, $J = 5.0$ Hz, 4H, $\underline{CH_2}$-py), 6.39 (s, 6H, ArpyH), 7.24 (m, 2H, ArpyH), 7.37 (d, $J = 7.6$ Hz, 4H, ArH), 7.41 (s, 4H, ArH), 7.72 (m, 2H, ArH), 8.58 (m, 2H, $\underline{NH}$py). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 10.07, 10.56, 13.17, 23.39, 31.00, 44.85, 76.76, 76.93, 122.30, 122.39, 127.59, 127.99, 128.07, 133.40, 136.35, 136.83, 148.95, 155.62, 156.90, 160.42, 167.71, 223.01. MS (EI) 860.45 m/e (M^+). Elemental analysis found: C, 74.77; H, 7.02; N, 6.27%. Calcd for ($C_{54}H_{60}O_6N_4$): C, 75.32; H, 7.02; N, 6.51%.

[‡] Crystals of **1** and **2** suitable for single-crystal X-ray diffraction were grown from ethanol. Data were collected on a Bruker–Nonius kappa CCD following standard procedures.

Crystal data for **1** $C_{54}H_{60}N_4O_6$, Mr = 861.06, $T = 120(2)$ K, monoclinic, space group $P2/c$, $a = 24.7998(5)$, $b = 16.6806(3)$, $c = 24.9057(5)$ Å, $\beta = 107.161(3)°$, $V = 9844.2(3)$ Å^3, $\rho_{calcd} = 1.162$ g cm^{-3}, $\mu = 0.076$ mm^{-1}, $Z = 8$, reflections collected: 89968, independent reflections: 17361 ($R_{int} = 0.1455$), final R indices [$I > 2\sigma I$]: $R_1 = 0.0626$, $wR_2 = 0.1491$, R indices (all data): $R_1 = 0.1401$. $wR_2 = 0.1796$.

Crystal data for **2** $C_{54}H_{60}N_4O_6$, Mr = 861.06, $T = 120(2)$ K, monoclinic, space group $C2/c$, $a = 20.5733(4)$, $b = 17.9742(3)$, $c = 25.3788(5)$ Å, $\beta = 101.582(3)°$, $V = 9193.7(3)$ Å^3, $\rho_{calcd} = 1.246$ g cm^{-3}, $\mu = 0.081$ mm^{-1}, $Z = 8$, reflections collected: 53571, independent reflections: 8120 ($R_{int} = 0.2019$), final R indices [$I > 2\sigma I$]: $R_1 = 0.0692$, $wR_2 = 0.1389$, R indices (all data): $R_1 = 0.2027$, $wR_2 = 0.1866$.

[§] An Origin 6.1 curve-fitting program used to evaluate the binding constants. The % saturation reached for most titrations in 0.5% DMSO-d_6/$CDCl_3$ was at least 80%. Errors were estimated from the curve-fitting program, with all curve fittings giving low χ^2 values.

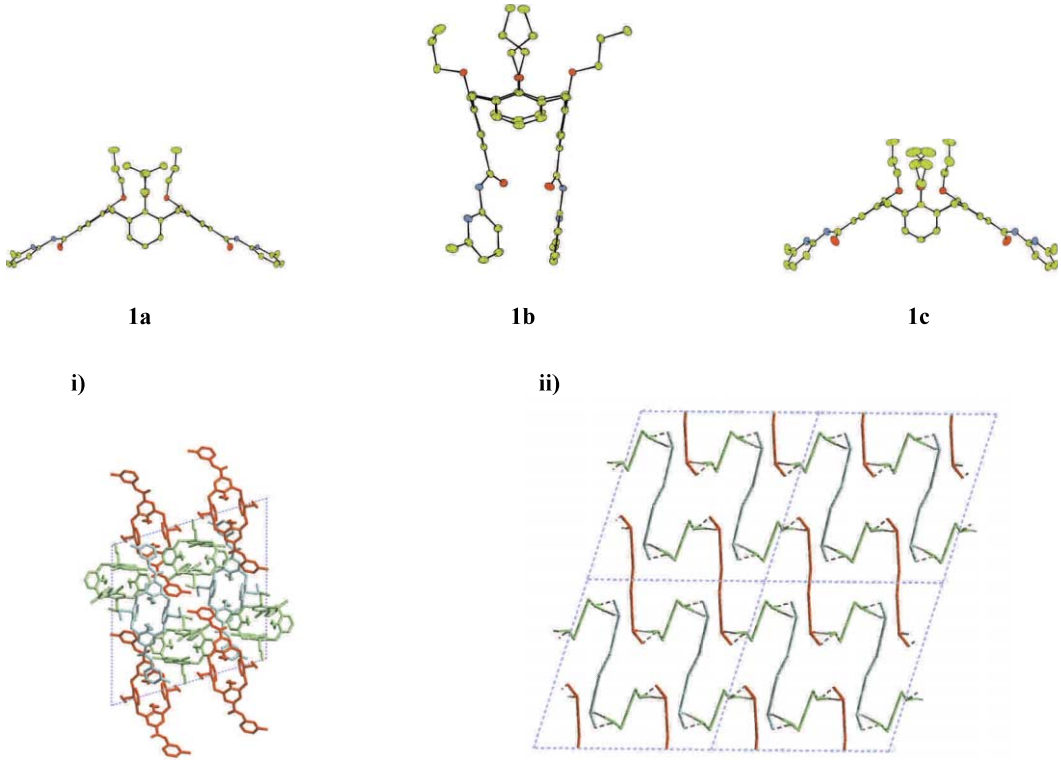


Figure 2. Three conformers **1a**, **1b** and **1c** observed in the X-ray crystal structure of compound **1**. (i) Cell packing diagram. (ii) Stylised representation of the hydrogen bonded chains looking down the *b* axis (**1a** red, **1b** green, **1c** turquoise).

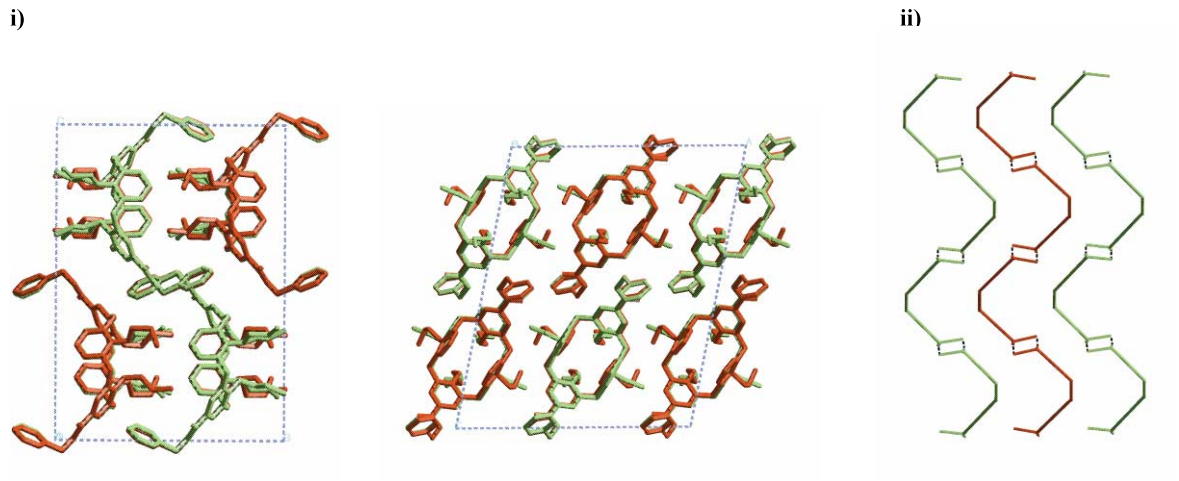


Figure 3. (i) Cell packing diagram of compound **2** containing two conformers **2a** and **2b**. (ii) Stylised representation of the two independent hydrogen bonded chains looking down the *a* axis (**2a** green, **2b** red).

to the changes in the chemical shift of the amido NH protons of **1** as a function of increased dicarboxylic acid concentration.[14] A representative example showing titration data for sebacic acid and a curve fit is depicted in Fig. 4(b). It is clear from the K_a values obtained with different lengths of alkyl spacer group ($n=3$–10) that there is a large distance dependence on the binding strength, with glutaric acid ($n=3$) giving the smallest value in this series. Binding constant values increase with increasing length of alkyl spacer group, up to a maximum with $n=10$ before the dominant stoichiometry changes to 1:2 at $n=12$.

It is likely that the conformation of the receptor, in particular that of the two hydrogen bonding sites with respect to the calixarene ring, plays an important role in determining binding strength. Fig. 5 shows two schematic representations of 1:1 complexes in which the dicarboxylic acid guest is bridged by the two amidopyridine groups of the calixarene receptor. A ditopic

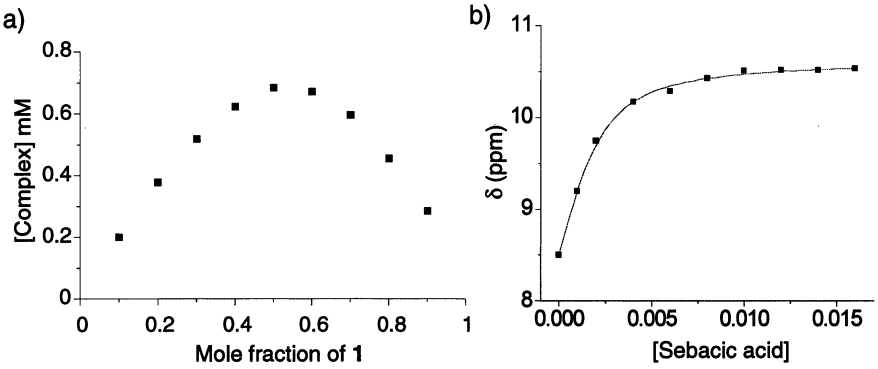
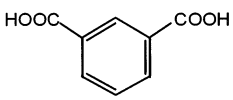
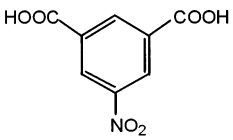
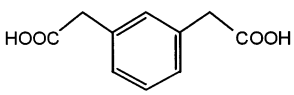


Figure 4. (a) Job plot for sebacic acid ($n=8$) and **1** (total concentration = 2 mM). (b) Titration curve and curve-fit for the addition of sebacic acid ($n=8$) to **1** (2 mM) in 0.5% DMSO-d_6/$CDCl_3$ at 298 K.

Table 1. Binding constants[a] (K_a) of bis(amidopyridine)-linked calixarene **1** with various dicarboxylic acids in 0.5% DMSO-d_6/$CDCl_3$ and 3% DMSO-d_6/$CDCl_3$ at 298 K

Guest molecules	0.5% DMSO-d_6 / $CDCl_3$	3% DMSO-d_6 / $CDCl_3$
	K_a/M^{-1}	K_a/M^{-1}
HOOC-$(CH_2)_n$-COOH		
n = 3	78	13
4	80	nd
5	133	20
6	392	39
8	1530	nd
10	*ca.* 3000[b]	nd
12	nd[c]	nd
	d	19
	d	23
	d	15

[a]Estimated errors were < 15%
[b]Exact value difficult to determine due to the presence of a small amount of 1:2 complex
[c]nd = not determined
[d]Hard to dissolve.

binding interaction with a small dicarboxylic acid such as glutaric acid would involve the two amidopyridine groups turning towards one-another (Fig. 5(a)). In such a conformation, steric hindrance between the guest and the phenyl groups on the calixarene ring would be minimised and also strain in the short alkyl chain would be reduced. As the guest becomes larger, the amidopyridine groups can turn away from one another to accommodate the guest without steric hindrance from the ring or strain in the spacer group (Fig. 5(b)). In this conformation, the two amidopyridine groups are virtually in the same plane as the phenyl groups to which they are attached, with the alkyl chain located largely outside of the calixarene cavity. It is interesting to note that in the X-ray structure of **1** (Fig. 2), the six amide units in the three conformers are almost as

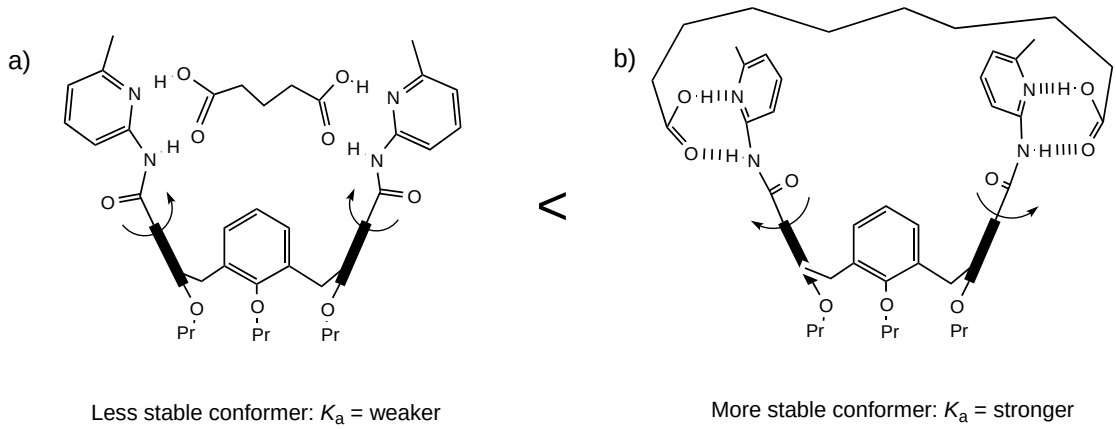


Figure 5. Schematic representations of cooperative binding by **1** of different lengths of alkyl dicarboxylic acids: (a) $n=3$, (b) $n=8$.

coplanar with their respective phenyl groups (range from 22.5 to 34.2°) as they are with their respective pyridine units (range from 9.3 to 28.0°). Clearly there must be a degree of conjugation between the amidopyridine unit and the phenyl ring to maintain this planarity. It is therefore likely that binding strength is maximised when disruption to this planarity is minimised, as expected for larger guests (Fig. 5(b)). Presumably for very large guests ($n \geq 10$), this conformation starts to become less favourable due to steric crowding in the alkyl chain, resulting in a change in the binding stoichiometry.

Aromatic diacids, isophthalic acid, 5-nitroisophthalic acid and 1,3-phenylene diacetic acid were chosen as guest molecules to compare with the aliphatic diacids, with solubility problems necessitating the use of a more polar solvent mixture (3% DMSO-d_6/$CDCl_3$). Isophthalic acid derivatives are known to self-organise in non-polar solvents.[15] However, in this relatively polar solvent mixture, no significant changes to the ^{1}H NMR spectrum of 5-nitroisophthalic acid were observed between 1 and 20 mM. All the resulting binding constants are small (Table 1) as expected by the choice of solvent mixture. Judging by the similarity between the values for aliphatic and aromatic guests, there is no π–π stacking between any of the aromatic di-acids and the phenyl groups of the calixarene ring. However, the relative acidity of these di-acids (i.e. 5-nitroisophthalic acid>isophthalic acid>1,3-phenylene diacetic acid) appears to play a role in determining complex strength.

In conclusion, we have succeeded in synthesising the bis(amidopyridine)-linked calix[4]arenes **1** and **2**, which exhibit interesting solid-state structures through intermolecular hydrogen bonds. In the case of **1**, cooperative binding of various dicarboxylic acids has been observed through hydrogen bonding interactions, with the binding strength strongly dependent upon the length of the spacer group between the carboxylic acid groups. Compared to other known receptors for neutral dicarboxylic acids,[4,9] calixarene **1** appears to be a suitable choice for the complexation of guests with relatively long alkyl spacer groups.

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