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Conformational Control of Selectivity and Stability in Hybrid Amide/Urea Macrocycles

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Abstract: The anion-binding properties of two similar hybrid amide/urea macrocycles containing either a 2,6-dicarboxamidophenyl or a 2,6-dicarboxamidopyridine group are compared. Significant differences in anion affinity and mode of interaction with anions are attributed to the presence of intramolecular hydrogen bonds in the pyridine system. In fact, remarkably, the phenyl macrocycle undergoes amide hydrolysis under *neutral conditions* in DMSO/water. The anion binding abilities of the receptors are compared to those of acyclic analogues of the macrocycles that show that the phenyl receptor behaves in a similar fashion to acyclic urea-containing receptors (i.e., showing little selectivity amongst oxo anions), whilst the pyridine-containing receptor shows a high affinity and selectivity for carboxylates.

Keywords: amides · anion binding · macrocycles · ureas

Introduction

Amides[1] and ureas[2] have been widely exploited in the design of receptors for anions.[3] Hybrid receptors containing both amides and ureas also been synthesised and in some cases shown to possess remarkably high anion affinities and high selectivity.[4] Our recent studies have shown that bis-ureas based on an *ortho*-phenylenediamine scaffold are particularly good receptors for carboxylates.[5] We wished to explore the use of "*ortho*-phenylenediamine-like" hydrogen-bond donor arrays in macrocyclic anion receptors. In 2000, Reinhoudt and co-workers reported the anion-binding ability of cyclic and acyclic receptors containing two *ortho*-phenylenediamine-based bis-urea units.[6] This work showed that these receptors were selective for dihydrogen phosphate in DMSO. In this paper, we report the anion-binding properties of two hybrid macrocycles containing urea and amide hydrogen bond donors.[7] We have compared the affinity of the macrocyclic receptors with a series of "fragments" **3**–**6** containing various combinations of the hydrogen-bonding motifs present in the macrocyclic systems. These results suggest dramatic differences in the mode of interaction of anions between the two macrocycles, which we attribute to the pre-organising influence of the pyridine group in receptor **1**.

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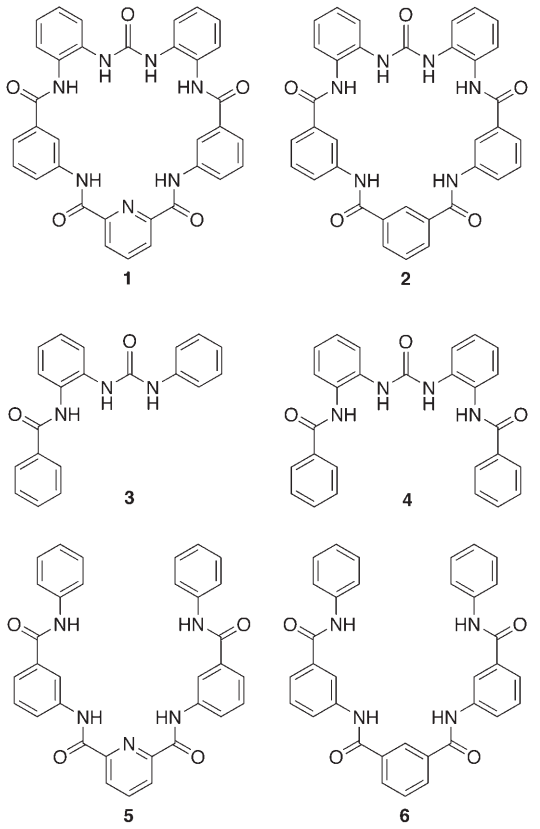
Results and Discussion

Macrocycle **1** was synthesised in 11% overall yield from 1,3-bis(2-aminophenyl)urea[8] (Scheme 1). The starting material was converted to compound **7** by an amide coupling reaction with 3-nitrobenzoic acid; compound **7** was subsequently reduced by using hydrazine hydrate/palladium on carbon to give 1,3-bis(2-aminophenyl)urea (**8**). The bis-amine was condensed with pyridine 2,6-dicarbonylchloride in the presence of 1.6 equivalents of tetrabutylammonium acetate. The latter reagent was used to solubilise compound **8** in dichloromethane and also function as a potential template for the formation of **1**. The macrocycle was purified by column chromatography on silica gel (60 Å) eluting with 92:8 CH_2Cl_2/MeOH followed by trituration in boiling ethylacetate.

Attempts to prepare macrocycle **2** using this methodology failed. Fortunately, an alternative route to obtain this receptor was found by the reaction of **8** with 1.1 equivalents of isophthaloyl dichloride in methanol and in the presence of 2.2 equivalents of concentrated sulfuric acid (Scheme 1). The macrocycle was purified by filtration and trituration in



water, followed by several washes with a mixture of methanol/dichloromethane (1:1).

The stability constants of macrocycle **1** with a variety of putative anionic guests were elucidated using ^{1}H NMR titration techniques (Table 1). The titration curves were fitted to 1:1 binding models (as confirmed by Job plot[9] analysis in the case of benzoate and acetate) using the EQNMR computer program.[10] The stability constant data shows that the macrocycle possesses a particularly high affinity for carboxylates. In fact the macrocycle binds acetate approximately 100 more strongly than dihydrogen phosphate both in [D$_6$]DMSO/0.5% water and in [D$_6$]DMSO/5% water solution.

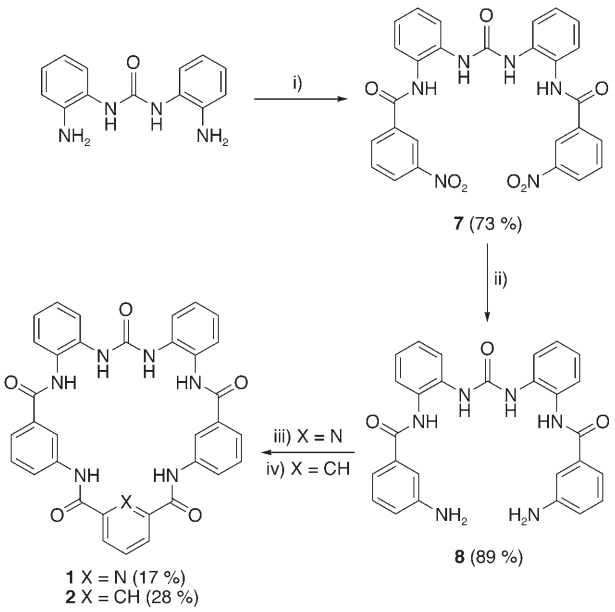
Table 1. Stability constants of compound **1** with a variety of anionic guests added as tetrabutylammonium salts as determined by ^{1}H NMR titration techniques performed in [D$_6$]DMSO/0.5% water and [D$_6$]DMSO/5% water at 298 K following NH (or CH)[a] resonances in the receptors.[b]

	Stability constants [M^{-1}]	
	[D$_6$]DMSO/0.5% water	[D$_6$]DMSO/5% water
Cl^-	194	42
Br^-	10	–
HSO_4^-	115	–
$H_2PO_4^-$	142[a]	51
NO_3^-	<10	–
$CH_3CO_2^-$	16500[c]	5170
$C_6H_5CO_2^-$	6430	1830
selectivity $K_a(CH_3CO_2^-)/K_a(H_2PO_4^-)$	116	101

[a] Due to NH broadening titration was conducted by following the shift of an ArH proton. [b] Errors estimated to be <15%. [c] This value is greater than 10^4 M^{-1}. As such the stability constant is at the upper limit that can be determined by this technique and should be treated with caution.

Figure 1 shows the shift of each NH group present in the macrocycle **1** upon addition of one equivalent of a variety of anions. The molecule contains a C_2 axis of symmetry that simplifies the ^{1}H NMR spectrum of the macrocycle, such that there are three NH resonances in the NMR spectrum. Proton NMR spectra of compound **1** in [D$_6$]DMSO/0.5% water in the absence (top) and presence (bottom) of 1.0 equivalents of tetrabutylammonium acetate are shown in Figure 2. The spectra show that the urea and 2,6-dicarboxamidopyridine NH groups shift significantly downfield upon addition of acetate, but that the amide groups adjacent to the urea are hardly influenced by the presence of the oxo anion.

Similarly Figure 3 shows the shifts of each NH group present in the macrocycle upon addition of aliquots of benzoate. The "linking" amide groups adjacent to the urea (Figure 1) appear to only interact very weakly with the carboxylate guests (if at all) as judged by the negligible shift of these protons. The 1:1 stoichiometry of carboxylate binding was confirmed by Job plot analysis. This leads us to propose the binding mode shown in Figure 3 for the interaction of the macrocycle with carboxylates in which one carboxylate oxygen atom binds to the two urea NH groups and the other binds to the 2,6-dicarboxamidopyridine NH groups leaving the amide NH groups next to the urea free. In contrast to these results, addition of one equivalent of dihydro-



Scheme 1. The synthesis of macrocycles **1** and **2**. i) 3-nitrobenzoic acid, PyBOP, Et$_3$N, HOBt, DMF (anhydrous); ii) $NH_2NH_2.H_2O$, Pd/C 10% cat., EtOH; iii) 2,6-pyridine dicarbonylchloride, tetrabutylammonium acetate, Et$_3$N, DMAP, CH_2Cl_2; iv) isophthaloyl dichloride, H_2SO_4, MeOH.

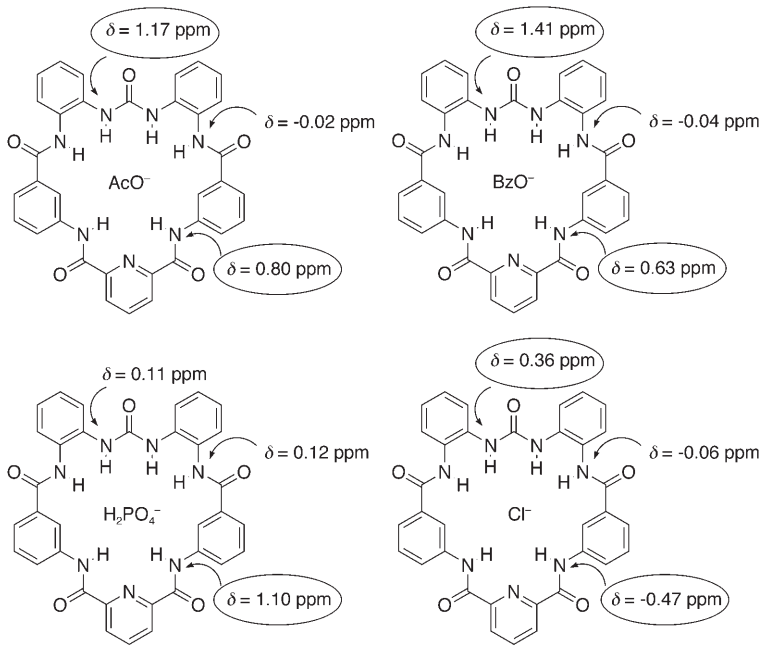


Figure 1. Shifts of the NH proton resonances in compound **1** in the presence of one equivalent of tetrabutylammonium anion salt in [D_6]DMSO/0.5% water. Downfield shifts are shown as positive numbers and upfield shifts as negative numbers. The most significant downfield shifts are circled.

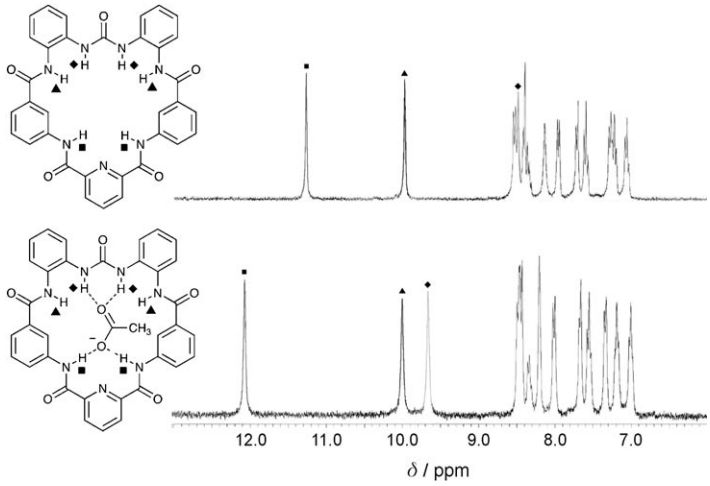


Figure 2. Downfield shifts of the NH proton resonances of compound **1** in the presence of 1.0 equivalents of tetrabutylammonium acetate in [D_6]DMSO/0.5% water.

gen phosphate causes a significant downfield shift of only the amide groups adjacent to the pyridine ring. The other NH groups in the macrocycle shift downfield by only approximately 0.1 ppm (see Figure 1). These results suggest that the predominant interaction in solution in this case is between the two convergent NH groups and presumably a single atom in the anion. Consequently the anion is bound considerably less strongly than the carboxylate guests. On the other hand addition of chloride causes a significant downfield shift of the urea NH groups and an upfield shift of the pyridine amide groups (Figure 1). These results lead us to suggest that this anion is bound predominantly by the urea NH groups, with the upfield shift of the pyridine amides caused presumably by either a desolvation effect as DMSO is displaced from the cavity by the anion or a conformational change in the receptor.

As previously reported[7] crystals of compound **1** were obtained by slow evaporation of a methanol solution of the macrocycle in the presence of excess tetramethylammonium salt. The crystal structure shown in Figure 4 reveals the acetate anion bound to the pyridine amide NH groups (N4−O7 2.975(5) Å; N6−O7 3.321(5) Å) and, in contrast to the solution binding evidence, to one linking amide NH group (N7−O6 2.804(5) Å).

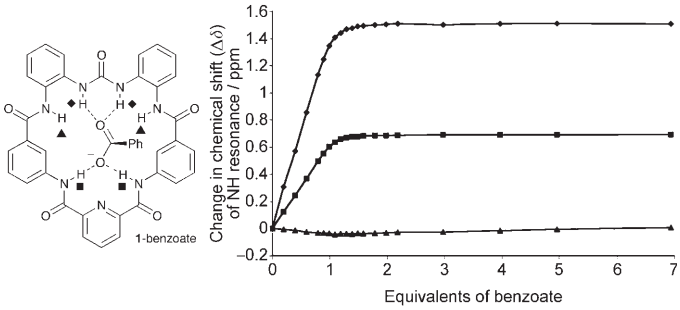


Figure 3. Shift of the NH protons in compound **1** upon addition of benzoate. The amide protons adjacent to the urea group do not shift significantly, whilst the 2,6-dicarboxamidopyridine NH groups and the urea NH groups shift downfield by $\delta = 0.63$ and 1.41 ppm, respectively, upon addition of excess tetrabutylammonium benzoate. A potential binding mode of benzoate to the macrocycle is shown on the left.

The crystals contain water of crystallisation and it is important to note that one of the water molecules is bound to the two urea NH groups within the macrocyclic cavity (N1−O8 2.983(6) Å; N2−O8 2.857(6) Å). Additionally a hydrogen bond is formed between this water and the bound acetate (O7−O8 2.668(6) Å). Thus O6 could be regarded as having been "displaced" from the urea NH groups by the bound water molecule. Thus, despite acetate being capable of binding in this mode to a linking amide group, it appears not to do so in solution.

The stability constants of macrocycle **2** with a variety of putative anionic guests were also elucidated using ^{1}H NMR titration techniques (Table 2). The titration curves were fitted to 1:1 binding models using the EQNMR computer program.[10] In contrast with the results obtained for macro-

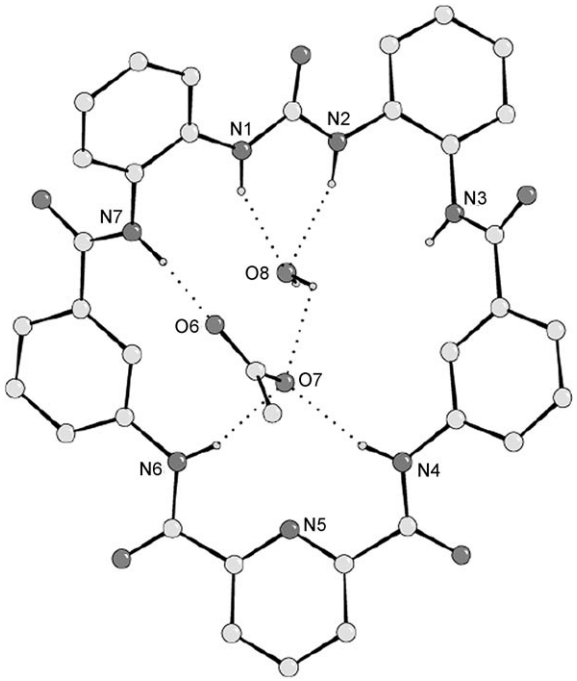


Figure 4. The X-ray crystal structure of the hydrated tetramethylammonium acetate complex of macrocycle **1**. Counterion, non-acidic hydrogen atoms and non-cavity bound water are omitted for clarity.

Table 2. Stability constants of compound **2** with a variety of anionic guests added as tetrabutylammonium salts as determined by ^{1}H NMR titration techniques performed in [D$_6$]DMSO/0.5% water at 298 K following NH (or CH)[a] resonances in the receptors.[b]

	Stability constants [M^{-1}] [D$_6$]DMSO/0.5% water
Cl^-	12
Br^-	< 10
HSO_4^-	< 10
$H_2PO_4^-$	609[a]
NO_3^-	< 10
$CH_3CO_2^-$	938
$C_6H_5CO_2^-$	321
selectivity	
$K_a(CH_3CO_2^-)/K_a(H_2PO_4^-)$	1.54

[a] Due to NH broadening titration was conducted by following the shift of an ArH proton. [b] Errors estimated to be < 15%.

cycle **1** its counterpart **2**, which contains the 2,6-dicarboxamidophenyl group, shows a lower affinity for carboxylates, with a significant difference between their stability constants of more than one order of magnitude (see Table 1 versus Table 2). Moreover, the affinity of macrocycle **2** for dihydrogen phosphate increases regarding its analogous **1** from 142 to 609 M^{-1} (see Tables 1 and 2). As a consequence compound **2** has a much lower selectivity for carboxylates than macrocycle **1**.

Figure 5 shows the shifts of each NH group present in macrocycle **2** upon addition of one equivalent of a variety of anions. As in the case of compound **1**, the urea NH group resonance shifts downfield significantly upon addition of acetate and benzoate. In contrast to what was observed with macrocycle **1**, the 2,6-dicarboxamidophenyl NH groups appear to interact very weakly with the carboxylate guests as judged by the small shifts of these protons (see Figure 1 versus Figure 5). Moreover, the shifts of the protons belonging to the amide groups adjacent to the urea are greater than that observed for macrocycle **1**.

On the other hand addition of one equivalent of dihydrogen phosphate to macrocycle **2** causes a significant downfield shift of the urea NH groups, as well as a moderate downfield shift of the protons of the amide groups adjacent to the urea. The other NH groups in the macrocycle only shift downfield by approximately 0.1 ppm. These results suggest that the predominant interaction in solution in this case is between the two urea NH groups and the anion, whether carboxylates or dihydrogen phosphate, together with a small contribution of the amide groups adjacent to the urea. In all the cases, the 2,6-dicarboxamidophenyl NH groups do not appear to interact with the anionic guests to a significant extent. The addition of one equivalent of chloride to this

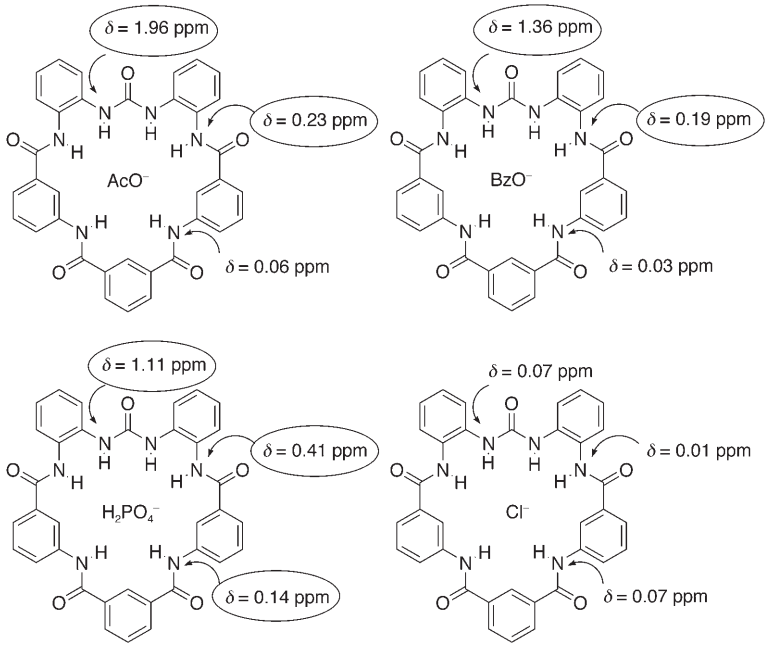
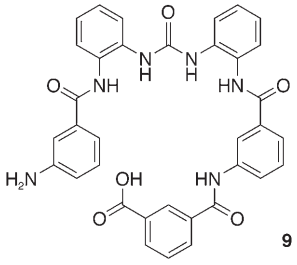


Figure 5. Shifts of the NH proton resonances in compound **2** in the presence of one equivalent of tetrabutylammonium anion salt in [D$_6$]DMSO/0.5% water. The most significant downfield shifts are circled.

macrocycle does not cause any significant change in the chemical shifts of the receptor NH groups (Figure 5), ($K_a = 12\,M^{-1}$; see Table 2).

We observed that macrocycle **2** was not stable in solution ([D_6]DMSO/0.5% water) over moderate periods of time. Figure 6 shows the ^{1}H NMR spectra of a 1.0 mM solution of macrocycle **2** in [D_6]DMSO/0.5% water over the course of 24 h. As can be observed after only 2 h in solution, new resonances appear (including a resonance at about $\delta = 5.3$ ppm corresponding to a free NH_2 group). Over time these signals become more intense and correspond predominantly to hydrolysis product **9**.[11] It has been shown that twisted amide



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groups are susceptible to hydrolysis under neutral conditions[12] leading us to suggest that in solution the hydrolysis-prone amide groups are significantly twisted. The smaller shifts of these groups in compound **2** than in the analogous groups in compound **1** upon addition of carboxylates suggests that the amides are not as predisposed to form a convergent hydrogen-bonding array. Presumably in compound **1** the involvement of the pyridine group in the formation of intramolecular hydrogen bonds with the amide groups in the 2- and 6-positions of the ring acts to stabilise a more linear arrangement of these groups than is possible in compound **2**, thus leaving compound **2** more prone to hydrolysis.

When the same experiment was repeated with a 1.0 mM solution of the macrocycle **2** in [D_6]DMSO/0.5% water in the presence of 5.0 equivalents of tetrabutylammonium acetate, the rate of decomposition was slowed significantly (Figure 7). In this case, no changes were observed in the spectra during the first 6 h, and only after 24 h is possible to detect a small amount of the decomposition product (signals at ca. $\delta = 10.1$, 6.7 and 5.3 ppm). The presence of the anion appears to increase the stability of macrocycle **2**, presumably due to complex formation conferring extra stability on the macrocyclic framework.

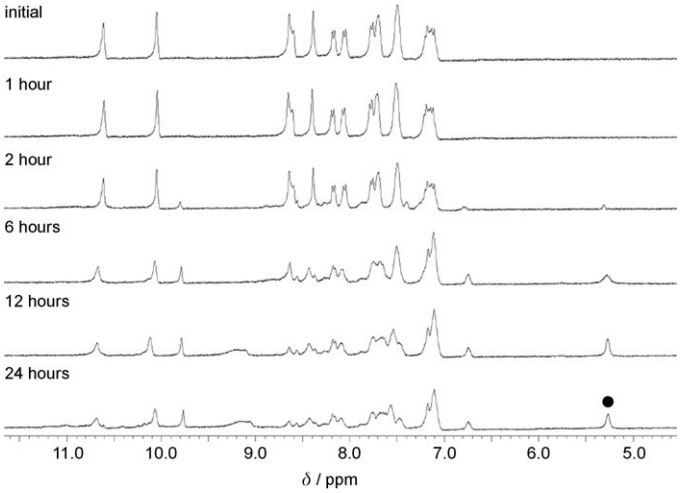

Figure 6. Decomposition of a solution of receptor **2** (1.0 mM) in [D_6]DMSO/0.5% water at 25°C as shown by ^{1}H NMR spectroscopy. The marked resonance corresponds to free NH_2 shown in structure of **9**.

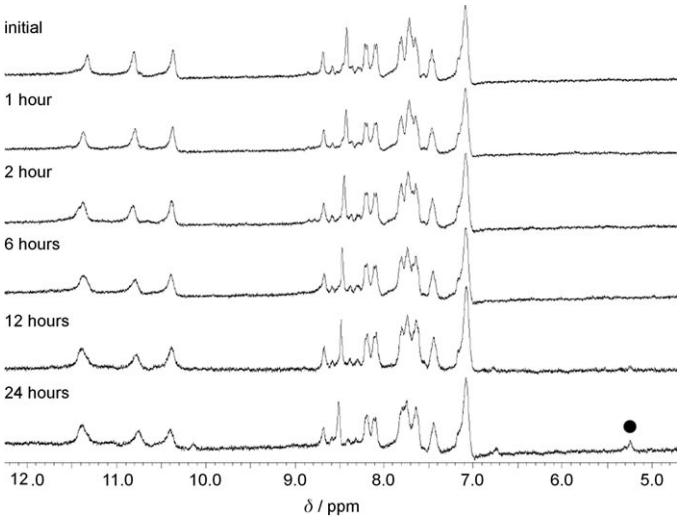

Figure 7. Decomposition of a solution of receptor **2** (1.0 mM) in [D_6]DMSO/0.5% water at 25°C as shown by ^{1}H NMR spectroscopy in the presence of 5.0 equivalents of tetrabutylammonium acetate. Decomposition is slower than in the absence of tetrabutylammonium acetate. The marked resonance corresponds to free NH_2 shown in structure of **9**.

We then synthesised a series of acyclic fragments **3**–**6** and the diphenylurea **10**[13] to investigate the interaction between the NH groups and anions in the acyclic fragments as compared the macrocycles. The syntheses of the fragments are discussed in the Experimental Section below. The crystal structure of compound **4** is discussed in the Supporting Information. Compounds **3** and **4** were synthesised as analogues for parts of the macrocycles containing the urea group. The stability constants with oxo anions show that the addition of an extra amide group in compound **4** as compared to compound **3** has a small but positive effect on the stability of the complex formed (Table 3). *N*,*N*′-Diphenylurea **10**[13] was also studied under these conditions and shows a similar affinity for benzoate but a significantly lower affinity for acetate and dihydrogen phosphate than compounds **3** or **4** (see Table 3).

This evidence leads us to suggest that the amide NH groups have a less significant interaction with oxo anions as compared to the urea. The less significant participation of the amide NH groups is also illustrated by plotting the change in chemical shift of the NH groups in the compound with increasing anion concentration. This is illustrated in Figure 8, which shows the shifts of the NH groups in compounds **3** and **4** upon addition of aliquots of tetrabutylam-

Table 3. Stability constants [M^{-1}] of compounds **3**–**6** and **10** with a variety of anionic guests added as tetrabutylammonium salts as determined by ^1H NMR titration techniques performed in [D_6]DMSO/0.5% water at 298 K following NH (or CH)[a] resonances in the receptors.[b]

	3	**4**	**5**	**6**	**10**
Cl^-	<10	<10	<10	$K_1=38$ $K_2=10$	31
Br^-	–	–	–	–	–
HSO_4^-	–	–	–	–	–
$H_2PO_4^-$	1290	1650	681	294	523
NO_3^-	–	–	–	–	–
$CH_3CO_2^-$	2360	2470	419	137	1261
$C_6H_5CO_2^-$	606	784	101	71	674
$K_a(CH_3CO_2^-)/K_a(H_2PO_4^-)$	1.84	1.49	0.62	0.47	2.41

[a] Due to NH broadening titration was conducted by following the shift of an ArH proton. [b] Errors estimated to be <15%.

monium benzoate in [D_6]DMSO/0.5% water at 298 K showing a much greater downfield shift for the urea NH groups than for the amide NH group(s). Potential binding modes for benzoate with compounds **3** and **4** are shown in Figure 8. The binding mode of carboxylates to compounds **3** and **4** is different from the binding mode in macrocycle **1** as the evidence leads us to suggest only one of the oxygen atoms in the carboxylate binds to this unit in the latter system. However, as the two oxygen atoms in the anion bind as shown in Figure 8, there is an interaction with the pendant amides resulting in the small downfield shift of these proton resonances. The receptors show a slightly higher affinity for oxo anions than macrocycle **2**, but with a similar selectivity for acetate versus dihydrogen phosphate. This finding supports the hypothesis that the predominant interaction of oxo anions with compound **2** is through the urea and adjacent amide groups.

Compounds **5** and **6** have a lower affinity for anions than the urea-containing receptors **3** and **4**, with the pyridine-containing receptor **5** having a slightly higher affinity for anionic guests than receptor **6**, presumably due to the preorganising influence of the pyridine group on the pendant bisamides favouring the formation of a cleft conformation (Table 3). Figure 9 shows the change in chemical shift of the NH groups in these compounds upon addition of benzoate. In these cases both the central and terminal amide NH groups shift downfield upon addition of benzoate and potential solution binding modes of this anion with the receptors are shown in Figure 9 (right). The receptors show a very weak interaction with chloride in solution binding this anion in a 1:2 receptor:anion stoichiometry (receptor **6**; see Table 3). Interestingly compound **6** is stable in solution under the conditions that would lead to the decomposition of compound **2**.

Crystals of the tetrabutylammonium benzoate complex of receptor **6** were grown by slow evaporation of a solution of the receptor in acetonitrile in the presence of excess anion salt. In contrast to the results obtained in solution, the receptor forms a 1:2 complex with benzoate (Figure 10). The central isophthalamide unit adopts a *syn–anti* conformation so forming two binding clefts each consisting of one central amide and one terminal amide group with each NH forming a single bond to a benzoate oxygen atom: N1–O8 3.021(4) Å, N2–O7 2.786(4) Å and N3–O5 2.923(4) Å, N4–O6 2.880(4) Å. Interestingly the binding mode of each benzoate to the receptor in the solid state is similar to the proposed structure of the solution complex species in that the anion is bound to both the central and terminal amide NH groups; however, in the solid state the *syn–anti* conformation of the central isophthalamide presents the two halves of the proposed solution binding site to different anionic guests.

Crystals of the tetrabutylammonium chloride complex of receptor **6** were obtained by slow evaporation of a solution of the receptor in acetonitrile in the presence of excess tetrabutylammonium chloride (Figure 11). One molecule of the receptor crystallises with three chloride and three counter tetrabutylammonium ions. The central isophthalamide

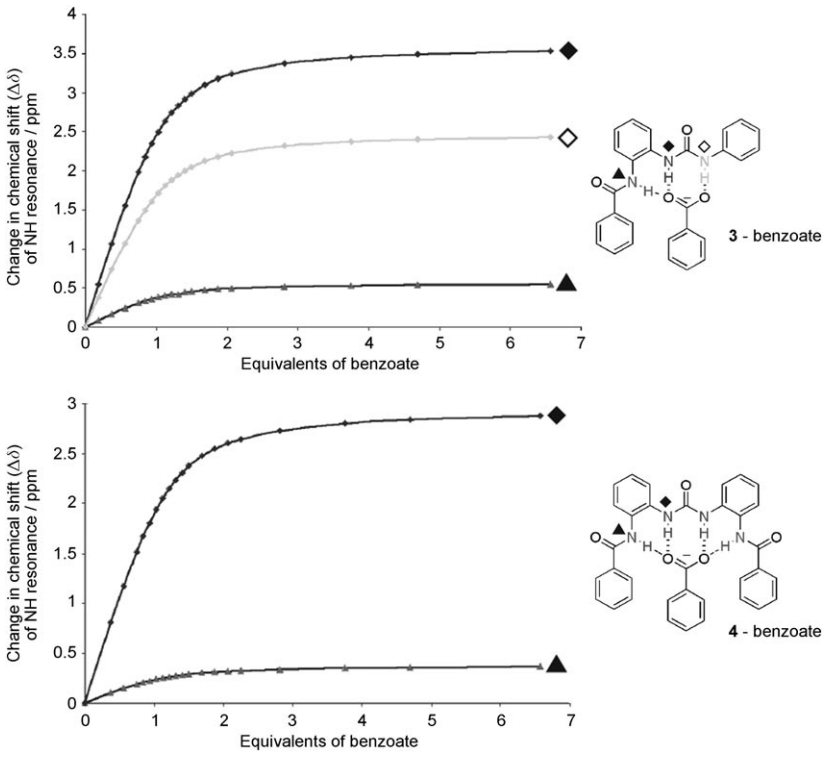

Figure 8. Shifts of the NH protons in compounds **3** (top) and **4** (bottom) showing downfield shifts upon addition of benzoate. In both cases the shift of the urea protons is greater than the amide NH groups. Potential binding modes of benzoate to the receptors (that are consistent with the NMR data) are shown on the right.

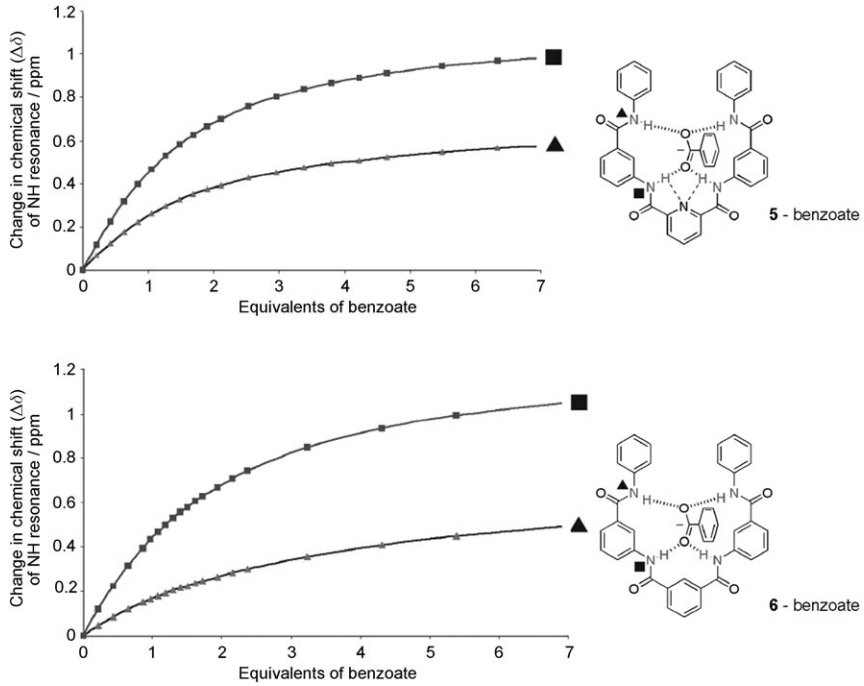

Figure 9. Shifts of the NH protons in compounds **5** (top) and **6** (bottom) showing downfield shifts upon addition of benzoate. Potential binding modes of benzoate to the receptors (that are consistent with the NMR data) are shown on the right. In both cases the downfield shift of the central amide groups is higher than that of the terminal NH groups.

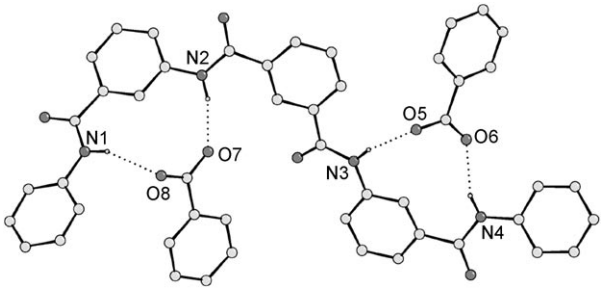

Figure 10. The X-ray crystal structure of the tetrabutylammonium benzoate complex of receptor **6**. Non-acidic hydrogen atoms and tetrabutylammonium counter cations have been omitted for clarity.

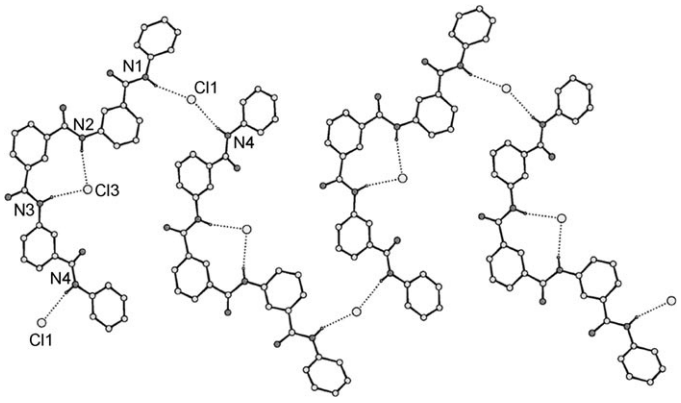

Figure 11. The X-ray crystal structure of the tetrabutylammonium chloride complex of receptor **6**. Non-acidic hydrogen atoms, tetrabuylammonium counter cations, non-bound chloride and water have been omitted for clarity.

unit adopts a *syn–syn* conformation binding a single chloride anion by means of two NH···Cl^- hydrogen bonds (N2···Cl3 3.3856(4) Å and N3···Cl3 3.289(4) Å). The other chloride bound to the receptor bridges between terminal NH groups in adjacent receptors (N1···Cl1 3.325(4) Å and N4···Cl1 3.412(4) Å). Another chloride anion in the structure forms a hydrated ion pair with a tetrabutylammonium cation and does not interact with the receptor.

Conclusion

Macrocycle **1** forms stable hydrogen-bonded complexes with carboxylate anions and displays a 100-fold selectivity for acetate versus dihydrogen phosphate in [D_6]DMSO/0.5% or 5% water. In contrast, macrocycle **2** shows a lower affinity and selectivity for carboxylates than **1** and in addition is unstable in [D_6]DMSO/water. We believe the difference in stability is due to the absence of the pre-organising influence of the pyridine group in compound **1** resulting in a twisted conformation of the isophthalamide group in compound **2** and consequently a higher propensity for amide hydrolysis under neutral conditions.[12] Whilst no X-ray structural data for this unstable compound has been obtained, anion-binding studies show significant differences in the mode of interaction of oxo anions with compounds **1** and **2**, data that supports the hypothesis of a distorted 2,6-dicarboxyamidophenyl group in macrocycle **2**. The more flexible acyclic receptors **3**–**6** form significantly less stable complexes with anions than macrocycle **1** and, like macrocycle **2**, do not display significant selectivity amongst oxo-anionic guests. These results show that a single change in a macrocyclic framework can result not only in significantly improved anion selectivity, but also in improved stability with macrocycle **1** showing excellent selectivity for carboxylates under partially aqueous conditions. We are continuing to explore the complexation properties of this new family of macrocyclic anion receptors.

Experimental Section

General remarks: All reactions were performed in oven-dried glassware under a slight positive pressure of nitrogen. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were determined on a Bruker AV300 or Bruker DPX 400 spectrometer, respectively. Chemical shifts

for ^{1}H NMR spectra are reported in parts per million, calibrated to the residual solvent peak set, with coupling constants reported in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm, relative to the central line of a septet at $\delta = 39.52$ ppm for deuterio-dimethylsulfoxide. Infrared (IR) spectra were recorded on a Mattson Satellite (ATR) FTIR and are reported in wavenumbers (cm^{-1}). Melting points were measured on a Gallenkamp melting point apparatus.

Macrocycle 1: An oven-dried 1 L three-necked round-bottomed flask was filled with dry dichloromethane (500 mL) to which triethylamine (0.49 mL, 3.43 mmol) and a catalytic quantity 4-dimethylaminopyridine (0.01 g) was added. Two additional solutions were prepared, the first of **8** (1.50 g, 3.12 mmol) and tetrabutylammonium acetate (1.50 g, 4.97 mmol) in dry dichloromethane (50 mL), the second of 2,6-pyridinedicarbonyl chloride (0.64 g, 3.12 mmol) in dry dichloromethane (50 mL), with both solutions were introduced into the reaction vessel by using a motor-driven syringe pump over a period of 6 h. After the addition the reaction was left stirring at ambient temperature for a further 72 h, before the volume of solvent was reduced by approximately 75% and reaction was extracted with water (3×200 mL). The retained organic phase was dried with $MgSO_4$ before removal of solvent under rotary evaporator. The light grey residue was dissolved in a small volume of 92:8 dichloromethane/methanol before purification by flash column chromatography. The white solid was further purified from hot ethyl acetate to give **1** as a white powder (0.32 g, 0.52 mmol, 17%). M.p. = 235 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 11.26$ (s, 2H; amide NH), 9.99 (s, 2H; amide NH), 8.54 (d, $J = 8.3$ Hz, 2H; ArH), 8.50 (s, 2H; urea NH), 8.43–8.32 (m, 3H; ArH), 8.16 (s, 2H; ArH), 7.97 (d, $J = 8.3$ Hz, 2H; ArH), 7.72 (d, $J = 8.3$ Hz, 2H; ArH), 7.60 (t, $J = 7.9$ Hz, 2H; ArH), 7.31–7.21 (m, 4H; ArH), 7.07 ppm (t, $J = 7.5$ Hz, 2H; ArH); ^{13}C{^{1}H} NMR (75 MHz, [D$_6$]DMSO): $\delta = 166.9$ (CO), 161.6 (CO), 153.2 (CO), 148.5 (C), 140.4 (CH), 138.0 (C), 136.0 (C), 134.9 (C), 129.1 (CH), 128.3 (C), 127.3 (CH), 126.5 (CH), 125.2 (CH), 123.4 (CH), 122.9 (CH), 122.8 (CH), 120.8 ppm (CH); IR (film): $\tilde{\nu} = 3245$, 3056, 1656, 1597, 1530, 1441, 1305, 747 cm^{-1}; LRMS (ES−): m/z: 646.3 [M+Cl]$^-$, 724.4 [M+TFA−H]$^-$; elemental analysis calcd (%) for $C_{34}H_{25}N_7O_5 \cdot 0.50\,CH_2Cl_2$: C 63.35, H 4.01, N 14.99; found: C 63.19, H 4.17, N 14.96.

Macrocycle 2: An oven-dried 500 mL three-necked round-bottomed flask was filled with **8** (1.50 g, 3.12 mmol) and isophthaloyl dichloride (0.70 g, 3.45 mmol) in anhydrous methanol (350 mL) to form a suspension when stirred. Concentrated sulfuric acid (0.375 mL, 6.870 mmol) was added to this stirred suspension. Following this addition the reaction was then heated to reflux under nitrogen for 30 minutes, after which the mixture was evaporated under low pressure. The resulting residue was then resuspended in water (100 mL) and filtered to afford a white solid that was washed with water (3×10 mL) and diethyl ether (3×10 mL). The white solid was triturated in MeOH/CH_2Cl_2 (1:1) to give **2** as a white powder (0.53 g, 0.87 mmol, 28%). M.p. = 224 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 10.61$ (s, 2H; amide NH), 10.05 (s, 2H; amide NH), 8.64 (s, 2H; urea NH), 8.58 (d, $J = 9.4$ Hz, 2H; ArH), 8.39 (s, 1H; ArH), 8.18 (d, $J = 8.1$ Hz, 2H; ArH), 8.05 (d, $J = 8.1$ Hz, 2H; ArH), 7.78–7.69 (m, 5H; ArH), 7.49 (m, 4H; ArH), 7.13 ppm (m, 4H; ArH); ^{13}C{^{1}H} NMR (75 MHz, [D$_6$]DMSO): $\delta = 165.3$ (CO), 165.1 (CO), 153.9 (CO), 139.3 (C), 134.9 (C), 134.8 (C), 133.2 (C), 130.8 (CH), 129.3 (C), 128.7 (CH), 128.6 (CH), 127.1 (CH), 126.7 (CH), 125.9 (CH), 123.6 (CH), 123.5 (CH), 123.0 (CH), 122.6 (CH), 120.2 ppm (CH); IR (film): $\tilde{\nu} = 3260$, 1651, 1592, 1530, 1483, 1451, 1303, 1254, 751 cm^{-1}; LRMS (ES−): m/z: 645.0 [M+Cl]$^-$, 721.1 [M+TFA−H]$^-$; elemental analysis calcd (%) for $C_{35}H_{26}N_6O_5 \cdot CH_2Cl_2$: C 62.17, H 4.06, N 12.08; found: C 62.39, H 4.27, N 12.06.

***N*-[2-(3-Phenylureido)phenyl]benzamide (3)**: *N*-(2-aminophenyl)benzamide (0.54 g, 2.5 mmol) dissolved in dry dichloromethane (40 mL) was placed into an oven-dried 100 mL three-necked round-bottomed flask and phenyl isocyanate (0.28 mL, 2.5 mmol) was then added dropwise. The reaction was left stirring for 16 h, after which time the resulting white precipitate was removed by filtration and washed with dichloromethane and diethyl ether to afford the product as a white powder (0.82 g, 2.5 mmol, 97.0%). M.p. = 198 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 9.21$ (s, 1H; NH), 8.08 (s, 1H; NH), 8.04 (d, $J = 1.4$ Hz, 2H; ArH), 8.01 (s, 1H; NH), 7.57 ppm (m, 3H; ArH); ^{13}C{^{1}H} NMR (75 MHz, [D$_6$]DMSO): $\delta = 165.8$ (CO), 152.9 (CO), 139.7 (C), 134.5 (C), 134.1 (C), 131.7 (CH), 128.8 (CH), 128.4 (CH), 128.1 (C), 127.8 (CH), 127.3 (CH), 126.3 (CH), 122.7 (CH), 122.1 (CH), 121.8 (CH), 118.2 ppm (CH); IR (film): $\tilde{\nu} = 3350$, 3200, 3143, 3044, 2995, 1638, 1565, 1478, 1438, 1322, 1226, 748 cm^{-1}; LRMS (ES−): m/z: 444.0 [M+TFA−H]$^-$, 775.1 [2M+TFA−H]$^-$; elemental analysis calcd (%) for $C_{20}H_{17}N_3O_2 \cdot 0.05\,CH_2Cl_2$: C 71.75, H 5.14, N 12.52; found: C 71.99, H 5.17, N 12.57.

1,3-Bis-(2-benzanilidephenyl)urea (4):[14] A solution of 1,3-bis-(2-aminophenyl)urea (0.35 g, 1.5 mmol), triethylamine (0.43 mL, 3.1 mmol) and DMAP (0.002 g, cat.) in dry dichloromethane (30 mL) was stirred for 15 minutes in an oven-dried 100 mL three-necked round-bottomed flask. After this benzoyl chloride (0.34 mL, 2.9 mmol) was added to the reaction in a dropwise manner with the reaction then left stirring for 18 h, after which solvent was removed by a rotary evaporator. The crude product was purified by flash column chromatography using dichloromethane/methanol 95:5 as eluent. The white product obtained was further purified by recrystalisation from hot ethanol which yielded compound **4** as a white powder (0.39 g, 0.87 mmol, 49%). M.p. = 194 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 10.00$ (s, 2H; NH), 8.61 (s, 2H; NH), 7.99 (m, 4H; ArH), 7.75 (dd, $J = 7.9$, 1.1 Hz, 2H; ArH), 7.50 (m, 8H; ArH), 7.22 (td, $J = 7.5$, 1.5 Hz, 2H; ArH), 7.11 ppm (td, $J = 7.6$, 1.5 Hz, 2H; ArH); ^{13}C{^{1}H} NMR (75 MHz, [D$_6$]DMSO): $\delta = 165.6$ (CO), 153.7 (CO), 134.3 (C), 133.5 (C), 131.6 (CH), 129.0 (C), 128.4 (CH), 127.7 (CH), 126.8 (CH), 126.0 (CH), 123.3 (CH), 122.9 ppm (CH); IR (film): $\tilde{\nu} = 3239$, 3058, 3027, 1704, 1638, 1593, 1514, 1472, 1437, 1296, 1261 cm^{-1}; LRMS (ES−): m/z: 562.9 [M+TFA−H]$^-$, 934.9 [2M+Cl]$^-$, 1386.2 [3M+Cl]$^-$; elemental analysis calcd (%) for $C_{27}H_{22}N_4O_3$: C 71.99, H 4.92, N 12.44; found: C 71.75, H 4.87, N 12.36.

Pyridine-2,6-dicarboxylic acid bis-[(3-phenylcarbamoylphenyl)amide)] (5): In an oven-dried 250 mL three-necked round-bottomed flask, a stirring solution of 3-aminobenzanilide (0.48 g, 2.26 mmol), triethylamine (0.35 mL, 2.49 mmol) and DMAP (0.004 g, cat.) in dry dichloromethane (50 mL) was left for 15 minutes before adding 2,6-pyridinedicarbonyl chloride (0.23 g, 1.13 mmol). The reaction was left stirring at ambient temperature for 18 h, after which the resulting white precipitated product was removed by filtration was washed with dichloromethane and water with **5** isolated as a white solid (0.32 g, 5.80 mmol, 52%). M.p. > 300 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 11.25$ (s, 2H; NH), 10.34 (s, 2H; NH), 8.47 (m, 2H; ArH), 8.45 (s, 2H; ArH), 8.34 (dd, $J = 8.7$, 6.8 Hz, 1H; ArH), 8.19 (m, 1H; ArH), 8.16 (m, 1H; ArH), 7.80 (m, 6H; ArH), 7.62 (t, $J = 7.9$ Hz, 2H; ArH), 7.37 (m, 4H; ArH), 7.12 ppm (m, 2H; ArH); ^{13}C{^{1}H} NMR (75 MHz, [D$_6$]DMSO): $\delta = 165.4$ (CO), 162.0 (CO), 148.7 (C), 140.1 (CH), 139.1 (C), 138.3 (C), 135.8 (C), 128.9 (CH), 128.6 (CH), 125.6 (CH), 124.2 (CH), 123.8 (CH), 123.4 (CH), 120.7 (CH), 120.5 ppm (CH); IR (film): $\tilde{\nu} = 3235$, 3135, 3058, 1646, 2584, 1528, 1422, 1324, 1237, 1142, 1079, 998, 902 cm^{-1}; LRMS (ES+): 578.1 [M+Na]$^+$, 1133.4 [2M+Na]$^+$, 1163.7 [2M+MeOH+Na]$^+$; elemental analysis calcd (%) for $C_{33}H_{25}N_5O_4 \cdot 0.25\,MeOH$: C 70.86, H 4.65, N 12.43; found: C 70.72, H 4.43, N 12.50.

***N*,*N*′-Bis-(3-phenylcarbamoylphenyl)isophthalamide (6)**: A solution of 3-aminobenzanilide (1.00 g, 4.7 mmol), triethylamine (0.72 mL, 5.2 mmol), DMAP (0.003 g, cat.) in dry dichloromethane (30 mL) was placed in an oven-dried 100 mL three-necked flask. The solution was then stirred for 30 minutes before slow portion wise addition of isophthaloyl dichloride (0.48 g, 2.3 mmol). Following the addition the reaction was left stirring for 16 h before precipitated white product was removed by filtration and subsequently washed with dichloromethane (2×10 mL) followed by water (2×10 mL). The precipitate was dried under high vacuum; however, ^{1}H NMR analysis revealed approximately 10% of mono-substituted isophthalic acid side product. The crude product was further purified by suspending in acidic MeOH (100 mL) and refluxing for 18 h. After this time reaction suspension was filtered hot and washed with MeOH (2× 20 mL). Compound **6** was obtained as a white solid (0.65 g, 1.17 mmol, 54%). M.p. > 300 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 10.63$ (s, 2H;

NH), 10.28 (s, 2H; NH), 8.33 (t, $J=1.8$ Hz, 2H; ArH), 8.21 (dd, $J=8.0$, 1.8 Hz, 2H; ArH), 8.07 (m, 2H; ArH), 7.78 (m, 4H; ArH), 7.72 (m, 3H; ArH), 7.54 (t, $J=7.7$ Hz, 2H; ArH), 7.36 (m, 4H; ArH), 7.10 ppm (m, 2H; ArH); $^{13}C\{^1H\}$ NMR (75 MHz, [D$_6$]DMSO): $\delta=165.5$ (CO), 165.1 (CO), 139.2 (C), 139.1 (C), 135.7 (C), 134.9 (C), 130.8 (CH), 128.7 (CH), 128.6 (CH), 127.1 (CH), 123.7 (CH), 123.3 (CH), 122.7 (CH), 120.4 (CH), 120.0 ppm (CH); IR (film): $\tilde{\nu}=3288$, 3061, 1689, 1645, 1534, 1451, 1326, 1253 cm^{-1}; LRMS (ES+): 555.0 $[M+H]^+$; elemental analysis calcd (%) for $C_{34}H_{26}N_4O_4$: C 73.19, H 4.65, N 10.35; found: C 73.24, H 4.68, N 9.97.

1,3-Bis-(2-(3-nitro)benzanilidephenyl)urea (7): A solution of 3-nitrobenzoic acid (3.13 g, 18.73 mmol), triethylamine (2.81 mL, 20.60 mmol), PyBOP (9.75 g, 18.73 mmol) was placed in an oven-dried 100 mL three-necked round-bottomed flask. HOBt (0.01 g) in anhydrous dimethylformamide (40 mL) with 1,3-bis-(2-aminophenyl)urea[8] (2.27 g, 9.37 mmol) was slowly added. Following the addition the reaction was left stirring at ambient temperature for 72 h, after which the solvent was removed using reduced pressure distillation to produce a brown solid residue. The residue was resuspended in methanol (50 mL) and filtered to afford a white solid **7** (3.70 g, 6.84 mmol, 73%) that was further washed with diethyl ether. M.p. = 217 °C; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta=10.37$ (s, 2H; NH), 8.78 (s, 2H; NH), 8.52 (s, 2H; NH), 8.39 (m, 4H; ArH), 7.84 (dd, $J=8.3$, 1.5 Hz, 4H; ArH), 7.75 (t, $J=7.9$ Hz, 2H; ArH), 7.40 (dd, $J=7.5$, 1.1 Hz, 2H; ArH), 7.25 (m, 2H; ArH), 7.10 ppm (m, 2H; ArH); $^{13}C\{^1H\}$ NMR (75 MHz, [D$_6$]DMSO): $\delta=163.6$ (CO), 153.3 (CO), 147.7 (C), 135.7 (C), 134.1 (CH), 130.0 (CH), 128.1 (C), 127.1 (CH), 126.5 (CH), 126.1 (CH), 123.1 (CH), 122.6 (CH), 122.4 ppm (CH); IR (film): $\tilde{\nu}=3260$, 1651, 1592, 1530, 1483, 1451, 1303, 1254, 751 cm^{-1}; LRMS (ES−): m/z: 653.1 $[M+TFA-H]^-$, 1193.7 $[2M+TFA-H]^-$, 1733.4 $[3M+TFA-H]^-$; elemental analysis calcd (%) for $C_{27}H_{20}N_5O_7$: C 60.00, H 3.73, N 15.54; found: C 59.70, H 3.83, N 15.60.

1,3-Bis-(2-(3-amino)benzanilidephenyl)urea (8): A suspension of 1,3-bis-(2-(3-nitro)benzanilidephenyl)urea (0.50 g, 0.93 mmol) in ethanol (150 mL) was place in an oven-dried three-necked round-bottomed flask and the suspension was stirred. Pd/C 10% (0.01 g, cat.) and hydrazine monohydrate (0.50 mL) were added dropwise to this suspension. The reaction was then heated to reflux and left stirring for 16 h, after which the reduced product was removed by filtration. The product was dissolved in dimethylformamide and filtered to remove Pd/C, after which the solvent was removed by reduced pressure distillation, resuspended in dichloromethane and washed with water to remove remaining dimethylformamide. The white precipitated product **8** was removed by filtration (0.40 g, 0.83 mmol, 89%). M.p. = 237 °C; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta=$ 9.79 (s, 2H; amide NH), 8.62 (s, 2H; urea NH), 7.65 (dd, $J=7.9$, 1.5 Hz, 2H; ArH), 7.49 (dd, $J=7.5$, 1.5 Hz, 2H; ArH), 7.22–7.09 (m, 10H; ArH), 6.75 (m, 2H; ArH), 5.27 ppm (s, 4H; NH$_2$); $^{13}C\{^1H\}$ NMR (75 MHz, [D$_6$]DMSO): $\delta=166.1$ (CO), 153.9 (CO), 148.8 (C), 135.1 (C), 132.9 (C), 129.7 (C), 128.8 (CH), 126.4 (CH), 125.7 (CH), 123.5 (CH), 123.1 (CH), 116.9 (CH), 114.5 (CH), 113.2 ppm (CH); IR (film): $\tilde{\nu}=3312$, 3285, 1641, 1509, 1441, 1308, 1293, 1275, 1233 cm^{-1}; LRMS (ES−): 515.2 $[M+Cl]^-$, 542.1 $[M+2MeOH-H]^-$, 559.1 $[M+Br]^-$, 593.3 $[M+TFA-H]^-$, 995.4 $[2M+Cl]^-$, 1041.4 $[2M+Br]^-$, 1073.6 $[2M+TFA-H]^-$; elemental analysis calcd (%) for $C_{27}H_{24}N_5O_3\cdot0.25\,CH_3OH$: C 67.00, H 5.16, N 17.20; found: C 66.80, H 5.11, N 17.06.

^{1}H NMR spectroscopic titrations: A Bruker AV300 NMR spectrometer was used to measure the ^1H NMR shifts of the NH protons of the receptors. Solutions of **1**–**6** and **10** were titrated with ≈10 mM anion salt in a ≈1 mM solution of the compounds in [D$_6$]DMSO/0.5% water or [D$_6$]DMSO/5% water at 25 °C. The titration data was plotted Δppm versus concentration of guest and fitted to a binding model using the EQNMR computer program.[10]

X-ray structure determinations: Cell dimensions and intensity data were recorded at 120 K, using a Bruker Nonius KappaCCD area detector diffractometer mounted at the window of a rotating Mo anode ($\lambda(Mo_{K\alpha})=$ 0.71073 Å). The crystal-to-detector distance was 30 mm and φ and Ω scans were carried out to fill the asymmetric unit. Data collection and processing were carried out using the programs COLLECT,[15] and DENZO[16] and an empirical absorption correction was applied using SADABS.[17] The structures were solved by direct methods[18] and refined by full-matrix least-squares methods on F^2. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were treated using a riding model.

Crystal data for ***6****(TBA benzoate)$_2$*: $C_{80}H_{108}N_6O_8$, $M_r=1281.72$, $T=$ 120(2) K, monoclinic, space group $P2_1/n$, $a=8.5260(2)$, $b=20.8328(11)$, $c=41.390(2)$ Å, $\beta=94.690(3)°$, $V=7327.1(6)$ Å^3, $\rho_{calcd}=1.162$ g cm^{-3}, $\mu=$ 0.075 mm^{-1}, $Z=4$, reflections collected: 41713, independent reflections: 13190 ($R_{int}=0.0973$), final R indices $[I>2\sigma(I)]$: $R1=0.0845$, $wR2=$ 0.2018, R indices (all data): $R1=0.1767$. $wR2=0.2511$.

Crystal data for ***6****(TBA Cl)$_3$·H$_2$O*: $C_{82}H_{136}N_7O_5Cl_3$, $M_r=1406.33$, $T=$ 120(2) K, orthorhombic, space group $P2_12_12_1$, $a=8.2548(3)$, $b=$ 20.2938(9), $c=48.724(2)$ Å, $V=8162.3(6)$ Å^3, $\rho_{calcd}=1.144$ g cm^{-3}, $\mu=$ 0.165 mm^{-1}, $Z=4$, reflections collected: 42045, independent reflections: 16936 ($R_{int}=0.1239$), final R indices $[I>2\sigma(I)]$: $R1=0.0956$, $wR2=$ 0.1666, R indices (all data): $R1=0.2121$. $wR2=0.2149$.

CCDC-609225 and CCDC-609227 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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