Anion-binding modes in a macrocyclic amidourea†

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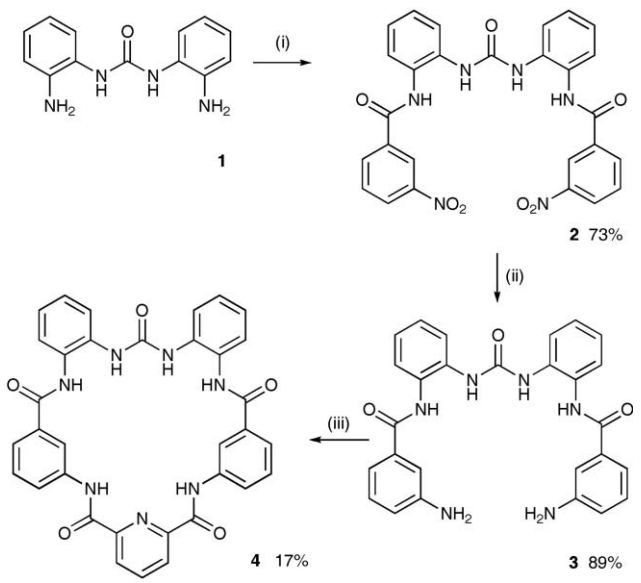
A macrocyclic amidourea shows anion dependent binding modes with a variety of different putative anionic guests.

Anion complexation chemistry is a rapidly evolving area of supramolecular chemistry currently receiving much attention.[1] There are a number of examples of anion receptors containing amide[2] and urea[3] containing hydrogen bonding groups. Macrocyclic amides and ureas are particularly effective hosts for a variety of guests finding applications in molecular recognition applications and self-assembling ensembles.[4] We have recently synthesised a series of oxo-anion selective bis-urea receptors based upon *ortho*-phenylenediamine.[5] We decided to combine a 2,6-dicarboxamidopyridine group and a urea in a macrocyclic receptor **4** containing two '*ortho*-phenylenediamine-like' 1,2-functionalised phenyl rings, designed to contain a convergent set of hydrogen bonds, and study the anion complexation properties of this new macrocyclic system.

Macrocycle **4** was synthesized in 11% overall yield from 1,3-bis(2-aminophenyl)urea[6] (Scheme 1). Compound **1** was converted to compound **2** *via* an amide coupling reaction with 3-nitrobenzoic acid which was subsequently reduced using hydrazine hydrate/palladium on carbon to give bis-amine **3**. The bis-amine was condensed with pyridine 2,6-dicarbonylchloride in the presence 1.6 equivalents of tetrabutylammonium acetate. The latter reagent was used to solubilise compound **3** in dichloromethane and also function as a potential template for the formation of **4** (earlier attempts at the synthesis of **4** using tetrabutylammonium chloride in DMF resulted in the cyclization reaction proceeding in less than 1% yield). 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.



Scheme 1 The synthesis of macrocycle **4**. (i) 3-Nitrobenzoic acid, PyBOP, Et_3N, HOBt, DMF (anhydrous); (ii) $NH_2NH_2{\cdot}H_2O$, Pd/C 10% cat., EtOH; (iii) 2,6-pyridine dicarbonylchloride, tetrabutylammonium acetate, Et_3N, DMAP, CH_2Cl_2.

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† Electronic supplementary information (ESI) available: Experimental section, binding data and supplementary X-ray figures. See DOI: 10.1039/b610938a

The stability constants of macrocycle **4** 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 using the EQNMR computer program.[7] The stability constant data shows that the macrocycle possesses a particularly high affinity for carboxylates. In fact the macrocycle binds acetate approximately 100 times more strongly than dihydrogen phosphate both in DMSO-d_6–0.5% water and in DMSO-d_6–5% water solution. Fig. 1 shows the shifts of each NH group present in the macrocycle upon addition of one equivalent of a variety of anions. The molecule contains a C_2 axis of symmetry which simplifies the ^{1}H NMR spectrum of the macrocycle such that there are three NH resonances in the NMR spectrum.

The 'linking' amide groups adjacent to the urea 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 Fig. 2 for the interaction of the macrocycle with carboxylates in which one carboxylate oxygen binds to the two urea NH groups and the other binds to

Table 1 Stability constants (M^{-1}) of compound **4** with a variety of anionic guests added as tetrabutylammonium salts as determined by ^{1}H NMR titration techniques performed in DMSO-d_6–0.5% water and DMSO-d_6–5% water at 298 K following NH (or CH[a]) resonances in the receptors. Errors < 15%

	Stability constants (M^{-1})	
Anion	DMSO-d_6–0.5% water	DMSO-d_6–5% water
Cl^-	194	42
Br^-	10	—
HSO_4^-	115	—
$H_2PO_4^-$	142[a]	51
NO_3^-	<10	—
$CH_3CO_2^-$	16500[b]	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] 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.

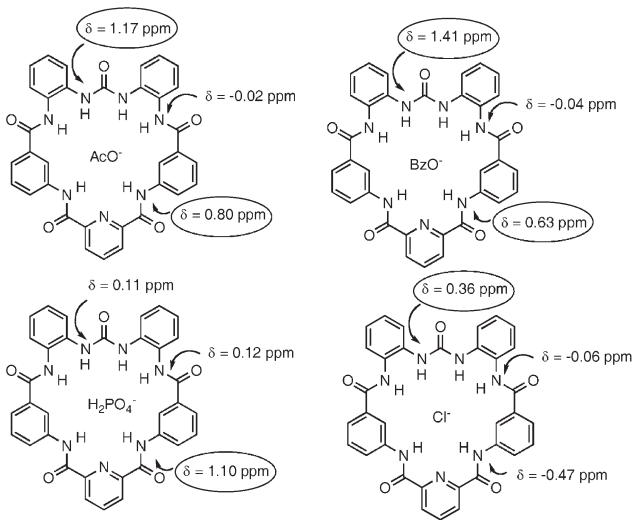

Fig. 1 Shifts of the NH proton resonances in compound **4** in the presence of one equivalent of tetrabutylammonium anion salt in DMSO-d_6–0.5% water. Downfield shifts are shown as positive number and upfield shifts as negative numbers. The most significant downfield shifts are circled.

the 2,6-dicarboxamidopyridine NH groups leaving the amide NH groups next to the urea free. In contradistinction to these results, addition of one equivalent of dihydrogen phosphate causes a significant downfield shift of only the amide groups adjacent to the pyridine ring. The other NH groups in the macrocycle shift

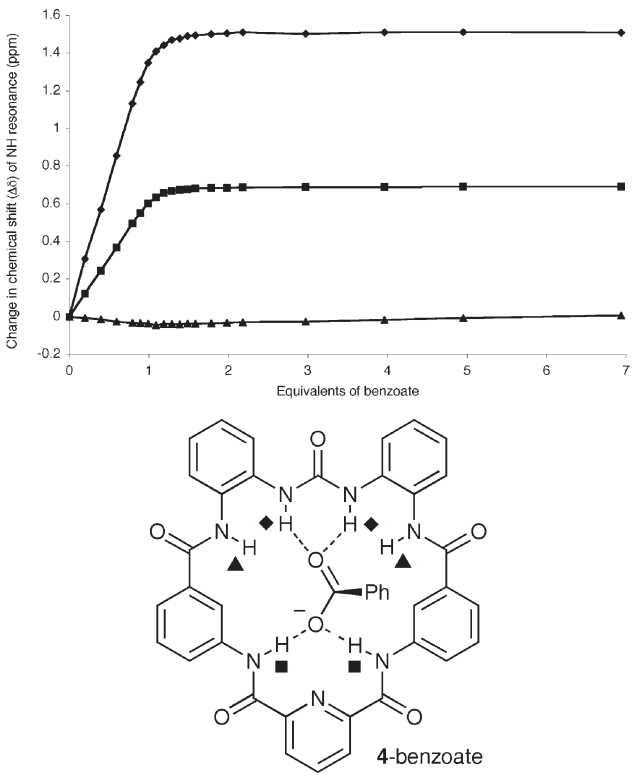

Fig. 2 Shift of the NH protons in compound **4** upon addition of benzoate. The amide protons adjacent to the urea group do not shift significantly whilst the 2,6-diamidopyridine NH groups and the urea NH groups shift downfield by 0.69 and 1.51 ppm respectively upon addition of excess tetrabutylammonium benzoate. A potential binding mode of benzoate to the macrocycle (bottom).

downfield by only *ca.* 0.1 ppm. 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. These results lead us to suggest that this anion is bound predominantly by the urea NHs 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.

Good quality crystals of tetrabutylammonium salts of the macrocycle have proven to be difficult to obtain. However small crystals were obtained by slow evaporation of a DMSO solution of the compound **4** in the presence of tetrabutylammonium fluoride.‡ The crystals proved to be a mixed tetrabutylammonium fluoride–carbonate salt with the formula $(\mathbf{4})_4((C_4H_9)_4N^+)_9(CO_3^{2-})_4(F^-)\cdot 4H_2O$ with the carbonate anions bound within the macrocycle as shown in Fig. 3. Carbonate was not present in the solution prior to crystallization, however, the crystallization vial was left open to the atmosphere and we presume that carbonate originated from CO_2 in the atmosphere which has been fixed by the tetrabutylammonium fluoride–macrocycle solution.[8] The carbonate anion is bound in the cavity *via* six N–H···O hydrogen bonds ranging in donor–acceptor distances of 2.725(13) to 2.840(11) Å. This involves each of the NH groups of the macrocycle as a donor and each oxygen of the carbonate accepting two hydrogen bonds from the macrocycle. Interestingly in the solid state the exocyclic fluoride is bound to four water molecules which form hydrogen bonding bridges to four of the 2,6-diamidopyridine O=C groups (Fig. 4) resulting in the formation of a porous lattice.† Subsequent attempts to measure carbonate binding in solution have so far been hampered by solubility problems.

More success was obtained with tetramethylammonium (TMA) acetate and crystals were obtained by slow evaporation of a methanol solution of the macrocycle in the presence of excess TMA salt.§ The crystal structure shown in Fig. 5 shows the acetate

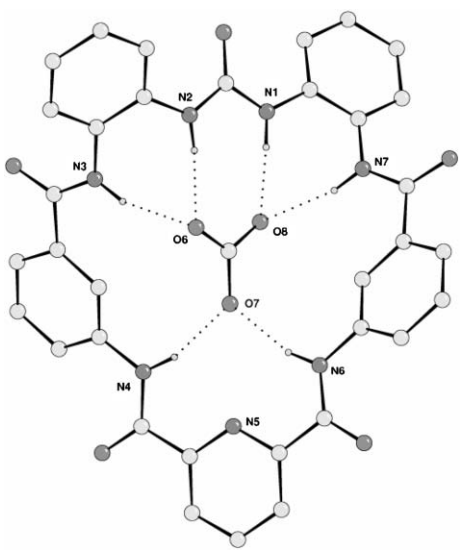

Fig. 3 The X-ray crystal structure of carbonate included within macrocycle **4**. Other components of the structure and non-acidic hydrogen atoms in the structure have been omitted for clarity.

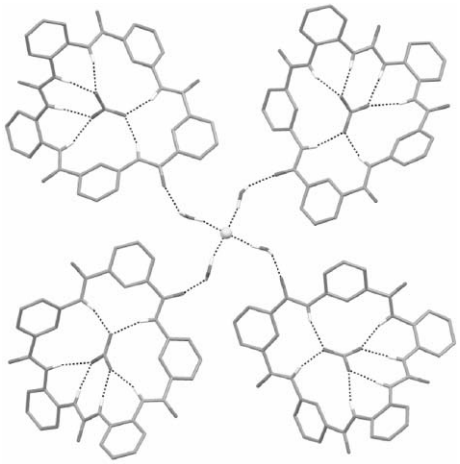

Fig. 4 The coordination environment around the exocyclic fluoride anion (shown in the centre of the figure) in the mixed carbonate–fluoride salt is shown with four water molecules forming hydrogen bonds to the 2,6-diamidopyridine amide CO groups.

anion bound to the pyridine amide NH groups (N4···O7 2.976(6) Å; N6···O7 3.318(6) Å) and, in contradistinction to the solution binding evidence, to one linking amide NH group (N7···O6 2.812(6) Å). However, it important to note that the crystals contain water with one of the water molecules bound to the two urea NH groups within the macrocyclic cavity N1···O8 2.978(7) Å; N2···O8 2.850(7) Å with a hydrogen bond formed between this water and the bound acetate O7···O8 2.673(6) Å. Thus O6 could be regarded as having been 'displaced' from the urea NH groups by the bound water molecule. It is interesting to note that despite acetate being capable of binding in this mode to the linking amide groups it appears not to do so in solution.

A new amidourea macrocycle **4** has been synthesised and shown to have a high selectivity for carboxylate anions over dihydrogen phosphate and chloride. NMR binding experiments lead us to suggest that carboxylates, dihydrogen phosphate and chloride interact differently with the macrocycle. We are continuing to explore the chemistry of macrocycle **4** and analogues of this system in the context of anion complexation and also CO_2 fixation. The results of these studies will be reported in due course.

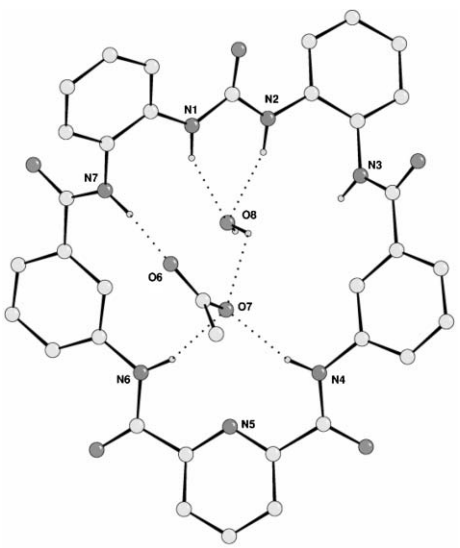

Fig. 5 The X-ray crystal structure of the hydrated tetramethylammonium acetate complex of macrocycle **4**. Counter cation, non-acidic hydrogen atoms and non-cavity bound water are omitted for clarity.

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Notes and references

‡ The crystals of $(\mathbf{4})_4(TBA^+)_9(CO_3^{2-})_4F^-\cdot 4H_2O$ were small (0.1 × 0.02 × 0.01 mm^3) and weakly diffracting and also contained channels of diffuse solvent. This resulted in a poor quality data set that was difficult refine. However, there remain no ambiguities in the correctness of the structure. Crystal data for $(\mathbf{4})_4(TBA^+)_9(CO_3^{2-})_4F^-\cdot 4H_2O$: $C_{284}H_{432}N_{37}O_{36}F$, Mr = 4959.67, T = 120(2) K, tetragonal, space group $P4/n$, a = 42.5993(11), c = 8.5359(2) Å, V = 15490.1(7) $Å^3$, ρ_{calc} = 1.063 g cm^{-3}, μ = 0.071 mm^{-1}, Z = 2, reflections collected: 90086, independent reflections: 11090 (R_{int} = 0.1600), final R indices [$I > 2\sigma I$]: $R1$ = 0.1722, w$R2$ = 0.4091, R indices (all data): $R1$ = 0.2726, w$R2$ = 0.4582. CCDC 608936. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b610938a

§ Crystal data for $(\mathbf{4})(TMA^+)(OAc^-)\cdot 2.75H_2O$: $C_{40}H_{46.5}N_8O_{10.25}$, Mr = 803.35, T = 120(2) K, monoclinic, space group $P2_1/c$, a = 16.9307(16), b = 10.1490(6), c = 23.890(2) Å, β = 102.098(3)°, V = 4013.9(6) $Å^3$, ρ_{calc} = 1.329 g cm^{-3}, μ = 0.098 mm^{-1}, Z = 4, reflections collected: 32236, independent reflections: 7007 (R_{int} = 0.0939), final R indices [$I > 2\sigma I$]: $R1$ = 0.1125, w$R2$ = 0.2288, R indices (all data): $R1$ = 0.1695. w$R2$ = 0.2562. CCDC 616448. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b610938a

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