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Dual-mode recognition of oxalate by protonated azacryptate hosts; conformational response of the guest maximizes π-stacking interactions

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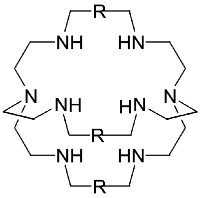
Exceptionally large complexation constants for oxalate encapsulated within azacryptand hosts are partly explained by π-stacking interactions between C=O and aromatic rings.

Small di- or tri-carboxylate anions are of particular interest in sensor technology on account of their biological significance.[1] The toxicity of the simplest dicarboxylate, the oxalate anion, a minor constituent of common foodstuffs, due, among other things, to its avidity for calcium scavenged from bone and other tissue, makes it a priority target. In addition, excessive generation and excretion of oxalate is characteristic of the metabolic disorder hyperoxaluria, so oxalate receptors are sought[2] for sequestration or monitoring purposes.

In previous studies[3,4] of the propensity of protonated azacryptands for oxoanion encapsulation we have demonstrated charge selectivity between mono- and di- negative tetrahedral AO_4^{n-} guests. Stability constants for complexation of such anions are consequent on the steric match arising from the shared trigonal symmetry of host and tetrahedral guest. With the hexaprotonated hosts, $[H_6L]^{6+}$,† we recorded log K_{app}‡ values ($[H_6L]^{6+} + AO_4^{n-}$) of *ca.* 3 for mono-, and in the range 5–7.5 for di-negative[5] tetrahedral AO_4^{n-} ions (A = Cl(VII), Re(VII), Se(VI), Cr(VI)). However, a highly significant step in complexation stability occurs for the dianion, oxalate: we determined the extraordinarily high log K_{app}‡ values of 10.5 ± 0.08 for **1** and 8.3 ± 0.06 for **2** in the present study.

To rationalise this dramatic enhancement of host–guest stability, we crystallised oxalate cryptates of the hexaprotonated ligands:[5]



L^1, R = *m*-xylyl
L^2, R = 2,5 furanyl

X-Ray structures§ $[H_6L.ox]^{4+}$ for L = L^1: **1** and L^2: **2**, are shown in Fig. 1. The oxalate anion is completely encapsulated, and just one oxygen of each carboxylate group is H-bonded, *via* 3 moderately strong H-bonds, to the set of three NH^+ donors from the appropriate end of the cryptand. The C–O distances within each cryptate complex fall into two sets: (a) 1.22–1.24 Å for the relatively double and (b) 1.27–1.28 Å for the relatively single CO bond. The longer C–O distances are involved in hydrogen bonding so the H-bonded oxygen atom presumably carries the negative charge in a relatively localised carboxylate function. We note also the existence of a second type of interaction, demonstrated *via* the close approach and parallel disposition of C=O and aromatic π-systems, Table 1. The oxalate has twisted out of plane to accommodate the most effective π-stacking arrangement. One end of the oxalate anion is sandwiched between two of the aromatic π-systems (red and green strands in Fig. 1), forming a triple π-stack. The other end is associated with the blue strand. Non-planarity of oxalate is rare, but not unprecedented;[6] indeed theoretical studies[6–8] indicate that in the gas phase the D_{2d} form of the ion is the most stable, although only slightly more so (0.015–0.3 eV per molecule) than the planar D_{2h} form. However, these authors[6] note that electrostatic interactions between the carboxylate oxygens and positively charged centres cause the oxalate ions to become flat, explaining the geometry usually observed in the solid state.

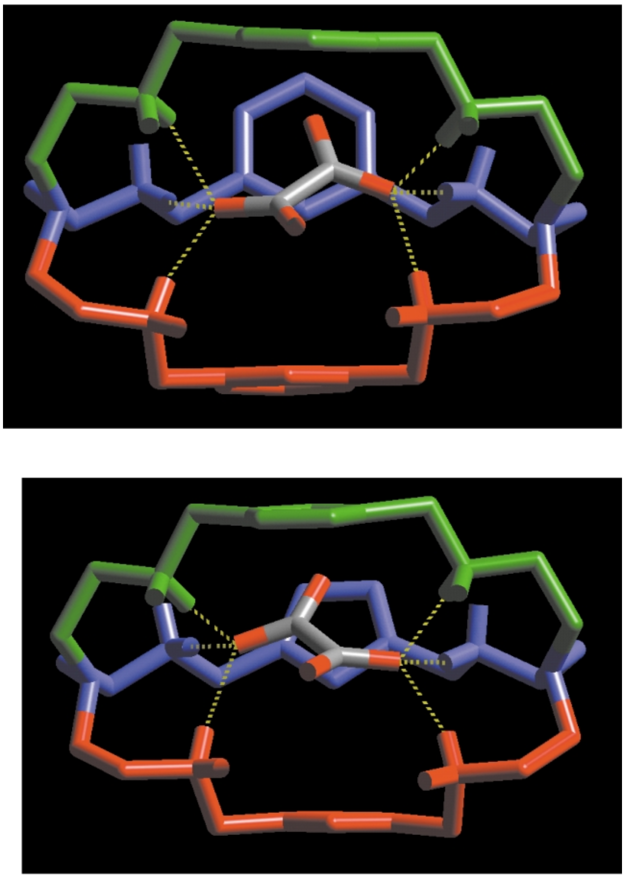


Fig. 1 X-ray structures of **1** (top) and **2** (bottom) illustrating the encapsulated oxalate anion. In both cases the individual cryptand strands have been highlighted in red, green and blue, and hydrogen atoms not involved in hydrogen bonds to the oxalate have been removed for clarity. Selected distances in Table 1.

Comparison of the internuclear distances within the guest illustrates the consequences of the various interactions in operation. C,O distances confirm some localisation of bonding within each encapsulated carboxylate entity, that is further emphasised by the oxalate twist which enables the most effective π-stacking interaction. The N–H···O^- intracryptate H-bond distances are short but not unusually so for anion encryptation.[3–5,9,12]

The stability constants for oxalate complexation by these hexaprotonated cryptands are as much as five orders of magnitude greater than for oxalate encapsulated within aliphatic

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Table 1 H-bonding, π-stacking, CO distances and C,C dihedral angle within the oxalate-cryptate complexes

Complex	N–O H-bond distances	C=O and C–O distances[c]/Å	Oxalate dihedral C,C angle	C=O to Ar distances[a]/Å
$[L^1H_6(COO)_2]^{4+}$ **1**	2.932; 2.769; 2.815; 2.825; 2.833; 3.039	1.230(7); 1.271(8); 1.271(8); 1.249(8)	−147.6(6)	3.172; 4.002; 4.172
$[L^2H_6(COO)_2]^{4+}$ **2**[b]	2.762; 2.840; 2.912; 2.740; 2.935; 2.834	1.281(8); 1.234(8); 1.236(8); 1.280(8)	148.7(6)	3.052; 3.410; 3.991

[a] Average of distance from centre of aromatic ring to carbonyl O. [b] Measured for cation A; the parameters for cation B are very similar. [c] CO distance in free oxalate ion[14] = 1.251 **Å**.

cryptates[10] where, incidentally, log K_{app}‡ values are of the same order as for other di-negative anions such as sulfate or hydrogenphosphate. Both results suggest a considerable stabilising effect for oxalate within our aromatic-linked hosts deriving from the π-stacking interactions. Indeed some of the C=O oxygen to aromatic ring distances in Table 1 are shorter than any previously observed C=O to aromatic contact.[11] In a similar dual mode recognition of terephthalate, involving the aromatic π-systems of host and guest in stacking,[12] the reported log K‡ values (at pH 6) fall in the range 4.4–4.8 depending on concentration. The larger stability constant for **1** *versus* **2** is to some extent the consequence of higher basicity of the cryptand host L[1] but a relatively short¶ intramolecular edge to face aromatic to aromatic π-contact may contribute to the greater stability of this cryptate.

The unprecedentedly high log K values for oxalate encapsulation in these systems are of considerable inherent interest as, to our knowledge, they are the highest recorded complexation constants for dicarboxylate or indeed for any dinegative anion. This should provide further insight into the factors defining anion coordination and recognition. In addition the differentiation from other di-negative anions may be exploitable *e.g.* in oxalate analysis, where a significant problem arises, in the normally used techniques, from interference of sulfate at low oxalate concentrations.[13] With our cryptate systems the large (up to 10^4) selectivity for oxalate over sulfate should suffice to ensure separation of these analytes in preliminary solvent extraction processes. In addition the ability of the cryptate to effectively compete for oxalate with cations, in terms of both absolute complex stability and its pH dependence, may indicate a possible detoxification application.

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Notes and references

† L = $[N(CH_2CH_2N{=}CRC{=}NCH_2CH_2)_3N]$.

‡ Conditional constant in aqueous solution, measured pH-potentiometrically, relative to that for tosylate medium, at 298 K, I = 0.1 M (see refs. 3 and 4 for experimental details).

§ Data were collected with a Bruker-AXS SMART diffractometer using the SAINT-NT[15a] software with graphite monochromated Mo-K_α radiation. A crystal was mounted on to the diffractometer at low temperature under nitrogen at *ca.* 120 K. The structure was solved using direct methods and refined with the SHELXTL version 5[15b] and the non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen-atom positions were added at idealised positions with a riding model and fixed thermal parameters ($U_{ij} = 1.2U_{eq}$ for the atom to which they are bonded). Hydrogen atoms were not located for the water molecules. The function minimised was $\Sigma[w(|F_o|^2 - |F_c|^2)]$ with reflection weights $w^{-1} = [\sigma^2 |F_o|^2 + (g_1P)^2 + (g_2P)]$ where $P = [\max |F_o|^2 + 2|F_c|^2]/3$. Additional material available from the Cambridge Crystallographic Data Centre comprises relevant tables of atomic coordinates, bond lengths and angles, and thermal parameters. CCDC 188702 and 188703. See http://www.rsc.org/suppdata/cc/b2/b207964j/ for crystallographic files in CIF or other electronic format.

Crystal data for $C_{38}H_{80}Cl_4N_8O_{30}$ (**1**): M = 1270.90, triclinic, space group $P1$, a = 11.402(4), b = 13.136(6), c = 20.757(7) Å, α = 77.440(8), β = 77.540(11), γ = 69.446(8), U = 2808.2(19) Å^{-3}, Z = 2, μ = 0.308 mm^{-1}, R_{int} = 0.0680, transmission range(max,min) = 0.928, 0.632. A total of 18384 reflections were measured for the angle range $3 < 2\theta < 50$ and 9684 independent reflections were used in the refinement. The final parameters were $wR2$ = 0.3097 and $R1$ = 0.0946 $[I > 2\sigma I]$.

Crystal data for $C_{32}H_{70.5}Cl_4N_8O_{31.25}$ (**2**): M = 1209.26, triclinic, space group $P1$, a = 10.4712(12), b = 19.570(2), c = 26.936(3) Å, α = 71.810(2), β = 89.512(2), γ = 81.701(2), U = 5185.2(10) Å^{-3}, Z = 4, μ = 0.331 mm^{-1}, R_{int} = 0.0724, transmission range(max,min) = 1.000, 0.619. A total of 36513 reflections were measured for the angle range $3 < 2\theta < 50$ and 17866 independent reflections were used in the refinement. The final parameters were $wR2$ = 0.3115 and $R1$ = 0.0998 $[I > 2\sigma I]$.

¶ Edge to face distance between C11 of strand B and centre of ring C is 4.112 Å.

1 J. Scheerder, J. F. J. Engbersen and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas*, 1996, **115**, 307.
2 V. V. Sorochinskii and B. I. Kurganov, *Appl. Biochem. Microbiol.*, 1997, **33**, 515.
3 M. Hynes, B. Maubert, J. Nelson, V. McKee and R. M. Town, *J. Chem. Soc., Dalton Trans.*, 2000, 2853.
4 B. Maubert, V. McKee, J. Nelson, I. Pál and R. M. Town, *J. Chem. Soc., Dalton Trans.*, 2001, 1395.
5 (*a*) I. Pál, PhD thesis QUB 2002; (*b*) I. Pál, R. Town and J. Nelson, to be published.
6 D. Y. Naumov, E. V. Boldyreva, N. V. Podberezskaya and J. A. K. Howard, *Solid State Ionics*, 1997, **101–103**, 1315.
7 M. Dewar and Y-J . Zheng, *J. Mol. Struct. (Theochem), 209*, 1990, 157.
8 R. E. Oakes and S. J. Bell, to be published.
9 G. G. Morgan, PhD, Open University, 1996.
10 B. Dietrich, J. Guilheim, J.-M. Lehn, C. Pascard and E. Sonveaux, *Helv., Chim. Acta*, 1984, **67**, 91.
11 (*a*) Cambridge Structural Database, January 2002 (*b*) O. Kennard and F. H. Allen, *Chem. Des. Automat. News*, 1993, **8**, 3137.
12 J.-M. Lehn, R. Meric, J.-P. Vigneron, I. Bkouche-Waksman and C. Pascard, *J. Chem. Soc., Chem. Commun.*, 1991, 62.
13 R. P. Singh, S. A. Smesko and N. M. Abbas, *J. Chromatogr. A*, 1997, **792**, 21–35; S. Peldzus, P. M. Huck and S. A. Andrews, *J. Chromatogr. A*, 1998, **793**, 198.
14 F. Allen, O. Kennard, D. Watson, L. Brammer, R. Orpen and J. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1.
15 (*a*) SAINT-NT, program for data collection and data reduction, Bruker-AXS, Madison, WI, 1998 (*b*) G. M. Sheldrick, SHELXTL Version 5.0, A System for Structure Solution and Refinement, Bruker-AXS, Madison, WI, 1998.