Solid-state and solution studies of bis-carboxylate binding by bis-amidinium calix[4]arenes †

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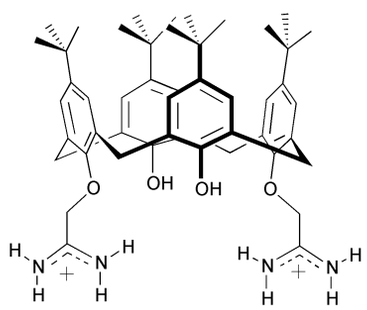
Bis-amidinium calix[4]arene receptors were shown to coordinate bis-carboxylate anions in DMSO solution; the crystal structure of the malonate salt of one of the receptors revealed a number of different amidinium–carboxylate interactions, demonstrating the propensity of these species to form complex hydrogen bonding networks.

Introduction

The coordination chemistry of anionic species by hydrogen bond donating receptors is an area of supramolecular chemistry that continues to attract the attention of chemists.[1] Amidinium (like guanidinium) forms salt bridges with carboxylate and phosphate anions and has been utilised in a variety of supramolecular systems including self-replicating molecules,[2] crystal engineered tapes[3] and ordered three dimensional aggregates.[4] The recognition of carboxylate anions has been the goal of a number of research groups world-wide.[5] Recently we reported the synthesis of bis-amidinium lower-rim substituted calix[4]arene derivatives (**1** and **2**).[6] As part of our research programme in anion complexation,[7] we decided to investigate the bis-carboxylate recognition properties of these receptors and, in particular, to compare the effect upon complexation of varying the chain length between the amidinium unit and the calixarene scaffold. In this communication, we present solution studies (in deuteriated DMSO) of the bis-carboxylate complexation properties of the hexafluorophosphate salts of **1** and **2** as well as X-ray crystallographic studies of the picrate complex of **1** and the malonate complex of **2**. Whilst this work was in progress, accounts of the recognition properties of bis-amidinium clefts and tetra-amidinium substituted resorcinarenes have been reported by Diederich and co-workers.[5]



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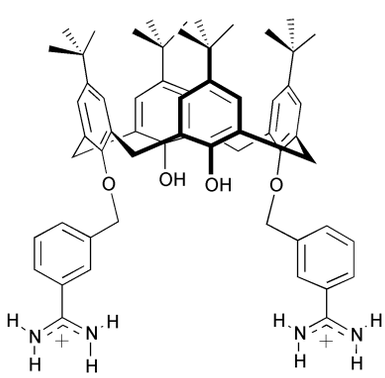

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Results and discussion

The chloride salts of the amidinium substituted calix[4]arenes **1** and **2** were prepared using the Garigipati method as reported previously[6] and converted to hexafluorophosphate salts by metathesis with $AgPF_6$. Yellow crystals of the picrate salt of **1**, amenable to structure determination by X-ray diffraction, were prepared as **3** by dissolving an excess of sodium picrate in an ethanol solution of the chloride salt of **1**, filtering and allowing the filtrate to evaporate slowly. The results of the structure determination are consistent with the formulation **1**(picrate)$_2$·~2.25 EtOH. The picrates are disposed in sheets about $z = 0$, with calixarenes opposed across $z = 0.5$, with the formulation forming a discrete ionic aggregate, excluding lattice solvent molecules, as shown in Fig. 1. The calixarene is in a distorted cone conformation [dihedral angles relative to the (methylene-C)$_4$ plane for rings 1–4 are 62.59(8), 58.92(8), 65.44(8) and 47.88(8)° respectively], with one of the ethanol solvent molecules included in the calixarene, oriented with the methyl group into the cavity. Interatomic distances are consistent with intramolecular hydrogen bonds between one H atom of each of the amidinium groups and the phenol O atoms (see Fig. 1 caption for relevant distances), and between phenol O atoms O(11, 41) and O(21, 31). It is interesting to note that the twist of the amidinium group–phenolic oxygen hydrogen-bonding network relative to the calixarene ring gives rise to enantiomers related by a centre of inversion. A picrate anion is linked to each of the two amidinium groups *via* a hydrogen bond network, similar to that observed in the picrate salt of L-arginine,[8] with further interactions with symmetry related picrates involving close

† Electronic supplementary information (ESI) available: NMR spectra of hexafluorophosphate salts of **1** and **2**, Job plots of **1** and **2**, and crystal structures of **3** and **4**. See http://www.rsc.org/suppdata/p2/b1/b102831f/

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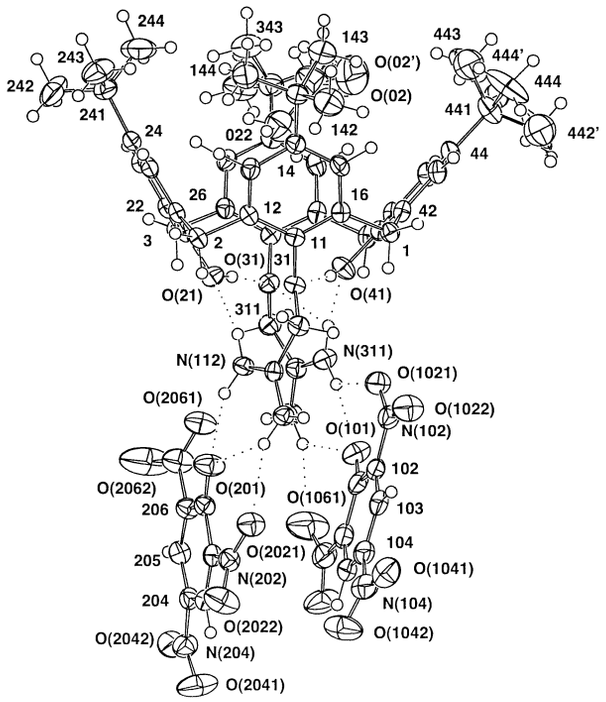


Fig. 1 Projection of the cation/anion array of **3** (the picrate salt of **1**); 50% displacement ellipsoids are shown for the non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0.1 Å (Fig. 4 similarly). O(11)···O(21) 2.993(3); O(21)···O(31), N(112) 2.736(3), 2.850(3); O(31)···O(41) 2.875(3); O(41)···O(11), N(311) 2.660(3), 2.772(3). N(111)···O(1041), O(201) 2.960(4), 2.850(3); N(112)···O(201) 2.779(4); N(311)···O(101), O(1021) 2.681(3), 2.829(3); N(312)···O(101), O(1061) 2.880(3), 2.967(4) Å.

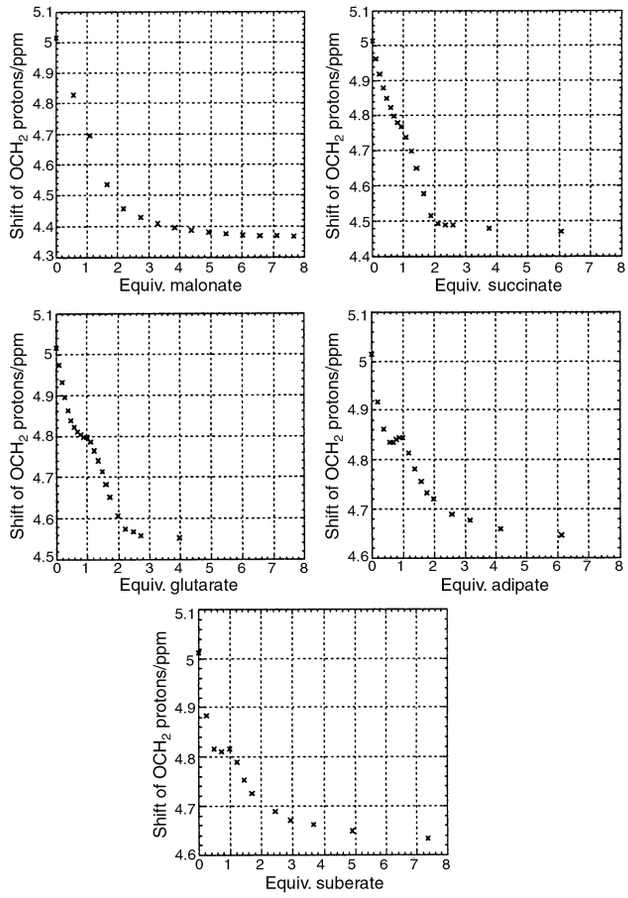


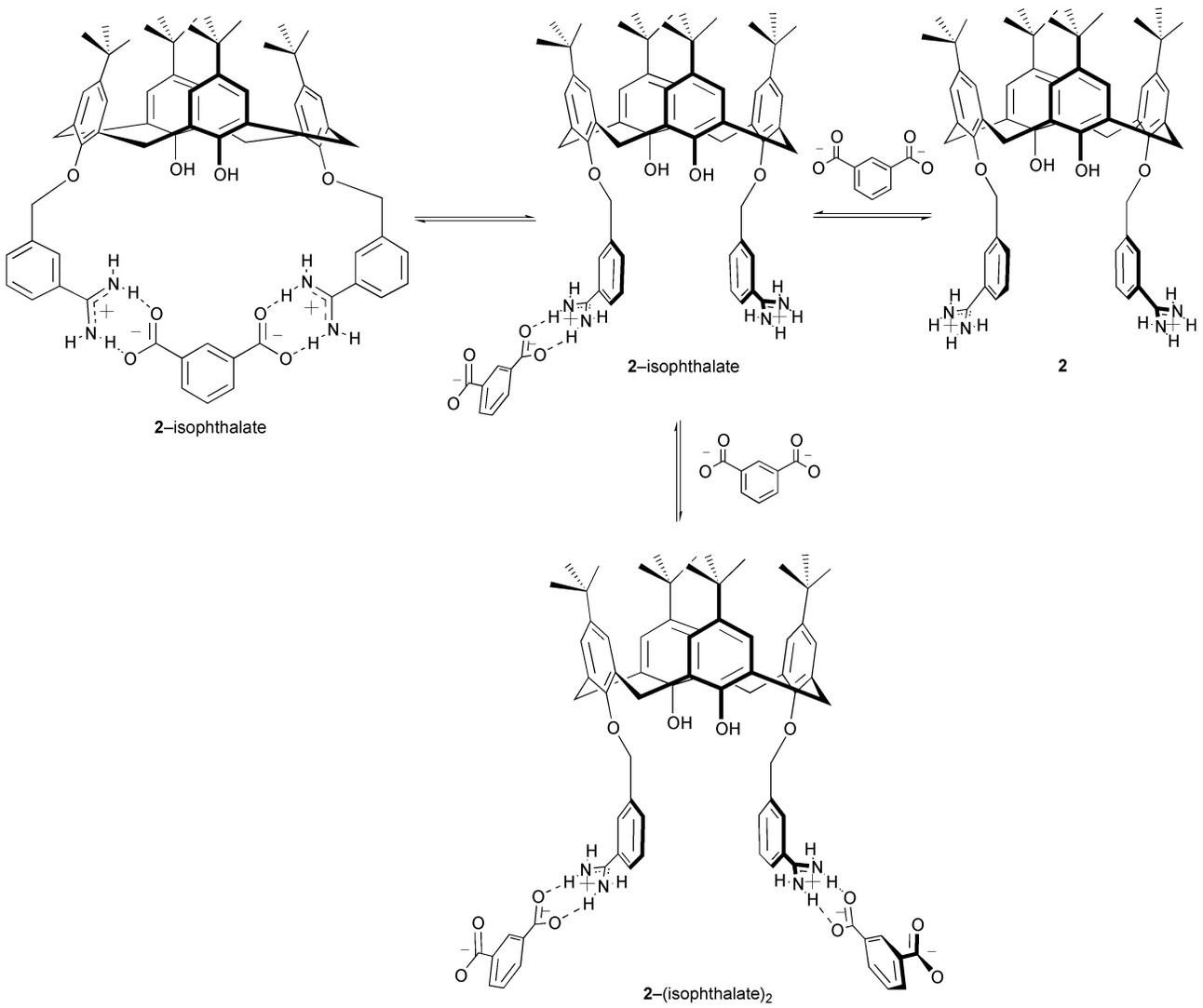
Fig. 2 The shift of the OCH_2 protons of compound **1** upon addition of various dicarboxylates, (a) malonate, (b) succinate, (c) glutarate, (d) adipate and (e) suberate, in deuteriated DMSO solution.

approach between one amidinium hydrogen atom and a nitro group of the picrate.

The solution complexation properties of the hexafluorophosphate salts of **1** and **2** were studied using ^{1}H NMR titration techniques in deuteriated DMSO solution. Hexafluorophosphate salts of the amidinium substituted calix[4]arenes were used, since the PF_6^- anion is relatively 'innocent' and does not significantly interact with hydrogen bond donating moieties. Initially a model study was conducted with compound **1** and acetate. Addition of aliquots of a solution of tetrabutylammonium acetate to a solution of **1**·PF_6 produced a titration curve (following the OCH_2 protons) consistent with 2 : 1 complex formation with $K_1 = 990$ M^{-1} and $K_2 = 960$ M^{-1}. It therefore appears that in this case the amidinium groups are acting independently and bind the two acetate anions with very similar stability constants. Addition of malonate, succinate, glutarate, adipate or suberate[9] to receptor **1** produced titration curves also indicative of a 2 : 1 anion–receptor stoichiometry, but which could not be fitted adequately to a simple 2 : 1 binding model.[10] Comparison of the NMR titration curves (Fig. 2) shows that as the length of the bis-carboxylate chain increases, from malonate to suberate, an increasingly noticeable 'stall' occurs in the titration curve. The curve 'stalls' at approximately one equivalent of anion. Our inability to fit these titration data to a simple binding model leads us to believe that there are multiple equilibria present in solution. We suggest that the 'stall' may be indicative of the formation of a 1 : 1 lower-rim bridged complex. Malonate appears to be too short to span the two amidinium groups that, by drawing an analogy to the solid-state structure observed in the picrate salt of **1**, and other crystal structures,[6b] may be oriented in a parallel but divergent manner due to hydrogen bonding to the lower rim phenolic oxygen atoms of the calixarene skeleton, so that in this case no 'stall' is observed. As the bis-carboxylate chain length increases, the acids form increasingly more stable lower-rim bridged complexes that, upon addition of further amounts of anion, form 2 : 1 anion–receptor species. A similar 'stall' was observed upon addition of isophthalate. Solubility problems precluded solution binding studies with **1** and terephthalate.

The amidinium groups in receptor **2** are further from the lower rim of the calixarene than those present in **1**. It is therefore less likely that the orientation of the amidinium moieties will be restricted by a hydrogen bond between them and the calixarene phenolic oxygens. ^{1}H NMR titrations of acetate, malonate, succinate, glutarate, adipate and pimelate with compound **2**, following the shift of the benzamidinium aromatic proton *meta* to the amidinium group, suggested the formation of 2 : 1 anion–receptor complexes. This binding stoichiometry was subsequently confirmed by Job plot analysis. Again the titration curves could not be fitted[10] adequately to a simple 2 : 1 binding model, suggesting multiple equilibria in solution. Interestingly, upon addition of isophthalate anions to the receptor, an unusual binding profile was observed (Fig. 3). The benzamidinium proton *para* to the amidinium group (followed due to the guest obscuring other receptor protons) shifts up-field at anion concentrations of less than one equivalent but reverses shift above one equivalent of anion. This behaviour was not observed upon addition of terephthalate; rather, a continuous down-field shift was seen. We believe this behaviour may be due to the formation of a bridged 1 : 1 complex at low concentrations of isophthalate (requiring a considerable conformational rearrangement of the receptor and, in particular, the orientation of the benzamidinium moieties) and the formation of a 2 : 1 complex at higher concentrations.

The malonate complex of receptor **2** was prepared by adding an aqueous solution of sodium malonate to an ethanol solution of **2**. The mixture was evaporated to dryness and extracted with dichloromethane. Crystals of **4** suitable for X-ray diffraction studies were formed by addition of an equal volume of ethanol



Scheme 1

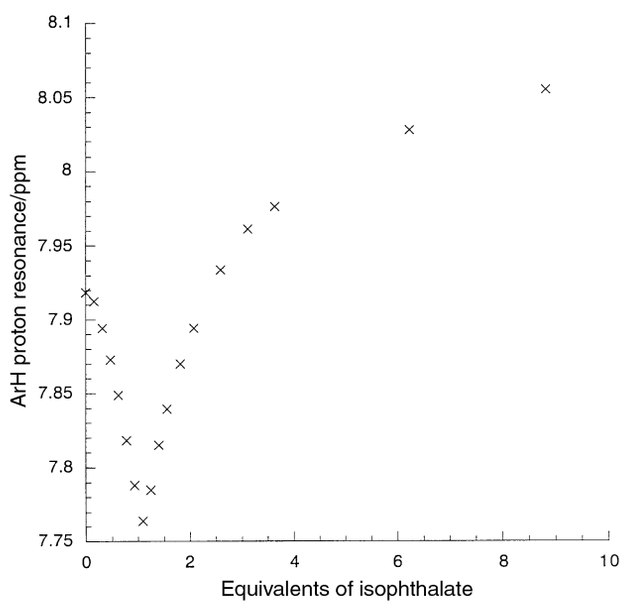


Fig. 3 The shift of a benzamidinium ArH proton of **2** upon addition of isophthalate in deuteriated DMSO solution.

to the dichloromethane extract, followed by slow evaporation of the solution. The results of the structure determination of **4** are consistent with the formulation $\mathbf{2}(CH_2(COO^-)_2)\cdot 4EtOH\cdot H_2O$. The structure of the calixarene cation with associated malonate anions is shown in Fig. 4; note that this figure shows all hydrogen bond links between the calixarene and malonate anions in the lattice, and thus does not reflect the stoichiometry of the salt. The calixarene again assumes the cone conformation, although in this case the cone is significantly pinched [dihedral angles relative to the (methylene-C)$_4$ plane for ring 1–4 are 77.5(2), 47.7(2), 86.5(2) and 44.8(2)° respectively] and the calixarene cavity is unoccupied. The amidinium groups do not form intramolecular hydrogen bonds. The cation, anion and water molecule are linked by a complex network of hydrogen bonds (Fig. 5). Of particular interest are the modes of interaction of the bis-amidinium cation with the malonate anion; three modes, each involving two hydrogen bonds, are shown schematically in Fig. 4(a). Mode (a) is the expected carboxylate–amidinium hydrogen bond interaction.[2] Mode (b) involves the dicarboxylate anion spanning the two amidinium moieties, with a single N···O hydrogen bond linking each pair of functional groups. Mode (c), with a single amidinium group spanning the dicarboxylate, is unusual and is presumably made possible by the short chain length of the dicarboxylate anion. The hydrogen-bonded network lies sandwiched about the *ab* plane between sheets of calixes, the *tert*-butyl groups at the periphery of each sandwich confronting about $z = 0.5$. The carboxylate and amidinium components lead to extension in the *b* and *c* dimensions as shown in Fig. 5; over and above this, the hydroxy components of the ethanol moieties support an intertwined solvent array: O,H(101)···O(301)($x-1$, $y+1$, z) 2.62(1), 1.7_2; O,H(301)···O(201) 2.72(1), 1.5_3; O,H(401)···O(201)(x, $y+1$, z) 2.66(1), 1.7_6 Å. Although H(201) was not

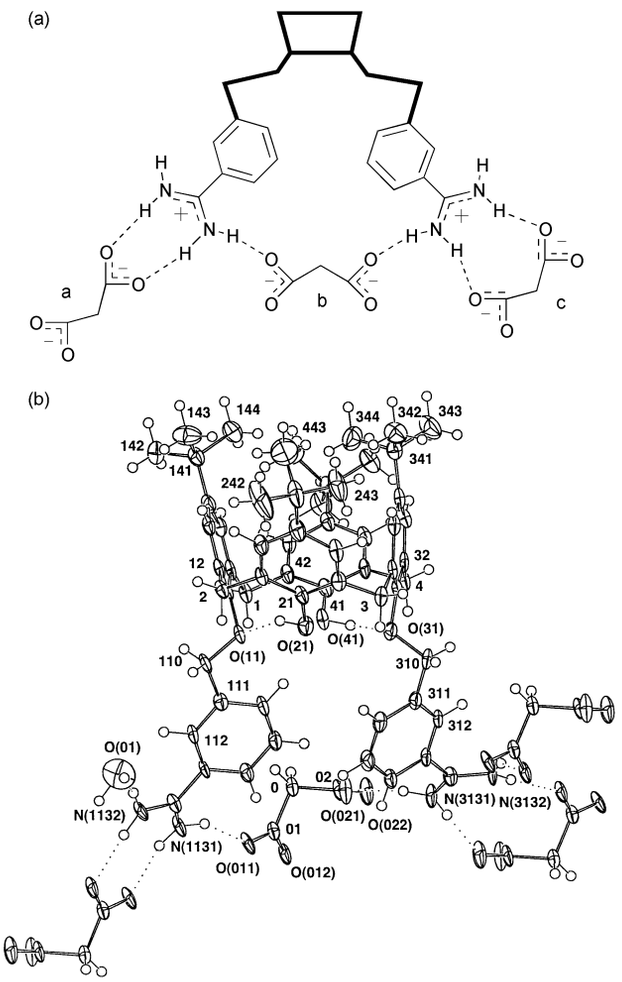


Fig. 4 (a) Schematic showing three different malonate coordination modes. (b) A projection of **4**. O(21)···O(11) 2.791(6); O(41)···O(31) 2.762(6); N(1131)···O(011), O(011)(2-x, $\bar{y}$, $\bar{z}$) 2.820(6), 2.746(8); N(1132)···O(012) (2−x, $\bar{y}$, $\bar{z}$), O(01) 2.843(6), 2.758(8); N(3131)···O(021), O(022)(1−x, $\bar{y}$−1, $\bar{z}$) 2.741(6), 2.792(7); N(3132)···O(012)(1−x, $\bar{y}$−1, $\bar{z}$), O(012)(x−1, y, z) 2.869(6), 2.924(6), O(01)(H(01a))···O(022)(x, y−1, z) 2.743(8)(1.83) Å.

resolved O(201) has no other close O···O contacts. The water molecule bridges between one of the carboxylate oxygens and an amidinium group as shown.

Solution studies have shown that the bis-amidinium receptors **1** and **2** coordinate bis-carboxylate anions, albeit with multiple equilibria present in solution. Nonetheless, NMR titration studies have been useful in elucidating processes occurring in solution. X-Ray crystallographic analysis of the picrate salt of **1** and the malonate salt of **2** reveals the propensity of these species to form complex hydrogen bonding networks. We are continuing to study the coordination properties of these and related species by other methods and the results of these studies will be presented in due course.

Experimental

Preparation of the hexafluorophosphate salts of 1 and 2

1–Cl^- (350 mg, 0.42 mmol) or **2**–Cl^- (432 mg, 0.44 mmol) was dissolved in methanol (30 mL). $AgPF_6$ (223 mg, 0.88 mmol) was added resulting in the formation of a white precipitate (AgCl). The white suspension was stirred for 30 minutes and allowed to stand for 2 hours. The AgCl was removed by filtration through a glass fibre filter (Millipore AP15), and the brown solution reduced *in vacuo*. The residue was purified by column filtration with methanol through Sephadex® LH-20 [240 mg of **1**–PF_6^- (54%) or 280 mg of **2**–PF_6^- (53%) were obtained].

Analytical data (compound 1–PF_6)

^{1}H NMR (300 MHz; DMSO-d_6) 1.22 (18H, s, Bu^t), 1.29 (18H, s, Bu^t), 3.67 (4H, d, J 12.7, Ar–CH_2–Ar), 4.14 (4H, d, J 12.7, Ar–CH_2–Ar), 5.01 (4H, s, O–CH_2), 7.32 (4H, s, ArH), 7.36 (4H, s, ArH), 9.14 (br s, NH_2). ^{13}C NMR (75.42 MHz; methanol-d_4) 31.4, 31.9, 32.2, 34.8, 35.2, 126.9, 127.7, 134.1, 145.1, 149.2, 149.9, 151.0, 168.5. +ve ESMS MH^+ 761.3 −ve ESMS 144 (PF_6^-). Microanalysis: Calc.[11] for $C_{48}H_{66}F_{12}N4O_4P_2$: 54.75, H 6.32, N 5.32. Found: C 53.49, H 6.60, N 4.92%.

Analytical data (compound 2–PF_6)

^{1}H NMR (300 MHz; DMSO-d_6) 1.21 (18H, s, Bu^t), 1.28 (18H, s, Bu^t), 4.20 (4H, d, J 12.7, Ar–CH_2–Ar), 5.2 (4H, s, O–CH_2), 7.23 (4H, s, ArH), 7.26 (4H, s, ArH), 7.64 (2H, d, J 8.2, ArH), 7.94 (2H, d, J 8.2, ArH), 7.64 (2H, s, ArH), 8.24 (2H, s, OH), 8.3 (2H, d, J 8.2, ArH). ^{13}C NMR (75.42 MHz, DMSO-d_6) 30.8, 31.4, 33.6, 34.0, 77.1, 125.4, 125.7, 127.2, 127.4, 127.9, 128.3, 129.4, 132.9, 137.6, 141.6, 147.4, 149.4, 149.9, 165.4. +ve ESMS 913.5 (MH^+) −ve ESMS 144 (PF_6^-). Microanalysis: Calc. [11] for $C_{60}H_{74}F_{12}N_4O_4P_2$: C 59.8, H 6.19, N 4.65, Found: C 58.01, H 6.35, N 4.63 %.

Preparation of 1(picrate)$_2$·2.25EtOH 3

An excess of sodium picrate (15 mg, 0.060 mmol) was added to a solution of **1**–Cl (10 mg, 0.012 mmol) in ethanol (10 mL) The solution was filtered and allowed to evaporate slowly to give yellow crystals of **3**.

Preparation of 2($CH_2(COO^-)2$)·4EtOH·H_2O 4

A solution of sodium malonate monohydrate (5 mg, 0.03 mmol) in water (5 mL) was added to a solution of **2**–Cl (10 mg, 0.010 mmol) in ethanol (5 mL). The mixture was evaporated to dryness and extracted with dichloromethane. Crystals of **4** suitable for X-ray diffraction studies were formed by addition of an equal volume of ethanol to the dichloromethane extract, followed by slow evaporation of the solution.

Structure determinations

Full spheres of CCD area-detector diffractometer data were measured (Bruker AXS instrument; ω scans, $2\theta_{max}$ as specified, monochromatic Mo-Kα radiation $\lambda = 0.71073_3$ Å; *T ca.* 153 K) yielding $N_{t(otal)}$ reflections, these merging to give N unique reflections (R_{int} quoted), N_o with $F > 4\sigma(F)$ being considered 'observed' and used in the large block least squares refinements [anisotropic thermal parameter forms for C, N, O; (x, y, z, U_{iso})$_H$ constrained at estimates]. Conventional residuals R, R_W on $|F|$ are quoted at convergence (reflection weights: $(\sigma^2(F) + 0.0004F^4)^{-1}$). Neutral atom complex scattering factors were employed, with computations performed using the Xtal 3.7 program system.[12] Full details of atom parameters are deposited (CCDC 155649 and 155650 for **3** and **4**, respectively). See http://www.rsc.org/suppdata/p2/b1/b102831f/ for crystallographic files in .cif or other electronic format.

Crystal/refinement data

Compound 3. $(C_{48}H_{66}N_4O_4)(C_6H_2N_3O_7)_2$·*ca.* $2.25C_2H_5OH$, $M = 1322.9$. Triclinic $P\bar{1}$, $a = 11.256(4)$, $b = 12.126(5)$, $c = 24.781(9)$ Å, $\alpha = 86.248(6)$, $\beta = 89.449(6)$, $\gamma = 85.085(6)°$, $V = 3362(4)$ Å^3. $D_C = 1.30_6$ g cm^{-3}. $\mu_{Mo} = 9.8$ cm^{-1}; specimen: 0.20 × 0.12 × 0.10 mm. $2\theta_{max} = 58°$; $N_t = 37455$, $N = 16219$ ($R_{int} = 0.053$), $N_o = 10356$, $R = 0.068$, $R_W = 0.072$. $|\Delta\rho_{max}| = 0.66(3)$ e Å^{-3}.

Variata. For this compound, application of an 'empirical'/multiscan absorption 'correction' ('T'$_{min,max} = 0.55$, 0.84) yielded a significant 'improvement' in the data, presumably in 'compensation' for absorption by the fibre mount and crystal deficiencies. *tert*-Butyl group 44 was modelled as rotationally

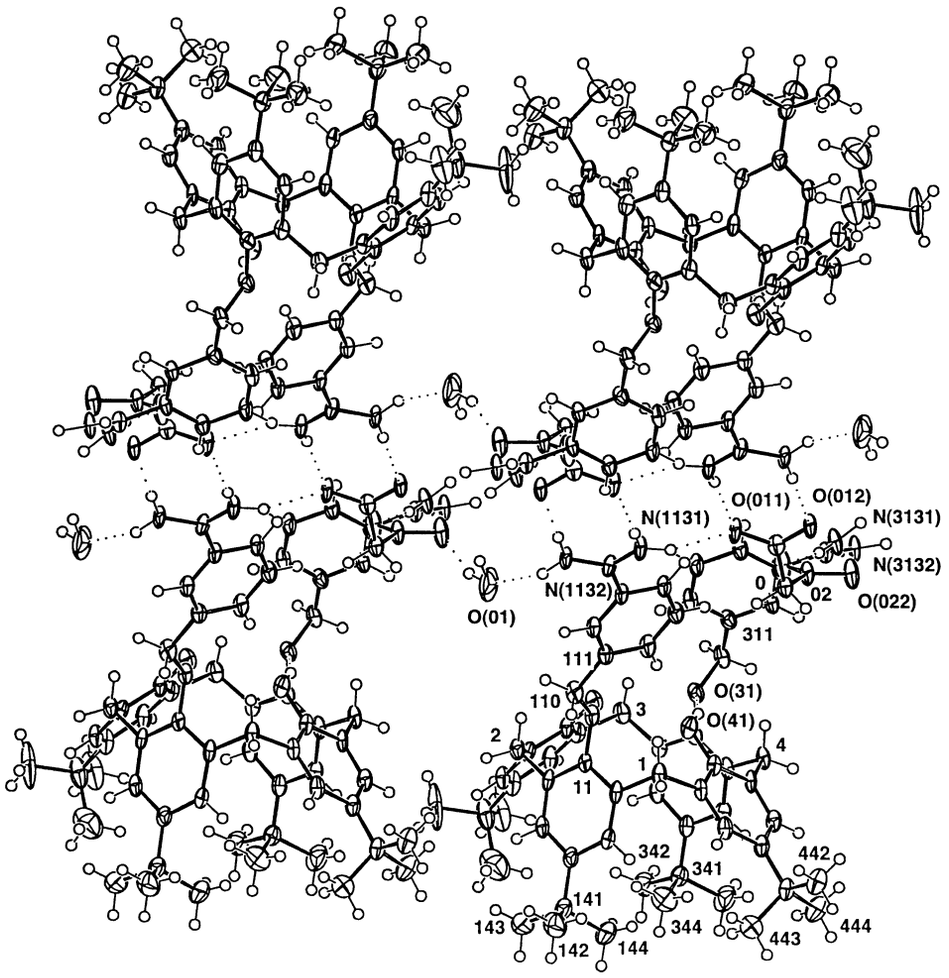


Fig. 5 A 'packing diagram' (viewed down the *a*-axis) showing the extended intermolecular hydrogen bonding network in **4**, mediated by malonate anions and water molecules (ethanol solvent molecules excluded).

disordered about its pendant bond, the methyl groups distributed over two sets of sites refining to occupancies 0.681(8) and complement. The hydroxy group of the included ethanol (#2) was modelled as disordered over two sets of sites, with occupancies set at 0.5 after trial refinement. Ethanol #3 was modelled as disordered about an inversion centre, with occupancy 0.5.

Compound 4. $(C_{60}H_{74}O_4N_4)(CH_2(CO_2)_2)_2{\cdot}4C_2H_5OH{\cdot}H_2O$, $M = 1219.6$. Triclinic $P\bar{1}$, $a = 10.569(3)$, $b = 12.071(3)$, $c = 27.334(7)$ Å, $\alpha = 94.522(5)$, $\beta = 100.971(5)$, $\gamma = 95.754(5)°$, $V = 3389(2)$ Å^3. $\mu_{Mo} = 8.1$ cm^{-1}; specimen: $0.50 \times 0.25 \times 0.08$ mm. $2\theta_{max} = 50°$; $N_t = 34058$, $N = 11868$ ($R_{int} = 0.079$), $N_o = 7123$; $R = 0.098$, $R_W = 0.11$. $|\Delta\rho_{max}| = 0.69(4)$ e Å^{-3}.

Variata. The hydroxylic hydrogen of ethanol #2 was not located.

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