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Molecular design using electrostatic interactions. Part 4: Synthesis and properties of flexible tetrapodand tetracations derived from naphthalene. Role of structured water in the electrostatic binding of polyanion guests: a model for interactions in biological systems

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Abstract—The 1,4,5,8-tetracations **5** and **11** have been prepared from 1,4,5,8-tetrakis(bromomethyl)naphthalene and 1,4,5,8-tetrakis-(bromomethyl)-2,3,6,7-tetramethylnaphthalene, respectively by treatment with DABCO in acetonitrile. Their interactions with the benzene-1,2,4,5-tetracarboxylate and naphthalene-1,4,5,8-tetracarboxylate tetraanions in water were investigated by ^{1}H NMR titration and both tetracations were found to have greater binding affinity to the benzene tetracarboxylate. Both also gave precipitates with ferricyanide but only the naphthalene tetracation **5** gave a precipitate with ferrocyanide. The X-ray structure of the crystalline ferricyanide tetracation **14** from tetramethylnaphthalene showed the methylDABCO cationic arms to be alternately above and below the naphthalene ring, which was itself distorted from the plane. The bound water in the non-charge-matched complex **14** appears to have a more intimate role in the crystal structure than does the bound water in the charge-matched ferricyanide **15** derived from 2,4,6-tris(DABCO-*N*-methyl)mesitylene tribromide which we reported previously. An analogy with interactions in biological receptors is made. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The study of the interaction of molecules in aqueous media is an area of major importance in that it mirrors events in the living cell.[1] Small molecule–protein,[2,3] protein–protein,[4–6] protein–DNA,[7–10] and antigen–antibody[11] binding all require the approach of the molecules in the cell in such an environment, first through the bulk water and then through the water layers that interact with the molecular surfaces. In this later phase of the interaction, water may be displaced from the surfaces into the bulk layer, the increase in entropy probably helping to balance other negative entropic events that occur as the molecules engage. An increasing number of interacting biological systems have, however, been shown to incorporate structured water at the binding surfaces and the entropy gain on binding will therefore be diminished. The water molecules also appear to be important in assisting site specific interaction between the complexing molecules and will thus make an enthalpic contribution to the stabilisation of the complex.[9] Initial close binding forces may also involve the reorganisation of bound water.[3]

We have investigated the interactions of synthetic polycation species with anions in water as a model for examining the interactions of charged biomolecules.[12,13] In some cases, crystals of the complex were obtained which requires that the complex is sufficiently long lived for it to aggregate.

These simple species, with their counterions, must follow the same series of operations as the interacting biomolecules. The final accretion of sufficient complexed molecules to allow for crystallisation probably has no intracellular equivalent but is equivalent to the crystallisation of interacting biomolecules. An X-ray crystallographic study of two of these crystalline polycation derivatives has been carried out at 100 K where the bound water molecules can be determined. Since the only hydrogen bond interactions are either those between the water molecules themselves or between the water protons and uncharged nitrogens of the polycation or polyanion, the function of the structured water would largely appear to be in space filling and as a dielectric medium for the interacting charges.

2. Results and discussion

2.1. Synthesis

We have previously described the synthesis of benzene

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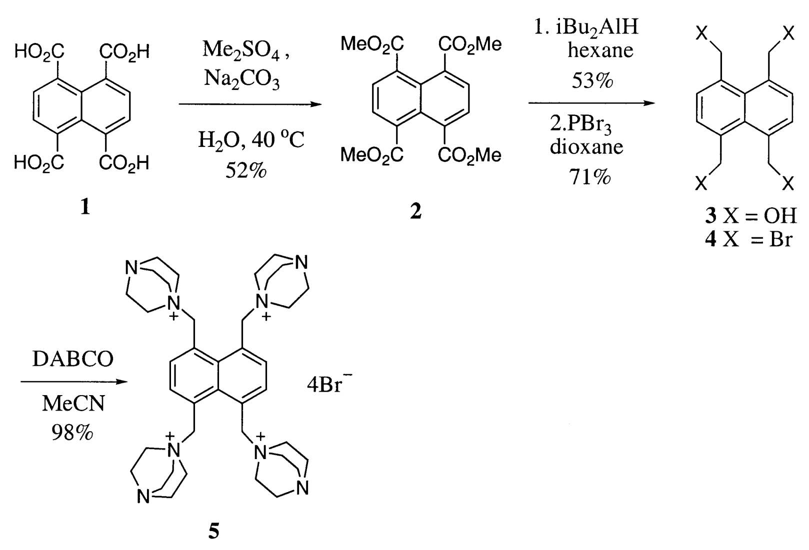
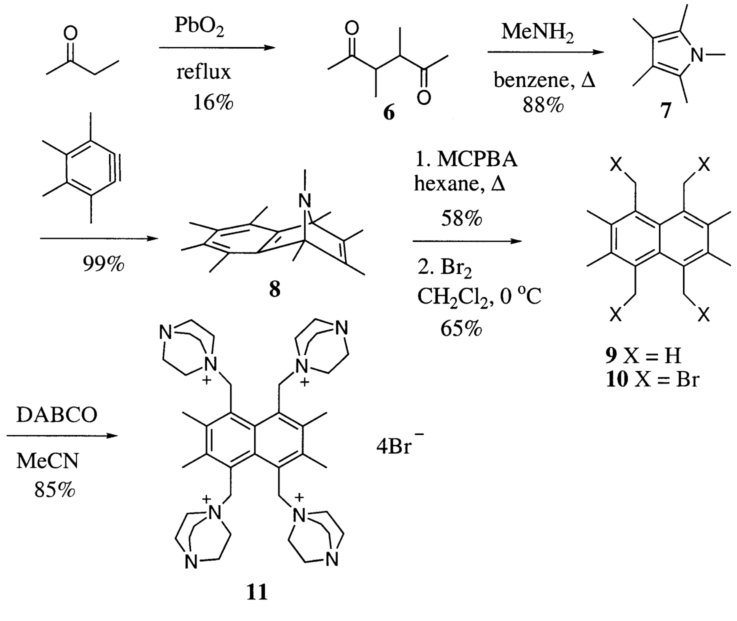


Scheme 1.

derivatives substituted with DABCO (1,4-diazabicyclo-[2.2.2]octane) and related bases to give polycation derivatives.[12,13] We have now applied the same method, the reaction of the appropriate bromomethyl derivative with the base, to prepare naphthalene derivatives. 1,4,5,8-Tetrakis(bromomethyl)naphthalene (**4**) was prepared from 1,4,5,8-naphthalene-tetracarboxylate (**1**) by a slight modification of the method of Kamada and Wasada (Scheme 1).[14] In our hands, the reduction of the tetraester **2** proceeded more readily with diisobutylaluminium hydride than with LAH as reported. Treatment of the tetrabromide **4** with DABCO gave the desired 1,4,5,8-tetrakis (DABCO-*N*-methyl)naphthalene (**5**) in 98% yield (19% overall yield from **1**).

The synthesis of 1,4,5,8-tetrakis(DABCO-*N*-methyl)-2,3,6,7-tetramethylnaphthalene (**11**) is shown in Scheme 2. The required tetrakis(bromomethyl)naphthalene (**10**) was prepared by the method of Hart et al. from butanone.[15,16] Oxidation with lead dioxide gave 3,4-dimethylhexan-2,5-dione (**6**) which on treatment with methylamine gave pentamethylpyrrole (**7**). The pyrrole was then added immediately to 1,3-dibromotetramethylbenzene in THF and the mixture treated with *n*-BuLi at −78°C to give the tetramethylbenzyne adduct **8**. Oxidation with *m*-chloroperoxybenzoic acid gave octamethylnaphthalene (**9**) which was converted to the desired tetrabromomethylnaphthalene **10** by treatment with bromine at 0°C. The tetrabromide **10** was then converted into **11** by treatment with DABCO in acetonitrile. Compound **11** was obtained in an overall yield of ca. 30% from **7**.

The ^{13}C NMR spectra and FAB mass spectra of the tetracations **5** and **11** were in accord with the assigned structures. The ^{1}H NMR spectrum of **5** showed the methylene protons as a singlet at δ 5.21 with the DABCO protons as two broad



Scheme 2.

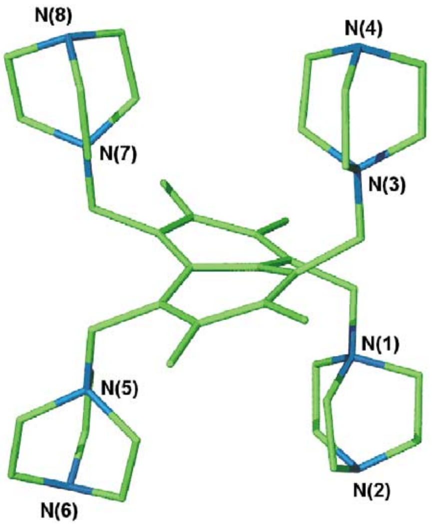
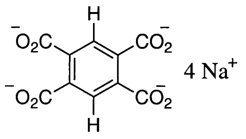


Figure 1. X-Ray crystal structure for the tetrakis(DABCO) organic cation in complex **14** (H atoms omitted for clarity).

triplets in the region δ 3.09–2.92. The ^{1}H NMR spectrum of **11** showed two doublets for the methylene groups indicating that their rotation is restricted in this tetracation. The tetrabromide was therefore converted, as previously described for benzene derivatives,[13] to the hexafluorophosphate salt which is soluble in dimethyl sulfoxide, but coalescence of the NMR signals was not observed up to 90°C.

2.2. Complexation studies

The association constants of the tetracations **5** and **11** with the tetrasodium benzene-1,2,4,5-tetracarboxylate (**12**) and tetrasodium naphthalene-1,4,5,8-tetracarboxylate (**13**) in water were determined by ^{1}H NMR titration studies[14] and the stoichiometry of the association by the method of continuous variation,[15] as we have described previously.[12] Both the anion and benzylic protons were monitored but the results given are for the anion proton chemical shifts. The stoichiometry in all cases was 1:1.



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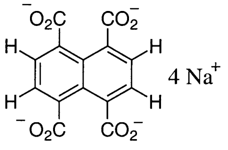

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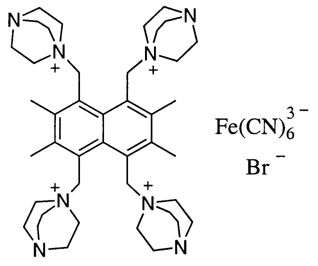

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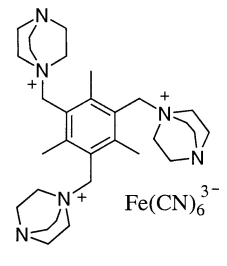

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For the tetracation **5** with the benzene tetraanion **12** the maximum change in chemical shift (Δδ) was 0.113 (±0.001) with log *K* 2.79 and with the naphthalene tetraanion **13** Δδ was 0.084 (±0.01) with log *K* 2.59. For tetracation **11** with tetraanion **12**, Δδ was 0.089 (±0.001) and log *K* was 2.66 and with tetraanion **13**, Δδ was 0.730 (±0.001) and log *K* was 2.14. The tetracation **5** thus binds more effectively to both the tetraanions **12** and **13** than does the tetracation **11**, suggesting that the methyl substituents on the naphthalene ring of **11** probably impede the assembly of the four positively charged DABCO groups on the same side of the ring. This is in accord with the observed multiplicity of the methylene signals of **11** in the ^{1}H NMR spectrum. Both **5** and **11** bind more effectively to the benzene tetraanion **12** than to the naphthalene tetraanion **13**, although this apparently has the better spatial fit. To obtain this fit, however, the cation and anion must be exactly aligned and it would appear that the less demanding tetraanion **12** is more often accommodated in a binding interaction.

2.3. Selective crystallisation

The tetracations **5** and **11** were treated with half-saturated solutions of the octahedral ferro- $[Fe(CN)_6^{-4}]$ and ferricyanide $[Fe(CN)_6^{3-}]$ ions as their potassium salts as described previously.[12,13] Precipitates were obtained with **5** for both anions, that with the ferrocyanide having an IR band at 2047 cm^{-1} and that with the ferricyanide at 2108 cm^{-1}, although only the ferricyanide complex was crystalline. Tetracation **11** gave no precipitate with ferrocyanide but a crystalline precipitate with ferricyanide with an IR band at 2111 cm^{-1}. In the competition experiment, **5** gave a precipitate which had IR bands at 2048 and 2110 cm^{-1}, whereas **11** gave a precipitate with only a band at 2111 cm^{-1}. Thus, charge matching does not, in these cases, seem a factor in the formation of the complex, the tetracation **11** forming a precipitate with the non-charge matching octahedral ferricyanide ion but not with charge matching octahedral ferrocyanide ion. Suitable crystals could not be obtained for an X-ray crystallographic study of the ferricyanide complex of **5** but suitable crystals were obtained for the complex of **11** with ferricyanide **14**.

An X-ray crystallographic study of **14** was carried out at 100 K where the bound water molecules can be determined. The crystal structure (Fig. 1) immediately suggests why charge matching is an unimportant selector in this case since the charged DABCO groups alternate on each side of the naphthalene moiety, which is itself considerably distorted from the plane, the ring atoms bearing the charged substituents being bent out-of-plane in the direction of the substituent. Fig. 1 shows the organic part of **14**.

Fig. 2 shows a part-structure of **14** which has the formula $C_{51}H_{92}BrFe_3N_{17}O_{12}$. Three ferricyanide ions each contribute 3/2 negative charges to the complex and the bromide ion, shared by two polycations, a 1/2 negative charge. These five negative units of charge are balanced by the four positive charges on the polycation and a proton from the hydroxonium ion. Eleven molecules of the bound water are associated with the polycation and the ferricyanide ions. Eight water molecules are bonded in a branched structure with an additional trimer, the last oxygen atom (O 11) of which is

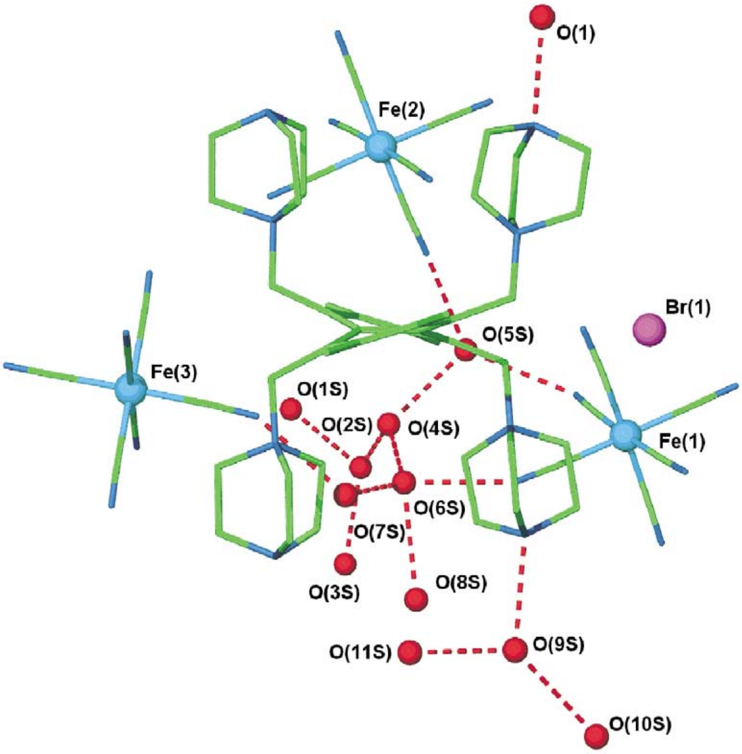

Figure 2. Partial crystal structure of ferricyanide complex **14**. Hydrogen atoms omitted, hydrogen bonds indicated by broken lines.

3.33 Å from the terminal oxygen of the longer chain. The eight water molecules project at one end (O 8) into a cleft along the centre of the naphthalene rings and between the cation–anion pairs on the same face of the naphthalene structure, with this oxygen probably involved in C–H–O hydrogen bonds. A single hydroxonium ion is associated with one of the uncharged DABCO nitrogen atoms. Hydrogen bonding between the water protons and the uncharged DABCO and cyanide nitrogens occurs.

The intimate part played by the bound water in this structure caused us to reinvestigate the X-ray crystal structure at 100 K of a charge matched complex **15** that we had reported previously.[12] The complex **15** has three cationic charges from the substituted DABCO moieties which balance the three charges of the ferricyanide anion. Unlike **14**, the three pendant arms of the cation are all on the same side of the molecule and the ferricyanide ion is centrally placed within the resultant pocket with one cyanide group pointing towards the benzene ring. The crystal contains 8 water molecules for each asymmetric unit and these are arranged in an ‘intermolecular’ fashion. Fig. 3 shows a part structure of complex **15** ($C_{36}H_{67}FeN_{12}O_8$). The 8 water molecules form a hydrogen-bonded chain which appears to serve a space filling role between the individual complexes, the two ions being bound together by the Coulombic charge.

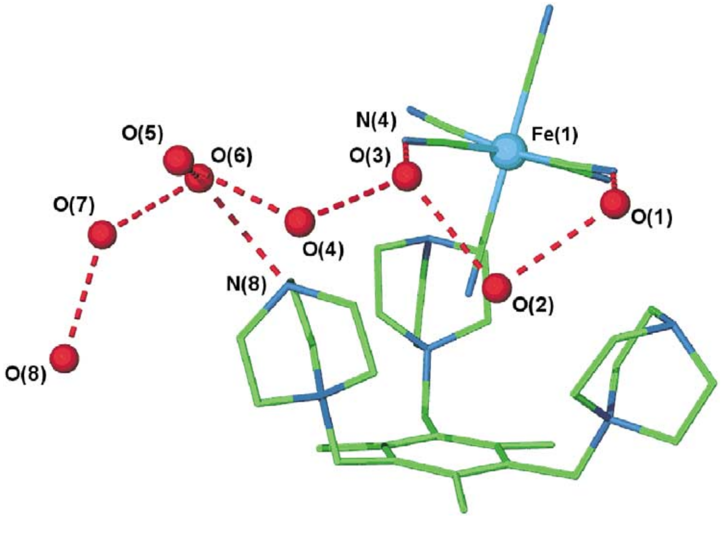

Figure 3. Molecular structure of ferricyanide complex **15**. Hydrogen atoms omitted, hydrogen bonds indicated by broken lines.

Further stabilisation is provided by hydrogen bonds between protons from the water chain and nitrogens of the DABCO and cyanide residues as for the complex **14**.

3. Conclusions

A comparison of the properties of the naphthalene tetracations **5** and **11** clearly indicates the profound effect that introduction of the methyl groups onto the naphthalene ring has. The tetramethyl derivative **11** is much less able to accommodate its structure to the interacting anionic species than can the hydrogen substituted system **5** and the X-ray structure of the ferricyanide complex **14** suggests that the likely ground state structure for **11** is that in which the charged groups alternate above and below the plane of the naphthalene ring. The trimethyl substituted benzene trication is clearly much less sterically crowded than **11** and the three charged groups can be accommodated on the same side of the ring, thus allowing charge matching with ferricyanide in **15** whereas **11** is not charge matched in **14**.

The crystal structures of **14** and **15** suggest that the function of the water molecules in these crystals is profoundly affected by the presence or absence of charge matching. The simpler structure **15**, with one ferricyanide to a trication, has the water molecules in an 'intermolecular' role helping to aggregate the individual 'neutral' molecules to form the crystal. In the more complex, non-charge matched structure **14**, the water molecules have an 'intramolecular' role and are interlaced between the two non-compensating ions. In terms of the biological model, system **14** represents a state in which the interacting molecules have progressed to the stage where there is bound, ordered water separating the species, whereas **15** represents the case in which all the water has been displaced, the function of the water molecules possibly not now having a biological counterpart though they could be considered as bound water on the surface between the biological molecule and the bulk water of the cell. With the involvement of water, and possibly spectator counterions, at the interacting ('active') site of the molecules, then charge or shape matching between the interacting units may be less important than originally thought. The OppA protein, which facilitates the entrance of peptides into Gram negative bacteria, uses water molecules to modify the binding site to fit the small peptide on offer,[17] but this is unusual as proteins generally use water molecules to bind ligands in a highly selective manner.[18] Receptors that have a variety of subtypes for the same ligand, a vital property in providing target-specific drugs, may involve different interactions for water and spectator counterions at the active sites. One would expect that receptor–ligand sites that incorporate water molecules as a structural feature would be less demanding on the nature of the ligand molecule than sites in which bound water is not involved.

The processes that occur when these relatively simple systems crystallise in water must follow the same sequence as those that occur between small, charged molecules and charged proteins in the cell. Electrostatic forces will make a major contribution to the initial stages of binding, with hydrogen and van der Waals bonding only occurring at a late stage in the process when the two systems are in close proximity. Where the interacting molecules have a good fit as regards shape and charge, then accessory molecules, such as water and counterions, are probably unimportant for the final docked complex whereas for molecules where the fit is less good, water and counterions can provide additional binding to stabilise the complex. The simple systems **15** and **14**, respectively, model these two types of complex.

4. Experimental

4.1. General

Melting points were determined on a Reichert melting point apparatus and are uncorrected. Mass spectra were recorded on a VG-ZAB mass spectrometer with Finnigan Incos II data system. ^{1}H NMR spectra were recorded at 400 and 300 MHz and ^{13}C NMR spectra were recorded at 100 and 75 MHz on a Varian VXR-400 and a Bruker AC300 instrument.

Elemental analyses were carried out by the microanalytical section of the Chemistry Department, University College London. The polycation bromide salts, which are deliquescent, were extensively dried in vacuo but water of crystallisation remained.

Chemical reagents were purchased from Aldrich Chemical Co., Lancaster Synthesis, ACROS and BDH. Solvents and reagents were used as received except for tetrahydrofuran which was distilled over sodium and benzophenone under an atmosphere of nitrogen immediately prior to use. Analytical thin layer chromatography (TLC) was performed on pre-coated aluminium backed plates (Merck Kieselgel 60 F_{254}) and visualised using ultraviolet light (254 nm), iodine or potassium permanganate solution as appropriate.

4.1.1. 1,4,5,8-Tetrakis(hydroxymethyl)naphthalene (3).[14] Tetramethyl 1,4,5,8-naphthalene-tetracarboxylate (**2**) (9.00 g, 25.0 mmol) was added in portions to a cooled (<30°C.) solution of diisobutylaluminum hydride (1.0 M solution in hexane) (365 mL, 365.0 mmol) under nitrogen. The resulting clear solution was stirred at room temperature for 30 h. Methanol (120 mL) was added cautiously, followed by hydrochloric acid (6 M, 275 mL). The precipitated solid was removed by filtration and recrystallised from dimethyl sulfoxide/chloroform to give **3** as a white solid (3.30 g, 13.3 mmol, 53%); mp 237–240°C, lit.[14] 231–233°C.

4.1.2. 1,4,5,8-Tetrakis(bromomethyl)naphthalene (4).[14] Prepared from phosphorous tribromide (10.4 mL, 29.64 g, 109.4 mmol) and 1,4,5,8-tetrakis(hydroxymethyl)naphthalene **3** (1.23 g, 5.0 mmol) in anhydrous dioxane under nitrogen as described. White solid (1.76 g, 3.5 mmol, 71%); mp 248–250°C (dec.), lit.[14] >220°C (dec.).

4.1.3. 1,4,5,8-Tetrakis(DABCO-*N*-methyl)naphthalene tetrabromide (5). 1,4,5,8-Tetrakis-(bromomethyl)-naphthalene (**4**) (0.42 g, 0.8 mmol) was added to a solution of DABCO (0.57 g, 5.1 mmol) in acetonitrile (100 mL). The resulting mixture was stirred for 72 h. The solid formed was removed by filtration, washed with acetonitrile, and dried under vacuum to give **5** as a white solid (0.79 g, 0.8 mmol, 98%); mp 281–285°C (dec.); ^{1}H NMR (D_2O) δ 8.00 (s, 4H,), 5.21 (s, 8H,), 3.09 (br, 24H), 2.92 (br, 24H); ^{13}C NMR (D_2O) δ 139.6, 128.0, 98.2, 71.2, 55.2, 46.8; IR 2962, 2891, 2371, 1648, 1459, 1363 cm^{-1}; MS *m/e* 869 (13, $M-Br^+$), 755 (3), 675 (8), 483 (45), 371 (52), 259 (23), 179 (52), 112 (100); $C_{38}H_{60}Br_4N_8\cdot 3H_2O$ requires C, 45.52; H, 6.63; N, 11.18. Found: C, 45.39; H, 6.58; N, 11.07.

4.1.4. Pentamethylpyrrole (7).[15] A mixture of 3,4-dimethyl-2,5-hexanedione (**6**) (20.00 g, 140.6 mmol), methylamine (40% aqueous, 75 mL, 27.18 g, 875.1 mmol) and benzene (300 mL) was refluxed for 6 h, water being removed continuously with a Dean and Stark trap. The resulting solution was dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The solid residue was dried under vacuum to give **7** as yellow solid (16.98 g, 123.7 mmol, 88%) which was used immediately.

4.1.5. Nonamethyl-1,4-dihydronaphthalen-1,4-imine (8).[15] *N*-Butyllithium (1.6 M solution in hexane) (30 mL, 48 mmol) was added dropwise over a period of 1 h to a suspension of 1,2-dibromo-3,4,5,6-tetramethylbenzene (10.64 g, 36.4 mmol) and pentamethylpyrrole (**7**) (5.00 g, 36.4 mmol) in anhydrous tetrahydrofuran (170 mL) at −78°C under nitrogen. After addition, the resulting mixture was kept at this temperature for an additional hour and left for 20 h at room temperature. Water (10 mL) and diethyl ether (20 mL) were added slowly, the layers were separated, and the aqueous layer was extracted with diethyl ether (20 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure. Petroleum ether 40–60°C (40 mL) was added to the residue, the solution was filtered, and the solvent was removed by rotary evaporation to give **8** as a yellow solid (9.66 g, 35.9 mmol, 99%); mp 90–92°C, lit.[15] 94–96°C.

4.1.6. Octamethylnaphthalene (9).[15] A mixture of nonamethyl-1,4-dihydronaphthalen-1,4-imine (**8**) (9.00 g, 33.4 mmol), anhydrous sodium carbonate (3.60 g, 34.0 mmol), *m*-chloroperoxybenzoic acid (57–86%, 11.22 g, 37.1 mmol) and benzene (200 mL) was heated under reflux for 15 h. Water (100 mL) was added, the layers were separated and the aqueous layer was extracted with chloroform (50 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The solid residue was triturated with methanol (55 mL) and filtered to give **9** as white needles (4.67 g, 19.4 mmol, 58%); mp 180–182°C, lit.[15] 181–182°C.

4.1.7. 1,4,5,8-Tetrakis(bromomethyl)-2,3,6,7-tetramethylnaphthalene (10).[16] A solution of bromine (3.84 mL, 11.98 g, 75.0 mmol) in dichloromethane (190 mL) was added dropwise to a solution of octamethylnaphthalene (**9**) (4.50 g, 18.7 mmol) in dichloromethane (560 mL) at 0°C. The resulting solution was left at room temperature for 2 h, then was washed with saturated aqueous sodium carbonate (3×600 mL) and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the solid residue was recrystallised from THF to give **10** as a white solid (6.79 g, 12.2 mmol, 65%); mp 178–181°C (dec.), lit.[16] 180°C (dec.).

4.1.8. 1,4,5,8-Tetrakis(DABCO-*N*-methyl)-2,3,6,7-tetramethylnaphthalene tetrabromide (11). 1,4,5,8-Tetrakis-(bromomethyl)-2,3,6,7-tetramethylnaphthalene (**10**) (2.40 g, 4.3 mmol) was added to a solution of DABCO (2.45 g, 21.8 mmol) in acetonitrile (200 mL). The mixture was stirred for 72 h. The solid formed was removed by filtration, washed with acetonitrile, and dried under vacuum to give **11** as a white solid (3.98 g, 3.6 mmol, 84%); mp 268–270°C (dec.); ^{1}H NMR (D_2O) δ 5.48 (d, J=15.2 Hz, 4H), 4.93 (d, J=15.2 Hz, 4H), 3.00 (m, 12H), 2.85 (m, 36H), 2.57 (s, 12H); ^{13}C NMR (D_2O) δ 147.5, 136.7, 123.8, 67.5, 55.3, 47.2, 22.6; IR 2960, 2884, 2074, 1636, 1459, 1358, 1191 cm^{-1}; MS *m/e* 923 (5, $M-Br^+$), 813 (2), 731 (7), 619 (13), 539 (28), 427 (37), 315 (17), 235 (38), 112 (100); $C_{42}H_{68}Br_4N_8\cdot 5H_2O$ requires C, 46.08; H, 7.18; N, 10.24. Found: C, 45.97; H, 7.08; N, 10.43.

4.2. Polyanions

These were prepared from the corresponding acids by treatment with sodium hydroxide followed by addition of acetone, isolation and drying under vacuum.

4.3. Crystallisation with ferro- and ferricyanide

A half saturated solution of either the potassium ferro- or ferricyanide was added to a dilute solution of the polycation (concentration ca. 10 mg mL^{-1}) and, after standing, the precipitate was removed by filtration.

For the competitive experiment, a solution was made from equal volumes of saturated potassium ferricyanide and saturated ferrocyanide and this was then added to a dilute solution of the polycation (concentration ca. 10 mg mL^{-1}). After standing, the precipitate was removed by filtration.

4.4. NMR titrations and Job plots

These were carried out as previously described.[12]

4.5. X-Ray structure analyses

Crystals were mounted on a thin glass fibre using a fast setting epoxy resin and cooled on the diffractometer to 100 K using an Oxford Cryostream low temperature attachment. A total of 90 oscillation frames each of width 2° in ϕ and of 30 s exposure time were recorded using a Nonius KappaCCD diffractometer, with a detector to crystal distance of 25 mm. Crystals were indexed from the first 10 frames using the DENZO-SMN package[19] and positional data were refined along with diffractometer constants to give the final unit cell parameters. Integration and scaling (DENZO, Scalepack[19]) resulted in unique data sets corrected for Lorentz and polarisation effects and for the effects of crystal decay and absorption by a combination of averaging of equivalent reflections and an overall volume and scaling correction. Structures were solved using SHELXS-97[20] and developed via alternating least squares cycles and difference Fourier synthesis (SHELXL-972) with the aid of the program XSeed.[21] All non-hydrogen atoms were modelled anisotropically, while hydrogen atoms are assigned an isotropic thermal parameter 1.2 times that of the parent atom (1.5 for terminal atoms) and allowed to ride.

All calculations were carried out with either a Silicon Graphics Indy workstation or an IBM compatible PC.

Crystal data for $C_{51}H_{92}BrFe_3N_{17}O_{12}$ **14**, CCDC 181099: $M=1382.2$, orthorhombic, $a=24.3713$ (5) Å, $b=26.5559$ (4) Å, $c=38.3438$ (7) Å, $T=100$ K, space group *Fdd*2, $Z=16$, $\mu=1.408$ mm^{-1}, 11846 reflections measured, independent 11846 ($R_{\text{int}}=0.0730$) which were used in all calculations, $R_1=0.0684$. The final $wR(F^2)$ was 0.1858 (all data).

Crystal data for $C_{36}H_{67}FeN_{12}O_8$ **15**, CCDC 181098: $M=851.87$, monoclinic, $a=13.1600$ (8) Å, $b=19.5629$ (6) Å, $c=16.4172$ (12) Å, $\beta=90.396$ (2)°, $T=100$ K, space group $P2_1/n$, $Z=4$, $\mu=0.420$ mm^{-1}, 23369 reflections measured, independent 7192 ($R_{\text{int}}=0.0524$) which were used in all calculations, $R_1=0.0534$. The final $wR(F^2)$ was 0.1122 (all data).

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