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Polyhalogenated heterocyclic compounds. Macrocycles from perfluoro-4-isopropylpyridine †

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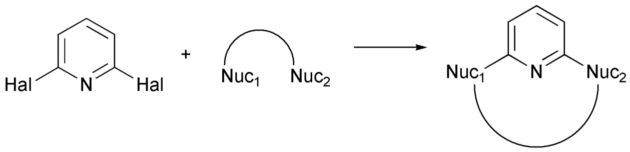
Received 26th March 2003, Accepted 1st May 2003
First published as an Advance Article on the web 15th May 2003

Perfluoro-4-isopropylpyridine was used as a building block for the two-step synthesis of a variety of macrocyclic systems bearing pyridine sub-units which were characterised by X-ray crystallography. Electrospray mass spectrometry revealed that complexation of either cations and, unusually, anions is possible depending on the structure of the macrocycle.

Introduction

Supramolecular chemistry is a major research field[2,3] and, for example, many macrocyclic polyether systems have been prepared since Pedersen's earlier synthesis of crown ether derivatives.[4] Macrocyclic compounds are now used for a variety of applications[3] such as sensors, imaging agents, catalysts and for ion analysis, providing further impetus for the development of this area. In particular, the incorporation of pyridine, or related heteroaromatic, sub-units into a macrocyclic ring has been the focus of much attention due to the often unusual chemical, physical and biological properties that such systems exhibit.[3]

Most commonly, the synthesis of macrocycles bearing heteroaromatic units involves side-chains that are attached to heterocyclic systems *via*, for example, nucleophilic displacement at saturated carbon, or addition–elimination reactions at carbonyl centres, in the ring-forming step.[5] However, syntheses of macrocycles by nucleophilic aromatic substitution processes involving the heteroaromatic ring are uncommon. In principle, halogenated pyridine derivatives in which the halogens are located at sites *alpha* to the ring nitrogen are possible building blocks and processes such as those depicted in Scheme 1 can be envisaged.

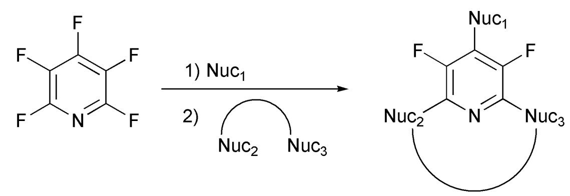


Scheme 1

Comparatively little work involving this synthetic approach has been reported. Newkome and co-workers[6] used 2,6-dibromopyridine in reactions with various polyethylene glycol derivatives and obtained a series of macrocyclic compounds, albeit in low yield, while Singh[7] used 2,6-dichloropyridine in similar processes to produce various macrocycles. In related systems, reactions of trichloro-*s*-triazine with a variety of difunctional nucleophiles provided a range of macrocyclic and cage derivatives.[8–10]

It is of course, well established that fluorine is generally more mobile in nucleophilic aromatic substitution reactions[11,12] than bromine or chlorine and we anticipated that reactions of difunctional nucleophiles with appropriately fluorinated heteroaromatic compounds would lead to macrocyclic systems.

Pentafluoropyridine **1** is a very versatile 'building block' because, in principle, all five fluorine substituents in pentafluoropyridine could be substituted by nucleophiles.[13] Therefore, potentially, a range of polysubstituted macrocyclic systems could be derived from this core molecule by a series of appropriate nucleophilic aromatic substitution steps. It is well documented[14,15] that, in general, the order of reactivity towards nucleophilic attack in pentafluoropyridine follows the sequence 4-fluorine > 2-fluorine > 3-fluorine. Consequently, for a succession of three nucleophilic substitution steps, where Nuc1 is the first nucleophile and Nuc2-Nuc3 is a bifunctional nucleophile, the order of substitution was anticipated to be as outlined below, presenting the opportunity of obtaining macrocyclic products (Scheme 2).



Scheme 2

Apart from our recent communication,[16] we are not aware of any reported syntheses of macrocycles involving highly fluorinated heterocyclic compounds as building blocks but the wide range of nucleophiles and dinucleophiles that are available (O, N, C, S centred) makes the theoretical number of macrocyclic derivatives bearing pyridine sub-units, that could be accessed by this approach, very large indeed. Therefore, in this paper, we establish the viability of using perfluorinated heterocyclic systems for the synthesis and characterisation of a family of macrocycles that derive from perfluoro-4-isopropylpyridine.

Results and discussion

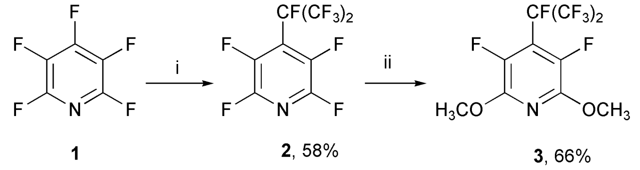
Synthesis

First, in accordance with the general approach outlined in Scheme 2, the reactive 4-position of pentafluoropyridine was 'blocked' by the introduction of a perfluoroisopropyl substituent at this site, which is also activating towards further attack by nucleophiles.

† Part 50. For part 49 see ref. 1.

DOI: 10.1039/b303443g

Fluoride-ion induced perfluoroalkylation of pentafluoropyridine was described many years ago[17] but more recent methodology,[18] which avoids the use of solvent, has enabled the chemistry of perfluoroalklypyridine derivatives to be developed on a preparatively useful scale. Reaction of pentafluoropyridine with hexafluoropropene and a trace amount of an amine catalyst, led to high yields of the perfluoro-4-isopropyl derivative **2**, following the literature procedure. Previous model studies[19] demonstrated that further nucleophilic attack involving **2** occurs at the 2- and 6-positions and, for example, reaction of **2** with sodium methoxide gave the dimethoxy derivative **3** in good yield (Scheme 3).



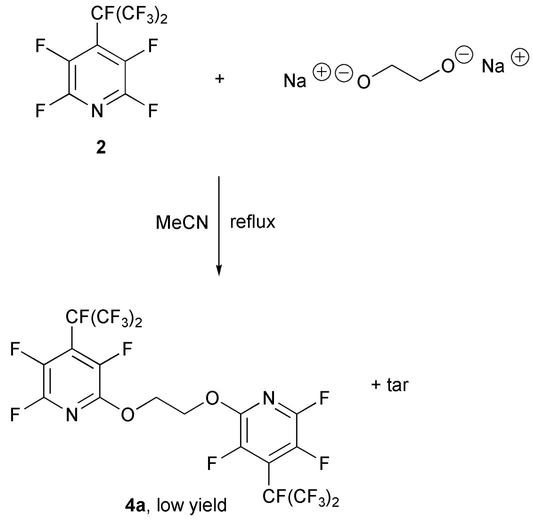
Scheme 3 *Reagents and conditions:* i, CF_2=CF–CF_3, $(Me_2N)_2$C=C-$(NMe_2)_2$, 60 °C, 14 h; ii, 2 MeONa, MeCN, reflux.

Given the efficiency of the substitution processes described above, reactions involving pyridine derivatives and di-sodium salts derived from appropriate diols were investigated. However, reaction of an excess of **2** with the di-sodium salt of ethylene glycol gave low yields of the desired bridged compound **4a** and considerable amounts of tar (Scheme 4).

Consequently, an alternative methodology, adapted from chemistry described by Farnham,[20] for the generation of dioxygen nucleophiles from trimethylsilylated derivatives of diols was explored, and we found that this fluoride ion catalysed procedure for the generation of oxy-anions was effective. For example, reaction of the bis-silylated derivative **5a** with an excess of **2** and a catalytic amount of caesium fluoride in acetonitrile, led to high yields of **4a** in a process that is outlined in Scheme 5.

Macrocycle formation (Scheme 6) was then accomplished by reaction of the bridged system **4a** with a further equivalent of **5a**, giving **6a** in surprisingly good yields considering the size of the ring being formed. Purification of the macrocycle **6a** was achieved by column chromatography and recrystallisation.

Several other macrocyclic systems **6b–d** were synthesised by analogous two step procedures, from appropriate bis-silyl derivatives **5b–d** (Table 1), by reaction with a further equivalent of **2**.



Scheme 4

In principle, there is a wide range of di-functional nucleophiles available that could be used to construct macrocycles, and, in the following discussion, we demonstrate the potential of the structural variety of macrocycles that may be accessed using the step-wise methodology described above.

N,*N′*-Dimethylethylene diamine **7** and **2** gave the bridged compound **8** by reaction in acetonitrile under reflux and the ring closure to macrocycle **9** was affected by heating with a further equivalent of **7** (Scheme 7).

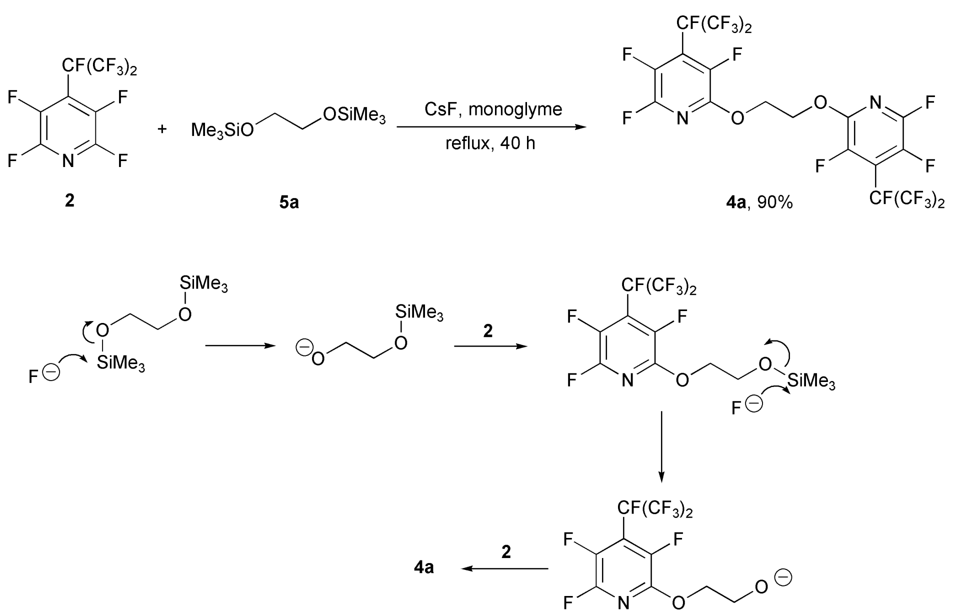
The bridged system **8** may be used as a building block for the construction of macrocycles in which the pyridine sub-units are connected by two different bridging groups. For example, cyclisation of **8** upon reaction with **5a** and **5b** gives macrocycles **10** and **11** respectively (Scheme 8).

Finally, macrocycle **15** was synthesised from ethanolamine **12**, **2** and **5a** in three steps (Scheme 9).

X-Ray crystallography

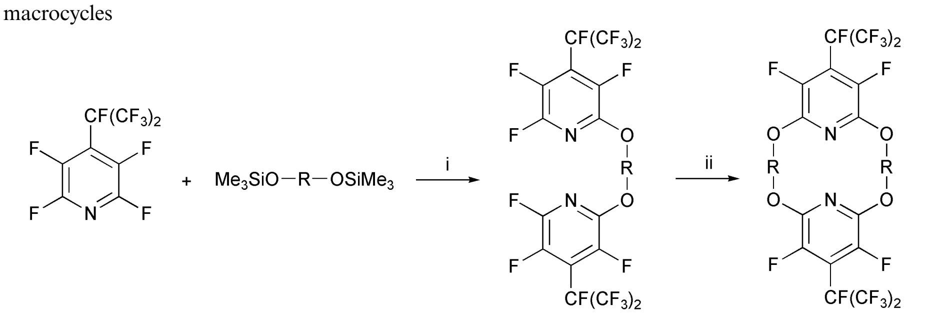
Single crystals of macrocycles **6a**,**b**,**d** were obtained that were suitable for X-ray crystallographic structural analysis. The geometric parameters and stepped *anti*-conformation of the centrosymmetrical molecule **6a** (Fig. 1) are very similar to that of a 2,6-pyridinophane reported by Newkome.[21]

The molecules **6a** in the crystal lattice form loose sheets parallel to the crystallographic *x*0*z* direction (Fig. 2) while adjacent

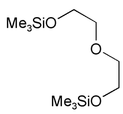
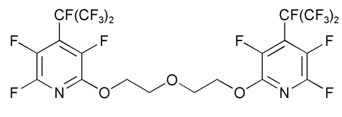
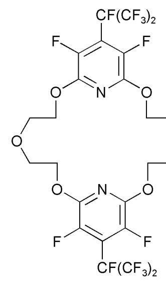
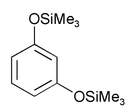
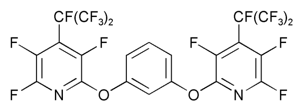
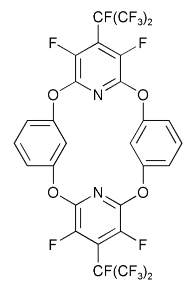
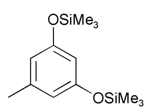
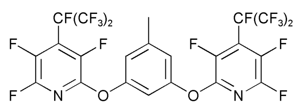
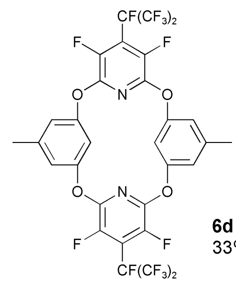


Scheme 5

Table 1 Synthesis of macrocycles



Reagents and Conditions: i, CsF, monoglyme, reflux, 40 h; ii, $Me_3SiO\text{-}R\text{-}OSiMe_3$, CsF, monoglyme, reflux, 5 d

$Me_3SiO–R–OSiMe_3$	Product yield(%)	Product yield(%)
 **5b**	 **4b**, 83%	 **6b** 40%
 **5c**	 **4c**, 70%	 **6c** 64%
 **5d**	 **4d**, 73%	 **6d** 33%

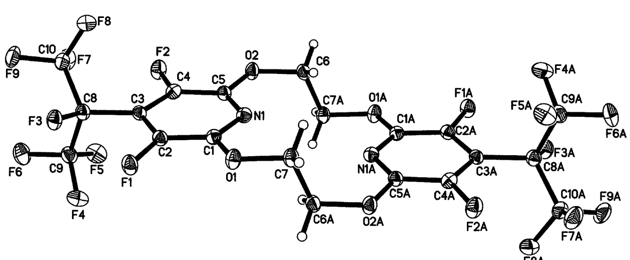


Fig. 1 Macrocycle **6a**.

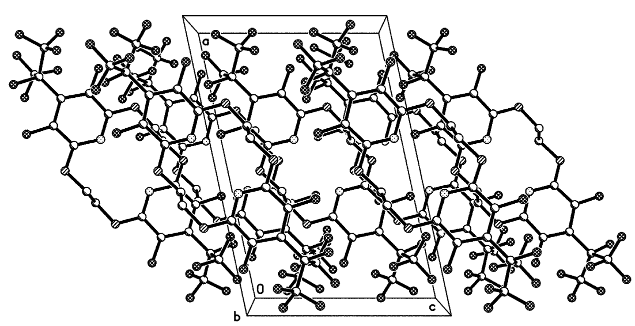


Fig. 2 Crystal lattice of macrocycle **6a**.

molecules in the sheets are connected by C–H ··· O interactions, the shortest one being C6–H62 ··· O1 (C ··· O 3.636 Å).

The larger heterocyclic polyether **6b** exists as two polymorphic modifications (**A** and **B**) both of which have a similar macrocyclic *syn*-conformation, with approximately parallel orientations of the heterocycles and perfluoroisopropyl groups in close proximity to each other (Fig. 3).

The two structures of macrocycle **6b** differ by the orientation of the terminal $CF(CF_3)_2$ groups in **A** and **B** (Fig. 4) and this leads to slightly different conformations of the polyether chains and different distances between the planes of aromatic rings in the molecules due to higher sterical repulsion in the molecule **B**. The distances between the planes of pyridyl rings in molecules **A** and **B** are 3.336 and 4.298 Å respectively. As one could expect, there are no strong intermolecular interactions in structures **A** and **B** and, in both structures, molecules form loose layers parallel to the (011) plane. The molecules in these layers

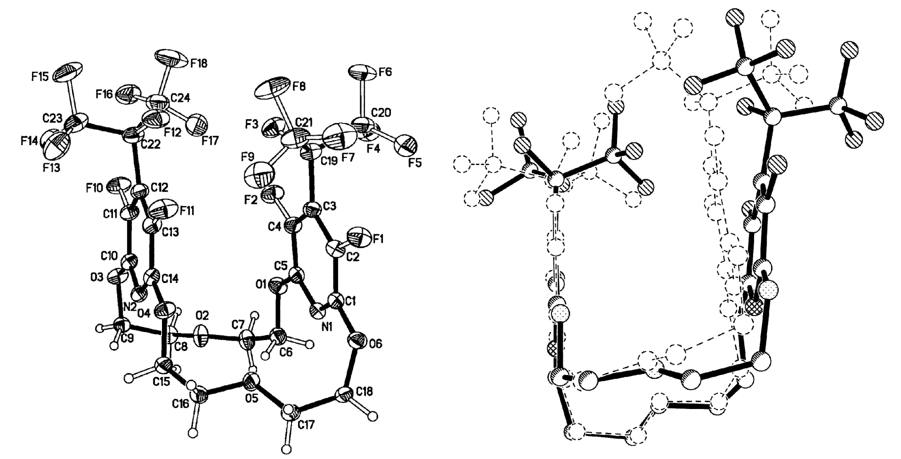
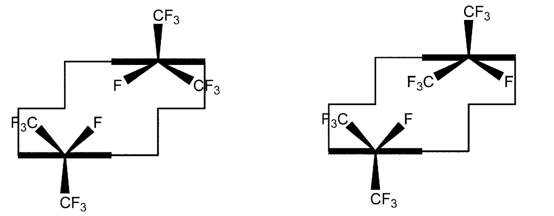
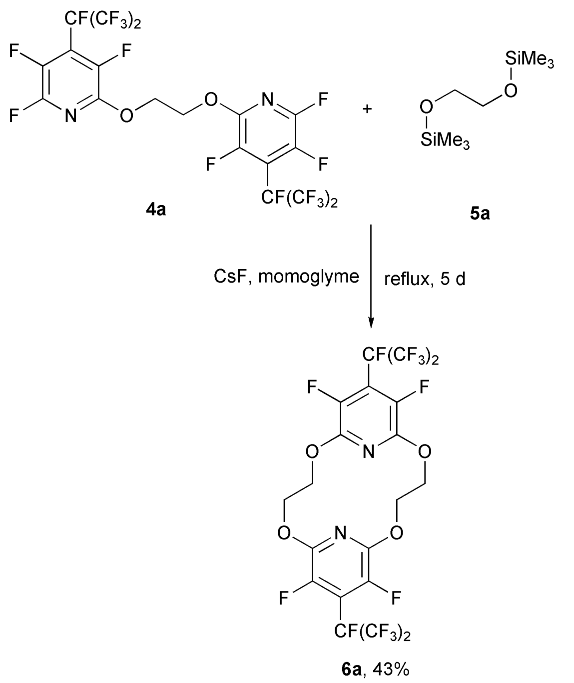


Fig. 3 Single crystal X-ray molecular structures of macrocycles **6b**. The two polymorphic modifications (A and B) are shown together for comparison (right).

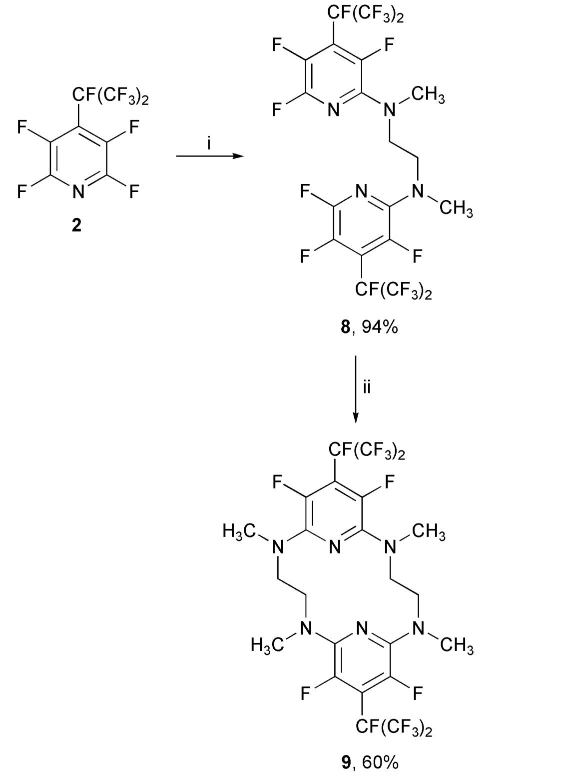


A B

Fig. 4 Schematic representation of the orientation of perfluoroisopropyl groups in the polymorphic modifications (**A** and **B**) of macrocycle **6b**.



Scheme 6



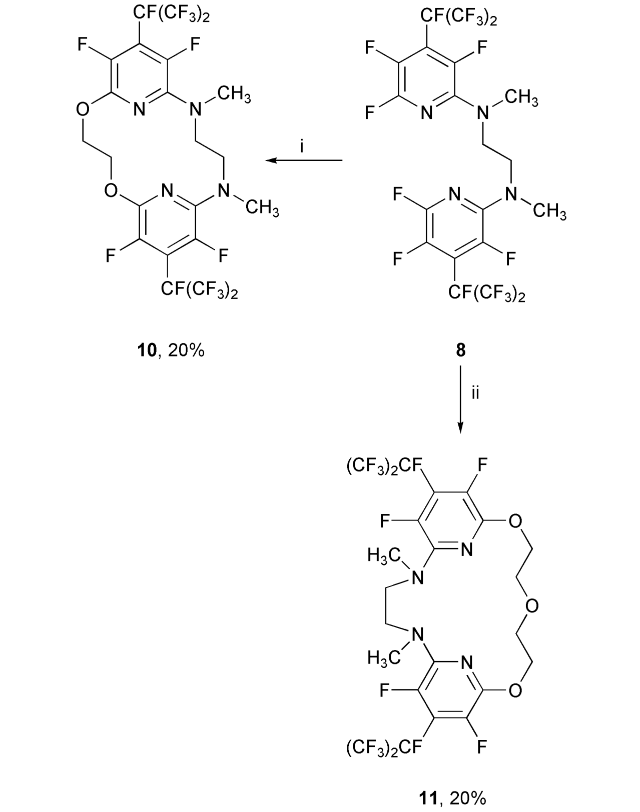
Scheme 7 *Reagents and conditions:* i, $MeNHCH_2CH_2NHMe$ **7**, THF, 75 °C, 1 d; ii, **7**, THF, rt, 20 h.

are connected by weak C–H ··· O interactions, the shortest one in structure **A** being C8–H81 ··· O6(x, $1.5 - y$, $-0.5 + z$) and in structure **B** C8–H82 ··· O1($-x$, $-y$, $1 - z$) with C ··· O distances 3.549 and 3.428 Å, respectively.

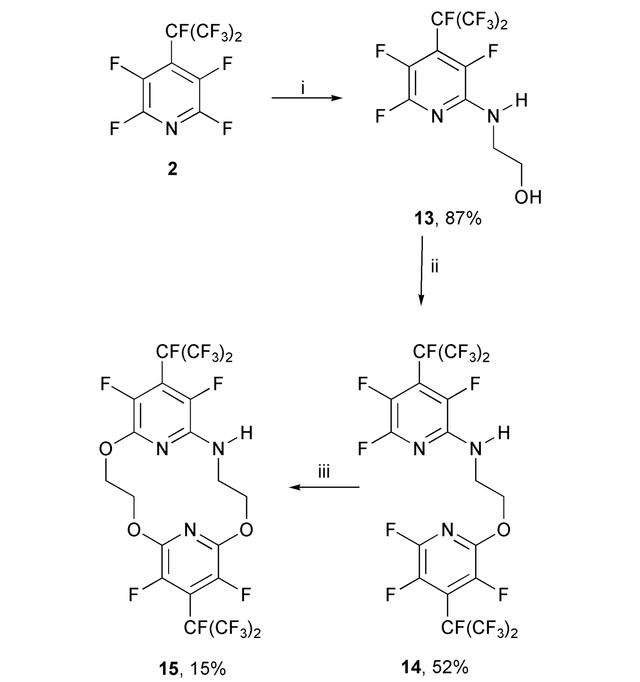
Most surprisingly, however, molecules in adjacent layers are arranged in head-to-head fashion with a number of F ··· F and C–H ··· F contacts between molecules in different layers (Fig. 5). It appears that the stacking of the molecules in the crystal lattice is best accomplished by the perfluoroisopropyl groups adopting positions that are adjacent to each other, forming fluorine-rich 'domains' within the unit cell.

To our knowledge, compound **6d** is the first structurally characterized tetra-oxo-calix[4]arene.[22] The two phenyl rings of the molecule are parallel to each other (dihedral angle between their planes is 1.0°) and almost perfectly overlapped with an interplanar distance of 4.39 Å (Fig. 6).

The symmetrical orientation of two pyridine rings makes the molecule close to possessing C_{2v} symmetry. It has been noted[23] that, in pyridyloxy-benzenes, the ether groups are usually parallel to the pyridyl ring but the orientation of phenyl groups varies considerably. Similar conformations of the ether group are observed in all three macrocycles **6a**,**b**,**d**. The orientation of the ether group in macrocycle **6d** makes its conformation quite different from those of the few known calix[4]pyridines, where either no conjugation exists between the pyridyl ring and the atoms of the bridge[24] or all four heterocycles interact with the bridge groups.[25]



Scheme 8 *Reagents and conditions:* i, **5a**, CsF, monoglyme, 85 °C, 5 d; ii, **5b**, CsF, monoglyme, 85 °C, 5 d.



Scheme 9 *Reagents and conditions:* i, $HOCH_2CH_2NH_2$ **12**, THF, 70 °C, 16 h; ii, **2**, NaH, THF, 70 °C, 16h; iii, **5a**, CsF, monoglyme, 85 °C, 5 d.

In the crystal cell, molecules **6d** form zigzag chains, parallel to the *c*-axis (Fig. 7) and molecules in the chains are connected by C–H ··· O interactions (the shortest C ··· O contact is 3.357 Å).

Conformational studies

^{1}H NMR studies of macrocycles dissolved in *d*-tetrachloroethane showed that the macrocyclic ring systems are highly flexible and rapidly interconvert between two conformations.

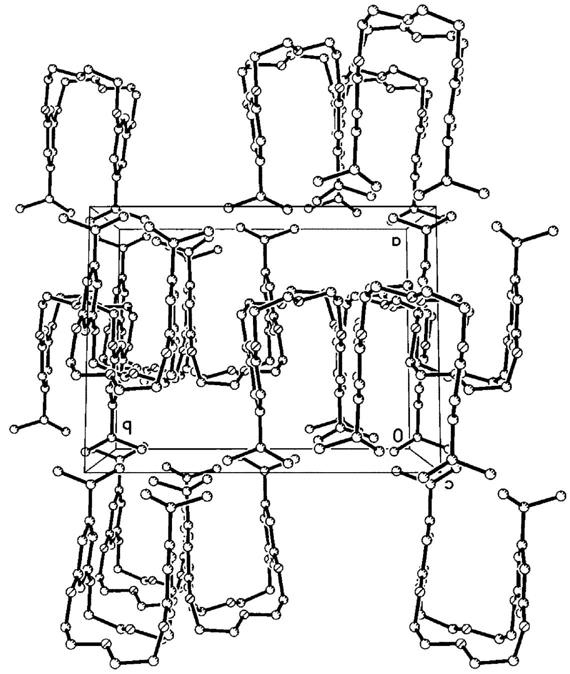


Fig. 5 Crystal lattice of macrocycle **6b**. (Fluorine atoms removed for clarity) showing the head-to-head arrangement of the molecules, forming fluorine-rich 'domains' within the unit cell.

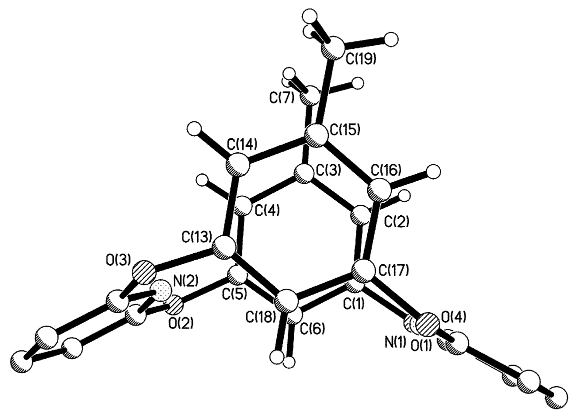
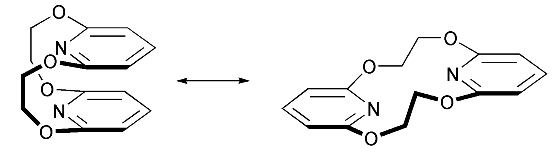


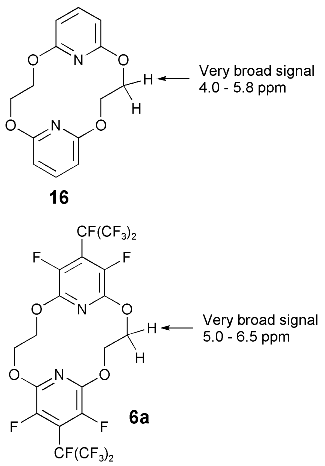
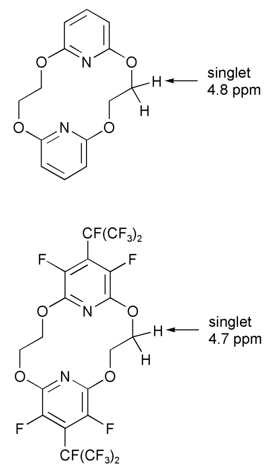
Fig. 6 Macrocycle **6d** (perfluoroisopropyl groups and fluorine atoms omitted for clarity).

For related systems, VT NMR studies by Newkome and coworkers[6] suggested that the 14-membered macrocycle **16** interconverts between a 'boat' and 'chair' conformation (Table 2). We have established that the conformation of **6d** in the crystal is similar to **16**, **boat**, while compound **6a** has a planar structure in the crystal, analogous to **16**, **chair**. For the case of **16**, at room temperature, the methylene protons gave a very broad signal located between 4.0 and 5.8 ppm whilst, at higher temperature, the same resonance appeared as a singlet at 4.8 ppm, indicating rapid interconversion on the NMR time-scale between the two conformations. Macrocycle **6a** gave similar results, for instance, a broad signal between 5.0–6.5 ppm at room temperature corresponding to CH_2, sharpens to a singlet centred at 4.7 ppm at higher temperature. Thus, similar interconversions between boat and chair conformations is likely.

The diethylene glycol **6b** and resorcinol **6d** based macrocycles, however, do not display any significant change in their ^{1}H NMR spectra over a temperature range of −25 to 90 °C. It is unlikely that such large molecules do not undergo any conformational change in solution and so we suggest that, for these more flexible systems, the interchange between conformational states is too rapid on the NMR time scale, even at lower temperatures.

Table 2 ^{1}H NMR studies of macrocycle **6a**



20 °C	90 °C
	

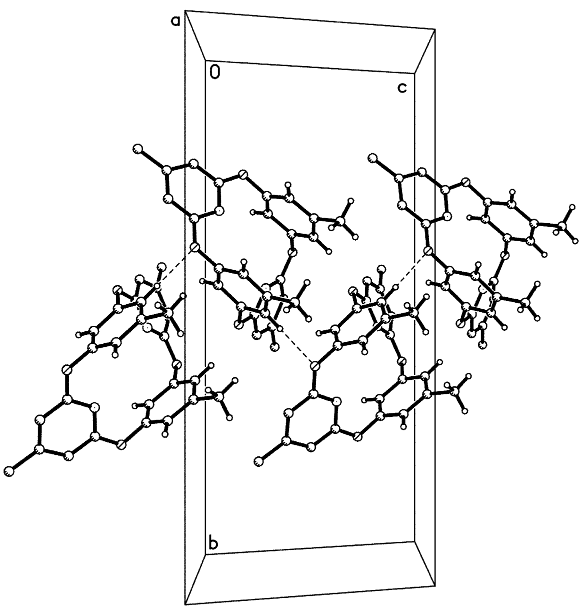


Fig. 7 Crystal cell of macrocycle **6d**.

Complexation studies

Electrospray mass spectrometry. Electrospray mass spectrometry has been used successfully to probe the ability of macrocyclic systems to coordinate a particular guest species.[26,27] Using this technique, a solution of macrocycle was mixed with a solution of the salt and this mixture was then subjected to ESMS analysis in both the positive and negative ion ionisation modes in order to observe positive and negatively charged complexed ions respectively.

Solutions of macrocycles **6a**,**b**,**d** in methanol were mixed with a solution of alkali metal acetates and, in a separate experiment, with a mixture of sodium halides; the results for ESMS analysis in both positive and negative ion ESMS modes are collated in Tables 3 and 4.

From these data, we conclude that macrocycle **6b** coordinates effectively with sodium, potassium and caesium ions, presumably by coordination of the oxygen atoms located in the polyether bridge of the molecule, whereas macrocycles **6a**,**d** do not coordinate with metal cations under these experimental conditions. Surprisingly, however, the results indicate that macrocycles **6a**,**d** form [M + Anion]$^-$ complexes. The ESMS spectrum of mixtures of macrocycles **6a**,**d** and sodium halides is shown in Fig. 8 and mass peaks corresponding to binding of these macrocycles with chloride, bromide and iodide can clearly be identified.

The nature of the binding between macrocycles **6a**,**d** and halide ions in the gas phase is difficult to rationalise. In general, there are far fewer synthetic anion hosts than cation receptors known and molecules capable of anion recognition,[28] such as polyammonium, guanidinium and pyrrole derivatives, bind through sites that are highly acidic and strong hydrogen bonding is possible. However, this mode of anion recognition is clearly not apparent in these cases. Farnham and co-workers[20] described binding of fluoride ion to polyfluorinated cyclic polyethers and it is possible that such systems involve hydrogen bonding with CH_2 sites that are made acidic by adjacent CF_2 groups. Also, Lagow and co-workers[29] reported that fluoride ion binds to some perfluorinated crown ethers but the nature of the interactions remains unclear. Again, however, both of these systems seem to be substantially different from those that we describe here.

Recent theoretical calculations[30] have shown that interactions between halide ions and electron poor heteroaromatic systems such as trichloro- and trifluoro-*s*-triazine are possible and are electrostatic in nature. Therefore, it seems reasonable to suggest that interactions of this type could explain the anion recognition displayed by macrocycles **6a**,**d** in the ES experiments described above.

Metal ion solution extraction studies. The binding ability of macrocycles may also be assessed by extraction of metal ions from an aqueous phase into an organic medium.[31] Macrocycles **6a**,**b**,**d** were dissolved in dichloromethane and shaken with an aqueous solution of either sodium or potassium picrate. The absorbance of the metal picrate solution before and after extraction by the organic macrocycle containing medium gives a value for the percentage of metal picrate extracted (Table 5, experiments using 18-crown-6 are included as a reference).

From these data, we see that all of these macrocycles are capable of extracting sodium and/or potassium picrate from aqueous solution into dichloromethane, most likely by binding to metal ions as we have no evidence to suggest that picrate anions bind with the macrocyclic systems.

Conclusions

Highly fluorinated pyridine derivatives may be used as effective building blocks for the construction of new macrocyclic systems that possess unusual structural and complexation phenomena. Further use of related perhalogenated heterocycles for the step-wise synthesis of a variety of structurally diverse macrocycles will be described in a subsequent publication.

Experimental

All starting materials were obtained commercially (Aldrich, Lancaster or Fluorochem). All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer operating at 400 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR) with tetramethylsilane and trichlorofluoromethane as internal standards. The existence of two rotamers of all systems bearing perfluoroisopropyl substituents leads to the observation of two sets of resonances in the ^{19}F NMR spectrum. This phenomenon is described in detail elsewhere for model perfluoroisopropyl-

Table 3 Macrocycles **6a**,**b**,**d** in the presence of metal acetates

Macrocycle	ESMS Mode	*m*/*z*	Major peaks (*m*/*z*)	Comment
6a	−ve	682	717	Chloride
			729	Acetate
			757	Unknown
6b	+ve	770	793	Sodium
			809	Potassium
			903	Caesium
6d	−ve	806	941	Chloride
			853	Acetate
18-crown-6	+ve	264	287	Sodium
			303	Potassium

Table 4 Macrocycles **6a**,**b**,**d** in the presence of sodium halides

Macrocycle	MS Mode	*m*/*z*	Major peaks (*m*/*z*)	Comment
6a	−ve	682	717	Chloride
			761	Bromide
			809	Iodide
6b	+ve	770	793	Sodium
6d	−ve	806	841	Chloride
			884	Bromide
			932	Iodide
18-Crown-6	+ve	264	287	Sodium

pyridine systems.[19] Mass spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25m HP1 (methylsilicone) column. Elemental analyses were obtained on a Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions were monitored by either 19F NMR or gas-chromatography on an Shimadzu GC8A system using an SE30 column. Distillation was performed using a Fischer Spaltrohr MS220 microdistillation apparatus. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040–0.063 nm) and TLC analysis was performed on silica gel TLC plates (Merck).

X-Ray crystal structures

All single crystal data were collected on a Bruker SMART-CCD diffractometer (ω-scan, 0.3°/frame) at 120.0(2) K using graphite monochromated Mo-K° radiation (λ = 0.71073 Å). The structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXL software.

Oxygen bridged compounds 4a–d

General procedure. Under an atmosphere of dry nitrogen, the bis-silyl derivative was added to a solution consisting of caesium fluoride, *2,3,5,6-tetrafluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)pyridine* **2** and monoglyme and heated to reflux temperature for 40 h. Water (250 ml) was added and the mixture was continuously extracted into ether. After drying the

Table 5 Extraction of metal picrates from aqueous to organic phase by macrocycles **6a**,**b**,**d**

	Sodium picrate			Potassium picrate		
Macrocycle	Abs_{Before}	Abs_{After}	$\%_{Extraction}$	Abs_{Before}	Abs_{After}	$\%_{Extraction}$
6a	0.0273	0.0124	54	0.0139	0.0832	40
6b	0.0273	0.0250	9	0.0139	0.1010	28
6d	0.0273	0.0125	27	0.0139	0.0147	0
18-Crown-6	0.0273	0.0271	6	0.0139	0.0390	72

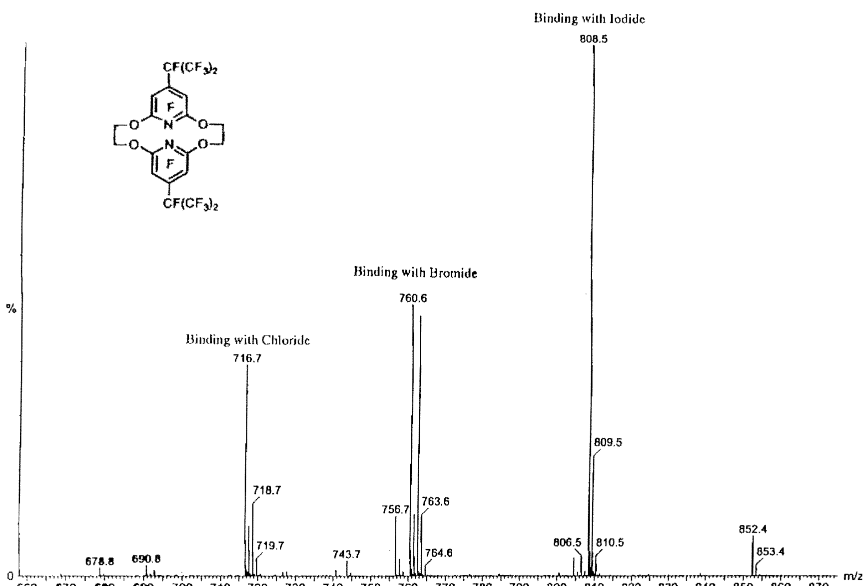


Fig. 8 Electrospray mass spectrometry (negative ion mode) of macrocycle **6a** (0.1 mM solution in methanol) after addition of a mixture consisting of NaF, NaCl, NaBr and NaI (0.1 mM solution of each salt in methanol).

ethereal layer ($MgSO_4$), excess **2** present in the ether fraction was recovered by extraction into perfluorocyclohexane. The ether layer was evaporated to give a crude product which was purified either by column chromatography on silica gel or recrystallisation.

2,3,5-Trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)-ethyl]-6-(2-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoro-methyl)ethyl](2-pyridyloxy)}ethoxy)pyridine 4a. 1-[2-(1,1-Dimethyl-1-silaethoxy)ethoxy]-1,1-dimethyl-1-silaethane **5a** (0.16 g, 0.79 mmol), **2** (5.0 g, 1.57 mmol) and caesium fluoride (0.12 g, 0.79 mmol) in monoglyme (50 ml), after column chromatography on silica gel using hexane–ethyl acetate (8 : 1) as the eluent, gave *2,3,5-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoro-methyl)ethyl]-6-(2-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyloxy)}ethoxy)pyridine* **4a** (0.47 g, 90%) as a colourless liquid; bp >300 °C (Found: C, 32.6; H, 0.6; N, 4.2. $C_{18}H_4F_{20}N_2O_2$ requires C, 32.7; H, 0.6; N, 4.2%); δ_H 4.8 (br s); δ_F −75.6 (6F, m, CF_3), −90.6 and −91.8 (1F, br s, F-6), −134.2 and −137.7 (1F, br s, F-5), −145.4 and −148.3 (1F, br s, F-3), −180.5 (1F, m, C**F**CF_3); δ_C 65.6 (s, CH_2), 91.8 (dsept, $^1J_{CF}$ 215, $^2J_{CF}$ 38.2, **C**FCF_3), 117.0 (m, C-4), 120.3 (qd, $^1J_{CF}$ 289, $^2J_{CF}$ 27.1, CF_3), 132.0–146 (br m, C-2,3,5,6); *m*/*z* (EI^+) 344 (100%), 318 (53), 275 (10), 249 (19), 69 (26).

2,3,5-Trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)-ethyl]-6-[2-(2-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoro-methyl)ethyl](2-pyridyloxy)}ethoxy)ethoxy]pyridine 4b. 1-{2-[2-(1,1-Dimethyl-1-silaethoxy)ethoxy]ethoxy}-1,1-dimethyl-1-silaethane **5b** (3.92 g, 15.7 mmol), **2** (10.0 g, 31.3 mmol) and caesium fluoride (4.75 g, 31.3 mmol) in monoglyme (50 ml), after column chromatography on silica gel using hexane and dichloromethane (4 : 1) as the eluent, gave *2,3,5-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-6-[2-(2-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyloxy)}ethoxy)ethoxy]pyridine* **4b** (9.17 g, 83%) as a colourless liquid; bp 280–282 °C (Found: C, 34.1; H, 1.1; N, 3.9. $C_{20}H_8F_{20}N_2O_3$ requires C, 34.1; H, 1.1; N, 3.9%); mp 207.6–209.0 °C (Found: C, 35.1; H, 1.2; N, 4.3. $C_{20}H_8F_{18}N_2O_4$ requires C, 35.2; H, 1.2; N, 4.1%); δ_H 3.9 (1H, m, CH_2OCH_2), 4.5 (1H, m, CH_2OAr); δ_F −75.8 (6F, m, CF_3), −91.2 and −92.8 (1F, br s, F-6), −134.5 and −137.2 (1F, br s, F-5), −146.6 and −149.9 (1F, br s, F-3), −180.6 (1F, m, C**F**CF_3); δ_C 67.5 (s, CH_2OCH_2), 69.2 (s, CH_2OAr), 91.9 (dsept, $^1J_{CF}$ 214, $^2J_{CF}$ 36.0, **C**FCF_3), 116.9 (m, C-4), 119.9 (qd, $^1J_{CF}$ 287, $^2J_{CF}$ 26.9, CF_3), 132.0–147 (br m, C-2,3,5,6); *m*/*z* (EI^+) 344 (100%), 318 (39), 249 (12), 69 (17).

2,3,5-Trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)-ethyl]-6-(3-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoro-methyl)ethyl](2-pyridyloxy)}phenoxy)pyridine 4c. 2-[3-(1,1-Dimethyl-1-silaethyl)phenyl]-2-methyl-2-silapropane **5c** (1.9 g, 7.1 mmol), caesium fluoride (2.5 g, 16.5 mmol), **2** (22.5 g, 70.5 mmol) and monoglyme (175 ml), after recrystallisation in cyclohexane, gave *2,3,5-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-6-(3-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyloxy)}phenoxy)pyridine* **4c** (3.5 g, 70%) as a white solid; mp 138.0–138.4 °C (Found: C, 37.3; H, 0.5; N, 3.9. $C_{22}H_4F_{20}N_2O_2$ requires C, 37.3; H, 0.6; N, 3.9%); δ_H 7.07 (1H, m, H-2), 7.14 (2H, dd, $^3J_{HH}$ 8.4, $^4J_{HH}$ 2.0, H-4), 7.50 (1H, t, $^3J_{HH}$ 8.4, H-5); δ_F −75.2 (6F, m, CF_3), −87.9 and −89.0 (1F, m, F-2), −132.8 and −135.3 (1F, m, F-3), −140.9 and −143.6 (1F, m, F-5), −180.3 (1F, m, C**F**CF_3); *m*/*z* (EI^+) 708 (M^+, 5%), 323 (6), 273 (8), 69 (29).

2,3,5-Trifluoro-6-(5-methyl-3-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyloxy)}phenoxy)-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine 4d. 2-[5-(1,1-Dimethyl-1-silaethyl)-3-methylphenyl]-2-methyl-2-silapropane **5d** (1.9 g, 7.1 mmol), caesium fluoride (2.5 g, 16.5 mmol), **2** (22.5 g, 70.5 mmol) and monoglyme (175 ml) after recrystallisation in cyclohexane, gave *2,3,5-trifluoro-6-(5-methyl-3-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyloxy)}phenoxy)-4-[1,2,2,2-tetrafluoro-1-(trifluoro-methyl)ethyl]pyridine* **4d** (3.7 g, 73%); mp 161–161.5 °C (Found: C, 38.0; H, 0.8; N, 3.9. $C_{23}H_6F_{20}N_2O_2$ requires C, 38.2; H, 0.8; N, 3.9%); δ_H 2.4 (3H, s, CH_3), 7.1 (3H, m, Ar-H); δ_F −76.2 (6F, m, CF_3), −90.8 and −91.9 (1F, m, F-2), −135.2 and −137.6 (1F, m, F-3), −143.8 and −146.4 (1F, m, F-5), −180.8 (1F, m, C**F**CF_3); *m*/*z* (EI^+) 722 (M^+, 31%), 406 (41), 387 (39), 378 (21), 301 (18), 253 (18), 236 (16), 89 (24), 78 (13), 69 (30).

Synthesis of macrocycles

19,20-Diaza-8,17-bis[1,2,2,2-(tetrafluoromethyl)ethyl]-7,9,16,18-tetrafluoro-2,5,11,14-tetraoxatricyclo[13.3.1.1^{6,10}]icosa-1(19),6,8,10(20),15,17-hexaene 6a. A mixture of **5a** (0.35 g, 1.7 mmol), dry CsF (0.5 g, 3.2 mmol) and **4a** (2.5 g, 3.8 mmol), in anhydrous monoglyme (150 ml) was heated to 85 °C under an atmosphere of dry nitrogen. The mixture was heated for 5 d, then allowed to cool and diluted with water (20 ml). Extraction into DCM (2 × 30 ml) enabled recovery of organic components. The combined organic phases were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. Column chromatography on silica gel, eluting with hexane and ethyl acetate 4 : 1 gave a white solid. Recrystallisation from toluene three times gave *19,20-diaza-8,17-bis[1,2,2,2-(tetrafluoromethyl)ethyl]-7,9,16,18-tetrafluoro-2,5,11,14-tetraoxatricyclo[13.3.1.1^{6,10}]icosa-1(19),6,8,10(20),15,17-hexaene* **6a** (43%, 0.5 g); mp 191–194 °C (Found: C, 35.4; H, 1.2; N, 4.1; $C_{20}H_8F_{18}N_2O_4$ requires, C, 35.2; H, 1.2; N, 4.1%); δ_H (20 °C) 5.2–6.8 (br s); δ_H (90 °C, $C_2H_4Cl_2$) 4.70 (s); δ_F −77.0 (6 F, s, CF_3), −145.1 and −147.9 (2 F, br s, ring F), −181.7 (1 F, m, C**F**CF_3); *m*/*z* (EI^+) 682 (M^+, 10%), 368 (75), 341 (100), 322 (32).

Crystal data for ***6a*** ‡. $C_{20}H_8F_{18}N_2O_4$, M = 682.28, monoclinic, space group $P2_1/c$, a = 14.2011(5), b = 8.4725(3), c = 9.4479(3) Å, β = 102.11(1)°, U = 1111.45(7) Å^3, F(000) = 672, Z = 2, D_c = 2.039 mg m^{-3}, μ = 0.240 mm^{-1}. Data were collected on a Bruker SMART-CCD 1K diffractometer (ω-scan, 0.3°/frame) using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). 12347 reflections (1.47 ≤ θ ≤ 30.31°) were collected yielding 3089 unique data (R_{merg} = 0.052). Structure was solved by direct method and refined by full-matrix least square on F^2 for all data. All non-hydrogen atoms were refined anisotropically, hydrogen atoms were located from the difference Fourier map and refined isotropically. Final $wR_2(F^2)$ = 0.1101 for all data (215 refined parameters), conventional $R(F)$ = 0.0429 for 3089 reflections with $I \geq 2\sigma$, GOF = 1.022. The largest peak on the residual map is 0.54 a/Å^3.

25,26-Diaza-11,23-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)-ethyl]-10,12,22,24-tetrafluoro-2,5,8,14,17,20-hexaoxatricyclo-[19.3.1.1^{9,13}]hexacosa-1(25),9,11,13(26),21,23-hexaene 6b. A mixture of **5b** (0.6 g, 2.0 mmol), dried CsF (0.6 g, 3.9 mmol) and **4b** (3 g, 4.3 mmol), in anhydrous monoglyme (600 ml) was heated to 85 °C under an atmosphere of dry nitrogen. The mixture was heated over 5 d before being allowed to cool to room temperature and water (20 ml) added. Extraction into dichloromethane (2 × 30 ml) enabled recovery of organic components. The combined organic extracts were dried ($MgSO_4$) and the solvent removed under vacuum. Column chromatography (hexane–ethyl acetate 5 : 1) gave a yellow solid, which after recrystallisation from toluene three times gave *25,26-diaza-11,23-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)-ethyl]-10,12,22,24-tetrafluoro-2,5,8,14,17,20-hexaoxatricyclo-*

‡ CCDC reference numbers 197403–197405, 208079. See http://www.rsc.org/suppdata/ob/b3/b303443g/ for crystallographic data in .cif or other electronic format.

[19.3.1.1^{9,13}]hexacosa-1(25),9,11,13(26),21,23-hexaene **6b** (0.62 g, 40%); mp 201–204 °C; (Found: C, 37.5; H, 2.0; N, 3.6; $C_{24}H_{16}F_{18}N_2O_6$ requires C, 37.4; H, 2.1; N, 3.6%); δ_H 3.88 (1H, m, CH_2O), 4.65 (1 H, m, CH_2OCH_2); δ_F −76.4 (6 F, m, CF_3), −147.1 and −150.0 (2 F, m, ring F), −180.7 (1 F, m, C**F**CF_3); δ_C 66.9 (s, CH_2), 69.9 (s, CH_2OCH_2), 92.9 (dsept, $^1J_{CF}$ 211, $^2J_{CF}$ 35.3, **C**FCF_3), 114.5 (m, C-4), 121.5 (qd, $^1J_{CF}$ 286, $^2J_{CF}$ 27.0, CF_3), 135–147 (br m, C-2,3); *m/z* (EI$^+$) 770 (M^+, 39%), 368 (29), 341 (100), 216 (21).

*Crystal data for **6bA** ‡.* $C_{24}H_{16}F_{18}N_2O_6$, *M* = 770.39, monoclinic (triclinic), space group *P* $2_1/c$ (*P*-1), *a* = 11.0542(4), *b* = 14.1784(5), *c* = 18.7552(6) Å, *α* =90, *β* = 102.960(1) *γ* = 90 °, *U* = 2864.6(2) Å^3, *F*(000) = 1536, *Z* = 4, D_c = 1.686 mg m^{-3}, *μ* = 0.182 mm^{-1}. 33009 reflections (1.89 ≤ *θ* ≤ 30.2°) were collected yielding 7801 unique data (R_{merg} = 0.029). Final $wR_2(F^2)$ = 0.1175 for all data (408 refined parameters), conventional *R*(*F*) = 0.0439 for 6566 reflections with *I* ≥ 2*σ*, GOF = 1.053.

*Crystal data for **6bB** ‡.* $C_{24}H_{16}F_{18}N_2O_6$, *M* = 770.39, monoclinic (triclinic), space group *P* $2_1/c$ (P-1), *a* = 10.771(1), *b* = 11.765(1), *c* = 12.279(1) Å, *α* = 69.53(1), *β* = 85.10(1), *γ* = 85.96(1)°, *U* = 1451.0(2) Å^3, *F*(000) = 768, *Z* = 2, D_c = 1.763 mg m^{-3}, *μ* = 0.199 mm^{-1}. 11550 reflections (1.77 ≤ *θ* ≤ 27.5°) were collected yielding 6561 unique data (R_{merg} = 0.088). Final $wR_2(F^2)$ = 0.1921 for all data (512 refined parameters), conventional *R*(*F*) = 0.0762 for 2734 reflections with *I* ≥ 2*σ*, GOF = 0.952.

1,11,18,28-Tetraoxadibenzena-bis-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridinophane 6c. Under an atmosphere of dry nitrogen, **5c** (0.36 g, 1.4 mmol) was added to a solution of caesium fluoride (0.35 g, 2.3 mmol), **4c** (1.0 g, 1.4 mmol) in monoglyme (300 cm3) and heated to reflux temperature for 40 h, before water (300 cm^3) was added. The mixture was continuously extracted into DCM, dried ($MgSO_4$) and evaporated to yield crude material. Column chromatography on silica gel using dichloromethane as the eluent gave *26,28-diaza-5,17-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-4,6,16,18-tetrafluoro-2,8,14,20-tetraoxapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(26),9,11,13(27),15,17,19(28),21,23-dodecaene* **6c** (0.71 g, 64%) as a white solid; mp 118.7–118.9 °C (Found: C, 43.0; H, 1.0; N, 3.6. $C_{28}H_8F_{18}N_2O_4$ requires C, 43.2; H, 1.0; N, 3.6%); δ_H 6.69 (1H, s, H-2), 6.86 (2H, m, H-4,6), 7.27 (1H, t, $^3J_{HH}$ 9.6, H-5); δ_F −75.3 (12F, m, CF_3), −140.8 and −143.7 (4F, m, ring F), −180.1 (2F, m, C**F**CF_3); *m/z* (EI$^+$) 778 (M^+, 49%), 292 (16), 243 (58), 200 (10), 100 (11), 93 (22), 92 (25), 76 (100), 69 (95).

26,28-Diaza-5,17-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)-ethyl]-4,6,16,18-tetrafluoro-11,23-dimethyl-2,8,14,20-tetraoxa-pentacyclo[19.3.1.^{13,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3,5,7(26),9,(27),10,12,15,17,19(28),21(25),22-dodecaene 6d. A mixture of **5d** (1.1 g, 3.8 mmol), dried CsF (1.3 g, 8.5 mmol) and **4d** (3 g, 5.8 mmol), in anhydrous monoglyme (150 ml) was heated to 85 °C under an atmosphere of dry nitrogen. The mixture was heated over 5 d before being allowed to cool to room temperature and water (20 ml) added. Extraction into DCM (2 × 30 ml) enabled recovery of organic components. The combined organic phases were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. Column chromatography on silica gel, eluting with hexane and ethyl acetate 5 : 1 gave a yellow solid. Recrystallisation from toluene three times gave *26,28-diaza-5,17-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-4,6,16,18-tetrafluoro-11,23-dimethyl-2,8,14,20-tetraoxapentacyclo-[19.3.1.^{13,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3,5,7(26),9,(27),10,12,15,17,19(28),21(25),22-dodecaene* **6d** (33%, 1.0 g); mp 201–204 °C (Found: C, 44.6; H, 1.7; N, 3.5. $C_{30}H_{12}F_{18}N_2O_4$ requires C, 44.7; H, 1.5; N, 3.5%); δ_H 2.33 (6H, s, CH_3), 6.58 (2H, s, H-2), 6.81 (4H, m, H-4,6); δ_F −75.5 (6 F, m, CF_3), −141.3 and −144.1 (4F, m, ring F), −180.3 (1F, m, C**F**CF_3); *m/z* (EI$^+$) 806 (M + 1, 100%), 403 (12).

*Crystal data for **6d** ‡.* $C_{30}H_{12}F_{18}N_2O_4$, *M* = 806.42, monoclinic, space group *Cc*, *a* = 13.473(3), *b* = 23.261(5), *c* = 11.079(2) Å, *β* = 113.78(3)°, *U* = 3177(1) Å^3, *F*(000) = 1600, *Z* = 4, D_c = 1.686 mg m^{-3}, *μ* = 0.182 mm^{-1}. 15431 reflections (1.75 ≤ *θ* ≤ 25.5°) were collected yielding 5778 unique data (R_{merg} = 0.028). Terminal $CF(CF_3)_2$ groups of the molecule are severely disordered which affected *R*-values. Final $wR_2(F^2)$ = 0.3100 for all data (408 refined parameters), conventional *R*(*F*) = 0.1168 for 4792 reflections with *I* ≥ 2*σ*, GOF = 1.095. The largest peak on the residual map (0.74 a/Å^3) is located in the disordered region.

Nitrogen bridged macrocycles

Methyl[2-methyl{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyl)}amino)ethyl]{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]2-pyridyl)}amine 8. A mixture of *N,N′*-dimethylethylenediamine **7** (1.4 g, 17 mmol) and **2** (10 g, 30 mmol), in anhydrous THF (75 ml) was heated to 75 °C under an atmosphere of dry nitrogen. The mixture was heated over 1 d before being allowed to cool to room temperature and sodium hydrogen carbonate solution (20 ml) added. Extraction into DCM (2 × 30 ml) enabled recovery of organic components. The combined organic phases were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. Reduced pressure distillation gave *methyl[2-methyl{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyl)}amino)ethyl]-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)-ethyl]2-pyridyl}amine* **8** (94%, 11 g); bp 140 °C (5 mbar); which was used in subsequent experiments without further purification.

2,5,11,14,19,20-Hexaaza-8,17-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-7,9,16,18-tetrafluoro-2,5,11,14-tetramethyl-tricyclo[13.3.1.1^{6,10}]icosa-1(18),6(20),7,9,15,(19),16-hexaene 9. Under an atmosphere of dry nitrogen, **7** (0.46 g, 5.2 mmol) was added to a solution of **8** (1.0 g, 2.6 mmol) in THF (50 ml) and the mixture was stirred at rt for 20 h before water (100 ml) was added. The organic material was continuously extracted with DCM, dried ($MgSO_4$) and then evaporated to yield crude material (1.98 g) which, after recrystallisation from toluene, afforded *2,5,11,14,19,20-hexaaza-8,17-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-7,9,16,18-tetrafluoro-2,5,11,14-tetra-methyltricyclo[13.3.1.1^{6,10}]icosa-1(18),6(20),7,9,15,(19),16-hexaene* **9** (1.1 g, 60%) as a white solid; mp 299.3–300.0 °C (Found: C, 39.1; H, 2.7; N, 11.5. $C_{24}H_{20}F_{18}N_6$ requires C, 39.2; H, 2.7; N, 11.4%); δ_H 2.8 (12 H, m, –CH_3), 3.2 (8 H, m, –CH_2); δ_F −76.1 (12 F, m, CF_3), −144.8 and −147.8 (4 F, s, F-3), −179.4 (2 F, m, *C*FCF3); δ_C 37.9 (m, –CH_2), 48.3 (s, –CH_3), 88.0–92.0 (broad overlapping m, *C*FCF_3), 113.9 (m, 8,17-C), 120.6 (qd, $^1J_{CF}$ 286.7, $^2J_{CF}$ 27.9, CF_3), 130.0–145.0 (broad overlapping m, ring C); *m/z* (EI$^+$) 734 (M^+, 5%), 380 (32), 367 (37), 360 (12), 354 (100), 324 (19), 255 (14), 69 (12).

11,14,19,20-Tetraaza-8,17-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-7,9,16,18-tetrafluoro-11,14-dimethyl-2,5-dioxatricyclo[13.3.1.1^{6,10}]icosa-1(19),6,8,10,(20),15, 17-hexaene 10. A mixture of **5a** (0.4 g, 1.9 mmol), dried CsF (0.5 g, 3.2 mmol) and **8** (3 g, 4.4 mmol), in anhydrous monoglyme (150 ml) was heated to 85 °C under an atmosphere of dry nitrogen. The mixture was heated over 5 d before being allowed to cool to room temperature and water (20 ml) added. Extraction into dichloromethane (2 × 30 ml) enabled recovery of organic components. The combined organic phases were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. Column chromatography on silica gel, eluting with hexane and ethyl acetate 5 : 1 gave a yellow solid. Recrystallisation from toluene three times gave *11,14,19,20-tetraaza-8,17-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-7,9,16,18-tetrafluoro-11,14-dimethyl-2,5-dioxatricyclo[13.3.1.1^{6,10}]icosa-1(19),6,8,10,(20),15,17-hexaene* **10** (20%, 0.27 g) as a white solid; mp 208–209 °C

(Found: C, 37.1; H, 1.95; N, 7.8. $C_{22}H_{14}F_{18}N_4O_2$ requires C, 37.3; H, 2.0; N, 7.9%); δ_H (TCE) 3.29 (3 H, s, CH_3), 3.30 (3 H, s, CH_3), 3.4–5.4 (8H, br s, CH_2O and CH_2N); δ_H (90 °C), 3.29 (6 H, m, CH_3), 3.75 (4 H, br s, CH_2N), 4.73 (4 H, br s, CH_2O); δ_F (TCE) −74.8 (12 F, m, CF_3), −139.5 (4 F, br m, F-3), 150.6 (4 F, br m, F-5), −178.6 (2 F, m, C*F*CF_3); δ_C (TCE, 90 °C), 38.0 (s, CH_3), 38.2 (s, CH_3), 49.0 (s, CH_2N), 62.4 (s, CH_2O), 92.0 (m, *C*FCF_3), 115.3 (m, C-4), 120.7 (qd, $^1J_{CF}$ 288, $^2J_{CF}$ 28, CF_3), 133.5 (m, C-6), 136.1 (m, C-2), 144.5 (m, C-3,5); *m*/*z* (EI^+) 708 (M^+, 32%), 688 (42), 381 (77), 355 (100), 69 (5).

2,5,22,23-Tetraaza-8,20-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-7,9,19,21-tetrafluoro-2,5-dimethyl-11,14,17-trioxatricyclo[16.3.1.1^{6,10}]-tricosa-1(22),6,8,10(23),18,20-hexaene 11. A mixture of **5b** (0.7 g, 4.4 mmol), dried CsF (0.6 g, 3.9 mmol) and **8** (3 g, 4.4 mmol), in anhydrous monoglyme (150 ml) was heated to 85 °C under an atmosphere of dry nitrogen. The mixture was heated over 5 d before being allowed to cool to room temperature and water (20 ml) added. Extraction into dichloromethane (2 × 30 ml) enabled recovery of organic components. The combined organic phases were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. Column chromatography on silica gel, eluting with hexane and ethyl acetate 5 : 1 gave a yellow solid. Recrystallisation from toluene three times gave *2,5,22,23-tetraaza-8,20-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-7,9,19,21-tetrafluoro-2,5-dimethyl-11,14,17-trioxatricyclo[16.3.1.1^{6,10}]-tricosa-1(22),6,8,10(23),18,20-hexaene* **11** (20%, 0.42 g); mp 207–210 °C (Found: C, 38.8; H, 2.5; N, 7.6. $C_{24}H_{18}F_{18}N_4O_3$ requires C, 38.3; H, 2.4; N, 7.45%); δ_H (TCE, 90 °C) 2.80 (4 H, m, CH_2O), 3.0 (4 H, m, CH_2O), 3.1 (6 H, br m, CH_3N), 3.4 (4 H, m, CH_2N); δ_F (TCE) −74.3 (12 F, m, CF_3), −133.3 (4 F, br s, F-3), −182.9 (2 F, m, C*F*CF3); *m*/*z* (EI^+) 752 (M^+, 20%), 732 (100), 341 (47), 448 (29), 69 (10).

Mixed N,O bridged compounds

2-({5,6-Difluoro-3-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-2-pyridyl}amino)ethan-1-ol 13. Ethanolamine **12** (2.9 g, 33.0 mmol) was added to a solution of **2** (15 g, 50 mmol) in THF (30 ml). The mixture was heated to 70 °C for 16 h and, after cooling, a saturated solution of aqueous sodium hydrogen carbonate (30 ml) was added. After extraction into dichloromethane (2 × 50 ml), the combined organic phases were dried ($MgSO_4$) before the solvent was removed under reduced pressure. Distillation under reduced pressure gave *2-({5,6-difluoro-3-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-2-pyridyl}amino)ethan-1-ol* **13** (10 g, 87%) as a colourless liquid; bp 50 °C at 5 mbar (Found: C, 33.0; H, 1.7; N, 7.8. $C_{10}H_6F_{10}N_2O$ requires C, 33.3; H, 1.7; N, 7.8%); δ_H 2.69 (1 H, br s, OH), 3.63 (2 H, m, CH_2), 3.81 (2 H, m, CH_2), 5.40 (1 H, br m, NH); δ_F −75.8 (6 F, m, CF_3), −92.2 (1 F, br m, F-6), −139.9 (1 F, br m, F-3), −155.3 (1 F, br m, F-5), −180.5 (1 F, m, C*F*CF_3); δ_C 43.5 (s, CH_2N), 61.4 (s, CH_2O), 92.0 (dsept, $^1J_{CF}$ 210, $^2J_{CF}$ 34.4, **C**FCF_3), 114.5 (m, C-4), 119.8 (qd, $^1J_{CF}$ 286, $^2J_{CF}$ 27, CF_3), 132.1 (dm, $^1J_{CF}$ 262, C-3), 140.0 (m, C-5), 143.1 (m, C-2), 147.0 (dd, $^1J_{CF}$ 234, $^2J_{CF}$ 15.5, C-6); *m*/*z* EI^+ 360 (M^+, 9%), 329 (100), 260 (64), 210 (22), 69 (21), 31 (13).

{3,5,6-Trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)-ethyl](2-pyridyl)}(2-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyloxy)}ethyl)amine 14. Sodium hydride (1.4 g, 58 mmol) was washed three times using dry hexane before being added slowly, under an atmosphere of dry nitrogen, to a solution of **2** (15 g, 47 mmol) and **13** (10 g, 29 mmol) in THF (30 ml). The mixture was heated to 70 °C for 16 h and, after cooling, water (30 ml) was added. After extraction into dichloromethane (2 × 50 ml), the combined organic phases were dried ($MgSO_4$) before the solvent was removed on a rotary evaporator. Distillation under reduced pressure gave *{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyl)}(2-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyloxy)}ethyl)amine* **14** (16 g, 52%) as a colourless liquid; bp 140 °C at 0.1 mbar (Found: C, 32.4; H, 0.74; N, 6.4. $C_{18}H_5F_{20}N_3O$ requires C, 32.8; H, 0.8; N, 6.4%); δ_H 3.90 (2 H, t, $^3J_{HH}$ 5.2, CH_2N), 4.58 (2 H, t, $^3J_{HH}$ 5.2, CH_2O), 5.15 (1 H, br s, NH); *m*/*z* (EI^+) 659 (M^+, 3%), 343 (23), 342 (38), 329 (100), 260 (31), 69 (18).

14,19,20-Triaza-8,17-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-7,9,16,18-tetrafluoro-2,5,11-trioxatricyclo-[13.3.1.1^{6,10}]icosa-1(19),6,8,10(20),15,17-hexaene 15. A mixture of **5a** (0.6 g, 2.9 mmol), dried CsF (0.7 g, 4.6 mmol) and **14** (3 g, 8 mmol), in anhydrous monoglyme (150 ml) was heated to 85 °C under an atmosphere of dry nitrogen for 5 d. After cooling, water (20 ml) was added. After extraction into dichloromethane (2 × 30 ml), the combined organic phases were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. Column chromatography on silica gel, eluting with hexane and ethyl acetate 5 : 1 gave a yellow solid. Recrystallisation from methanol three times gave *14,19,20-triaza-8,17-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-7,9,16,18-tetrafluoro-2,5,11-trioxatricyclo[13.3.1.1^{6,10}]icosa-1(19),6,8,10(20),15,17-hexaene* **15** (15%, 0.27 g) as a white solid, mp 155–159 °C (Found: C, 35.5; H, 1.3; N, 6.2. $C_{20}H_9F_{18}N_3O_3$ requires C, 35.3; H, 1.4; N, 6.2%); δ_H 3.78 (2 H, m, CH_2N), 4.70 (6 H, m, CH_2O); δ_F (TCE) −75.0 (12 F, m, CF_3), −144.7 (4 F, br m, F-3), −147.9 (4 F, br m, F-5), −179.2 (2 F, m, C*F*CF_3); *m*/*z* (EI^+) 681 (M^+, 31%), 366 (41), 339 (100), 242 (13), 69 (14).

Metal picrate extraction studies

Aqueous solutions containing picric acid (5.0 mM) and the alkali metal fluoride (50.0 mM) were prepared. Into a capped vial was placed 1.0 ml of the metal picrate solution and 1.0 ml of the macrocycle (5.0 mM) in DCM. The resulting two-phase system was then mixed together for 30 minutes using a mechanical shaker. The samples were then allowed to stand for 1 hour before a sample (10 µl) of the aqueous phase was then removed and made up to a 5.0 ml sample using acetonitrile. The absorption spectrum of the solution was then measured, in a 1.0 cm silica-cell, using a UV2 UV/VIS spectrometer at 275 nm. This was referenced to a blank solution containing DCM and the metal picrate under investigation to account for any slight solubility of the metal picrate in DCM.

Acknowledgements

We thank the University of Durham (PH and AK) and EPSRC (PR).

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