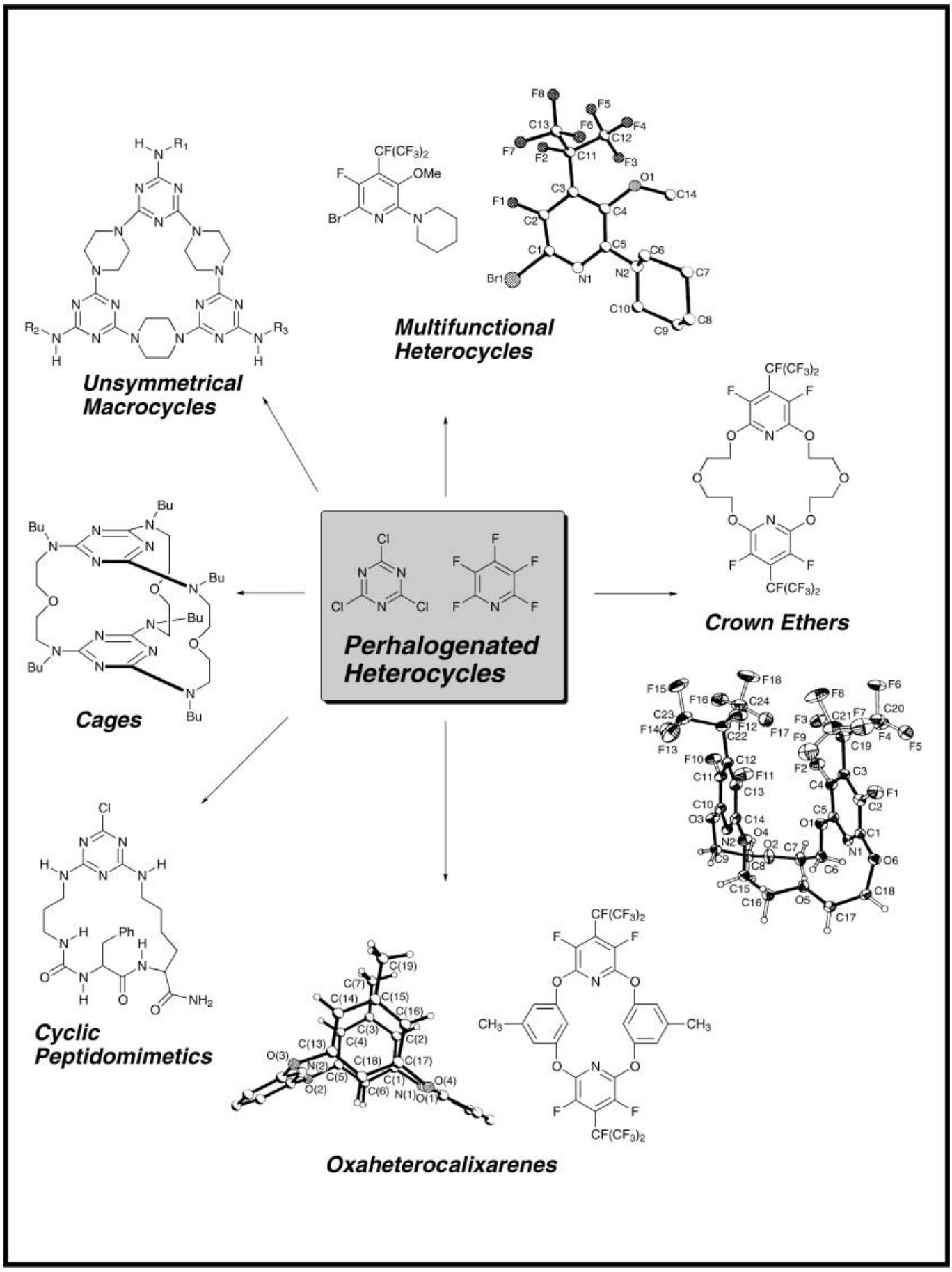

0947-6539/03/0907-1464 $ 20.00+.50/0 *Chem. Eur. J.* **2003**, *9*, No. 7

Macrocycles from Perhalogenated Heterocycles

Graham Sandford*[a]

Abstract: Perhalogenated heteroaromatic systems, such as trichloro-*s*-triazine and pentafluoropyridine, are multifunctional "building blocks" that react with a number of appropriate difunctional nucleophiles to provide access to a variety of macrocyclic and even cage-like molecular architectures. Unusual structural and complexation characteristics of the systems reported so far, such as the recognition of anions, provide a further stimulus for the development of this area.

Keywords: anion receptors · fluorinated ligands · fluorine · heterocycles · macrocyclic ligands

Introduction

Supramolecular chemistry has developed into a major research field[1] since the synthesis and complexation properties of the first crown ethers[2] (Pedersen[1]), cryptands[2] (Lehn[3]) and spherands (Cram[4]) were published. In particular, host–guest systems involving noncovalent interactions between a synthetic host and either a cationic, anionic or neutral guest have been extensively studied[1, 5] with a view to understanding, and mimicking, the types of directed interactions prelevant in nature. Furthermore, numerous macrocyclic derivatives have been adapted for use as, for example, sensors, imaging agents, catalysts and ion analysis[1]

Most commonly, the synthesis of macrocycles involves nucleophilic substitution reactions at sp^3-hybridised carbon atoms or nucleophilic addition–elimination reactions at carbonyl groups in the ring-closing step.[6] The formation of macrocyclic systems by nucleophilic aromatic substitution processes has not generally been adopted, although some syntheses have been reported[7, 8] that indicate the possibilities of this approach.

In this context, perhalogenated heterocyclic systems, in which all ring carbon atoms are attached to a halogen, may, in fact, be used for the construction of a range of novel supramolecular derivatives. This brief account aims to introduce and summarise recent work involving the use of perchloro- and perfluoro-heteroaromatic starting materials for the synthesis of novel polyfunctional macrocyclic systems. No special handling procedures are required for syntheses involving perhaloheterocyclic derivatives and, consequently, the chemistry that is discussed here could readily be used by the general organic chemistry community. A variety of highly halogenated heterocyclic derivatives are commercially available and, indeed, some are prepared on the industrial scale for use as fibre-reactive dyes and as intermediates for the life-science industry.[9]

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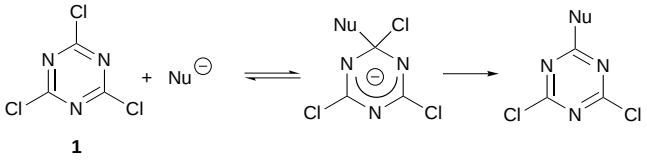
Perchloroheteroaromatic "Building Blocks"—Trichloro-*s*-triazine

Perchlorinated heterocycles are highly susceptible to nucleophilic attack because of the activating influence of the electron-withdrawing chlorine substituents, and substitution occurs via the well-known Meisenheimer type complexes in a two-step addition–elimination process (Scheme 1).



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Scheme 1. Nucleophilic substition of trichloro-s-triazine.

In principle, all three chlorine atoms in trichloro-*s*-triazine **1** may be sequentially replaced by nucleophiles, as shown in Scheme 2, in which Nu^1 is the first nucleophile to react with the triazine, Nu^2 is the second and so on. This polyfunctionality has, indeed, been utilised to prepare a library of triazine derivatives each bearing three different substituents by parallel chemistry techniques.[10, 11] For example **2**, a triazine ring bearing a carbohydrate and two peptide residues, was prepared by a three-step process as part of a wide-ranging study involving the synthesis of a library of over 40000 compounds, which were accessed by reaction of the triazine scaffold with a range of nucleophilic species.

A polyfunctional system such as trichloro-s-triazine should, therefore, be a very suitable "building block" for the synthesis

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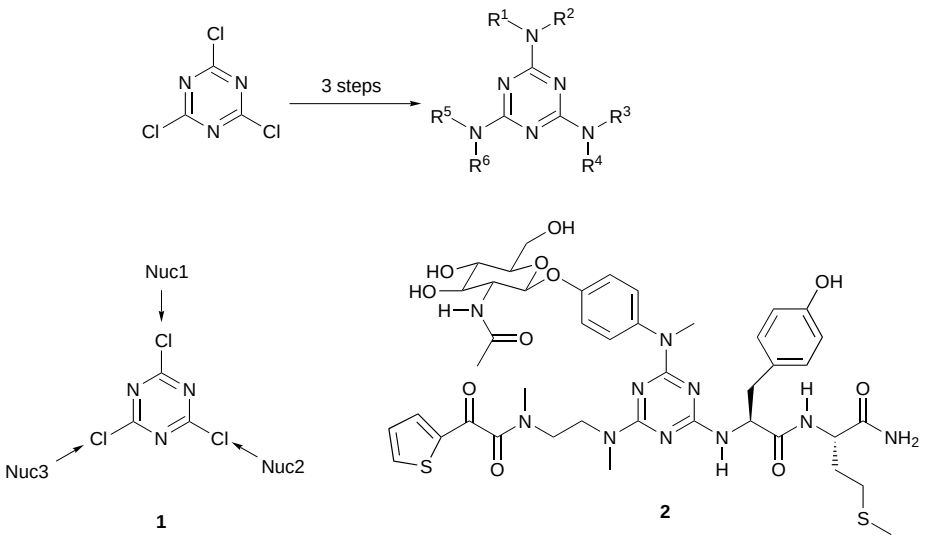
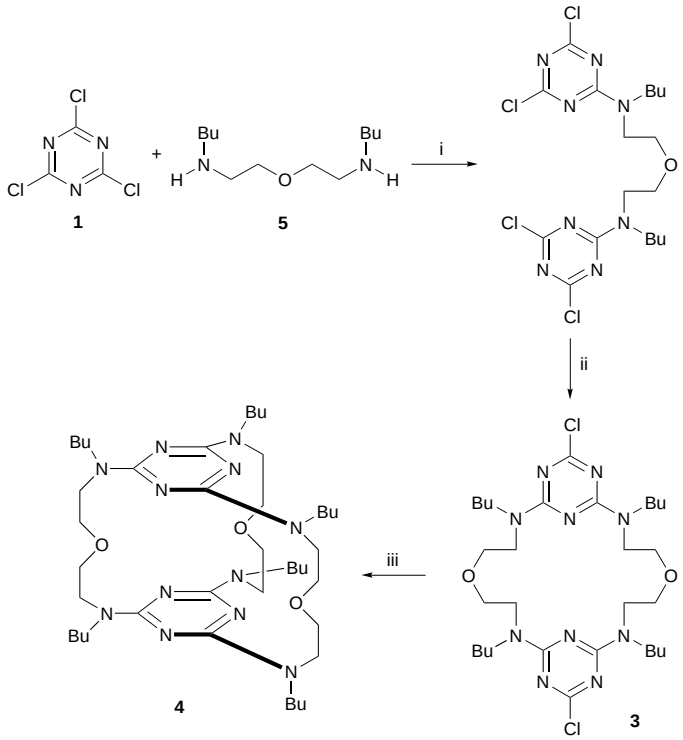


Scheme 2. Sequential controlled tri-substitution of the trichloro-s-triazine system.

of macrocycles after treatment with appropriate difunctional nucleophiles. Anelli and co-workers[12] were the first to synthesise both macrocyclic **3** and caged structures **4** by reaction of two and three equivalents of a diamine linker **5**, respectively, Scheme 3. The reaction temperature required for each nucleophilic substitution reaction becomes higher as the triazine unit becomes more substituted and, consequently, less activated towards nucleophilic attack.

These early findings have been developed by Lowik and Lowe for the synthesis of a variety of triazine-based receptors.[13, 14] The flexibility of the synthetic approach outlined in Scheme 4 allows each triazine to be functionalised separately and macrocycles of various sizes to be obtained, depending upon the choice of diamine linker. The synthesis of asymmetrical macrocycles is less accessible by normal synthetic routes, although a number of systems have been prepared.[15, 16] Binding studies indicate the affinity of some of these large macrocyclic rings towards carbohydrate guests.

Macrocycles incorporating triazine units in their structures may also be synthesised on the solid phase, and a range of cyclic peptidomimetics, which contain rings of between 11 and 37 atoms, has been reported.[17] Treatment of a solid-phase-supported polypeptide with **1** gives the monosubstituted triazine derivative, which undergoes cyclisation with an appropriate pendant nucleophile located on a remote position on the peptide strand (Scheme 5). Subsequent photoinduced decoupling of the peptide yields the peptidomimetic. Of course, the polypeptide chain length may be varied, and cyclic peptidomimetics bearing 3–10 amino acid residues, such as compounds **7**–**9**, have been described.



Scheme 3. Synthesis of macrocycles and cages from trichloro-s-triazine. i) 0–5 °C, KOH, acetone/H_2O, 46%; ii) 50–70 °C, KOH, THF/H_2O, 63%; iii) 160–180 °C, K_2CO_3, DMSO/H_2O, 14%.

Macrocycles from Pentafluoropyridine

Several factors make perfluorinated heterocyclic systems potentially much more preferable substrates for macrocyclic synthesis than the corresponding chlorinated derivatives:

- The vastly increased reactivity of carbon–fluorine bonds in heterocylic systems towards nucleophiles compared with corresponding carbon–chlorine bonds.
- The enhanced selectivity of perfluorinated heterocycles towards nucleophilic attack as compared with corresponding perchlorinated derivatives. (For example, pentachloropyridine gives a mixture of 2- and 4-substituted products on reaction with sodium ethoxide whereas pentafluoropyridine gives 4-substitution exclusively.[18, 19])
- The possibility for using ^{19}F NMR as a structural probe. Pentafluoropyridine, **10**, is a very versatile building block because, in principle, all five fluorine substituents could be substituted by nucleophiles. Therefore, potentially, a range of polysubstituted systems could be derived from this core molecule by nucleophilic aromatic substitution processes. Furthermore, it is well established[18, 19] that, in general, the order of activation towards nucleophilic attack follows the sequence 4-fluorine > 2-fluorine > 3-fluorine. Consequently, for a succession of five nucleophilic substitution steps, in which Nu^1 is the first nucleophile, Nu^2 is the second, etc., the order of substitution is predicted to be selective as

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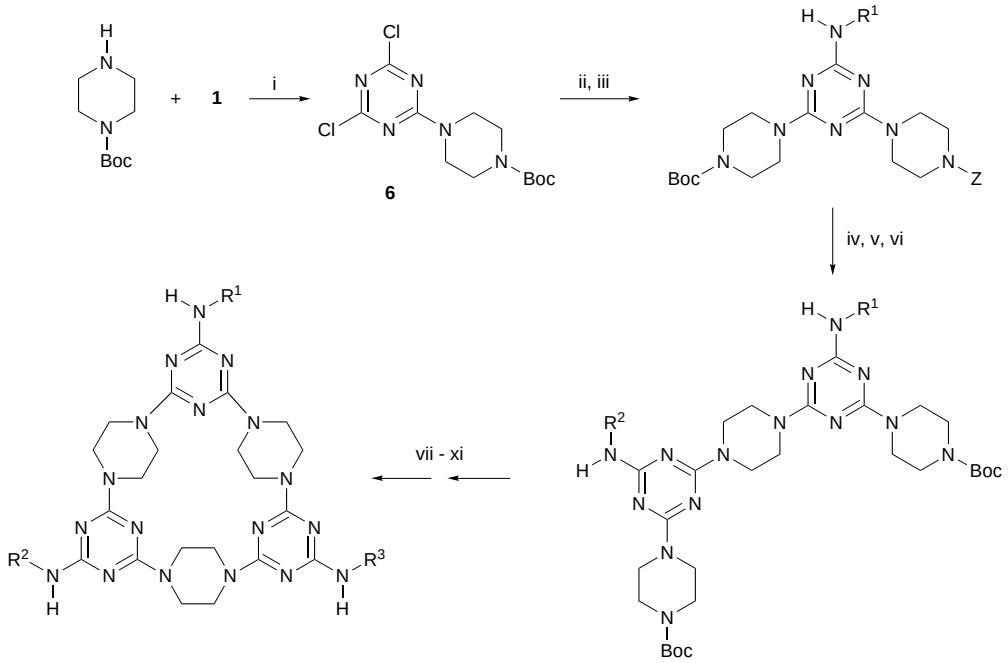
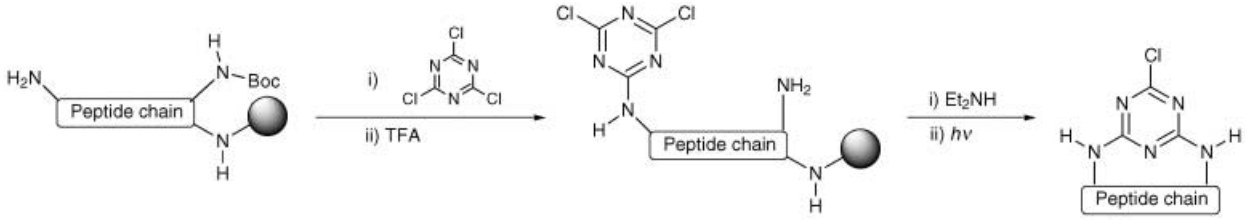
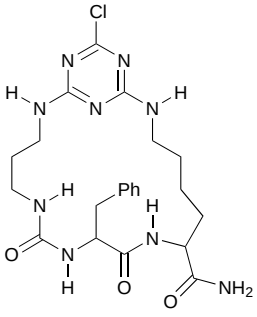


Scheme 4. Large macrocyclic rings from **1**. i) $NaHCO_3$, H_2O/acetone, 93%; ii) (*Z*)-NC_4H_8N-H, H_2O/acetone, $NaCO_3$, 95%; iii) R^1-NH_2, THF, 75–99%; iv) TFA, CH_2Cl_2; v) **6**, Et_3N, CH_2Cl_2, 78–100%; vi) R^2-NH_2, THF, 92–96%; vii) H_2, Pd/C, THF, EtOH; vii) **1**, $NaHCO_3$, H_2O/acetone, 54–85%; ix) HCl, dioxane; x) Et_3N, DMF, 40–85%; xi) R^3-NH_2, THF, 60–90%.



Scheme 5. Synthesis on the solid phase of cyclic peptidomimetics incorporting triazine units.



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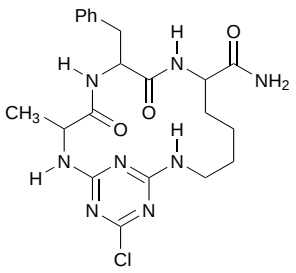

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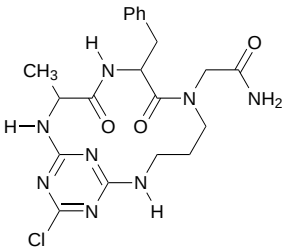

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outlined below, although a few exceptions to these general rules have been reported.[20] This idea has permitted the synthesis of a variety of pyridine derivatives bearing five different substituents, such as **11**, by a sequence of nucleophilic substitution processes (Scheme 6).[21] This demonstrates the polyfunctionality and synthetic utility of this system.

At Durham University, pentafluoropyridine **10** has been used as the starting material for the synthesis of a variety of structurally diverse macrocycles.[22] The general strategy for macrocyclic synthesis is outlined in Scheme 7. The first nucleophile "blocks" the most reactive 4-position, and then the dinucleophile leads to the bridged derivative **12**. Macrocycles **13** are then formed by the reaction of **12** with an equivalent of a third difunctional nucleophile.

Many macrocycles could be synthesised by using this methodology, and two examples are given in Scheme 8. Perfluoroalkylation of **10** by heating it with hexafluoropropene and a catalytic amount of tetrakis(bisdimethylamino)ethane (TDAE) yields the perfluoroisopropyl derivative **14**. Model studies indicated that **14** reacts with nucleophiles to give products that arise from substitution at the 2- and 6-positions.[23] A two-step reaction sequence involving firstly the synthesis of the bridged derivative **15**, by reaction of a dioxygen anion (generated in situ from bistrimethylsilylated diethylene glycol and a fluoride ion) and **14**, followed by ring closure with a further equivalent of the

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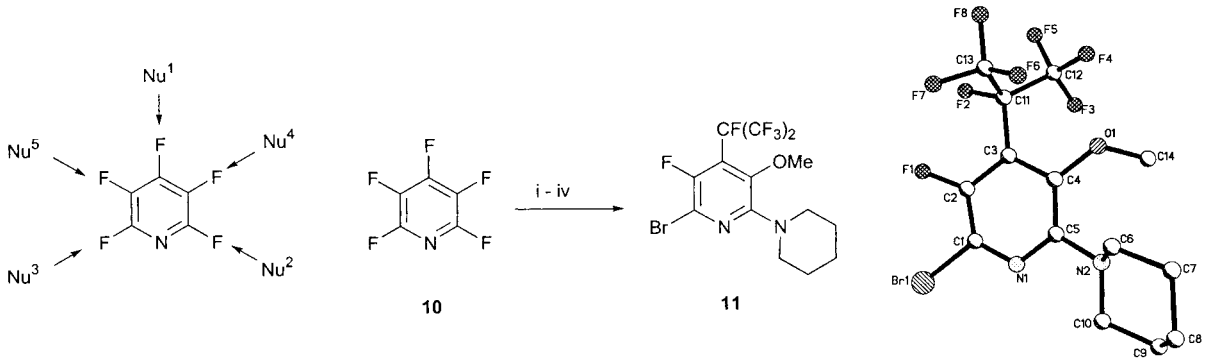
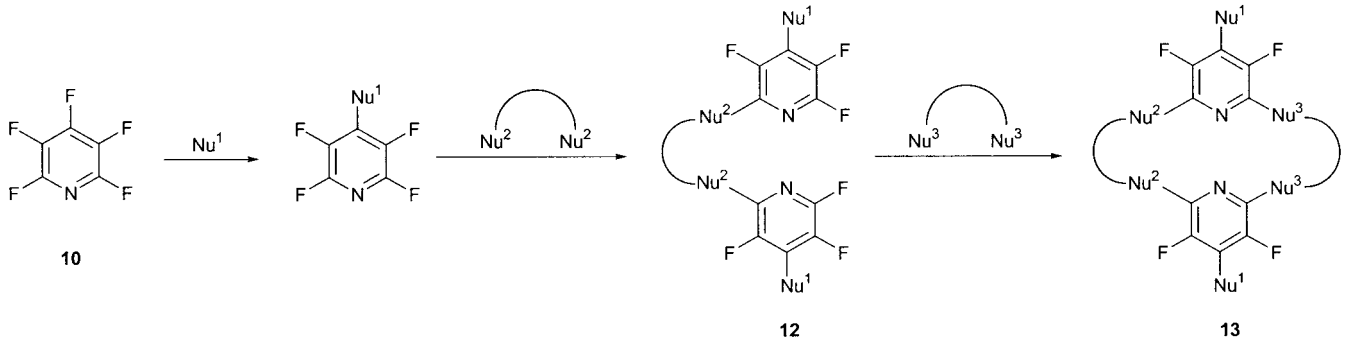
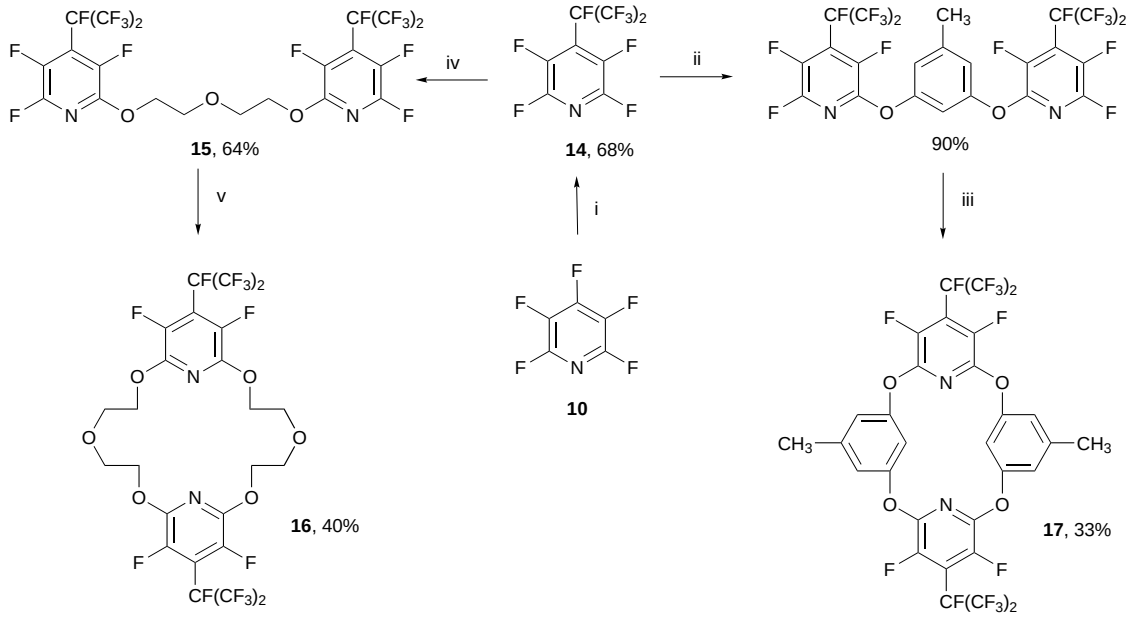


Scheme 6. Polysubstitution on pentafluoropyridine allows the synthesis of pyridine systems **11** bearing five different substituents. i) CF_2=CF-CF_3, TDAE, 60 °C, 68 %; ii) HBr, $AlBr_3$, 160 °C, 74 %; iii) piperidine, MeCN, 80 %; iv) NaOMe, MeOH, reflux, 80 %.



Scheme 7. Synthetic strategy for the construction of macrocycles from pentafluoropyridine.



Scheme 8. Macrocycles from pentafluoropyridine. i) CF_2=CF-CF_3, TDAE, 60 °C, 16 h; ii) CH_3–$C_6H_3(OSiMe_3)_2$, CsF, monoglyme, reflux, 4 d; iii) CH_3–$C_6H_3(OSiMe_3)_2$, CsF, monoglyme, reflux, 4 d; iv) $MeSiOCH_2CH_2OCH_2CH_2OSiMe_3$, CsF, monoglyme, reflux, 4 d; v) $MeSiOCH_2CH_2OCH_2CH_2OSiMe_3$, CsF, monoglyme, reflux, 4 d.

difunctional glycol nucleophile, provides an effective route to macrocycle **16**. The oxoheterocalixarene derivative **17**, in which the four aromatic rings are connected by two-bond linkages in a similar manner to the well-known calixarenes,[24] was also synthesised by the three-step strategy outlined above.

Macrocycles **16** and **17** exhibit some remarkable structural and solution-phase properties. Two types of crystal for macrocycle **16** (cubes and plates), which correspond to different polymorphic crystalline modifications showing two different orientations of the terminal $CF(CF_3)_2$ groups, were observed by X-ray analysis (Figure 1). It is surprising that

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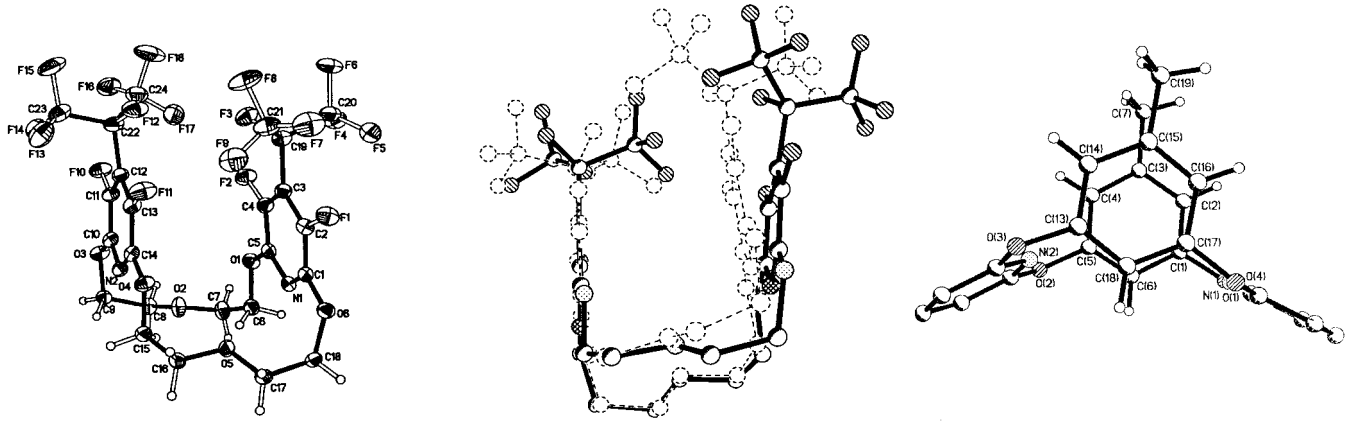

Figure 1. Single-crystal X-ray molecular structures of macrocycles **16** (left and centre) and **17** (right). For structure **17**, the perfluoroisopropyl groups have been omitted for clarity due to the structural disorder caused by rapid rotation.

solid-state **16** exists in the form (Figure 1) in which the two bulky perfluoroisopropyl groups adopt positions that are in close proximity, and solution-phase conformational studies are in progress.

Electrospray mass spectrometry studies indicate that, while macrocycle **16** binds cations, macrocycle **17** binds anions! Mixing a solution of macrocycle **17** with a mixture of aqueous sodium chloride, bromide and iodide led to the observation by negative ion mass spectrometry of macrocycle/anion complexes. Whilst the number of macrocyclic derivatives that bind cations is now quite extensive, the number of macrocycles capable of anion recognition is considerably smaller. Systems that form complexes with anionic guests, such as polyammonium, guanidinium and pyrrole-based systems[25] usually contain sites that are capable of directed hydrogen bonding, a situation that is not present in **17**. However, recent theoretical studies have indicated that interactions between the centre of electron-deficient heterocyclic rings, such as trifluoro-s-triazine, and anions are possible; this may provide a clue to the type of complexation occurring in these cases.[26]

Conclusion

Perhalogenated heteroaromatic systems may be used for the construction of a variety of structurally diverse macrocycles by a sequence of nucleophilic aromatic substitution processes. The availability of perhalo-heterocyclic compounds and a great many suitable difunctional nucleophiles makes the number of supramolecular systems that is available through this approach virtually limitless. The structural and complexation phenomena exhibited by just the relatively few systems that have been reported so far, indicate the opportunities that are provided by these multifunctional systems.

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