

Imide linked '4 + 4' macrocycles formed by condensation of isophthaloyl dichloride and tetra- or penta-fluoroaniline†

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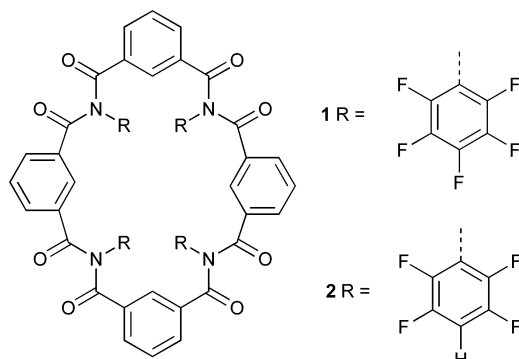
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Condensation of isophthaloyl dichloride and pentafluoroaniline or 2,3,5,6-tetrafluoroaniline results in the formation of imide linked '4 + 4' macrocycles.

Crabtree and co-workers' studies of the anion complexation properties of isophthalamides revealed how very simple hydrogen bond donor systems could function as effective anion receptors.¹ Our interest in anion complexation and anion templated assembly led us to study the anion binding properties of isophthalamides containing electron withdrawing groups. We found that 3,5-dinitrophenyl derivatives form double helices around fluoride anions.² We therefore wished to investigate the structural properties of isophthalamides containing other electron withdrawing groups and so attempted to synthesise a variety of these molecules containing fluorinated phenyl moieties by condensation of isophthaloyl dichloride with fluorinated anilines. Fluorinated isophthalamides have previously been synthesised by Hunter and co-workers.³ Using alternate reaction conditions (*i.e.* carrying out the reaction in the presence of a base), we found that along with the expected fluorophenylisophthalamides, in the case of pentafluoroaniline and 2,3,5,6-tetrafluoroaniline, unexpected imide-linked macrocycles **1** and **2** were formed by a 4 + 4 isophthaloyl dichloride/aniline condensation reaction, albeit in moderate yield. We therefore investigated the syntheses of these unusual macrocycles.

Macrocycles **1** and **2** were synthesised by a 1:1 condensation of isophthaloyl dichloride and pentafluoroaniline or 2,3,5,6-tetrafluoroaniline in dry dichloromethane in the presence of excess triethylamine and a catalytic quantity of DMAP (see supplementary information for details). The macrocycles were isolated from the reaction mixtures by column chromatography on silica gel eluting with dichloromethane (and in the case of **2** a subsequent filtration through a Sephadex® LH-20 column in acetonitrile and crystallisation from acetonitrile) in 13% and 3% respective yields. An analogous reaction was attempted with 2,3,4,5-tetrafluoroaniline but no macrocyclic product could be obtained in this case. Crystals suitable for X-ray crystallographic determination were obtained by slow evaporation of chloroform and acetonitrile solutions of **1**‡ and **2**§ respectively. The crystal structures, shown in Figs. 1 and 2,



† Electronic supplementary information (ESI) available: ¹H, ¹³C and ¹⁹F NMR spectra of **1** and **2** and a combined CIF file. See <http://www.rsc.org/suppdata/cc/b4/b401614a/>

reveal that the macrocyclic skeletons of **1** and **2** adopt similar saddle-like conformations in the solid state.

Imide formation from these reactions presumably results from the acidity of the polyfluorinated anilines allowing intermediate amide species to deprotonate and react with a further isophthaloyl dichloride (the gas phase acidity of pentafluoroaniline is similar to

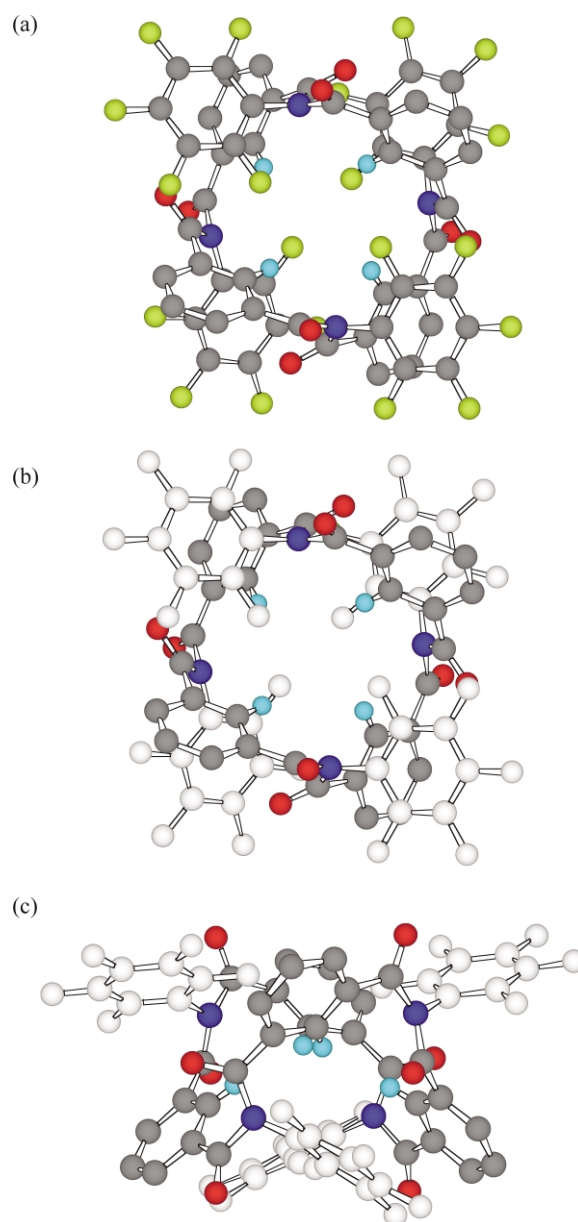


Fig. 1 Three views of the X-ray crystal structure of macrocycle **1** (a) top view, (b) top view with pentafluorophenyl groups in white and (c) side view with pentafluorophenyl groups in white revealing the saddle conformation of the macrocyclic skeleton. Key: carbon – grey; oxygen – red; nitrogen – blue. Certain hydrogen atoms have been omitted for clarity.

that of acetic acid).⁴ The fact that the analogous reaction with the presumably⁵ less acidic 2,3,4,5-tetrafluoroaniline did not result in any detectable quantities of macrocycle in our hands, supports this hypothesis. The formation of macrocycles in not insignificant yields in the absence of a template led us to examine the crystal structures for possible mechanisms of 'self-templation'. The macrocycles both adopt saddle-like conformations that orientate the acidic protons between the imide groups on the isophthalic rings to point into the macrocyclic cavity. Similarly the pendant

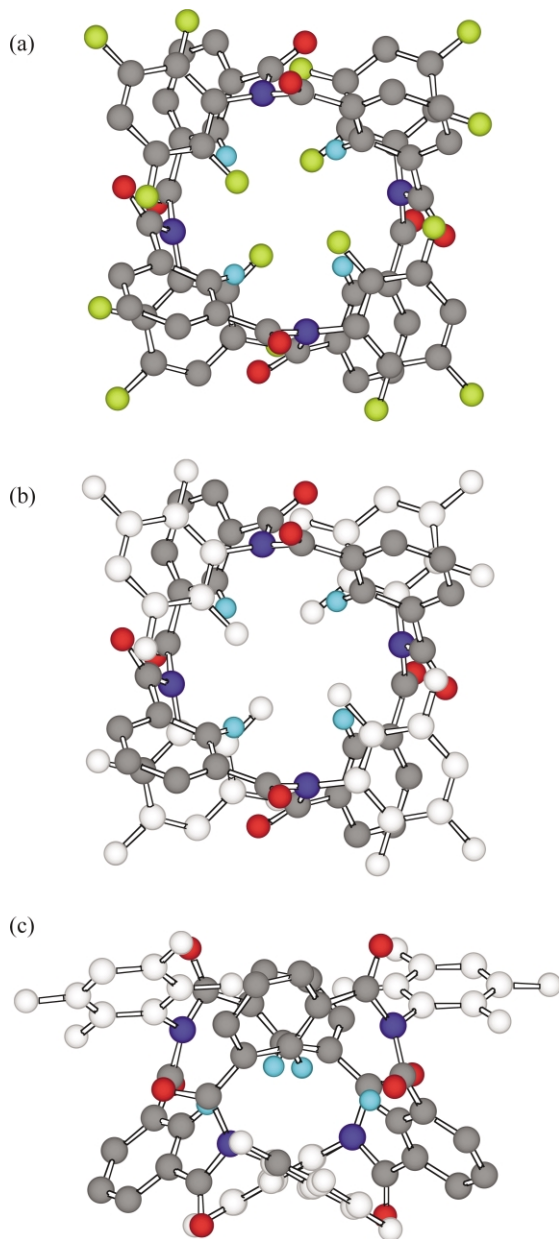


Fig. 2 Three views of the X-ray crystal structure of macrocycle **2** (a) top view, (b) top view with tetrafluorophenyl groups in white and (c) side view with tetrafluorophenyl groups in white revealing the saddle conformation of the macrocyclic skeleton. Key: carbon – grey; oxygen – red; nitrogen – blue. Certain hydrogen atoms have been omitted for clarity.

fluoroaniline groups are oriented such that four electronegative *ortho*-fluorine substituents point into the annulus of the macrocycle. These groups form a distorted cube-like array of trifurcated H...F interactions between 2.81 Å and 3.65 Å in length in macrocycle **1** and 3.04 Å and 3.59 Å in **2**. Whilst these interactions are rather long,⁶ it may be that they acted to stabilise the acyclic precursors to **1** and **2** in conformations suitable for cyclisation. Solution studies of **1** in CDCl₃ and **2** in DMSO-d₆ by ¹⁹F NMR spectroscopy reveal that the fluoroaniline rings are not rotating freely in solution as five or four ¹⁹F resonances are observed respectively for **1** and **2** suggesting that the conformation of the macrocycles persist in solution at room temperature. Variable temperature ¹H and ¹⁹F NMR spectra of macrocycle **2** in DMSO-d₆ show a sharpening of the ¹H NMR spectrum into four resonances and the coalescence of the four fluorine resonances observed at room temperature to two at 70 °C presumably indicating conformational flexibility in solution at raised temperatures (see electronic supplementary information).

Imide-linked macrocycles **1** and **2** have been synthesised in one step in the absence of a template. X-ray crystallographic analysis has shown that these macrocycles adopt saddle-like conformations in the solid state that orient the acidic isophthalamide CH protons and the *ortho*-fluorine atoms on the pendant fluorophenyl groups into the annulus of the macrocycle. We are continuing to investigate aspects of the chemistry of this, to the best of our knowledge, new class of macrocycle. The results of these studies will be reported in due course.

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Notes and references

‡ Crystal data for **1**: C₅₆H₁₆F₂₀N₄O₈·1.5CHCl₃, *M*_r = 1396.25, *T* = 120(2) K, monoclinic, space group *C2/c*, *a* = 14.6087(5), *b* = 31.9021(15), *c* = 24.1559(10) Å, α = 90°, β = 98.010°, γ = 90°, *V* = 11148.0(8) Å³, ρ_{calc} = 1.664 Mg m⁻³, μ = 0.323 mm⁻¹, *Z* = 8, reflections collected: 15228, independent reflections: 7955 (*R*_{int} = 0.0533), final *R* indices [*I* > 2σ(*F*²)]: *R*1 = 0.0733, *wR*2 = 0.2009, *R*indices (all data): *R*1 = 0.1250, *wR*2 = 0.2283. CCDC 228208.

§ Crystal data for **2**: C₅₆H₂₀F₁₆N₄O₈·CH₃CN, *M*_r = 1221.81, *T* = 120(2) K, monoclinic, space group *P2₁/n*, *a* = 17.9621(5), *b* = 13.2143(3), *c* = 23.3857(6) Å, α = 90°, β = 112.58°, γ = 90°, *V* = 5125.1(2) Å³, ρ_{calc} = 1.583 Mg m⁻³, μ = 0.145 mm⁻¹, *Z* = 4, reflections collected: 45287, independent reflections: 11319 (*R*_{int} = 0.0489), final *R* indices [*I* > 2σ(*F*²)]: *R*1 = 0.0524, *wR*2 = 0.1344, *R*indices (all data): *R*1 = 0.0820, *wR*2 = 0.1512. CCDC 228209. See <http://www.rsc.org/suppdata/cc/b4/b401614a/> for crystallographic data in .cif or other electronic format.

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