Non-classical [1_4]Metaheterophanes Containing Betaine Units. Synthesis, NMR Spectroscopy and X-Ray Crystallography

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The *N*-diphenylmethyl derivative **4** is the immediate precursor of the *N*-substituted dipolar [1_4]metaheterophane **3**, and allows the convenient synthesis of the unsubstituted macrocycle **5**, which can be transformed into the quadrupolar or dipolar heterophanes **1** and **2**; the molecular structures of **1** and **2** were confirmed by single-crystal X-ray analysis.

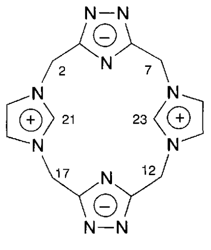
Amongst the fascinating variety of molecular architectures within cyclophanes, phanes and heterophanes,[1] and different types of calixarenes,[2] none are related to the title quadrupolar heterophanes **1** and dipolar heterophanes **2**.[†][3] The ring components present in heterophanes[1] are normally uncharged heteroaromatic moieties; however, in a few cases quaternary pyridinium moieties have been used.[‡][5,6] In this communication we report the synthesis of the first examples of macrocyclic systems containing heterocyclic betaines as building blocks:[7] the bis-betaine **1** and betaine **2**.

An efficient synthesis of the *N*-unsubstituted key intermediate **5** has been accomplished—*i.e.* by deprotection of the *N*-diphenylmethyl heterophane **4**. The macrocycle **5** was then transformed into the quadrupolar and dipolar heterophanes **1** and **2**.

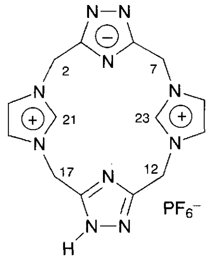
The synthetic route to the metaheterophane **4** is shown in Scheme 1. The protophane **9** was obtained by a three-step procedure starting from 4-amino-3,5-bis(hydroxymethyl)-1,2,4-triazole **6**.[4b,8a,b] Condensation of compound **9** with the bischloromethyl derivative **10**[8c] afforded the *N*-diphenylmethyl macrocycle **4**, in a remarkable yield (63%) for a macrocyclization. The title heterophanes **1–3** were prepared from the key heterophane **4** as shown in Scheme 2.

The eluates resulting from the treatment of the macrocycle **4** with an anion-exchange Amberlite IRA-401 resin (OH$^-$ form)[§] were carefully acidified to pH 6 using an aqueous solution of HPF_6 to yield the dipolar heterophane **3**.

On the other hand, removal of the *N*-diphenylmethyl group was achieved by treatment of **4** with trifluoroacetic acid, affording the ditrifluoroacetate **5**, from which the quadrupolar and dipolar heterophanes **1** and **2** were obtained.[§]



1



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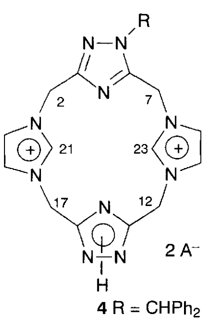
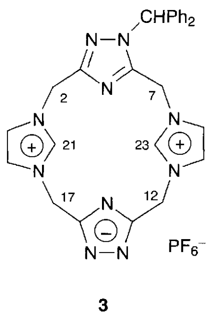


4 R = CHPh$_2$
5 R = H



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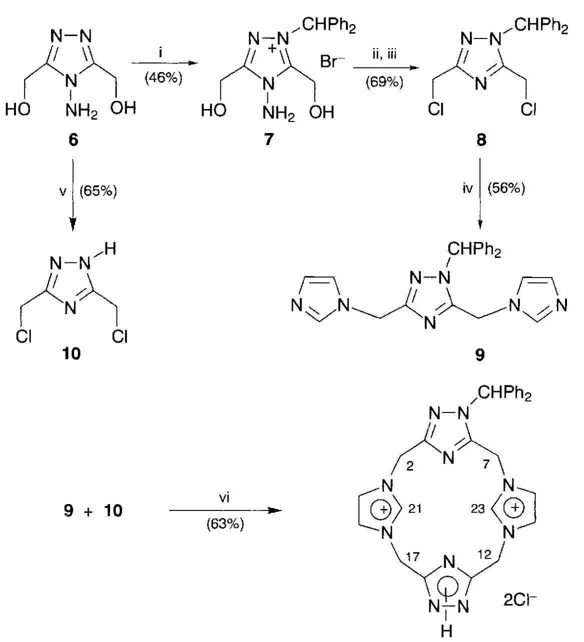
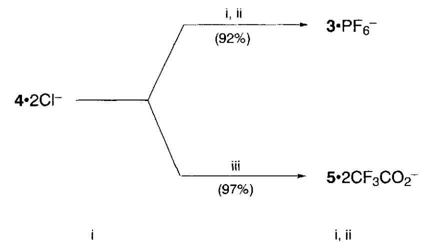
The structures of the new compounds were unambiguously characterized by their microanalytical and spectroscopic data. Individual assignments were made using the appropriate ^1H and ^{13}C NMR techniques (HMQC, HMBC and ROESY), except for the NH protons.

The molecular structures of compounds **1** and **2** were confirmed by X-ray crystallography.[¶] Fig. 1 shows the perspective molecular diagram of **1** with the corresponding atom numbering.[||] Bond distances and angles are well correlated with those for dipolar compound **2** (*vide infra*). The weighted least-squares plane defined by C(2), C(7), C(12) and C(17) methylene carbon atoms has a side length of 4.96 Å.



Scheme 1 *Reagents and conditions:* i, Ph_2CHBr (1 equiv.), dry DMF, sealed tube, 90 °C, 48 h; ii, $NaNO_2$, 1 mol dm^{-3} HCl, 25 °C, 20 h; iii, Na_2CO_3 to pH 7, the precipitate was collected and dried; $SOCl_2$, reflux, 4.5 h; iv, imidazole, dry DMF, KOH, 80 °C, 48 h; v, as ref. 8*c*; vi, dry MeCN, reflux, 48 h



Scheme 2 *Reagents and conditions:* i, Anion-exchange resin IRA-401 (OH$^-$ form); ii, the neutral eluates were immediately collected, 1% aqueous hexafluorophosphoric acid to pH 6; iii, TFA, phenol, reflux, 1 h

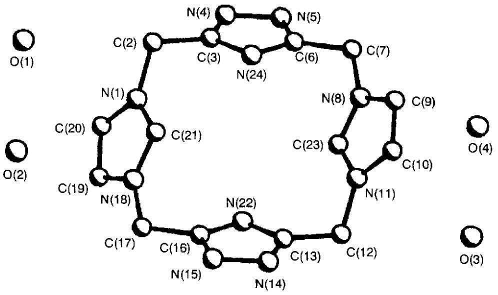


Fig. 1 Perspective molecular diagram (PLUTO[10e]) of quadrupolar heterophane **1**

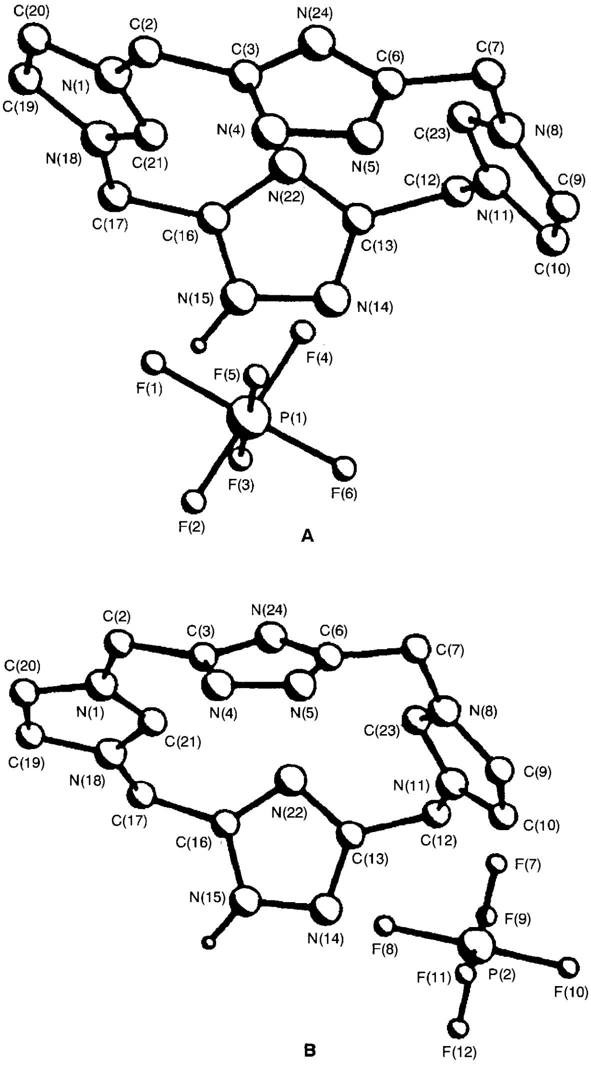


Fig. 2 Perspective molecular diagram (PLUTO[10e]) of dipolar heterophane **2**

The molecular structure of **2** is shown in Fig. 2: the asymmetric unit contains two independent molecules (cations) and their associated PF_6^- counterions. Bond distances and angles for both molecules **2A** and **2B** are similar, and the macrocyclic dimensions are similar to those observed for **1**.

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Footnotes

† The recently synthesised parent aromatic molecule [1.1.1.1]metacyclophane[3] serves as a reference compound for the development of unusual [1$_4$]metaazolophanes; only a few examples of related heterophanes[1] and heterocalix[4]arenes[2] have been reported so far, *e.g.* the azaporphyrinogen-type models containing 2,6-pyridino [4a] and azole[4b] rings.

‡ Prime examples of cyclophanes derived from 4,4′-bipyridinium units have been independently reported by Stoddart *et al.*[5] and Hünig *et al.*[6]

§ The use of an ion-exchange Amberlite IRA-401 resin (OH^- form) is the method of choice for the preparation of imidazolium(pyridinium) azolate inner salts with several interannular spacers,[9] for instance the methyleneimidazolium 3(5)-1,2,4-triazolate.[7]

¶ Appropriate single crystals were grown by slow evaporation of an ethanolic solution of **1**, and by recrystallization of **2** from $Pr^iOH–H_2O$.

Crystal data for **1**: $C_{14}H_{14}N_{10}{\cdot}4H_2O$, M = 394.4, T = 293 K, monoclinic, $P2_1/n$, a = 1515.8(2), b = 634.5(1), c = 939.3(3) pm, β = 99.65(2)°, V = 0.890(1) nm^3, Z = 2, F(000), = 416, D_c = 1.471 g cm^{-3}, μ = 0.904 cm^{-1}. Data collected on a Siemens-Stoe AED automatic diffractometer using Cu-Kα radiation, graphite monochromator and ω/θ scan up to 2θ = 120° provided 1349 independent reflections of which 1207 with $I > 3\sigma(I)$ were corrected for Lorentz and polarization factors and used for structure solution and refinement. For **2**: $C_{14}H_{15}N_{10}{\cdot}PF_6$, M = 468.3, T = 293 K, monoclinic, $P2_1/c$, a = 1533.3(2), b = 1502.4(3), c = 1674.5(1) pm, β = 106.59(1)°, V = 3.697(1) nm^3, Z = 8, F(000) = 1904, D_c = 1.679 g cm^{-3}, μ = 2.130 cm^{-1}. Data collected as above yielded 3811 reflections with $I > 3\sigma(I)$ that were used for structure solution and refinement after correction for Lorentz and polarization factors. Both structures were solved by direct methods (SHELXS86)[10a] and refined by F full-matrix least squares techniques (XRAY76).[10b] Hydrogen atoms were found by Fourier difference synthesis, including those of the solvents molecules in **1**. For both structures anisotropic thermal parameters were refined for all non-hydrogen atoms and fixed coordinates and isotropic thermal parameters were used for hydrogen atoms. A weighting scheme for obtain flat dependence Δ^2F *vs.* F_o and sin θ/λ was used (PESOS).[10c] Final R = 0.039 and Rw = 0.047 for **1** and R = 0.070 and Rw = 0.085 for **2**. Geometric calculations were performed with PARST.[10d] Atomic coordinates, bond lengths and angles, and thermal parameters for both **1** and **2** have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

|| The atom numbering system is not the same as that obtained from the X-ray analysis because **1** has a centrosymmetric structure.

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