Synthesis and X-ray structure of a new sterically hindered cyclophane containing chiral spirobiindanol phosphonates and phosphate units

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The synthesis, as well as the stereochemical and solid-state structure characterization of a novel sterically congested cleft-like receptor molecule, fully equipped for multipoint recognition and containing a chiral spirobiindanol phosphonate unit, is reported.

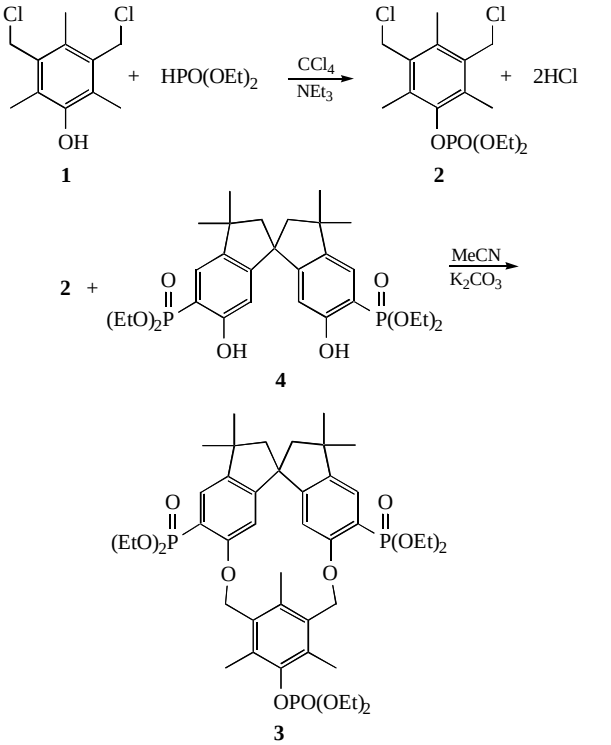
The search of rigid receptor molecules for organic dicationic guests is a very fertile field in chemistry. In particular, there exists a need to develop three-dimensional building blocks containing selected functional groups in order to introduce binding sites suitable for biologically relevant molecules into small stereochemically rigid cyclophanes.[1–5]

Recently, we have reported[6] on the synthesis and conformational characterization of sterically congested cyclophanes containing the spirobiindanol phosphonate moiety, and some of these compounds were used as chiral sensors for arginine and lysine.[7]

To improve the complexing properties of these sensors, specially for longer biologically relevant α,ω-diamine dications, we wanted to introduce an additional binding site into one of the congested cyclophanes in a particularly strategic position, *i.e.*, we synthesised compound **3** according to Scheme 1.

Thus, in this paper we present the synthesis, NMR characterization and X-ray structure of a new cleft-like receptor molecule based on bisphosphonate **4**, which is fully equipped for the multipoint recognition of dicationic substrates.

By condensing spirobiindanol phosphonates **4** with phosphate mesityl unit **2**† under high dilution, macrocycle **3**‡ was synthesised in good yield (>60%). Scheme 1 gives a description of the synthetic strategy employed for the preparation of cyclophane **3**, which was characterised in solution by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The data confirmed that macrocycle **3** is stereochemically rigid on the NMR time scale. In particular, the restricted rotation of the 1,3-bridged mesityl ring renders the molecule asymmetric, as evidenced by the fact that all nuclei are chemically and magnetically different. The two bridging benzylic groups, as well as the two phosphorus atoms attached to the C_2-symmetrical spirobiindane unit, are no longer homotopic. Thus, their hydrogens, which are diastereotopic, give rise to two different doublets of doublets, while the phosphorus atoms give rise to two sharp singlets at δ 18.97 and 17.74 ppm, respectively.



Scheme 1

The molecular structure of compound **3** (Figure 1)§ almost completely coincides with that of bis-(5,5′-diethyloxyphosphonyl)-6,6′-(2,4,5-trimethyl-1,3-benzyloxy)-3,3,3′,3′-tetramethyl-1,1′-spirobiindane.[6] Although the molecule of **3** is chiral, it is regularly alternated with its optical antipode in the centrosymmetric $P2_1/c$ space group, giving a racemic crystal. The macrocycle

† Triethylamine (0.011 mol) was added dropwise to a mixture of compound **1**[8] (0.01 mol) and diethyl phosphite (0.011 mol) in carbon tetrachloride (20 ml) with stirring at 0 °C. Then, the mixture was stirred overnight at room temperature, the treatment and purification on silica gel (cyclohexane–ethyl acetate, 1:1) gave derivatives **2**.

Ethyl 3,5-bis(chloromethyl)-2,4,6-trimethylbenzenephosphate **2**: yield 45%, mp 101–102 °C. ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, 6H, OCH_2Me, J_{HH} 7 Hz), 2.42 (s, 6H), 2.45 (s, 3H), 4.19 (m, 4H, OCH_2Me), 4.65 (s, 4H). ^{13}C NMR, δ: 13.50, 14.84, 16.14 (d, J_{CP} 6.7 Hz), 41.41, 64.58 (d, J_{CP} 6.0 Hz), 107.81 (d, J_{CP} 10.6 Hz), 130.96 (d, J_{CP} 3.0 Hz), 133.71 (d, J_{CP} 1.9 Hz), 134.17 (d, J_{CP} 2.2 Hz), 146.35 (d, J_{CP} 7.9 Hz). ^{31}P NMR, δ: – 5.18. FAB–MS, *m*/*z* (%): 369 (85, M + H$^+$), 333 (100, M + H$^+$ – Cl$^–$), 371 (45, M + H$^+$ + 2).

‡ Solutions of equimolar amounts of **2** and spirobiindanol phosphonates[6] **4** were added dropwise at equal rates from two dropping funnels to a suspension of a molar excess of dried K_2CO_3 in anhydrous MeCN (200 ml) at a refluxing temperature with stirring. Then, the reaction mixture was refluxed and stirred overnight and filtered. The solvent was evaporated to give a powder, which was collected with hexane by filtration and washed several times with water. The product was purified on silica gel (ethyl acetate–methanol, 9:1), to give **3** as white prismatic crystals.

Bis-(5,5′-diethyloxyphosphonyl)-6,6′-(1,3-benzyloxy-2,4,6-trimethyl-5-diethylphosphate)-3,3,3′,3′-tetramethyl-1,1′-spirobiindane **3**: yield 60%, mp 150 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ: 1.19 (s, 3H, spiro-Me), 1.21 (t, 3H, $OPOCH_2Me$, J_{HH} 7 Hz), 1.25 (t, 3H, $OPOCH_2Me$, J_{HH} 7 Hz), 1.33 (s, 3H, spiro-Me), 1.35 (s, 3H, spiro-Me), 1.39 (s, 3H, spiro-Me), 1.42 (m, 12H, $POCH_2Me$), 1.57 (s, 3H, Ar*Me*), 1.83 (d, 1H, J_{HH} 12.5 Hz), 1.92 (d, 1H, J_{HH} 12.5 Hz), 2.28 (d, 1H, J_{HH} 13.0 Hz), 2.39 (d, 1H, J_{HH} 13.0 Hz), 2.49 (s, 3H Ar*Me*), 2.55 (s, 3H, Ar*Me*), 4.02–4.32 (m, 12H), 5.19 (dd, 2H, J_{HH} 13.5 Hz), 5.33 (dd, 2H, J_{HH} 13.5 Hz), 5.65 (d, 1H, $^4J_{HP}$ 6.0 Hz), 5.97 (d, 1H, $^4J_{HP}$ 6.5 Hz), 7.48 (d, 1H, $^3J_{HP}$ 15 Hz), 7.68 (d, 1H, $^3J_{HP}$ 14.5 Hz). ^{13}C NMR, δ: 13.74, 14.57, 16.12 (m), 16.42 (m), 30.34, 30.52, 30.80, 31.06, 43.03, 43.07, 57.21, 57.93, 57.95, 61.71 (d, J_{CP} 5.9 Hz), 61.93 (d, J_{CP} 5.9 Hz), 62.20 (d, J_{CP} 5.9 Hz), 62.69 (d, J_{CP} 5.9 Hz), 64.32 (m), 64.83, 108.35 (d, $^3J_{CP}$ 11 Hz), 115.56 (d, $^1J_{CP}$ 188.4 Hz), 120.94 (d, $^3J_{CP}$ 10.9 Hz), 122.01 (d, $^1J_{CP}$ 186.6 Hz), 128.45 (d, $^2J_{CP}$ 7.3 Hz), 128.85 (d, $^2J_{CP}$ 7.7 Hz), 131.56, 131.84 (d, J_{CP} 3.2 Hz), 132.08, 132.38 (d, J_{CP} 3.7 Hz), 133.82, 143.26 (d, J_{CP} 14.1 Hz), 147.61 (d, J_{CP} 7.7 Hz), 149.33 (d, J_{CP} 14.1 Hz), 154.55, 155.55, 157.63, 159.81 (d, J_{CP} 4.1 Hz). ^{31}P NMR, δ: –5.52, 17.74, 18.97. FAB–MS, *m*/*z* (%): 876.9 (40, M$^+$), 580.8 (90), 240.9 (100).

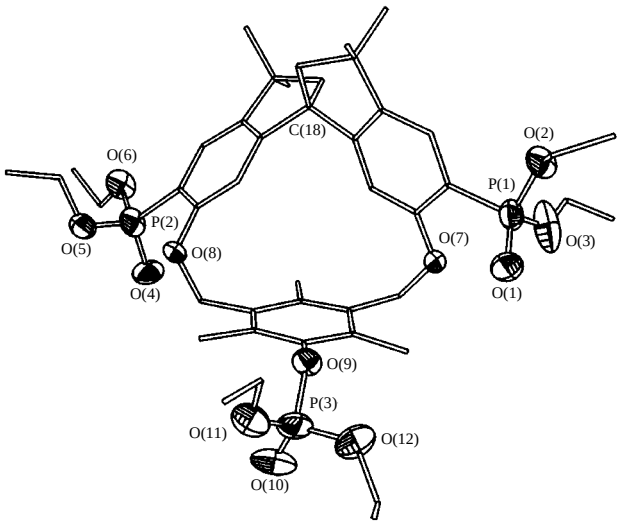


Figure 1 The molecular structure of macrocyle **3**. P and O thermal ellipsoids are represented at 30% probability. C and H atoms are omitted for clarity. For the same reason, only the sticks corresponding to the more populated positions of disordered ethyl groups are shown.

§ *Single-crystal X-ray diffraction analysis*. A single crystal (0.50×0.28× ×0.16 mm) of **3** suitable for an X-ray study was prepared by slow evaporation of a toluene–isooctane solution. Crystal data: $C_{44}H_{63}O_{12}P_3$, M = 876.85, monoclinic, space group $P2_1/c$, a = 12.656(3), b = 27.409(7), c = 13.741(3) Å, β = 103.20(1)°, V = 4641(2) Å^3, Z = 4, d_{calc} = 1.255 g cm^{-3}, μ = 0.187 mm^{-1}. The data were collected on a Siemens P4 diffractometer ($2.1 < \theta < 22.4°$, monochromated MoKα radiation, λ = 0.71073 Å, T = = 293 K); a redundant set of 6372 reflections was collected from which, after Lorentz, polarisation and absorption corrections and after merging the equivalents (R_{int} = 0.0868), 5005 unique reflections were obtained. The structure was solved by a combination of direct and Fourier methods and refined by a full-matrix least-squares technique. The abnormally elongated thermal ellipsoids, together with inconsistencies in bonds geometry and the presence of a residual electron density, suggested the presence of disorder in some terminal ethyl groups. In the final refinement cycle, the two ethyl groups connected to P(1) and one of the ethyl groups connected to P(2) were refined as disposed in two different conformations, with isotropic thermal factors for C atoms and fixing to 1 the total occupancy for each group. All other non-hydrogen atoms were refined with anisotropic thermal parameters, giving the reliability factors R_1 = 0.0868 and wR_2 = 0.2001 for 523 variables with 1 restraint. Calculations were performed using the SHELXTL program.[9] Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun*., Issue 1, 2000. Any request to CCDC should quote the full literature citation and the reference number 1135/72.

shows its usual heart-like shape with the O(7) and O(8) atoms 6.59 Å apart and with the spiro carbon C(18) 5.44 Å away from the centroid of the xylyl ring. As pointed out earlier,[6] the steric hindrance of the ring atoms does not allow guest molecules to be enclathrated. Moreover, some degree of tension is present in the macrocycle that slightly twists the mesityl group, which is not exactly planar. In spite of a conformational disorder in some of the terminal ethyl groups, the crystal packing is slightly more efficient than that in the related structure,[6] so that no solvent molecules are found in the structure.

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