Synthesis and characterization of conformationally flexible phosphonated cyclophanes

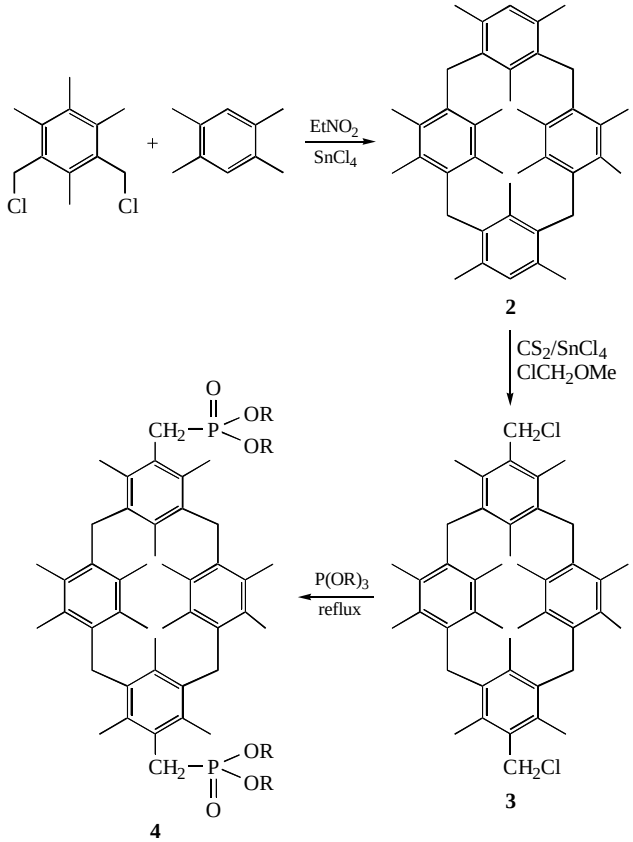
Giuseppe A. Consiglio,[a] Salvatore Failla[b] and Paolo Finocchiaro*[a]

[a] *Istituto Chimico, Facoltà di Ingegneria, Università di Catania, 95125 Catania, Italy.*
Fax: +39 095 738 2798; e-mail: pfinocchiaro@ic.ing.unict.it
[b] *Dipartimento di Ingegneria Chimica, dei Materiali delle Materie Prime e Metallurgiche, Università di Roma 'La Sapienza', 00161 Rome, Italy*

The phosphorylated calix[4]arenoid *para*- and *meta*-substituted cyclophane tetramers, which were synthesised in good yields starting from parent cyclic hydrocarbons, show a 'saddle-shaped' rigid conformation in solution, and the methylenephosphonic acid dialkyl ester groups are in a strategic position for complexation with neutral guests.

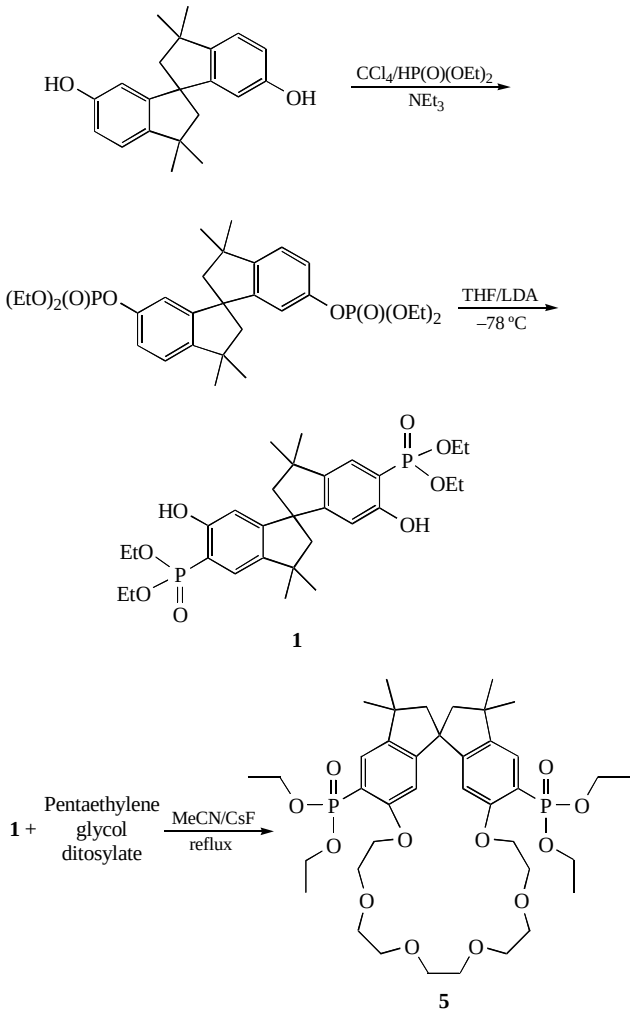
Conformationally flexible medium-sized cyclophanes are macrocycles of great importance for supramolecular chemistry and thus the attention of chemists has been focused on a synthetic route towards such molecules.[1–3] In particular, great interest was created in the synthesis and characterization of constrained macrocycles for the use as specific receptors for the selective complexation of neutral guests[3–5] with the emphasis on the binding of a wide variety of biologically relevant molecules. Moreover, chemically robust aromatic macrocycles able to complex cations, in particular, lanthanides, are needed as luminescent sensors and for diagnostic bioassay[6,7] in medicine.

Previously, we have performed the synthesis of tetrameric aryl macrocycles connected by methylene bridges and prepared spirobiindane bis(phosphonate)[8] unit **1**. We decided on the use of this synthon for preparing macrocycles that possess ancillary groups such as phosphonic ones in order to produce suitable hosts for a wide variety of neutral guests and for transition elements.



4a R = Me
4b R = Et
4c R = Pr^i

Scheme 1



Scheme 2

It has been shown previously[9] that crystalline, high-melting tetrameric methaparacyclophane **2** possesing two mesitylene and two durene units connected by methylene bridges can be easily synthesised by Friedel–Crafts procedures. Chloromethylation[10] of **2** yielded **3**, which gave phosphorylated calix[4]arenoid tetramers **4a**–**c** by the Arbuzov reaction using trialkyl phosphites (Scheme 1).†

We found by NMR investigations at room temperatures that macrocycles **4a**–**c** show restricted rotation of the durene rings as evidenced by the presence of two sharp singlets for the durene methyl groups at δ 1.43 and 2.34 ppm in the ratio 1:1. Furthermore, these data reveal that one set of signals is strongly upfield shifted by the aromatic ring current effect. Analogous shielding is evidenced by the mesitylene methyl groups posi-

tioned inside the methylene bridging groups which resonate at δ 0.87 ppm, *i.e.*, *ca*. 1.46 ppm upfield compared to the relevant methyl groups in the linear parent subunit model 2,4,6-trimethylbenzylphosphonic acid dialkyl ester. These data are consitent with the conformation of macrocycles **4a**–**c** in solution as an 1,3-alternated saddle-shaped geometry in which two durene units are perpendicular to the plane identified by the four bridging methylene groups, whereas the mesityl rings are alternatively up and down with their inner methyl groups pointing inward the aromatic ring current of the durene rings. Thus, the methylenephosphonic groups are also alternatively up and down of the cage in strategic positions for complexing with neutral guests.

Due to the skeleton symmetry, the bridging methylene protons appear as two doublets at *ca*. 4.08 ppm; the methylene groups attached to the phosphonic groups appear as a sharp doublet due to the coupling with phosphorus ($^2J_{HP}$ 21.5 Hz), whereas the methyls or methylenes of alkyl groups R in the $-P(O)(OR)_2$ moiety, due to the tetrahedral geometry of the phosphorus, reside in a diastereotopic environment when R is Pr^i or Et, whereas they are enantiotopic for R = Me. It follows that the $-P(O)(OMe)_2$ protons in **4a** appear as a sharp doublet due to the coupling with phosphorus ($^3J_{HP}$ 10.5 Hz); the methyl protons of the ethoxy groups in **4b** appear as a triplet, whereas the methylene protons manifest themselves as two distinct multiplets, (AB systems coupled with phosphorus); and the methyl protons of the isopropyl groups in **4c** appear as two doublets ($\Delta\nu$ 0.10 ppm, $^2J_{HH}$ 6 Hz).

By condensing spirobiindane monomer **1** with pentaethylene glycol ditosylate under conditions of high dilution, macrocycle **5** was synthesised in good yield (> 40%, Scheme 2).‡ The NMR investigations of host **5** at room temperature showed that it possesses a C_2 symmetry in solution and the sets of signals due to the methylenes of the crown and the spirobiindane moiety are in the expected range.

Macrocycle **5** is a novel chiral crown ether possessing phosphonate moieties in strategic positions, which may enhance the possibility of hydrogen bonding in three-dimensional chiral recognition.

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† *General procedure for the synthesis of phosphorylated methaparacyclophanes* **4a**–**c**. To 2 mmol (1.45 g) of chloromethyl methaparacyclophane derivative **2** was added, under a nitrogen atmosphere, 50 ml of trialkylphosphite. The reaction mixture was refluxed for 6 h, until no more unreacted starting material was observed by TLC. After evaporation of the solvent, the residue was refluxed with cyclohexane, then cooled, filtered and dried to give the diphosphonate derivative as a white powder, which was crystallised from dichloromethane–cyclohexane.

4,18-Bis(dimethoxyphosphorylmethyl)-3,5,7,10,11,13,14,17,19,21,24,25,27,28-tetradecamethyl[1.1.1.1]methaparacyclophane **4a**, (1.32 g, 83%), mp > 300 °C. ^{1}H NMR ($CDCl_3$) δ: 0.87 (s, 6H, int ArMe), 1.43 (s, 12H, int DureneMe), 2.34 (s, 12H, ext DureneMe), 2.51 (s, 12H, ext ArMe), 3.45 (d, 4H, CH_2P, $^2J_{HP}$ 21.5 Hz), 3.66 (d, OMe, $^3J_{HP}$ 11 Hz), 4.08 (dd, 8H, $ArCH_2$, J_{HH} 15.5 Hz). ^{13}C NMR, δ: 16.56, 17.43, 17.82, 18.85, 29.05 (d, $^1J_{CP}$ 137.4 Hz), 30.03, 52.67, 125.5 (d, J_{CP} 10 Hz), 131.67, 132.8 (d, J_{CP} 6 Hz), 135.31 (d, J_{CP} 3.7 Hz), 136.96, 139.36 (d, J_{CP} 3.7 Hz). ^{31}P NMR δ: 30.88. CI-MS (NH_3) *m*/*z*: 801 (8%, M^+), 819 (100%, $[M + NH_4]^+$).

4,18-Bis(diethoxyphosphorylmethyl)-3,5,7,10,11,13,14,17,19,21,24,25,27,28-tetradecamethyl[1.1.1.1]methaparacyclophane **4b**: (1.37 g, 80%), mp 206–208 °C. ^{1}H NMR ($CDCl_3$) δ: 0.87 (s, 6H, int ArMe), 1.28 (t, 12H, OCH_2*Me*, J_{HH} 7 Hz), 1.43 (s, 12H, int DureneMe), 2.34 (s, 12H, ext DureneMe), 2.51 (s, 12H, ext ArMe), 3.43 (d, 4H, CH_2P, $^2J_{HP}$ 22 Hz), 4.04 (m, 16H, $ArCH_2$ + OCH_2Me). ^{13}C NMR, δ: 16.56, 17.43, 17.82, 18.85, 29.05 (d, $^1J_{CP}$ 137.4 Hz), 30.03, 52.67, 125.5 (d, J_{CP} 10 Hz), 131.67, 132.8 (d, J_{CP} 6 Hz), 135.31 (d, J_{CP} 3.7 Hz), 136.96, 139.36 (d, J_{CP} 3.7 Hz). ^{31}P NMR, δ: 30.88. CI-MS (NH_3) *m*/*z*: 857 (10%, M^+), 875 (100%, $[M + NH_4]^+$).

4,18-Bis(diisopropyloxyphosphorylmethyl)-3,5,7,10,11,13,14,17,19,21,24,25,27,28-tetradecamethyl[1.1.1.1]methaparacyclophane **4c**, (1.46 g, 80%), mp 250–252 °C. ^{1}H NMR ($CDCl_3$) δ: 0.86 (s, 6H, int ArMe), 1.22 (d, 12H, OCH*Me*, J_{HH} 6.5 Hz), 1.31 (d, 12H, OCH*Me*, J_{HH} 6 Hz), 1.44 (s, 12H, int DureneMe), 2.34 (s, 12H, ext DureneMe), 2.51 (s, 12H, ext ArMe), 3.36 (d, 4H, CH_2P, $^2J_{HP}$ 21.5 Hz), 4.06 (dd, 8H, $ArCH_2$, J_{HH} 15 Hz), 4.66 (m, 2H, OCH). ^{13}C NMR, δ: 16.65, 17.38, 18.00, 18.77, 23.89, 24.08, 30.79 (d, $^1J_{CP}$ 139.8 Hz), 32.97, 126.4 (d, J_{CP} 9 Hz), 131.51, 132.78 (d, J_{CP} 6 Hz), 134.8 (d, J_{CP} 3.5 Hz), 136.98, 139.05 (d, J_{CP} 3.5 Hz). ^{31}P NMR, δ: 26.85. CI-MS (NH_3) *m*/*z*: 913 (15%, M^+), 931 (100%, $[M + NH_4]^+$).

‡ *6,6′-Bis(diethoxyphosphoryl)-7,7′-spirobiindano-23-crown-6* **5**. Solutions of **1** (0.58 g, 1 mmol) and pentaethylene glycol ditosylate (1 mmol) in freshly distilled MeCN (200 ml in total) were added dropwise, at equal rates over a period of 6 h from two different dropping funnels, to a stirred suspension of anhydrous CsF (0.91 g, 6 mmol) in anhydrous MeCN (400 ml) at a refluxing temperature for 48 h; next, the solvent was evaporated to give a white powder, which was collected with diethyl ether by filtration and washed several times with water. The product was purified by crystallisation from cyclohexane–ethyl acetate to give crown compound **5** (0.32 g, 40%), mp 148–150 °C. ^{1}H NMR ($CDCl_3$) δ: 1.34 (s, 6H), 1.35 (t, 6H, OCH_2*Me*, J_{HH} 7 Hz), 1.37 (m, 12H), 2.11 (d, 2H, J_{HH} 13 Hz), 2.37 (d, 2H, J_{HH} 13 Hz), 3.59 (m, 12H), 3.61 (m, 2H), 3.77 (m, 2H), 3.83 (m, 2H), 3.99 (m, 2H), 4.2 (m, 10H), 6.34 (d, 2H, $^4J_{HP}$ 6.5 Hz), 7.64 (d, 2H, $^3J_{HP}$ 15 Hz). ^{13}C NMR, δ: 16.45 (d, J_{CP} 6.4 Hz), 30.30, 31.37, 43.15, 62.05 (m), 68.64, 69.11, 70.29, 70.51, 70.63, 107.81 (d, J_{CP} 10.6 Hz), 116.14 (d, $^1J_{CP}$ 187.3 Hz), 128.77 (d, J_{CP} 7.6 Hz), 144.6 (d, J_{CP} 14.4 Hz), 156.42 (d, J_{CP} 2 Hz), 160.51 (d, J_{CP} 3.5 Hz), ^{31}P NMR, δ: 18.34. FAB-MS, *m*/*z*: 784 (100%, $[M + H]^+$).