Phosphorotropic rearrangement in synthesis of asymmetrically-substituted calix[4]arenes

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Monosodium derivatives of 1,3-bis(diethoxyphosphoryl)calix[4]arenes undergo *O,O*-phosphorotropic rearrangement into corresponding 1,2-bis(diethoxyphosphoryl)calix[4]arenes which are useful reagents in the synthesis of asymmetrically substituted calix[4]arenes with AABH-type substitution of the lower rim.

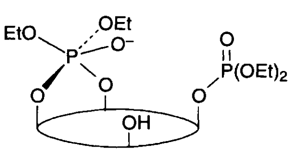
The design of highly selective artificial receptors based on calixarenes[1] is an intensively developing area of supramolecular chemistry,[2] within which the synthesis of chiral calixarenes is a promising method for obtaining 'host' molecules capable to enantio- or diastereo-selective recognition.[3] These were first obtained by functionalization of calixarenes by chiral reagents,[4] but recently a new approach based on asymmetric placement of achiral substituents on the upper[5] or lower[6] rims of the calix[4]arene macrocycle has been developed. The latter[6] allows the macrocyclic cavity to be fixed in one of four possible conformations:[7] cone, partial cone, 1,3-alternate or 1,2-alternate. Here a new method for the synthesis of phosphorus containing asymmetrically substituted calix[4]arenes with AABH substitution type of the lower rim is described.

Calix[4]arenes **4** and **5**† (Scheme 1) were synthesized in good yield by a one pot procedure consisted of successive treatments of 1,3-bis(diethoxyphosphoryl)calix[4]arenes[8] **1a,b** in the cone conformation with sodium hydride (in benzene or THF, reflux, 5 min) and such electrophilic reagents as benzoyl chloride or methyl monobromoacetate. The use of diethylchlorophosphate as the electrophilic reagent leads to triphosphorylated calixarenes **6**.‡

The synthesis proceeds *via* the formation of the unstable 1,3-diphosphorylcalix[4]arene monoanion **2**, which undergoes fast *O,O*-phosphorotropic rearrangement into the proximal 1,2-diphosphorylation[4]arene monoanion **3**.†

The key step of this process is the *O,O*-phosphorotropic rearrangement brought about by the advantageous spatial orientation of the phenolate anion oxygen for intramolecular nucleophilic attack at the phosphorus atom.[9] The phosphorotropic rearrangement intermediate is phosphorane **A**, which is not been detected by ^{31}P NMR due to its short lifetime.

The ^{1}H NMR spectra of compounds **4** and **5** (Table 1) show four doublets of doublets for the methylene bridge protons Ar–CH_2–Ar ($^2J_{HH}$ 13–15 Hz). The spectrum of **4b** shows four equal singlets from *tert*-butyl groups, three doublets of doublets for the AB spin system of the three aromatic moieties ($^4J_{HH}$ 1.4–2.4



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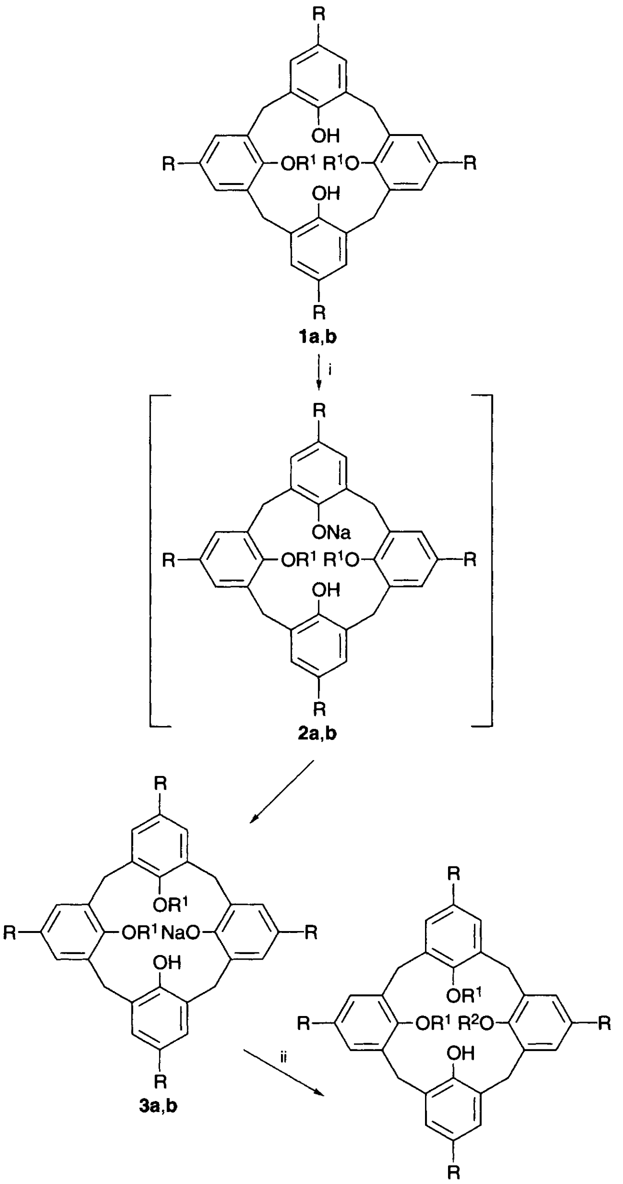

4a,b R^2 = PhCO
5a R^2 = $CH_2C(O)OMe$
6a,b R^2 = $P(O)(OEt)_2$
7a,b R^2 = H

a R = H, **b** R = Bu^t, R^1 = $P(O)(OEt)_2$

Scheme 1: *Reagents*: i, NaH, THF or benzene; ii, R^2X (X = Cl, Br).

Table 1 Selected spectroscopic data for compounds **3a**, **4–7**[a]

Compound	$^{31}P\{^1H\}$ NMR	Ar–CH$_2$–Ar ^1H NMR	Ar–CH$_2$–Ar $^{13}C\{^1H\}$ NMR
3a	−5.04	3.11, 4.26 (2 H); 3.16, 4.60 (4 H); 3.49, 5.00 (2 H)	—[b]
4a	−3.20, −3.52	3.31, 4.67 (2 H); 3.36, 4.08 (2 H); 3.38, 5.08 (2 H); 3.40, 4.34 (2 H)	30.93, 31.13 31.55, 31.61
4b	−3.10, −3.68	3.34, 4.66 (2 H); 3.37, 4.12 (2 H); 3.39, 5.02 (2 H); 3.46, 4.42 (2 H)	31.38, 31.84 31.96[c]
5a[d]	−3.59	3.31, 4.96 (2 H); 3.35, 4.59 (2 H); 3.35, 4.94 (2 H); 3.35, 5.02 (2 H)	31.80,[e] 32.13 32.37
6a	−3.10	3.33, 4.34 (4 H); 3.42, 5.09 (4 H)	32.18, 32.49
6b	−3.10	3.34, 4.35 (4 H); 3.39, 5.09 (4 H)	—[b]
7a	−3.10	3.46, 4.23 (2 H); 3.49, 4.64 (4 H); 3.49, 5.05 (2 H)	31.47, 31.76 32.52
7b	−3.10	3.47, 4.20 (2 H); 3.49, 4;61 (4 H); 3.49, 5.03 (2 H)	32.48, 32.95[c]

[a] ^1H, ^{31}P and ^{13}C NMR determinations were carried out on a Gemini VXR-200 instrument, in $(CD_3)_2CO$, 20 °C. [b] For this compound the $^{13}C\{^1H\}$ NMR spectrum was not recorded. [c] The signal is overlapped with that of a *tert*-butyl group. [d] Carried out in $CDCl_3$. [e] The chemical shifts for the two methylene bridges are overlaped.

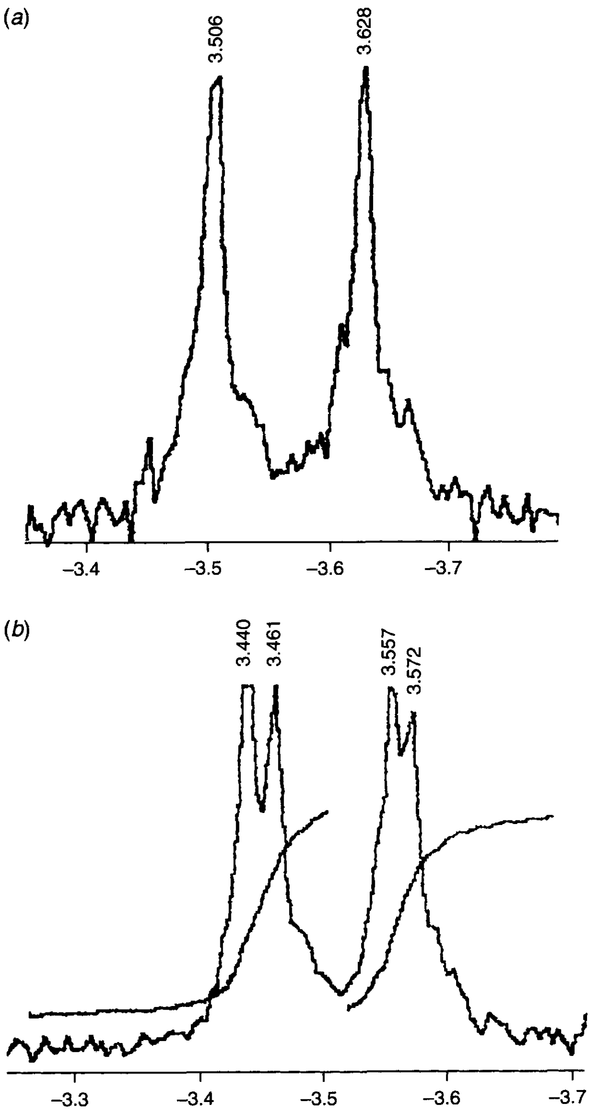

Fig. 1 $^{31}P\{^1H\}$ NMR spectra of compound **1b** recorded in (*a*) DL-α-phenylethylamine–C_6D_6 (95:5), and (*b*) L-α-phenylethylamine–C_6D_6 (95:5)

Hz) and a broad signal for the protons of the fourth aromatic fragment of the macrocyclic skeleton.

Thus, spectral data leave no doubts about the C_1 symmetry of compounds **4** and **5**; which are racemates as proved by the doubling of the phosphorus signals ($\Delta\delta$ = 0.01 ppm) in the $^{31}P\{^1H\}$ NMR spectra recorded in a solution of 1-phenylethylamine and deuterobenzene (95:5) (Fig. 1).‡

Compounds **3a** and **4–7** exist in the cone conformation. This is proved by the typical sets of signals of the methylene bridges in the ^1H NMR spectra,[1a] the distinctive signals of the carbon atoms of these groups in ^{13}C NMR spectra[10] (Table 1) and by X-ray analysis of triphosphorylated calix[4]arene **6b**§ (Fig. 2).

The molecule **6b** has a symmetry plane through atoms C(11), C(16), P(1B), O(1C), C(13) and C(14). The slope angles of the phenolic ring (1) and opposite phosphorylated phenolic ring (2) to the main macrocyclic plane formed by the methylene bridge carbons are 35.0 and 48.5°, respectively. The other two aromatic moieties (3) and (4) are oriented nearly perpendicular to the main plane and form equivalent slope angles of 88.5°. The angles between the benzene rings are: (2)–(3) −89.4°, (3)–(1) −88.5°, (1)–(2) −83.5°.

The distances of the lower rim macrocycle oxygens O(1A), O(1A*), O(1B) and O(1C) from the main plane are 1.357, 1.357, 1.353 and 0.860 Å, respectively. The oxygen atom O(1C) is 3.156 Å from O(1A) or O(1A*) What can point to the hydrogen bond formation led to the hydrogen atom oscillation between O1A and O1A*.

The carbon atoms C(17) and C(19) of the *tert*-butyl groups placed at the upper rim of the macrocycle are 2.478 and 3.132 Å, respectively, from the main plane. Both of these groups are disordered, in two conformations rotated at 60° to each other about the bond to the phenyl ring. The ethoxy group bonded to the phosphorus atom P(1B) is also disordered, into three positions. The bond angles at the phosphorus atoms range from 100.7 to 121.8°. The averaged bond lengths formed by the phosphorus atoms are: P=O, 1.456; P–OEt, 1.531; P–OAr, 1.581 Å.

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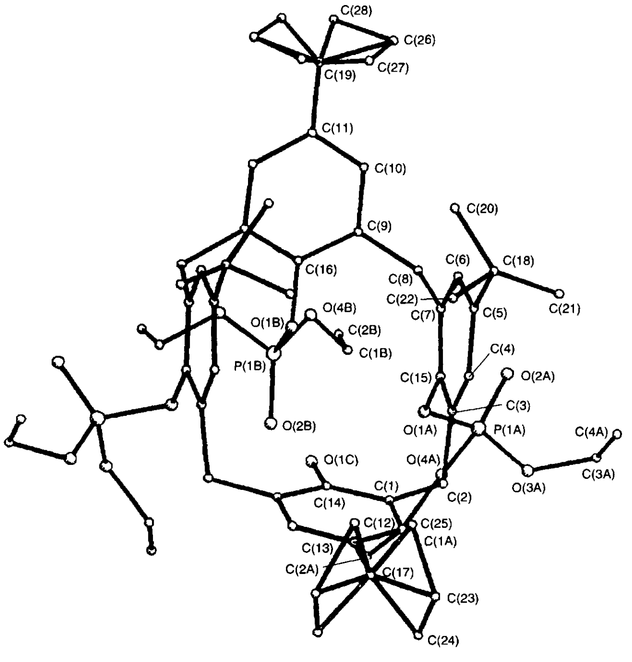

Fig. 2 Molecular structure of **6b**

Footnotes

† ^1H, ^{31}P, ^{13}C NMR and elemental analysis data confirm the identity of the new compounds (Table 1). *Selected data* for **4a**: mp 178–179 °C, yield 61%. For **4b**: mp 100–102 °C, yield 55%. For **5a**: mp 62–64 °C, yield 32%. For **6a**: mp 139–140 °C, yield 53%. For **6b**: mp 158–159 °C, yield 75%. For **3a**: mp 167–168 °C, yield 85%. For **7a**: mp 177–178 °C, yield 84%; **7b**: mp 161–162 °C, yield 82%. 1,2-bis(diisopropoxyphosphoryl)calix[4]arenes with the unestablished conformation was synthesized by the reduction of the 1,2-bis(diisopropoxyphosphoryl)monospirodienonecalix[4]arene.[11]

‡ The $^{31}P\{^1H\}$ NMR spectra recorded in the following conditions: 80.95 MHz, spectral width = 2770 Hz, number of points 32 000 (digital resolution 0.17 Hz), pulse width 75°.

§ *Crystal data* for **6b** $C_{56}H_{83}O_{13}P_3$, M_r = 1057.14, colourless rhombic crystal, space group *Pnma* (No. 62), a = 27.519(5), b = 17.776(5), c = 12.841(3) Å, V = 6281.53 Å^3, Z = 4, D_c = 1.118 g cm^{-3}, μ(Cu-Kα) = 16.88 cm^{-1}, X-ray data for **6b** were obtained on a CAD-4 diffractometer, no. unique reflections: 6827, no. of reflections with [$I > 3\sigma(I)$]: 5749. The structure was solved by direct methods and refined in anisotropic approximation. Final $R(R_w)$ 0.076 (0.089). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors.

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