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Calix[4]arenes Bearing α-Amino- or α-Hydroxyphosphonic Acid Fragments at the Upper Rim

Andrew Solovyov,[1] Sergey Cherenok,[1] Ivan Tsymbal,[1] Salvatore Failla,[2] Giuseppe A. Consiglio,[3] Paolo Finocchiaro,[3] and Vitaly Kalchenko[1]

[1]*Institute of Organic Chemistry, National Academy of Sciences of the Ukraine, Murmanskaya str. 5, 02094 Kiev-94, Ukraine*

[2]*Dipartimento di Ingegneria Chimica, dei Materiali, delle Materie Prime e Metallurgiche, Università di Roma "La Sapienza," Via del Castro Laurenziano 7, I-00161 Rome, Italy*

[3]*Istituto Chimico, Facolta di Ingegneria, Universita di Catania, Viale A. Doria 6, I-95125 Catania, Italy*

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ABSTRACT: *By the reaction of para-formylcalix[4]arenes* **1–6** *with trialkyl phosphites in the presence of dry hydrogen chloride, calix[4]arenes* **7–13** *possessing dialkylphosphoryl-hydroxymethyl groupings at the upper rim were synthesized. Calix[4]arenes* **18–23** *functionalized with dialkylphosphoryl-alkyl(aryl)aminomethyl groups were obtained by sodium-promoted addition of dialkyl phosphites to C=N bonds of para-iminocalix[4]arenes* **14–17**.

The consecutive treatment of α-hydroxy- or α-aminophosphonic acid dialkyl esters of calix[4]arenes **7, 10, 18**, *and* **21** *with bromotrimethylsilane and methanol gave dihydroxyphosphoryl derivatives of calix[4]arenes* **24–27**.

It was shown that calix[4]arenes bearing at the macrocyclic upper rim hydroxymethylphosphonic fragments, as well as bis-hydroxymethyl(aminomethyl)phosphonic fragments, are able to undergo self-assembly with formation of dimeric OH···O=P hydrogen bonded associates. © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:58–67, 2001

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INTRODUCTION

The calixarenes are a group of phenolic macrocyclic compounds that play a significant role in supramolecular chemistry [1,2]. This interest is connected with the ability of calixarenes to bind organic and inorganic species with formation of host-guest-type complexes [3]. The latter are stabilized by noncovalent interactions (coulombic, dipole-dipole forces, CH-π, solvatophobic interactions, etc.) [4,5], which play an important role in biochemical processes. Calixarenes can also mimic natural enzyme action [6] and serve as lipophilic containers for the transport of a bioactive guest through cell membranes [7]. One of the most important routes to the synthesis of new bioactive compounds consists of functionalization of the calixarene skeleton with fragments of natural or artificial biologically active compounds [8–11].

α-Hydroxy and α-aminophosphonic acid deriv-

atives being metabolites of natural aminoacids [12], are known to belong to the class of bioactive compounds. These compounds inhibit specifically some fermentative reactions [13] and possess high cancerostatic, bacteriostatic, and cytotoxic activity [13,14].

In our previous paper, we described a convenient synthetic procedure for insertion of α-hydroxy and α-aminophosphonic acid dialkyl ester fragments at the upper rim of a macrocycle [15]. It was shown that mono- and bis-(dialkylphosphoryl-hydroxymethyl)-calix[4]arenes are able to associate with formation of supercavities, caused by formation of strong intermolecular hydrogen bonds CH–OH···O=P at the upper rim. The present investigation deals with the preparation of new α-hydroxy- and α-aminophosphonic acid diesters and with the synthesis of calix[4]arenes bearing the fragments of free α-hydroxy- or α-aminophosphonic acids.

RESULTS AND DISCUSSION

The reaction of formyl compounds with trialkyl phosphites, which have been developed recently [16], is a convenient synthetic procedure for introduction of phosphonyl-hydroxymethyl fragments at the calixarene upper rim [15]. By the interaction of *para*-formylcalix[4]arenes **1–6** (cone conformers) with trialkyl phosphites in 1,4-dioxane solution, saturated with dry hydrogen chloride at room temperature, calixarenes **7–13** possessing one, two, or four dialkylphosphoryl-hydroxymethyl moieties at the upper rim were obtained (Scheme 1).

The most important methods of the synthesis of α-aminophosphonous acid derivatives are based on Pudovik [17], Mannich [18], and Kabachnik-Fields reactions [19]. The advantages of phosphorylation using the Pudovik method are high regioselectivity and stereoselectivity, good yields, and accessibility of reagents. We used this method for functionalization of the calixarene upper rim with dialkylphosphoryl-aminomethyl fragments.

The precursors, *para*-iminomethylcalixarenes **14–17**, were obtained by refluxing stoichiometrical quantities of formylcalixarenes **1, 2**, and **4** with amines in *meta*-xylene in the presence of molecular sieves, which bind the evolved water as described in the literature [15]. The preparation of dialkylphosphoryl-aminomethyl moieties at the upper rim was performed by reaction of *para*-iminomethylcalixarenes **14–17** with dialkyl phosphites in the presence of sodium. Unlike the phosphorylation of *para*-iminodialkoxycalix[4]arenes **14, 16**, and **17** in the presence of an excess of sodium, in the reaction with a *para*-iminotetraalkoxycalix[4]arene **15**, a catalytic quantity of sodium is sufficient. Yields of calix[4]arenes **18–23** were in the range of 60–65% (Scheme 2).

Calixarene phosphonic acids **24–27** were obtained by reaction of calixarene dialkyl phosphonates **7, 10, 18**, and **21** with bromotrimethylsilane (in dry chloroform), and subsequent alcoholysis of the silyl esters was obtained with methanol (Scheme 3).

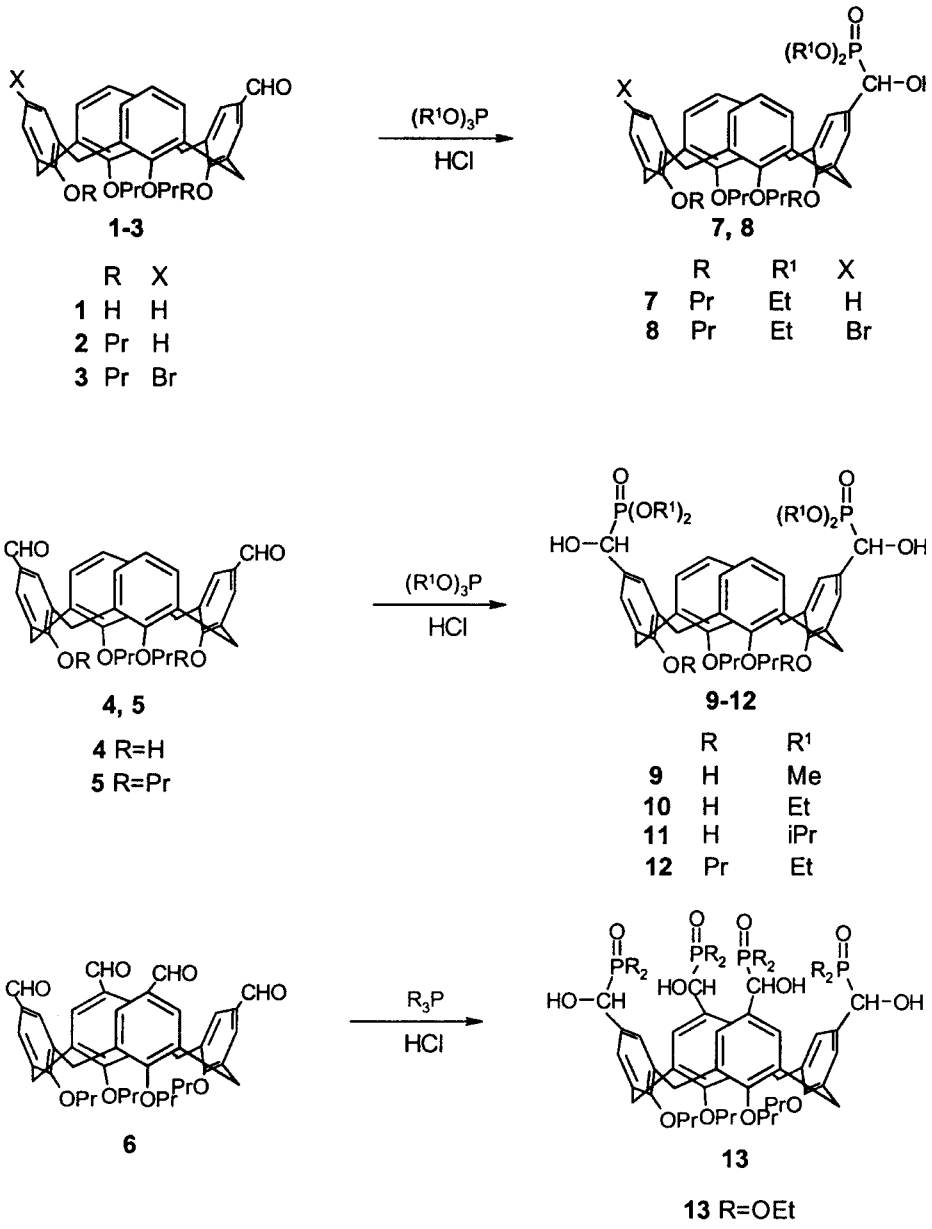
Dialkylphosphoryl-hydroxymethyl-calix[4]arenes **7–13** and dialkylphosphoryl-aminomethyl-calix[4]arenes **18–23** are colorless crystalline compounds soluble in many organic solvents. Calix[4]arenes **24–27** containing the fragments of free α-amino(hydroxy)phosphonic acids are soluble in polar solvents (DMSO, DMF, and alcohols). Calix[4]arene monoaminophosphonic acids **25** are also soluble in chloroform.

The syn-orientation of the benzene rings of phosphorylated calixarenes **7–13** and **18–27** was demonstrated by the presence of an AB spin system of nonequivalent axial and equatorial protons of the $ArCH_2Ar$ methylene bridges in the ^1H NMR spectra.

Phosphorylated dipropoxycalix[4]arenes **9–11, 18, 20–23**, and **25–27** adopt the flattened cone conformation, characteristic of dialkoxycalix[4]arenes [2,20]. In the ^1H NMR spectra, the signals of OH protons are found at low field more than 8.00 ppm due to formation of two strong hydrogen bonds OH···OPr between proximal fragments on the macrocyclic lower rim. The distance ($\Delta\delta$) between nonequivalent axial and equatorial protons of $ArCH_2Ar$ methylene links of calixarenes **9–11, 18, 20–23**, and **25–27** in ^1H NMR spectra, reflecting the dihedral angles formed by neighboring benzene fragments, are in the range of 0.54–0.97 ppm. The values of $\Delta\delta$ are characteristic for dialkoxycalix[4]arenes in the flattened cone (C_{2v} symmetry) conformation. In this conformation, phosphorylated benzene fragments are forced to a coplanar orientation due to formation of the intramolecular hydrogen bonds OH···OPr. Alkoxylated fragments are nearly perpendicular to the main molecular plane of the macrocycle. This conformation was confirmed by means of a molecular mechanics calculation (Program PCMODEL) (Figure 1).

The values $\Delta\delta$ 1.24–1.31 ppm for tetraalkoxycalix[4]arenes **7, 8, 12, 13, 19**, and **24** indicate the cone conformation (symmetry C_{4v}) [2]. This conformation can be considered as a transition structure in a fast interconversion flattened cone–flattened cone, characteristic of tetraalkoxycalix[4]arenes [21].

An important feature of bis-phosphorylated calix[4]arenes **9–12, 20–23, 26**, and **27** is the presence of two chiral carbon atoms of methylol or aminomethyl groups at the upper macrocyclic rim and the possibility of the formation of *d,l*-racemic and (or)



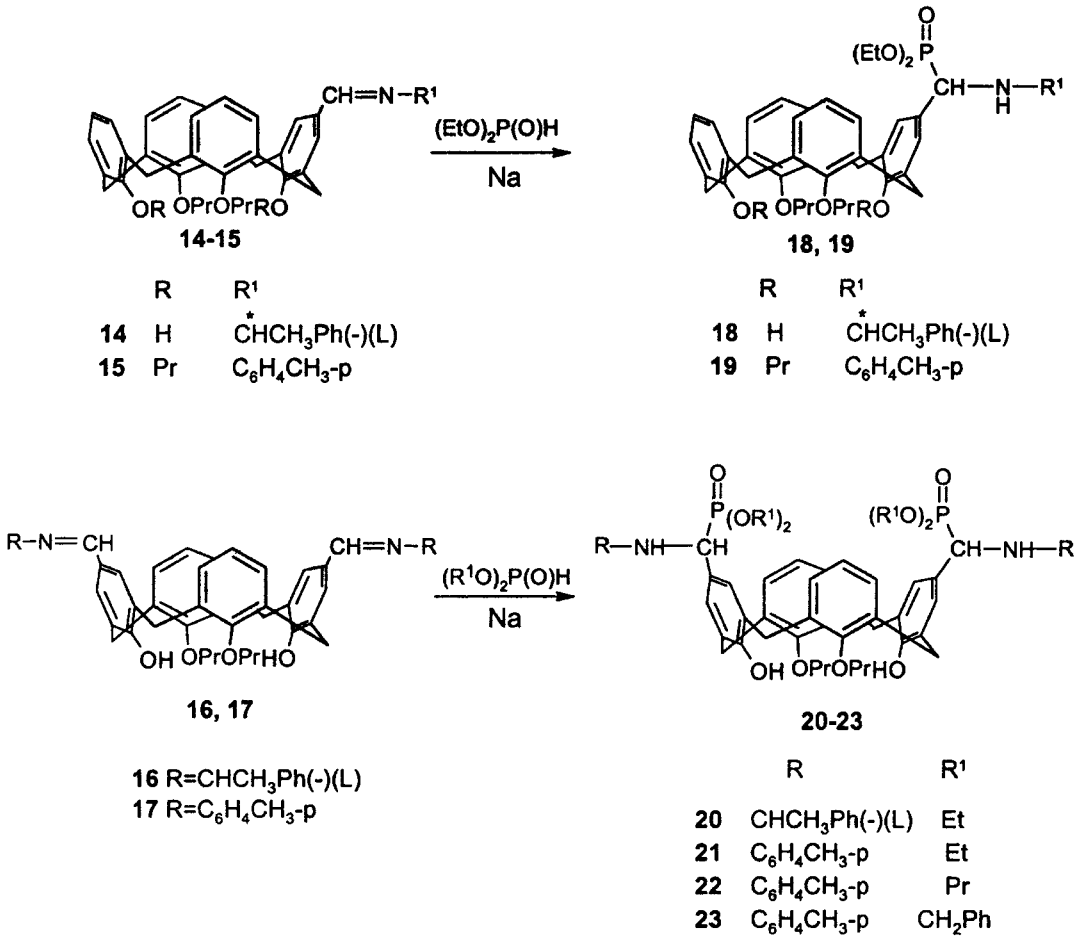
SCHEME 1

meso-forms in the process of their synthesis (Figure 2).

The addition of dialkyl phosphites to C=N bonds of iminocalix[4]arenes **14–17** is highly stereospecific, as previously observed in similar reactions [22]. In the case of bis-phosphorylation, only one of two possible diastereomers was obtained. This result was proved by the fact that only one set of signals in the ^{1}H and ^{31}P NMR spectra of calixarenes **21** and **22** is present.

Analogous stereospecificity in phosphorylation of monoimino-calix[4]arene **14** containing a chiral carbon bonded to the nitrogen atom of the imine group takes place. Formation of only one diastereoisomer of compound **18** is confirmed by the ^{1}H and ^{31}P NMR spectra.

Unlike observations with aminophosphonate derivatives of calixarenes, doubling of signals is observed in the ^{1}H and ^{31}P NMR spectra of bis-hydroxyphosphonates. The ratio of intensity of signals in the ^{1}H NMR spectra is dependent on the size of the alkyl groups at phosphorus atoms and the conditions of the reactions. The observed spectral data in bis-hydroxyphosphonates **9–12** can be explained from the point of view of the formation of a stereoisomeric mixture of *d,l*-racemic and *meso*-forms. One of the



SCHEME 2

diastereomers formed can be isolated by crystallization [15].

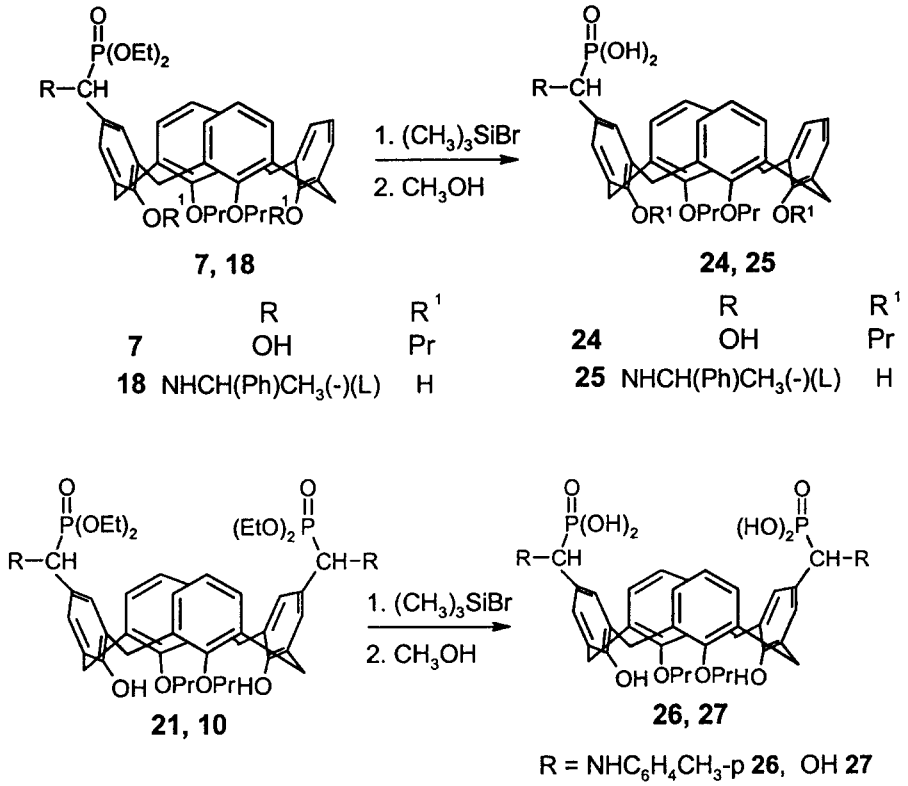
Derivatives of α-hydroxyphosphonic acids can form dimeric associates caused by intermolecular hydrogen bonds CH–OH···O=P [23]. In accordance with fast atom bombardment (FAB) mass spectra ($[2M]^+$ peaks) and IR spectra (associated CH–OH groups at 3310–3360 cm^{-1}), all mono(dialkylphosphoryl-hydroxymethyl) calix[4]arenes **7** and **8** as well as bis(dialkylphosphoryl-hydroxymethyl) calix[4]arenes **9–11** existing in the stereochemically rigid flattened cone conformation, with a large distance (near 13 Å) between the opposite phosphorus atoms, form the CH-OH···O=P hydrogen bonded dimers (Figure 3).

The sterochemically flexible cone conformation of bis or tetrakis(dialkylphosphoryl-hydroxymethyl)tetrapropoxycalix[4]arenes **12** and **13** allows the formation of two types of associates, with both intermolecular (dimeric structure, similar to that shown in Figure 3) or intramolecular (monomeric structure, Figure 4) hydrogen bonds.

It should be noted, in accordance with molecular modeling data, that this association is possible only in the case of the same configuration of the chiral carbon atoms of the phosphonomethylol fragments (*R* + *R* or *S* + *S* but not *R* + *S*). The association is confirmed by CH–OH···O=P hydrogen bonds at 3310–3360 cm^{-1} in the IR spectra. A more detailed investigation of association of tetrapropoxycalixarenes **7**, **8**, **12**, and **13** is in progress.

In contrast to dialkylphosphoryl-hydroxymethyl-calixarenes **7–13**, calix[4]arenes **18–23** possessing dialkylphosphoryl-aminomethyl groups are unable to form strong CH–NH···O=P associates [15]. No dimers were observed in their FAB mass spectra. Unlike the esters **18–23**, the aminophosphonic acid **25** forms a dimeric structure caused by strong intermolecular P=O···HO–P bonds. This process was confirmed by the presence of peaks of the dimer in the FAB mass spectra.

In conclusion, calix[4]arenes bearing dialkylphosphoryl-hydroxymethyl fragments at the macrocyclic upper rim, as well as bis(dialkylphosphoryl-



SCHEME 3

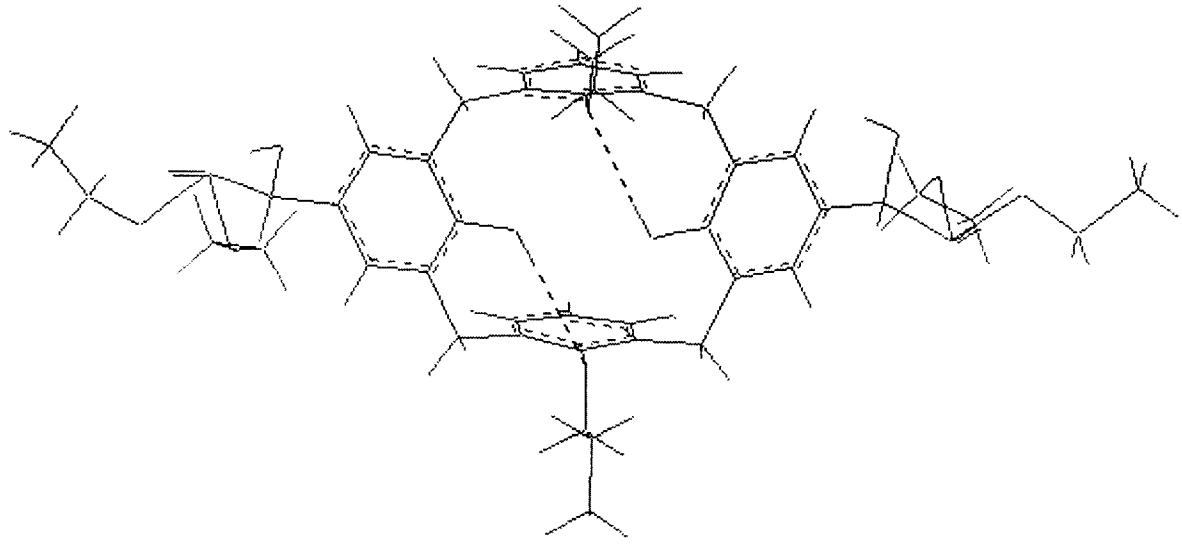


FIGURE 1 Energy minimized structure of calixarene **10**.

hydroxymethyl(aminomethyl)) fragments, are similar to calix[4]arenes functionalized with carboxylic [24], acetamide [25], and (thio)urea [25,26] groups and are able to undergo self-assembly with formation of dimeric hydrogen bonded associates. Formation of capsule type complexes of the compounds with bioactive molecules and their transport through biomembranes is therefore possible.

EXPERIMENTAL

^{1}H NMR and ^{31}P NMR spectra were recorded on a VXP 300 instrument operating at 300 MHz and 121.5

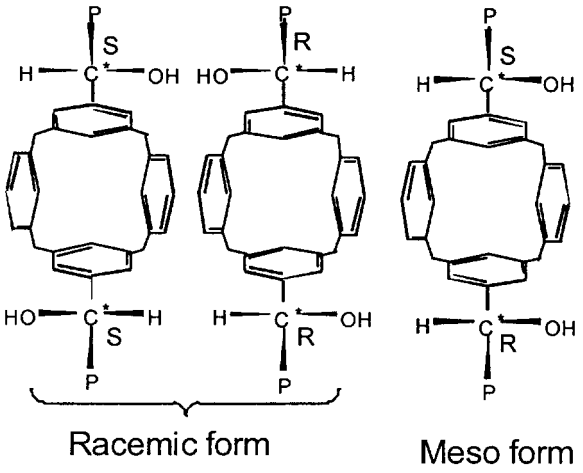


FIGURE 2 *d,l*-Racemic and *meso*-forms of bis(dialkylphosphoryl-hydroxymethyl)-calixarenes

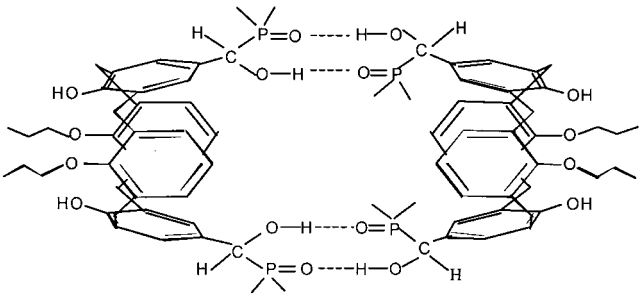


FIGURE 3 Dimeric association of bis(dialkylphosphoryl-hydroxymethyl)dipropoxycalixarenes **9–11**

MHz, respectively. The chemical shifts are reported from internal tetramethylsilane and external 85% H_3PO_4 standards. The FAB mass spectra were obtained with a double focusing Kratos MS 50S instrument equipped with a standard FAB source and a DS 90 data system, using *m*-nitrobenzyl alcohol as a matrix. The melting point determinations were performed on a Boetius apparatus and are uncorrected. IR spectra were recorded on a spectrometer M-80. CCl_4 for spectroscopy measurements was distilled over P_2O_5 and stored over molecular sieves (3Å) to obtain the condition in which water absorption bands ν_a and ν_{as} in this solvent (with thickness of absorptions layer 10 cm) were absent. 1,4-Dioxane was distilled over CaH_2 and stored over molecular sieves (3Å). Bromotrimethylsilane was freshly distilled. All reactions were carried out under dry argon. Purification of compounds **18–23** was achieved by column chromatography on silica gel (Silufol L 40/100). Formylcalix[4]arenes **1–6** were synthesized according to literature procedures [27]. A detailed procedure for the preparation of iminocalix[4]arene **17** has been described in the literature [15].

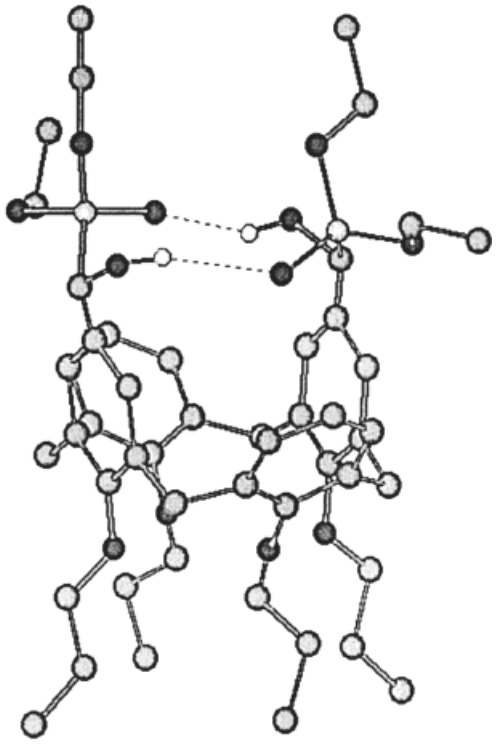


FIGURE 4 Energy minimized structure of calixarene **12** (*S,S*-diastereoisomer) (hydrogen atoms are omitted for clarity).

5-Bromo-17-formyl-25,26,27,28-tetrapropoxycalix[4]arene **3**

Compound **3** was obtained as a by-product in the synthesis of diformylcalix[4]arene **5** in accordance with the method described in Ref. [27d] by the reaction of the dibromotetrapropoxycalixarene with butyllithium and DMF. Isolation by column chromatography, R_f 0.6 (CH_2Cl_2/EtOH 10:1). Colorless crystalline compound: yield 34%, m.p. 130–132°C. ^{1}H NMR ($CDCl_3$), δ 1.02 (m, 12H, $CH_2CH_2CH_3$), 1.98 (m, 8H, $CH_2CH_2CH_3$), 3.16, 3.23 (two d, 2H + 2H, *J* 13.5 Hz, $ArCH_{2\ eq}$), 3.85 (m, 8H, OCH_2), 4.44, 4.49 (two d, 2H + 2H, *J* 13.5 Hz, $ArCH_{2\ ax}$), 6.42 (s, 2H, ArH), 6.60–6.77 (m, 6H, ArH), 6.99 (s, 2H, ArH), 9.57 (s, 1H, CHO).

General Procedure for the Preparation of Calixarenes **7–13**

To a suspension of monoformyl-, diformyl-, or tetraformylcalixarenes (0.1 mmol) in dioxane (or THF) (5 mL), the trialkyl phosphites (1 mmol, 2 mmol, or 4 mmol, respectively) were added. Gaseous hydrogen chloride (dried by $CaCl_2$) was bubbled through the reaction mixture with stirring at room temperature over a period of 0.5 hours. The resulting clear solu-

tion was stirred for 1 hour. The reaction mixture was evaporated in vacuum to give an oil. The oil was washed with petroleum ether (or with diethyl ether in the case of dimethylphosphoryl-hydroxymethyl derivatives). White powders were obtained and dried in deep vacuum at room temperature over a period of 5–10 hours. Yields were 85–90%.

5-Diethylphosphoryl-hydroxymethyl-25,26,27,28-tetrapropoxycalix[4]arene **7**

A colorless crystalline compound: yield 85%, m.p. 134–136°C (cyclohexane). ^{1}H NMR ($CDCl_3$), δ: 1.04 (m, 12H, $CH_2CH_2C\boldsymbol{H}_3$), 1.30 (m, 6H, $OCH_2C\boldsymbol{H}_3$), 2.00 (m, 8H, $CH_2C\boldsymbol{H}_2CH_3$), 3.19 (d, 4H, *J* 12.9 Hz, $ArCH_{2eq}$), 3.90 (m, 10H, OCH_2) 4.10 (m, 2H, $OC\boldsymbol{H}_2CH_3$), 4.50 (d, 4H, *J* 12.9 Hz, $ArCH_{2ax}$), 4.73 (d, 1H, *J* 19.8 Hz, CHP), 6.44–7.04 (m, 11H, ArH). ^{31}P NMR δ ($CDCl_3$) 22.05.

5-Bromo-17-diethylphosphoryl-hydroxymethyl-25,26,27,28-tetrapropoxycalix[4]arene **8**

A colorless crystalline compound: yield 80%, m.p. 130–132°C (hexane). ^{1}H NMR ($CDCl_3$), δ 0.93 (m, 12H, $CH_2CH_2C\boldsymbol{H}_3$), 1.30 (m, 6H, $CH_2C\boldsymbol{H}_3$), 1.84 (m, 8H, $CH_2C\boldsymbol{H}_2CH_3$), 3.07 (d, 4H, *J* 12.9 Hz, $ArCH_{2eq}$), 3.67–4.11 (m, 12H, OCH_2), 4.37 (d, 4H, *J* 13 Hz, $ArCH_{2ax}$), 4.67 (d, 1H, *J* 13.8 Hz, CHP), 6.34 (s, 2H, ArH), 6.45–6.68 (m, 6H, ArH), 6.73, 6.92 (two s, 1H + 1H, diastereotopic ArH).

5,17-Bis(diethylphosphoryl-hydroxymethyl)-25,26,27,28-tetrapropoxycalix[4]arene **12**

A colorless crystalline compound: yield 90%, m.p. 110–112°C (cyclohexane). ^{1}H NMR ($CDCl_3$), δ: 0.84, 1.02 (two m, 6H + 6H, $OC_2HC\boldsymbol{H}_3$), 1.14 (t, 6H, *J* 7.2 Hz, $CH_2CH_2C\boldsymbol{H}_3$), 1.31 (t, 6H, J 7.2 Hz, $CH_2CH_2C\boldsymbol{H}_3$), 1.83 (m, 8H, $CH_2C\boldsymbol{H}_2CH_3$), 3.10 (d, 4H, *J* 13.2 Hz, $ArCH_{2eq}$), 3.55–4.40 (m, 16H, OCH_2) 4.37 (d, 4H, *J* 13.2 Hz, $ArCH_{2ax}$), 4.81, 4.85 (two d, 1H + 1H, *J* 12.9 Hz and *J* 13.5 Hz, PCH), 6.20 (m, 6H, ArH), 7.00–7.17 (m, 4H, ArH). MS (FAB) *m/z*; 769[M-H_2O–$HPO(OC_2H_5)_2$ + H]$^+$, 907[M − H_2O + H]$^+$, 925[M + H]$^+$. Calculated: M 924.0.

5,11,17,23-Tetrakis(diethylphosphoryl-hydroxymethyl)-25,26,27,28-tetrapropoxycalix[4]arene **13**

Colorless crystalline compound: yield 90%, m.p. 80–85°C (cyclohexane). ^{1}H NMR ($CDCl_3$), δ: 0.92–1.40 (m, 36H, CH_3), 1.92 (m, 8H, $CH_2C\boldsymbol{H}_2CH_3$), 3.20 (m, 4H, $ArCH_{2eq}$), 3.66–4.43 (m, 28H, $ArCH_{2ax}$ + OCH_2), 4.80 (m, 4H, PCH), 7.30 (wide s, 8H, ArH). MS (FAB) *m/z*; 946[M − $2H_2O$–2H P $O(OC_2H_5)_2$ + H]$^+$, 1258[M + H]$^+$. Calculated: M 1257.5.

General Procedure for the Preparation of Iminomethylcalix[4]arenes **14–16**

To a suspension of monoformyl- or diformylcalix[4]arene (2 mmol) in *meta*-xylene (40 mL), the amine (4 mmol or 6 mmol accordingly) was added. The reaction mixture was refluxed over molecular sieves (3Å) for 30 hours. The resulting clear solution was separated from the molecular sieves and evaporated in a vacuum to give a yellow solid. The solid was washed with hot hexane (60°C). A yellow powder was obtained and dried in a vacuum (0.05 mm, 2 hours).

5-N-(L)-α-Phenylethylmetylenimino-25,27-dipropoxycalix[4]arene **14**

A colorless crystalline compound: yield 80%. m.p. 160–165°C. ^{1}H NMR($CDCl_3$), δ: 1.30 (t, 6H, J 7.2 Hz, $CH_2CH_2C\boldsymbol{H}_3$), 1.60 (d, 3H, *J* 7.2 Hz, $CHC\boldsymbol{H}_3$), 2.10 (m, 4H, $CH_2C\boldsymbol{H}_2CH_3$), 3.38, 3.45 (two d, 2H + 2H, *J* 13.2 Hz, $ArCH_{2eq}$), 3.98 (t, 4H, *J* 7.2 Hz, OCH_2), 4.29, 4.31 (two d, 2H + 2H, *J* 13.2 Hz, $ArCH_{2ax}$), 4.50 (q, 1H, *J* 7.2 Hz, $C\boldsymbol{H}CH_3$), 6.07 (t, 1H, *J* 7.2 Hz, ArH), 6.74 (t, 2H, *J* 7.2 Hz, ArH), 6.93 (m, 3H, ArH), 7.05 (d, 4H, *J* 7.2 Hz, ArH), 7.33 (t, 2H, *J* 7.2 Hz, ArH), 7.41 (d, 2H, *J* 7.2 Hz, ArH), 7.51 (s, 2H, ArH), 8.22 (s, 1H, OH), 8.23 (s, 1H, OH), 8.69 (s, 1H, CH=N).

5-N-tolylmetylenimino-25,26,27,28-tetrapropoxycalix[4]arene **15**

A colorless crystalline compound: yield 75%, m.p. 160–165°C. ^{1}H NMR($CDCl_3$), δ: 1.04 (m, 12H, $CH_2CH_2C\boldsymbol{H}_3$), 1.94 (m, 8H, $CH_2C\boldsymbol{H}_2CH_3$), 2.38 (s, 3H, $ArCH_3$), 3.17, 3.26 (two d, 2H+2H, *J* 13.2 Hz, $ArCH_{2eq}$), 3.80–4.01 (m, 8H, OCH_2), 4.47, 4.50 (two d, 2H + 2H, *J* 13.2 Hz, $ArCH_{2ax}$), 6.52–6.74 (m, 9H, ArH, *NS*), 7.10, 7.19 (two d, 2H + 2H, *J* 8.1 Hz, C_6H_4), 7.28 (s, 2H, ArH, S), 8.23 (s, 1H, CH=N)

5,17-Bis-(N-(L)-α-phenylethylmetylenimino)-25,27-dipropoxycalix[4]arene **16**

A colorless crystalline compound: yield 76%, m.p. 150–153°C. ^{1}H NMR ($CDCl_3$), δ: 1.30 (t, 6H, *J* 7.5 Hz, $CH_2CH_2C\boldsymbol{H}_3$), 1.59 (d, 6H, *J* 6.6 Hz, $CHC\boldsymbol{H}_3$), 2.05 (m, 4H, $CH_2C\boldsymbol{H}_2CH_3$), 3.44 (d, 4H, *J* 13.2 Hz, $ArCH_{2eq}$), 3.98 (t, 4H, *J* 6.8 Hz, OCH_2), 4.28 (d, 4H, *J* 13.2 Hz, $ArCH_{2ax}$), 4.49 (q, 2H, *J* 6.6 Hz, $C\boldsymbol{H}CH_3$), 6.72 (t, 2H, *J* 7.2 Hz, ArH-*p* NS), 6.92 (d, 4H, *J* 7.2 Hz, ArH-m

NS), 7.22–7.50 (m, 14H, ArH-m S + C_6H_5), 8.22 (s, 2H, CH = N), 8.52 (s, 2H, OH).

General Procedure for the Preparation of Calixarenes **18–23**

To a given dialkyl phosphite (3 mL), sodium (3.2 mmol) was added by portions (with caution). To the solution of the sodium dialkyl phosphite formed, monoimino- or diiminodipropoxycalix[4]arenes (0.4 mmol for calixarenes **14** or 0.8 mmol for calixarenes **16–17**) were added. (In the case of monoformylcalix[4]arene **15**, just a catalytic quantity of sodium was used). The mixture was stirred at room temperature for 3 hours. The reaction was quenched by addition of water (100 mL). A white precipitate was filtered off, washed with water, hexane, and diethyl ether, and purified by column chromatography.

5-Diethylphosphoryl-aminomethyl-25, 27-dipropoxycalix[4]arene **18**

Purification by column chromatography ($CHCl_3$/C_2H_5OH 10:1), R_f 0.8. Colorless crystalline compound: yield 60%, m.p. 120–123°C. ^{1}H NMR ($CDCl_3$), δ: 0.85, 1.32 (two d, 3H + 3H, *J* 7.5 Hz, diastereotopic OCH_2CH_3), 1.30, 1.31 (two t, 3H + 3H, *J* 7.5 Hz, diastereotopic CH_2CH_3), 1.33 (m, 3H, diastereotopic $CHCH_3$), 2.01 (m, 4H, $CH_2CH_2CH_3$), 3.32, 3.34 (two d, 2H + 2H, *J* 13.2 Hz, $ArCH_{2eq}$), 3.75, 4.15 (two m, 2H + 2H, diastereotopic $POCH_2$), 3.96, 3.98 (two t, 2H + 2H, *J* 7.5 Hz, OCH_2), 4.24, 4.26, 4.28, 4.31 (four d, 4H, *J* 13.2 Hz, diastereotopic $ArCH_{2ax}$), 6.30 (d, 1H, *J* 23 Hz, PCH), 6.80–7.40 (m, 11H, ArH), 8.40 (s, 2H, OH). ^{31}P NMR ($CDCl_3$), δ 26.4.

5-Diethylphosphoryl-aminomethyl-25,26,27,28-tetrapropoxycalix[4]arene **19**

Purification by column chromatography ($CHCl_3$/C_2H_5OH 5:1), R_f 0.6. Colorless crystalline compound: yield 60%, m.p. 106–109°C. ^{1}H NMR ($CDCl_3$), δ: 0.80–1.40 (m, 18H, diastereotopic OCH_2CH_3 + CH_2CH_3), 1.95 (m, 8H, $CH_2CH_2CH_3$), 2.18 (s, 3H, $ArCH_3$), 3.12, 3.13, 3.16, 3.19 (four d, 4H, J 12.3 Hz, diastereotopic $ArCH_{2eq}$), 3.69, 4.02 (two m, 4H + 4H, diastereotopic OCH_2), 3.89, 4.20 (two m, 2H + 2H, diastereotopic $POCH_2$), 4.42, 4.45, 4.47, 4.49 (four d, 4H, *J* 12.3 Hz, diastereotopic $ArCH_{2ax}$), 4.75, 4.80 (two d, 1H, *J* 21 Hz, PCH), 5.82 (d, 1H, *J* 8.7 Hz, NH), 6.20 (m, 5H, ArH), 6.63, 6.97 (two d, 2H + 2H, *J* 8.1 Hz, C_6H_4), 6.65 (m, 1H, ArH), 6.89 (t, 1H, *J* 7.5 Hz, ArH), 7.10 (d, 2H, 7.5 Hz, ArH), 7.14, 7.20 (two s, 1H + 1H, diastereotopic ArH) ^{31}P NMR ($CDCl_3$), δ 24.14.

5,17-Bis(diethylphosphoryl-aminomethyl)-25,27-dipropoxycalix[4]arene **20**

Purification by column chromatography ($CHCl_3$/C_2H_5OH 10:1), R_f 0.5. A colorless crystalline compound: yield 65%, m.p. 80–83°C. ^{1}H NMR ($CDCl_3$), δ: 0.66, 1.32 (two t, 6H + 6H, *J* 7.5 Hz, diastereotopic OCH_2CH_3), 1.33 (m, 6H, CH_2CH_3), 2.01 (m, 4H, $CH_2CH_2CH_3$), 2.10 (d, 6H, $CHCH_3$), 3.36 (d, 4H, *J* 13.0 Hz, $ArCH_{2eq}$), 3.70, 4.15 (two m, 4H + 4H, diastereotopic $POCH_2$), 3.97, 3.98 (two t, 2H + 2H, *J* 7.5 Hz, diastereotopic OCH_2), 4.31 (d, 4H, *J* 13.0 Hz, $ArCH_{2ax}$), 6.35 (m, 2H, PCH), 6.68–7.11 (m, 20H, ArH), 8.20 (s, 2H, OH). ^{31}P NMR ($CDCl_3$), δ 25.7.

5,17-Bis(dibenzylphosphoryl-aminomethyl)-25,27-dipropoxycalix[4]arene **23**

A colorless crystalline compound: yield 65%. m.p. 96–100°C (cyclohexane). ^{1}H NMR ($CDCl_3$), δ; 1.28 (m, 6H, CH_2CH_3), 2.01 (m, 4H, CH_2CH_3), 2.17 (s, 6H, $ArCH_3$), 3.24, 3.29 (two d, 2H + 2H, *J* 12.6 Hz diastereotopic $ArCH_{2eq}$), 3.89 (m, 4H, OCH_2), 4.17, 4.23 (two d, 2H + 2H, *J* 12.6 Hz diastereotopic $ArCH_{2ax}$), 4.46, 4.99 (two m, 4H + 4H, CH_2Ph), 4.70 (d, 2H, *J* 21.6 Hz, PCH), 6.45–6.90 (m, 14H, ArH), 7.16, 7.23 (two s, 2H + 2H, diastereotopic ArH-m *S*), 8.28 (s, 2H, O H).^{31}P NMR ($CDCl_3$), δ 25.2.

General Procedure for Synthesis of Calixarene Phosphonic Acids **24–27**

To a solution of mono- and diphosphorylated calix[4]arenes **7, 10, 18**, and **21** (0.1 mmol) in 5 mL of dry chloroform, bromotrimethylsilane (1 and 2 mmol respectively) was added. The reaction mixture was stirred at room temperature for 30 hours. The reaction mixture was evaporated under reduced pressure. An excess of absolute methanol was added to the residue. The methanol solution was heated at 50°C for 2 hours, and the solvent was evaporated. A solid residue was dried in vacuum (0.05 mm) for 10 hours.

5-Dihydroxyphosphoryl-hydroxymethyl-25,26,27,28-tetrapropoxycalix[4]arene **24**

Colorless crystalline compound: yield 85%, m.p. 250–260°C (dec.). ^{1}H NMR (DMSO-d6), δ: 0.95 (m, 12H, $CH_2CH_2CH_3$), 1.93 (m, 8H, $CH_2CH_2CH_3$), 3.07 (d, 4H, J 13 Hz, $ArCH_{2eq}$), 3.67–3.84 (m, 8H, OCH_2), 4.37 (d, 4H, $ArCH_{2ax}$), 6.33–6.68 (m, 9H, ArH), 6.73, 6.93 (two s, 1H + 1H, diastereotopic ArH). ^{31}P NMR (CD_3CN), δ 16.7.

5-Dihydroxyphosphoryl-N-(L)α-phenylethyl-aminomethyl-25,27-dipropoxycalix[4]arene **25**

A colorless crystalline compound: yield 85%. ^{1}H NMR ($CDCl_3$), δ: 0.98 (m, 9H, C***H***$_3$CH + CH_2CH_2C***H***$_3$), 1.65 (m, 4H, CH_2C***H***$_2CH_3$), 3.10 (d, 4H, 12.6 Hz, $ArCH_{2eq}$), 3.16 (q, 1H, 7.2 Hz, CH_3C***H***), 3.67 (m, 4H, OCH_2), 3.97 (m, 4H, $ArCH_{2ax}$), 6.4–7.2 (m, 16H, ArH), 8.00 (s, 1H, OH), 8.20, 8.60 (two s, 1H + 1H, POH), 10.0 (s, 1H. OH)^{31}P NMR ($CDCl_3$), δ 14.4 MS (FAB) *m/z*; 640[M - HP $O(OH)_2$ + H]$^+$, 723[M + H]$^+$, 1444[2M + H]$^+$. Calculated: M 722.0.

5,17-Bis(dihydroxyphosphoryl-N-tolylamino-methyl)-25,27-dipropoxycalix[4]arene **26**

A colorless crystalline compound: yield 88%. ^{1}H NMR (DMSO-d6), δ: 1.70 (m, 6H, CH_2CH_2C***H***$_3$), 1.95 (m, 4H, CH_2C***H***$_2CH_3$), 2.07 (s, 6H, $ArCH_3$), 3.50, 3.60 (two d, 2H + 2H, 12.6 Hz, $ArCH_{2eq}$), 3.94 (m, 4H, OCH_2) 4.10, 4.14 (two d, 2H + 2H, 12.6 Hz, $ArCH_{2ax}$), 7.10–7.88 (m, 18H, ArH), 9.44–9.56 (two s, 1H + 1H, OH). ^{31}P NMR (DMSO-d6), δ 16.7.

5,17-Bis(dihydroxyphosphorylhydroxymethyl)-25,27-dipropoxycalix[4]arene **27**

A colorless crystal compound: yield 85%, m.p. 250–260 °C (dec.). ^{1}H NMR (DMSO-d6), δ: 1.35 (m, 6H, CH_2CH_2C***H***$_3$), 2.05 (m, 4H, CH_2C***H***$_2CH_3$), 3.35 (d, 4H, J 13 Hz, $ArCH_{2eq}$), 3.90 (d, 4H, OCH_2) 4.20 (d, 4H, *J* 13 Hz $ArCH_{2ax}$), 6.65 (m, 2H, ArH), 6.95 (m, 4H, ArH), 7.10 (m, 4H, ArH). ^{31}P NMR (DMSO-d6), δ 19.7. MS (ES) *m/z*; 651[M − HP $O(OH)_2^+$, 693[M − $2H_2O$]$^+$, 729[M]$^+$. Calculated M 728.0.

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