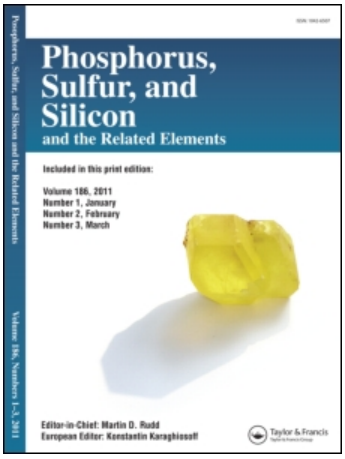


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS, NMR AND X-RAY STRUCTURE OF PHOSPHORYLATED TETRAM ERIC METACYCLOPHANES

Giuseppe A. Consiglio[a]; Paolo Finocchiaro[a]; Salvatore Failla[b]; Ante Albert[c]; Dietrich Mootz[c]
[a] Istituto Chimico - Facoltá di Ingegneria- Universitá di Catania, Catania, Italy [b] Dipartimento di Ingegneria Chimica, dei Materiali delle Materie Prime e Metallurgiche, Universitá di Roma La Sapienza, Rome, Italy [c] Institut für Anorganische Chemie and Strukturchemie, Heinrich-Heine-Universität Düsseldorf, Dässeldorf, Germany

To cite this Article Consiglio, Giuseppe A. , Finocchiaro, Paolo , Failla, Salvatore , Albert, Ante and Mootz, Dietrich(1999) 'SYNTHESIS, NMR AND X-RAY STRUCTURE OF PHOSPHORYLATED TETRAM ERIC METACYCLOPHANES', Phosphorus, Sulfur, and Silicon and the Related Elements, 149: 1, 29 — 38
To link to this Article: DOI: 10.1080/10426509908037020
URL: http://dx.doi.org/10.1080/10426509908037020

Phosphorus, Sulfur and Silicon, 1999, Vol. 149, pp. 29-38
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS, NMR AND X-RAY STRUCTURE OF PHOSPHORYLATED TETRAMERIC METACYCLOPHANES

GIUSEPPE A. CONSIGLIO[a], PAOLO FINOCCHIARO[a*], SALVATORE FAILLA[b†], ANTJE ALBERT[c] and DIETRICH MOOTZ[c‡]

[a]*Istituto Chimico – Facoltà di Ingegneria- Università di Catania – Viale A. Doria 6 – 95125 Catania, Italy,* [b]*Dipartimento di Ingegneria Chimica, dei Materiali delle Materie Prime e Metallurgiche – Università di Roma La Sapienza – Via del Castro Laurenziano, 7 – 00161 Rome, Italy and* [c]*Institut für Anorganische Chemie and Strukturchemie, Heinrich-Heine-Universität Düsseldorf, D-40225 Düsseldorf, Germany*

(Received 14 December, 1998)

The synthesis of mesitylene-derived 1,3 alternate [1.1.1.1] metacyclophanes functionalized with pendant methylene-phosphonic acid diethyl ester groups is described. The compounds were fully characterized by ^{1}H, ^{13}C and ^{31}P-NMR spectra and by FAB-MS spectroscopy.

The preferred conformation in solution was established by NMR methods, whereas the solid state conformation of one of them, solved by X-ray diffraction techniques, is also reported. The macrocycle forms a lattice clathrate with cyclohexane in the ratio 1:2 (macrocycle over guest) and alternates with an additional molecule of water in a hydrogen-bonded 1D array.

Keywords: Conformationally preorganized synthetic receptors; Lattice clathrate; Hydrogen-bonded structures; Phosphorylated tetrameric metacyclophanes

INTRODUCTION

The selective recognition of biologically relevant molecules, as well as cations and especially anions, by synthetic receptors is a very fertile and interesting field of investigation in Supramolecular Chemistry.[1] In particular, high emphasis is devoted to the synthesis of conformationally preor-

* Correspondence Author: e-mail: pfinocchiaro@ic. ing. unict. it
† Correspondence Author: e-mail: sfailla@ic ing. unict. it
‡ Correspondence Author: e-mail: mootz@uni-duesseldorf.de

ganized building blocks from which specific hosts with desired properties can be prepared by appropriate and selective functionalization reactions. Furthermore, chemically robust macrocycles able to complex cations, and in particular lanthanides, are needed as luminescent sensors and for diagnostic bioassays,[2–4] not least for the use in powerful screening techniques such as Magnetic Resonance Imaging (MRI) and Proton Emission Computed Assisted Tomography (SPECT), or Proton Emission Tomography (PET) once complexed with radioactive lanthanides and actinides.

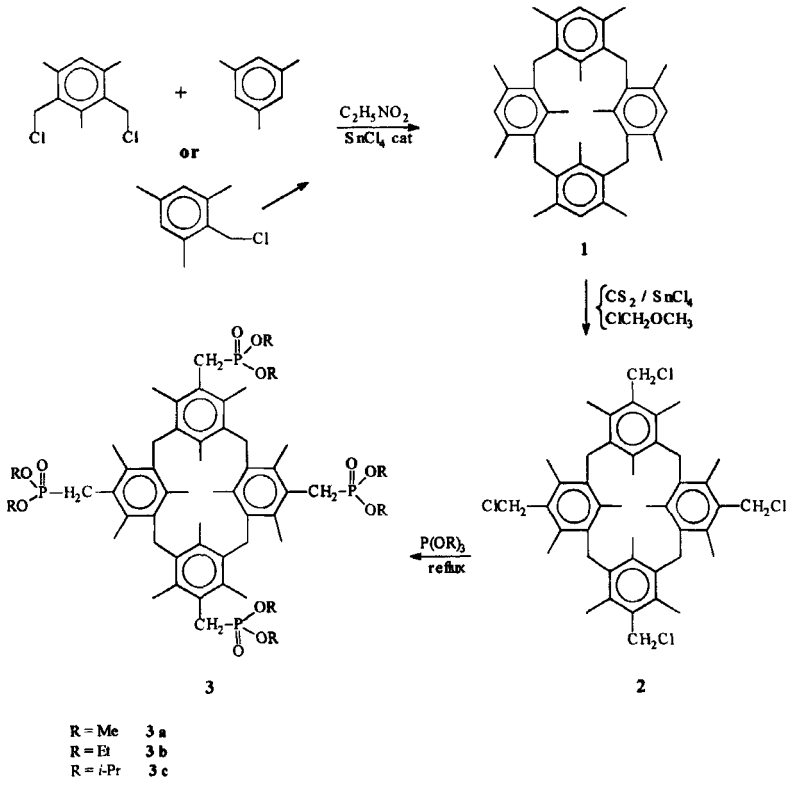
Among the various possible functionalization procedures, the introduction of phosphonic or phosphinic groups into the molecule, specially as pendant arms, appears to be the most promising route. Therefore, in this paper we shall describe the synthetic approach to mesitylene-derived 1,3-alternate [1.1.1.1] metacyclophanes which are functionalized by pendant methylene-phosphonic acid dialkyl ester groups. The stereochemistry in solution of such calix[4]arenoid type macrocycles will be discussed and the solid-state conformation of one of them, solved by X-ray diffraction techniques, will be also reported, together with its host properties.

RESULTS AND DISCUSSIONS

Tetrameric metacyclophane **1**, having four mesitylene units connected by methylene bridges, was easily synthesized by Friedel-Crafts procedures.[5] Chloromethylation[6] of **1** yielded **2** which, by Arbuzov reaction using trialkyl phosphites, produced the phosphorylated calix[4]arenoid tetramers **3a-c** (see scheme 1).

In previous reports[6,7] it was demostrated that macrocycle **1** exists in solution on the NMR time-scale in a fixed "saddle-shape"[6] or 1,3-alternate[7,8] conformation in the temperature range of –60 to 150 °C, substantiated by an upfield resonance for the intra-annular methyl groups which are strongly shielded ($\Delta\delta \sim 1.0$ ppm) by the aromatic ring current of the two adjacent flanking mesitylene subunits.

^{1}H-NMR investigations reveal that this type of conformation is maintained also for the phosphorylated macrocycles **3a-c.** In fact, due to the skeleton symmetry (D_{2d}), the bridging methylene protons appear as a sharp singlet at *ca.* 4.6 ppm, and the annular methyl groups show up with



SCHEME 1 Synthetic Procedure for the Calix[4]Arene Type Phosphonates All Meta Substituted

two signals at δ 2.4 ppm and ca. δ 1.13 ppm* in the ratio 2:1, assigned to external and internal methyl groups, respectively. The methylene groups attached to the phosphonic groups appear as a sharp doublet due to the coupling with phosphorus ($^2J_{HP}$ = 22.0 Hz), whereas the methyls or the methylenes of alkyl groups R in the -P(O)(OR)$_2$ moiety, due to the tetrahedral geometry of the phosphorus, reside in diastereotopic environment

* The inner methyl groups are shifted up-field by Δδ = 1.13 ppm with respect to the pertinent methyl group in the linear subunit model 2,4,6-trimethyl benzyl phosphonic acid diisopropyl ester, whose ^{1}H-NMR is δ ($CDCl_3$) ppm: 1.12 (d, 6H, $CH(\underline{CH_3})_2$, $^3J_{HH}$= 6.2 Hz), 1.28 (d, 6H, $CH(\underline{CH_3})_2$, $^3J_{HH}$ = 6.0 Hz), 2.23 (d, 3H $ArCH_3$, J_{HP} = 2.6 Hz), 2.38 (d, 6H, J_{HP} = 1.6 Hz), 3.14 (d, 2H, CH_2P, $^2J_{HP}$ = 22.2 Hz), 4.59 (m, 2H, $\underline{CH}(CH_3)_2$), 6.83 (s, 2H, ArH).

when R is *i*-Pr or Et, whereas are enantiotopic for R = Methyl. It follows that in **3a** the -P(O)$(OMe)_2$ protons appear as a sharp doublet due to the coupling with phosphorus ($^3J_{HP}$ = 10.5 Hz); in **3b** the methyl protons of the ethoxy groups appear as a triplet, whereas the methylene protons show up as two distinct multiplets (AB systems coupled with phosphorus); and in **3c** the methyl protons of the isopropyl groups appear as two doublets ($\Delta\nu$ = 0.145 ppm, $^2J_{HH}$ = 6 Hz).

A further point of interest in our phosphorylated macrocycles is their tendency to generate clathrate inclusion compounds with small organic molecules in the solid state, a property which may render these compounds also of relevant interest as receptors towards hydrophobic guests,[9] or as watersoluble macrocyclic hosts once the phosphonic group is hydrolized to the corresponding mono-ester or to the free acid, with pH depending binding properties.

Rewarding enough, macrocycle **3b** was found to form an inclusion compound with cyclohexane, whose stoichiometry, determined both by ^{1}H-NMR integration and by X-ray diffraction techniques (see below), was found in the molar ratio 1:2 (macrocycle to guest). The compound was found by ^{1}H-NMR to crystallize with some water; the importance of such finding, together with the relevance to the molecular architecture of our host, will be discussed in the X-ray section.

The crystal structure of **3b** · 2 C_6H_{12} · H_2O has been determined by X-ray analysis at −50°C. The calixarene molecule, with its bond lengths and bond angles all in the normal range*, lies around a twofold rotation axis of the space group, parallel [100], through one pair of opposite methylene C atoms in the inner macrocycle. From the latter, the arene systems are protruding *alternately up and down* (Figure 1), with the dihedral angle between two across from each other at 34.8(2)°. This 1,3-alternate or saddle conformation is distincly different from the more frequent cone or bowl form of calixarenes with the arenes oriented all to the same side of the macrocycle.

A molecule of water, also present in the crystal structure, is situated on the same type of symmetry axis as the calixarene. The two molecules are consecutively *hydrogen-bonded* to each other in a one-dimensional array along [010]. The geometry of the one independent hydrogen bond,

* Therefore bond lengths and bond angles of the macrocycle are not given here; they are deposited as supplementary material.

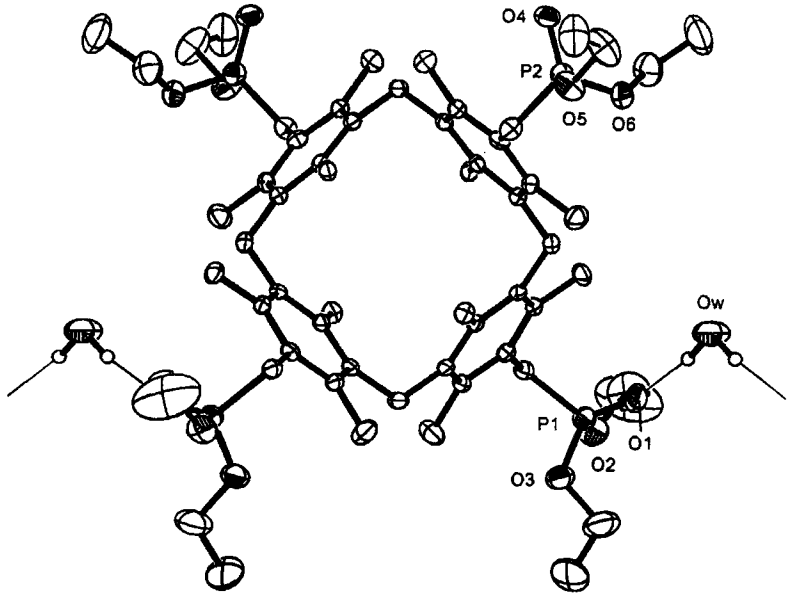


FIGURE 1 The calixarene molecule **3b** and the two water molecules to which it is O–H·····O hydrogen-bonded. Crystallographic twofold rotation axes through all molecules vertical and parallel to the plane of the drawing, H atoms except those of water molecules omitted for clarity, 25% ellipsoids for C, P, O

donated by the water molecule and accepted by one of the P=O functions, is again in the usual range (Ow···O1: 2.72(1) Å).

A cyclohexane molecule with a likewise acceptable *chair* geometry (C-C: 1.54–1.59(3) Å, C-C-C: 102–113(3)°, C-C-C-C: absolute values 61–69(3)°) was found in a general position (*i.e.*, two of these per calixarene and water molecule). Its incorporation into the crystal structure, with the calixarene conformation as observed, does not appear as an inclusion on a molecular level, but rather indicates a *lattice clathrate*, Specifically, and as an unusual feature, the cyclohexane molecules are arranged in a *tetrahedron-like cluster of four* (Figure 2) around a 222-D_2 position of the space group at 1/4, 3/4, 1/2 (and 3/4, 1/4, 1/2).

Considering the interest of our macrocycles also as potential molecular receptor, it is interesting to characterize the cavity by some geometric parameters. Figure 3 reveals that with the opening angle of 34.8° the molecular cavity is quite large and wide at the entrance and gets smaller

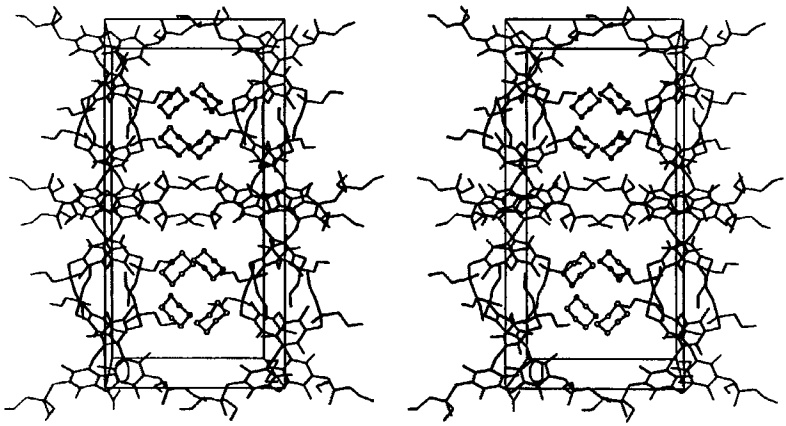


FIGURE 2 Stereoscopic view of a larger part of the crystal structure, showing the tetrahedron-like cluster of four cyclohexane molecules each around two equivalent 222-D_2 position at ¼, ¾, ½ and ¾, ¼, ½. Calixarene molecules **3b** by lines only, water molecules (at z = 0 and 1, *i.e.* far from the cyclohexane molecules) and all H atoms omitted for clarity

going inside down, typical for a cone conformation. The distance between the two opposite aryl carbon atoms carrying the -CH_2-P(O)$(OEt)_2$ groups is 6.88 Å, whereas for the methyl-substituted inner aryl carbon atoms the distance is reduced to 5.14 Å (Figure 3). The distances between opposite methylene C atoms in the inner macrocycle are 7.18(2) and 7.13(2) Å. The shortest distance between two adjacent methylene carbons is 4.55(1) Å.

EXPERIMENTAL

3, 5, 7, 10, 12, 14, 17, 19, 21, 24, 26, 28-Dodecamethyl [1.1.1.1]metacyclophane (**1**) and 4, 11, 18, 25-tetrakis(chloromethyl)-3, 5, 7, 10, 12, 14, 17, 19, 21, 24, 26, 28-dodecamethyl[1.1.1.1]metacyclophane (**2**) were synthesized according to a literature procedure[5,6] by reacting equimolar quantities of mesitylene and bis(chloromethyl)mesitylene in $EtNO_2$ solution in the presence of catalytic amounts of $SnCl_4$ at 60 °C for 1 h and then overnight at room temperature. The precipitate so obtained was filtered off and recrystallized from toluene. Chloromethylation of (**1**) with chloromethyl methyl ether in CS_2 at −15 °C in the presence of $SnCl_4$ produces (**2**) in good yield, as reported[6].

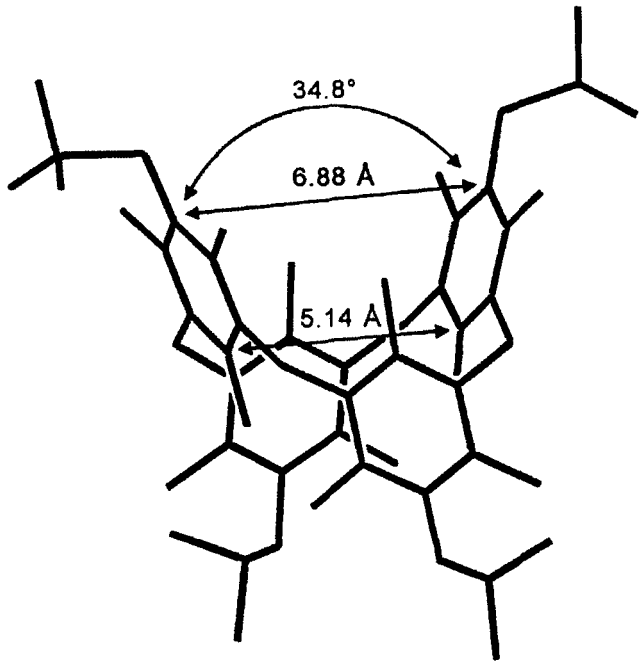


FIGURE 3 Line diagram with geometric parameters for the molecular cavity of **3b**. Macrocycle viewed largely side-on, ethyl groups and all H atoms omitted

Unless otherwise noted, commercially available chemicals were used as supplied: trialkyl phosphites, 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene, mesitylene, tin(IV) chloride, chloromethyl methyl ether were obtained from Aldrich. All reactions were performed under an inert atmosphere of nitrogen, and the solvents were distilled before use.

^{1}H-, ^{13}C-, ^{31}P-NMR spectra were recorded in $CDCl_3$ solution with TMS as internal standard and 85% H_3PO_4 as external standard, respectively, using a Varian-Inova 500 instrument operating at 500, 125, and 200 MHz, respectively. Mass spectra were obtained using a double-focusing Kratos MS 50S instrument equipped with a standard FAB source and DS 90 data system. 3-Nitrobenzyl alcohol was used as matrix.

The melting point determinations were performed on a Büchi 530 melting point apparatus and are uncorrected.

General Procedure for the Synthesis of Phosphorylated Metacyclophanes 3a-c

To 2 mmol (1.45 g) of the chloromethyl metacyclophane derivative (**2**) were added, under nitrogen atmophere, 30 ml of trialkylphosphite and heated to reflux temperature; then more trialkylphosphite was added until a homogeneous solution was obtained. The reaction mixture was refluxed for 4–6 hrs, 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 tetraphosphonate derivative as a white powder, which was crystallized form a mixture of ethylacetate/cyclohexane.

4, 11, 18, 25-Tetrakis(dimethoxyphosphonylmethyl)-3, 5, 7, 10, 14, 17, 19, 21, 24, 26, 28-dodecamethyl[1. 1.1. 1]methacyclophane (3a)

White prisms (1.68 g, 83 %), mp > 300 °C (ethylacetate/cyclohexane); ^{1}H-NMR ($CDCl_3$, δ ppm): 1.119 (s, 6H, int Ar$\underline{CH_3}$), 1.124 (s, 6H, int Ar$\underline{CH_3}$), 2.409 (s, 12H, ext Ar$\underline{CH_3}$), 2.411 (s, 12H, ext Ar$\underline{CH_3}$), 3.32, (d, 8H, CH_2P, $^2J_{HP}$ = 22.0 Hz,), 3.56 (d, 24H, PO$\underline{CH_3}$, $^3J_{HH}$ = 10.5 Hz), 4.01 (s, 8H, Ar$\underline{CH_2}$Ar); ^{13}C-NMR ($CDCl_3$, δ ppm): 18.07 (s), 18.38 (s), 29.04 (d, $^1J_{CP}$ = 137.4 Hz), 33.56 (s), 52.59 (d, $^2J_{CP}$ = 6.6 Hz), 126.23 (d, J_{CP} = 9.9 Hz), 132.74 (d, J_{CP} = 6.0 Hz), 134.55 (d, J_{CP} = 4.6 Hz), 138.05 (d, J_{CP}= 4.0 Hz); ^{31}P{^{1}H}-NMR ($CDCl_3$, δ ppm): 30.19; FAB-MS: 1016.8 (98, M^+), 1038.9 (40, M+Na^+), 396.9 (60), 255 (100).

3b · $2C_6H_{12}$ · H_2O: 4, 11, 18, 25-Tetrakis (diethyloxyphosphonylmethyl)-3, 5, 7, 10, 14, 17, 19, 21, 24, 26, 28-dodecamethyl[1.1.1.1] methacyclophane (3b)

White prisms (1.8 g, 80 %), mp = 225 °C (ethylacetate/cyclohexane); ^{1}H-NMR ($CDCl_3$, δ ppm): 1.13 (s, 12H, int Ar$\underline{CH_3}$), 1.20 (t, 24H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ = 6.5 Hz), 1.43 (s, 24H, cyclohexane), 2.42 (s, 24H, ext Ar$\underline{CH_3}$), 3.32, (d, 8H, $\underline{CH_2}$P, $^2J_{HP}$ = 22.0 Hz), 3.92 (m, 16H, PO$\underline{CH_2}CH_3$), 4.02 (s, 8H, Ar$\underline{CH_2}$Ar); ^{13}C-NMR ($CDCl_3$, δ ppm) 16.35 (s), 18.19 (s), 18.49 (s), 26.90 (cyclohexane), 29.91 (d, $^1J_{CP}$ = 135.8 Hz), 33.65 (s), 61.82 (d, $^2J_{CP}$ = 6.1 Hz), 126.66 (d, $^3J_{CP}$ = 9.2 Hz), 132.68 (d,

$^2J_{CP}$ = 5.4 Hz) 134.34, 137.99; ^{31}P-NMR ($CDCl_3$, δ ppm) 27.79; FAB-MS: 1129.2 (100, M^+), 227 (22).

4, 11, 18, 25-Tetrakis(diisopropyloxyphosphonylmethyl)-3, 5, 7, 10, 14, 17, 19, 21, 24, 26, 28-dodecamethyl[1.1.1.1]methacyclophane (3c)

White prisms (1.9 g, 78 %), mp = 170 °C dec. (ethylacetate/cyclohexane); ^{1}H-NMR ($CDCl_3$, δ ppm): 1.10 (d, 12H, CH($\underline{CH_3}$)$_2$, $^3J_{HH}$ = 6.0 Hz,), 1.13 (s, 6H, int Ar$\underline{CH_3}$), 1.14 (s, 6H, int Ar$\underline{CH_3}$), 1.25 (d, 12H, CH($\underline{CH_3}$)$_2$, $^3J_{HH}$ = 6.0 Hz,), 2.411 (s, 12H, ext Ar$\underline{CH_3}$), 2.413 (s, 12H, ext Ar$\underline{CH_3}$), 3.25, (d, 8H, $\underline{CH_2}$P, $^2J_{HP}$ = 22.0 Hz), 4.00 (s, 8H, Ar$\underline{CH_2}$Ar), 4.59 (m, 8H, CH($\underline{CH_3}$)$_2$); ^{13}C-NMR ($CDCl_3$, δ ppm): 18.29 (s), 18.65 (s), 23.79 (d, $^3J_{CP}$= 4.6 Hz), 24.04 (d, $^3J_{CP}$ = 4.5 Hz), 30.95 (d, $^1J_{CP}$ = 138.9 Hz), 33.58 (s), 70.14 (d, $^2J_{CP}$ = 6.9 Hz), 127.08 (d, J_{CP} = 9.1 Hz), 132.59 (d, J_{CP} = 5.3 Hz) 134.25 (d, J_{CP} = 3.8 Hz), 137.87 (d, J_{CP} = 3.8 Hz); ^{31}P{1H}-NMR ($CDCl_3$, δ ppm): 26.16; FAB-MS: m/z 1241.5 (28, M^+), 453.1 (38), 369.1 (47), 227.1 (100).

Crystal structure analysis

A single crystal of **3b** · 2 C_6H_{12} · H_2O of approximate dimensions 0.3 × 0.3 × 1.0 mm was sealed in a thin-walled glass capillary and mounted on a Siemens-Stoe AED 2 diffractometer operating with graphite-monochromatized MoKα radiation (λ = 0.71073 Å) and equipped for measurements at low temperature. The unit cell dimensions and (unique) space group were determined in the usual way and the intensities collected with a variable Ω/θ scan: *a*= 32.20(2) Å, *b* = 15.10(1) Å, *c* = 15.51(1) Å, *V* = 7541(8) Å^3 at −50°C; *Pban*, Z = 4; *d*(calcd)= 1.146 mg mm^{-3}, μ = 0.16 mm^{-1}; 2θ(max) = 44°, 4578 independent reflections of which 2629 were observed (|Fo| ≥ 4 σ_F), no correction for absorption.

The structure was solved by direct methods. The cyclohexane and also a water molecule were located in a difference Fourier map. In a later stage, the H atom positions, except those for the cyclohexane molecule and ethoxy groups, were obtained in the same way. Refinement was done on F^2, for the calixarene and water non-H atoms with anisotropic displacement parameters and for the located H atoms with isotropic ones, kept at 1.2 times the equivalent isotropic values of the respective C atoms. For the cyclohexane C atoms, an *overall* isotropic displacement parameter was

refined. The final residuals are $R(F) = 0.089$ for the observed and $wR(F^2) = 0.309$ for all reflections. The minimum and maximum residual electron densities are –0.30 and 0.45 eÅ^{-3}. The program system SHEXTL PLUS[10] was used on a VAX Station 3200 (Digital) and SHELXL-93[11] on a PC. Complete crystallographic data are deposited with the Cambridge Crystallographic Data Centre.

Acknowledgements

We thank C.N.R. and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for financial support.

References

[1] *Comprehensive Supramolecular Chemistry,* Edited by J.-M. Lehn, J.L. Atwood, J.E.D. Davies, D.D. MacNicol and F. Vögtle, Pergamon – Oxford UK 1996.
[2] S.W.A. Bligh, N. Choi, D.ST.C. Green, H.R. Hundson, C.M. McGrath, M. McPartlin, *Polyhedron,* **12,** 2887 (1993) and reference therein.
[3] R.A. Bulman, in *"Trace Metals and Fluorine in Bones and Teeth"*, edited by N.O. Priest and F.L. van de Vyver (CRC Press. Boca Ration, FL), p. 271 (1990); R. Engel, *Chem. Rev.,* **77,** 349 (1977).
[4] S. Aime, A.S. Batsanov, M. Botta, R.S. Dickins, S. Faulkner, C.E. Foster, A. Harrison, J.A.K. Howard, J.M. Moloney, T.J. Norman, D. Parker, L. Royle and J.A.G. Williams, *J. Chem. Soc., Dalton Trans,* 3623 (1997).
[5] F. Bottino, G. Montaudo and P. Maravigna, *Ann. Chim.* (Rome) **57,** 972 (1967).
[6] S. Pappalardo, G. Ferguson and J.F. Gallagher, *J. Org. Chem.,* **57,** 7102 (1992).
[7] S. Pappalardo, F. Bottino and G. Ronsisvalle, *Phosphorus and Sulfur,* **19,** 327 (1984).
[8] L.C. Groenen, J.D. van Loon, W. Verboom, S. Harkema, A. Casanati, R. Ungaro, A. Pochini, F. Ugozzoli and N. Reinhoudt, *J. Am. Chem. Soc.*, **113,** 2385 (1991).
[9] G.A. Consiglio, S. Failla, P. Finocchiaro, M. Visi and K.I. Herdcastle, *Supramolecular Chemistry,* in press.
[10] SHELXTL PLUS, Structure Determination System, Revision 4.21/V; Siemens Analytical X-Ray Instruments, Inc.; Madison, WI, USA, 1990.
[11] SHELXL-93, G.M. Sheldrick, Crystal Structure Refinement, Universität Göttingen, 1993.