

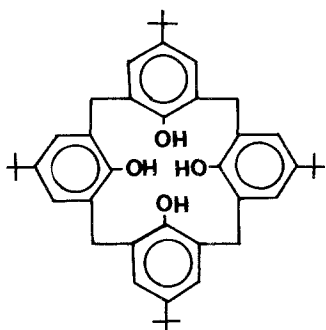
NEW IONIZABLE LIGANDS FROM p.t-BUTYLCALIX [4] ARENE

R. Ungaro,* A. Pochini
Institute of Organic Chemistry
G.D. Andreetti
Institute of Structural Chemistry of the
University
Via Massimo D'Azeglio 85
43100 Parma
Italy

ABSTRACT. The introduction of acetic acid units on p.t-butylcalix[4]arene, in a controlled way, leads to a series of new lipophilic complexones (3,5,7) with different structures and properties. The tetraacid derivative (3) shows a "cone" structure and its alkali and ammonium salts are soluble in water whereas the other two ligands (5) and (7) show a "flattened cone" structure. All new ligands are able to extract divalent metal cations from water to methylene chloride.

1. INTRODUCTION

p.t-Butylcalix[4]arene (1) is a cyclic tetramer derived from the condensation of p.t-butylphenol and formaldehyde, usually in basic conditions¹. This compound belongs to a class of phenolic macrocycles recently called calixarenes¹ which are experiencing new interest, especially after their structures have been firmly established. Compound (1) has a special interest because it is able to form inclusion complexes with several organic molecules, in the solid state^{2,3}.



In fact, although it has a mobile structure in solution and experiences a pseudo rotation process whose energy has been measured^{1,4}, in the solid state it has a "cone" structure determined by four intramolecular hydrogen bonds, which create a cavity suitable for the inclusion of neutral molecules. Several inclusion complexes between (1) and aromatic guest molecules have been isolated and their X-ray crystal structure determined. These complexes show either a 1:1 or 2:1 host/guest stoichiometry, although the X-ray structures are rather similar in the two cases.

In the 1:1 complexes the guest is held inside an intramolecular cavity (created by the hydrogen bonds) mainly by interactions between the butyl groups and the aromatic nucleus of the guest and more or less the same situation is observed in the 2:1 complexes³.

This inclusion behaviour seems to be so far restricted to p.t-butylcalix[4]arene (1), since other calixarene macrocycles either are not able to form any inclusion complex⁵ or give clathrates^{6,7}, with the guest held inside intermolecular voids of the crystal lattice.

Another interesting aspect of calixarenes is their high lipophilicity which, together with their macrocyclic nature, led us to use them as **ordered building blocks** for open chain⁸ and cyclic⁹ cation ligands, and other authors¹⁰ to employ them as such for the transport of alkali cations through bulk liquid membranes.

Continuing our studies in the functionalization of calixarene macrocycles to build up new specific ligands for ions and neutral molecules we have synthesized three new carboxylic acid derivatives (3-5) of p.t-butylcalix[4]arene (1), determined their structures and checked their complexing ability.

2. MATERIALS AND METHODS

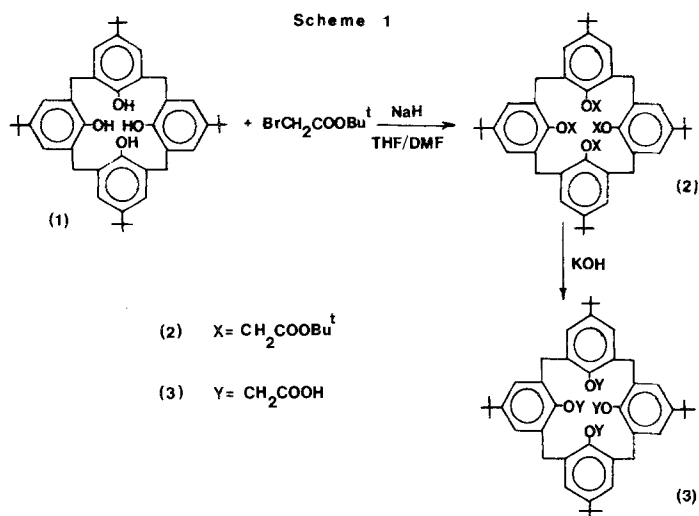
¹H NMR spectra were registered (at 60 MHz) on a Varian EM 360 and (at 200 MHz) on a Bruker CSP 200 spectrometer using tetramethylsilane as internal standard. All compounds synthesized gave satisfactory elemental analysis and spectral data consistent with the proposed structures.

The experimental details for their synthesis and characterization will be reported elsewhere.

3. RESULTS AND DISCUSSION

3.1 p.t-butylcalix[4]arene-Tetraacetic Acid (3)¹¹

With the aim of synthesizing a suitable derivative of (1)



which, preserving the "cone conformation" of the parent matrix could make it water soluble, allowing to study the inclusion of neutral molecules in this solvent and to compare the results with that obtained in the solid state, we have prepared the tetracarboxylic acid (3) (Scheme 1).

The tetraester (2) has been obtained in 70% yield and its ^1H and ^{13}C NMR spectra show a very simple pattern. The former (Fig. 1.) shows singlets for all the t.butyl groups, for the $-\text{CH}_2\text{COOR}$ and aromatic protons whereas the bridging

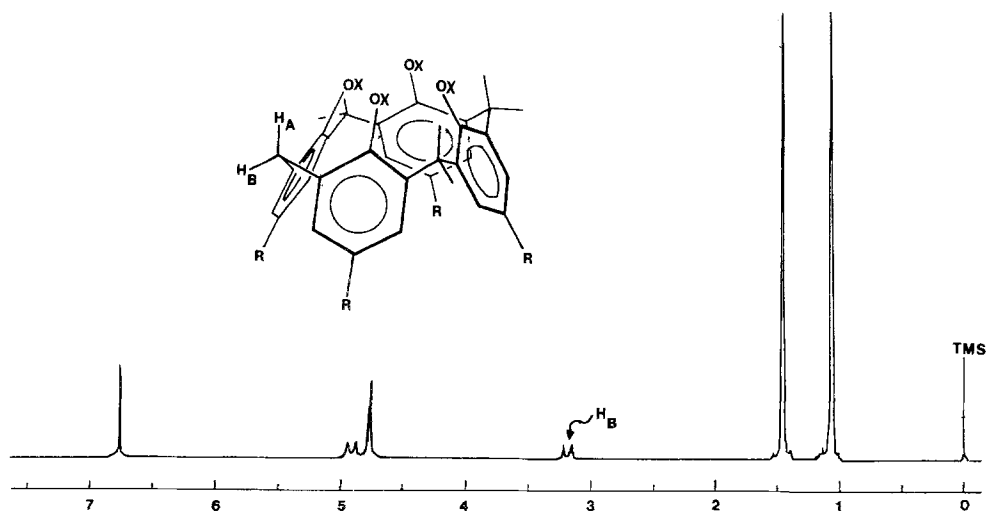


Fig. 1. ^1H NMR spectrum of p.t-butylcalix[4]arene tetraester (2) showing the "cone" conformation.

methylenes of the macrocycle gives two doublets typical of an AB system ($J_{AB} = 13 \text{ Hz}$). The high field doublet at $\delta 3.18$ has been assigned to the equatorial proton H_B on the basis of Nuclear Overhauser effect and pyridine-induced shift experiments on (2), (3) and other simple derivatives of the Calix[4]arene (1) whereas the low field signal at 4.89δ is due to the axial proton H_A .

The NMR data suggest a symmetrical "cone" structure in solution for compounds (2) and (3), which is obtained after simple hydrolysis from (2) and shows similar NMR data.

The attainment of the desired "cone" structure was not an obvious result to be expected since more often the functionalization of calix[4]arenes at the phenolic oxygen atoms leads to compounds with less symmetrical structures,^{1,6,8} although compounds in a cone conformation have been reported¹.

The X-ray crystal structure determination (Figure 2) confirms the cone structure for compound (2) although the hydrophobic cavity assumes in the solid state a less symmetrical shape compared with the solution, probably to minimize the repulsion between the four t.butyl groups of the ester moiety and to fill the space on the top of the macrocycle.

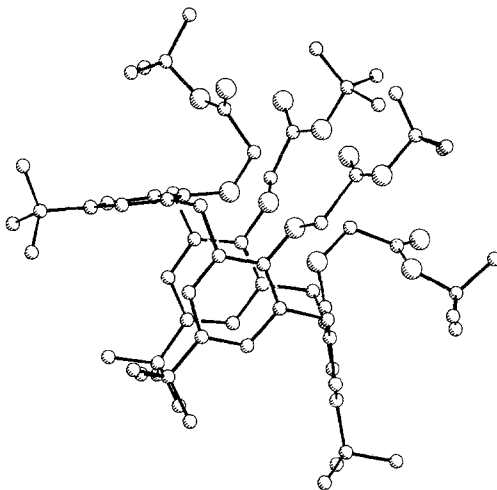


Fig. 2. X-ray structure of the tetraester (2). Perspective view.

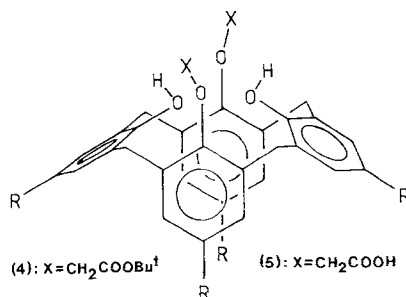
The four carboxylic groups of the tetraacid (3) can be easily neutralized by the proper base in ethanol/water and therefore salts of several cations could be prepared without difficulties. They show in water at 20°C a solubility (mmol/l) of 5.0 for lithium, 2.2 for ammonium, 2.0 for cesium and potassium, 0.5 for sodium and 0.2 for barium cations.

The lithium salt is the most soluble and has been chosen for binding studies. Its ^1H NMR spectrum in D_2O is rather sharp even at a concentration very close to saturation

indicating that no micellar aggregate is formed in these conditions. However no evidence has been reached so far that benzene, toluene, p-xylene and other aromatic molecules which were easily included in the solid state by the p-t-butylcalix[4]arene (1) are complexed by the lithium salt of the tetraacid (3) in D_2O .

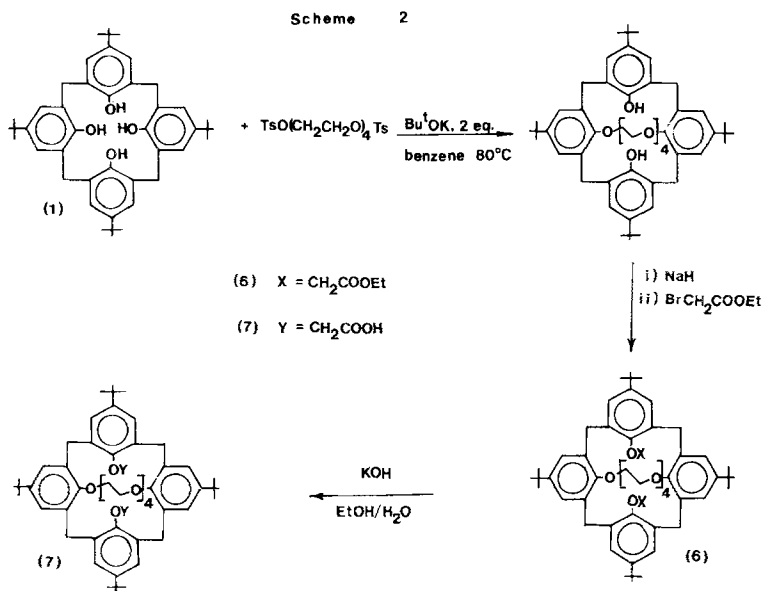
3.2. p-t-Butylcalix[4]arene -Diacetic Acid (5)

This compound has been obtained in 40% overall yield by treating compound (1) with t.butyl bromoacetate and t.BuOK in benzene and hydrolysing the ester (4). It shows (1H and ^{13}C NMR) a "flattened cone" structure (Cf sec. 3.3 and Fig. 3.).



3.3 p,t-Butylcalix[4]arene - Crown-5-Diacetic Acid (7) and its 1:1 Calcium complex.

This compound has been obtained in 20% overall yield through the sequence of reactions depicted in Scheme 2.



The 1H NMR spectrum of (7) (Fig. 3) indicates a "flattened cone structure" for this new macrobicyclic compound^{9,13}. The two carboxylic groups are located on the opposite sides of the polyetheral ring in a position

suitable to interact and neutralize the charge of a divalent cation included in the polyetheral ring. Treatment of the crown (7) with a suspension of CaCO_3 in methanol gives, after evaporation of the solvent, a 1:1 complex between (7) and calcium ion.

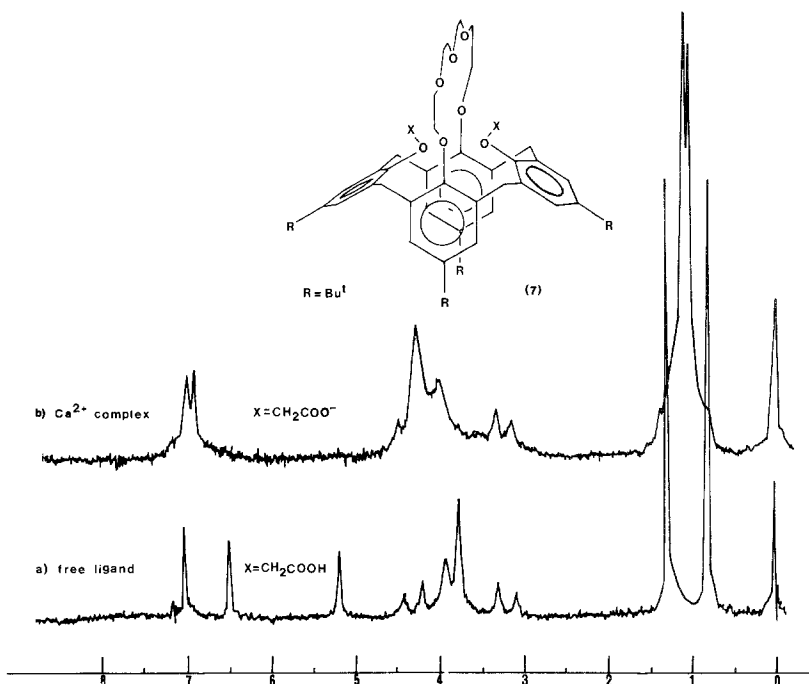


Fig. 3. ^1H NMR spectrum (60 MHz, CDCl_3) of a) crown-5-diacid (7) and b) its 1:1 complex with Ca^{2+} .

The ^1H NMR spectrum of this complex gives evidence for the inclusion of the calcium cation inside the polyetheral cavity even at 60 MHz (Fig. 3). In particular the low field shift experienced by all the etheral protons indicates a strong interaction of the oxygens with the cation. Other signals of the complexed host experience large shifts compared with the free ligand, and in particular that of the two methylenes linked to the carboxylic groups which go upon complexation ca. 1 ppm upfield.

The fact that the two signals observed in the free ligand for the t-butyl groups and the aromatic protons (Fig. 3a) approach each other in the calcium complex (Fig. 3b) indicates that the conformation of the calixarene macrocycle is less flattened in the complex and tends to become closer to the "cone" structure shown by the tetracid (1).

3.4 Extraction of divalent metal cations.

A great deal of effort has been devoted in the last few years to synthesize new ligands bearing ionizable groups capable to interact with cations forming a neutral ion-pair, which eventually can be extracted into organic media^{14,15}. This will result in a great improvement of their ability to extract cations and transport them through bulk liquid membranes, since the counter anion does not need to follow the cation into the organic phase passively. It is well known the strong anion effect on cation extraction and transport phenomena¹⁶.

In this context the ligands synthesized (3,5,7) were rather attractive as new acidic complexones for the extraction of divalent cations because of the carboxylic groups present on their lipophilic backbones. In particular for the crown ether (7) a double control of selectivity in complex formation could be expected, one deriving from charge interaction between the two carboxylate groups and cations and the second from the cavity size.

The results of simple extraction experiments by the three new ligands synthesized are reported in Table I. For comparison the data obtained with the parent macrocycle (1) and the acyclic p.t-butyl-phenoxyacetic acid, both of which are unable to extract in organic media most of the cation tested, are also shown.

Table I. Extraction ($\text{H}_2\text{O} \rightleftharpoons \text{CH}_2\text{Cl}_2$) of divalent Metal Acetates.

Acid Ligand	Fraction of Cation Extracted(%)					
	Mg ²⁺	Ca ²⁺	Sr ²⁺	Ba ²⁺	UO ₂ ²⁺	Pb ²⁺
Calix 4 arene (1)	←----- no extraction -----→					
p.t-Butylphenoxyacetic	0	0	10	0	6	10
Tetraacid (3)	5	81	79	63	83	98
Diacid (5)	10	61	42	32	69	95
Crown-5-Diacid (7)	0	83	33	37	16	87

$[\text{Mac}_2]_{\text{H}_2\text{O}} = 5 \times 10^{-4} \text{ M}$; $[\text{Ligand}]_{\text{CH}_2\text{Cl}_2} = 10^{-3} \text{ M}$ for all compounds except (3) ($5 \times 10^{-4} \text{ M}$).

The results show that the three ligands (3,5,7) are quite effective in extracting divalent cations (except magnesium) from water to methylene chloride. The most effective seems to be the tetraacid (3) which extracts lead almost

quantitatively and uranyl and alkaline earth cations to a large extent, even at $[ligand]/[cation]=1$. However ligands (3) and (5) do not appear to be very selective and a much better selectivity towards lead and calcium is obtained with the crown ether (7). As observed with other carboxylic acid ligands the selectivity in cation extraction and transport can be remarkably effected by "external factors", such as pH of the source phase, presence of suitable additives both in the aqueous and organic phases and by performing competitive instead of single ion experiments. We are currently investigating all these effects to find conditions for a better selectivity and to clarify the nature of the extracting species.

References

1. C.D. Gutsche, Acc. Chem. Res. **16**, 161 (1983).
2. G.D. Andreetti, R. Ungaro and A. Pochini, J. Chem. Soc. Chem. Commun. 1005 (1979).
3. R. Ungaro, A. Pochini, G.D. Andreetti and P. Domiano, J. Chem. Soc. Perkin Trans 2, 000 (1984).
4. G. Happel, B. Mathiasch, H. Kämmerer, Makromol. Chem., **176** 3317 (1975).
5. G.D. Andreetti, R. Ungaro, and A. Pochini, J. Chem. Soc. Chem. Commun. 533 (1981).
6. C. Rizzoli, G.D. Andreetti, R. Ungaro and A. Pochini, J. Mol. Struct. **82**, 133 (1982).
7. M. Coruzzi, G.D. Andreetti, V. Bocchi and R. Ungaro, J. Chem. Soc. Perkin Trans 2 1133 (1982); G.D. Andreetti, A. Pochini and R. Ungaro, J. Chem. Soc. Perkin Trans 2 1773 (1983); R. Ungaro, A. Pochini, G.D. Andreetti and V. Sangermano, J. Chem. Soc. Perkin Trans 2 0000 (1984).
8. V. Bocchi, D. Foina, A. Pochini, R. Ungaro, Tetrahedron **38**, 373 (1982); R. Ungaro, A. Pochini, G.D. Andreetti and P. Domiano, J. Inclusion Phenomena **2**, 000 (1984).
9. C. Alfieri, E. Dradi, A. Pochini and G.D. Andreetti, J. Chem. Soc. Chem. Commun. 1075 (1983).
10. R.M. Izatt, J.D. Lamb, R.T. Hawkins, P.R. Brown, J.J. Christensen, J. Am. Chem. Soc., **105**, 1782 (1983).
11. Preliminary report: A. Arduini, A. Pochini, S. Reverberi and R. Ungaro, J. Chem. Soc. Chem. Commun. 981 (1984).
12. E. Dradi, A. Pochini and R. Ungaro unpublished results.
13. C.D. Gutsche, B. Dhawan, J.A. Levine, K.H. No, L.J. Bauer, Tetrahedron **39**, 409 (1983).
14. R.A. Bartsch et al., J. Org. Chem. **48**, 4864 (1983).
15. K. Hiratani et al., Bull. Chem. Soc. Jpn., **57**, 1976 (1984).
16. Y. Takeda in Host-Guest Complex Chemistry, F. Vögtle, E. Weber Ed., Springer-Verlag Berlin 1984, p. 1.