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Water-soluble calixarenes as synthetic receptors. Remarkable influence of stereochemistry on the coordination properties of two new conformational isomers of a calix[4]arene tetracarboxylate[1]

Giuseppe Arena[a]; Raffaele P. Bonomo[a]; Rosario Calì[a]; Fabio G. Gulino[b]; Gaetano G. Lombardo[a]; Domenico Sciotto[a]; Rocco Ungaro[c]; Alessandro Casnati[c]
[a] Dipartimento di Scienze Chimiche, Università di Catania, Catania, Italy [b] Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico, CNR, Catania, Italy [c] Dipartimento di Chimica Organica ed Industriale, Università di Parma, Parma, Italy

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Water-soluble calixarenes as synthetic receptors. Remarkable influence of stereochemistry on the coordination properties of two new conformational isomers of a calix[4]arene tetracarboxylate[1]

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[a]Dipartimento di Scienze Chimiche, Università di Catania, Viale A. Doria 8, 95125 Catania, Italy, [b]Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico, CNR, Viale A. Doria 8, 95125 Catania, Italy and [c]Dipartimento di Chimica Organica ed Industriale, Università di Parma, Viale delle Scienze, Parma, Italy

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Two new water-soluble calix[4]arene tetracarboxylic acids in the *cone* and *partial cone* blocked conformations were synthesized. Conformational assignment was made on the basis of their Ar-CH_2-Ar ^1H and ^{13}C NMR patterns. Their proton and Cu(II) coordination properties were studied by several techniques to evaluate the role played by the different stereochemistry of the two isomers. The combination of potentiometric, calorimetric and spectroscopic (NMR, ESR and UV-visible) results gives a detailed and coherent description of the complex formation processes. The NMR analysis of the *partial-cone* isomer highlights the role played by solvophobic forces on the degree of inclusion of the carboxylic group inside the apolar calixarene cavity. The results show that the protonation of the *cone* isomer significantly differs from that of the *partial cone* isomer, indicating that hydrogen bonding, involving oxygen atoms of two adjacent carboxylate groups, occurs only in the *cone* isomer. Also the complex formation with copper(II) is strongly affected by the different conformations of the two calixarenes which produce not only species with different stabilities but also different species.

INTRODUCTION

Chemically modified calixarenes[2] have attracted the attention of a number of researchers in the last few years. Unmodified calixarenes, which are phenol-formaldehyde cyclic oligomers, are practically insoluble in water. This is a rather crucial limitation which is not encountered, for instance, in cyclodextrins, another class of cavity-shaped host molecules that has been extensively used to partly mimic the action of enzymes.[3] The attachment of polar groups to calixarenes has circumvented this limitation. It has also been stressed that water solubility renders it possible an accurate pK_a determination of calixarenes.[4] These observations have led researchers to synthesize water-soluble calixarenes, by functionalyzing them both at the upper rim (aromatic nuclei) and at the lower rim (phenolic OH groups).[5-15]

Shinkai *et al.* have also succeded in the regioselective cleavage of ribonucleoside 2',3'-cyclic phosphates by using water-soluble calix[4]arenes.[16] The same Author has proposed water-soluble calix[4]arene-5,11,17,23-tetrasulfonate as an analytical reagent for cerium(III) ions.[17] Williams *et al.* have extracted fullerene-C_{60} from toluene into the aqueous phase, by using a water soluble calix[8]arene.[15]

Since the knowledge of the acid-base characteristics of calixarenes is crucial for the design of more sophisticated calixarene-based receptors, some time ago we started a systematic study of the proton complex formation of

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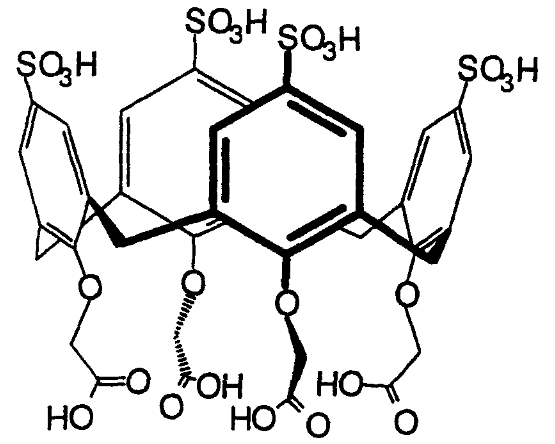
*To whom correspondence should be addressed.



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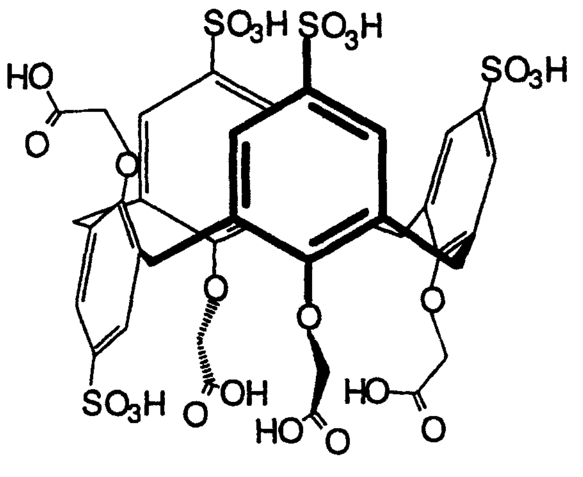

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Figure 1 1: *Cone* Conformation; 2: *Partial Cone* Conformation

water-soluble calix[4]arenes.[9] Previously we demonstrated that in calix[4]arene-*p*-tetrasulfonate (i) only two protons dissociate up to pH 11 and (ii) that the stabilization of the pentaanion in the *cone* conformation and, consequently, the remarkable acidity of the first ionizable OH group is due to the presence of strong adjacent hydrogen bonds.[9] A recent re-investigation of this system by Shinkai *et al.*[18] has confirmed our results. We herein report the results of our investigation on two conformationally blocked isomers *1* and *2* in which the basic skeleton of the calix[4]arene-*p*-tetrasulfonate was chemically modified by attaching four carboxylic groups to the phenolic OH functionalities (see Figure 1).

The formation constants were determined potentiometrically in aqueous solution at I=0.1 mol dm^{-3} ($NaNO_3$). Following the methodology, successfully used for calix[4]arene-*p*-tetrasulfonate, we also dissected the ΔG° values into the compounding ΔH° and ΔS° values to have additional information about the factors governing the protonation process. The combination of thermodynamic and NMR results gives a detailed description of the protonation process. The *cone* and *partial cone* isomers were synthesized and studied in order to evaluate the role played by their different stereochemistry not only in the acidity but also in the complexing properties of the two ligands. To this end the copper(II) complex formation with both isomers was investigated potentiometrically under the same experimental conditions used for the determination of the protonation constant values. EPR measurements were carried out on both systems to know how the donor atoms are involved in the coordination to copper(II).

RESULTS AND DISCUSSION

The ^{1}H NMR spectrum of the *cone* isomer (Figure 2) indicates that the Ar-CH_2-Ar methylenes show a single

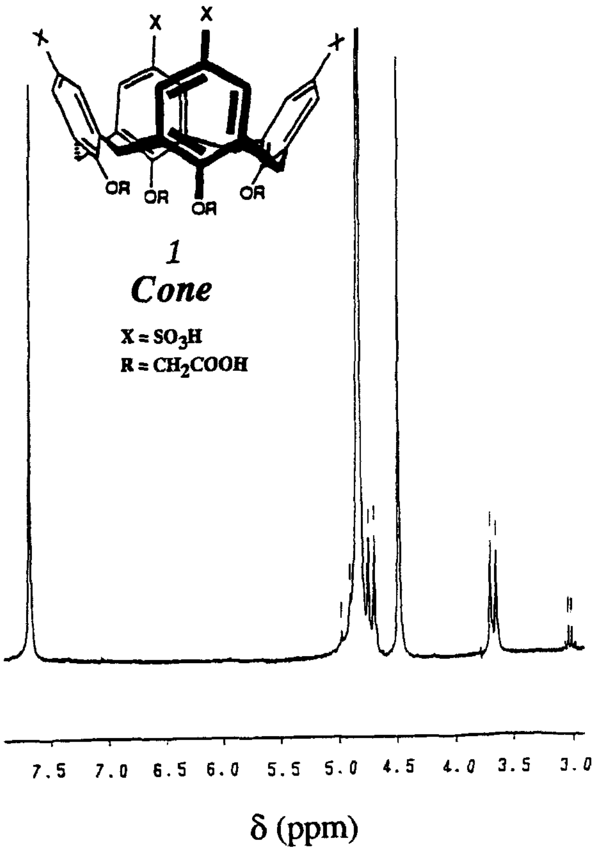


Figure 2 250 MHz ^{1}H NMR spectrum of the *cone* isomer in D_2O.

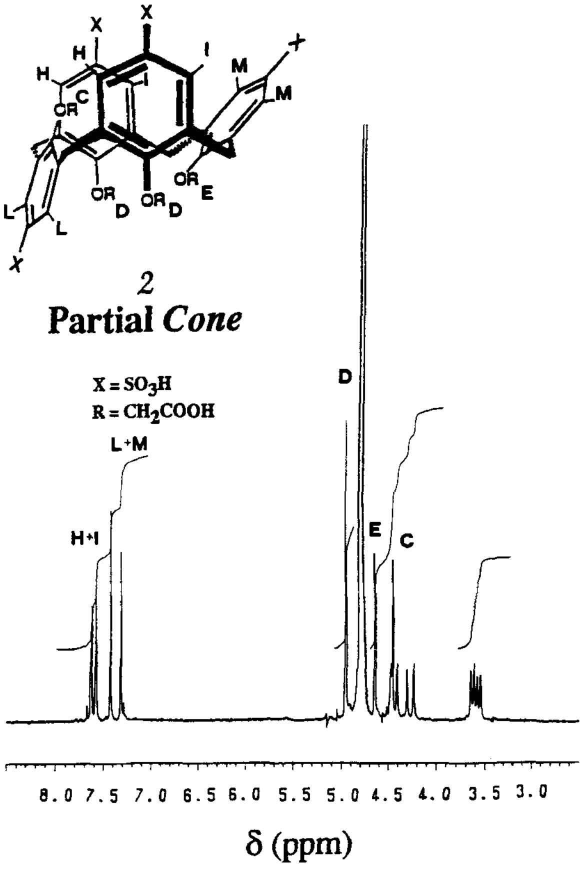


Figure 3 250 MHz ^{1}H NMR spectrum of the *partial cone* isomer at pH=6.

AX system, which is distinctive of a blocked *cone* conformation.[2] Only one signal is detected for the O-CH_2-protons as well as for the aromatic protons, owing to the symmetry of the molecule.

The ^{1}H NMR spectrum of product *2* (Figure 3) shows that the Ar-CH_2-Ar methylene pattern consists of two different AX systems, which could suggest a *partial cone* structure.[2]

However, the appearance of these signals is rather unique and has not been observed previously in calix[4]arene derivatives in the *partial cone* structure.[2] The chemical shifts of the axial protons of the two methylenes which link the *anti* oriented aromatic nuclei are very different from that of the corresponding equatorial ones, thus giving an AX system, whereas usually they appear as a singlet or give two very close doublets (AB system).[2,19] This can be explained by assuming a more rigid structure for compound *2* in aqueous solution (Figure 4), with methylene group C held inside the aromatic cavity (*self*-inclusion) and the corresponding aromatic nucleus almost parallel to the ideal plane of the bridging methylenes.

The molecular structure is also confirmed by the presence of three different signals for the O-CH_2-methylenes which have been assigned as shown in the picture. Methylene C, in fact, is shielded by the cavity, thus resonating at higher fields than methylenes D and E. The aromatic protons give rise to a pattern of four signals (ratio 1:1:1:1), namely a pair of doublets (J_{meta}=2 Hz) and a pair of singlets. This allows us to assign these signals as shown in Figure 3. The presence in the ^{13}C NMR spectrum of two signals at δ 33.4 and 34.4 for the bridging methylenes also agrees with a *partial cone* structure.[20]

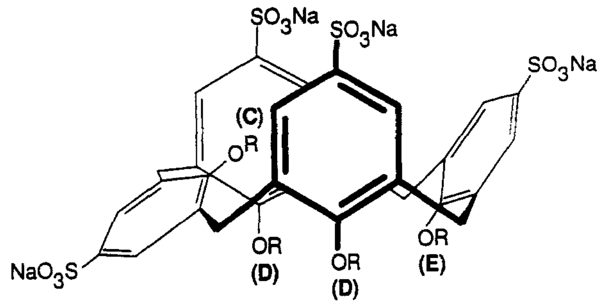
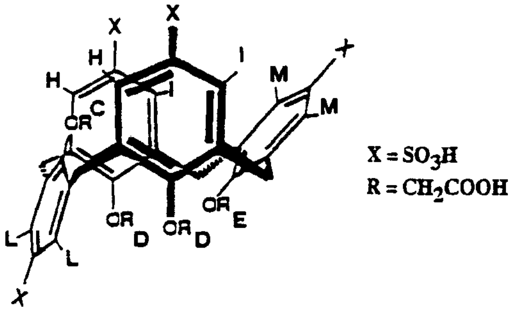


Figure 4 Schematic representation of the *partial cone* structure in aqueous solution.

We also carried out a series of ^{1}H NMR measurements for both ligands as a function of the pH, covering the pH range where the four carboxylates protonate. Whereas the spectra of the *cone* isomer remain virtually unchanged in going from pH 6 to pH 2, the spectra of the *partial cone* isomer show interesting features which deserve some comments. The chemical shifts (δ) observed for the *partial cone* isomer as a function of the pH are reported in Table 1. Going from pH 6 to pH 2 methylene C undergoes the most significant change (Δδ=0.28), whilst methylenes D and E show no significant variations. This suggests that as the protonation degree increases, methylene C is increasingly influenced by the shielding effect of the cavity. Clearly, the more hydrophobic carboxyl group accomodates into the cavity more easily than the unprotonated carboxylate anion. Unfortunately, no indication of the protonation order of the four carboxylates can be given at the present, since i) the four carboxylates protonate within 2.4 pH units and ii) the overall shift (Δδ=0.28) of methylene C occurs within a relatively large pH range, therefore not allowing any correlation of the observed shift with a given pK.

The thermodynamic parameters for ligands *1* and *2* are reported in Table 2. Enthalpy values were obtained by direct calorimetry. Incidentally, it has to be mentioned that the purity, determined by means of potentiometric experiments agreed well with the water content determined by thermogravimetric analysis. Table 2 indicates that for both ligands deprotonation is practically complete around pH 6. However, whereas for the *cone* isomer the protonation constants are grouped roughly within 1.5 pH units, for the *partial cone* derivative the proto-

Table 1 ^1H NMR chemical shifts (δ) of the *partial cone* isomer as a function of pH



Protons	pH=6	pH=5	pH=4	pH=3.5	pH=3	pH=2	pH=1
C	4.47	4.46	4.38	4.30	4.24	4.20	4.19
E	4.65	4.65	4.61	4.60	4.60	4.60	4.61
D	4.95	4.95	5.04	5.04	5.05	5.04	5.04
H+I	7.62	7.63	7.61	7.62	7.62	7.61	7.61
	7.57	7.58	7.61	7.61	7.62	7.61	7.61
A	3.58	3.58	3.74	3.75	3.78	3.79	3.79
X	4.27	4.27	4.23	4.20	4.17	4.17	4.17
A'	3.60	3.61	3.78	3.80	3.82	3.82	3.82
X'	4.45	4.44	4.31	4.30	4.27	4.26	4.25
L+M	7.31	7.31	7.48	7.49	7.49	7.48	7.48
	7.42	7.42	7.56	7.56	7.57	7.57	7.56

nation constants cover 2.4 pH units, indicating that the different stereochemistry does play a role on the acid-base properties of the two ligands.

As to the *cone* derivative, the first two carboxylate groups protonate at pH values which are significantly higher than those of the last two carboxylates. Interestingly, the log Ks of the last two steps closely resemble the log K for the protonation of phenoxyacetate (3.16).[21] The enthalpic and entropic contributions can help in understanding the reasons for such a difference. Usually for the formation of a complex between an acetate (*hard* donor) and a proton (*hard* acceptor), strong bonds between these and the water molecules of their hydration shells have first to be broken. This takes much energy which is not completely regained by the formation of the O-H bond. The net reaction tends to be endothermic. On the other hand, the resulting liberation of several water molecules from the hydration shells implies a large gain of entropy which in fact constitutes the driving force of the reaction between *hard* particles.[22] There is a sizable difference between the enthalpy values of the first two and last two protonation steps. Such a difference cannot be correlated to any remarkable conformational change, since, as already said, no such change is observed in the ^1H NMR over the entire protonation range. This leads us to think that each one of the first two protons interact with two adjacent carboxylate groups, thus determining an enthalpic contribution that is more favourable than one would expect for a "hard acid-hard base" interaction.[22] The entrance of the third as well as the fourth proton destroys such a hydrogen bonding, and this accounts for the unfavourable enthalpic contributions observed for both the last two steps. The entropic contribution of the last protonation step, which is sur-

Table 2 Thermodynamic parameters for the protonation of *cone* and *partial cone* isomers at 25°C and I=0.1 mol dm^{-3} ($NaNO_3$).

Reaction			*log K*	*ΔG^0 kcal mol^{-1}*	*ΔH^0 kcal mol^{-1}*	*ΔS^0 cal mol^{-1} deg^{-1}*
			cone			
L^{4-}	$+ H^+$	$= HL^{3-}$	4.57[a]	-6.23	-0.5(1)	19.1(3)
HL^{3-}	$+ H^+$	$= H_2L^{2-}$	3.97[a]	-5.41	-1.1(1)	14.7(5)
H_2L^{2-}	$+ H^+$	$= H_3L^-$	3.27[a]	-4.46	0.4(2)	16.3(5)
H_3L^-	$+ H^+$	$= H_4L$	3.03[a]	-4.13	3.0(2)	24.0(5)
			partial cone			
L^{4-}	$+ H^+$	$= HL^{3-}$	5.11(1)	-6.97	2.0(1)	30.2(4)
HL^{3-}	$+ H^+$	$= H_2L^{2-}$	4.61(1)	-6.23	0.9(1)	24.2(4)
H_2L^{2-}	$+ H^+$	$= H_3L^-$	3.35(1)	-4.57	1.1(2)	19.2(5)
H_3L^-	$+ H^+$	$= H_4L$	2.71(1)	-3.70	-0.4(2)	11.0(6)

a Data from ref. 9
σ in parentheses

Table 3 Copper(II) formation constants of *cone* and *partial cone* isomers at 25°C and I = 0.1 mol dm^{-3} ($NaNO_3$).

Reaction					Log β
				cone	
Cu^{2+}	+	L^{4-}	+ $2H^+$	= $[CuLH_2]$	11.27(5)
Cu^{2+}	+	L^{4-}	+ H^+	= $[CuLH]^-$	8.45(2)
Cu^{2+}	+	L^{4-}		= $[CuL]^{2-}$	4.63(3)
				partial cone	
Cu^{2+}	+	L^{4-}	+ $2H^+$	= $[CuLH_2]$	12.01(3)
Cu^{2+}	+	L^{4-}	+ H^+	= $[CuLH]^-$	7.87(2)
Cu^{2+}	+	L^{4-}		= $[CuL]^{2-}$	3.25(2)
Cu^{2+}	+	L^{4-}	+ H_2O	= $[CuL(OH)]^{3-}$+ H^+	-2.61(3)

σ in parentheses

prisingly large (more positive) for a ligand that is already largely desolvated, indicates that the carboxylic groups are no longer held together by the formation of hydrogen bonds.

The thermodynamic parameters concerning the protonation of the *partial cone* isomer are significantly different from those of the *cone* conformer. The trend of the enthalpic and entropic contributions is what one would predict for a classical "hard acid-hard base" interaction. In fact, the first protonation step is accompanied by a large desolvation which results in the large entropic contribution and unfavourable enthalpic value, due to the breaking of ion-water molecules bonds. This also applies to the following protonation steps; the protonation of a molecule, which is progressively less solvated, results in less unfavourable enthalpic contributions and less favourable entropic contributions. In opposition to the *cone* isomer, there seem to be no intramolecular hydrogen bonds in the less symmetrical and presumably more distorted *partial cone* isomer.

Copper(II) complex formation. For both ligands we have also studied complex formation with copper(II). We restricted our study to the pH range 2.5-7.5, essentially for two reasons: i) we are interested in enzyme mimicking systems, and therefore, going to higher pHs would not be of any practical advantage; ii) the description of the system, above pH 7.5 is complicated by the simultaneous presence of hydrolitic and binuclear species and iii) very often (99% of cases, depending on the metal/ligand ratio) a precipitate forms around this pH.

The complex formation constants, obtained potentiometrically, are reported in Table 3. This table shows that, up to a given pH, both systems are best described by the same set of species, i.e. a bis-protonated, mono-protonated and 1:1 species. However, two points deserve some comment. First of all, the complexes detected for the *partial cone* isomer are in general weaker than those of the *cone* derivative. In addition, whilst the 1:1 species prevails for the *cone* isomer, a competing hydroxo species is detected for the *partial cone* in the same pH region (Figure 5a and 5b).

Clearly, as mentioned for the protonation, the different stereochemistry does play a role in complex formation.

In order to have a better picture of the copper(II) species which form in solution, we carried out optical visible and EPR measurements on both systems. Frozen

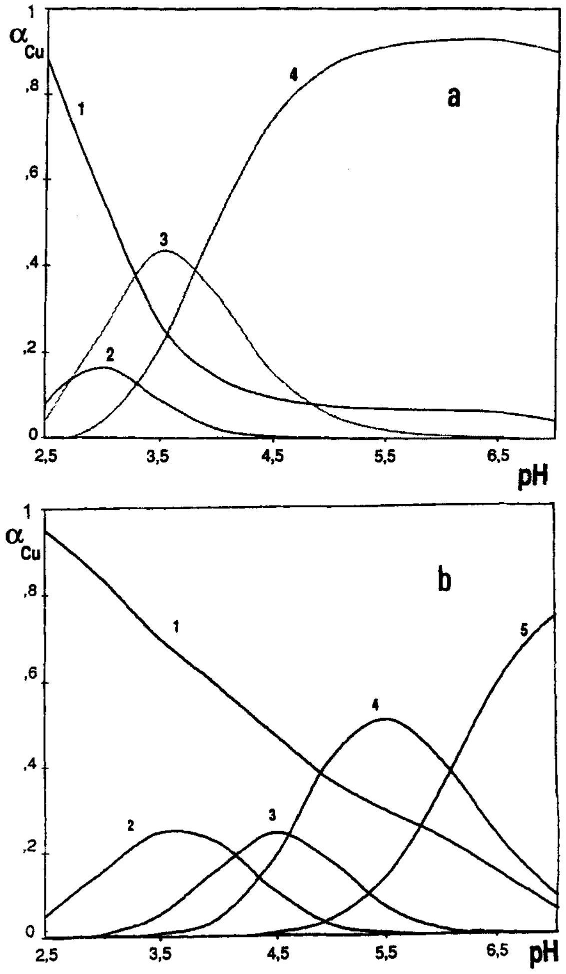


Figure 5 Distribution diagrams for the Cu(II)-*cone* (a) and *partial cone* (b) systems; (a) 1 = Free metal ion, 2 = $[CuLH_2]$, 3 = [CuLH], 4 = [CuL]; (b) 1 = Free metal ion, 2 = $[CuLH_2]$, 3 = [CuLH], 4 = [CuL], 5 = [CuLOH], [Cu] = [L] = 5.10^{-3} mol dm^{-3}. Charges are omitted for simplicity.

Table 4 Spin Hamiltonian and U.V.-Vis Parameters for the Cu (II)-*Cone* Isomer System

Species	*pH*	$g_{\parallel}$	$A_{\parallel}$	$g_{\perp}$		$A_{\perp}$		λ, ε
$[Cu(H_2O)6]^{2+}$	3.0	2.427	130	2.088				833, 11[23]
$[CuLH_2]$	3.5–3.9	2.387(2)	145(3)	2.076(2)				784, 25
		g_1	A_1	g_2	g_3	A_2	A_3	
$[CuL]^{2-}$	6.9	2.358(1)	150(1)	2.172(1)	2.065(1)	28(1)	7(1)	758, 35

Estimated errors in parentheses

Units for A: 10^4 cm^{-1}
Units for λ: nm
Units for ε:dm^3 mol^{-1} cm^{-1}

solution EPR spectra can give information on the number of donor atoms involved in coordination to copper(II) as well as on the geometrical features of the complexes. Table 4 shows the spin hamiltonian parameters, λ_{max} and ε_{max} values for the Cu(II)-*cone* system, obtained at various pHs. As shown in this table, the assignment of the spin hamiltonian parameters to each species formed in the pH range 4-5.5 turned out to be impossible whereas it was possible to determine the magnetic parameters below pH 4 and above pH 5.5. This is very likely to be ascribed to the simultaneous presence of equally important species, having a relatively high degree of formation, as also indicated by the distribution diagram (Fig. 5a). The spin hamiltonian parameters calculated below pH 3.5 almost exclusively indicate the presence of free copper(II), whereas those obtained for the species forming at pH 3.5 indicate that copper(II) is in a $d_{x^2-y^2}$ ground state and the complex has the characteristics of a typical axially elongated octahedron formed by oxygen donors. The shifts of the magnetic parameters, compared to those associated with the hexaquo ion, indicate that copper(II) probably coordinates two of the four carboxylate oxygens. The magnetic parameters are not sizably different from those found for the copper(II) complexes with substituted malonates, for which two oxygen atoms have been shown to be involved in the coordination to copper(II).[24] In the neutral region, in which, as indicated by the *emf* measurements, all four carboxylic oxygens are deprotonated, a new species forms and its EPR spectrum shows remarkable rhombicity. The spin hamiltonian parameters were obtained through a careful simulation (Figure 6) of the EPR spectrum. The presence of a rhombic component in the EPR spectrum could be an indication of a copper (II) complex polyhedron, having a strong tetrahedral distortion.

Indeed in the presence of four carboxylate oxygens, only a tetrahedral distortion reasonably justifies the appearance of a rhombic component in the EPR spectrum. In fact, if for such a complex we were dealing with either a regular square-planar or octahedral geometry i) such a rhombic distortion would not be detected and ii) the decrease of $g_{\parallel}$ and the increase of $A_{\parallel}$ values would be larger than those found, since the coordination of two carboxylate oxygens causes the negative charge on the coordination site to increase.[25-27] The spectrophotometric data support the presence of a tetrahedrally distorted copper(II) complex. In fact, the maximum of the visible band shifts to higher frequencies, as expected for a

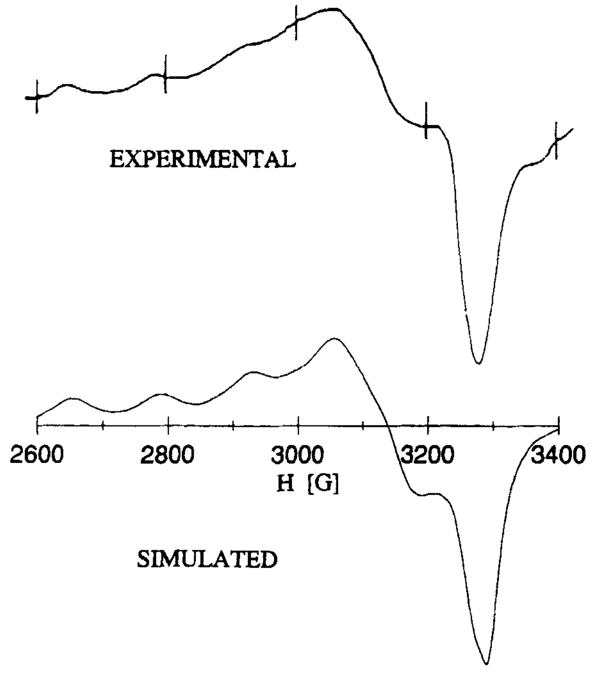


Figure 6 Experimental and simulated EPR spectrum for the Cu(II)-*cone* system at pH=6.9.

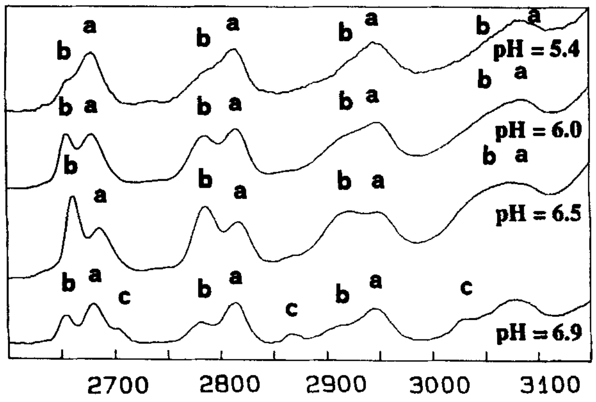


Figure 7 pH dependence of the EPR spectra (parallel part) of the Cu(II)-*partial cone* system.

Table 5 Spin Hamiltonian Parameters for the Cu (II)-*Partial Cone* Isomer System

Species	*a*		*b*		*c*	
pH	$g_{\parallel}$	$A_{\parallel}$*	$g_{\parallel}$	$A_{\parallel}$*	$g_{\parallel}$	$A_{\parallel}$
4.6	2.348	146				
5.4	2.348	146	2.372	144		
6.0	2.348	146	2.372	144		
6.5	2.348	146	2.372	144		
6.9	2.348	146	2.372	144	2.291	17g
Cu^{2+}	2.427	130				

* units for $A_{||}$: 10^4 cm^{-1}
errors in $g_{||} \approx 0.003$
" " in $A_{||} \approx 0.0002$ cm^{-1}

stronger complex, while the absorptivity increases, as predictable for a distorted complex.[28]

For the Cu(II)-*partial cone* system, the EPR investigation indicates that we are dealing with a picture that is rather different from that describing the Cu(II)-*cone* system, as also indicated by the potentiometric results (Figure 5 b). At pH 4.6 the EPR spectrum reveals the presence of a single species, whilst two more species appear in the pH range 5.4-6.9. The frozen solution EPR spectra at different pHs are shown in Figure 7; the parallel magnetic parameters extracted from these experiments are listed in Table 5. The spin hamiltonian parameters suggest that two carboxylate oxygens are coordinated to copper(II) at pH 4.6, as also found for the *cone* isomer. As we raise the pH a second species appears accompanied by an increase in $g_{\parallel}$ and a slight decrease in $A_{\parallel}$ values. Very likely a tetrahedral distortion occurs[29] and this is due to copper(II) having to accomodate three carboxylate oxygens, the fourth position being occupied by a water molecule. In line with the potentiometric results, as the pH is raised, a third species appears whereas the two species discussed above become progressively less important. This species, which becomes significant at pH 6.9, is characterized by significantly low $g_{\parallel}$ and great $A_{\parallel}$ values, respectively, thus indicating that we are in the presence of a copper(II) complex having a quite regular geometry. In addition, the $A_{\parallel}$ value, remarkably high for a copper(II) complex with oxygen donor atoms, is indicative of the coordination of a negatively charged group. Interestingly, this species forms at the expense of the species formed in the pH region below 6.5. This suggests that a carboxylate oxygen is forced to leave the coordination sphere, thus permitting the in-plane coordination of a hydroxo group. Consequently, the strain imposed by the simultaneous coordination of the three carboxylate oxygens is released and a stronger equatorial plane is experienced by copper(II). The existence of this hydroxo species has also been proved by means of *emf* measurements. The optical visible spectra support the EPR results. In fact, at pH 3.5 we have a λ_{max} and an ε_{max} value of 786 nm and 29, respectively, which are typical of octahedral complexes with oxygen donor atoms. λ_{max} and an ε_{max}, obtained at pH 6.5 (753 nm and 181, respectively) can be attributed to a copper(II) complex in a tetrahedral environment.[28]

EXPERIMENTAL SECTION

General methods. NMR spectra were obtained in D_2O at 25°C with a Bruker AC-250 spectrometer. Chemical shifts (δ, ppm) were externally referenced to sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) in order to avoid any possible interaction with the calix[4]arene derivatives. Coupling constants (J) are reported in hertz (Hz). Infrared spectra were performed on a Perkin-Elmer 684 IR spectrophotometer. The thermogravimetric analysis was performed on a Mettler TA 3000 (Sensitivity = 2.5×10^{-6} g).

EPR spectroscopic measurements were carried out on a Bruker ER 200 D spectrometer driven by the ESP 3220 data system and equipped with a standard low temperature apparatus. Frozen solution spectra were run at 150 K after the addition of about 5% methanol to increase resolution. Parallel spin hamiltonian parameters ($g_{\parallel}$ and $A_{\parallel}$) were calculated directly from enlarged scale experimental spectra, after the klystrom frequency was standardized by means of the DPPH radical (g = 2.0036). The magnetic field was monitored by a gauss meter Bruker ER 035.

Electronic spectra were carried out on a Hewlett-Packard 8452A diode-array spectrophotometer.

Materials. The synthesis of calix[4]arene-p-tetrasulfonate[30] and 5,11,17,23-tetrasulfonato-25,26,27,28-tetrakis(hydroxycarbonylmethoxy)calix[4]arene, *1*(*cone* conformation)[31] has been previously reported.

5,11,17,23tetrasulfonato25,26,27,28tetrakis(hydroxycarbonylmethoxy)calix[4]arene (sodium salt), *2* (*partial cone* conformation.). Calix[4]arene-*p*-tetrasulfonate (1.25 g, 1 mmol), NaOH (1.20 g, 30 mmol) and monobromoacetic acid (2.08 g, 15 mmol) in 15 mL of water were heated at 90°C for 72 hrs. Reaction progress was monitored by TLC. The reaction mixture was evaporated to dryness *in vacuo*. The white solid obtained was

Table 6 Experimental conditions of potentiometric measurements for the *partial cone* isomer at 25°C and I=0.1 mol dm^{-3} ($NaNO_3$)

C°_L/(mmol dm^{-3})	*Titrant (mol dm^{-3})*		*pH range*	*N°. of points*
7.0	NaOH	0.1017	2.4–6	65
5.8	NaOH	0.1017	2.4–6	57
5.9	NaOH	0.1017	2.4–6	55
6.1	NaOH	0.1017	2.4–6	60
5.6	NaOH	0.1012	2.4–6	59

Table 7 Experimental conditions of calorimetric measurements for compounds *1* and *2* at 25°C and I=0.1 mol dm^{-3} ($NaNO_3$)

C°_L/(mmol dm^{-3})	*Titrant*	*(mol dm^{-3})*	*pH range*	*N°. of points*
Cone				
4.2	HNO_3	0.1919	2.4–5.2	8
4.1	HNO_3	0.1919	2.4–5.2	9
4.1	HNO_3	0.1919	2.4–5.2	7
4.8	HNO_3	0.2011	2.4–5.2	8
3.6	HNO_3	0.2011	2.4–5.2	8
Partial cone				
4.4	HNO_3	0.0810	2.4–6	7
3.8	HNO_3	0.0810	2.4–6	7
3.8	HNO_3	0.0810	2.4–6	7
3.9	HNO_3	0.0810	2.4–6	7
3.7	HNO_3	0.0810	2.4–6	7

dissolved in 15 ml of 0.01 N aqueous NaOH solution and heated at 80°C for 8 hrs to decompose the polyester formed from monobromoacetic acid. The solution was evaporated to dryness *in vacuo* to give a white powder that was washed with hot methanol to remove NaBr. After washing with methanol, compound *2* was isolated from the reaction products by reverse phase column chromatography using water as eluent. Yield = 60%; m.p.>250°C. IR (KBr) 3700-3100(bs), 1610(s), 1200(s), 1050 cm^{-1}; ^{1}H NMR (D_2O) δ 3.58 (d, 2H, Ar-CH_2-Ar, H_{eq} J=13.8 Hz), 3.61 (d, 2H, Ar-CH_2-Ar, H'_{eq}, J=13.2 Hz), 4.26 (d, 2H, Ar-CH_2-Ar, H_{ax}), 4.43 (d, 2H, Ar-CH_2-Ar, H'_{ax}), 4.45 (s, 2H, OCH_2CO), 4.64 (s, 2H, OCH_2CO), 4.95 (s, 4H, OCH_2CO), 7.31 (s, 2H, ArH), 7,42 (s, 2H, ArH), 7.58 (d, 2H, ArH, J=2.0Hz), 7.63 (d, 2H, ArH, J=2.0 Hz); ^{13}C NMR (D_2O) δ 33.4 (t, Ar-CH_2-Ar), 34.4 (t, Ar-CH_2-Ar), 76.8 (t, $O\underline{C}H_2CO$), 128.8, 129.1, (d, Ar *meta*), 131.7, 131.9, 132.3, 135.4 (s, Ar *ortho*), 136.5, 136.7, 141.1 (s, Ar *para*), 157.3, 158.9, 159.1 (s, Ar *ipso*), 179.2, 179.4, (s, C=O). Atomic absorption spectroscopy (Na) and elemental analysis showed the product to be an octasodium salt. Thermogravimetric analysis showed that water loss is complete below 200 °C. The amount of water lost (approximately 16%) indicates that this compound crystallizes with 10 water molecules. The anhydrous compound undergoes decomposition above 250°C. Anal.[($C_{36}H_{24}Na_8O_{24}S_4$)$10H_2O$]C,H.

E.M.F. measurements. These measurements were carried out by means of homemade fully automatic apparatuses, which make use of Metrohm components (meter, E 654; dispenser, E 665; combined glass electrode, EA 125) and IBM or IBM compatible PCs. The experiments were always run simultaneously in two cells (2.5 mL) both to avoid systematic errors and check for reproducibility. Values of E°, E_j and slope of the electrode system were determined in separate experiments by titrating 2.5 mL of standard HNO_3 with CO_2-free standard NaOH. In all the experiments the ionic strength was maintained at 0.1 mol dm^{-3} ($NaNO_3$) by adding the appropriate amount of sodium nitrate. Experimental details are given in Table 6.

Calorimetric measurements. The calorimetric experiments were performed at 25±0.0002 °C using a LKB TAM equipped with a 2.5 mL stainless steel cell. As indicated in Table 7, the experiments were always performed by adjusting the pH of the ligand solution to the desired value and titrating with standard HNO_3. It was done so to minimize the formation of water, which would have "masked" the heat of protonation. The titration data (a total of 40 and 35 for the *cone* and *partial cone* isomer, respectively) were corrected for all non-chemical energy terms, determined in separate experiments, and refined simultaneously to obtain the final ΔH° values. Experimental details are given in Table 7.

Calculations. Two computer programs, namely ACBA[32] and SUPERQUAD[33], were used to handle the potentiometric data. By using these two programs, which refine the data by minimizing respectively the error square sum in added volumes and the error square sum in measured electrode potentials, the risk of fitting systematic errors is drastically reduced. E°, slope and E_j were calculated by using ACBA[32].

The protonation enthalpies were obtained by using the computer program DOEC[34].

A general computer programx[35] was used to treat the experimental EPR spectra to obtain the spin Hamiltonian parameters. Other experimental details are reported in references 9 and 36.

CONCLUSIONS

Two new blocked *cone* and *partial-cone* isomeric tetracarboxylated calix[4]arenes were obtained by two original routes. Both isomers were obtained by carefully choosing experimental conditions for the preparation and separation with a degree of purity desirable for potentiometric, calorimetric and spectroscopic measurements. The disposition of the carboxylic residue within the hydrophobic calixarene cavity, which changes with pH, suggests that its inclusion reaches a maximum when the carboxylic group is protonated.

The thermodynamic trend (ΔG°, ΔH° and ΔS°) of the protonation of both isomers strongly supports the presence of intramolecular hydrogen bonding in the *cone* isomer, whilst surprisingly, the *partial-cone* isomer, which does not exhibit the fourth carboxylate group on the same side, but pointing towards the cavity, does not show any hydrogen bonding.

The stabilities of the copper(II) ion species with the two isomers predictably differ because of the differing stereochemistries of the two ligands. Carboxylate oxygen donor atoms only give rise to weak copper(II) complexes. Moreover, the EPR frozen solution spectra indicate that different geometrical arrangements of the carboxylate oxygens around the copper(II) ion are encountered as the carboxylic groups are progressively deprotonated. The different stabilities of the complex species can be interpreted in terms of different complex structures. The peculiar tetrahedral arrangement of four carboxylate oxygens in the *cone* isomer, or of three carboxylate oxygens in the *partial-cone* isomer, are clear examples of the well known coordination "plasticity" of the copper(II) ion, which is accomodated in the preorganized structure of the tetracarboxylated calix[4]arene ligands. Interestingly, in the *partial-cone* isomer, one of the carboxylate oxygens leaves the coordination sphere to allow the coordination of a hydroxo group, thus leading to the formation of the less constrained and more symmetrical complex structure of the hydroxo species. Moreover, it is noteworthy that owing to the steric constraints present in these systems, only the coordination of the third carboxylate oxygen is enough to cause the copper(II) complex to assume a tetrahedral geometry as pointed out by the results of the EPR on the *partial-cone* isomer coordination.

We would like to stress that the combination of different techniques, in particular of the thermodynamic and spectroscopic techniques (NMR and EPR), gives a detailed picture of molecular phenomena as well as a better knowledge of the coordination features, namely stabilities and geometrical structures, and the inclusion properties of these systems.

We are currently continuing our investigation of these molecules in order to optimize the role played by different stereochemistries in their coordination properties and in the encapsulation of organic compounds inside the apolar cavity of the calixarene.

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