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Synthesis and Complexing Properties of a Double-Calix[4]arene Crown Ether

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Abstract. Treatment of *p-tert*-butylcalix[4]arene with tetraethyleneglycol ditosylate in the presence of potassium carbonate in acetonitrile afforded the first example of a double-calixcrown (**1**) in 52% yield. The double-calixcrown (**1**) was shown to form 1 : 1 complexes with potassium and rubidium picrates in the solid state and in solution in chloroform. The stability constants of the alkali complexes have been determined in acetonitrile, as well as the phase transfer parameters from water to dichloromethane.

Key words. Calix[4]arene, complexation of alkali cations, stability constants, biphasic transfer.

1. Introduction

One branch of supramolecular chemistry consists of the design and synthesis of chemical molecular systems able to recognize organic guest molecules and/or to selectively bind ionic species [1]. Since the first report of Gutsche on calixarenes and their possible application as enzyme mimics in host-guest chemistry, calixarenes have been used as ordered building blocks for the synthesis and design of selective complexing agents [2]. For example, the bridging of *p-tert*-butylcalix[4]arene with tetra- and pentaethylene glycol ditosylates leads to *calixcrowns* [3] which are preorganized ligands, selective towards potassium cations. Similarly, the bridging of *p-tert*-butylcalix[4]arene with a terphenyl unit lead to *calixspherands* [4], which are able to form kinetically stable complexes with sodium, potassium, and rubidium cations.

We report here our recent results on the isolation of the first *double-calixcrown* (**1**) which has been obtained from *p-tert*-butylcalix[4]arene which was chosen because of its facile preparation in high yields [5]. Complex formation of (**1**) and M^+Pic^- ($M^+ = K^+$ and Rb^+) is reported and discussed on the basis of ^{1}H-NMR spectra. The stability constants of (**1**) with alkali cations have been determined in acetonitrile. Extraction data from water to dichloromethane are also presented.

2. Experimental Section

2.1. MATERIALS FOR THE SYNTHETIC PART

p-tert-Butylcalix[4]arene was prepared according to reference [5]. The alkali picrates were prepared according to reference [6]. Tetraethylene glycol ditosylate,

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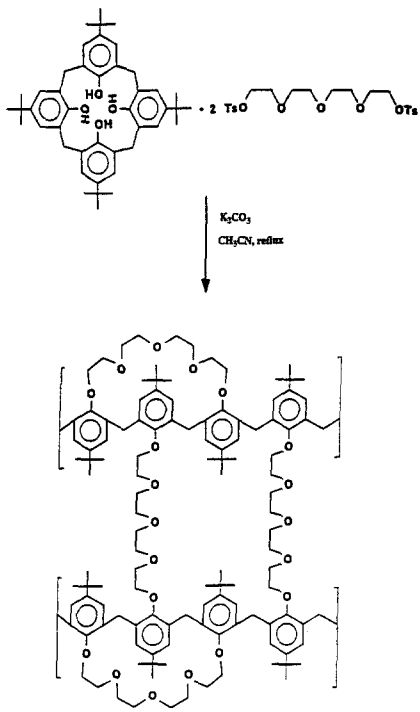
potassium carbonate, and the solvents were commercial reagents and used without further purification.

2.2. ANALYTICAL PROCEDURES

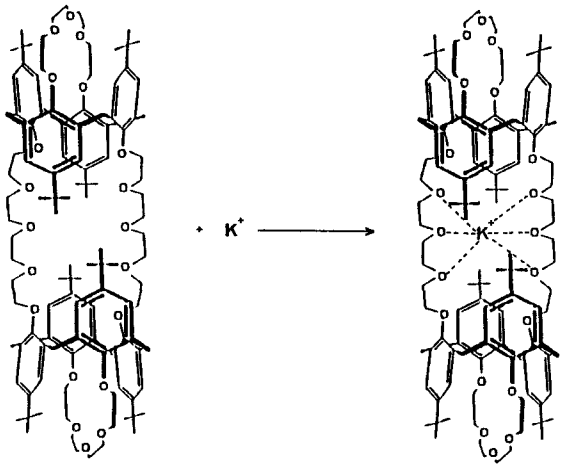
The melting points (mps) were taken on a Büchi 500 apparatus in capillaries sealed under nitrogen. TLC analyses were run on Kieselgel Merck 5515 plates. The eluent is specified in the experimental procedures. Elemental analyses were carried out at the Service de Microanalyse of the Institut de Chimie de Strasbourg. The ^{1}H-NMR spectra were recorded at 200 MHz on a Bruker SY 200 spectrometer. The mass spectra were obtained on a VG-Analytical ZAB HF apparatus.

2.3. PREPARATION OF DOUBLE-CALIXCROWN (1)

A suspension of *p-tert*-butylcalix[4]arene (2.60 g; 4 mmol), tetraethylene glycol ditosylate (2.01 g, 4 mmol), and potassium carbonate (7.44 g; 40 mmol) in 300 mL of dry acetonitrile was heated under reflux for 5 days. A new crop of tetraethylene glycol ditosylate (4.02 g; 8 mmol) and potassium carbonate (7.44 g; 40 mmol) was then added to the reaction mixture and the reflux was continued for 4 days. After filtration, the solvents were removed under reduced pressure (15 mmHg). The solid obtained was dissolved in 200 mL of dichloromethane and 200 mL of 1N HCl solution was added. The organic layer was separated and dried over sodium sulfate.



Scheme I. Synthesis of the double-calixcrown (**1**).



Scheme II. Complexation of K^+ ion by double-calixcrown (**1**).

After removing the solvents the crude reaction mixture was precipitated with methanol to give pure (**1**) as a white solid ($m = 1.55$ g; 52%. Mp 199–200°C; FAB mass spectrum $M^+ + Na$ ($m/z = 1953.2$), the sodium complex signal is probably observed due to the presence of sodium cation in the calibrating phase; ^{1}H-NMR (200 MHz) in $CDCl_3$ (7.27 ppm) in ppm from TMS: 7.03 (*s*, 16H, ArH), 3.89 (*s*, 16H, $ArCH_2Ar$), 3.64–3.60 (*m*, 16H), 3.45–3.37 (*m*, 32H), 2.95–2.87 (*m*, 16H) no assignment was given for the multiplets corresponding to the methylene protons of the glycolic chains, 1.39 (*s*, 72H, *p-tert*-butyl).

Anal. Calcd. for $C_{120}H_{168}O_{20}$: C, 74.05; H, 8.77. *Found* C, 73.92; H, 8.56.

2.4. PREPARATION OF THE COMPLEX (1) K^+·Pic$^-$

Ligand (**1**) (106 mg) was dissolved in 10 mL of dry chloroform and stirred for 24 h in the presence of an excess of solid potassium picrate. After filtration, the solvent was evaporated to give yellow microcrystals, $m = 126$ mg. Mp 83–85°C; FAB mass spectrum $M^+ + K$ ($m/z = 1969.0$); ^{1}H-NMR in $CDCl_3$ in ppm from TMS: 8.89 (*s*, 2H, picrate) 7.15 (*s*, 8H, ArH), 7.13 (*s*, 8H, ArH), 3.89 (*s*, 16H, $ArCH_2Ar$), 3.80–2.87 (*m*, 64H, OCH_2CH_2O), 1.40 (*s*, 36H, *tert*-butyl), 1.33 (*s*, 36H, *p-tert*-butyl).

2.5. PREPARATION OF THE COMPLEX (1) Rb^+·Pic$^-$

The preparation started with 110 mg of ligand (**1**) and proceeded under similar conditions. After filtration and evaporation of the solvent, microcrystals were obtained $m = 122$ mg. Mp 94–96°C; FAB mass spectrum $M^+ + Rb$ ($m/z = 2014.2$); ^{1}H-NMR in $CDCl_3$ in ppm from TMS: 8.91 (*s*, 2H, picrate) 7.14 (*s*, 8H, ArH), 7.12 (*s*, 8H, ArH), 3.90 (*s*, 16H, $ArCH_2Ar$), 3.80–2.87 (*m*, 64H, OCH_2CH_2O), 1.40 (*s*, 36H, *p-tert*-butyl), 1.31 (*s*, 36H, *p-tert*-butyl).

2.6. STABILITY CONSTANT DETERMINATIONS

Stability constants, K, of alkali complexes of (**1**), equal to the concentration ratios $[ML^+]/[M^+][L]$ ($M^+ = Li^+$, Na^+, K^+, Rb^+, and Cs^+) were determined in acetonitrile (Merck, Uvasol), at 25°C, by UV absorption spectrophotometry as described previously [6, 7]. A constant ionic strength ($I = 0.01$ M) was provided by Et_4NClO_4. The metallic salts were introduced as perchlorates: $LiClO_4$ and $NaClO_4$ (Fluka purum), $KClO_4$ (Prolabo, Normapur), and chlorides: RbCl and CsCl (Merck). Extraction data, expressed as the percentage of alkali picrates transferred from an aqueous solution (2.5×10^{-4} M) to a dichloromethane solution containing the calixarene ($c_L = 2.5 \times 10^{-4}$ M), were determined according to the procedure already reported [6]. In our case the extraction equilibrium was reached after 10 min vigorous shaking by hand and one hour magnetic stirring.

3. Results and Discussion

Following a known procedure [8], *p-tert*-butylcalix[4]arene and tetraethylene glycol ditosylate were refluxed for 9 days in acetonitrile in the presence of an excess of potassium carbonate. After the usual work up, the reacting mixture was precipitated with methanol to afford (**1**) in 52% yield as a pure product as detected by TLC. Compound (**1**) was identified by positive ion FAB mass spectrometry of its sodium complex ion (m/z (M^+Na) = 1953) and by ^{1}H-NMR spectroscopy to consist of two crowned *p-tert*-butylcalix[4]arenes in the 1,3-alternate conformation (one singlet is observed at 1.39 ppm for the *tert*-butyl groups, one singlet at 7.03 ppm for the aromatic protons, and one singlet at 3.89 ppm for the methylene protons of the calixarene moiety), connected by two glycolic chains in diammetrically opposite positions (see Experimental Section).

The mechanism of the formation of (**1**) can be rationalized as follows: in a preliminary step and according to literature data, *p-tert*-butylcalix[4]arene probably reacts with the ditosylate to produce the 1,3-dihydroxy-*p-tert*-butylcalix[4]arene crown-5 in the cone conformation [9]. Then, the remaining free 1,3-dihydroxy functional groups react with the excess ditosylate. During that process, inversion from the cone conformation to the 1,3-alternate occurs *via* the oxygen through the annulus mechanism [10], to afford a double-calixcrown in which the calixcrown units have the 1,3-alternate conformation. A double-crowned *p-tert*-butylcalix[4]arene in the 1,3-alternate conformation related to (**1**) has been reported in reference [3].

In a separate experiment, ligand (**1**) was reacted in chloroform with potassium picrate (K^+Pic^-) to give the complex compound as thin yellow crystals. Mp 83–85°C. Figure 1 presents the ^{1}H-NMR spectra of (a) the free ligand and of (b) the complex compound (**1**)·K^+Pic^- (two singlets at 1.33 and 1.39 ppm for the *tert*-butyl groups, two singlets at 7.12 and 7.15 ppm for the aromatic protons) in deuteriated chloroform. The signals of both double-calixcrown (**1**) and picrate are detected at room temperature indicating the complex to have the 1 : 1 stoichiometry based on the integration ratio of the aromatic protons of picrate and the aromatic protons of (**1**). The double-calixcrown (**1**) is a tritopic receptor molecule. Crowned *p-tert*-butylcalix[4]arenes are known to complex potassium in the glycolic shaped

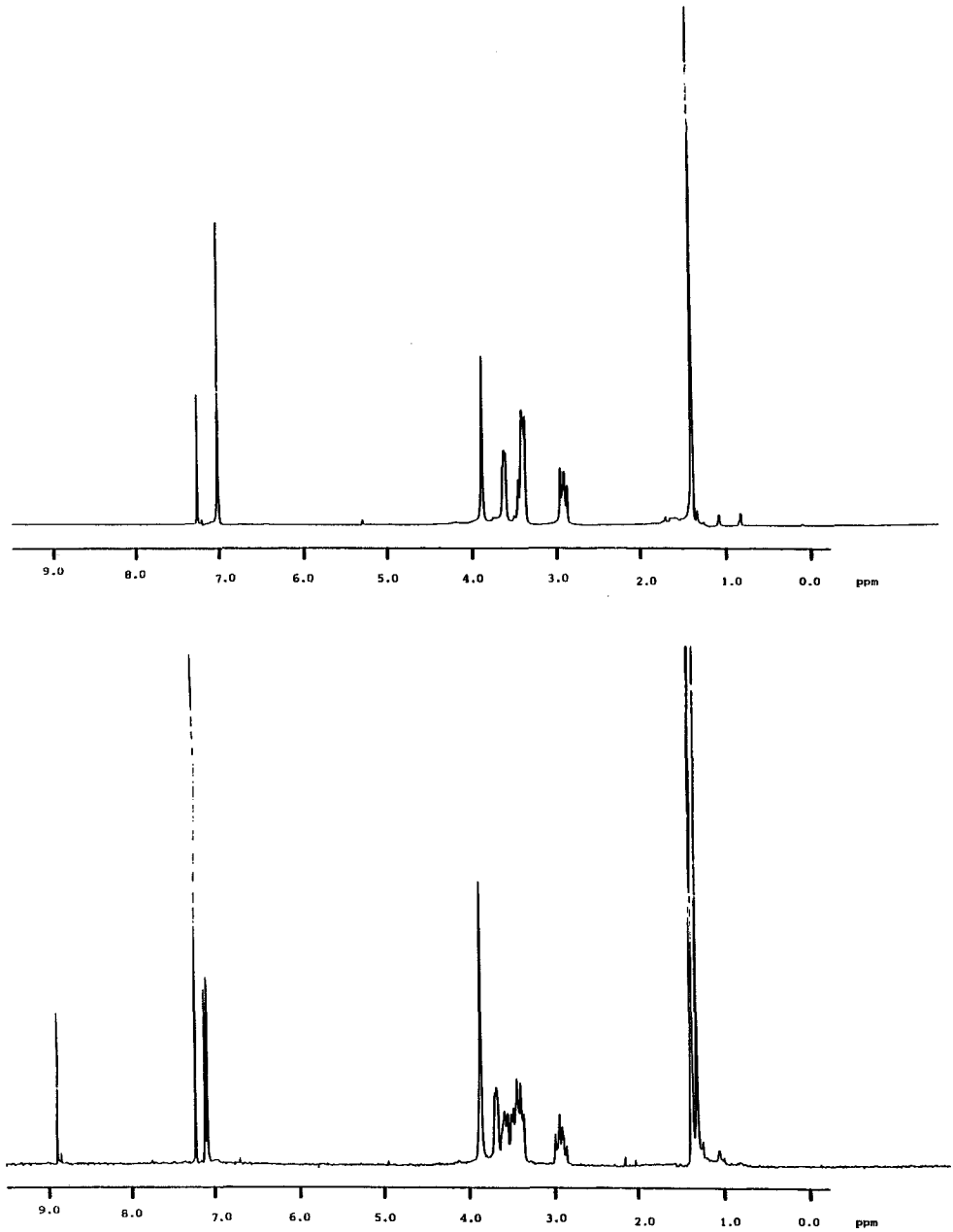


Fig. 1. (a) ^{1}H-NMR of double-calixcrown (**1**) (top). (b) ^{1}H-NMR of the 1:1 (**1**)·K^+Pic^- complex (bottom).

cavity and one expects ligand (**1**) to be capable of binding potassium cations in three possible location sites (two in the calixcrown cavities and one in the polyether-like central region of (**1**)). The formation of a 1:1 complex compound suggests that the potassium cation is located in the central cavity between the two

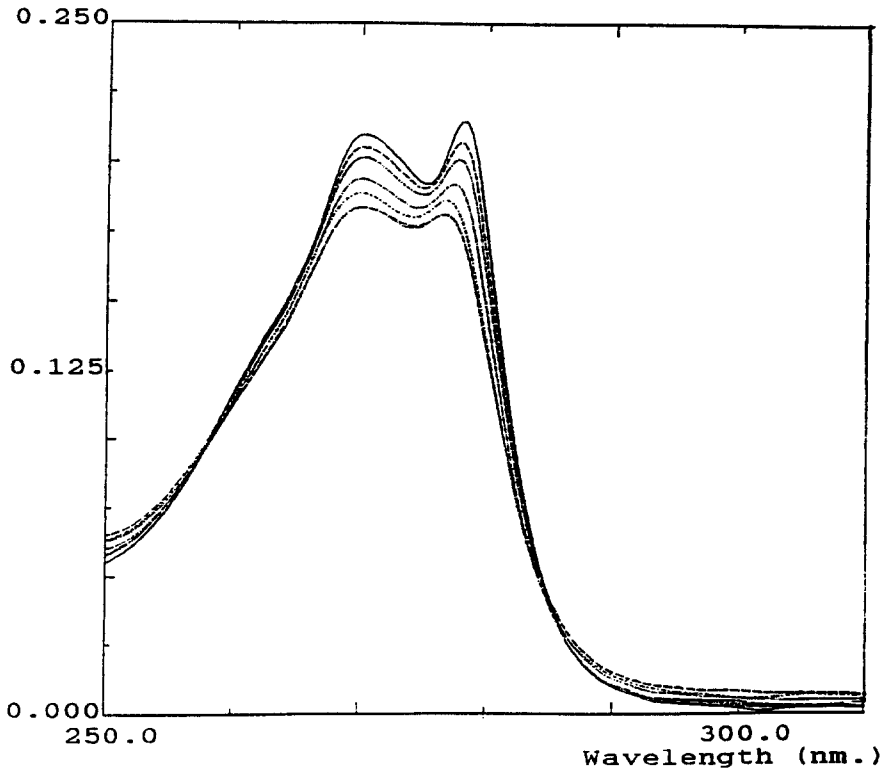


Fig. 2. Change in UV absorption spectrum of (**1**) (upper curve) upon addition of $KClO_4$ in acetonitrile: concentration of (**1**): 2.5×10^{-5} M, $0 \leqslant R \leqslant 20$, cuvettes of 2 cm path length.

opposite glycolic chains linking the calixarene units as depicted in Scheme II. Similar results were obtained when rubidium picrate was used instead of the potassium salt and a 1 : 1 complex was also isolated (see Experimental Section). Experiments carried out with lithium, sodium, and cesium picrates respectively did not afford any complexes.

The formation of 1 : 1 complexes in acetonitrile was established with all the alkali cations by UV absorption spectrophotometry. The case of K^+ ion complexation is illustrated in Figure 2, which shows the spectral changes induced in the wavelength range from 250 to 300 nm by stepwise addition of $KClO_4$ to a solution of (**1**) in acetonitrile up to a cation to ligand molecular ratio of $R = 20$. A decrease of the intensity of the absorption maxima of the ligand at 270 and 280 nm is observed as well as a small hypsochromic shift of the latter band and two isosbestic points at 258 and 285 nm. The experimental data could be described by assuming the formation of a 1 : 1 complex with $\log K = 4.9$. The logarithms of the stability constants of the complexes with the complete series of alkali cations are reported in Table I, together with the percentage of cation extracted. Both sets of data are parallel and show a maximum of binding with K^+ and Rb^+. For comparison purposes K^+ is less strongly complexed by (**1**) than by the crown ethers 18C6 and DC18C6, which are known to be selective for these cations (log K, respectively, 5.70

Table I. Complexation and extraction of alkali cations by ligand (**1**): values of log K in acetonitrile[a] at 25°C, $I = 0.01$ M (Et_4NClO_4) and percentage (%) of extraction of picrates from water to dichloromethane[b].

	Li^+	Na^+	K^+	Rb^+	Cs^+
Log K	2.2	1.8	4.9	5.2	2.5
%	3	2	35	45	7

[a] Arithmetic mean of at least two experiments. Precision corresponding to the 95% confidence interval: 0.1–0.2.

[b] Arithmetic mean of at least six runs. Precision corresponding to the 95% confidence interval: 1.

and 6.60 in acetonitrile) [11]. However, (**1**)·K^+ is as stable as its homologue with DB30C10 (log $K = 4.70$ in the same medium) which has the same number of oxygen donor atoms as the central cavity of (**1**). This observation is in good agreement with the previously assumed location of the potassium cation. Figures given in Table I enable the calculation of the M^+/M'^+ complexation selectivities as the ratio, s, of the stability constants of the corresponding complexes: (**1**) displays a very high K^+/Na^+ selectivity ($s = 1260$) as compared to 222, 18C6 and the natural antibiotic dinactin for which $s = 40$, 8 and 6, respectively [11]. The Rb^+/Cs^+ selectivity of (**1**) ($s = 450$) is also unusually high.

A molecular model of (**1**) suggests that the central, or *major* cavity is the largest and easiest binding site in macrocycle (**1**) and that the calixcrown, or *minor* cavities are inhibited from complexation by the presence of the *tert*-butyl groups because of the 1,3-alternate geometry of the calix[4]arene units. Synthetic work is currently under investigation to prepare the molecule related to receptor (**1**) and bearing no *tert*-butyl groups.

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