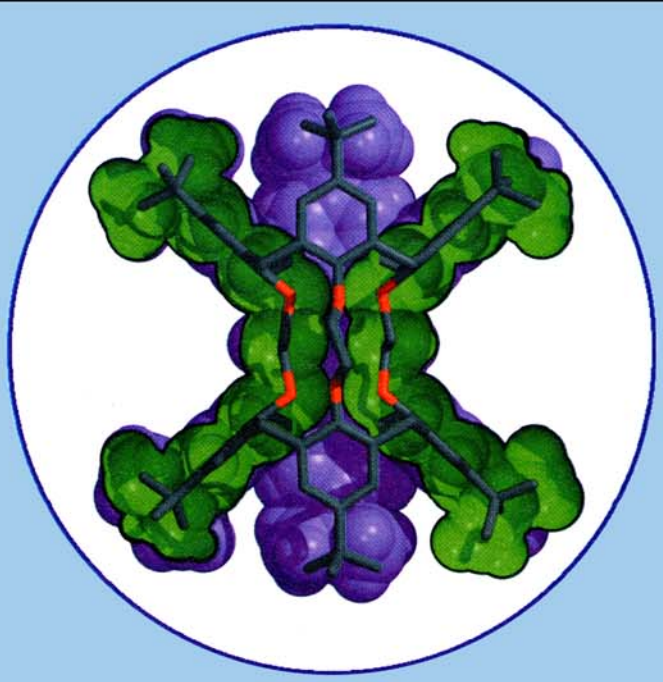
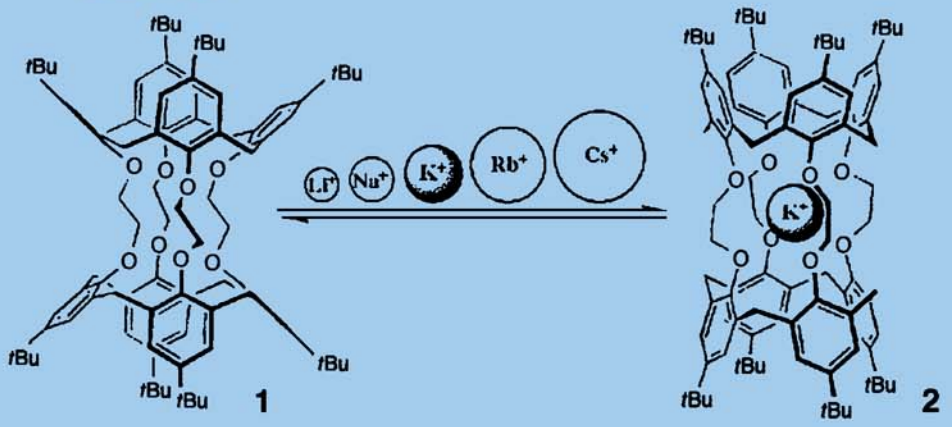
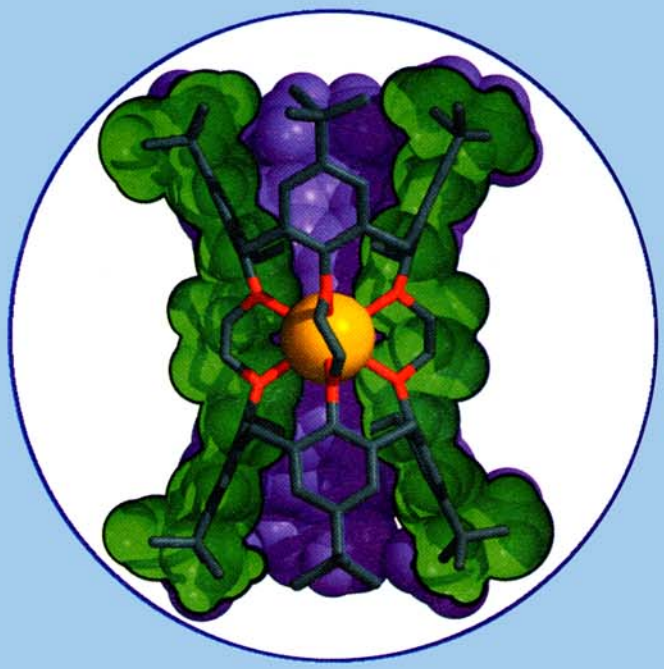


A new cage molecule possessing an eight-coordinate binding site displays a remarkable affinity for the potassium cation over any other alkali metal.





The two inserts, taken from crystal structures of **1** and **2** , illustrate the channel-like nature of the ligand and the gating of one potassium ion as it travels along the molecule's main (vertical) axis. More about **calix[4]tube** on the following pages.

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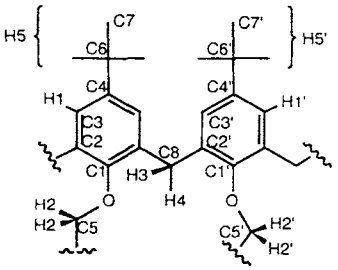
Calix[4]tube: A Tubular Receptor with Remarkable Potassium Ion Selectivity**

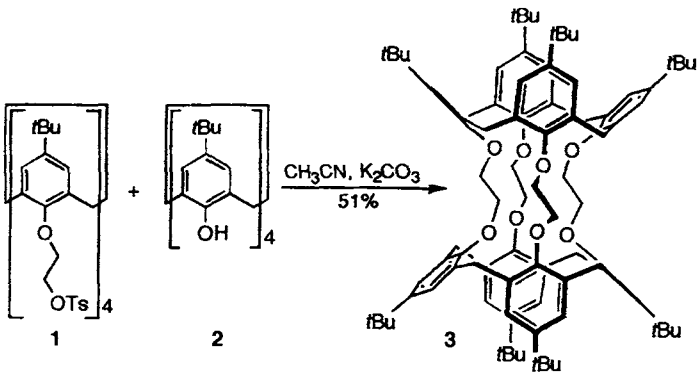
Philippe Schmitt, Paul D. Beer,* Michael G. B. Drew, and Paul D. Sheen

Potassium channel proteins have been investigated intensely in the last decade and a great deal of information about their structure/function relationships has been elucidated.[1] A very exciting, and still controversial, aspect focuses on how these proteins transport potassium ions through the cell membrane at high rates and with almost perfect selectivity (K^+ transported 1000 times more efficiently than Na^+).[2] The region of the channel pore responsible for the selection of the alkali metal ion, termed the selection filter, contains a square-planar array of four converging tyrosine residues.[3] The results of experimental and ab initio studies suggest that an *en face* cation-π interaction between K^+ ions and the arene surfaces of the tyrosine residues could be determinant for such a unique selectivity pattern.[4]



Despite the involvement of numerous research groups in the development of synthetic channels,[5, 6] it appeared to us that a biomimetic approach focusing in particular on the selection of alkali metal ions had not been fully investigated. In an effort to accredit the cation–π interaction hypothesis, we designed a novel biomimetic calix[4]arene-based tubular receptor whose access to metal cations may be controlled by filtering gates based on a square-planar array of arene surfaces.[7]

The template-driven condensation of the *p-tert*-butyl-calix[4]arene **2** with the pertosylated derivative **1**[8] in acetonitrile furnished the novel calix[4]tube **3** in fairly good yields (Scheme 1). Surprisingly this compound was found to be insoluble in all common organic solvents with the exception of chloroform and carbon tetrachloride. After crystallization from a chloroform/benzene mixture, **3** was submitted to crystal structure analysis (Figure 1) and found to exhibit C_i symmetry in the solid state.[9] The molecule contains two calix[4]arene units in a flattened, C_2-symmetrical *cone* conformation. Within the same calixarene macrocycle, each phenyl ring intersects the plane of the four methylene carbon atoms at angles of 89.6(2), 41.3(2), 87.3(2), and 43.7(2)°, respectively. It is noteworthy that the ethylene linkages alternate in two different geometries. Two of them present an *anti*-like conformation (O-C-C-O torsion angle



Scheme 1. Synthesis of the calix[4]tube **3**.

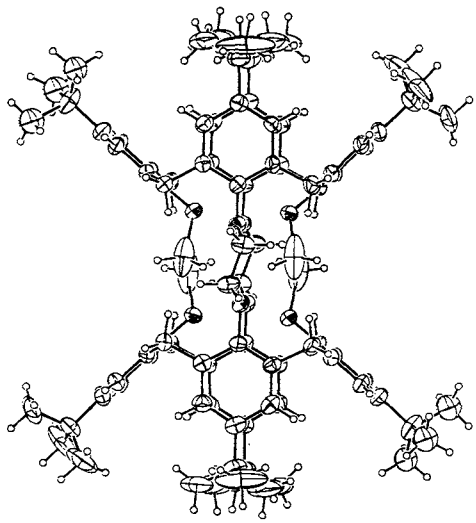


Figure 1. Crystal structure of the centrosymmetric calix[4]tube **3** in $3 \cdot 2.5\,C_6H_6$, with ellipsoids at 30% probability. Hydrogen atoms are included with small arbitrary radii. The benzene solvent molecules are not shown.

of 161.2(6)°), whereas the remaining two display a *gauche*-type conformation (O-C-C-O torsion angle of 47.8(8)°). As a consequence of this particular arrangement, the central cage composed of eight oxygen atoms is unsuitable to form an inclusion complex.

Interestingly, on the NMR time scale, this conformational symmetry is conserved in solution. The ^1H and ^{13}C NMR spectra of **3** in deuterated chloroform are consistent with the freezing of the calixarenes in a flattened *cone* conformation. All the signals, with the exception of those for the methylene groups, are split into two singlets of equal intensity. Moreover, the ^1H NMR spectra were found to be temperature independent up to 55°C. The absence of any coalescence or even peak broadening, features indicative of a time-averaged D_{4h} symmetry, suggests the calix[4]tube **3** is an extremely rigid molecule in solution.

As a consequence of the solubility limitations of **3**, a mixture of deuterated chloroform and methanol (8:2) was employed as solvent for the NMR spectroscopic investigations of the complexation of metal ions by **3**. Solid alkali metal iodide (10 μmol ($\approx$10 equiv)) was added to 1 mL of a solution of the calix[4]tube in this solvent mixture ([**3**] = 1 mM) at 25°C. The samples were sonicated briefly and ^1H NMR spectra were recorded at various times.

Compound **3** underwent a dramatic change when treated with potassium iodide. Within the first hour after mixing, the initial spectrum disappeared and was replaced by a new set of peaks suggestive of an increase of the ligand symmetry (Figure 2). The

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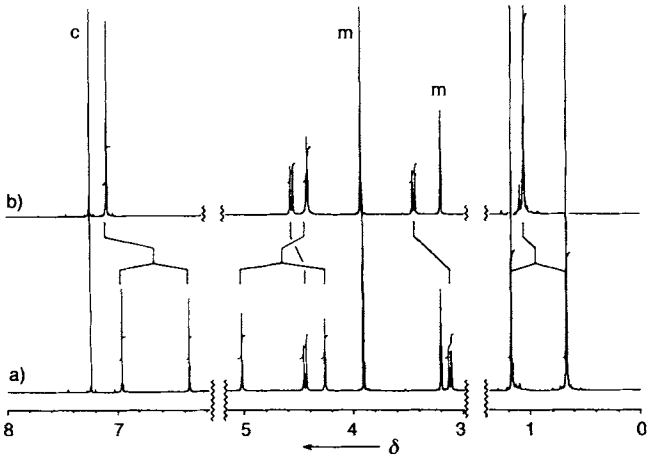

Figure 2. ^{1}H NMR spectrum of **3** [500 MHz, $CDCl_3/CD_3OD$ 4/1 (v/v)]: a) pure, b) with 10 equivalents of solid potassium iodide (c, m: solvent peaks corresponding to chloroform and methanol, respectively).

structural degeneracy of **3** after K^+ complexation, characterized by a fourfold symmetry along the molecule's main axis, is consistent with the opening of the binding cavity driven by the complexation of the potassium ion within the cage consisting of eight oxygen atoms.

Analogous experiments with other alkali metal iodides (LiI, NaI, RbI and CsI) failed to exhibit any significant cation uptake. Estimated by integration of the NMR signals, less than 7% of **3** was complexed after more than three days in presence of 10 equivalents of RbI; in the cases of LiI, NaI, and CsI the complexation after three days was less than 5% (Figure 3). Such a preference for potassium ions over any of the other alkali metal ions is remarkable for a synthetic receptor.[10]

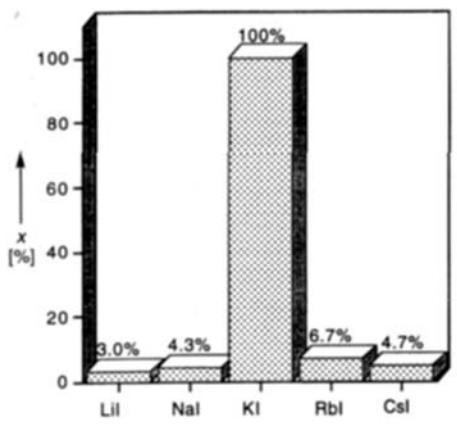

Figure 3. Uptake of alkali metal ions by **3** after treating its chloroform-methanol solution (4/1, [**3**] = 1 mM) with 10 equivalents of alkali metal iodide. The complexation ratio x was determined by integration of the ^{1}H NMR spectra after the samples had been left to stand for 90 h. In the case of KI, equilibrium was reached within an hour.

To investigate the potassium complexation process quantitatively, the uptake of 1 μmol of KI ([KI] = 10^{-3} M) by one equivalent of **3**, in homogeneous solution at 25 °C, was monitored as a function of time. After 24 h the system was evaluated to have reached equilibrium (86% of **3** was complexed), the formation of a 1:1 complex was established, and a stability constant of 4×10^4 L mol^{-1} was estimated. The complexation halftime, defined by the time necessary for the system to reach half the equilibrium conversion ratio, was measured to be 18 minutes. Although these are preliminary results, this experiment reveals the complexation process is kinetically slow and may be a consequence of an important intramolecular reorganization necessary for the cation uptake.

Comparison of the chemical shifts values of **3** and of its potassium complex (**4**), shows in general low-field shift deviations of all the calix[4]arene-related peaks ($\Delta\delta$ *t*-Bu: +0.923, Ph: +0.426, CH_2: +0.216), whilst the signals of the ethylene protons exhibit an average high-field variation (− 0.228, Figure 2). This feature is consistent with a displacement of the electron density of the ligand towards the molecule's equatorial plane caused by the close proximity of the positive charge of the complexed metal ion.

The geometry of the complex was confirmed by X-ray analysis.[11] As predicted by NMR spectroscopy, **4** is highly symmetrical and contains an approximate C_4 element of symmetry along the main axis of the molecule. All ethylene linkages present a *gauche* conformation (O-C-C-O torsion angles vary from 51.7 to 68.00°) and the potassium ion is located at the center of a slightly flattened cube; the K−O distances range from 2.759(6) to 2.809(6) Å (Figure 4). The angles of intersection of the phenyl rings with the mean plane of the four methylene carbon atoms vary between 64.6(2) and 67.9(2)°.

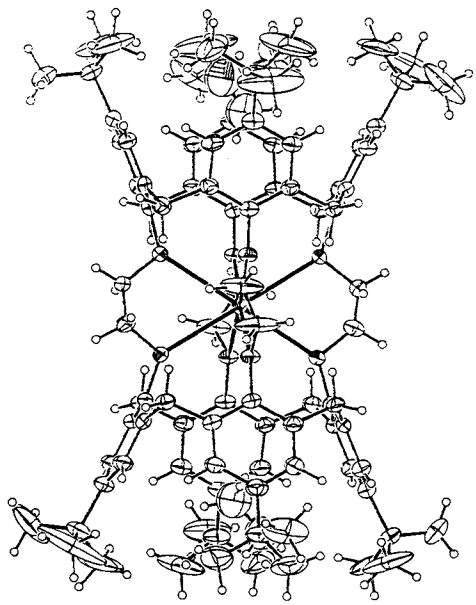

Figure 4. Structure of the K^+ complex **4** of the calix[4]tube **3** in crystals of **4**·I·3 $CHCl_3$·4 CH_3OH·H_2O. A potassium ion is located in the center of **3**, and two methanol molecules in the cone cavities. Ellipsoids are drawn at 30% probability. Hydrogen atoms are included with small arbitrary radii. The chloroform and water solvent molecules are not shown.

Of relevance to K^+ selective channel transportation, the assumption that the calixarene units provide the preferred cation-accessing gates was tested by using constrained molecular mechanics calculations.[12, 13] Preliminary calculations suggested that indeed the complexation of the potassium ion would require an activation energy about 10 kJ mol^{-1} larger by accessing the cavity across rather than along the main axis of the molecule and may involve a prior weak complexation of the cation in the calixarene cone (Scheme 2).[14] Our current efforts are directed in the collection of experimental evidence of such a behavior and in the derivatization of **3** as a potential new class of membrane-spanning compounds.

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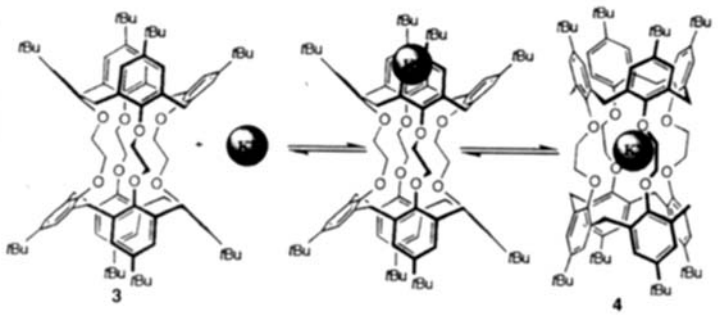

Scheme 2. Schematic representation of the uptake of K^+ ions by **3** based on molecular mechanics calculations.

Experimental Section

3: A suspension of *p-tert*-butyl-calix[4]arene (451 mg, 0.70 mmol) and potassium carbonate (480 mg, 3.5 mmol) in dry acetonitrile (100 mL) was stirred under nitrogen. After 2 h at room temperature, **1** (1 g, 0.70 mmol) was added and the reaction mixture brought to reflux for five days. The solvent was then removed in vacuo and the solid suspended in a 1:1 ethanol-water mixture. The suspension was heated to reflux overnight and hot filtered. The crude mixture was then dissolved in chloroform (50 mL) and the solution carefully paper filtered to yield a clear solution to which acetone (40 mL) was added. Filtration of the microcrystalline material obtained after the solution had been allow to stand for a few hours, followed by its drying in vacuo yielded **3** (500 mg) as an analytically pure product (51%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.09 (s, 8H; H1/H1′), 6.48 (s, 8H; H1/H1′), 5.15 (s, 8H; H2/H2′), 4.57 (d, ^3J(H,H) = 13 Hz, 8 H; H3), 4.39 (s, 8 H; H2/H2′), 3.25 (d, ^3J(H,H) = 13 Hz, 8 H; H4), 1.31 (s, 36H; H5/H5′), 0.80 (s, 36 H, H5/H5′); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 156.0 (C1/C1′), 152.8 (C1/C1′), 144.5 (C2/C2′), 144.3 (C2/C2′), 135.1 (C4/C4′), 131.9 (C4/C4′), 125.5 (C3/C3′), 124.8 (C3/C3′), 73.0 (C5/C5′), 72.5 (C5/C5′), 34.1 (C6/C6′), 33.5 (C6/C6′), 32.4 (C8), 31.7 (C7/C7′), 31.0 (C7/C7′); C,H,Cl analysis ($C_{96}H_{120}O_8 \cdot CHCl_3$): calc.: C 76.58, H 8.02, Cl 6.99; found: C 76.32, H 8.17, Cl 8.09.

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Keywords: alkali metals · calixarenes · ion channels · potassium · supramolecular chemistry

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[11] a) Crystal data for **4**·I·3$CHCl_3$·4CH_3OH·H_2O, crystal dimensions: 0.45 × 0.30 × 0.45 mm, yellowish color, monoclinic, $P2_1/a$, a = 24.46(2), b = 12.334(13), c = 36.65(4) Å, β = 96.902(10)°, V = 10976(19) Å^3, Z = 4, ρ_{calcd} = 1.268 mg m^{-3}, $2\theta_{max}$ = 50.260, $\lambda(Mo_{K\alpha})$ = 0.71073 Å, T = 293(2) K. 27485 reflections were measured on a MARresearch Image Plate. 17598 were independent [R(int) = 0.825]. Data analysis and refinement of structure as for **3** [9]. The iodide was disordered over two sites with occupation factors of 0.74 and 0.26, respectively. Two water molecules were refined with 50% occupancy. The final R and wR^2 values are 0.0826 and 0.2893, respectively, for 9655 data with $I > 2\sigma(I)$. Largest peak and hole in the final difference Fourier map were 1.029, −0.713 e Å^{-3}, respectively. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100240. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code + (1223) 336-033; e-mail: deposit@chemcrys.cam.ac.uk).

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Coordination Arrays: Tetranuclear Cobalt(II) Complexes with [2 × 2]-Grid Structure**

Garry S. Hanan, Dirk Volkmer, Ulrich S. Schubert, Jean-Marie Lehn,* Gerhard Baum, and Dieter Fenske

A major goal in inorganic supramolecular chemistry is the self-assembly of polynuclear coordination arrays through the suitable design of ligands and choice of metal ions in order to generate well-defined architectures in a controlled fashion.[1] In

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