Calix[5]arene-Based Molecular Vessels for Alkylammonium Ions**

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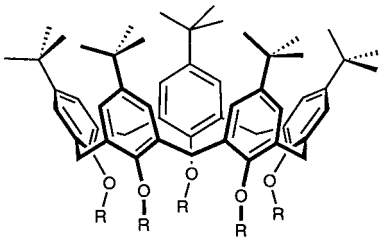
Dedicated to Professor Francesco Bottino on the occasion of his 70th birthday



	R
1a	H
1b	$(CH_2)_3CH(CH_3)_2$
1c	$(CH_2)_2OCH(CH_3)_2$
1d	$CH_2CO_2CH(CH_3)_2$
1e	$CH_2CO_2C(CH_3)_3$

Cation–π-electron interactions are known to play an important role in the recognition of positively charged guests by the electron-rich π-systems of natural[1] and synthetic hosts.[2] Calixarenes,[3] when suitably functionalized, can provide three-dimensional, rigid, π-rich cavities for the selective inclusion of organic cations in nonpolar media.[4] Recently we have shown that triether derivatives of (1,3)-*p*-*tert*-butylcalix[5]arene crown-6 are able to discriminate between linear and branched alkylammonium ions by means of *endo* complexation.[5] The low association constants (K_{ass} = 48–86 M^{-1}) observed for the selective inclusion of nBuNH$_3^+$ ions are probably related to the shape of the cavity of these host molecules (C_s symmetry) and their pronounced tendency to fill the cavity by canting a *tert*-butylphenyl residue inwards.[5]

To develop more powerful receptors, these calixarenes with distorted *cone* conformations should be replaced by compounds with an improved shape and preorganized, permanent *cone* conformations. Although the shape of the calix[5]arene cavity can, in principle, be tuned by changing the nature and bulkiness of substituents on both the upper and lower rims,[6] the presence of *tert*-butyl substituents on the upper rim is essential to keep the molecule in a *cone* conformation and ensure selective inclusion of RNH$_3^+$ ions. Therefore, structural modifications to the lower rim of *p*-*tert*-butylcalix[5]arene (**1a**) have been addressed. We have found that the attachment of long-chain pendant groups (bulkier than ethoxyethoxy)[7] on the lower rim of **1a**—by exhaustive alkylation with appropriate electrophiles—produces derivatives **1b**–**e**, which have a fixed and quite regular C_{5v} *cone* conformation. These receptors bind linear RNH$_3^+$ ions much more efficiently and selectively than the neutral synthetic host systems reported to date.

Host–guest binding affinities were investigated by ^{1}H NMR titration experiments of $CDCl_3/CD_3OD$ (9/1, v/v) solutions of **1b**–**e** with the four isomeric butylammonium picrate salts. Upon addition of increasing amounts of salts, the spectra consistently showed, from the first aliquot onwards, distinct sets of signals for the free and complexed species, indicating that exchange between the complexed and uncomplexed guests is slow on the NMR time scale. Consequently, the formation of 1:1 inclusion complexes was directly assessed by comparing the signal intensities of solutions containing equimolar amounts of host and guest. *endo* Complexation is unambiguously supported by the dramatic upfield shifts (complexation-induced shifts, CIS, up to $\Delta\delta$ = 4.1) of the resonances of the cavity-included alkyl chain of the guest. Due to the high preorganization of the host cavities prior to guest inclusion, the CIS of the receptors are lower ($\Delta\delta$ = 0.1–0.4).

The percentage of *endo* complexation for each butylammonium salt was determined by direct ^{1}H NMR analysis of equimolar solutions (5×10^{-3} M) of host and guest. Hosts **1b**–**e** show a remarkable affinity for the linear nBuNH$_3^+$ ion (68–95%) and a much lower affinity for the branched iBuNH$_3^+$ (6–38%) and sBuNH$_3^+$ (5–28%) ions. No interaction could be detected with the bulky tBuNH$_3^+$ ion, even when a large excess (10 equiv) of the salt was added under standard experimental conditions (15 min equilibration at 21°C before the spectrum was recorded). Furthermore, a direct NMR competition experiment has shown that when **1e** is mixed with equimolar mixtures of the four butylammonium picrates, only nBuNH$_3^+$ (95%) and iBuNH$_3^+$ (5%) ions undergo *endo* complexation. Owing to the high degree of *endo* complexation for the nBuNH$_3^+$ ion, relevant K_{ass} values could not be reliably assessed by ^{1}H NMR spectroscopy[8] and were determined in $CHCl_3$ saturated with water by using the picrate extraction method developed by Lein and Cram.[9]

The association constants of **1b**–**e** with the isomeric butylammonium picrates are summarized in Table 1. High lgK_{ass} values ($4.63 \le \lg K_{ass} \le 6.47$) are always found with the nBuNH$_3^+$ ion and receptors **1b**–**e**, while with the other branched cations and specifically with the tBuNH$_3^+$ ion they are significantly lower ($\lg K_{ass} \le 3.5$). For a given butylammonium picrate isomer, the stability of the complexes generally decreases in the following order: **1e** > **1b** > **1c** > **1d**. Accordingly, calix[5]arenes **1b** and **1e** appear to bind the nBuNH$_3^+$

Table 1. Association constants ($\lg K_{ass} \pm \sigma$) of isomeric BuNH$_3^+$ ions (picrate salts) with **1b**–**e**, obtained by UV spectroscopy.[a]

	nBuNH$_3^+$	iBuNH$_3^+$	sBuNH$_3^+$	tBuNH$_3^+$
1b	5.80 ± 0.02	3.72 ± 0.01	3.68 ± 0.01	3.16 ± 0.02
1c	4.68 ± 0.02	3.26 ± 0.06	3.24 ± 0.02	3.02 ± 0.03
1d	5.32 ± 0.01	3.69 ± 0.02	3.6 ± 0.1	3.5 ± 0.2
1e	6.47 ± 0.08	4.09 ± 0.01	3.8 ± 0.2	3.49 ± 0.02

[a] Measured in $CHCl_3$ at 25°C (σ: standard deviation of a minimum of three independent determinations).

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ion more selectively than the other isomeric cations. For instance, the selectivity of **1e** for nBuNH$_3^+$ over tBuNH$_3^+$, expressed as the ratio $K_{ass}(n\text{BuNH}_3^+)/K_{ass}(t\text{BuNH}_3^+)$ approaches 10^3. This is, to the best of our knowledge, the highest selectivity so far observed for this pair of isomers. It is higher than the values reported for [18]crown-6[10] and calix[6]arene hexaesters[11] by about three and two orders of magnitude, respectively. Kubo et al. have recently reported a reversed selectivity for tBuNH$_3^+$ ions [$K_{ass}(t\text{BuNH}_3^+)/K_{ass}(n\text{BuNH}_3^+ = 11$] by a chromogenic 1,1′-binaphthyl-derived calix[4]crown. In this case complexation is presumed to involve the crown ether moiety and a phenolate group.[12]

Since the structural motif of nBuNH$_3^+$ is present in biologically important amines, calix[5]arenes **1b**–**e** can also act as biomimetic host systems. A screening with a number of α-amino acid methyl esters (including Phe-OMe · HCl, Arg-OMe · 2 HCl, Val-OMe · HCl) and small peptides has shown that receptors **1b** and **1e** form specifically 1:1 inclusion complexes only with N^{α}-Ac-Lys-OMe · HCl and Lys-Gly-OMe · 2 HCl. Noteworthy, in the latter the ε-butylenammonium group is recognized by the cavity and complexed in the presence of an unprotected α-ammonium group. In addition, the methyl ester hydrochlorides of the neurotransmitter γ-aminobutyric acid (GABA)[13] and the plasmin inhibitor ε-aminocaproic acid (ε-Ahx)[14] are also strongly included with degrees of complexation up to 80 % (Figure 1).

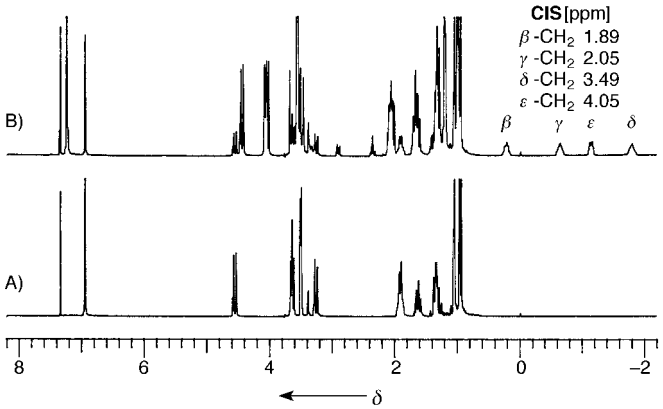

Figure 1. ^{1}H NMR spectra (300 MHz, $CDCl_3/CD_3OD$ 9/1, 21 °C) of receptor **1b** (A) and its 1:1 inclusion complex with ε-Ahx-OMe · HCl ([**1b**] = [ε-Ahx-OMe · HCl] = 5×10^{-3} M) showing characteristic CIS values for the included guest (B).

The calix[5]arene derivatives described here, which are frozen in a C_{5v}-symmetric *cone* conformation, are the most selective molecular receptors for linear alkylammonium ions reported to date. These receptors display an enzymelike selectivity[15] towards biologically important ammonium substrates. Enhancement of their efficacy as biomimetic host systems is currently in progress.

Experimental Section

1b: A stirred mixture of **1a**[16] (0.405 g, 0.50 mmol), isohexyl tosylate (1.923 g, 7.50 mmol), and anhydrous K_2CO_3 (1.037 g, 7.50 mmol) in dry CH_3CN (50 mL) was refluxed under N_2 for 16 h. After cooling, the precipitate was collected by filtration, washed with water, dried, and recrystallized from CH_3CN/CH_2Cl_2 to give **1b** in 72 % yield, m.p. 221–224 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 6.6$ Hz, CHMe_2, 30 H), 1.03 (s, tBu, 45 H), 1.32 (m, $OCH_2CH_2CH_2$, 10 H), 1.60 (septet, $J = 6.6$ Hz, CHMe$_2$, 5 H), 1.89 (m, $OCH_2CH_2CH_2$, 10 H), 3.25, 4.54 (d, $J = 13.8$ Hz, $ArCH_2Ar$, 10 H), 3.63 (t, $J = 7.2$ Hz, $OCH_2CH_2CH_2$, 10 H), 6.92 (s, Ar H, 10 H); FAB MS (positive ion): m/z (%) 1248 [100, $(M + NH_4)^+$].

Calixarene **1c** was obtained analogously from **1a** and 2-isopropoxyethyl tosylate in 84 % yield, m.p. 180–185 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.02$ (s, tBu, 45 H), 1.19 (d, $J = 6.1$ Hz, CHMe_2, 30 H), 3.26, 4.56 (d, $J = 13.8$ Hz, $ArCH_2Ar$, 10 H), 3.70 (septet, $J = 6.1$ Hz, CHMe$_2$, 5 H), 3.78–3.89 (m, OCH_2CH_2, 20 H), 6.88 (s, Ar H, 10 H); FAB MS (positive ion): m/z (%) 1258 [100, $(M + NH_4)^+$].

Calixarenes **1d** and **1e**[17] were prepared similarly by treating **1a** with the appropriate alkyl bromoacetate. After the reaction mixture had been heated for 24 h at reflux, the inorganic salts were filtered off and washed with $CHCl_3$. The combined organic layers were concentrated to dryness, and the oily residue (mostly the K^+ complex)[17] was treated with petroleum ether. KBr was filtered off and the solvent removed to afford the free calixarenes. **1d**: 70 % yield, m.p. 184-186 °C (hexane/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.01$ (s, tBu, 45 H), 1.27 (d, $J = 6.2$ Hz, CHMe_2, 30 H), 3.35, 4.84 (d, $J = 14.5$ Hz, $ArCH_2Ar$, 10 H), 4.62 (s, $OCH_2C{=}O$, 10 H), 5.08 (septet, $J = 6.2$ Hz, CHMe$_2$, 5 H), 6.87 (s, Ar H, 10 H); FAB MS (positive ion): m/z (%) 1333 [100, $(M + Na)^+$]. The physical and spectral data of **1e** were identical to those in the literature.[16]

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Controlling the Structure of Supramolecular Porphyrin Arrays**

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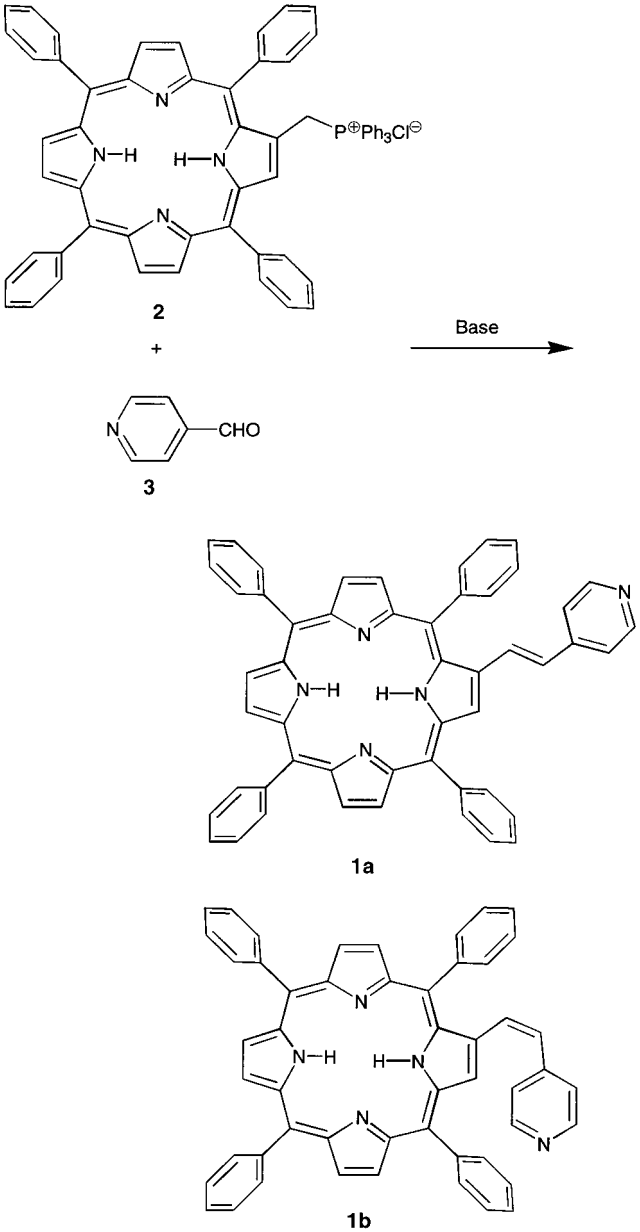
The importance of multichlorin assemblies in photosynthetic reaction centers and light-harvesting antenna complexes has inspired considerable interest in the synthesis of porphyrin arrays. Several synthetic strategies are employed for the assembly of multiporphyrin systems. A wide variety of porphyrin arrays of ever-increasing size have been constructed by the traditional methodology of covalently linking porphyrins.[1] More recently the incorporation of porphyrins into supramolecular assemblies has proven to be an attractive method for array formation. With careful choice of materials, the supramolecular structure of the array can be engineered. However, there is currently no porphyrin array system that can be "switched" from one ordered assembly to another. Here we report the first porphyrin system where the structure of the supramolecular assembly can be altered by a noninvasive technique such as photolysis.

With some notable exceptions,[2] the majority of the self-assembling porphyrin arrays are based upon metal – ligand interactions.[3] To a large extent this work has concentrated upon the coordination chemistry of *meso*-pyridyl porphyrins. Porphyrin assemblies prepared from *meso*-pyridyl porphyrins range from dimeric through to polymeric complexes.[3] Of particular interest are the ordered structures formed by a single component interacting with itself. The most common motif in this area is the use of pyridyl-functionalized metalloporphyrins; for example, the metal center of a zinc porphyrin will readily coordinate another ligand, such as pyridine. If the zinc porphyrin is also functionalized by a pyridine, the possibility for zinc – pyridine (inter-[4] or intramolecular[5]) interactions exist. The orientation of the pyridine functionality on the porphyrin macrocycle has a profound influence on the resulting superstructure, providing either dimeric[4f, 6] or oligomeric and polymeric[3j–l, 4] compounds. We have recently become interested in the formation of porphyrin arrays using coordination chemistry as a construction technique and the possibility that simple geometric changes, such as *cis/trans* alkene isomerization, would provide a method to control array superstructure.

As an introduction to this area we prepared the β-vinylpyridine functionalized porphyrin **1**. This compound can be obtained in 82% yield from the reaction of **2**[7] with 4-pyridinecarboxaldehyde (**3;** Scheme 1). The product isolated



Scheme 1. Synthesis of **1a** and **1b**.

is an isomeric mixture of *trans* **1a** (62%) and *cis* **1b** (20%) that can be separated by careful chromatography. The ^{1}H NMR spectra for both **1a** and **1b** are consistent with the structures reported. As expected **1a** is the more favored isomer, and solutions of **1b** convert into **1a** when heated in chloroform or if left exposed to light. Based on the X-ray

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