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Cryptocalix[6]arenes; Molecules with a Large Cavity

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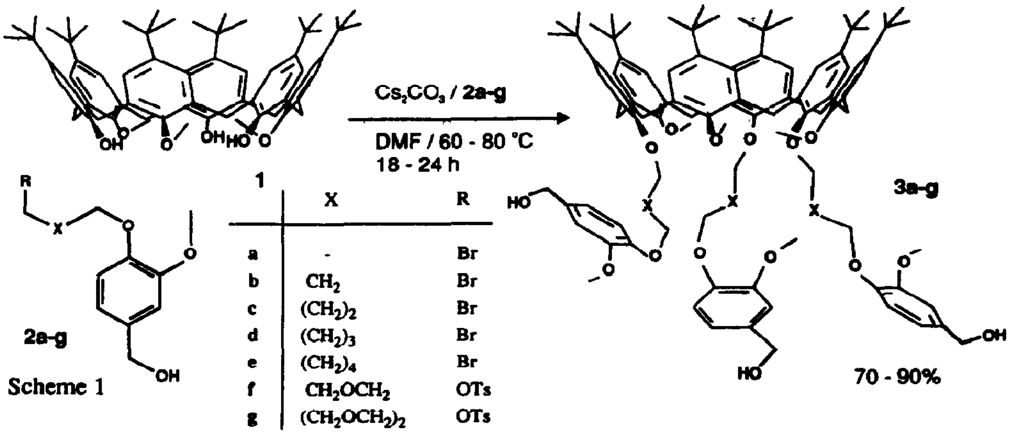
Abstract: A new type of cavitand molecules with large cavities (**4a-g**) has been synthesized by the covalent three-point linking of a *p-tert*-butylcalix[6]arene to a cyclotriveratrylene (CTV) and their dynamic behavior has been studied by ^{1}H NMR spectroscopy.

A useful way for the synthesis of synthetic receptors is to start from readily available building blocks like cyclodextrins,[1] recorcin[4]arenes,[2] cyclotriveratrylenes,[3] and calix[n]arenes.[4] In our group we have mainly used selectively functionalized calix[4]arenes for the synthesis of highly specific and effective ionophores.[5] In order to make also calix[6]arenes suitable as building blocks we are studying, in collaboration with the groups of Ungaro and de Mendoza, the selective functionalization of calix[6]arenes. This has resulted in novel procedures for the selective alkylation[6] and phosphorylation[7] of *p-tert*-butylcalix[6]arene. Capping of calix[4]arenes via the upper- or lower rim with simple aromatic moieties,[8] polyoxyethylene glycol- or alkyl chains[9] or terphenyls[10] results in a strongly increased rigidity in these calix[4]arene derivatives and in a high ordering of functional groups. As calix[6]arenes are even more flexible than calix[4]arenes, capping would provide a method to obtain conformationally more defined calix[6]arene structures. Recently Gutsche et al. have capped calix[6]arenes via proximal positions with aromatic moieties.[11] Rigidification of the structure by *three-point* capping would lead to symmetric, bowl-shaped molecules. In a detailed study of the conformational properties and dynamic behavior of calix[6]arenes, we have found that *p-tert*-butylcalix[6]arenes which are alternately substituted with methoxy groups and bulky substituents predominantly exist in a flattened cone conformation.[12] The *syn* arrangement of the bulky substituents in space provides an ideal situation to cap the lower rim of calix[6]arene via an intramolecular cyclotrimerization. Veratryl alcohol can be easily derivatized and cyclotrimerized to cyclotriveratrylenes in reasonable to good yields and these derivatives have been used by Collet et al. in the synthesis of cryptophanes.[3,13] In this communication we present our preliminary results on the preparation of cryptocalix[6]arenes, which contain both a calix[6]arene and a cyclotriveratrylene unit.

Veratryl alcohol was reacted with an excess of an α,ω-alkyl dibromide or polyoxyethylene ditosylate and K_2CO_3 as a base in refluxing acetonitrile to give the alkyl bromides **2a-e** and alkyl tosylates **2f,g** in

40-70% yield. The veratryl units **2a-g** (4 equiv) were subsequently coupled to 1,3,5-trimethoxy-*p*-*tert*-butyl-calix[6]arene **1**[12] with 6 equiv of Cs_2CO_3 as a base in DMF at 60 - 80 °C to give the precursors **3a-g** in 70-90% yield (Scheme 1).



	X	R
a	-	Br
b	CH_2	Br
c	$(CH_2)_2$	Br
d	$(CH_2)_3$	Br
e	$(CH_2)_4$	Br
f	CH_2OCH_2	OTs
g	$(CH_2OCH_2)_2$	OTs

Scheme 1

After purification by recrystallization from methanol or ethanol, the final cyclizations were performed by slowly dripping (2-3 h) of an 0.1 mM solution of the precursors **3a-g** in glacial acetic acid in an ice-cooled mixture of glacial acetic acid and perchloric acid (2:1 v/v). After workup, the crude products were subjected to column chromatography (silica gel, mixtures of EtOAc/hexanes) and subsequent trituration or recrystallization from methanol or ethanol to give the cryptocalix[6]arenes **4a-g** in 30-73% yield.[14]

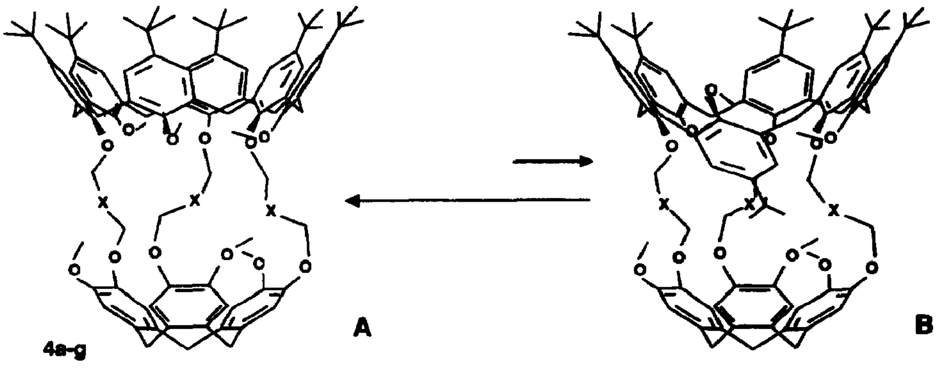


Figure 1: Equilibrium between the major (A) and minor (B) conformer of cryptocalix[6]arenes **4c**, **4d** and **4f**.

The ^1H NMR spectra of **4a-g** show two signals for the *tert*-butyl groups, two AB systems for the methylene bridges of the calix[6]arene skeleton, and one AB system for the methylene bridges of the cyclotriveratrylene moiety. The methoxy groups of the calix[6]arene moiety are deeply embedded in the calix[6]arene annulus, as can be concluded from the large upfield shift of the signals by the ring currents of the aromatic rings. These features, together with the symmetry of the aromatic region clearly prove the C_3 symmetry of these molecules. In order to investigate the dynamics of **4a-g**, variable temperature ^1H NMR spectra were recorded. The low temperature ^1H NMR spectra of **4c,d** and **4f** clearly showed the existence of a minor conformer (B) beside the major C_3 conformer (A), whose resonances coalesce upon raising the temperature. The upfield shift of one *tert*-butyl group of the minor conformer (B) indicates that one anisole moiety has rotated in such a way that its *tert*-butyl group is located in the cavity, and is subjected to the ring current of the CTV aromatic system (Figure 1). From the ratio A/B conformer, the Gibbs free energy differences (ΔG°) were calculated. From intensities of the exchange connectivities in the NOESY spectra the activation Gibbs free energies (ΔG^{*}) for the interconversion process were calculated (Table 1). By increasing the length of the spacer of **4c** with one methylene group or oxygen atom, the activation Gibbs free energy decreases with 7 (**4d**) and 3 (**4f**) kJ mol^{-1}, respectively. The ^{1}H NMR spectra of the long spacered **4e** and **4g** did not change upon increasing the temperature from 223 to 323 K, which indicates that the interconversion is fast on the chemical shift timescale with a $\Delta G^{*} < 56$ kJ mol^{-1}. It is assumed that for **4c**, **4d** and **4f** the interconversion process is sterically controlled by the passage of a *tert*-butyl group through a portal, while for **4e** and **4g** this is the breaking of favorable CH...π interactions[12] when a methoxy group is pulled from the annulus. The ^{1}H NMR spectra of cryptocalix[6]arenes **4a** and **4b**, having short spacers, also did not change upon varying the temperature, as accomodation of the *tert*-butyl group in their cavities is sterically unfavorable, which results in a concentration of minor conformer which is less than the detection limit. The size of the cavity of **4c** is thus approximately that of a *tert*-butyl group. The capping of calix[6]arene with a cyclotriveratrylene unit is the first example of the three-point capping of calix[6]arenes and creates molecules with an increased rigidity and a well-defined conformational and dynamic behavior. Complexation studies of neutral guests in these new cryptocalix[6]arenes as well as the exploration of the concept of intramolecular cyclotrimerizations to create new molecular shapes are currently under investigation.

Table 1: Yields, thermodynamic and kinetic data of cryptocalix[6]arenes **4a-g** at 223 K in CD_2Cl_2.

	Yield %	$\Delta G^{\circ a}$ kJ mol^{-1}	ΔG^{*b} kJ mol^{-1}
4a	30	c	c
4b	30	c	c
4c	49	8.3	63
4d	46	7.6	56
4e	41	d	d
4f	73	6.9	60
4g	72	d	d

[a] Difference in Gibbs free energy between the major (A) and minor (B) conformer.

[b] Activation Gibbs free energy for the interconversion between the major (A) and minor (B) conformer.

[c] Fast interconversion.

[d] Concentration of minor conformer is below the detection limit.

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