

Tetrahedron Letters 42 (2001) 7465-7468

TETRAHEDRON LETTERS

Synthesis of biscalix[4]arene with enhanced binding ability to a cationic guest

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Received 11 June 2001; revised 6 August 2001; accepted 24 August 2001

Abstract—The biscalix[4]arene showed remarkably enhanced inclusion ability for the *N*-methylpyridinium ion due to the increasing π -basicity of the benzene rings, which interact with the guest in an edge-to-face manner, in calix[4]arene skeletons. © 2001 Elsevier Science Ltd. All rights reserved.

Calixarenes, a new class of synthetic macrocycles having phenolic units linked by methylene groups, have received considerable attention for host guest chemistry in the last decade.¹ The architecture of the calixarene can provide a π -basic cavity. Hence, they are useful for designing a globular π -basic cavity by connecting the upper rims of two calixarenes.^{2–10} We previously demonstrated that conformational isomers derived from calix[4]arenes are very useful for estimating the contribution of the cation- π interaction¹¹ to the host–guest complexation process,¹² and biscalix[4]arene **1** prepared by connecting two conformationally immobile calix[4]arenes with two spacers at the upper rims has significant inclusion ability for positively charged aromatic guests with a disk shape.¹³ The rigid conformation of the biscalix[4]arene skeleton permits prediction of the complex structure as shown in Fig. 1. Two possible orientation modes of cation- π interaction can be seen in the complex. One is the edge-to-face type interaction between the flattened benzene rings in the biscalix[4]arene and the guest protons that are vertically in contact with them. The other is the face-to-face interaction between the benzene rings, which are connected with the spacers at the *p*-positions and stand in parallel, in the biscalix[4]arene and the guest π -system sandwiched with them (Fig. 2). To clarify the contribution of these two interactions to the binding



Figure 1. Schematic representation for the proposed complex structure.

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edge-to-face type interaction

Figure 2. The edge-to-face and face-to-face type interaction in the biscalix[4]arene complex.

Keywords: calixarenes; cation- π interaction; host-guest complexation.

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force on the complexation of the biscalix[4]arene, we designed a new biscalix[4]arene 2 with four phenol units that will interact with the peripheral protons of a disk-shaped guest in an edge-to-face manner. If the edge-to-face type interaction is the predominant interaction as the intermolecular attractive force for the complexation with the cationic guests, 2 would show enhanced inclusion ability for the cationic guests because the phenol units in 2 provide increasing π -basicity compared with the propoxybenzene units in 1. We now report the synthesis and the inclusion properties of the biscalix[4]arene 2.



The biscalix[4]arene **2** was synthesized from cone-25,27dibenzyloxycalix[4]arene¹⁴ **3a** according to Scheme 1. The products were identified by IR, ¹H NMR and mass

$$\begin{array}{c} \overbrace{QR_{1}}^{OR_{1}} & \overbrace{QR_{2}}^{OR_{2}} \\ \overbrace{X}^{OR_{1}} & \overbrace{QR_{2}}^{OR_{2}} \\ \overbrace{X}^{CH_{2}} & \overbrace{X}^{CH_{2}} \\ \overbrace{X}^{CH_{2}} & \overbrace{QR_{1}}^{CH_{2}} \\ \overbrace{R_{1}}^{CH_{2}} & \overbrace{R_{1}}^{CH_{2}} \\ \overbrace{R_{1}}^{H} = Bn, R_{2} = H, X = Br \\ \overbrace{3c}^{CR_{1}} = Bn, R_{2} = Pr, X = Br \\ \overbrace{3d}^{CR_{1}} = Bn, R_{2} = Pr, X = OH \\ \overbrace{3e}^{R} R_{1} = H, R_{2} = Pr, X = OH \\ \overbrace{3f}^{CR_{1}} = Bn, R_{2} = Pr, X = COH \\ \overbrace{3g}^{CR_{1}} = Bn, R_{2} = Pr, X = CH_{2}OH \\ \overbrace{3h}^{CR_{1}} = Bn, R_{2} = Pr, X = CH_{2}OH \\ \overbrace{3h}^{CR_{1}} = Bn, R_{2} = Pr, X = CH_{2}OH \\ \overbrace{3h}^{CR_{1}} R_{1} = H, R_{2} = Pr, X = CH_{2}OH \\ \overbrace{3h}^{CR_{1}} R_{1} = H, R_{2} = Pr, X = CH_{2}OH \\ \overbrace{3h}^{CR_{1}} R_{1} = H, R_{2} = Pr, X = CH_{2}Br \\ \overbrace{3a}^{I} & \overbrace{97\%}^{VII} \\ \overbrace{97\%}^{VII} \\ \overbrace{95\%}^{VIII} \\ \overbrace{95\%}^{VIII} \\ \overbrace{97\%}^{VIII} \\ \overbrace{97\%}^{VIII} \\ \overbrace{97\%}^{VIII} \\ \overbrace{97\%}^{VIII} \\ \overbrace{97\%}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{92\%}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{92\%}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{91}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{91}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{91}^{VIII} \\ \overbrace{91\%}^{VIII} \\ \overbrace{91}^{VIII} \\ \overbrace{$$

Scheme 1. Synthesis of 2. *Reagents and conditions*: (i) Br_2 , CHCl₃, 0°C; (ii) *n*-PrBr, NaH, DMF, 0°C; (iii) *n*-BuLi, THF, -78°C, 1 h; (iv) B(OCH₃)₃; (v) AcOH, H₂O₂; (vi) TMSBr, CHCl₃, rt, 1 h; (vii) CO₂; (viii) LiAlH₄, THF, reflux, 24 h; (ix) Cs₂CO₃, THF, reflux, 2 days.

spectral evidence and elemental analysis. The ¹H NMR spectrum of **2** shows two sets of doublets for the $ArCH_2Ar$ methylene protons, indicating that both of the two calix[4]arene skeletons adopt the cone conformation.

The inclusion properties of 2 to N-methylpyridinium (4) iodide were examined using ¹H NMR measurements. It is reported that the chemical shifts for the protons in the quaternary ammonium ions are only slightly shifted to a higher magnetic field in the presence of calix[4] arenes, and the cation- π interaction between the calix[4]arenes and the cationic guests is quite weak.¹² The ¹H NMR spectrum of 4 iodide (10.0 mM) in the presence of 2 (5.0 mM), on the other hand, gave two separated peaks for each proton at 25°C in CDCl₃, which are assigned to the complexed and uncomplexed 4. These peaks did not coalesce into an average peak even at 130°C in 1,1,2,2-tetrachloroethane- d_2 . This remarkably high coalescence temperature, $T_{\rm c}$, reveals that the dynamic process during the complexation and the decomplexation is much slower than the NMR time scale, suggesting that 4 is tightly encapsulated in the inner sphere of 2 and the complex is quite stable.

The peaks for all the protons in 4 were shifted to the upper magnetic field upon complexation, i.e. the chemical shifts of the α -, β -, γ - and *N*-methyl protons in the complexed 4 were 3.82, 4.08, 4.91 and 1.61 ppm and those in the free 4 were 9.38, 8.12, 8.48 and 4.73 ppm, respectively. These significant upfield shifts rationalized by the shielding effect of the benzene rings in 2 imply that 4 is included in the inner sphere of 2. Indeed, these upfield shifts caused by the complexation were not observed for nonionic guests such as pyridine, picoline, benzene or toluene. The essential cationic charge in the guests establishes the significant contribution of the cation- π interaction to the formation of the complex in 2.

The association constants K_a of 1 and 2 for 4 picrate were estimated using UV-vis spectroscopy. For example, the UV-vis spectra of 4 gave an absorbance maximum at 361 nm in the absence of 2 in CHCl₃. With the addition of 2, the absorbance at 361 nm decreased and that at 378 nm assigned to the complex increased. This bathochromic shift indicates that 4 and the picrate anion form a separated ion pair and the picrate is left outside of **2**. This behavior of **2** as a molecular capsule is characterized by the steric shielding of 4 from contact to the picrate. The plot of the absorbance versus [2]/[guest] gave a gradual curve indicating the 1:1 stoichiometry of the host and guest for the complex. The $K_{\rm a}$ values were determined by the curve fit method for these plots using the computer-assisted nonlinear leastsquare procedure. The K_a for the complex of 1 with 4 was 1.55×10^4 dm³ mol⁻¹, whereas that of **2** was $5.13 \times$ 10⁶ dm³ mol⁻¹, which is greater by 330-fold than that of 1. Obviously, this significant enhancement in K_a is attributed to the increasing π -basicity of the flattened

benzene rings, which interact with the guest protons in an edge-to-face manner.

Computational studies using molecular mechanics and semiempirical molecular orbital calculations with PM3 approximation predicted the pinched cone conformation for both calix[4]arene skeletons in 2. The significant enhancement in K_a for the complex of 2 cannot be explained by a similar structure predicted for 1. The plane canting angle, which is defined as a dihedral angle between the phenyl plane and the mean plane of the bridging methylene carbons, for 2 is larger than that for 1. However, the CPK model and computer-assisted calculation examination revealed that 1 possessed a suitable room of the inner cavity to form the tightly fit complex with N-methylpyridinium whereas the cavity of 2 was somewhat large to suitably include it. In spite of this disagreement on the size of 2 and the guest, the fact that the K_a for 2 is larger than that for 1 will support the explanation by not the steric factor but by an electrostatic factor.

The most definitive proof for the structure of 2 came from an X-ray crystallographic analysis.¹⁵ The single crystal was obtained as a $2 \cdot 3$ CHCl₃ complex from the CHCl₃ solution. One CHCl₃ molecule occupies the inner sphere of 2 and the others are in the crystal lattice. As shown in Fig. 3, both calix[4]arenes in 2



Figure 3. X-Ray crystal structure of 2. The hydrogen atoms are omitted for clarity.

adopt the pinched cone conformation with C_{2v} symmetry, i.e. the two benzene rings connected with the spacers at the *p*-positions stand almost parallel and the other two phenol units are flattened in each calix[4]arene skeleton. When 2 forms the complex with a disk-shaped guest, the guest is probably sandwiched between the perpendicular benzene units, and consequently the highly directional C–H bond in the guest will be in contact with the phenol units in 2 in an edge-to-face manner.

The UV-vis spectra of 4 iodide (0.5 mM) gave an absorbance maximum at 371 nm in the absence of 2 in CHCl₃ which is assigned to the charge-transfer (CT) band from the iodide anion to the pyridinium cation. By the addition of 2 (0.5 mM), the absorbance at 371 nm disappeared and no other band assigned to the CT band appeared. Although the CT band for the complex of 2 with a stronger acceptor molecule, 1,1'-dimethyl-4,4'-bipyridinium, was observed as a shoulder at longer wavelengths than 400 nm, the chemical shift changes in the ¹H NMR spectra were not observed for the 1,1'dimethyl-4,4'-bipyridinium upon the complexation, indicating that 2 formed the *exo*-complex with the guest molecule and it was located outside of 2. The π - π interaction of the face-to-face type in the complex of 2 can be reasonably regarded as the CT interaction, because it is the π - π stacking between the acceptor aromatic molecule with a positive charge and dialkoxybenzene. However, the UV-vis data obviously support the extremely weak possibility that the main driving force for the complexation of 2 with the N-methylpyridinium is the CT interaction of the face-to-face type.

The C–H bonds have been considered to weakly interact with a molecular fragment bearing a partial negative charge or polarized electron cloud, because they generally have a small dipole moment with a positively charged hydrogen atom. The positive charge significantly enhances the polarity of the C–H bonds and the acidity of the hydrogen atom in the guests. Therefore, the positive charge in the guests is essential for the host–guest systems of the biscalix[4]arenes. The preorganized phenol units in **2** behave as a π -base. The property of the hydroxy group as an electron-donating substitution is not much different from that of the propoxy group; Hammett constant $\sigma_p = -0.37$ and $\sigma_m =$ 0.12 for OH, $\sigma_p = -0.27$ and $\sigma_m = 0.12$ for OMe. However, the hydroxy groups in **2** form the hydrogen bonding to the neighboring propoxy groups and the hydrogen bonding must enhance their polarization.

In conclusion, the present study showed that the biscalix[4]arene involving the phenol units has improved inclusion ability for the *N*-methylpyridinium ion due to the cation- π interaction, and the contribution of the CH- π interaction with the edge-to-face contact to the cation- π interaction is important. An appropriate molecular design for the calixarene host proved that the edge-to-face interaction was useful as an intermolecular attractive force for molecular recognition.

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- 15. Crystal data: C₇₃H₇₅Cl₉O₁₀, M=1431.47, monoclinic, a = 13.3236(3), b = 13.2853(2), c = 19.8984(4) Å, $\beta =$ $101.6628(4)^{\circ}$, $V = 3449.4(1) \text{ Å}^3$, T = 93 K, space group Pc (no. 7), Z=2, μ (Mo K α)=4.23 cm⁻¹, 30622 reflections measured, 7905 unique ($R_{int} = 0.039$) which were used in all calculations. The final $R(F^2)$ was 0.103 (all data). One chloroform molecule is disordered, showing two different orientations with 50% statistical distribution in the inner sphere of 2. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 164699. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].