

Communications

First Calix[8]arene with Regioselectively Functionalized Upper Rim. Apparent Observation of Intramolecular Hydrogen-Bond Flipping

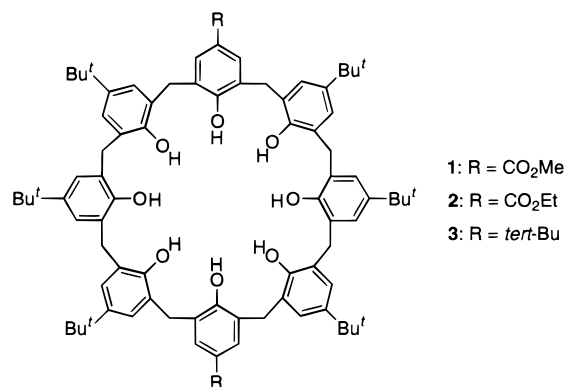
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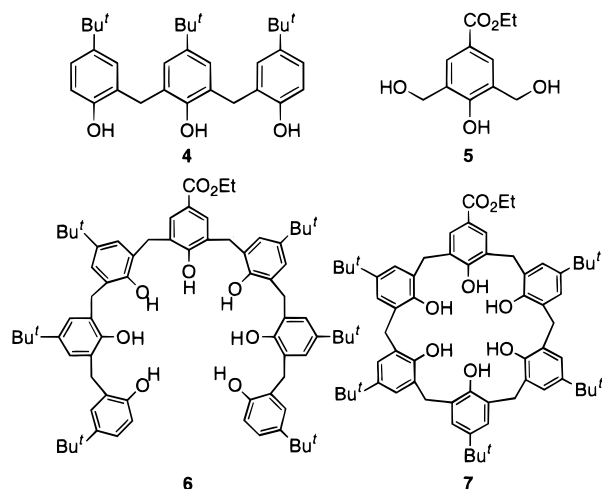
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“Calixarene” is a general term for a series of macrocyclic phenol condensates connected with methylene bridges and holds a significant position in host–guest chemistry together with crown ether and cyclodextrin.¹ Especially, calix[8]arene serves as a fascinating candidate for supramolecular chemistry because of its inherent large diameter of 8.6 Å and the noticeable properties such as the double incorporation of metal ions,^{2a} C₆₀ isolation from fullerene soot,^{2b,c} and the formation of ion-sensing film.^{2d} Chemical modifications of the framework enable us to control the static and dynamic natures of the molecule.^{1a,b} However, the great difficulty in achieving regioselective functionalization of the framework, mainly due to the complete equivalence of the reactive sites, has hampered the growth of its chemistry compared with the smaller calixarenes. As for the lower rim, Neri has recently reported regioselective control with the aid of weak inorganic base.³ On the other hand, modification at the upper rim has so far been performed only by the introduction of eight uniform substituents, and therefore, the regioselective functionalization at the upper rim is unprecedented to date. Here, we report a convenient and general method for constructing the calix[8]arene regioselectively modified at the upper rim, followed by the successful preparation of **1** and **2**, which serve as building blocks for supramolecules because the regioselectively introduced ester moieties are easily functionalizable. In addition, we also report the variable-temperature NMR showing a novel dynamic process of which observation was intrinsically impossible in the highly symmetrical *p*-*tert*-butylcalix[8]arene **3**. To the best of our knowledge, **1** and **2** are the first examples of calix[8]arene derivatives carrying different substituents at the upper rim.

To accomplish regioselective modification at the upper rim, Böhmer’s “3 + 1” methodology,⁴ which successfully yielded asymmetric calix[4]arenes, was extended for the preparation of calix[8]arenes **1** and **2** and designated as convergent “7 + 1” fragment condensation. The “7” fragment



6 was synthesized in 35% yield by acid-catalyzed condensation between *p*-*tert*-butylphenol condensate **4**⁵ and bisalcohol **5**.⁶ Subsequent acid-promoted ring closure using equimolar amounts of the “7” fragment **6** and “1” fragment **5** afforded calix[8]arene **2** in 9.1% yield. The fairly low yield reflects the fact that this “7 + 1” condensation was associated with the formation of various linear and cyclic byproducts. Very interestingly, one of them was found to be a ring-shrunk calix[6]arene **7** (7.3%). Mendoza reported a similar side reaction that involved direct transformation from a calix[6]arene to a calix[4]arene under acidic conditions.⁷ However, the formation of **7** is not likely to be via the direct [8]-to-[6] pathway because no changes of **2** were detected under the same conditions used for the **5** + **6** → **2** reaction. Finally, an additional calix[8]arene **1** was prepared by transesterification of **2** with methanol in an autoclave (32%).



Dynamic NMR spectra of calix[8]arenes **1** and **2** were measured in a sealed tube using chloroform-*d* as solvent. Although both compounds revealed almost the same spectral changes over the range of –50 to +90 °C, ethyl ester **2** was found to be unsuitable for extensive analyses because of the complicated superposition of the methylene signals of the

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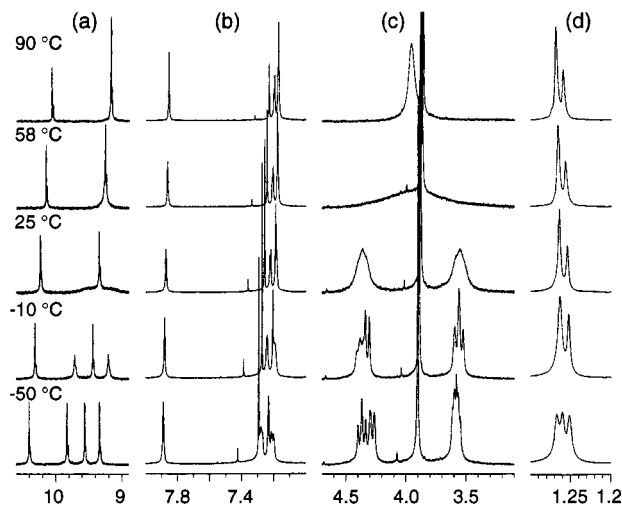


Figure 1. Enlarged ^1H NMR spectra (400 MHz) of **1** at relevant temperatures in CDCl_3 : (a) hydroxyl, (b) aromatic, (c) benzylic and CO_2Me , and (d) *tert*-butyl regions. The intensity scales are different for each region.

ethyl groups and the benzylic bridges. Alternatively, methyl ester **1** had enough separation to investigate the dynamic process of the calix[8]arene in detail. On increasing the temperature from -50 to $+90$ $^\circ\text{C}$, drastic and gradual changes in the signal shape were observed in the phenolic hydroxyl, benzylic, and *tert*-butyl regions as shown in Figure 1. The hydroxyl groups appeared as four singlets at -50 $^\circ\text{C}$, but with a rise in temperature two of them were subjected to chemical exchange (T_c 30 $^\circ\text{C}$), whereas another two remained unaltered (Figure 1a). As can be seen from Figure 1c, the benzylic region at -50 $^\circ\text{C}$, which was assigned to be four pairs of AB doublets from the resolution-enhanced spectrum by a mathematical treatment of the FID signal, turned into a broadened singlet (T_c 58 $^\circ\text{C}$).⁸ Moreover, three singlets in 1:1:1 ratio of the *tert*-butyl groups changed to two singlets in a 2:1 ratio as shown in Figure 1d.

Comparison of the dynamic NMR spectra of **1** and **3** revealed large differences such that the spectral changes of **1** opened from -30 $^\circ\text{C}$ while that of **3** was almost undetectable up to 10 $^\circ\text{C}$.⁹ Thorough assignments with the aid of 2D NMR experiments at -50 $^\circ\text{C}$ (COSY and phase-sensitive ROESY) led to the conclusion that the temperature-dependent spectra of **1** were rationally interpreted by a combination of two kinds of dynamic processes, i.e., (1) macrocyclic ring inversion of the pleated loop conformation¹⁰ of calix[8]arene and (2) directional change of the intramolecular hydrogen bond array.¹¹ The activation energy (ΔG^\ddagger) of the former process was estimated from the changes in the benzylic region to be 15.2 kcal/mol,¹² which agrees very closely with that of the parent calix[8]arene **3** (15.7 kcal/mol).⁹ At -50 $^\circ\text{C}$, the appearance of the four sharp singlets of the hydroxyl groups along with the three singlets of the *tert*-butyl groups implied the presence of a C_2 axis perpendicular to the molecular plane, which classified the aromatic systems into four types denoted as A, B, C, and D as shown in Scheme 1.

(8) Two singlets rather than a broadened singlet are expected for the structurally different methylene bridges. Two singlets were observed at room temperature when pyridine- d_5 was used as solvent.

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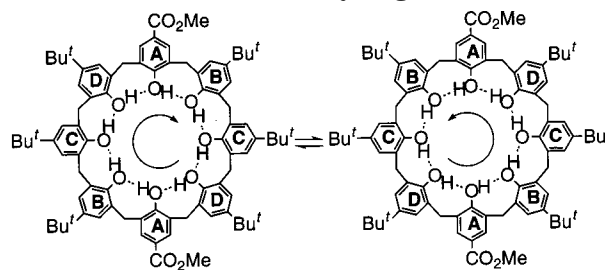
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(11) Hydrogen-bond reversal can be induced either by disrupting the hydrogen bonds sequentially or by a tunneling mechanism as mentioned in ref 15.

(12) Almost the same ΔG^\ddagger values were obtained from the four pairs of benzylic AB doublets (T_c 58 $^\circ\text{C}$) of which parameters were as follows: (a) ΔG^\ddagger 15.2 kcal/mol, $\Delta\delta$ 275 Hz, and $J = 13.3$ Hz, (b) 15.2 kcal/mol, 277 Hz, 14.0 Hz, (c) 15.1 kcal/mol, 321 Hz, 13.1 Hz, and (d) 15.1 kcal/mol, 315 Hz, 13.3 Hz.

Scheme 1. Directional Change of the Cyclic Array of Intramolecular Hydrogen Bonds



The depicted intramolecular hydrogen bond array was confirmed by an IR signal of 3237 cm^{-1} and the phase-sensitive ROESY spectra.¹³ Judging from the sharp signals of the hydroxyl and *tert*-butyl groups, such directional flipping between clockwise and counterclockwise arrays was frozen at -50 $^\circ\text{C}$, while it was facilitated with a rise in temperature. Here, it is worth noting that only protons attached to the B and D rings were exposed to chemical exchange and those of the A and C rings remained unchanged. In other words, hydroxyl functionalities of the A and C rings form hydrogen bonds only to adjacent *p*-*tert*-butylphenol residues irrespective of the direction, whereas those of the B and D rings are very sensitive to the direction that switches the hydrogen bond acceptors with different electron density, that is, *p*-*tert*-butylphenol or *p*-hydroxybenzoate residues. Therefore, only the B and D rings are anticipated to be exchangeable. The ΔG^\ddagger for the hydrogen bond reversal was calculated to be 14.1 kcal/mol from the spectral changes in the hydroxyl region (T_c 30 $^\circ\text{C}$ and $\Delta\delta$ 201 Hz).¹⁴ This relatively large ΔG^\ddagger in comparison with that of a calix[6]arene derivative (10.6 kcal/mol)¹⁵ suggests that the strength of the hydrogen bond should play a crucial role in the conformational stability of calixarenes.

Although the presence of hydrogen-bond flipping in the known calix[8]arenes has so far been unobserved due to the intrinsic symmetrical reason, the present compounds **1** and **2** with lower symmetry shed some light on the nature for the first time in calix[8]arene chemistry. The host ability of **1** and **2** as well as the transformation into supramolecules using these compounds as building blocks are being investigated in our laboratory.

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Supporting Information Available: Experimental procedures, characterization data, spectral data for all new products, and the dynamic NMR spectra of compounds **1** and **2** (25 pages).

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(13) In the phase-sensitive ROESY spectra at -50 $^\circ\text{C}$, each of the hydroxyl groups showed NOEs with the two neighboring ones.

(14) The activation energy for the hydrogen-bond flipping was also estimated from the spectral changes in the *tert*-butyl region (ΔG^\ddagger ca. 14 kcal/mol, T_c ca. -20 $^\circ\text{C}$, and $\Delta\delta$ 2.2 Hz). The reviewer of this paper pointed out that the energy barrier was too high. The calix[8]arene skeleton may adopt the appropriate conformation for the formation of hydrogen bonding, but we cannot further specify the exact reason only on a basis of the NMR data at present.

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