The *Cone*-to-*Cone* Interconversion of Partially O-Methylated Calix[4]arenes: First Experimental Values for the Energy Barriers

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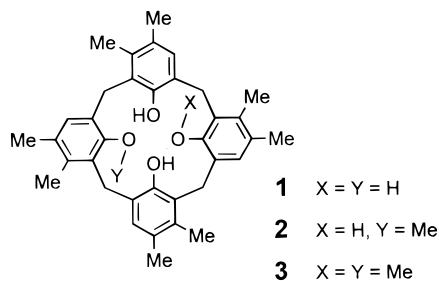*Nagoya University, Fuo-Cho, Chikusa-Ku*
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Calix[4]arenes,[1] macrocyclic compounds in which four phenolic units are linked via methylene bridges *ortho* to their hydroxy groups, assume the so-called *cone* conformation, which is stabilized by a cyclic array of intramolecular hydrogen bonds. However, the molecules are not entirely rigid, and the two identical *cone* conformations interconvert with a rate roughly comparable to the usual NMR time scale.[2] In contrast, tetramethyl ethers of calix[4]arenes exist in various conformations, where the *partial cone* conformation is usually predominant,[3] since intramolecular hydrogen bonding cannot contribute to the stabilization of any conformation. Again, the molecule is flexible, showing that the methoxy groups are still small enough to pass through the annulus.

Interesting properties are found for the partially O-methylated calix[4]arenes,[4] especially the mono- and the 1,3-dimethyl ethers, which exist exclusively in a *cone* conformation. This conformation is stable on the NMR time scale up to the highest temperatures studied (125 °C in d_2-tetrachloroethane).[5] The obviously higher energy barriers of the *cone* → *cone* interconversion in comparison to calix[4]arenes and their tetramethyl ethers must be due to a combination of two effects, the stabilization by hydrogen bonding and the larger steric requirements of the methoxy group in comparison to the hydroxy group. While this explanation is qualitatively plausible, quantitative experimental values for the energy barrier[6] are as yet unknown.

Figure 1. Resolution of **2** by chromatography on Chiralpak AD.

Calix[4]arenes (e.g. **1**)[7] composed of meta-substituted phenols such as 3,4-dimethylphenol are chiral in their *cone* conformation[8] and their *cone* → *cone* inversion[9] converts one enantiomer into its mirror image. Thus, investigation of this thermal racemization by measurement of rate constants as a function of temperature should enable the experimental determination of the energy barriers for the chiral partial methyl ethers **2** and **3** which again exist as pure *cone* conformers.
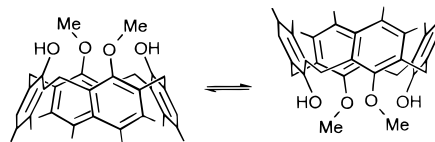
The resolutions of **2** an **3** were achieved by chromatography with use of chiral stationary phases.[10] An example is shown in Figure 1. The separation factor α is distinctly higher for **3** than for **2**.[11] The CD spectra of the resolved materials could then be followed as a function of time[12] (Figure 2a) and the decrease of the e.e. follows the expected first-order rate law up to 85% conversion (Figure 2b). Thus, the rate constant *k* for the ring inversion is derived (−ln(ee) = 2 kt). Arrhenius plots (Figure 2c) and the Eyring equation finally lead to the activation data collected in Table 1.

1 X = Y = H
2 X = H, Y = Me
3 X = Y = Me

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(1) For reviews see: Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745. Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, 1989, *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, 1998.
(2) From variable-temperature NMR energy barriers of $\Delta G^{\ddagger}$ = 14.6−15.7 kcal mol^{-1} (*T* = 303−325 K) were derived for calix[4]arenes in CDCl$_3$. See ref 1 and references cited there.
(3) For a recent computational and NMR spectroscopic study see: van Hoorn, W. P.; Briels, W. J.; van Duynhoven, J. P. M.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Org. Chem.* **1998**, *63*, 1299−1308.
(4) For an early study see: Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409−426.
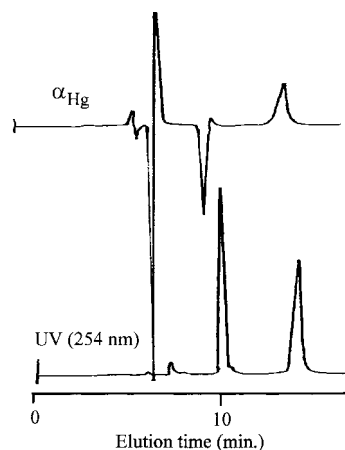
(5) Groenen, L. C.; Steinwender, E.; Lutz, B. T. G.; van der Maas, J. H.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1893−1898.
(6) A recent computational study predicts barriers of 35.1 (monomethoxy), 32.2 (1,2-dimethoxy), 30.3 (1,3-dimethoxy), and 27.0 kcal mol^{-1} (trimethoxy calix[4]arene): van Hoorn, W. P.; Morshuis, M. G. H.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Phys. Chem. A* **1998**, *102*, 1130−1138.
(7) (a) Wolff, A.; Böhmer, V.; Vogt, W.; Ugozzoli, F.; Andreetti, G. D. *J. Org. Chem.* **1990**, *55*, 5665−5667. (b) Andreetti, G. D.; Böhmer, V.; Gordon, J. G.; Tabatabai, M.; Ugozzoli, F.; Vogt, W.; Wolff, A. *J. Org. Chem.* **1993**, *58*, 4023−4032.
(8) The 1,2-alternate conformation (*C_i*-symmetry) and the 1,3-alternate conformation (*S$_4$*-symmetry) would be achiral.
(9) An energy barrier of $\Delta G^{\ddagger}$ = 13.4 kcal mol^{-1} (*T* = 291 K) was found for **1** in CDCl$_3$; this is slightly lower than that for *p*-methylcalix[4]arene ($\Delta G^{\ddagger}$ = 14.6 kcal mol^{-1} at *T* = 323 K) under analogous conditions; see ref 7b.
(10) The resolutions of **2** and **3** were carried out by HPLC on amylose tris(3,5-dimethylphenylcarbamate) as the chiral stationary phase (Daicel Chiralpak AD) with hexane/2-propanol (9:1) as the eluent: column size 25 × 0.46 cm i.d.; flow rate 0.5 mL/min; detection by UV (JASCO MD-910) and polarimetry (JASCO OR-990). Separation characteristics: for **2**, k_1' = 0.67, k_2' = 1.36, α = 2.04(−); for **3**, k_1' = 2.28, k_2' = 9.99, α = 4.38(−).
(11) The separation factors are also distinctly better than those formally reported for mono- and 1,3-diethers of **1**: Pickard, S. T.; Pirkle, W. H.; Tabatabai, M.; Vogt, W.; Böhmer, V. *Chirality* **1993**, *5*, 310−314.
(12) To measure the racemization rates the enantiomers resolved by HPLC were directly collected in an optical cell (c ≈ 0.06−0.18 g/L) where their circular dichroism was monitored with a JASCO J-720.
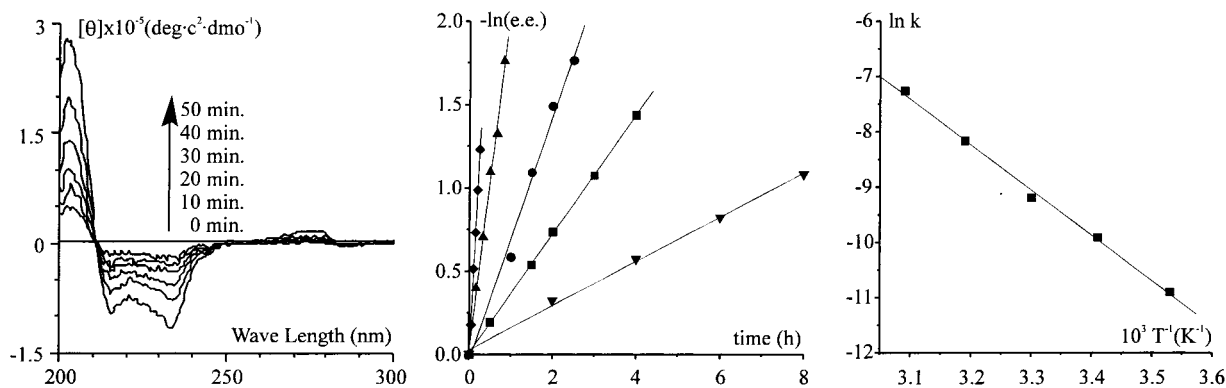
Figure 2. Racemization kinetics of **2** in hexane/2-propanol (from the left to the right): (a) CD spectra of (−)-**2** as a function of time at 313.8 K; (b) first-order plots of −ln(ee) versus time at 283.2, 293.5, 303.2, 313.8, and 323.9 K; and (c) Arrhenius plot of ln k versus 1/T.

Table 1. Activation Parameters for the Racemization (*Cone*-to-*Cone* Interconversion) of Chiral Calix[4]arenes

	2	**3**
E_A (kcal mol^{-1})[a]	21.3	16.2
ln A[a]	24.6	17.8
$\Delta H^{\ddagger}$ (kcal mol^{-1})[b]	20.7	15.6
$\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})[c,e]	−11.7	−25.3
$\Delta G^{\ddagger}$ (kcal mol^{-1})[d,e]	24.3	23.3

[a] $\ln k = \ln A - E_A/(RT)$. [b] $\Delta H^{\ddagger} = E_A - RT$. [c] $\Delta S^{\ddagger} = R \ln(Ah/(ekT))$. [d] $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$. [e] T = 303 K.

As expected, distinctly higher values for $\Delta G^{\ddagger}$ are found for **2** and **3** in comparison to **1**.[9] However, they are by far not as high as those calculated for the corresponding derivatives of the basic (unsubstituted) calix[4]arene.[6] Comparison of the $\Delta G^{\ddagger}$ values determined by variable-temperature ¹H NMR for **1** and *p*-methyl calix[4]arene ($\Delta\Delta G^{\ddagger}$ = 1.2 kcal mol^{-1})[9] makes it unlikely that this difference is caused by the *m*-methyl groups. In agreement with the theoretical expectations the barrier is higher for the monomethyl ether **2** (with three intramolecular hydrogen bonds) than for the dimethyl ether **3** (with two intramolecular hydrogen bonds). This difference is more pronounced in $\Delta H^{\ddagger}$ than in $\Delta G^{\ddagger}$

(around room temperature), due to a strong compensation by $\Delta S^{\ddagger}$. It is unclear at the moment why the transition state for the interconversion of dimethyl ether **3** is distinctly higher ordered in comparison to the ground state than that for **2**. However, an overintepretation of the activation parameters, which most probably are also solvent dependent, should not be attempted at this time.

In conclusion, we have demonstrated for the first time an experimental procedure to determine the activation parameters for the conformational interconversion of partially O-methylated calix[4]arenes. We are presently extending these studies to the 1,2-dimethyl and the trimethyl ether of calix[4]arene **1**, to other chiral calix[4]arenes having no *m*-substituent,[13] as well as to different solvents. We hope to obtain in this way a more detailed understanding of the delicate balance between steric requirements (OMe vs OH) and hydrogen bonding (OH···OH and OH···OMe), a problem that is also of general interest.

(13) Böhmer, V.; Wolff, A.; Vogt, W. *J. Chem. Soc., Chem. Commun.* **1990**, 968−970.