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On the Conformational Isomers in Tetra-O-alkylcalix[4]arenes

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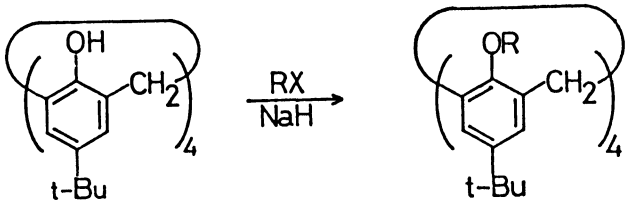
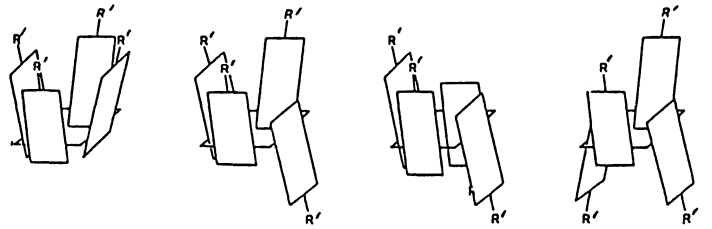
p-t-Butylcalix[4]arene (1_4H) was alkylated with RX (R= Me, Et, Pr, and Bu) and the products (1_4R) were analyzed by HPLC and ^{1}H NMR. It was found that (i) ring inversion arising from the oxygen-through-the-annulus rotation can be inhibited by R greater than Et, (ii) "cone" and "partial cone" result in a 1:1 ratio, and (iii) thermodynamically, the "partial cone" conformation is most stable.

Calixarenes are cyclic oligomers made up of benzene units just as cyclodextrins are made up of glucose units. Although these two macrocyclic compounds have a similar cavity-shaped architecture, there exists a basic difference: the cyclodextrin cavity is conformationally fixed, whereas the conformational freedom still remains in the calixarene cavity.[1-3] It is known that introduction of alkyl or acyl substituents into the OH groups suppresses the conformational freedom because of steric hindrance (i.e., inhibition of the oxygen-through-the-annulus rotation) and affords conformational isomers.[2,4,5] However, a relation (if any) between the substituent effect and the isomer distribution is hardly understood. For example, two isomers, "partial cone" and "1,3-alternate" were isolated from tetra-O-acetylation of calix[4]arene[6] whereas only "cone" isomers were isolated from tetra-O-butylation of p-sulfonatocalix[4]arene[7] and tetra-O-(t-butoxycarbonyl)methylation of p-t-butylcalix[4]arene,[8] but the reason for the isomer distribution has never been explained. In order to establish the possible relation between the substituent effect and the isomer distribution we carried out a reaction of RX (R=Me, Et, Pr, and Bu) with p-t-butylcalix[4]arene (1_4H) and analyzed the products in detail by HPLC and ^{1}H NMR.



1_4H 1_4R

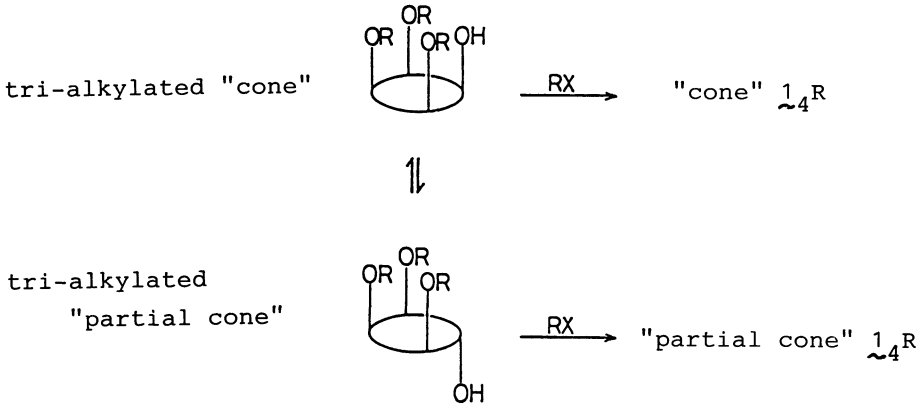
Basically, there can exist four different conformational isomers for calix[4]arenes (as illustrated below). These isomers can be differentiated by ^{1}H NMR: the $ArCH_2Ar$ methylene protons in the "cone" isomer give a pair of doublets, those in the "1,3-alternate" isomer give a singlet resonance, and those in other two isomers give more complex patterns because of low symmetry of their ring systems.[9]



cone partial cone 1,2-alternate 1,3-alternate

$\underset{\sim}{1}_4$H (1.0 g, 1.54 mmol) in THF(35 ml)-DMF(3.5 ml) mixed solvent was treated with oil-dispersed NaH (1.0 g, 25 mmol) at reflux temperature for 4 h. After cooling RX (80 mmol) was added dropwise and then the mixture was refluxed for 2 h. The raw products were subjected to HPLC analysis to determine the isomer distribution. The isomers were separated by a preparative TLC method. The conformations were assigned by ^{1}H NMR spectra reported by Gutsche et al.[6] The results are summarized in Table 1.

$\underset{\sim}{1}_4$Pr and $\underset{\sim}{1}_4$Bu prepared by the reaction with RBr contained "cone" and "partial cone" approximately in a 1:1 ratio (Fig. 1). Even though the two isomers isolated by TLC were heated in 1,1,2,2-tetrachloroethane at reflux temperature for 12 h, the isomerization did not take place. This establishes that these alkyl substituents can sterically inhibit the oxygen-through-the-annulus rotation. Thus, the product distribution is kinetically controlled when the fourth alkyl group comes in. The decrease in the "cone" fraction for PrI (Table 1) suggests that tri-alkylated "cone" is more crowded than tri-alkylated "partial cone".



In contrast, $\underset{\sim}{1}_4$Me gave a single peak in HPLC. The ^{1}H NMR spectrum was temperature-dependent: the split pattern ascribable to "partial cone" at low temperature coalesces at about 60 °C to a singlet resonance. Thus, the methyl group is too small to fix the calix[4]arene ring and each benzene unit can

rotate in a speed comparable with the NMR time-scale. One can thus conclude that among four isomers of $\underset{\sim}{1}_4$Me "partial cone" is the most stable isomer from a thermodynamic viewpoint.

$\underset{\sim}{1}_4$Et is just intermediary between $\underset{\sim}{1}_4$Me and $\underset{\sim}{1}_4$Pr. The product obtained in refluxing THF (67 °C) was "partial cone". When heated in 1,1,2,2-tetrachloroethane (>100 °C), it gradually isomerized to "1,2-alternate".[6] By

Table 1. Distribution of conformational isomers

RX	Product	Yield[a] /%	Isomer distribution/% Cone	Partial cone
MeI	$\underset{\sim}{1}_4$Me	100	0	100[b]
EtI	$\underset{\sim}{1}_4$Et	100	0	100
PrI	$\underset{\sim}{1}_4$Pr	100	19	81
PrBr	$\underset{\sim}{1}_4$Pr	100	45	55
BuBr	$\underset{\sim}{1}_4$Bu	100	53	47

a) Determined by an HPLC method.

b) This isomer is a mixture of "inside" and "outside" partial cones.[9]

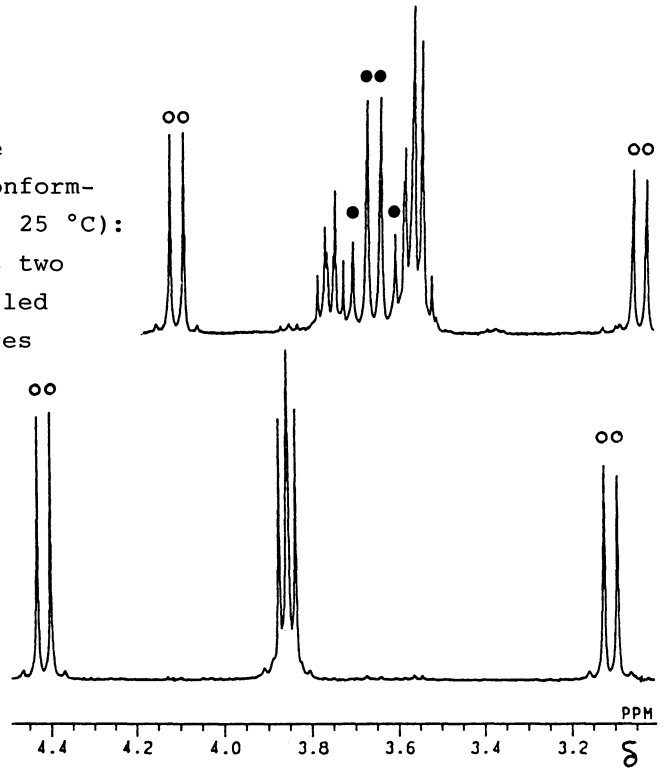


Fig. 1. Partial ^{1}H NMR for the $ArCH_2Ar$ methylene protons in conformational isomers of $\underset{\sim}{1}_4$Bu ($CDCl_3$, 25 °C): "partial cone" (upper) features two pairs of doublets (open and filled circles); "cone" (lower) features a pair of doublets (open circles).

following the progress of the reaction by HPLC we determined the rate constants for the forward reaction (partial cone $\longrightarrow$1,2-alternate: k_f) and the reverse reaction (1,2-alternate$\longrightarrow$ partial cone: k_r) and the equilibrium constants ($K = k_f/k_r$) at 125, 134, 143, and 146 °C, from which we computed activation parameters and thermodynamic parameters: k_f (at 398.2 K) = 2.73 x 10^{-5} s^{-1}, $\Delta H^{\ddagger}$ = 28.6 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -8.0 e.u.; k_r (at 398.2 K) = 3.04 x 10^{-5} s^{-1}, $\Delta H^{\ddagger}$ = 27.2 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -11.5 e.u.; K (at 398.2 K) = 0.898, ΔH = 1.4 kcal mol^{-1}, ΔS = 3.5 e.u. These parameters establish that "partial cone" is more stable than "1,2-alternate" in the enthalpy term whereas the reverse is true in the entropy term. Anyway, the fraction of "partial cone" increases with lowering medium temperature indicating that thermodynamically, "partial cone" is the most stable conformation.

In conclusion, the present study established for the first time the relation lying between the substituent effect and the isomer distribution. Further interesting is the finding on the order of the stability, partial cone > 1,2-alternate > cone. We are now trying to explain the stability order on the basis of theoretical calculations. Anyway, the "cone" isomer, which has frequently been isolated,[7,8] results only in kinetically-controlled systems. Böhmer et al.[10] and Vicens et al.[11] synthesized asymmetrically-substituted calix[4]arenes, but the optical resolution failed because of facile ring inversion or the formation of several conformational isomers. Our preliminary results indicate that when alkyl groups larger than Et are introduced into asymmetrically-substituted calix[4]arenes, they actually behave as optical isomers.

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