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Calix[4]arenes with Alkylidene Bridges, Synthesis and Conformational Properties

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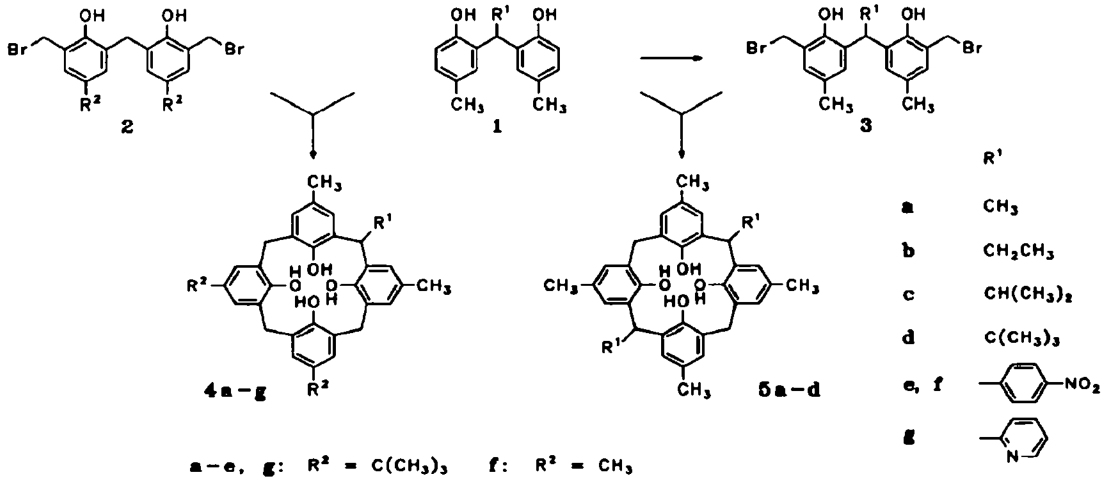
Abstract: Calix[4]arenes with one or two alkylidene bridges were synthesized by "2+2" fragment condensation. As predicted by molecular mechanics calculations aliphatic residues at the bridging carbon atom(s) prefer the equatorial position.

Calixarenes, usually prepared by alkaline condensation of t-butyl-phenol with formaldehyde, can be converted into various derivatives by chemical modification[1]. Obvious places to introduce additional functionalities are the phenolic oxygens, which can be converted to ether or ester groups and the p-positions, which are available for all types of electrophilic substitutions after removal of the t-butyl groups. Other potential sites, the methylene groups, are not as easily amenable to chemical modifications although their oxidation to carbonyl groups and the subsequent reduction to alcohol functions have been described[2]. "2+2" Fragment condensations of bisbromomethylated dinuclear compounds with other dinuclear compounds have been widely used to synthesize calix[4]arenes with different phenolic units[3] including compounds with "annelated" calix[4]arene systems[4] and occasionally also to obtain calix[4]arenes having one alkylidene bridge[5, 6]. We recently started to study this synthetic possibility in more detail. A publication by Italian colleagues[7] prompts us to report some preliminary results.



Alkylidene diphenols of type **1** with two free o-positions are easily prepared by condensation of the appropriate aldehyde and excess of p-cresol or p-t-butylphenol. Condensation of **1** with **2** leads to calix[4]arenes **4** with a single alkylidene bridge. Bromomethylation of **1** gives **3** and subsequent condensation with **1** results in the formation of calix[4]arenes **5**, in which two opposite methylene bridges are replaced by alkylidene bridges. The yields in the last step are in the range of 20 to 35% making these compounds available in reasonable quantities.

The first compounds of type **4** were synthesized, starting with various aromatic aldehydes. Their ^{1}H NMR spectra at low temperature are in agreement with the existence of two diastereomeric cone conformations. For instance, at 230 K for **4e** two singlets for t-butyl groups (1.17/1.18 ppm), for methyl groups (2.04/2.19 ppm) and for the methine proton (5.27/6.11 ppm) are found with nearly equal intensity. The pattern observed for the methylene protons can be understood as the superposition of two times two pairs of doublets (ratio 2:1) for the methylene bridges adjacent and opposite to the alkylidene bridge. The aromatic protons show four resolved (6.71/6.89/6.95/7.07 ppm) and four overlapping signals (around 7.02 ppm) for the phenolic units and four doublets (7.38/7.50 and 8.15/8.20 ppm) for the p-nitrophenyl residue. Finally two signals for the OH groups (10.01/10.16 ppm) are found. From variable temperature measurements in CDCl$_3$ an energy barrier of $\Delta G^{\ddagger}=15.3\pm0.1$ kcal/mol can be derived at 307 K (coalescence temperature of the methyl protons) for the cone to cone ring inversion process involving two diastereomeric conformations. The ratio of these diastereomers is 1.1 : 1 at 230 K and 1.03 : 1 at 275 K[8]. Similar results were obtained with **4f** ($\Delta G^{\ddagger}=14.9\pm0.1$ kcal/mol in CDCl$_3$)[9]. It should be mentioned that the diastereomerisation process changes the axial and equatorial protons, but that in contrast to a usual calixarene with only methylene bridges these protons remain diastereotopic in **4**. At fast exchange conditions (400 K) the methylene pattern of **4f** has the appearence of an asymmetric quintet, which is the result of the partial overlap of the two AB systems (in a 2:1 ratio) expected for these protons (Fig.1).

Against the usual intuition, the aromatic residue R in **4e,f** obviously has neither a strong influence on the barrier of the cone to cone ring inversion nor has it any distinct preference for the axial or equatorial position. In fact, molecular mechanics calculations reveal only small energy differences for the diastereomeric cone conformations with axial and equatorial positions of the residue R = phenyl. (A free energy difference of 0.24 kcal/mol would lead to a ratio of 1.55:1 at 275 K for the diastereomers). However, aliphatic residues show a strong preference of the equatorial position with energy differences of 1.9 to 2.4 kcal/mol, which would correspond to ratios of 32:1 to 81:1. The reason is found mainly in the angle bending term (see Table 1), where in the axial conformer larger deviations from the tetrahedral arrangement of the bridging methine occur.

To test this prediction we synthesized the calix[4]arenes **4a-d**. In all cases we found in the ^{1}H NMR spectrum at room temperature (400 MHz, CDCl$_3$) only one set of signals, in agreement with either the presence of a single cone conformation, or with two diastereomeric cone conformations rapidly interconverting on the NMR timescale[10]. Lowering the temperature to 220 K did not result in any change, suggesting that the spectrum observed corresponds to a single conformation frozen on the NMR timescale[11]. 2D-NOESY spectra show that the substituent R, as predicted by the calculations, adopts in all cases the equatorial position. This is evidenced by the NOE observed between the substituent and one aromatic signal as well as between the bridging methine and the hydroxylic protons. In all cases the population of the axial conformer was too low to allow its detection in the NMR spectra. It is not yet clear if this is entirely due to the energy difference between the two cone conformations, or if in addition a high energy barrier for the ring inversion exists, but obviously the sp^3 carbon atom of the aliphatic residues makes these groups more "voluminous" than the sp^2 carbon atom in the planar phenyl groups[12].

This observation of a strong conformational preference suggests that only one diastereomer should be formed in the synthesis of calixarenes **5a-d**. Indeed in all cases we obtained a single product[10], in which both residues assume the equatorial position, while in the case of R = phenyl two diastereomers with *cis* and *trans* arrangement of the two residues R would be expected[7].

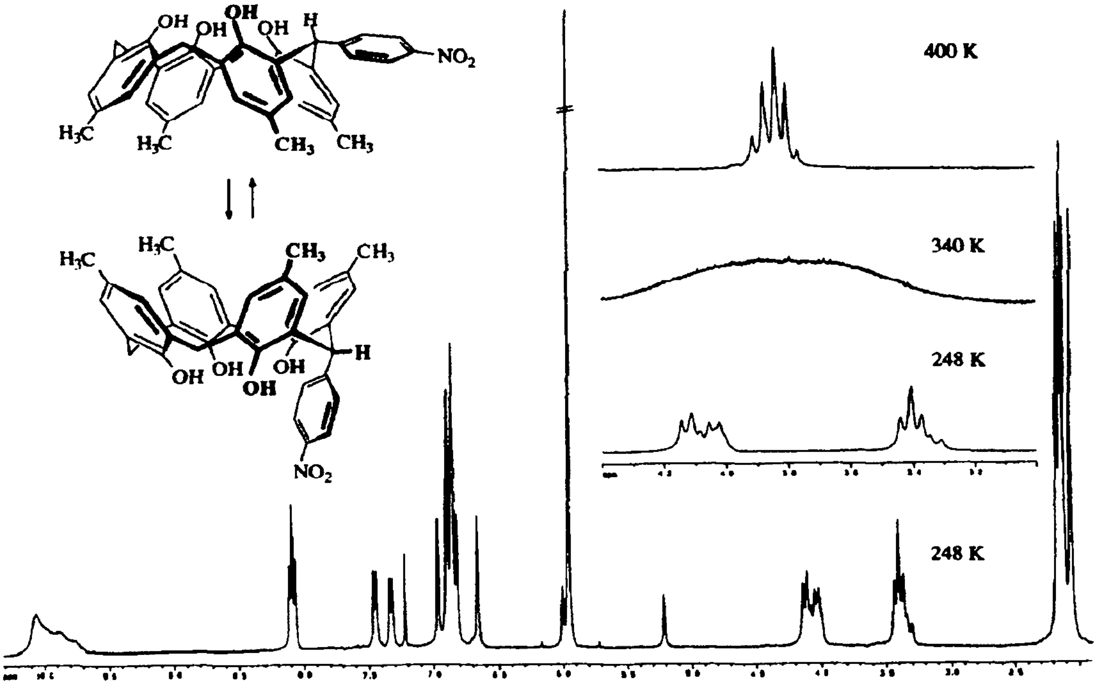


Fig. 1. Temperature dependent ^1H NMR spectra of compound **4f** in $Cl_2CDCDCl_2$

Compounds **4a-d** and **5a-d** to the best of our knowledge, are the first examples of calix[4]arenes with a strong conformational bias for the cone conformation with an equatorial position of the residue R. The situation may be compared to the all-*cis* isomer of resorcarenes which adopts exclusively the cone conformation with axial arrangement of the residues at the bridges[13,14]. In both cases this prefered conformation avoids an interaction of R and the OH groups which are *endo* in calixarenes and *exo* in resorcarenes. So far "conformational fixation" in calix[4]arenes has been achieved by bridges between the p-positions (at the upper rim)[15] or by the attachment of bulky substituents to the phenolic oxygens (at the lower rim)[1]. We are presently studying how the properties of calix[4]arenes (e.g. inclusion phenomena) are influenced by this, whether a similar stabilization of the cone conformation is also possible in calix[5]arenes, and if conformational preferences are exhibited by even larger members of the calixarene family.

Table 1. Differences $\Delta E = E_{equ} - E_{ax}$ in kcal/mol of the calculated energies[16] for the diastereomeric cone conformers of **4** with equatorial and axial position of the residue R.

Compound [R]	ΔE_{bs}	ΔE_{ab}	ΔE_{tors}	ΔE_{vdw}	ΔE_{elec}	ΔE_{total}
4a [CH_3]	-0.04	-1.98	-0.12	-0.38	0.41	-2.09
4b [CH_2CH_3]	-0.05	-1.93	-0.11	-0.43	0.52	-1.98
4c [$CH(CH_3)_2$]	-0.05	-1.89	-0.10	-0.32	0.45	-1.89
4d [$C(CH_3)_3$]	-0.09	-2.39	-0.34	-0.74	1.14	-2.36
4e [*p*-$NO_2C_6H_4$]	-0.04	-1.00	0.12	0.08	0.57	-0.24
4g [α-C_5H_4N]	-0.03	-1.07	0.12	0.04	0.66	-0.26

Abbreviations used: $E_{total} = E_{bs} + E_{ab} + E_{tors} + E_{oop} + E_{vdw} + E_{elec}$, E_{bs} = bond stretching energy, E_{ab} = angle bending energy, E_{tors} = torsional energy, E_{vdw} = van der Waals energy, E_{elec} = electrostatic energy.

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8. In $Cl_2CDCDCl_2$ a ratio of 1.5:1 was found for **4e** at room temperature.
9. The diastereomerisation barrier is somewhat solvent dependent. A value of $\Delta G^{\ddagger} = 15.6 \pm 0.1$ kcal/mol was found for **4f** in $Cl_2CDCDCl_2$.
10. For specific example the ^1H NMR data (200 MHz, $CDCl_3$, 293 K) of compounds **4a** and **5a** are as follows: δ_H, (ppm)
    4a. 1.20 (18 H, s, $C(CH_3)_3$), 1.67 (3 H, d, J=7.2, CH_3), 2.15 (6 H, s, CH_3), 3.43 and 4.20 (each 2 H, d, J=13.9, CH_2), 3.47 and 4.24 (each 1 H, d, J=13.8, CH_2), 4.70 (1 H, q, J=7.2, CH), 6.82 (2 H, s, ArH), 6.93 (2 H, s, ArH), 7.00 (2 H, d, J=2.3, ArH), 7.04 (2 H, d, J=2.3, ArH), 10.20 (4 H, s, OH);
    5a. 1.66 (6 H, d, J=7.2, CH_3), 2.16 (12 H, s, CH_3), 3.40 (2 H, d, J=13.9, CH_2), 4.17 (2 H, d, J=13.9, CH_2), 4.67 (2 H, q, J=7.2, CH), 6.80 (4 H, d, J=1.5, ArH), 6.91 (4 H, d, J=1,6, ArH), 10.06 (4 H, s, OH).
11. At the highest temperature studied (320 K) we observed in the less crowded systems broadening of the methylene signals, probably resulting from mutual exchange with the low populated axial conformer (the "hidden partner"); compare: Anet, F. A. L.; Basus, V. J., *J. Mag. Res.* **1978**, *32*, 339-343.
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