Conformational Dynamics of Calixarenes. Kinetics of Conformational Interconversion in 5,11,17,23-Tetra-*p*-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene under Entropic Control

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Abstract: The kinetics of interconversions of the four conformers of the title compound (partial cone (pc); cone (c); 1,2-alternate (alt,2); 1,3-alternate (alt,3)) were studied in chloroform and in a 50:50 binary mixture of chloroform and acetonitrile by 2D-EXSY ^{1}H NMR spectroscopy. The results are fully consistent with the coexistence of three one-step processes involving the partial cone conformation (pc ⇄ alt,2; pc ⇄ c; pc ⇄ alt,3). The rate constants for the forward processes are, for chloroform and the binary mixture, respectively, at 270 K, 0.0040 and 0.12, 1.6 and 3.4, and 2.1 and 4.7 s^{-1}. All the values of the activation enthalpies are close ($\Delta H^{\ddagger} \approx 60$ kJ mol^{-1}), while the entropies of activation are, respectively, −70, −16, and −29 J mol^{-1} K^{-1} in chloroform, indicating that the conformational exchange is under entropy control.

Introduction

Calixarenes,[1] cyclic oligomers of phenolic units linked through the ortho positions, are a fascinating class of receptacle molecules showing recognition properties both of metal or organic cations and of neutral molecules.[2] Variations in the structure result mainly from the number of oligomeric units, the nature of the bridges between the aromatic rings, or the type of substitution at the para and at the phenolic positions.[1a-c] Depending upon the relative orientations of the para and phenolic sites, the tetramer can adopt four different conformations: cone (c), partial cone (pc), 1,2-alternate (alt,2), and 1,3-alternate (alt,3).[1a] Among the myriad of possible structural variations, 5,11,17,23-tetra-*p*-*tert*-butyl-25,26,27,28-tetramethoxy calix[4]arene (**1**) is particularly interesting since it is one of the most simple derivatives of the series and the simultaneous presence of the four conformers can be detected on the ^{1}H NMR spectrum.[3] This allowed the determination of the relative stabilities of the four conformers in $CDCl_3$: pc ≫ alt,2 > c > alt,3 (at 243 K[3a,b] and 248 K[3b,c]; the order alt,2 > c is reversed at and above 258 K[3b]). However, no variable temperature, quantitative studies on the kinetics and mechanistic pathways of conformer interconversion have been published so far[4] on simple members of the calixarene family.

In this paper, it is demonstrated that *the kinetics of interconversion of the various conformers is controlled by entropic factors*, since the enthalpies of activation lie in a very short range of values. Moreover, the most thermodynamically unstable conformer (alt,3) is the kinetically preferred intermediate in the self-interconversion of the most thermodynamically stable conformer (pc ⇄ pc).

Since the four conformations of **1** in $CDCl_3$ solutions are in slow equilibrium on the ^{1}H NMR time scale until 320 K at 500 MHz, a complete kinetic analysis of all the interconversion processes could be done by 2D exchange spectroscopy.[5] The system was studied also in a more polar environment, namely, a binary mixture of acetonitrile and chloroform, which favors the cone conformer with its higher dipole moment.[3c]

Experimental Section

Chemicals and Solutions. 5,11,17,23-Tetra-*p*-*tert*-butyl-25,26,27,-28-tetramethoxycalix[4]arene (**1**) was synthesized from the tetrahydroxy derivative (Aldrich, 99%), following the procedure of Gutsche *et al.*[6]

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but with only a 2-fold excess of NaH and MeI. It was obtained with a purity of 99+% (as shown by the absence of any impurity on the 500 MHz ^{1}H NMR spectrum), after recrystallization in a chloroform/methanol mixture. A differential scanning calorimetry (DSC) measurement on **1** under nitrogen gave a maximum of the endothermic peak for the melting at 248.2 °C, with an onset at 239.6 °C, a value in good agreement with the literature value.[2b] The compound started to decompose at around 280 °C.

Acetonitrile-d_3 (99.5%) was purchased from Aldrich and chloroform-d (99.8%) from Cambridge Isotope Laboratories. Both solvents were dried over molecular sieves 4 Å. The binary mixtures of $CDCl_3$ and CD_3CN were 50:50 by volume. The $CDCl_3$ solution was 0.13 M in **1**, which is close to saturation at the lowest temperature of this study. In the case of the $CDCl_3/CD_3CN$ mixture, two solutions were used with concentrations of **1** of 36 and 72 mM. The latter concentration is close to saturation at the lowest temperature of this study.

NMR Measurements. The ^{1}H NMR spectra were recorded on a Bruker AMX-500 NMR spectrometer at 500.14 MHz. The samples were contained in 5 mm outer diameter tubes, and the spectra were recorded in deuterium locked mode without spinning to reduce T_1 noise. The temperature calibration was done with a thermocouple inserted in a nonspinning tube containing chloroform. The temperature was estimated to be reliable at ±0.5 K.

The longitudinal relaxation times of the methoxy and methylenic protons were measured in chloroform at all temperatures using the inversion-recovery pulse sequence. They ranged from 0.65 to 0.78 s for the methoxy and from 0.31 to 0.53 s for the methylenic protons. They were slightly higher in the acetonitrile/chloroform mixture. A standard NOESY pulse sequence was used for the 2D exchange (2D-EXSY) experiments.[5] The NMR parameters were chosen to obtain quasi quantitative spectra: relaxation delay time 2 s ($\geq 3T_1$), 90° pulse 6.1 μs, sweep width 3.8 kHz, acquisition time 0.136 s, 16 scans of 1024 points by 256 slices with a total measuring time per spectrum of 2.5−3 h. The spectra were recorded every 10 K, from 220 to 300 K (from 250 to 290 K for the mixed solvent). At each temperature, a series of six 2D-EXSY spectra were recorded, with mixing times (τ_m) ranging from 50 to 500 ms (from 20 to 300 ms for the mixed solvent).

Data Treatment. The 2D spectra were symmetrized, and the methoxy cross-peaks integrated using standard Bruker software. Each cross-peak intensity was referenced against the total intensity of the methoxy and methylenic region (for example, from 2.7 to 4.5 ppm at 270 K). In all the cases, the methoxy cross-peak intensities were then multiplied by the factor f, given in eq 1, in order to (a) reference them

$$f = (5/3)e^{-[\tau_m/T_1(\text{methoxy})-\tau_m/T_1(\text{methylene})]} \quad (1)$$

to the total intensity of the methoxy peaks only and (b) take into account the differences in T_1's for the methoxy and the methylenic protons. The term 5/3 originates from the number of methoxy and methylenic protons in **1**. The factor f decreases from 1.67 at mixing time 0 to ~1.3 at τ_m = 500 ms. This correction was not used for the binary mixture since shorter mixing times were used. The resulting corrected cross-peak intensities where then plotted against the mixing times and the rate constants extracted using the initial rate method. At low exchange rates (k < 0.05 s^{-1}, or 0.3 s^{-1} for mixed solvent) there is a linear relationship between the cross-peak intensities and the mixing time:[5c] $I_{j\to i} = k_{i\to j}p_i\tau_m$ where p_i is the equilibrium percentage of conformer i (see Figure 3, $T \leq 260$ K). For faster exchange an equation of the form[7c] $I_{j\to i} = A(1 - e^{-B\tau m})$ was fitted to the data (see Figure 3 for $T \geq 270$ K) and the slope of the tangent at the origin (mixing time 0) was calculated ($k_{i\to j} = AB/p_i$). Both the $I_{i\to j}$ and $I_{j\to i}$ integrals were used for the analysis to decrease the errors from the integration. As the partial cone conformer gives three peaks (ratio 2:1:1) the rate constant for the exchange involving this conformer could be determined using a total of six peaks. These peaks could be processed either simultaneously to give one rate constant or separately to give a number of rate constants equal to the number of processed peaks. The latter approach was preferred since the eventual overlaps with other exchange peaks or with NOESY peaks can make the quality of the various peaks quite different. It is only at the final stage of the data processing (Eyring plots) that a linear regression is done on all the data. All the curve fitting was done using standard nonlinear regression procedures. It was sometimes necessary to add a constant term to correct for overlaps, in which case the equation becomes $I_{j\to i} = A(1 - e^{-B\tau m}) + C$. The rate constants were then plotted in Eyring plots and the activation parameters calculated using a regression procedure by fitting to both the linearized and the exponential forms.[7]

(7) $\Delta S^{\ddagger}_{1,2}$ is lower than $\Delta S^{\ddagger}_{1,3}$ and $\Delta S^{\ddagger}_{c}$ with a confidence level of 99%. An exponential fit on the Eyring equation gave identical results in the limit of the experimental error (1 σ); in this case the confidence level mentioned above was 90%.

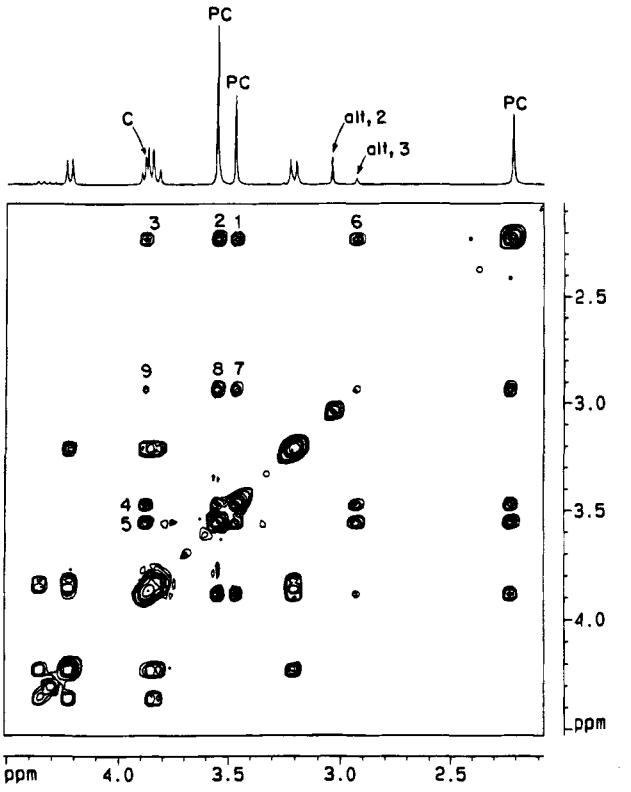

Figure 1. 1D ^{1}H and 2D ^{1}H EXSY NMR spectra (500 MHz) of the methoxy and methylene regions of calixarene **1** at 250 K (mixing time 500 ms, symmetrized data) in $CDCl_3$. The methoxy cross-peaks used in the analysis are numbered: partial cone−partial cone (1, 2); partial cone−cone (3−5); partial cone−1,3-alternate (6−8), and cone−1,3-alternate (9). Their mirror images (across the diagonal) where also used to give an idea of the accuracy of the integration.

Results and Discussion

Figure 1 shows a typical 2D-EXSY NMR spectrum at 250 K, in chloroform-d, in the region of the methylene and of the methoxy signals. The cross-peaks analyzed at that temperature are indicated. The cross-peaks for the exchanges involving alt,2 start appearing only at 260 K, under the conditions of this study. The methoxy cross-peaks were used for all calculations as they have a high intensity and are well resolved. Similarly, Figure 2 shows a 2D-EXSY NMR spectrum at 280 K for the binary mixture chloroform/acetonitrile. Figure 3 shows an example of the cross-peak volume analysis for the pc−pc exchange in chloroform (see Experimental Section, Data Treatment).

The rate constants for the various conformational exchanges were obtained on the basis of the model of Scheme 1 and, as such, constitute also a test of this model. The model assumes that only one conformational flip of an aromatic unit is allowed for the interconversion processes. In this model, suggested previously by Shinkai et al.[3b] to account for their equilibrium data, concerted processes in which an interconversion of two or more aromatic units would take place simultaneously are not considered.

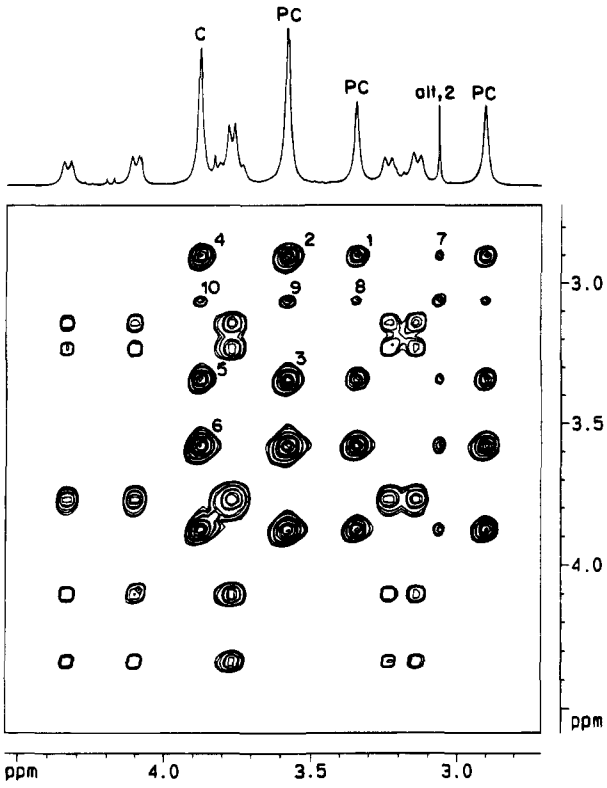

Figure 2. 1D ^1H and 2D ^1H EXSY NMR spectra (500 MHz) of the methoxy and methylene regions of calixarene **1** at 280 K (mixing time 300 ms, symmetrized data) in a binary mixture. The methoxy cross-peaks used in the analysis are numbered: partial cone−partial cone (1−3); partial cone−cone (4−6); partial cone−1,3-alternate (7−9), and cone−1,2-alternate (10). Their mirror images (across the diagonal) where also used to give an idea of the accuracy of the integration.

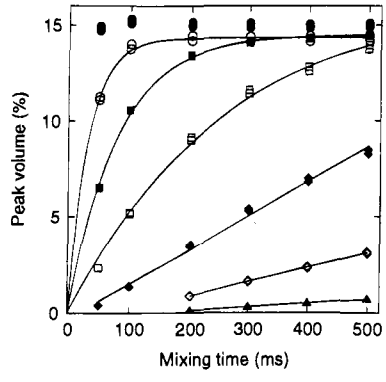

Figure 3. Cross-peak volumes as a function of the mixing times obtained from 240 to 300 K, in the case of the partial cone−partial cone exchange for cross-peak 2 in Figure 1.

In the range of temperature studied, a complete kinetic analysis could be performed, in the case of chloroform, for the three one-step processes (Scheme 1), as well as for the self-interconversion of the partial cone, and for the alt,3-cone two-step exchange. The cross-peaks for the alt,2−c exchange could only be seen in the binary mixture.

Since the rate constants can be obtained for each one-step process, since the thermodynamic equilibrium constants can be obtained from the integrations of the various species at each temperature, a complete thermodynamic and kinetic picture of the various conformational exchanges can be drawn. The thermodynamic data obtained in this study are in good agreement with those previously published.[3] Figure 4 shows the Eyring plots of the various processes, and Table 1 gives the values of the kinetic parameters for the one-step processes. In

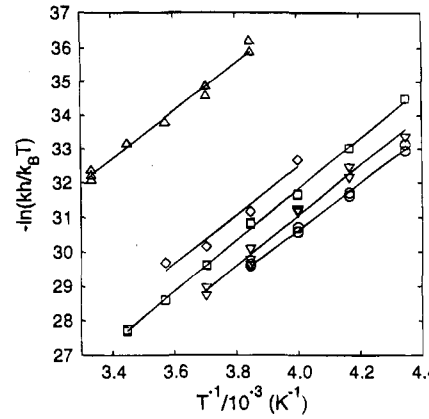

Figure 4. Eyring plots of the various conformational exchange rates of calixarene **1** in $CDCl_3$: (△) partial cone−1,2-alternate; (◇) cone−1,3-alternate; (○) partial cone−1,3-alternate; (□) partial cone−partial cone; (▽) partial cone−cone.

Scheme 1

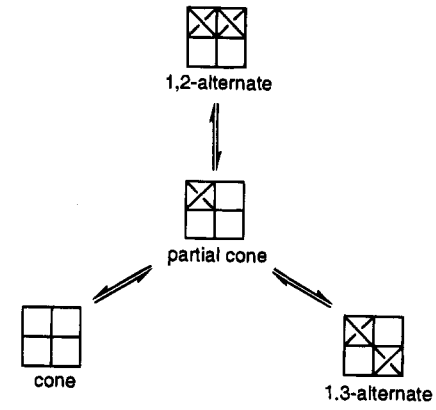

Table 1

exchange	solvent	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})	k_{270} (s^{-1})
partial cone−	$CDCl_3$	56(2)[a]	−29(6)	2.1[b]
1,3-alternate	$CDCl_3/CD_3CN$	62(9)	−3(30)	4.7[b]
partial cone−	$CDCl_3$	61(3)	−16(10)	1.6[b]
cone	$CDCl_3/CD_3CN$	56(2)	−28(5)	3.4[b]
partial cone−	$CDCl_3$	59(3)	−70(8)	0.0040[b]
1,2-alternate	$CDCl_3/CD_3CN$			0.12[c]

[a] Error limits (1 σ) are given within parentheses. [b] Calculated from $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. [c] Directly measured at 270 K.

the case of the binary mixture, the temperature range in which the pc−alt,2 conversion could be studied was too narrow to allow a reliable determination of the activation parameters in that case.

The following main conclusions arise from these data: (i) the alt,2−pc exchange is very slow compared to the alt,3−pc and c−pc exchanges;[3a] (ii) the fastest self-exchange path for the most stable conformer, pc ⇄ pc, involves the alt,3 conformer, which is thermodynamically the most unstable conformer; (iii) the rate-limiting steps of the two-step processes alt,3−c and pc−pc are, respectively, the one-step processes pc−c and pc−alt,3; (iv) the Eyring plots are roughly parallel; all the values of the enthalpies of activation are the same within the errors of measurement (~59 kJ mol^{-1}), corresponding plausibly to the steric hindrance associated with the aromatic ring flip; (v) the one-step exchange processes given in Table 1 are faster when the polarity of the solvent increases, the increase being the largest in the case of the pc−alt,2 conversion; (vi)

the interconversion processes are kinetically controlled by the entropies of activation.[7]

Not only is the cone conformation, characterized by the highest dipole moment, more thermodynamically stable in the more polar solvent ($K_{c \rightleftharpoons pc} = 12$ (chloroform) and 2.1 (chloroform/acetonitrile)), but it is also kinetically more stable: the rate constants for the cone to partial cone conversions are, respectively, 19 s^{-1} in chloroform and 7.1 s^{-1} in the binary mixture at 270 K.

It is quite unusual for conformational processes to be controlled by entropic factors. The fact that the 1,2 conformer is kinetically stable results from a large negative entropy of activation compared to the other conformers. The most probable interpretation of this entropy loss is a larger organization, in the transition state, of the solvent molecules forming the solvation cage of the calixarene. This effect cannot be due to the formation of a larger dipole moment, since this should mainly be observed in the case of the partial cone to cone exchange. One can speculate that the global shape of the conformation is playing a key role: while the shape of the calixarene is roughly globular in all three other conformers, it is flattened in the case of the alt,2 conformer. As a result, during the conformational change, the solvent cage is strongly perturbed and expanded in the case of alt,2, leading to the reorganization of a larger number of solvent molecules with an accompanying loss of translational entropy.

The kinetics and the mechanisms of complexation of a variety of guests, particularly alkali-metal cations, by calixarenes in solution are now being investigated in our laboratory.

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