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Activation Parameters for Calixarene Ring Inversion As Determined by Computer-Assisted Spectrum Simulation

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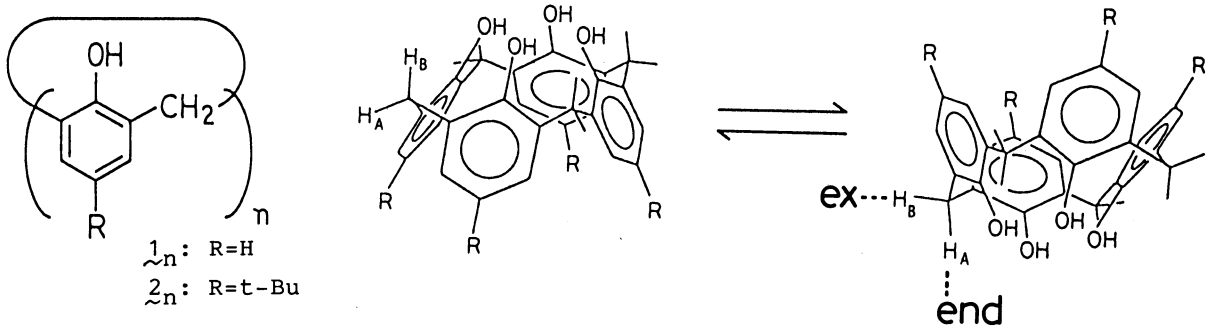
Activation parameters for calixarene ring inversion were determined for the first time by computer-assisted simulation of the ^{1}H-NMR spectra. It was found that the process is governed by the enthalpy term and features small, negative $\Delta S^{\ddagger}$ for calix[4]arenes and positive $\Delta S^{\ddagger}$ for calix[8]arenes. These data are of great significance to understanding the nature of calixarene conformations.

Calixarenes are cyclic oligomers made up of benzene units just as cyclodextrins are made up of glucose units. Although these two compounds have a similar cavity-shaped architecture, there exists an essential difference: the cyclodextrin cavity is conformationally fixed, whereas the conformational freedom still remains in the calixarene cavity. In order to apply calixarenes as a basic skeleton for functionalized host molecules, it is important to obtain an insight into the conformational freedom. The situation is conveniently monitored by temperature-dependent ^{1}H-NMR: for instance, the spectrum of calix[4]arene displays a singlet resonance for the $ArCH_2Ar$ methylene protons at high temperature and a pair of doublets at low temperature.[1,2] Thus, the coalescence temperature (T_c) appears at intermediary temperature, from which one can estimate the rate of ring inversion.[1-3] The method is very convenient; however, it only provides a rate constant at T_c and thus one can neither compare $\Delta G^{\ddagger}$ at constant temperature nor determine activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. Such data present only qualitative information about calixarene conformations. We here report an application of computer-assisted spectrum simulation to calixarene ^{1}H-NMR spectra (complete line shape analysis method).[4] By this method we could determine for the first time $\Delta G^{\ddagger}$ at desired temperature and activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for ring inversion.



^{1}H-NMR spectra were measured by a JEOL GX-400 (400 MHz) apparatus. We used calix[4]arene ($\underset{\sim}{1}_4$) or p-t-butylcalix[n]arene ($\underset{\sim}{2}_n$:n=4,8). At -30 °C in $CDCl_3$, $\underset{\sim}{1}_4$ gave a pair of doublets for the $ArCH_2Ar$ protons at 3.54 and 4.25 ppm with J_{gem} = 13.9 Hz (A in Fig. 1). This indicates that these two protons are magnetically nonquivalent, H_{ex} and H_{end} being assigned to the higher and lower magnetic field, respectively.[5] With increasing temperature the peaks are gradually broadened and finally coalesce into one peak at 44 °C. The temperature-dependent spectral change was simulated assuming the life time (τ) for each temperature (B in Fig. 1). Excellent agreement is seen between the observed and the simulated spectra. The reliability of the present simulation is guaranteed by the linearity of the Arrhenius plot. As shown in Fig. 2, a plot of log k (rate constant for ring inversion) vs. T^{-1} afforded an excellent linear relationship ($r>0.999$). By least-squares computation we obtained $A = 1.48 \times 10^{12}$ s^{-1} and E_a = 14.8 kcal mol^{-1}. From these values we calculated $\Delta G^{\ddagger}_{298}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$. Similar simulation was conducted for $\underset{\sim}{2}_4$ and $\underset{\sim}{2}_8$. The results are summarized in Table 1.

Examination of Table 1 reveals that activation parameters for calixarene ring inversion feature large $\Delta H^{\ddagger}$ and relatively small (mostly negative) $\Delta S^{\ddagger}$. As shown in Fig. 3, a $\Delta H^{\ddagger}$-$\Delta S^{\ddagger}$ plot shows a linear, compensation relationship ($r=0.97$): the large isokinetic temperature (β=475 K) indicates that the process is governed by the enthalpy term. It is known that calixarenes give high T_c in nonpolar solvents and low T_c in polar, particularly basic solvents such as acetone and pyridine.[1,2] The solvent effect supports the view that the "cone" conformation is stabilized by intramolecular hydrogen-bonding interactions among OH groups. One can conclude, therefore, that scission of hydrogen-bonds is reflected by $\Delta H^{\ddagger}$. For example, $\Delta G^{\ddagger}_{298}$ for $\underset{\sim}{2}_4$ in $CDCl_3$ (16.4 kcal mol^{-1}, $k=5.84$ s^{-1}) is greater by 2.1 kcal mol^{-1} than that in pyridine-d_5 (14.3 kcal mol^{-1}, $k=203$ s^{-1}). The difference is mainly due to the difference in $\Delta H^{\ddagger}$ (4.6 kcal mol^{-1}).

$\underset{\sim}{2}_8$ also gave a pair of doublets at 3.52 and 4.34 ppm at -20 °C in $CDCl_3$. However, the activation parameters are somewhat different from those for $\underset{\sim}{2}_4$: $\Delta H^{\ddagger}$ is greater by 1.5 kcal mol^{-1} than that for $\underset{\sim}{2}_4$ and $\Delta S^{\ddagger}$ is positive. $\underset{\sim}{2}_8$ can

Table 1. Activation parameters for calixarene ring inversion in various solvents

Calixarene	Solvent	T_c / °C	$\Delta G^{\ddagger}_{298}$ /kcal mol^{-1}	$\Delta H^{\ddagger}$ /kcal mol^{-1}	$\Delta S^{\ddagger}$ /e.u.
1_4	$CDCl_3$	44	15.7	14.2	-5.0
2_4	$CDCl_3$	>55	16.4	15.9	-1.7
2_4	Toluene-d_8	70	16.1	15.8	-1.0
2_4	Benzene-d_6	60	15.8	14.6	-6.0
2_4	Pyridine-d_5	19	14.3	11.3	-10
2_8	$CDCl_3$	>55	16.8	17.4	2.0

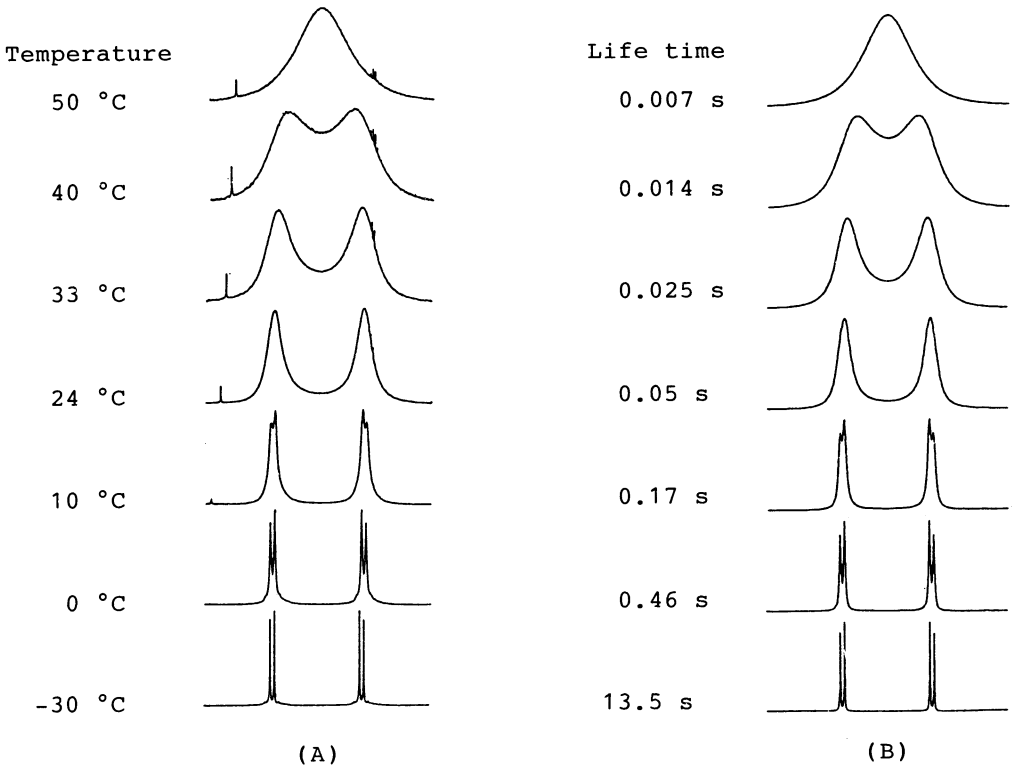


Fig. 1. Observed (A) and simulated spectra (B) of $\underset{\sim}{1}_4$ (1.94×10^{-2} mol dm^{-3}) in $CDCl_3$.

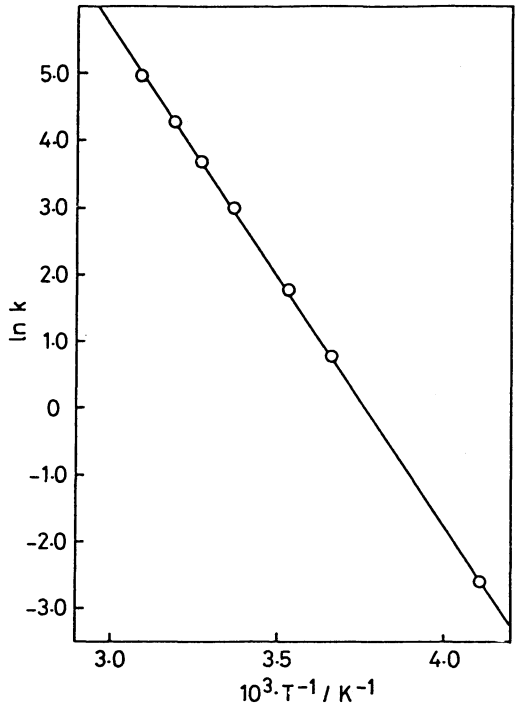


Fig. 2. Arrhenius plot for the rate of $\underset{\sim}{1}_4$ ring inversion.

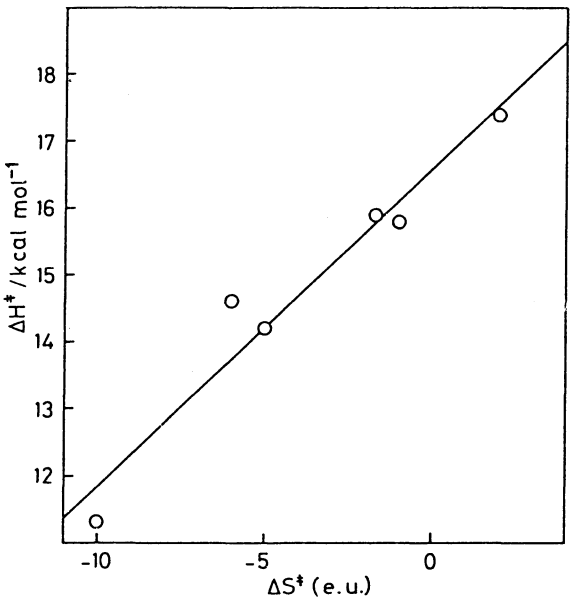


Fig. 3. $\Delta H^{\ddagger}$-$\Delta S^{\ddagger}$ compensation relationship.

form (at least) 8 hydrogen-bonds, twice as much as $\underset{\sim}{2}_4$. Thus, the $\Delta H^{\ddagger}$ augmentation of 1.5 kcal mol^{-1} is rather small. The discrepancy is accounted for by the strong, intramolecular hydrogen-bonds attained in $\underset{\sim}{2}_4$.[6] According to the IR spectroscopic studies, the OH groups in calixarenes are all intramolecularly hydrogen-bonded and $\underset{\sim}{2}_4$ has the strongest hydrogen-bonds.[6] The negative $\Delta S^{\ddagger}$ values for $\underset{\sim}{1}_4$ and $\underset{\sim}{2}_4$ imply that the transition state is more sterically-hindered than the initial state. In contrast, the positive $\Delta S^{\ddagger}$ observed for $\underset{\sim}{2}_8$ indicates the reverse situation. It is known that the calix[8]arene ring is very flexible.[1,2,7] Examination of Corey-Pauling-Koltun molecular models suggests that $\underset{\sim}{2}_8$ is so flexible that one can build even "flat calix[8]arene" without any steric hindrance. We believe that ring inversion of calix[8]arene does not accompany perceptible steric hindrance.

Finally, it is worthwhile to reconsider why the ^{1}H-NMR resonance changes from a singlet peak to doublet peaks. It has been believed that the spectral change is related to a conformational change from "cone" to "alternate".[1,2,7,8] The continuity in the Arrhenius plot clearly indicates that such a conformational transition does not exist and the spectral change is related to the rate change in ring inversion between "cone" conformations.

In conclusion, the present study has addressed activation parameters for calixarene ring inversion for the first time. These parameters well reflect the nature of calixarene rings and provide a novel insight into calixarene conformations.

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