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Dynamic structure of inclusion complexes of monodeoxycalix[4]arene with small organic guests in solution

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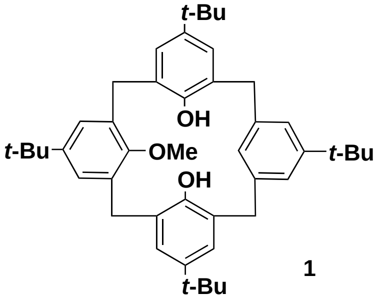
Abstract—Structure elucidation of the inclusion complexes of monodeoxycalix[4]arene with small organic guests was carried out by X-ray crystallographic analysis and molecular dynamic simulation. Although the guest moves rapidly in the host cavity, the time averaged structure resembles the one obtained by the X-ray crystallography. Chemical shift simulation succeeded to reproduce the observed complexation induced shift. © 2001 Elsevier Science Ltd. All rights reserved.

There has been intense activity in the investigation of synthetic receptors capable of binding small organic molecules.[1] The essential aspect of molecular recognition is understanding the nature of the interaction of one molecule with another. There should be a specific arrangement of the two molecules for which the energy is lower than that of other possible orientations. It is thus important to identify the exact arrangement of the two molecules in solution, so that detailed understanding is obtained of the factors that affect the way the molecules arrange. However, it is not easy to determine the precise arrangement of the two molecules of a complex in which non-directional forces (van der Waals, CH–π, π–π interactions, etc.) played an important role in binding the two components in solution. The restriction of the guest motion imposed by the host cavity wall is usually not so severe in such complexes. The guest can thus be moved or rotated in the host cavity. How can we determine the precise structure of such a complex in solution? To address this important issue, we selected the molecular dynamic (MD) simulations.[2] In a previous paper,[3] we reported that methyl ether of monodeoxycalix[4]arene (**1**) can bind neutral small organic guests[4] in CCl_4 solution. The solvent molecule is too large to reside in the cavity of the host and, hence it does not compete with the small guests.[5] In this paper, we report on the dynamic structure of the inclusion complexes of **1** and X–CH_2–Y type guests.



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A crystallographic analysis of the inclusion complex of **1** and CH_2Cl_2 gave the structure in the solid state.[6] In this structure the deoxy aromatic ring inclines outwards extensively, so as to widen the cavity for the guest. At the same time, two proximal phenol rings lean inwards to squeeze the planar guest. In this complex, the host changes its structure to control the orientation of the guest; an induced-fit type adjustment[7] of the host cavity for the guest shape is seen in the structure. The molecular mechanics calculations fully reproduced the structural change of the host. In this structure, the two protons of the guest are both facing to the deoxy ring.[8] The structure having a similar guest orientation but facing to other aromatic ring was not obtained by the calculation. This can be explained by freedom of movement of the host aromatic wall. In the deoxy ring there is less severe inner annular steric repulsion when it leaned outwards, and hence greater freedom of movement than for any other aromatic ring. In other words, movement of the deoxy ring is the most favorable of

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Keywords: dynamic structure; calix[4]arene; molecular dynamics; chemical shift simulation.

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the four possible outward movements of the aromatic rings, which adjust the cavity for the size and shape of the guest (Fig. 1).

The other structural feature worthy to note is the positional disorder of the guest. The disorder of the guest can be attributable either to static or dynamic, the latter of which suggests that the thermal motion of the guest in the crystal. It has been shown that the latter is the case, since the analysis of the temperature-dependent NMR spectral patterns of the crystalline complex of **1** and deuterated dichloromethane suggested that a dynamic multiple sites jump of the guest is operative in the host cavity.[9] The dynamic movement of the guest in the host cavity is more extensive in solution because the forces that keep the shape of the host as tight as in the crystalline state (such as packing forces) do not work effectively in solution.

In order to analyze the dynamic motion of the complex, MD simulation study on the complex was carried out with a stochastic dynamic treatment using AMBER* force-field at 300 K. The MacroModel V6.5[10] was applied with GB/SA chloroform solvation.[11] In such a weak complex, rapid diffusion permits the frequent exchange of the host/guest partners in solution. Reflecting this behavior, the complex is not stable and the guest sometimes leaves the host cavity during the MD simulation. To keep the host/guest complex together, flat-bottom restraints were used between the host and guest. Using these restraints, if the guest strayed away from the host, it was gently pushed back toward the host. The structure and the movement of the inclusion complex can be monitored by the interatomic distances as a function of time in MD calculation. The guest moves rapidly within the host cavity as is clearly found in the trajectory of the distance between the averaged position of the two methylene protons and the centroid of the deoxy aromatic ring (Fig. 2a). The time average of the distance (3.66±0.64 Å) is apparently shorter than the corresponding distance towards the anisole ring (4.25±0.81 Å, Fig. 2b). The distance to the deoxy aromatic ring is the shortest among the four possible distances (Fig. 3). This clearly indicates that the time averaged position of the methylene group of the guest is very close to the deoxy aromatic ring preferentially to other aromatic rings, reproducing the trend of the static simulation by the molecular mechanics calculations. The preferential orientation of the guest to the deoxy ring was shown in all the complexes examined.

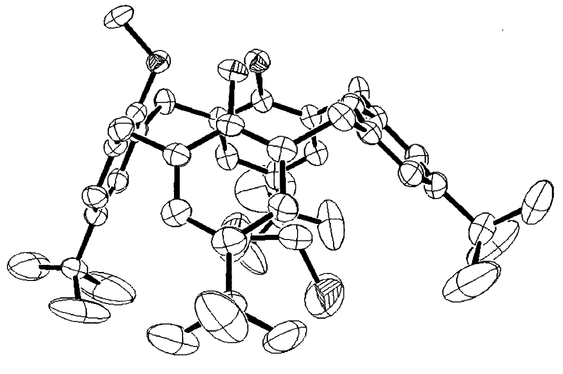

Figure 1. Ortep drawing of **1** and CH_2Cl_2 complex. Minor disordered atoms are omitted for clarity.

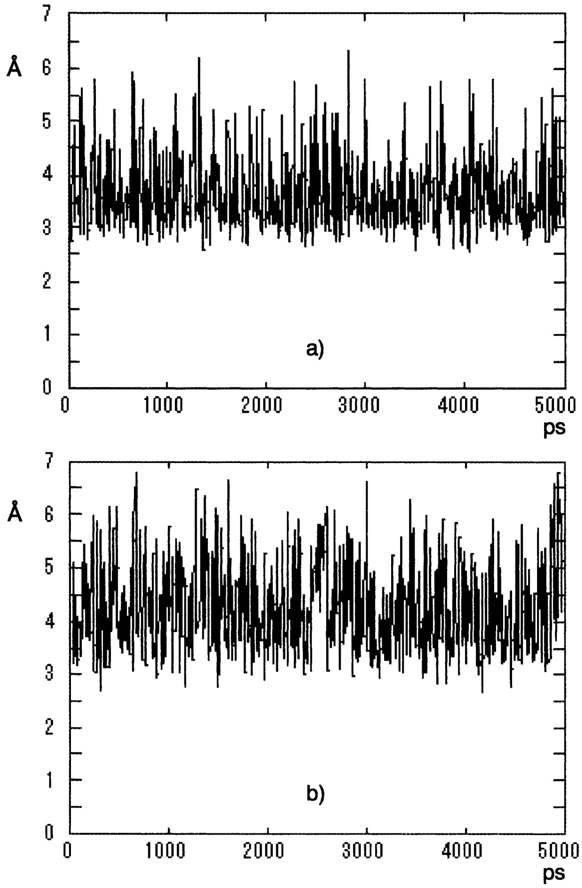

Figure 2. The distance between the averaged position of guest protons and (a) centroid of the deoxy aromatic ring and (b) centroid of anisole as a function of the time at 300 K.

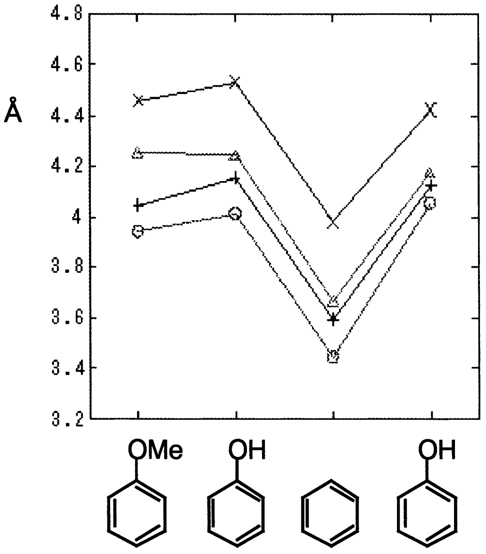

Figure 3. Averaged distance between aromatic rings of **1** and methylene of CH_2Cl_2 (△), CH_2Br_2 (X), CH_2ClCN (○) and CH_2BrCN (+).

Table 1. Observed and calculated CIS (ppm)

	CH_2Cl_2	CH_2Br_2	CH_2ClCN	CH_2BrCN
Obsd[a]	3.97±0.25	3.20±0.12	4.15±0.05	3.85±0.06
Calcd	3.72±1.09	3.27±1.27	4.12±0.85	3.92±1.04

[a] See Ref. 3.

Table 2. Observed and calculated enthalpy changes (kcal/mol)

	CH_2Cl_2	CH_2Br_2	CH_2ClCN	CH_2BrCN
Obsd[a]	−4.35	−3.96	−5.75	−5.12
Calcd	−2.86	−4.00	−4.55	−5.05

[a] See Ref. 3.

The MD simulation also gave the theoretical time averaged CIS value of the guest proton in the host cavity.[12] The averaged induced shift of the guest proton was estimated from 1000 structures monitored at every 5 ps intervals during the simulation period (5 ns). The CIS value at each structure was estimated using the ring current effect of the four benzene rings and the magnetic shielding effect of the oxygen containing functional groups.[13] The averaged CIS values reproduced satisfactorily the observed CIS values of the guest (Table 1). The validity of the MD calculation was further shown by the calculated enthalpy of complexation. As can be seen in Table 2, the calculation well reproduced the observed values for the complexation in solution.

Acknowledgements

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