Mechanism and Thermodynamics of Guest Escape from a Carcerand

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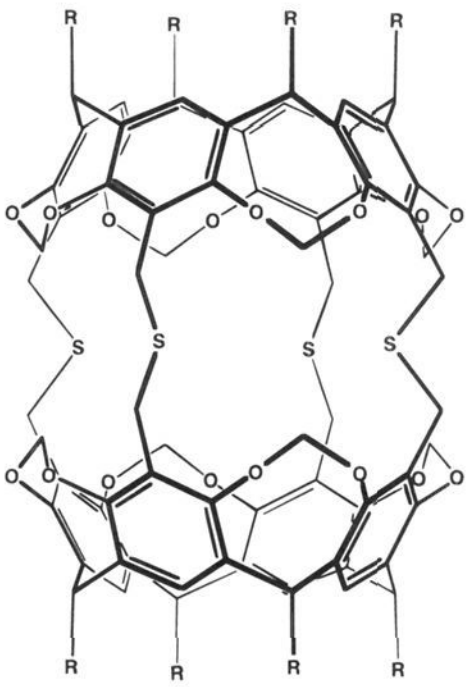
Received August 12, 1994

Cram and co-workers created the concept of container molecules (carcerands) and have begun to explore the novel structures and dynamic processes of carceplexes, which are carcerands with guest molecules trapped inside by constrictive binding.[1,2] We report here the first theoretical investigations of structures and dynamics of carceplexes. Information not available from space-filling model inspection or experiments is obtained. These computations provide a quantitative analysis of this novel type of molecular recognition and a method for the design of new carceplexes.

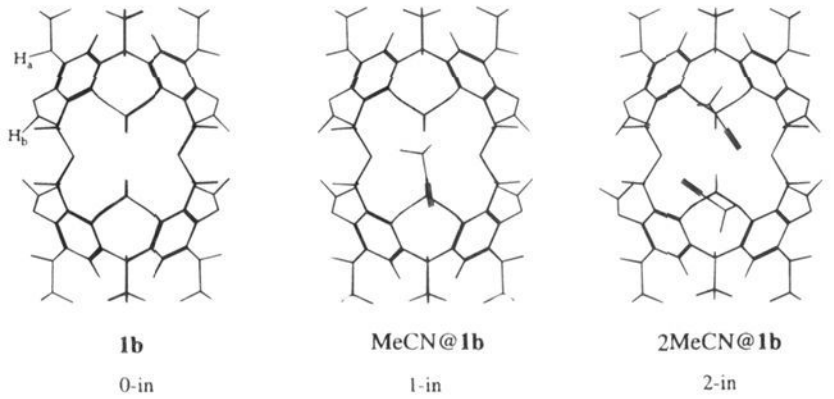
Carcerand **1a** is formed with one or two acetonitrile molecules inside during the synthesis.[3] The complex with two acetonitriles ($2CH_3CN$@**1a**, 2-in) loses one upon heating at 110 °C for 3 days and leaves a complex with a single acetonitrile inside (CH_3-CN@**1a**, 1-in). Kinetic studies gave an activation energy for



1a R = $(CH_2)_2Ph$
1b R = Me

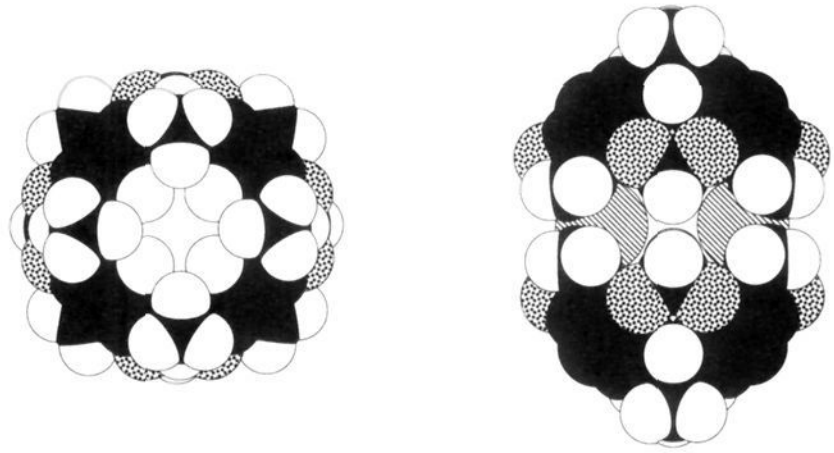
the decomplexation process of ~20 kcal/mol.[3] It was proposed that the acetonitrile escapes through the top (polar) portal rather than the side (equatorial) portal, since the top portal is larger in a CPK model. Escape of a second acetonitrile from 1-in to form a carcerand molecule without guest (**1b**, 0-in) and incarceration by 0-in or 1-in in acetonitrile solution to form 1-in or 2-in are not observed.

Force field calculations were carried out using the Macromodel program[4] with the AMBER* force field.[5,6] The AMBER



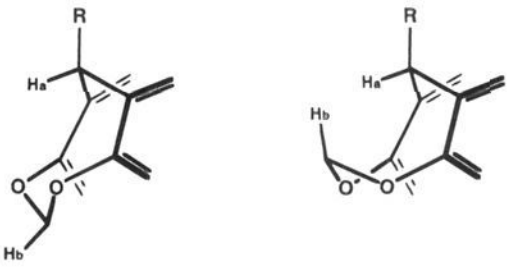
1b 0-in | MeCN@**1b** 1-in | 2MeCN@**1b** 2-in

Figure 1. Optimized structures of carcerand **1b** with no (0-in), one (1-in), and two (2-in) acetonitrile molecules inside.



4.0 program[7] was employed for the free energy perturbation (FEP) and potential of mean force (PMF) calculations by molecular dynamics simulations.[8] MD-display[9] and Macromodel were used as graphic interfaces for the AMBER program. To reduce the computational effort, we studied carcerand **1b**, with methyl groups instead of phenylethyl groups.[10]

We first carried out force field calculations to optimize the possible structures of the carceplexes and molecular dynamics to investigate the motions of incarcerated acetonitriles. Figure 1 illustrates optimized structures of **1b**, CH_3CN@**1a**, and $2CH_3$-CN@**1a** with the AMBER* force field. MM2* and MM3* give similar results to AMBER*. Each of the eight-membered rings in **1b** has the CH_2-in conformation. A CH_2-out conformation



CH_2-in | CH_2-out

is ~7 kcal/mol higher in energy, due to the steric repulsion between two hydrogens (H_a and H_b) in the CH_2-out conformation. The lowest energy geometry has the two acetonitriles aligned antiparallel (2-in); a conformer with one of the acetonitriles oriented in the opposite direction (2-in′) was found to be 1 kcal/mol higher in energy.

Molecular dynamics simulations of 2-in at room temperature show that there is free rotation of guest acetonitriles around the

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(6) The $C_{Ar}-C_{Ar}-O-C_R$ torsional parameters of AMBER were altered to the values in AMBER* to provide comparable results.
(7) Pearlman, D. A.; Case, D. A.; Caldwell, J. C.; Seibel, G. L.; Singh, U. C.; Weiner, P. A.; Kollman, P. A. *AMBER 4.0*, UCSF; Department of Pharmaceutical Chemistry, University of California: San Francisco, CA, 1991.
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(9) Callahan, T.; Swanson, E.; Lybrand, T. University of Washington, Seattle, WA, 1991. (Available from QCPE)
(10) Preliminary results indicate a negligible difference between portal sizes in octamethyl and octakis(phenylethyl) carcerands; the polar portal is somewhat constricted in the latter.

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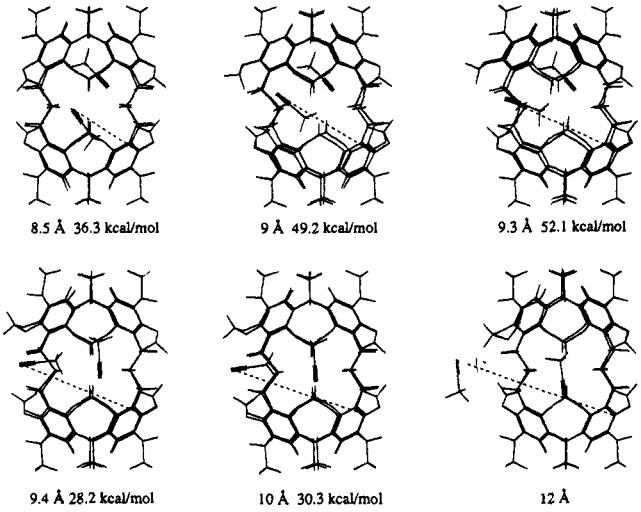


Figure 2. Snapshots along the equatorial escape pathway.

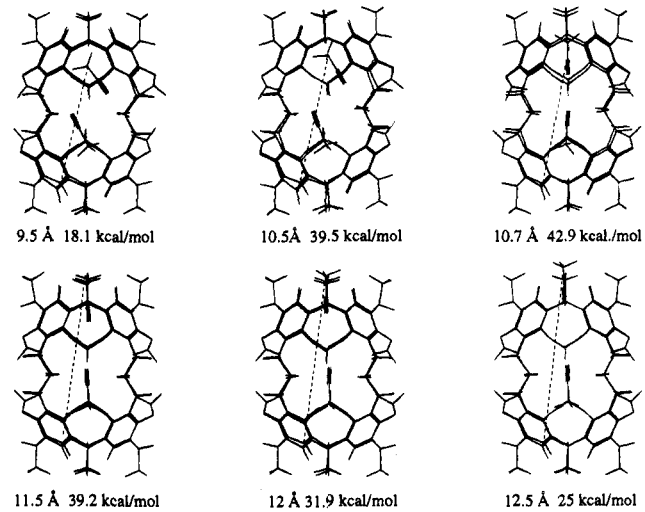
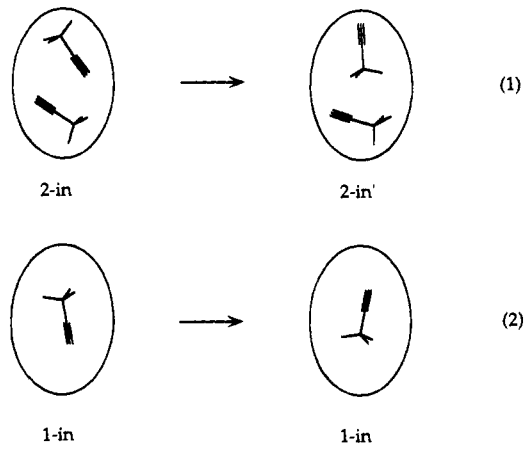


Figure 3. Snapshots along the polar escape pathway.

vertical (polar) axis. We raised the temperature of 2-in to 3000 K, but no processes such as exchange or escape of acetonitriles or isomerization to 2-in′ were observed during the time scale of computer simulations (~1000 ps).

An FEP calculation was performed on the mutation, 2-in → 2-in′. One acetonitrile of 2-in was mutated into the one with the opposite orientation over 40 windows. The free energy of 2-in′ is 3 kcal/mol higher than that of 2-in. The 2 kcal/mol extra free energy of stabilization of 2-in relative to 2-in′ is probably due to the fact that the 2-in conformation allows freer motion of the guest molecules inside the carcerand. The prediction that 2-in has the acetonitrile methyl groups close to the aromatic rings most of the time is in accord with the deduction from the experimental NMR spectrum.[3]



Constrained optimizations were employed to obtain potential energy surfaces for escape pathways. The distance between one of the phenyl carbons of the host molecule and either the nitrogen or the methyl carbon of an acetonitrile molecule was taken as reaction coordinate as illustrated by the dotted lines in Figures 2 and 3. The activation energies for escape from the side and top portals (Figures 2 and 3, respectively) were calculated to be 52 and 46 kcal/mol, respectively. However, the conformational flip of two adjacent CH_2 groups to CH_2-out conformations increases the side-portal size and drastically lowers the activation energy for MeCN escape. Consequently, we predict that an acetonitrile escapes from 2-in via the side opening by conformational flip of two $-OCH_2O-$ moieties ($E^{\ddagger}$ = 22, 26 kcal/mol),[11] followed by escape from the widely opened portal (22 kcal/mol). This process is different from speculations based upon CPK models,[3] since this conformational process cannot be performed with the CPK models.

FEP calculations were carried out with MD to estimate the difference in free energy change for the first (2-in → 1-in) and second (1-in → 0-in) escape processes. An acetonitrile molecule was mutated away over 40 windows (2 ps/window, 0.2 ps equilibrium, 1.8 ps sampling) at 383 K. The first process was calculated to be exergonic by 11 kcal/mol, while the second escape was calculated to be endergonic by 3 kcal/mol. This does not represent the reaction energies of these two processes in solution, because it does not include the solvation energy of acetonitrile; nevertheless, the calculations show that the 2-in → 1-in conversion is 14 kcal/mol more favorable than 1-in → 0-in. It is likely that the first process is exothermic and the second is endothermic.

The potential energy of incarceration was also calculated from the optimized structures. The first escape (2-in → 1-in) process is endothermic by 1 kcal/mol, and the second process (1-in → 0-in) is endothermic by 11 kcal/mol. Hence, $\Delta\Delta E$ = 10 kcal/mol. The calculated difference between $\Delta\Delta G$ and $\Delta\Delta E$ is due to the $T\Delta S$ term, which makes the second escape energetically more difficult by 4 kcal/mol. The $P\Delta V$ term calculated for the volume change of 1 mol of acetonitrile at atmospheric pressure is approximately 0.5 kcal/mol. Carceplex 2-in involves a tight fit of two acetonitriles, and the motion of guest molecules is restricted; this is entropically unfavorable. Carceplex 1-in is less crowded, and the guest molecule can move relatively freely, an entropically favorable factor.

In order to understand fully the experimental results, we need to carry out a potential of mean force calculation to get a free energy surface for the escape of acetonitrile from the carceplex. We have not yet achieved stable results for all pathways, mainly because of the difficulty in defining the reaction coordinate. The free energies of activation for the first and second escapes from the top portal were calculated as 30 and 37 kcal/mol, respectively. Although this is not the lowest energy pathway for acetonitrile escape, it does show the relative free energies of activation for one pathway of escape of the first and second acetonitriles.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this research and to Donald J. Cram for many helpful and inspiring discussions. We also thank the Office of Academic Computing at UCLA for generous support.

JA942677Q

(11) The activation energy for the ring flip was estimated by optimizing the structure with the (phenyl carbon)−oxygen−(methylene carbon)−oxygen torsion angle constrained to 0°.