# Molecular Dynamics Calculation for the Complexes of a Macrotricyclic Receptor with Organic Substrates

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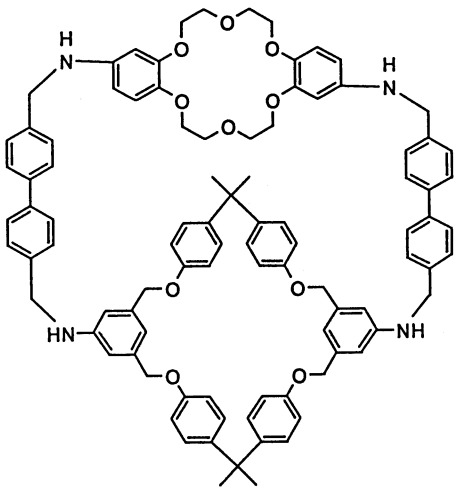
Molecular dynamics calculation was performed in order to obtain structural information about the complexes of a macrotricyclic receptor (**1**), which has crown ether and cyclophane subunits as binding sites, with organic substrates, ω-(phenylalkyl)ammonium picrates (**2**; the methylene number, $n$=4, 5, 7), taking account of solvent effect. The resulting equilibrium structures were in good agreement with experimental data; among the three complexes, the complex of **1** with **2** ($n$=5) gave the largest stability constant. Furthermore, the quantitative evaluation of the difference in Gibbs free energy between two complexes, calculated by the perturbation method, was also consistent with the experimental data.

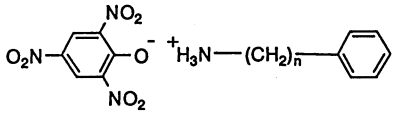
It is well-known that bioprocesses, such as enzymatic reactions, antigen-antibody reactions, and ion transportations, proceed selectively and/or specifically with molecular recognition. A mimicking of these reactions by artificial compounds would be valuable not only for understanding of the underlying factors in bioprocesses but also for development of new, selective and/or specific organic reactions. Recently, we found that macrotricyclic receptor (**1**), having crown ether and cyclophane subunits as binding sites, recognized the methylene chain length of ω-(phenylalkyl)ammonium picrates (**2**; the methylene number, $n$=3—9).[1] The largest stability constant ($K$s') of the complex of **1** with **2** was observed when the methylene number, $n$, of **2** was five or six, which was 3—4 times larger than those of the complexes with **2** ($n$=4, 7). However, no structural information was obtained for the complexes since the complexes gave very complicated $^1$H NMR spectra and the growth of a single crystal for X-ray structural analysis was in failure.

On the other hand, the computational method has a high potential for getting structural information, which is difficult to be obtained by experimental methods. For isolated "gas phases" system, a lot of calculations were carried out by molecular orbital and molecular mechanical methods.[2] However, some calculations indicated that the (de)solvation of a cation upon complexation played an important role in the complex-formation process.[2b] Recently, molecular dynamics studies incorporating the effect of solvents were reported.[3,4] Grootenhuis and Kollman, for example, employed free energy perturbation theory in order to simulate properties of macrocyclic dibenzocrown ethers.[5] Their results showed that the perturbational technique is very useful to obtain thermodynamic data for a complexation process.

In this paper, we report the molecular dynamics calculations for the complexes of tricyclic receptor **1**, which has crown ether and cyclophane subunits, with ω-(phenylalkyl)ammonium picrates (**2**, $n$=4, 5, 7) and



**1**



**2**

the difference in Gibbs free energy (ΔΔG) calculated on the basis of the perturbation method proposed by Grootenhuis and Kollman.[5]

## Computational Details

For molecular dynamics calculation, the AMBER package[6] was used, in which the energy function is of the form

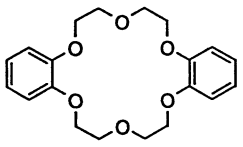
$$E_{\text{total}} = \sum_{\text{bonds}} K_r(r-r_{\text{eq}}) + \sum_{\text{angles}} K_\theta(\theta-\theta_{\text{eq}}) + \sum_{\text{dihedrals}} \frac{V_n}{2}[1+\cos(n\phi-\gamma)] + \sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}\right] + \sum_{\text{H-bonds}}\left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}}\right]$$

All of the force field parameters were taken from the literatures.[5,7] Through the molecular dynamics calculation, the all-atom force field was used and the SHAKE algorithm[8] was applied to C-H bonds. In the calculation, the optimized potentials for liquid simulation (OPLS)[9] parameters for water were used for solvent models. The point charges used in the molecular dynamics were taken by the molecular orbital calculation MNDO in the MOPAC package. Picrate anion was ignored in the molecular dynamics calculation in order to simplify the system.

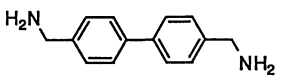
The starting geometry of the receptor for molecular dynamics calculation was determined by molecular mechanics calculation, which was performed with MMP2 program.[10] Because of the difficulty in optimizing the whole structure of receptor **1** at a time, **1** was divided into three parts; dibenzo-18-crown-6 **3**, bis(aminomethyl)biphenyl **4**, and diaminocyclophane **5**.

The starting geometry of **3** for molecular mechanics calculation was adopted from the X-ray data in the literatures.[11] Both of two independent molecules in a unit cell were individually optimized by MMP2 calculation. The molecules of solvent in the X-ray data were ignored.

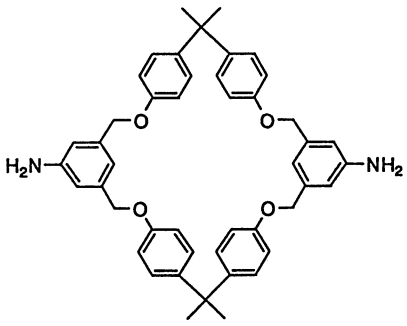
The starting geometry of **4** for molecular mechanics calculation was made by MOLDA5[12] on a personal computer NEC PC9801VX21, and MMP2 calculation was performed.



**3**




**4**




**5**

The starting geometry of **5** for molecular mechanics calculation was based on the X-ray data of dinitrocyclophane.[13] Since the other parts of receptor **1** could not be connected with the X-ray determined structure of $C_i$ symmetry, the structure of the dinitrocyclophane was assumed to take $C_2$ symmetry. Moreover, the nitro groups in the dinitrocyclophane was replaced by amino groups. There were 36 possible conformations for **5** in $C_2$ symmetry: *Anti* and two *gauche* conformations for $Ar^1$-O-C-$Ar^2$; cisoid and transoid conformations between the oxygen of the skeleton and the nitrogen attached to $Ar^2$; i.e., 3×2×3×2 in total. MMP2 calculations were carried out for all of the structures, and the most stable structure (*anti*-cisoid; *gauche*-cisoid was used as the starting geometry of **5**.

The connection of the three parts, i.e., **3**, **4**, and **5**, was carried out by using MOLDA5 program. There were 72 possible connecting modes (two faces of the crown ether subunit; *anti* and two *gauche* conformations for $Ar^1$ (crown ether subunit)-N-C-$Ar^2$ (bridge subunit) and for $Ar^3$ (cyclophane subunit)-N-C-$Ar^4$ (bridge subunit), respectively; inside and outside the cavity for each methylene in the bridge subunit; namely, 2×3×3×2×2). Connection could be achieved for 16 structures, for which molecular mechanics calculation was performed. Among them, the most stable structure, where the crown ether subunit bends inside the cavity, each Ar-N-C-Ar is *gauche* (right-handed screw), and each methylene is inside, was regarded as the starting geometry of the receptor molecule for molecular dynamic study.

The nitrogen atom of the substrate molecule was taken as $sp^3$ with no charge, and its energy was minimized by MMP2 calculation.

For the starting geometry of the complex, we located the nitrogen atom of the substrate molecule by MOLDA5 program to interact through ordinary hydrogen bonds with the oxygen atoms of the crown ether subunit in the receptor molecule, obtained by MMP2 calculation.

In our solvent model, 20—25 molecules of OPLS water were placed around the receptor molecule or complex, and water molecule (s) closer than 2.0 Å to the atoms of the receptor molecule or complex was removed. For the molecular dynamics calculation, the windowing technique[14] was used, in which 500 equilibration steps and 500 data collection steps were performed with a $2\times10^{-3}$ ps timestep at 300 K and constant pressure of 1.0 atm. The total time length for the simulation was 160 ps, i.e., $8\times10^4$ steps, to equilibrate the structure of the receptor and complex.

The perturbation calculation was carried out forward ($\lambda$: 1→0) and backward ($\lambda$: 0→1) with $\Delta\lambda$=0.05.

Since the ensembles were generated at constant temperature (300 K) and pressure (0 atm), the calculated energy may be regarded as Gibbs free energy. The substrate molecule, ω-(phenylalkyl)ammonium ion, was taken as the perturbing group.

The molecular dynamics and molecular mechanics calculations were carried out on a HITACHI S-820 supercomputer and HITACHI M-680/M-682 computers, respectively, in the Computer Centre of the University of Tokyo.

## Results and Discussion

The molecular dynamics calculations were carried out for receptor **1** alone and for the complexes of **1** with ω-(phenylalkyl)ammonium picrate (**2**, $n$=4, 5, 7). The equilibrium structures are shown in Fig. 1.

The equilibrium structure of the receptor molecule in the complex with **2** ($n$=7) is elongated in comparison with those of the receptor molecule alone and of the complex with **2** ($n$=5). The elongation of the receptor molecule in the complex with **2** ($n$=7) may result in the complex being less stable than the complex with **2** ($n$=5) in enthalpy term, although there exists the interaction between the phenyl group in **2** and the cyclophane subunit in **1** in both cases of the complexes with **2** ($n$=5) and with **2** ($n$=7).

In order to evaluate quantitatively the difference in the stability of the receptor molecule between the complexes with **2** ($n$=5) and with **2** ($n$=7), MMP2 calculation was performed. The calculation showed that the receptor molecule in the complex with **2** ($n$=7) was less stable than that in the complex with **2** ($n$=5) by 15.63 kcal mol$^{-1}$.

These results on the molecular dynamics and molecular mechanics calculations are in agreement with the experimental data[1] that the stability constant ($K$s′) of the complex of **1** with **2** ($n$=5) is 2.8 times larger than that with **2** ($n$=7) at 20 °C (Table 1).

The benzene ring of the substrate molecule is located outside the cavity of the cyclophane subunit of the receptor molecule in the case of the complex with **2** ($n$=4). In contrast, in the case of the complex with **2** ($n$=5), the benzene ring of the substrate molecule is located in the cavity of the cyclophane subunit to interact each other. Moreover, the structures of the

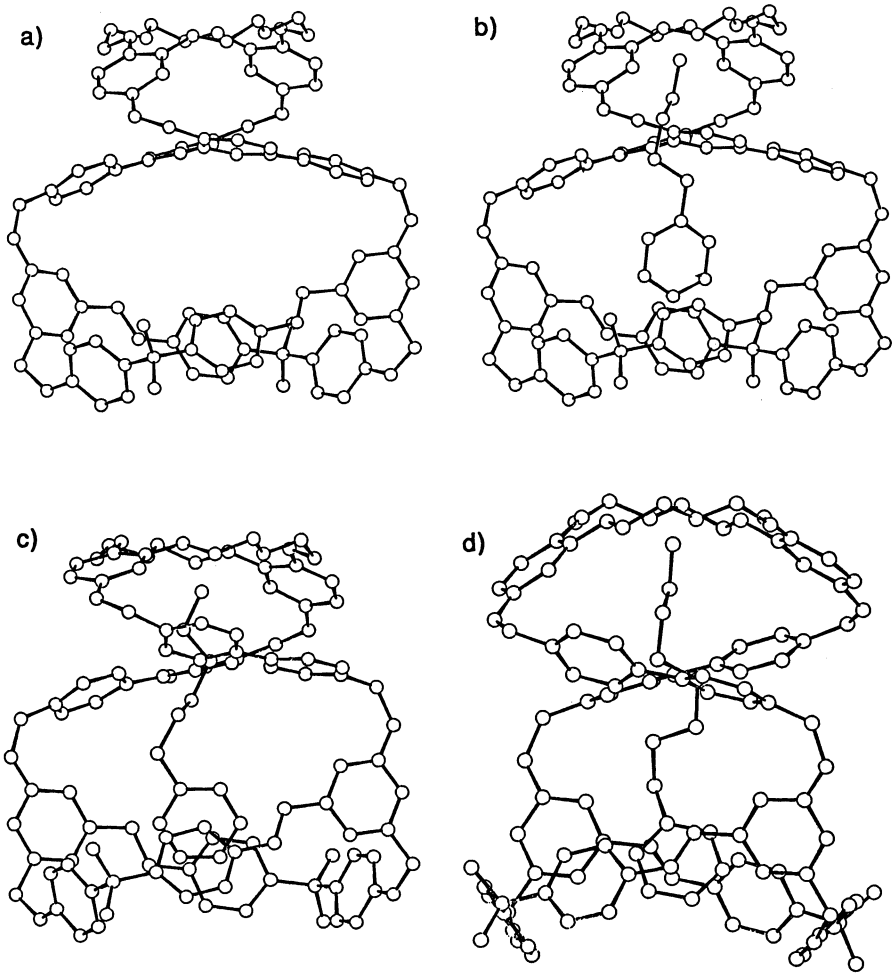



Fig. 1. The equilibrium structures of a) receptor **1**, b) the complex of **1** with **2** ($n$=4), c) the complex of **1** with **2** ($n$=5), and d) the complex of **1** with **2** ($n$=7), calculated by molecular dynamics.

Table 1. The Observed Stability Constant ($Ks' \times 10^{-2}$ $M^{-1}$) for the Complexes of **1** with **2** ($n$=4, 5, 7) at 20 °C[1)]

| $n$ | $Ks'$ |
|---|---|
| 4 | 4.4 |
| 5 | 17.3 |
| 7 | 6.2 |

Table 2. The Difference in Gibbs Free Energy ($\Delta\Delta G$) between the Complexes of **1** with **2** ($n$=5) and with **2** ($n$=4) at 300 K

| | $\Delta\Delta G$/kcal $mol^{-1}$ |
|---|---|
| Calcd by Perturbation Method | 0.81 |
| Obsd[1)] | 0.71 |

receptor molecule in the complexes are little different from that of the receptor molecule alone. These molecular dynamics results may account for the experimental fact[1)] that the complex with **2** ($n$=5) is more stable than the complex with **2** ($n$=4) as given in Table 1. Namely, the difference in the stability between the complexes with **2** ($n$=4) and with **2** ($n$=5) may be due to the absence or presence of the interaction between the benzene ring in **2** and the cyclophane subunit in **1**.

The perturbation study was carried out by changing parameters for ω-(phenylalkyl)ammonium cation with five methylenes into the parameters for the cation with four methylenes in order to calculate the difference in Gibbs free energy ($\Delta\Delta G$) between the complexes with **2** ($n$=5) and with **2** ($n$=4). The result is listed in Table 2 with the observed value.[1)] The calculated value is highly consistent with the experimental result. This suggests that the quantitative value of $\Delta\Delta G$ can be reproduced by the molecular dynamics calculation and that the equilibrium structures calculated by molecular dynamics represent the actual phases of the complexes.

Furthermore, the quantitative evaluation was performed by using MMP2 calculation for the contribution of the hydrophobic interaction between the phenyl group in **2** and the cyclophane subunit in **1** to the stabilization of the complex with **2** ($n$=5). The enthalpy for the interaction was found to be 0.82 kcal $mol^{-1}$, which is almost equal to the observed $\Delta\Delta G$. This indicates that the complex of **1** with **2** ($n$=5) is stabilized more than the complex of **1** with **2** ($n$=4) by the additional hydrophobic interaction between the phenyl group in **2** and the cyclophane subunit in **1** other than the primary electrostatic interaction between the ammonium group in **2** with the crown ether subunit in **1**.

## Conclusion

The equilibrium structures of the complexes of receptor **1** with organic substrates **2** ($n$=4, 5, 7), calculated by molecular dynamics, are in good agreement with the fact that among them the complex with substrate **2** ($n$=5) is the most stable. Furthermore, the quantitative value of $\Delta\Delta G$ in the process, calculated by the perturbation method, is also consistent with the experimental data.

Present studies indicate that the molecular dynamics calculation and perturbation method are very useful to get the structural information, which is difficult to get by experimental methods, for large, complex macropolycyclic systems.

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