Molecular Dynamics Simulation for Liquid-liquid Distribution of Spirobenzopyran Derivatives Bearing a Monoazacrown Ether Moiety

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The distribution of spirobenzopyran derivatives incorporating a crown ether moiety in water/1,2-dichloroethane two-phase system was simulated using a molecular dynamics method. Regardless of the size of crown ether moiety of the compounds, the steric energy was changed with the length of their alkyl chains. The steric energy in aqueous phase was increased with lengthening the alkyl chain, while the steric energy in the organic phase remained almost unchanged. As a result, these difference in the steric energy between the two phase were increased with the alkyl chain length and the compounds are, therefore, energetically stable in the organic phase. The snapshot obtained by the calculation showed that the compounds at the interface push their alkyl chain into the organic phase to stabilize them.

Key Words: molecular dynamics, distribution, steric energy, spirobenzopyran, alkyl chain length

Introduction

Various spirobenzopyran derivatives bearing a monoazacrown ether moiety with a different ring size, which we call crowned spirobenzopyran, had been synthesized so far, and extensive discussion has been made with their photochemical characteristics in the presence of specific metal ions. Meanwhile, in the liquid-liquid extraction using crowned spirobenzopyran as the extraction reagent as well, highly selective extractability was found for specific metal ions. Thus several reports have been published with respect to the photochromism, metal-ion complexation, and liquid-liquid extraction of crowned spirobenzopyrans by irradiation of UV and visible lights.1,4

Sophisticated molecular modeling that has never been believed to be attainable until now has become

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feasible thanks to the dramatic enhancement of processing ability of computers. For the molecular simulation to elucidate the structure and physical properties of substances, Molecular Mechanic method (MM), Monte Carlo method (MC), and Molecular Dynamic (MD) are often used. The molecular dynamics is a calculation method in which molecular mechanics develop, and it is calculated on the basis of the classical dynamics and Newton's motion equation. It is possible that this method requires a time-dependent molecular assembly. The molecule simulation has been used for the qualitative evaluation of the electric charge density on the atom in an extraction reagent or the chemical properties of organic solvent and extraction equilibrium constant in the field of solvent extraction. There are, however, not so many examples for the study on simulation of liquid-liquid extraction procedures available until now. In the field of the solvent extraction, simulations of nickel extraction in pentane/water phase and uranium extraction with tributyl phosphate in chloroform/water phase have been reported. 

In this paper, we report the MD simulation concerning the distribution of crowned spirobenzopyrans between two phases of water and 1,2-dichloroethane. The extraction reagent for the calculation is illustrated in Figure 1.

![Chemical Structure of Extraction Reagent](image)

\[ \text{Fig. 1 Chemical Structure of extraction reagent in this study.} \]

**Calculation method**

The MD calculation was conducted by using Win Masphyc Pro ver.2 offered by Fujitsu. With both the water and 1,2-dichloroethane phases, a structure-mitigation calculation was carried out under the condition of constant volume and temperature (NVT) by placing 256 molecules into the water phase and 119 molecules into the 1,2-dichloroethane phase. The aqueous and organic phases have a density of 1.00g/cm³ and 1.25g/cm³, respectively, in a cubic body with one side of 25 Å. Furthermore, a cell-size adjustment calculation was carried out under the condition of constant pressure and temperature (NPT). Finally, the main calculation was performed under the condition of the boundary circulation.

MOPAC(PM3) was used for constructing the initial structure of the extraction reagent, the optimized structure of which were obtained by a molecular mechanic and a semi-experimental molecular orbital method. For filing the potential, the Organic and Dreiding files were used. The extraction reagent molecule was placed in the center of these unit cells, at an arbitrary angle. Thus, 100-ps calculations were carried out by using the Nose method for the temperature controlling under the condition of constant volume and constant temperature (NVT) in a simulation box as shown in Figure 2. The cut-off distance was 10 Å. With the two-phase interfacial model, the same calculation

![MD Simulation Box](image)

\[ \text{Fig. 2 MD simulation box of spirobenzopyran in water phase.} \]
was carried out by inserting an extraction reagent in the interface between both the phases.

**Result and Discussion**

For the model with which a 100-ps calculation was performed, a 100-steps calculation was again carried out under the condition of constant volume and constant temperature (NVT) with a calculation time interval of 0.001fs, thus, yielding the energy $U_{\text{total}}$. When the computation started, the energy changed roughly. However, within about 40 ps, the energy reached an approximately constant value. Therefore, 100 ps is an enough time for the simulation time to obtain the energy. Meanwhile, the same calculation was conducted in vacuo (without any solvent) with the extraction reagent molecule reproduced from the model calculated for 100ps, thus, affording the energy $U_{\text{ext}}$. Furthermore, the steric energy $U_{\text{in\ phase}}$ of the extraction reagent was obtained from the energy brought from the solvent itself $U_{\text{phase}}$.

$$U_{\text{in\ phase}} = U_{\text{phase}} + U_{\text{ext}} - U_{\text{total}} \quad (1)$$

The difference in the steric energy between the individual phases was determined to be variation $\Delta U$.

$$\Delta U = U_{\text{in\ water}} - U_{\text{in\ organic}} \quad (2)$$

In general, the difference in the steric energy between the bulk phase and interface is closely related to the interfacial adsorption equilibrium constant for a given compound. Thus, it is widely recognized that the difference in the steric energy between the two bulk phases is closely related to the distribution constant of the compound. The NVT ensemble (constant number of particle, volume, and temperature) is used for this simulation. Therefore, it is possible to assume that the change of the entropy (the disorder of particle) is approximately constant because there is no change in the heat and the particle number. Since it is thought that the entropy effect was small in the calculation of this energy, it can be removed from the object of the discussion.

The variation in the steric energy for the aqueous and organic phases of the spirobenzopyran extraction reagent bearing a monoaza-15-crown-4 moiety is shown in Figure 3.

Fig. 3 Steric energy of 15-crown-5 spirobenzopyran. ( □: in water, △: in 1,2-dichloroethane phase )

The steric energy of the extraction reagent in organic phase is almost constant regardless of the length of the alkyl chain, while the steric energy in aqueous phase is increased as the alkyl chain is elongated. This tendency was found not only with the model of 15-crown-5 shown here but also with the model of 12-crown-4 and with the model of 18-crown-6. Furthermore, the steric energy obtained from the difference between the two phases is increased as the alkyl chain is elongated. It is clear from the calculation that the compounds are stabilized energetically in the organic phase than in the aqueous phase (Figure 4).

The compound used for this simulation consists of two moieties, that is, spirobenzopyran and crown ether moieties. Each of the moieties was independently simulated, and the stability for each of the phases was calculated. The simulation results are shown in Figures 5 and 6.

Fig. 4 Change of steric energy for crowned spirobenzopyran. ( □: 12-crown-4, △: 15-crown-5, ▽: 18-crown-6 )
The steric energy of the crown ether moiety increased by introducing the alkyl chain to the moiety for both of the aqueous and organic phases. As a result, the difference in the steric energy did not change very much, even if the introducing alkyl chain was lengthened. This was the case with the other crown ether moiety with a different ring size. In the meantime, the steric energy of the spirobenzopyran moiety for the aqueous phase increased by introducing a long-chain alkyl group, while the steric energy for the organic phase remains almost unchanged.

The calculation indicates the spirobenzopyran moiety is stabilized in the organic phase by lengthening the alkyl chain, much more than the crown ether moiety.

For the crowned spirobenzopyran derivatives, the difference in the steric energy between the aqueous and organic phases shows that the variation in the steric energy is independent of the size of the crown ether ring. The steric energy difference becomes greater as the incorporating alkyl group is elongated. The stability of the compounds is greater for the organic phase than for the aqueous phase. The difference in the steric energy that depends on the size of the crown ether ring is considered to be due to some balance between the hydrophilicity and hydrophobicity of the crown ether moieties themselves. Likewise, details are given with the steric energy of spirobenzopyran derivative bearing a 12-crown-4 moiety in the organic phase and the energy in the water/1,2-dichloroethane interface, together with the variation of the steric energy (Figures 7 and 8).
The figures show that the steric energy at the interface possesses more than two times of the energy in the organic phase. Definitely, the compounds are energetically unstable at the interface. Also, the variation also becomes greater and therefore the compounds are in a less stable state at the interface as their incorporated alkyl group is elongated. This might be because the alkyl chain is inserted into the organic phase, and the instability is caused by the liability of the compounds to move to the organic phase. On the other hand, the energy at the interface is greater than that for the aqueous phase, and the compounds are less stable than for the aqueous phase. However, since the energy is decreased in the order, the interface > the aqueous phase > the organic phase, it can be therefore imagined that the compounds at the interface tends to be transferred to organic phase to be energetically more stable. Figure 9 is a typical snapshot for the interface model for the 100-ps calculation of the spirobenzopyran derivative bearing a monoaza-12-crown-4 moiety and a decyl group. The snapshot indicates that the alkyl chain introduced to the extraction reagent is pushed into the organic phase to stabilize the compound energetically at the interface.

**Fig. 9** Snapshot of 12-crown-4 spirobenzopyrans obtained by 100-ps calculation. (upper: aqueous phase, lower: organic phase)

**Conclusions**

The stability of the spirobenzopyran derivatives bearing a crown ether moiety with a different ring size, which are photoresponsive extraction reagents, was calculated in the two-phases system of water/1,2-dichloroethane by using molecular dynamics. Regardless of the crown-ether ring size, the steric energy for the aqueous phase is increased as the alkyl chain introduced into the spirobenzopyran is elongated. Therefore, the compounds are relatively stabilized in the organic phase more than in the aqueous phase. Furthermore, the steric energy of the compounds for the aqueous phase depends on the size of the crown ether ring. The energy difference might be derived from the physical properties of the crown ether itself. The introduction of the alkyl group was effective to stabilize the spirobenzopyran moiety in the organic phase. The calculation at the interface between the two phases exhibits that the energy of the compounds is high at the interface. The snapshot showed that the compounds at the interface push their alkyl chain into the organic phase to stabilize themselves.

**References**

クラウンエーテル部位を持つスピロベンゾピランの液液分配に関する分子動力学シミュレーション

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クラウンエーテル部位を持つスピロベンゾピランの水と1,2ジクロロエタン二相系における分配を分子動力学法を用いてシミュレーションした。クラウンエーテルの大きさに関係なく、スピロベンゾピランに導入したアルキル鎖の長さにより、立体エネルギーは変化を見せた。立体エネルギーは、どのモデルとも有機相ではほぼ一定であったのに対し、水相での立体エネルギーは、導入したアルキル基が長鎖になるに従い大きくなった。結果として、両者の差はアルキル基が長くなるに伴い大きくなり、相対的に有機相で安定となっていた。また、計算後のスナップショットにおいて、界面に置かれた配位子は、長鎖のアルキル基から有機相へと入り込み、安定化する様子が確認された。

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