– Reviews –

Computational Chemistry in Solvent Extraction

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Recent rapid advances in computer hardware and software for computational chemistry enable molecular modeling and molecular simulations to be achieved up to the level of practical applications. Even in solvent extraction, the applications of computational chemistry to the molecular design of high-performance extractants as well as the simulations of extraction processes have gradually been increasing during the last decade. Combining the quantitative structure-property relationship between the molecule properties calculated by the computational chemistry with the thermodynamic properties obtained from experiments, researchers can precisely predict the next generation of extractants and novel extraction processes. In this review, the concept of computational chemistry, such as molecular mechanics, molecular orbitals and molecular dynamics calculations, frequently used in the field of solvent extraction, are outlined. Our systematic researches on the computational chemistry for solvent extraction utilizing molecular mechanics and molecular dynamics calculations are also presented.

1. Introduction

Computational chemistry is now widely recognized as a powerful tool for designing new molecules with specific properties, and for interpreting their stabilities, reactivities and other physicochemical properties. Computing of the structures and properties of chemical compounds is gaining increasing importance as computational techniques become increasingly accurate as high-performance computing and molecular graphics become available at relatively low cost.

Molecular mechanics (MM) calculations are among the simplest and fastest techniques, and are therefore extremely useful when considering very large molecules (e.g. biopolymers) or a large number of structures (e.g. a whole set of conformers of complex molecules). Though the first MM models were set up and used in the field of coordination chemistry [1], it was not until recently that inorganic chemists rediscovered the power of this approach, which in the mean time had been developed as a routine tool in the field of organic chemistry. A renewal of interest among inorganic chemists came with the development of functions and parameterizations, which allowed for the modeling of higher coordination numbers, variable coordination geometries and electronic effects exerted by the central metal atom. The interest in and acceptance of the technique is leading to an increasing number of books and reviews that have been devoted to this subject [2-7].

Just as for MM calculations, molecular orbital (MO) calculations are frequently used to elucidate the most stable structures of molecules *in vacuo* as well as in a dense phase. There are 2 types of MO methods, i.e., the semi-empirical MO method (SMO), such as MOPAC, and the non-empirical MO method, such as the *ab initio* method, and density functional theory (DFT). Even when we use a high-performance computer, however, only small molecules can be treated with the MO methods, because large numbers of Schrödinger equations must be solved. Since the semi-empirical MO method can not be used to calculate a molecule including an atom without an empirical Hamiltonian parameter of the Schrödinger equation, applications of this calculation method to metal complexes have been delayed due to a lack of empirical Hamiltonian parameters for metals.

Molecular dynamics (MD) simulations using empirical potential functions and their parameters are being widely applied to elucidate the dynamic behavior and the thermodynamic properties of molecules in dense phases, such as aqueous and organic solutions. MD simulations have also been widely utilizing in the field of molecular simulations of inorganic matter and gas in catalysts and membrane phases.

Even in solvent extraction, many researchers have been applying computational chemistry to understand the extraction processes and design high-performance extractants during the last decade. The research trends over the past 5 years are listed in Table 1. In this paper, we briefly introduce the progress of computational chemistry in the field of solvent extraction. Our systematic research on the solvent-extraction process utilizing MM and MD calculations is also presented.

2. Molecular Modeling of Extractants and Their Complexes

2.1 Molecular modeling of novel bi-functional organophosphorus extractants for lanthanoid separation [8]

Lanthanoids are important elements in the production of advanced materials such as superconductors, ultramagnets and laser crystals. However, their chemical and physical similarities make the mutual separation of adjacent elements among the lanthanoids quite difficult. We have synthesized novel organophosphorus extractants as shown in Fig.1. These extractants have two functional phosphoric groups in a molecule based on a new concept to introduce an appropriate spacer between the bi-functional groups. Using the extractants, we have investigated the extraction behavior of nine lanthanoids and compared our results with those for conventional mono-acidic organophosphorus extractants. The structural effects of the extractants on the extraction behavior of the lanthanoids were then evaluated by using both the molecular mechanics and semi-empirical molecular orbital methods.

Based on slope analysis and Job's analysis methods of the experimental data, the extraction equilibrium of lanthanoids for each extractant can be expressed as follows.

For EG3PA and o-type;

 $Ln^{3+} + 2(H_2R)_2 = LnRHR(H_2R)_2 + 3H^+,$ (1) For *p*-type;

 $Ln^{3+} + 2(H_2R)_3 = Ln(HR)_3(H_2R)_3 + 3H^+$, (2) where Ln^{3+} and H_2R denote the lanthanoid elements and the bi-functional organophosphorus extractants.

Author (year)	Method	Extractant / extract / solvent	Objective	Ref.
Yoshizuka et al. (2006)	MM	phosphate / UO ₂ ²⁺ , Th ⁴⁺ / toluene	Complex structure in vacuo	21
Yoshizuka <i>et al</i> . (2006)	SMO	phenylboric acid, quaternary ammonium / monosaccharide / 1-octanol, hexane	Complex structure in solvent	22
Uezu et al. (2006)	ММ	β -diketone / Al ³⁺ , In ³⁺ / benzene	Complex structure in vacuo	9
Uezu et al. (2006)	ММ	diphosphonate ester / lanthanoids / chloroform	Complex structure in vacuo	23
Sieffert et al. (2006)	MD	calix[4]crown-6 / alkali metal ion / ionic liquid	Complex formation in solvent	24
Galand <i>et al.</i> (2005)	MD	β -diketone, tributyl phosphate / UO ₂ ²⁺ / supercritical carbon dioxide	Complex formation in solvent	25
Uezu et al. (2005)	SMO, DFT	calix[4]arene derivative / Li ⁺ , Na ⁺ , K ⁺ / toluene	Complex structure in solvent	26
Krishna et al. (2004)	DFT	tributyl phosphate / Hf ⁴⁺ , Zr ⁴⁺ / methyl isobutyl ketone	Complex structure in vacuo	27
Oshima <i>et al.</i> (2004)	SMO, DFT	calix[6]arene derivative / amino acid ester / chloroform	Complex structure in vacuo	28
Watarai et al. (2003)	MD	5-octyloxymethyl-8-quinolinol / - / chloroform	Extractant behavior at the oil-water interface	29
Coupez et al. (2003)	MD	dithiophosphinic acid, tributyl phosphate / lanthanoids / chloroform	Complex formation at the oil-water interface	30
Zushi et al. (2003)	MD	β -diketone, neutral phosphate ester / Li ⁺ / heptane	Complex formation at the oil-water interface	31
Baaden <i>et al.</i> (2002)	MD	tributyl phosphate / UO ₂ ²⁺ / chloroform, supercritical carbon dioxide	Complex formation in solvent	16
Boehme <i>et al.</i> (2002)	DFT	carbamoyl phosphine oxide (CMPO) / lanthanoids	Complex structure in vacuo	32
Lumette et al. (2002)	ММ	diamide derivative / Eu ³⁺ / <i>tert</i> -butylbenzene	Complex structure in vacuo	33

Table 1 Research trends of computational chemistry in solvent extraction over the past 5 years



Fig.1 Structures and abbreviation of novel bi-functional organophosphorus extractants

Since the extraction equilibrium constants (K_{ex}) of the *p*- and *o*-types have different values, we cannot directly compare the results to evaluate the extractability and selectivity for the two extractants. Thus, the pH value at 50 % extraction, pH_{0.5}, was employed to evaluate the extraction behavior of all the bi-functional extractants as shown in Fig.2. The spacer structure in the extractants strongly affects not only the extractability but also the selectivity in the lanthanoid extractions. For enhancement of the selectivity, a rigid-segment spacer appears to be more effective than a flexible one, because EG3PA



Fig.2 pH_{0.5} values for novel bi-functional organophosphorus extractants for lanthanoids

having the most flexible spacer shows the lowest selectivity towards the lanthanoids. The *p*-type exhibits the highest selectivity, in particular for heavy lanthanoids.

The MM calculation program "MOMEC", which possesses lanthanoid force field parameters, enables us to analyze stable conformations in a series of lanthanoid complexes. The extractant structures are found to be quite different from each other. In particular, the conformational difference between *o*-type and *p*-type extractants is quite interesting, which is caused by the different substituent positions and the rigidity of the phenolic group in the spacer. From the comparison of the extractant structures optimized by MOMEC calculations, the steric hindrance of the *p*-type extractant is higher than that of the *o*-type. Meanwhile, from the electric point of view, we cannot explain why the *p*-type has a high selectivity for all the lanthanoids, because these three extractants have similar electron densities on all the functional atoms. This also suggests that the enhancement of the selectivity comes from a steric effect not an electrical effect.

In general, lanthanoid complexes with an organic ligand have nona coordination with tricapped trigonal prismatic (TCTP) geometry. Thus, we have calculated the nona coordinated lanthanoid complexes with EG3PA, *o*-type and *p*-type by MOMEC. Figure 3 exhibits the lowest strain energy structure of the La-*p*-type complex.

The difference in complex formation energy between La^{3+} and the corresponding lanthanoid ion is expressed by the following equations:



Fig.3 The lowest strain energy structure of the La-*p*-type complex calculated by MOMEC

$$\Delta U_{\rm Ln} - \Delta U_{\rm La} = (U_{\rm Lncom} - U_{\rm Ln}) - (U_{\rm Lacom} - U_{\rm La}), \qquad (3)$$

where U_i (i = Ln³⁺ (= lanthanoid), La³⁺ (= lanthanum), Lncom (= lanthanoid complex), Lacom (= lanthanum complex)) is the energy of the respective molecules.

Figure 4 shows the relation between $(\Delta U_{Ln} - \Delta U_{La})$ and the inverse of the ionic radius. Increasing rigidity of the spacer in the bi-functional organophosphorus extractants can be seen to lead to increasing selectivity among the lanthanoids. It is also concluded that the large difference in complex formation energy between a lanthanoid ion and La³⁺ provides for high selectivity. Based on the above results, we can design novel extractants having a large energy difference in complex formation by using molecular modeling with the molecular mechanics calculations before synthesizing them. Furthermore, the physicochemical meaning of these values should be clarified in the near future from a thermodynamic viewpoint.



Fig.4 The relation between $(\Delta U_{Ln} - \Delta U_{La})$ and the inverse of ionic radius

2.2 Molecular Modeling of β -Diketones for the Separation of Aluminum(III) and Indium(III) [9]

β-diketones are widely used as extracting and masking reagents for chelatometric titration because they form stable complexes with various metal ions. There is a lack of systematic studies on the correlation between the structure of β-diketones and their selectivity for metal ions, although much attention has been paid to the structure of the metal - β-diketone complexes. The important factors determining the metal-ion selectivity of the ligands are the "geometry of the oxygen atoms coordinating with the metal ion" and the "ligand-ligand interaction in the complex" [10]. If the structure of β-diketones could be modified by introducing bulky groups into suitable positions, the O---O distance could be intentionally controlled to improve their extractability and separability. According to this strategy, we synthesized several β-diketones as shown in Fig.5, to examine the solvent extraction of Al³⁺ and In³⁺ which have large differences in their ionic radii, *i.e.*, Al³⁺, r = 0.53 Å; In³⁺, r = 0.80 Å, for a coordination number of six. We then evaluated how the O---O distance and other factors in the structure of the β-diketones affected their complexation reactions. These factors could lead to a quantitative methodology for the design of more high-performance ligands. We attempt to explain and predict the

	Ligand	R_1	R_2	R ₃
R ₃	HL1	CH₃	CH₃	Н
l -	HL2	CH₃	CH₃	Ph
B_1 , \downarrow B_2	HL3	CH₃	Ph	Н
	HL4	CH₃	Ph	Ph
	HL5	Ph	Ph	Н
ő d	HL7	CH₃	CF₃	Н
	HL8	Ph	CF ₃	Н
H	HL9	Ph	CF_3	CH₃

Fig.5 The structures and abbreviations of β -diketones derivatives

extraction behavior of β -diketones by using the quantitative structure-property relationship (QSPR) [11].

The extraction equilibrium and the strain energy of each component can be expressed as

$$M(H_2O)_6^{3+} + 3HL = ML_3 + 3H^+ + 6H_2O,$$

$$U_M \qquad 3U_{HL} \qquad U_{Mcom} \qquad 3U_H \qquad 6U_{aq},$$
(4)

where U_i (i = M (= Al³⁺ or In³⁺), HL, Mcom (= metal complex), H⁺, and aq) is the strain energy of the respective molecule from the molecular mechanics (MOMEC) calculations.

The strain energy contribution to complex formation is given by

$$\Delta U_{\rm M} = (U_{\rm Mcom} + 3U_{\rm H} + 6U_{\rm aq}) - (U_{\rm Mcom} + 3U_{\rm HL}).$$
(5)



Fig.6 The QSPR for the extractability with β -diketones of Al³⁺ and In³⁺

If the entropy changes during extraction are negligible, the relationship between the strain energy contribution to the complex formation and the extraction constants, K_{ex} , can be expressed by the following two equations.

$$\Delta U_{\text{Al or In}} = \beta \log K_{\text{ex,Al or In,}}$$
(6)

$$\Delta U_{\rm Al} - \Delta U_{\rm Ia} = \alpha \log(K_{\rm ex,Al} / K_{\rm ex,In}), \tag{7}$$

where α and β are the apparent QSPR constants in the above relationships.

Figure 6 shows the relationships between $\Delta U_{\rm M}$ and $\log K_{\rm ex,M}$ for the seven extracting ligands. The plot shows a strong linear relationship. Since the $\Delta U_{\rm In}$ values for InL2₃ and InL4₃ are too high (88 kJ/mol and 78 kJ/mol, respectively), the plot no longer shows a linear relationship. Since HL2 and HL4 do not extract In³⁺, these calculation results are quite reasonable. The relative strain energy for the ligands reflects the extractability of Al³⁺ or In³⁺ with β-diketones.

A plot of $(\Delta U_{Al} - \Delta U_{In})$ vs $\log(K_{ex,Al}/K_{ex,In})$ for the five extracting ligands as shown in Fig.7 also reveals a good linear relationship with a slope (α) of 0.88. This relationship shows the selectivity of β -diketones for Al³⁺ or In³⁺. For the complexation of transition metal ions with polyamine ligands and lanthanoid ions with organophosphate ligands, a similar linear slope has been obtained (α = 1.15 for transition metal-polyamines [11, 12], 1.26 for lanthanoid-organophosphates) [13]. The small but significant deviation may be due to the neglect of terms for entropy, ion pairing, and solvation in Eq.(7). However, the high degree of linearity suggests that the neglected terms are either constant or linearly dependent on the strain energy over the whole series of compounds described here. The QSPR also



Fig.7 The QSPR for the selectivity of $\beta\text{-diketones}$ for Al^{3+} and In^{3+}

allows us to design new extractants with structural properties similar to those of the seven ligands, with improved separation properties.

3. Molecular Simulations of Extraction Processes

3.1 How to apply MD simulations to solvent extraction

The MD calculations can handle not only systems consisting of large numbers of atoms and molecules, but also the time-dependent properties and behavior of a system [7]. The MD calculations generate a series of time-dependent properties (positions and velocities) of all atoms and molecules in the system by solving Newton's equations of motion. "Initial state" and "potential energy functions" are required as input information. The initial state consists of the initial configurations and velocities of all particles. Especially in the case of a simulation of molecules in the liquid phase with a random-structure, the initial configurations have a great influence on the success or failure of the simulation. Setting the initial velocities corresponds to setting the kinetic energy on each atom in the initial configuration. The sum of the kinetic energy on each atom is related to the temperature in the system that is thermodynamically in equilibrium; the initial velocity of each atom is related to a designated temperature in the system that is in equilibrium. Potential functions" and "parameter sets". Functional forms are greatly dependent on the bond properties and structures of the molecules. The parameter sets in the potential functions are determined to reproduce either experimental data or results from high-accuracy calculations based on quantum mechanics. The validity of the potential functions is the

most dominant factor in a successful simulation. Figure 8 shows the relationship between the potential energy and atomic distance in the classical mechanics potential system used for the MD simulations in solvent extraction processes. When the classical mechanics potential system, such as the harmonic-type bond stretching deformation potential and the Lennard-Jones type Van der Waals potential, is applied to the MD calculations, long-range non-bonding interatomic interactions are not estimated. Particularly, the parameters electrostatic (Columnb) for and hydrogen bonding potentials must be obtained ab initio.



Fig.8 Classical mechanics potential systems used for MD simulations

In the solvent-extraction process, not only the stability of the extracted complex, but also the orientation of the extractant and the intermediate complex at the interface govern the extractability, selectivity and kinetics. In order to simulate the extraction behavior, the interface between the organic

and aqueous phases should be precisely reproduced so as to clarify the dynamic behavior and structural change of the reactant species near to the interface. Moreover, when the MD simulation of the extractant and/or its complex in the interface system will be carried out, computational resources are indispensable for the calculations for several thousand atoms and molecules.

The basic cells of aqueous and organic phases generated by the MD calculations are pasted together to produce the interface cell as shown in Fig.9. In this interface cell, both solvent molecules are commingled with each other over a distance of 1 nm width. This commingled zone indicates the "interphase". The extractant and/or its complex are inserted into the interface cell and the dynamic behavior and structural variation profile can be simulated.

3.2 MD Simulations of Interfacial Adsorption of N-8-Quinolylsulfonamides

Sophisticated research involving MD simulations in the field of solvent extraction has been published by Watarai *et al.* [14] and Wipff *et al.* [15,16]. Watarai *et al.* elucidated that the extractant structure at the interface between toluene and water is different from that at a heptane interface, and this difference in structure controls the extraction kinetics. Wipff *et al.* have simulated the extraction behavior of cesium in the chloroform-water system. They elucidated that the cesium complex is stable adjacent to the interface like a surfactant. Particularly, they have succeeded in MD simulations involving the behavior and structural changes of tributylphosphate (TBP) and its uranium complex in supercritical carbon dioxide [16].

We carried out MD simulations of the phenomenon that the interfacial activity increases with



N-8-quinolylsulfonamide

Fig.9 MD simulations of the adsorption of *N*-8-quinolylsulfonamide adjacent to the interface between water and toluene phases under NTP(1000ps) + NTV(1000ps) ensembles; cell size: $3 \text{ nm} \times 6 \text{ nm}$, left side: aqueous phase (892 molecules), center: *N*-8-quinolyl-*p*-octadecylbenzene sulfonamide (1 molecule), right side: toluene phase (157 molecules), density: 0.930 g/cm³ (25 °C)

increasing alkyl chain length of N-8-quinolylsulfonamides [17]. A liquid-liquid boundary cell (3 x 3 x 6 nm³) was prepared by two adjoining rectangular boxes of pure water and toluene having the real densities of a mixture of the solvents. After setting one molecule of a N-8-quinolylsulfonamide at the center of the interface. the rectangular liquid-liquid cell was calculated under NTP(1000ps)+NTV(1000ps) ensembles with the MD method. For this purpose, a set of potential functions and their parameters specialized for this system was constructed in advance, in the same manner as in constructing the MM force field [18].

Figure 9 shows a snapshot of the dynamic behavior of *N*-8-quinolyl-*p*-octadecylbenzene sulfonamide adjacent to the interface between toluene and water phases after 2000 ps. The extractant molecule is observed as a bending structure orienting the alkyl chains toward the toluene phase and a coordination group toward the water phase. Alternatively, when the MD simulations were carried out under the condition wherein an extractant molecule is inserted into the center of the toluene phase, the extractant takes on a linear structure. This indicates that the extractant molecule is stabilized by the orientation in which the lipophilic group faces to the organic phase, whilst the hydrophilic group faces the aqueous phase.

The relationship between the difference in the steric energy of N-8-quinolylsulfonamides $(-\Delta U_{\rm HR})$ obtained by the MD calculation and the interface adsorption equilibrium constant ($K_{\rm ad}$) of N-8-quinolylsulfonamides is shown by

$$-\Delta U_{\rm HR} (= U_{\rm in \ toluene} - U_{\rm at \ interface}) = \alpha \ln K_{\rm ad} , \qquad (8)$$

where α is the apparent QSPR constant in the interface adsorption equilibrium relationship.



Fig.10 Quantitative structure-property relationship of interfacial adsorption of *N*-8-quinolylsulfonamides between toluene and water phases

The plot of $-\Delta U_{\text{HR}}$ vs. $\ln K_{\text{ad}}$ in Fig.10 reveals a good linear relationship with a slope (α) of -2.64. This QSPR technique using the MD calculations becomes an effective prediction tool of the interfacial adsorption properties of extractants.

3.3 MD simulations of distribution coefficients of metal complexes

By using MD simulations in the liquid-liquid binary system, the hydrophilic-lipophilic balance of the molecule can be estimated from the difference in the calculated internal energies of the solute located in either the aqueous phase or the organic phase. We are now developing novel MD simulations of pharmaceutical metal complexes for estimating the partition coefficient of these complexes between 1-octanol and water (log*P*) [19]. Especially, since the lipophilicity of radiotracer complexes is well correlated to their biodistribution [20], it is important to develop a novel estimation method for log*P* as a virtual molecule design tool for developing a new radiotracer for targeting therapy.

We have carried out MD simulations for several types of oxorhenate and oxotechnate complexes of dimercaptosuccinic acid (DMSA), $\text{ReO}(\text{DMSA})_2^-$ (DMSA-Re) and $\text{TcO}(\text{DMSA})_2^-$ (DMSA-Tc), in the 1-octanol-water system. Figure 11 shows a snapshot of the dynamic behavior of DMSA-Re in the 1-octanol phase after 200 ps. From these MD simulations, the differences in internal energy of DMSA-Re both in the 1-octanol phase and in the water phase can be obtained.

The internal energy difference stabilized by inserting DMSA-metal complex into the 1-octanol-water system, ΔU , can be expressed by

$$\Delta U = U_{\rm all} - U_{\rm sol} - U_{\rm com}, \tag{9}$$

where U_i (i = all, sol, com) are the relevant internal energies of all molecules and solvent molecules in the system, and the DMSA-metal complex alone, respectively.



Fig.11 Estimation of log*P* values by using MD simulation of DMSA-Re in the 1-octanol-water system in NTP(100ps) + NTV(100ps) ensemble; cell size: 1.6 nm × 1.6 nm × 6.1 nm, left side: 1-octanol phase (25 molecules), center: DMSA-Re (1 molecule), right side: water phase (267 molecules), density: 0.914 g/cm³ (25 °C)

From these internal energy differences, the QSPR equation for estimating log*P* can be derived:

$$\Delta \Delta U = \Delta U_{1-\text{octanol}} - \Delta U_{\text{water}} = \alpha \log P, \qquad (10)$$

where α is the apparent QSPR constant for the above relationship, and subscript "1-octanol" and "water" indicate the internal energy difference in the DMSA-metal complex existing either in the 1-octanol phase or the water phase in the interface boundary cell.

Figure 12 shows the relationship between the internal energy difference, $\Delta\Delta U$ and the experimentally measured log*P* values for DMSA-Re and DMSA-Tc. The plots reveal a good linear relationship with a slope (α) of -11.2. The MD simulations also indicate that the QSPR so obtained relates the internal energy difference between the DMSA metal complexes in the 1-octanol phase and that in the water phase with the log*P* value. We emphasize that this QSPR technique using the MD calculations can apply to the estimation of log*P* values for various RI complexes.



Fig.12 Quantitative structure-property relationship of $\log P$ values for DMSA-Re and DMSA-Tc.

4. Conclusions

Nowadays, by appropriately combining MM, MO or MD calculations, the solvent extraction process can be simulated with reasonable accuracy. In addition, QSPR theory can easily elucidate the relationship between the properties of molecules and the thermodynamics involved in solvent extraction. Our final goal is to estimate the real constant of the extraction equilibria and kinetics by simulating all the extraction processes. However, improvements in the potential functions and their parameters as well as the development of high-speed computing methods optimized to liquid-liquid extraction system are

still required. Furthermore, the calculation methods described here will become important as the global standard of computational chemistry for many fields of separation processes such as, ion exchange, adsorption, and membrane separation.

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