Computation of Redox Potential of Molecule by Energy Representation Method

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Abstract. *We have been applied the conventional approach based on the molecular dynamics simulation to estimate the redox potential so far. In this study, we have focused the computational conditions in order to estimate standard redox potential by using the energy representation method: we calculate excess chemical potential increasing the number of solvent molecules and sampling data for the preparation of energy distribution functions. From these results, we have found that the computational value of the standard redox potential is close to the experimental value in the case of the system with larger number of solvent molecules unaffected by the behavior of counter-ion when we take a sufficient sampling data for the energy distribution functions.*

Keywords: redox potential, molecular dynamics simulation, thermodynamics cycle, excess chemical potential, energy representation method

1   Introduction

Understanding of redox (reduction and oxidation) mechanisms with electron transfer in biological systems has borne great importance in wide-ranged areas. Analyzing the detailed value of redox potential has been key element technology to apply the redox reaction in biological system to the industrial field such as the bio-fuel cells [1] and artificial photosynthesis [2] as well as the interest in biology [3]. In order to estimate the value of redox potential of molecules, several computational models and methods base on the quantum mechanics (QM) [4, 5] and QM/molecular mechanics (MM) hybrid methods [6, 7] has been developed with the recently growth of computer architecture. However, it is not easy to estimate the redox potential because the redox reaction is associated with the free energy change in electron transfer process in the condensed system, much less the computation of redox potential of large molecules including proteins due to the computational cost. The development of theoretical models and methods to estimate the redox potential for the biological systems is still challenging topics in the field of computational science.

In the previous report, we have suggested a simple calculation method by using molecular dynamics (MD) and density functional theory (DFT) calculations according to thermodynamic cycle to estimate the redox potential of molecules, and we have showed the efficiency of our conventional approach to estimate the difference of the standard redox potential of molecules relative to the normal hydrogen electrode (NHE) potential, which mean the difference of the absolute redox potential of molecules, comparing with the experimental data [8]. However, in the view of each molecule's standard redox potential, the computational values have large discrepancies comparing with the experimental values. To compute accurate value of standard redox potential should be important for the understanding of molecular-specific redox mechanism and the exactly discussions of the redox potential with the difference of that of molecules.

In this study, we compute the standard redox potential of simple small molecule, acetone, relative to the NHE potential. Then, in order to investigate the proper conditions to get more accurate value of standard redox potential, we improve the computational method of excess chemical potential, which is required to estimate the absolute oxidation free energy in thermodynamic cycle, in

the frame work of the energy representation (ER) method [9, 10]: specifically, we calculate the dependence of the standard redox potential on the number of solvent molecules in the simulation cell, and we evaluate the excess chemical potential increasing the sampling data for the description of the energy distribution function. From these results, we have discussed the computational approach by using the ER method to estimate the standard redox potential of molecule.

2   Computational procedures

The computation of the standard redox potential of molecule employs the Nernst equation. The standard redox potential $E°$ is associated with the absolute oxidation free energy change, ΔG, and the absolute potential of normal hydrogen electrode (NHE), E^{NHE}, which has -4.44 V for the experimental data [8, 11], as follow,

$$E° = \frac{\Delta G}{nF} + E^{NHE},$$ (1)

where, n and F are the number of electrons and the Faraday constant, respectively. According to the thermodynamic cycle as shown in Figure 1, the ΔG is given by

$$\Delta G = \Delta E + \left\{ \Delta \mu_{(N-1)} - \Delta \mu_{(N)} \right\},$$ (2)

where, ΔE is the ionization free energy, $\Delta \mu_{(N)}$ and $\Delta \mu_{(N-1)}$ are excess chemical potential of molecules in reduced and oxidized states, respectively. The ionization free energy is evaluated by the difference of the average of total energies of reduced and oxidized configurations, which are obtained from the molecular dynamics (MD) simulations of the molecules in solvation. The excess chemical potential is calculated by the energy representation (ER) method by utilizing the energy representation module (ERmod) program packages [12]. In the ER method, the excess chemical potential is given by the energy distribution functions for the solution and reference solvent systems. These energy distribution functions are obtained from the different MD simulations. The actual form of the excess chemical potential using these energy distribution functions and the details of computational methodology are presented in Refs. [9, 10].

In this report, we have used the previous result of equilibrium MD simulations for the configurations of the neutral and radical cationic molecule in solvation, and we also have used the values of ionization free energy ΔE, which is obtained by the density functional theory (DFT) calculations with B3LYP method and 6-31+G(d,p) basis set in the previous study [8]. The excess chemical potentials in the neutral and radical cationic states, $\Delta \mu_{(N)}$ and $\Delta \mu_{(N-1)}$, have been reevaluated
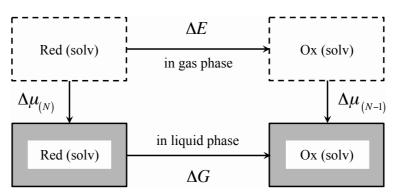

Figure 1. Conventional approach to calculate the absolute oxidation free energy change ΔG based on the thermodynamic cycle

relative to the different number of solvents system. In this study, we prepare the simulation boxes including 1425, 2850 and 4275 solvents molecules; then these system sizes are $36.5 \times 34.3 \times 34.6$ Å, $45.7 \times 43.4 \times 43.9$ Å and $52.3 \times 50.0 \times 50.0$ Å, respectively. The MD simulation for the calculation of energy distribution function is performed utilizing the AMBER 11 program packages [13]. Langevin thermostat and barostat are used to control system temperature ($T = 300$ K) and pressure ($P = 1$ atm). The TIP3P model [14] is adopted for the solvent molecule. Particle mesh Ewald method [15] is used for the calculation of coulomb interaction. Cut-off lengths for the real-space coulomb and van der Waals (vdW) interactions are 12 Å. The time step for the MD simulation is 2 fs. The AMBER force field 03 (parm99) parameters [16, 17] are used for the vdW and torsion interactions of solute molecules. On the other hands, for the bond stretching, angle bending and partial charge in acetone molecule, we have applied the previous results obtained from the quantum chemical calculations [18]. It is noted that for the MD simulations of the radical cationic acetone under the periodic boundary conditions, a chloride-ion is inserted into the simulation cell as counter-ion.

For the calculation of energy distribution function for the solution system, the sampled structure of the solute molecule obtained from the equilibrium MD simulation is put in the center of the MD cell, and the water molecules are arranged around the solute molecule. The *NPT*-MD simulation of the solution system is performed for 1 ns to prepare total 100×10^3 snapshots. The configuration of the solute molecule is fixed in this simulation. On the other hands, for the calculation of energy distribution function for the reference solvent system, the pure solvent system, which has the same number of water molecules as the solution system, is prepared. The *NPT*-MD simulation of the reference solvent system is performed for 100ps to obtain 100 snapshots. After that, the sampled structures are randomly inserted 1000 times into the pure solvent system of each snapshot: a total of 100×10^3 sampling data are prepared for the reference solvent system. It is noted that we have confirmed that the number of sampling data for the reference solvent system is sufficient to estimate the excess chemical potential of molecule in the neutral and radical cationic states.

3   Results and discussions

Table 1 show the computational results of the dependence of absolute oxidation free energy ΔG and the standard redox potential $E°$ of an acetone on the number of solvent molecules in the simulation cell. The average values of ΔG or $E°$ are 186.7, 187.6 and 188.5 kcal/mol or the 3.65, 3.69 and 3.73 V for the 1425, 2850 and 4275 solvents systems, respectively. These results show that the computational value of standard redox potential is more different from the experimental value (0.16 V [19]) even if the number of solvent molecules increases in the simulation cell. The average values of excess chemical potential in neutral state, $\Delta\mu_{(N)}$, are -2.3 kcal/mol for all of the solvents systems, showing that there is no dependence of the $\Delta\mu_{(N)}$ on the number of solvent molecules. On the other hands, the

Table 1. Dependence of the absolute oxidation free energy ΔG and the standard redox potential $E°$ on the number of solvent molecules, N^{water}. The units are kcal/mol for ionization free energy ΔE, excess chemical potential in neutral and radical cationic molecules, $\Delta\mu_{(N)}$ and $\Delta\mu_{(N+1)}$, ΔG and V for the $E°$, respectively. The values in parentheses show the standard deviation.

N^{water}	ΔE [a]	$\Delta\mu_{(N)}$	$\Delta\mu_{(N-1)}$	ΔG	$E°$
1425		-2.3 (0.2)	-36.4 (1.5)	186.7 (2.1)	3.65 (0.09)
2850	220.8 (1.4)	-2.3 (0.2)	-35.5 (1.4)	187.6 (2.0)	3.69 (0.09)
4275		-2.3 (0.2)	-34.6 (2.4)	188.5 (2.8)	3.73 (0.12)

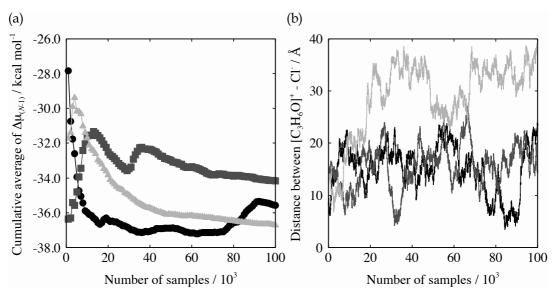[a] Previous computational result from Refs. [8]

(a)

(b)

Figure 2. (a) Cumulative average of excess chemical potential in radical cationic state $\Delta\mu_{(N+1)}$ for one configuration and (b) change of distance between the radical cationic acetone and chloride-ion as a function of the number of samples; black, black ash and gray lines indicate these for the 1425, 2850 and 4275 solvents systems, respectively.

average values of excess chemical potential in radical cationic state, $\Delta\mu_{(N-1)}$, are -36.4, -35.6 and -34.6 kcal/mol for the 1425, 2850 and 4275 solvents systems, respectively, denoting the same tendency of the computational values of ΔG or $E°$. This results show that the radical cationic acetone is less soluble in larger solvents system.

In order to investigate the reason of this results, we have analyzed the cumulative average of $\Delta\mu_{(N-1)}$, as shown in Figure 2 (a), for just only a configuration of solute molecule, which is pick up from equilibrium molecular dynamics (MD) simulation for 10 ns. Additionally, we here plot change of distance of counter-ion (chloride-ion) from the center of mass of the solute molecule in Figure 2 (b). Comparing the Figure 2 (a) with (b), we find that the $\Delta\mu_{(N-1)}$ become positively large value when the counter-ion exists within the distance about 15 Å around the solute molecule; for instance, in the Figure 2 (a), the cumulative average of $\Delta\mu_{(N-1)}$ for the 1425 solvents system increase positively from about 75×10^3th sampling data, then, the distance between solute molecule and counter-ion become short as shown in Figure 2 (b). From this result, we assume that the behavior of the counter-ion artificially put in the simulation cell has a negative effect on the evaluation of the excess chemical potential of charged solute molecule.

Based on this assumption, we focus on one configuration and compute the $\Delta\mu_{(N-1)}$ increasing the number of sampling data until 1000×10^3 snapshots for the calculation of energy distribution function. Figure 3 (a) and (b) shows the probability distribution of the distance between the solute molecule and the counter-ion for the 100×10^3 and 1000×10^3, respectively. These figures indicate that we can estimate the $\Delta\mu_{(N-1)}$ with widely coordinate sampling of the counter-ion in the simulation cell because we can get distortion-free probability distribution between 0 – 15 Å at some level.

The results of the value of $\Delta\mu_{(N-1)}$ are shown in Figure 4. In this Figure, we plot the average of the difference of $\Delta\mu_{(N-1)}$ ($\Delta(\Delta\mu_{(N-1)})$) for 1425 solvents system from that for 2850 or 4250 solvents systems. In the case of 2850 – 1425 solvents systems, the average of $\Delta(\Delta\mu_{(N-1)})$ become negative value from outside of 400×10^3th sampling data. From the result, we find that the value of $\Delta\mu_{(N-1)}$ for 2850 solvents system is smaller than that for 1425 solvents system, and specifically, the value of absolute oxidation free
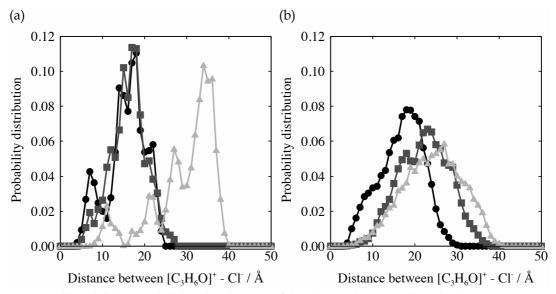
(a)

(b)

Figure 3. (a) and (b) are probability distributions of the distance between the radical cationic acetone and chloride-ion for the 100×10^3 and 1000×10^3, respectively; black, black ash and gray lines indicate these for the 1425, 2850 and 4275 solvents systems, respectively.

$14{,}488 / (145.30 + x)^{1.5562}$
-0.7393
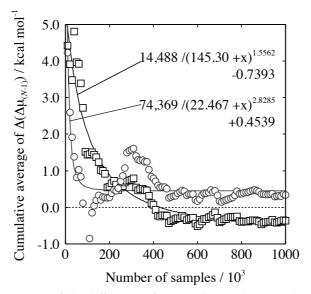
$74{,}369 / (22.467 + x)^{2.8285}$
$+0.4539$

Figure 4. Cumulative average of the difference of excess chemical potential in radical cationic state $\Delta\mu_{(N-1)}$, which is showed as $(\Delta(\Delta\mu_{(N-1)}))$ in the Figure, between the 1425 and 2850 solvents systems (black square points) and between the 1425 and 4250 solvents systems (black ash circle points); lines are fitting results of these points.

energy ΔG (or also standard redox potential E°) is close to the experimental value for 0.7 kcal/mol. This value is obtained from fitting calculation of all the values of $\Delta(\Delta\mu_{(N-1)})$. On the other hands, in the case of 4275 – 1425 solvents systems, the average of $\Delta(\Delta\mu_{(N-1)})$ is still positive value even if we have

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take the 1000×10^3 sampling data. From the result, it is considered that the computation of $\Delta\mu_{(N-1)}$ for the 4275 solvents system is still not satisfied only by 1000×10^3 sampling data due to the widely system size; actually, the probability distribution for 4275 solvents system has larger part than that for 2850 solvents system between the distances from 0 to 15 Å. In order to become negative value for the $\Delta(\Delta\mu_{(N-1)})$ and close to the experimental data for the ΔG, we should sufficiently take sampling data for the calculation of energy distribution function, and we should compute the average of $\Delta\mu_{(N-1)}$ including the other configurations; these treatments would be a future work. Thus, these results suggest that the computational approach by using the energy representation (ER) method has the possibility of discussion for the standard redox potential of molecule under the condition of the sufficiently number of solvent molecules and sampling data to obtain the energy distribution function unaffected by the counter-ion.

4   Summary

We have computed the standard redox potential of molecule by using our conventional approach with energy representation (ER) method. To compute the absolute oxidation free energy, we have investigated the proper conditions for the calculation of excess chemical potential increasing the number of solvent molecules and sampling data to get the energy distribution functions in the frame work of the ER method.

We have discussed about the computational approach by using the ER method to estimate the standard redox potential of molecule in relation to the behavior of counter-ion in the simulation cell. The computational value of the standard redox potential is close to the experimental value in the case of larger system when we take a sufficient sampling data for the calculation of the energy distribution functions. These results suggest that the computational approach by using the ER method has the possibility of discussion for the standard redox potential of molecule under the condition of the sufficiently number of solvent molecules in the simulation cell and sampling data to obtain the energy distribution functions unaffected by the counter-ion.

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