POTENTIAL OF MEAN FORCE BY THERMODYNAMIC INTEGRATION: MOLECULAR-DYNAMICS SIMULATION OF DECOMPLEXATION

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"Umbrella sampling" has been incorporated in the thermodynamic integration method to obtain a potential of mean force by *slow growth* molecular-dynamics simulations. The method was tested for liquid argon, for which good agreement was obtained with a standard potential of mean force, as derived from the radial pair-correlation function. For a sodium chloride ion-pair in aqueous solution the calculations showed resonable agreement with a literature result. The method was also applied to the decomplexation of 18-crown-6 and a potassium cation in aqueous solution.

1. Introduction

Simulations of host–guest complexation or – more generally – binding of two species in solution, with the Monte Carlo and molecular-dynamics methods, have often been restricted to equilibrium states, yielding enthalpies and (relative) free energies of solvation and binding [1–8]. Simulations of a process, such as the (de)complexation reaction, involving the crossing of barriers, are relatively expensive in terms of computing resources. Several studies, however, have been reported in which a potential of mean force is determined along a certain (reaction) coordinate, such as the distance between two species in solution [9–17], or an internal coordinate [18–23], e.g. a dihedral angle. Usually a simple system was involved, of which the coordinate of interest was covered with "umbrella sampling". Recently, larger host–guest systems were treated with these methods, yielding reaction paths and barriers for (de)complexation [24,25].

In host–guest complexation 18-crown-6 is one of the most widely studied hosts. Besides the experimental work, a number of computational studies have been reported. Molecular-mechanics studies of the isolated host and of complexes with alkali-metal cations and neutral molecules have been performed [26–28], as well as molecular-dynamics simulations of alkali-metal cation complexes in solution, which

yielded relative free energies of complexation [5–7]. As a next step, it seemed worthwhile to study the (de)complexation process of 18-crown-6 with alkali-metal cations.

2. Method

Empirical force-field methods yield potential energies of single conformations or enthalpies of systems in thermal equilibrium. Free energies cannot be calculated from standard Monte Carlo or molecular-dynamics simulations. The problem is in the entropy, for which in principle sampling of all possible configurations of the system in its phase space is necessary. This is practically not feasible. Several methods have, however, been developed for the calculation of free energy *differences*, a review of which has been given [29].

The difference in free energy between two systems, characterized by Hamiltonians H_0 and H_1, can be calculated with the thermodynamic perturbation [1,30–32] and integration [33] methods. In this last approach a continuous perturbation is defined with a parameter λ that couples the two systems in the perturbation Hamiltonian $H(\lambda)$. The free energy of the system (G in the isothermic–isobaric ensemble [34]) is a function of λ, $G(\lambda)$, of which the derivative with respect to λ is calculated as

$$\delta G(\lambda)/\delta\lambda = \langle \delta H(\lambda)/\delta\lambda \rangle_\lambda . \qquad (1)$$

Integration is performed by evaluation of the ensemble average $\langle \ \rangle_\lambda$ at a limited number of λ values, with subsequent numerical integration, or by *slow growth*, i.e. λ is changed slowly at every timestep, so that the system remains essentially in equilibrium, and the averaging can occur during integration using the instantaneous values of the derivative.

With "umbrella sampling" [9,10] a system can be forced to sample in phase space (transition) regions that are of interest but normally only infrequently encountered. This is accomplished by the addition of a constraining (umbrella) potential to the Hamiltonian, or by the use of a weighting function in the sampling procedure. The "umbrella" allows the exploration of a (reaction) coordinate r, for which, after correction for the imposed constraint, a probability distribution $g(r)$ can be calculated. Associated with a probability distribution $g(r)$, such as the radial pair-correlation function, a potential of mean force $W(r)$ can be defined,

$$W(r) = -kT \ln g(r) . \qquad (2)$$

The derivative of the potential of mean force yields the mean (ensemble-averaged) force along the coordinate r, hence the name [34].

(De)complexation can be studied by the evaluation of a free energy along a complexation reaction coordinate. With umbrella sampling two (de)-complexing species can be constrained at a specified distance along the coordinate. To use this method within the thermodynamic integration scheme, a constraining potential was added as a function of λ to the Hamiltonian H_0,

$$H(\lambda) = H_0 + \tfrac{1}{2} k_c [r - r_0(\lambda)]^2 . \qquad (3)$$

The behavior of r_0 as a function of λ determines the reaction coordinate. If the constraining force constant k_c is large, the instantaneous value of r will be approximately equal to the constraint value r_0.

The free energy difference between two arbitrary points along the reaction coordinate r can be calculated by integration, with eqs. (1) and (3),

$$\Delta G = \int \langle \delta H(\lambda)/\delta\lambda \rangle_\lambda \, \mathrm{d}\lambda$$

$$= \int \langle -k_c [r - r_0(\lambda)] \, \delta r_0(\lambda)/\delta\lambda \rangle_\lambda \, \mathrm{d}\lambda$$

$$= \int \langle -k_c (r - r_0) \rangle_{r_0} \, \mathrm{d}r_0 . \qquad (4)$$

Thus ΔG equals the integral of the mean force exerted on the two species, along the reaction coordinate, i.e. the potential of the mean force. The constraining potential allows averaging at a specified value of the reaction coordinate, and at the same time it yields the force along this coordinate. This method for calculating a potential of mean force is not exact, because the averaging at r_0 requires $r = r_0$, whereas the force is calculated as $k_c(r - r_0)$. But a large k_c will give $r \approx r_0$. A detailed analysis yields a second-order correction. The method requires the absence of (relative) motion of the two species, which was achieved by scaling their velocities to (nearly) zero. In connection with this, the value of the constraining force constant, k_c, was chosen as large as possible without giving numerical problems. For definition of the reaction coordinate r two points are required. For an interatomic potential of mean force, the coordinates of the two atoms involved define these points. In case of a more complicated reaction, such as the decomplexation of 18-crown-6 and a cation, a virtual atom has to be defined. The center of the macrocyclic cavity of 18-crown-6 is a natural choice; its coordinates are calculated as the arithmetic mean of the coordinates of all 18-crown-6 (O and CH_2) atoms. The constraining force acting on this center is transferred to all atoms equally, as though 18-crown-6 were a rigid body. This applies only to the reaction coordinate, otherwise 18-crown-6 retains its macrocyclic flexibility, which is essential in (de)complexation.

Molecular-dynamics simulations were performed with the GROMOS package [35].

3. Results and discussion

3.1. Potential of mean force of liquid argon

As a first test of the method, calculations were performed on liquid argon, a system thoroughly studied

with experimental, theoretical, and computational methods [36]. For this system of homogeneous composition the argon–argon potential of mean force (PMF) can easily be derived with eq. (2) from the radial pair-correlation function (RPCF), obtained from an equilibrium molecular-dynamics simulation. This serves as a reference for the results from thermodynamic integration.

For the simulation of liquid argon a truncated octahedron with a volume of 5.5 nm^3 was constructed, containing 110 atoms. Standard Lennard-Jones 12–6 parameters for the argon pair-potential were used [36]. A timestep of 0.010 ps was applied in an equilibrium run, whereas in the thermodynamic integration runs the timestep was 0.005 ps; it was not investigated whether this reduction in timestep is essential for thermodynamic integration runs. Temperature was maintained at 100 K, by velocity scaling [37] with a time constant of 0.5 or 0.25 ps. Nonbonded interactions were calculated for all pairs of atoms within a cutoff distance of 0.95 nm. After extensive equilibration of the liquid-argon box at 100 K, a 100 ps molecular-dynamics run was performed, from which the RPCF was determined. In fig. 1 the corresponding reference PMF is shown and compared with the argon pair-potential. The PMF shows the familiar picture with two minima, the contact-pair and the solvent-separated minimum. The statistical error in this reference PMF is low (± 0.01 kJ/mol): curves calculated for the first and second 50 ps of the run showed complete overlap.

Then *slow growth* thermodynamic integration runs were performed, after equilibration of the system, with a specified argon–argon pair constrained at a distance of 0.33 nm. Preliminary runs indicated the need for long simulation times to obtain reproducible results and reasonable agreement with the reference. In fig. 1 the result is shown of a 4000 ps run, that covered with linear increment the range 0.33–0.83 nm for the interatomic distance within the pair. The PMF curve can be shifted vertically at liberty, because the integration constant, which should yield a PMF value of zero at infinite separation, is unknown. Comparison of the reference PMF to the result of the 4000 ps run, which was shifted so as to give the best fit, shows good agreement. There is a slight underestimation of the depth of the contact pair minimum; for high r values also some deviation is
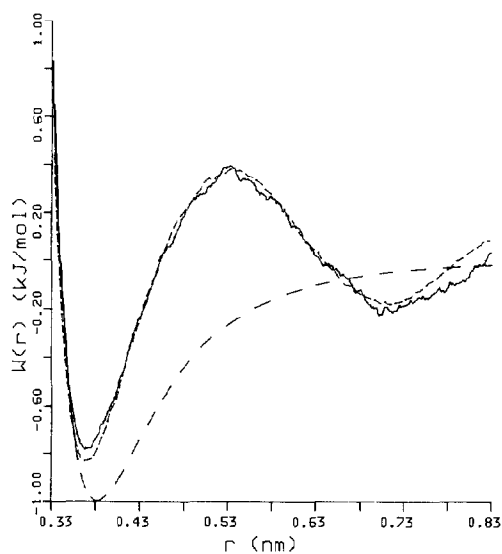

Fig. 1. Liquid argon potential of mean force at 100 K, obtained by thermodynamic integration in a 4000 ps molecular-dynamics run (———). Reference (– – –) calculated from the radial pair-correlation function, derived from a 100 ps molecular-dynamics equilibrium run. The argon pair-potential (– – –) is shown for comparison. The thermodynamic integration PMF is shifted vertically for best fit with the references.

observed, which may be an effect due to the cutoff of nonbonded interactions at 0.95 nm [38]. From the average deviation between the precise reference PMF and the thermodynamic integration PMF, an error of the order of 0.05 kJ/mol in the latter is estimated. In a similar study the argon–argon PMF was calculated from molecular-dynamics simulations with the thermodynamic perturbation method [16]; a qualitatively comparable result was obtained, with an estimated error of 0.1 to 0.3 kJ/mol, in considerably shorter simulation times as compared with the present work.

3.2. Potential of mean force of a sodium chloride ion-pair in aqueous solution

Next a system of inhomogeneous composition was considered, viz. one sodium chloride ion-pair in aqueous solution. The potential of mean force for the ion-pair cannot be obtained from the radial pair-correlation function, because in a normal molecular-dynamics run of this system there is no adequate sampling of the relevant coordinate, the distance between

the two ions; therefore no reliable RPCF can be calculated.

For the simulation of sodium chloride in water an equilibrated aqueous solution of Na^+ was taken [5,39], in which a water molecule near Na^+ was replaced by a Cl^-, yielding a truncated octahedron with one Na^+–Cl^- ion-pair and 178 water molecules. The parameters for Cl^- were those used in studies of the aqueous solvation of the anion [40]; other simulation parameters are as reported before [5]. After 40 ps equilibration of the system at 298 K, with the ion-pair constrained at a distance of 0.25 nm, a 160 ps thermodynamic integration run was performed, in which the distance between the ions was linearly increased by *slow growth* from 0.25 to 0.65 nm. With the ions at 0.65 nm the system was again equilibrated for 40 ps, and then the 160 ps run was repeated in the reverse direction ($r=0.65\rightarrow0.25$ nm). The resulting PMFs are shown in fig. 2a, with the minimum shifted to the origin of the abscissa; a result from Berkowitz et al. [11] is included for comparison. They obtained their result by application of an umbrella potential for sampling at a number of specified interionic distances in molecular-dynamics simulations; they used somewhat different parameters, especially for Na^+, which is reflected in fig. 2a by a discrepancy of approximately 0.02 nm in the location of the contact-pair minimum. Therefore their PMF has been shifted in an ad hoc fashion 0.02 nm along the ordinate, for comparison (see fig. 2b). All curves have the characteristic shape, as observed for argon. The two thermodynamic integration runs show a rather different behavior for the larger values of r. The forward run ($r=0.25\rightarrow0.65$ nm) rises to a second maximum, higher than the barrier between the contact-pair and solvent-separated regions; this is an unexpected result, probably due to a lagging of the system behind the perturbation. The backward run ($r=0.65\rightarrow0.25$ nm) shows a low second maximum in the same region. Averaging of the two runs, that show the same behavior for small r values, appears to yield a reasonable result, due in part to a cancelation of hysteresis. A statistical error is estimated, from the deviations between the two runs, as 1 to 3 kJ/mol. The shifted result of Berkowitz et al. compares well with the averaged PMF of the two 160 ps runs. From the results the barriers for dissociation of the ion-pair (from contact to solvent-separated
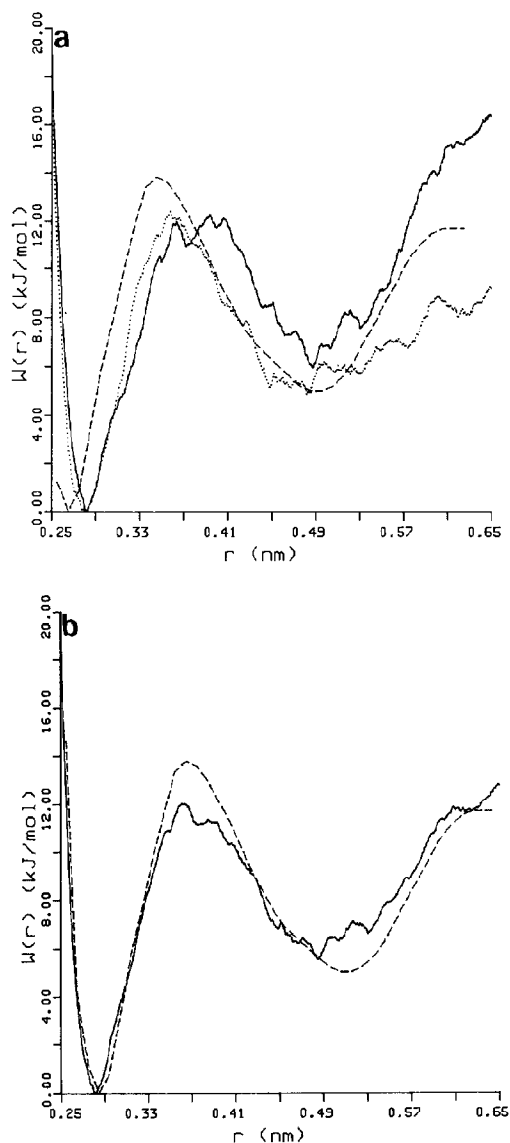

Fig. 2. Na^+–Cl^- potential of mean force at 298 K: (a) calculated from 160 ps thermodynamic integration molecular-dynamics runs ($r=0.25\rightarrow0.65$ nm, ——; $r=0.65\rightarrow0.25$ mm, ···), compared with a literature result (- - -, redrawn from Berkowitz et al. [11]); (b) average of the two runs (——), compared with the literature result (- - -, shifted 0.02 nm to the right). The minimum of each curve is positioned at the origin of the abscissa.

minimum), and for association (vice versa) are estimated as 12 and 6 kJ/mol, respectively. Berkowitz et al. report values of 14 and 8 kJ/mol, with an error of 1 to 2 kJ/mol. The differences between the present molecular-dynamics results and those of Berko-

witz et al. are within estimated error, and may reflect the difference in model parameters.

3.3. Decomplexation of 18-crown-6 and a potassium cation

Finally, the thermodynamic integration method was applied to the 18-crown-6·K^+ complex in aqueous solution. This presents a more complicated case than sodium chloride because one of the species involved is a flexible macrocycle. Decomplexation will most likely involve conformational changes. From previous simulations it was clear that for the complex longer simulation times were needed than for a single cation, in order to obtain a comparable precision [35].

The 18-crown-6·K^+ system was taken from an equilibrated configuration, containing one complex and 225 water molecules [5,39], with details for the simulations the same as described previously [5]. The 18-crown-6·K^+ complex was constrained at $r=0.0$ mm, i.e. with K^+ in the center of the macrocyclic cavity. After 40 ps of equilibration at 298 K, a *slow growth* run of 280 ps was performed, in which linearly the range $r=0.0$–0.7 nm was covered. The potential of mean force, calculated as the free energy change along this decomplexation coordinate, is shown in fig. 3. In a short, preliminary run qualitatively the same features were observed. The PMF exhibits a minimum at low r values, consistent with the thermodynamic stability of the complex. Several interesting details are observed. The minimum of the curve is not found at exactly $r=0.0$ nm, i.e. with K^+ in the center of the cavity, but at approximately 0.1 nm. This is in line with the calculated coordination of K^+ in the 18-crown-6 complex by three water molecules [39], interpreted as two waters coordinating to K^+ at one side of the macrocyclic plane and one at the other, which will result in a displacement of the cation towards the two waters at one side; hence the minimum is found for $r>0.0$ nm. Around $r=0.4$ nm a plateau in the curve of the PMF is observed, which is ascribed to a solvent-separated state, with a water oxygen coordinated to the cation and its hydrogen atoms hydrogen-bonded to crown-ether oxygens; besides 18-crown-6 will have gained some conformational flexibility, as the cation has left the cavity. Beyond this solvent-separated state, which
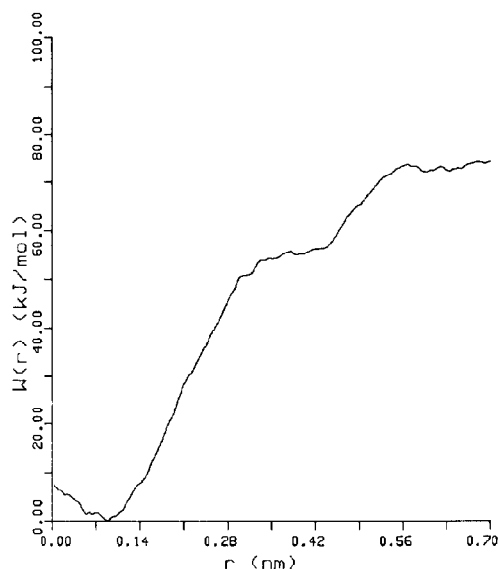

Fig. 3. Potential of mean force for the decomplexation of 18-crown-6·K^+ at 298 K, in a 280 ps thermodynamic integration molecular-dynamics run; the minimum of the curve is positioned at the origin of the abscissa.

does not really exhibit a local minimum, the PMF rises until a second plateau in the region 0.6–0.7 nm is reached. It is not clear whether this is the global maximum, or that the curve will rise again beyond 0.7 nm. Further simulation, from $r=0.7$ nm onwards, will not yield a reliable result, because of the cutoff of the nonbonded interactions at 0.85 nm. From the present result the barrier to the "solvent-separated" state is estimated as 50 kJ/mol, and toward the second maximum as 75 kJ/mol; and no barrier for complexation is observed within the range of the simulation. Experimentally a free energy barrier to decomplexation of 39 kJ/mol was calculated from the measured barrier to complexation of 27 kJ/mol [41], and the free energy of complexation of −12 kJ/mol. The present calculation may not be representative of an equilibrated decomplexation, even more so than the sodium chloride system, because of the conformational changes during the simulation. A longer run may yield a more reliable estimate of the barrier. Then also a more detailed analysis of the results, e.g. in terms of a reaction path, will be performed.

4. Conclusions

The results for liquid argon demonstrate the agreement between the standard potential of mean force, obtained from the radial pair-correlation function, and the result calculated by thermodynamic integration. For the sodium chloride ion-pair it is concluded that 160 ps runs apparently are rather short to cover the relevant range of the reaction coordinate adequately. Averaging of the forward and backward runs yields a reasonable result. For the decomplexation of 18-crown-6 and potassium cation the simulation obviously is too short to adequately describe the decomplexation process with the conformational reorganization, but the resulting curve shows some interesting aspects, e.g. the supposed solvent-separated state.

The results for liquid argon and the sodium chloride ion-pair in aqueous solution show that by thermodynamic integration meaningful results can be obtained with respect to the potential of mean force.

Recently a similar approach to calculating the free energy along a specified coordinate by thermodynamic integration has been described by van Gunsteren [42].

Acknowledgement

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