

Ion-Water Interaction Potentials Derived from Free Energy Perturbation Simulations

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A consistent set of empirical interaction parameters for the alkali and alkaline-earth metal cations is derived by performing free energy perturbation simulations in aqueous solution. The resulting parameters reproduce the observed hydration free energies as well as radial distribution functions for these ions. The minimum energies for gas-phase alkali metal ion monohydrates are also examined for this (liquid phase) potential and found to be in reasonable agreement with experiments. It is argued that calculations of *differential* ion solvation energies are not enough to assess the validity of a given potential and that the most reliable way to obtain parameters for use in simulations of solutions and biomolecules is to calibrate the calculated *absolute* hydration free energies against observed ones.

Introduction

With modern computational resources it has become possible to evaluate the energetics of complex molecular systems by direct microscopic simulations. In particular, the free energy perturbation (FEP) approach¹ has become very popular in recent years (see, e.g., ref 2 for an overview) and can now be applied even to large biomolecular systems for calculating, e.g., binding energies, intrinsic pK_a 's, and enzyme catalytic barriers.³⁻⁹ The FEP technique in combination with molecular dynamics (MD) or Monte Carlo (MC) simulations appears to be a very promising route for addressing energetic questions in a quantitative way, as a wealth of recent studies suggest.²

Many interesting problems in biomolecular and biomimetic chemistry involve interactions with metal (or other) ions in one way or another. Metalloenzymes, ion-binding proteins, ion channels, and ion-selective macrocycles are just a few examples in which the interaction between ions and organic groups plays a central role. To understand such phenomena as binding and rate selectivity in these systems, it is of great interest to be able to model the relevant ion-ionophore interactions on a microscopic level. While considerable efforts have been devoted to deriving consistent empirical interaction potentials for proteins, nucleic acids, and various solvents, there are still no such potentials available for ion-solvent or ion-ionophore interactions whose validity has been verified by calculations of *absolute* solvation free energies.

In most molecular mechanics/dynamics studies of ion-solvent systems the relevant interaction parameters were obtained either from *ab initio* SCF calculations^{10,11} or by fitting a Lennard-Jones potential to experimental gas-phase energetics for ion monohydrates.¹² Such procedures do not, however, guarantee that the resulting parameters are actually the most adequate ones for simulations of condensed phases. Apart from the problems associated with SCF calculations in this context, transferability problems between different phases are not unusual for two-body pair potentials. This point has been clearly illustrated in two recent studies of ionic hydration by Straatsma and Berendsen¹³ and by

Migliore et al.,¹¹ where *ab initio* potentials were found to give hydration free energies that differed considerably from observed ones. In fact, it appears that to be confident with any set of ion interaction parameters, e.g., when studying differential binding of ions to host molecules, it is necessary to first verify that correct solvation free energies in water are obtained. Of course, the water potential should likewise be consistent with the rest of the general force field.

In the present paper, we take the approach that the most consistent way to obtain a useful and operational set of ion-solvent interaction parameters for condensed-phase simulations is to calibrate the calculated *hydration free energy* against the observed one, using a water model that is an integral part of a general molecular mechanics force field. This is, however, not the only parameter constraint that should be invoked as it is not enough to determine the structural properties of the system. The most natural additional constraint on the parameters is therefore that they simultaneously reproduce the observed radial distribution function (RDF) in water. By performing extensive FEP/MD calculations in water we derive a consistent set of interaction parameters, which fulfill the criteria above, for the alkali (Li^+ , Na^+ , K^+ , Rb^+ , Cs^+) and alkaline-earth (Mg^{2+} , Ca^{2+} , Sr^{2+} , Ba^{2+}) metal ions.

The simulations are performed with the widely used SPC water model,¹⁴ and results are presented both for the original rigid version as well as for a flexible variant of this water model, which does not require the use of constraints in the MD algorithm. The SPC model is particularly attractive since it has been parametrized in conjunction with the more general GROMOS force field¹⁵ for proteins and nucleic acids. For comparison, we also report results for Na^+ calculated with the TIP3P water model.²⁷

We compare the performance of our Na^+ and Ca^{2+} potentials to those used in some other FEP/MD studies, and as an additional check of our parameters, we also contrast these to experimental and *ab initio* SCF results on ion monohydrates in the gas phase. It turns out that the potentials derived from solution simulations give ion-water minimum energies that agree rather well with gas-phase experiments and are at least as close to these as the corresponding *ab initio* potentials.

Methods

Boundary Conditions. A pertinent problem when calculating solvation free energies of charged molecules and ions is how to treat the system boundaries. In the present work we have chosen to employ the constrained spherical boundary model developed by Warshel and King,^{16,17} viz., the SCAAS (surface constraint

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all-atom solvent) model. We will still refer to it as the SCAAS model, although the actual water parameters used here correspond not to those reported in ref 17 but to the SPC parameters.¹⁴ In the SCAAS model the solvent is represented as an isolated sphere of water molecules surrounding the solute. The surface layer of this sphere is subjected to harmonic radial and angular (polarization) constraints. The radial constraint ensures that the appropriate density is maintained, while the angular constraints applied to the dipole moment vector of the surface molecules forces these to have the average polarization that would be expected in a corresponding infinite system (this polarization is calculated by using the Langevin function as described in refs 16 and 17). It should be noted that for any finite system or periodic system with a finite interaction cutoff radius, one must include a correction to the calculated hydration energy due to the surrounding (infinite) medium. This correction can be calculated from the Kirkwood formula¹⁸ or, if higher than monopole moments of the charge distribution are neglected (which is on average warranted), from Born's formula (in kcal/mol and Å)

$$\Delta G_{\text{Born}} = -332 \frac{Q_1^2}{2r_{\text{Born}}} \left(1 - \frac{1}{\epsilon}\right) \quad (1)$$

where Q_1 is the net charge of the solute and r_{Born} is the radius of the cavity in the macroscopic medium with dielectric constant ϵ in which the charge is embedded.

There are several considerations that make the spherical boundary more suitable than the often used periodic boundary conditions (PBC). First, the use of PBC requires a rather large number of water molecules to avoid artificial distortions of the electric fields near the boundaries of the central image. It is also well-known that the calculated free energies are quite sensitive to the choice of cutoff radii in the simulations.¹³ Not only the ion-water cutoff ($R_{\text{I-w}}^c$), the effect of which can be taken into account by eq 1, but also the water-water cutoff radius ($R_{\text{w-w}}^c$) can have a pronounced effect on the calculated ΔG_{hydr} . Straatsma and Berendsen examined the dependence of the calculated free energy of transforming Ne to Na^+ , on different choices of cutoff radii.¹³ They found that the difference in free energy between using $R_{\text{I-w}}^c = 9$ Å and $R_{\text{I-w}}^c = 12$ Å was -8.8 kcal/mol, with $R_{\text{w-w}}^c = 9$ Å. With $R_{\text{w-w}}^c = 12$ Å the corresponding quantity became -6.0 kcal/mol. The prediction from the Born equation (1) using $r_{\text{Born}} = R_{\text{I-w}}^c$, on the other hand, is -4.6 kcal/mol for the situation above. In our case it appears that $R_{\text{w-w}}^c$ must be extended to about 14 Å to remove the influences of the cutoff radii on the hydration free energy. We therefore decided not to use any cutoff radii at all ($R_{\text{I-w}}^c = R_{\text{w-w}}^c = \infty$) in the calculations reported here. With a spherical boundary model for the explicit (microscopic) water and $R_{\text{I-w}}^c = R_{\text{w-w}}^c = \infty$, one can assume that the cavity radius in eq 1 should correspond simply to the radius of the SCAAS sphere (R_{SCAAS}). As is demonstrated below (and also in ref 17), this assumption proves to be correct within the accuracy of the simulations, i.e., with this choice of Born radius the calculated ΔG_{hydr} does not display any significant system size dependency. With the use of PBC, however, the Born radius becomes less well defined since, even if $R_{\text{I-w}}^c$ would appear to be the most suitable choice for the cavity radius, the water-water interaction energy due to molecules outside of the cutoff sphere centered on the ion are included in the total energy of the system. In other words, some polarization of waters outside $R_{\text{I-w}}^c$ (which the Born correction is assumed to take care of) is already included in the Hamiltonian of the microscopic system, which makes the use of eq 1 with $r_{\text{Born}} = R_{\text{I-w}}^c$ somewhat questionable.

Finally, and perhaps most importantly, when performing calculations on larger systems such as proteins the size of the computational problem tends to become overwhelming if PBC are used. The spherical boundary model offers a more convenient way for calculation of free energies in such larger systems, without the need to "solvate" the entire protein.

TABLE I: Final Lennard-Jones Parameters, Calculated Hydration Free Energies, and Ion-Water Oxygen RDF Peaks for the Alkali-Metal Ions^a

ion	A_1	B_1	$\Delta G_{\text{hydr}}^{\text{calc}}$	$R_{\text{I-w}}^{\text{calc}}$	$\Delta G_{\text{hydr}}^{\text{obs}}$	$R_{\text{I-w}}^{\text{obs}}$
Li^+	25.0	2.60	-122.2 ± 0.6	2.03	-122.1	2.00-2.08
Na^+	143.7	3.89	-98.5 ± 0.5	2.39	-98.2	2.35-2.42
K^+	522.7	4.35	-80.9 ± 1.0	2.75	-80.6	2.73-2.80
Rb^+	824.4	4.64	-75.5 ± 0.9	2.89	-75.5	2.88
Cs^+	1647.9	5.44	-67.7 ± 0.7	3.10	-67.8	3.09-3.15

^a The errors in $\Delta G_{\text{hydr}}^{\text{calc}}$ denote the accumulated FEP/MD hysteresis errors (note that the errors in $\Delta \Delta G_{\text{hydr}}^{\text{calc}}$ are considerably smaller). Observed ΔG_{hydr} values are taken from ref 23 and the observed $R_{\text{I-w}}$ values from refs 24 and 25 (the lower limit of $R_{\text{I-w}}$ is the sum of the Pauling radii).

TABLE II: Final Lennard-Jones Parameters, Calculated and Observed Hydration Free Energies, and Ion-Water Oxygen RDF Peaks for Alkaline-Earth-Metal Ions

ion	A_1	B_1	$\Delta G_{\text{hydr}}^{\text{calc}}$	$R_{\text{I-w}}^{\text{calc}}$	$\Delta G_{\text{hydr}}^{\text{obs}}$	$R_{\text{I-w}}^{\text{obs}}$
Mg^{2+}	37.0	8.32	-455.9 ± 2.6	2.00	-455.5	2.05-2.10
Ca^{2+}	264.1	18.82	-380.6 ± 1.3	2.40	-380.8	2.39-2.42
Sr^{2+}	613.5	20.54	-345.9 ± 1.8	2.58	-345.9	2.53
Ba^{2+}	1341.5	24.13	-314.6 ± 1.9	2.77	-315.1	2.75

Simulation Procedure. The free energy of hydration for a given ion, I^{n+} , can be computed in the following way:

$$\Delta G_{\text{hydr}}(\text{I}^{n+}) = \Delta G_{\text{FEP}}(\text{I}^0 \rightarrow \text{I}^{n+}) + \Delta G_{\text{Born}} + \Delta G_{\text{cav}} \quad (2)$$

where $\Delta G_{\text{FEP}}(\text{I}^0 \rightarrow \text{I}^{n+})$ denotes the free energy of *charging* the ion in water, obtained from an FEP/MD simulation in N discrete steps as

$$\Delta G_{\text{FEP}}(\text{I}^0 \rightarrow \text{I}^{n+}) = \sum_{m=0}^{m=N-1} -RT \ln \langle \exp(-(V_{m+1} - V_m)/RT) \rangle_m \quad (3)$$

where the potential V_0 , corresponding to $Q_1 = 0$, is successively transformed into the potential V_N , corresponding to $Q_1 = +n$. Typically, one uses $V_m = (1 - \lambda_m)V_0 + \lambda_m V_N$, incrementing λ in a number of steps from 0 to 1. The term ΔG_{Born} is the correction due to the finite size of the system, discussed above, and is in our case calculated with $r_{\text{Born}} = R_{\text{SCAAS}}$. The last term in eq 2 denotes the free energy of creating the uncharged ion "cavity" in water.

The ion-water potential energy function (V_m in eq 3) is of the standard electrostatic plus Lennard-Jones form (in kcal/mol and Å):

$$V_{\text{I-w}} = 332 \sum_j \frac{Q_1 q_j}{r_{1j}} + \sum_j \frac{A_1 A_j}{r_{1j}^{12}} - \frac{B_1 B_j}{r_{1j}^6} \quad (4)$$

where the index I denotes the ion and the sums run over all atoms, j , of the solvent molecules. As the ion charge (Q_1), the SPC water partial charges ($q_O = -0.82$, $q_H = +0.41$) and van der Waals' parameters ($A_O = 793.3$, $B_O = 25.01$, $A_H = B_H = 0.0$) are given, we are left with finding suitable values for the A_1 and B_1 parameters.

For comparison, we also report some calculations with a flexible SPC water model having the same partial charges and van der Waals' parameters as the original rigid version. In this case the additional intramolecular potential energy terms are given by

$$V_{\text{w}}^{\text{intra}} = \frac{1}{2} k_b (b - b_0)^2 + \frac{1}{2} k_\theta (\theta - \theta_0)^2 \quad (5)$$

with $k_b = 750$ kcal/(mol Å²), $b_0 = 1.00$ Å, $k_\theta = 120$ kcal/(mol rad²), and $\theta_0 = 109.47^\circ$.

All calculations were carried out with a modified version of the MOLARIS program.¹⁹ In the simulations with rigid SPC water the SHAKE procedure²⁰ was used to satisfy the bond-length and

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TABLE III: Comparison of $\Delta G_{\text{hydr}}^{\text{calc}}$ and $R_{\text{I-W}}^{\text{calc}}$ for Na^+ and Ca^{2+} Obtained with Different Parameter Sets

ion	A_1	B_1	water model	source	$\Delta G_{\text{hydr}}^{\text{calc}}$	$R_{\text{I-W}}^{\text{calc}}$	$\Delta G_{\text{hydr}}^{\text{obs}}$	$R_{\text{I-W}}^{\text{obs}}$
Na^+	143.7	3.89	rig. SPC	this work	-98.5 ± 0.5	2.39	-98.2	2.35-2.42
Na^+	143.7	3.89	flx SPC	this work	-99.0 ± 0.4	2.40	-98.2	2.35-2.42
Na^+	143.7	3.89	TIP3P	this work	-98.8 ± 0.8	2.39	-98.2	2.35-2.42
Na^+	107.0	4.60	TIP3P	ref 26	-102.0 ± 0.4	2.32	-98.2	2.35-2.42
Na^+	89.0	7.50	TIP3P	ref 28	-107.5 ± 0.6	2.26	-98.2	2.35-2.42
Ca^{2+}	264.1	18.82	rig. SPC	this work	-380.6 ± 1.3	2.40	-380.8	2.39-2.42
Ca^{2+}	150.0	3.30	rig. SPC	ref 29	-388.2 ± 0.9	2.28	-380.8	2.39-2.42
Ca^{2+}	2210.0	192.00	flx SPC	ref 30	-341.6 ± 0.6	2.74	-380.8	2.39-2.42

angle constraints. The MD time-step used was $\Delta t = 0.002$ ps (except in the calculations of ΔG_{cav} , where $\Delta t = 0.001$ ps was used) and the simulations were performed at constant temperature ($T_0 = 298$ K) using the temperature scaling algorithm of Berendsen et al.²¹ Two different sizes of the SCAAS water sphere, containing 202 and 460 water molecules, respectively, were used to examine the possible system size dependency of the calculated free energies.

Results and Discussion

We started the parametrization by finding pairs (A_1 , B_1) for Na^+ and Ca^{2+} that reproduce the observed values of ΔG_{hydr} and the ionic radius. For both of these ions the experimental value for the hydration energy²² of Ne (+2.5 kcal/mol) was used as an initial approximation for ΔG_{cav} [the value of ΔG_{cav} was recalculated once the (A_1 , B_1) for Na^+ and Ca^{2+} had been determined and found to be within 1.0 kcal/mol of $\Delta G_{\text{hydr}}^{\text{obs}}(\text{Ne})$]. As a check of the possible system size dependency of the calculated ΔG_{hydr} 's, we evaluated these quantities for Na^+ and Ca^{2+} using two different sizes of the SCAAS sphere containing 202 and 460 water molecules, respectively. The total hydration free energies including the cavity and Born corrections for Na^+ are $\Delta G_{\text{hydr}}^{202\text{w}} = -98.5$ kcal/mol and $\Delta G_{\text{hydr}}^{460\text{w}} = -98.7$ kcal/mol for these two cases, respectively, with hysteresis errors of $\leq \pm 0.5$ kcal/mol. For Ca^{2+} , the corresponding numbers are $\Delta G_{\text{hydr}}^{202\text{w}} = -380.6$ kcal/mol and $\Delta G_{\text{hydr}}^{460\text{w}} = -379.2$ kcal/mol, with hysteresis errors of $\leq \pm 1.3$ kcal/mol. This indicates that the errors due to system size dependencies are not very severe and, at any rate, comparable to the accuracy (or convergence) of the FEP/MD calculations. This conclusion was also reached by King and Warshel¹⁷ from calculations of the "charging energy" of Na^+ .

Once the Na^+ and Ca^{2+} parameters were established the other alkali and alkaline-earth metal ion parameters were determined by perturbation simulations with Na^+ and Ca^{2+} as starting points. The total simulation length was 80 ps to obtain $\Delta G_{\text{hydr}}(\text{Ca}^{2+})$ and 80 ps each for the $\text{Ca}^{2+} \leftrightarrow \text{Ba}^{2+}$ and $\text{Ca}^{2+} \leftrightarrow \text{Mg}^{2+}$ transformations, while the corresponding three trajectory lengths for the alkali-metal ions were 50 ps each. In addition to this, the RDF calculation for each ion covered a length of 20 ps. However, if one also considers the simulations that resulted in unacceptable parameters the total trajectory length covered well over a nanosecond.

The final interaction parameters, hydration energies and ion-oxygen RDF peaks for the alkali-metal ions are given in Table I together with the relevant experimental numbers. The observed values of ΔG_{hydr} are taken from ref 23. As can be seen from the table two values of the observed ion-water oxygen distance are given; the lower value corresponds to the Pauling radii²⁴ and the higher one to the experimentally determined RDF peak (if available). The latter values are taken from ref 25 and references

therein. The final results for the alkaline-earth-metal ions are given in Table II together with the experimental numbers. As can be seen from Tables I and II the calculated hydration free energies are all in good agreement with the observed ones. The calculated ion-water RDF peaks also generally fall within the observed range. The errors in this quantity vary depending on the size and valency of the ion. For Ca^{2+} and Mg^{2+} the RDF peak errors are estimated to be about ± 0.02 Å, while for Cs^+ they are of the order of ± 0.05 Å. However, the value of $R_{\text{I-W}}^{\text{calc}}$ for Mg^{2+} show a less good agreement with the observed distance than for any of the other ions and appears to be slightly too small. It seems, in fact, rather difficult to obtain a larger Mg^{2+} radius while maintaining a value of $\Delta G_{\text{hydr}}^{\text{calc}}$ close to the observed one. One reason for this problem may be the use of a rigid unpolarizable water model. That is, for the first solvation shell ligands one might expect a significant increase of the dipole moment due to the strong interaction with the ion, which is suppressed by the use of a rigid water model. This effect would be more pronounced for Mg^{2+} than for any of the other ions, since it is the smallest divalent one treated here.

As a preliminary attempt to examine the effect of releasing the water intramolecular constraints we calculated $\Delta G_{\text{hydr}}(\text{Na}^+)$ with a flexible but otherwise identical SPC model (see above for intramolecular energy parameters). The resulting hydration free energy, given in Table III, is $\Delta G_{\text{hydr}} = -99.0 \pm 0.4$ kcal/mol and the corresponding RDF peak is 2.40 Å. The main effect associated with making the SPC model flexible is a slight compression (on average) of the water bond angle, which leads to an increase of the dipole moment by about 4%. The difference in $\Delta G_{\text{hydr}}(\text{Na}^+)$ between the rigid and flexible models, however, is not that large and is within the hysteresis errors of the simulations. This may be due to the fact that even if the increased dipole moment of the flexible water strengthens the ion-water interaction, it will also inevitably strengthen the water-water interactions and these two energy terms contribute with opposite signs to the free energy of hydration. The close agreement between $\Delta G_{\text{hydr}}(\text{Na}^+)$ for the rigid and flexible versions might be taken as an indication that the parameters given in Tables I and II can be directly used also with a flexible SPC model. In this context it is also interesting to examine the transferability of the ion Lennard-Jones parameters to water models other than SPC. To address this issue, FEP calculations on Na^+ were carried out using the TIP3P water model²⁷ together with the parameters given in Table I. These results, which are given as the third entry in Table III, are very similar to those obtained with the SPC model and thus suggest that the ion parameters may be directly transferable between the two water models.

In Table III we also present the results from absolute hydration energy calculations for Na^+ and Ca^{2+} using parameters that have been reported by other authors. The second set of Na^+ parameters in Table III was used by Grootenhuis and Kollman in a recent study of ion binding to crown ethers,²⁶ and these are rather close to those derived in the present work. The calculated hydration energy using their parameters and the TIP3P water model²⁷ is -102.0 ± 0.4 kcal/mol and the corresponding ion-water RDF peak is found at 2.32 Å. Thus, the Na^+ parameters given in ref 26 for use with TIP3P water appear quite reasonable, and the slightly too negative value of the hydration energy is consistent with a

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TABLE IV: Comparison of the Minimum Energies for Gas-Phase Alkali-Metal Ion Monohydrates Obtained with the Parameters in Table I and Those Obtained from Experiments and ab Initio Calculations

ion	E_{\min}^{calc}	$E_{\min}^{\text{obs } a}$	$E_{\min}^{\text{calc } b}$
Li ⁺	-31.7	-34.0	-37
Na ⁺	-22.8	-24.0	-27
K ⁺	-17.8	-17.9	-18
Rb ⁺	-16.3	-15.9	
Cs ⁺	-14.3	-13.7	

^aTaken from ref 31. ^bTaken from ref 32.

somewhat smaller ion radius. The third set of TIP3P-Na⁺ parameters was used in a recent study of (differential) ion solvation in three different solvents by Rao and Singh.²⁸ Our calculation with these parameters (and TIP3P water) give about 10 kcal/mol too negative hydration energy and an ion radius that is significantly smaller than that observed for Na⁺. The second set of Ca²⁺ parameters given in Table III were used by Teleman and Ahlström in an MD study of a Ca²⁺-EDTA complex.²⁹ As can be seen these parameters give about 7 kcal/mol too negative hydration energy, which again is consistent with a too short Ca²⁺-oxygen distance of 2.28 Å. The last set of Ca²⁺ parameters examined in Table III are due to Sussman and Weinstein³⁰ and were used in a study of the ion-selective cyclic peptide (-L-Pro-Gly)₃. These parameters give a hydration energy that differs about 40 kcal/mol from the experimental value for Ca²⁺ and a corresponding ion radius that is considerably larger than the observed value.

As a final exercise it is interesting to examine the transferability of our empirical pair potential, derived in solution, to the gas phase. We therefore calculated the minimum interaction energy for isolated ion monohydrates involving the alkali-metal ions. The

results of these calculations are shown in Table IV together with experimentally determined gas-phase enthalpies for the corresponding monohydrates.³¹ In Table IV we have also included results from ab initio SCF calculations reported by Kollman and Kuntz³² for Li⁺, Na⁺, and K⁺. As can be seen from the table, the interaction potential derived in aqueous solution gives rather decent results for gas-phase monohydrates as well and compares favorably with the ab initio results. One might therefore expect pair potentials derived by fitting the Lennard-Jones parameters to gas-phase experiments to yield reasonable absolute hydration free energies. In general, however, it would seem more reliable to derive the parameters in aqueous solution if they are to be used in condensed phases, even though this requires a considerable computational effort.

In view of the rather large number of recent studies^{12,26,28,30,33} addressing the issue of *differential* solvation or binding of ions, one finds it rather surprising that so few attempts have been made to actually check the parameters used with respect to *absolute* solvation free energies. It appears, however, that the fact that observed binding or solvation free energy differences can often be well reproduced might have been taken as evidence for the "correctness" of the particular potential used. In principle, it is of course possible to obtain "correct" free energy differences even if the absolute values are totally wrong. Therefore, we would argue that it is safer, if not necessary, to first evaluate the absolute solvation free energies if the relevant parameters are to be used to ask quantitative questions concerning energetics.

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