Accurate Free Energy Perturbation Calculation of the Hydration Free Energies of Fe^{3+} and Fe^{2+}

Joseph J. Urban and James R. Damewood, Jr.*†

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, USA

Molecular dynamics/free energy perturbation (MD/FEP) calculations have resulted in free energies of hydration and time-average coordination numbers for Fe^{3+} and Fe^{2+} that are in excellent agreement with previously determined experimental values.

Remarkable agreement with experiment has been obtained for the free energy perturbation (FEP),[1] molecular dynamics calculation of the free energy of hydration for Fe^{3+} and Fe^{2+}. The calculated free energies and the time-average coordination numbers for both systems are in excellent agreement with previously determined experimental values. In this communication, we report the details of our FEP simulations and critically compare our results with the available experimental data.

All FEP simulations in this work were performed with the program AMBER (3.0)[2] using the TIP3P[3] water model, and periodic boundary conditions at constant pressure (1 atm) and temperature (300 K). The windowing technique[1] was used for parameter transformation and selected perturbations were peformed in both the forward ($\lambda = 0 \rightarrow 1$) and reverse ($\lambda = 1 \rightarrow 0$) directions. A 2 fs time step was employed with 200 steps of equilibration and 300 steps of sampling for each perturbation window and simulation times of between 26 and 81 ps were employed. For Fe^{3+} and Fe^{2+}, atom-centred point charges were employed and R and ε parameters[4][‡] were derived for these atoms using the previously reported *ab initio* calculated structures and energies[5] of the respective hexahydrates. Cut off radii of either 7.5 or 10.0 Å were employed and residual interactions beyond the cut off radius were

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[†] *Present address*: ICI Pharmaceuticals Group, Structural Chemistry Section, Medicinal Chemistry Department, Wilmington, Delaware 19897, USA.

[‡] For Fe^{3+}: $R = 0.85718$ Å, $\varepsilon = 0.01119$ kcal mol^{-1}; for Fe^{2+}: $R = 1.30002$, $\varepsilon = 0.00837$. These parameters are optimized to reproduce the *ab initio* binding energies and obtain $Fe^{n+}\cdots O$ binding distances upon complete optimization that are *ca.* 5% (Fe^{2+}) and *ca.* 9% (Fe^{3+}) shorter than those calculated by *ab initio* methods. Average $Fe\cdots O$ distances during the simulations are similar. The parameterization procedure employed in obtaining these parameters is described ref. 4.

Table 1 Data for Fe^{2+} and Fe^{3+} hydration simulations[a]

	Simulation time		26 ps		51 ps		81 ps	
		R[b]	$\Delta\Delta G_{\text{pert}}$	$\Delta\Delta G_{\text{calc}}$[c]	$\Delta\Delta G_{\text{pert}}$	$\Delta\Delta G_{\text{calc}}$[c]	$\Delta\Delta G_{\text{pert}}$	$\Delta\Delta G_{\text{calc}}$[c]
(*I*)	Fe^{2+}(aq) $\rightarrow$ Fe^{3+}(aq)	7.5	-467.6 ± 1.0	-576.9 ± 1.0	-464.6 ± 0.5	-573.9 ± 0.5	-465.2 ± 0.4	-574.5 ± 0.4
	(exptl.[d] -579.1)	10.0	-486.7 ± 1.3	-568.6 ± 1.3	-487.9 ± 0.7	-569.8 ± 0.7		
(*II*)	Fe^{3+}(aq) $\rightarrow$ Fe^{2+}(aq)	7.5	464.5 ± 1.0	573.8 ± 1.0	465.0 ± 0.6	474.3 ± 0.6		
	(exptl.[d] 579.1)							
(*III*)	Fe^{3+}(aq) $\rightarrow$ 0	7.5			846.7 ± 3.7	1043.3 ± 3.7		
	(exptl.[d] 1036.4)							
(*IV*)	Fe^{2+}(aq) $\rightarrow$ 0	7.5			378.7 ± 1.8	466.1 ± 1.8		
	(exptl.[d] 457.3)							

[a] Energies in kcal mol^{-1} $\pm$ hysteresis errors for simulations; 1 cal = 4.184 J. [b] Cut off radius in Å. [c] Using Born correction as described in text. [d] Experimental values from ref. 7.

approximated using the Born equation[6] and a dielectric constant of 78.4.§ Energetic results from the various simulations are reported in Table 1.

The relative hydration free energy ($\Delta\Delta G^{\text{hyd}}$) of Fe^{3+} and Fe^{2+} can be calculated by an Fe^{3+} $\rightarrow$ Fe^{2+} free energy perturbation in aqueous solution (*I*, Table 1). We performed this perturbation in a box of 172 waters using a cut off radius of 7.5 Å. Results obtained directly from the perturbation ($\Delta\Delta G_{\text{pert}}$) and those corrected for contributions beyond the cut off radius ($\Delta\Delta G_{\text{calc}}$) are reported for 26, 51 and 81 ps in Table 1. The reverse perturbation, Fe^{2+} $\rightarrow$ Fe^{3+} (*II*), is similarly shown Table 1. The reversibility of the 51 and 81 ps simulations within acceptable error limits, and the only slightly larger differences for forward and reverse perturbations at 26 ps, indicates that the 51 and 81 ps calculations are equilibrated. The 51 ps simulation time was, therefore, adopted for all future simulations.

To test the effects of increased cut off radius on the calculations, we performed simulation *I* in a box of 404 waters with a cut off radius of 10.0 Å. As expected, the $\Delta\Delta G_{\text{pert}}$ data (Table 1) reveal that the Fe^{2+} $\rightarrow$ Fe^{3+} perturbation is calculated to be more energetically favourable with this larger cut off radius. Correspondingly, the Born correction decreases for the 10.0 Å calculations, leaving $\Delta\Delta G_{\text{calc}}$ for the 7.5 and 10.0 Å simulations quite similar (Table 1).

The corrected perturbations ($\Delta\Delta G_{\text{calc}}$) of Fe^{2+} $\rightarrow$ Fe^{3+} (*I*) at the 7.5 and 10.0 Å cut offs are all in very good to excellent agreement with the experimental value[7] of -579.1 kcal mol^{-1} [errors $\leqslant 1\%$ at 7.5 Å, $\leqslant 1.8\%$ at 10.0 Å].

Perturbation of Fe^{3+} $\rightarrow$ Fe^{2+} (*II*) over 51 ps with a cut off radius of 7.5 Å leads to a value of 574.0 ± 0.6 kcal mol^{-1} which suggests that the statistical error for these perturbations is of the order of the hysteresis error observed for each individual perturbation and well within acceptable error limits. Indeed, these are the first reported molecular dynamic simulations for $\Delta\Delta G^{\text{hyd}}$ of the iron(II)–iron(III) system that may be considered to be competitive with experiment.[8]

Hydration free energies (ΔG^{hyd}) can be calculated for Fe^{3+} and Fe^{2+} by perturbing the respective iron atoms to nothing in an aqueous environment (*III* and *IV*, Table 1). The electrostatic and van der Waals parameters, in that order, were perturbed to zero in separate simulations for each iron.[1] These two energies were then summed to obtain the ΔG^{hyd} values for Fe^{3+} and Fe^{2+}. As can be seen from Table 1, agreement with the corresponding experimental values[7,9] is good to excellent in both cases, even though the the ΔG values are large. These calculations show that, for both ΔG^{hyd} and $\Delta\Delta G^{\text{hyd}}$ (see above), the iron parameters reported in this communication function extremely well in describing the energetics of Fe^{3+} and Fe^{2+} in aqueous solution.

The time-average coordination number of both Fe^{3+} and Fe^{2+} in these simulations is also of interest and is found to be six (octahedral), in complete accord with experimental findings.[10] Previous molecular dynamics studies of Fe^{3+} and Fe^{2+} using *ab initio* pair potentials[8a] have obtained eight- rather than the experimental six-coordination. By deriving our AMBER parameters for Fe^{3+} and Fe^{2+} using data on the respective hexahydrates, we implicitly account for solvent polarization in the first solvation shell. Others have suggested[8a] that the implicit consideration of polarization in their empirical potentials allows for the accurate simulation of Fe^{3+} and Fe^{2+} coordination numbers. Our findings support this previously presented position.

Initially, it was surprising that such excellent agreement with experiment could be obtained in these simulations without employing a polarizable water model. While our parameterization of Fe^{3+} and Fe^{2+} accounts for the polarization of the first solvation shell (see above), polarization beyond this radius must also be important. Its neglect should result in an underestimation of the stability of the respective hydrate. It is reasonable to assume that the Born equation overestimates the energetic correction beyond the cut off radius since it is, in general,[11] known to overestimate the hydration energy of ions. We suggest that the accuracy obtained in the present calculations is, in part, due to the apparent cancellation of the energetic underestimation of solvent polarization beyond the first solvation shell and energetic overestimation of the Born correction beyond the 7.5 to 10.0 Å cut off radius. In addition, we emphasize the importance of deriving the potential energy functions for ions in the manner described above to the accuracy of these calculations.[12] Recent FEP simulations for ion hydration[13] which used *ab initio* pair potential-derived parameters together with Born corrections beyond the simulation cut off radii obtained results which deviated from the experimental hydration energies by as much as *ca.* 20%. We, therefore, agree with the previous suggestion[8a] that *ab initio* pair potentials for ions can yield unacceptable results in dynamic simulations.

The Born-corrected FEP calculations described in this work allow for surprisingly accurate calculation of the very large free energy changes involved in the hydration of Fe^{3+} and Fe^{2+}. The observation that this level of accuracy can be obtained, at equilibrium, for such large $\Delta\Delta G$ values in only 51 ps of simulation, supports the position[6,13] that the limits on perturbation step size are system-dependent, and not limited

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§ The experimental value of 78.4 was employed; however, the magnitude of this parameter has little effect on the calculated Born correction.

to the previously suggested $2RT$.[14] The application of these iron potentials to other systems of interest is in progress.

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