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Free energy MD and QM parameterization of the Fe^{+} force field in water

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The free energy difference between the states *B* and *A*, $\Delta G(A \to B) \equiv G_B - G_A$, is expressed in the FEP method as $\Delta G_{BA}^{FEP} = -\ln\left\langle e^{-\beta\Delta U} \right\rangle_A / \beta$, where $\beta = 1/RT$, *R* is the gas constant, *T* is the absolute temperature. Here we employed the double-end (DE) FEP technique that calculates $\Delta G(A \to B)$ as an average from simulations at both states (e.g., refs.[S1,S2]), $\Delta G_{BA}^{DEFEP} = -\frac{1}{2\beta}\left(\ln\left\langle e^{-\beta\Delta U} \right\rangle_A - \ln\left\langle e^{+\beta\Delta U} \right\rangle_B\right) \equiv \frac{1}{2}\left(\Delta G_{AB} - \Delta G_{BA}\right)$. The standard error (*SE*) for ΔG_{BA} and ΔG_{AB} terms was determined from standard error from the corresponding block averages, SE_{bl}, where trajectory points were fragmented in three blocks. Calculations of ΔG_{BA}^{DEFEP} were split in a number of steps between the end states. The potential energy of the intermediate state at step *m* is expressed then as a linear combination of the end-point potentials using coupling parameter λ, $U_k = (1-\lambda_k)U_A + \lambda_k U_B$, $\lambda_k, (k = 1,...,K)$. The total free energy $\Delta G_{BA,tot}^{DEFEP}$ from the *K* steps, $\Delta G_{BA,tot}^{DEFEP}$, is an average of two sums $\Delta G_{BA,tot}^{FEP} = -\sum_k \ln\left\langle e^{-\beta\Delta U_k} \right\rangle_A / \beta$ and $\Delta G_{AB,tot}^{FEP} = -\sum_k \ln\left\langle e^{\beta\Delta U_k} \right\rangle_B / \beta$. Standard error for the $\Delta G_{BA,tot}^{DEFEP}$ function of two variables $\Delta G_{BA,tot}^{FEP}$ and $\Delta G_{AB,tot}^{FEP}$ was expressed as $SE\left(\Delta G_{BA,tot}^{DEFEP}\right) = \frac{1}{2}\left|\Delta G_{AB,tot}^{FEP} + \Delta G_{BA,tot}^{FEP}\right| + \frac{1}{2}\sqrt{SE_{bl,tot}\left(\Delta G_{AB,tot}^{FEP}\right)^2 + SE_{bl,tot}\left(\Delta G_{BA,tot}^{FEP}\right)^2}$. Collective $SE_{bl,tot}$ errors of $\Delta G_{BA,tot}^{FEP}$ and $\Delta G_{AB,tot}^{FEP}$ were determined as square roots from the sum of squares of $SE_{bl,k}$ terms. Besides, separate MD simulations were carried out for atom mutations considered for independent trajectories in the forward and reverse directions between the end states. The final numbers for $\Delta G(A \to B)$ were taken as average from these trajectories. The joint statistical error for the forward and reverse runs includes the hysteresis in these runs and is calculated similar to the expression for $SE\left(\Delta G_{BA,tot}^{DEFEP}\right)$.

The free energy MD simulations were performed using the adapted for GNU Fortran-9.2.0 and OpenMPI-5.08 parallel version of the Q5.06 program [S3]. The MD simulations of ions were carried out for water sphere with 460 TIP3P water molecules and the radius r_{mod} = 15 Å. Infinite cutoff radii were used for ion–water and water–water interactions. The MD time step was 2 fs. The MD simulations were done for T=298 K using Berendsen's thermostat with the temperature coupling constant of τ_T=200 fs. In this case the number for the ratio $\rho = \tau_T/\Delta t$ is 100[S4]. Besides test free energy calculations were performed with several smaller ρ that increases coupling with thermostat. The obtained $\Delta G(Fe^+ \rightarrow Ne)$ for ρ in the range from 50 and up to 5 show small deviations within statistical uncertainty of calculations from the value given in Table 1. Separate scaling of water molecules and ion was employed in most cases however it had a little effect on the FEP results in comparison with regular scaling of the whole system.The bond lengths of water molecules were constrained using SHAKE. The ion was restrained to the center of the sphere with a harmonic force 1.0 kcal/mol. Soft-core LJ potential in the operational form employed in Q5 (e.g., refs.[S5]) was applied to avoid numerical singularities at the end point in atom annihilation.

The system was equilibrated for 500 ps of MD prior to the production phase of free energy calculations. The number of λ-steps K was 50 in this work; λ_k changed linearly from 0 to 1. The mutation scheme involved 50 ps of MD at every step. Equilibration part involved 5 ps and production part – 45 ps at each λ-step. The energies were collected at each 20 fs of MD. An equilibration phase of 100ps of MD was used between trajectories for mutations in the forward and reverse directions. The total free-energy difference $\Delta G_{BA,tot}^{DEFEP}$ is calculated by summing over the free-energy contributions from the intermediate λ–steps. $\Delta G_{BA,tot}^{DEFEP}$ were calculated also for 1 ns of MD equilibration phase in selected runs in order to estimate the convergence of simulations. The difference between the corresponding free energies was less than 0.1 kcal mol^{-1}.

The procedure of scanning the $\Delta G_s(Fe^+)$ surface included mutations of $Fe^+ \rightarrow Ne$. The employed LJ parameters for Ne were ($r_I/2$ = 1.5428 Å, ε_I = 0.07074 kcal mol^{-1}). Validation of the obtained FF parameters was carried out via independent direct annihilation of ions (Table 1S). The RDF data were collected from 0.5 ns MD trajectories after 1ns equilibration. The RDF plots were built with a step of 0.05 Å.

Quantum mechanical calculations have been carried out at the MP4(SDQ)/def2-QZVPP level of theory using Gaussian-09[S6] program. The reference single-determinant wave function in

the MP4 method was obtained using unrestricted HF method. Stable wave function was taken in the calculations of the Fe^+ electronic states with different spin multiplicities. The program outputs with spin properties are given below. The electron correlation calculations involved all explicitly given electrons with option 'Full' in Gaussian-09. The cube file with electron density was generated by means of *cubegen* utility in Gaussian-09 with the settings *kind* FDensity='MP4' and *npts*=500. Isodensity surface was generated using linear interpolation along the points in cube file.

Gaussian-09 output of the calculated spin properties of Fe+ *M*=4 at the UMP4(SDQ,Full)/def2-QZVPP level of theory:

```
**********************************************************************
<Sx>= 0.0000 <Sy>= 0.0000 <Sz>= 1.5000 <S**2>= 3.7581 S= 1.5020
 <L.S>= 0.000000000000E+00
 Annihilation of the first spin contaminant:
 S**2 before annihilation     3.7581,   after     3.7500
**********************************************************************
```

Gaussian-09 output of the calculated spin properties of Fe+ *M*=6 at the UMP4(SDQ,Full)/def2-QZVPP level of theory:

```
**********************************************************************
<Sx>= 0.0000 <Sy>= 0.0000 <Sz>= 2.5000 <S**2>= 8.7512 S= 2.5002
 <L.S>= 0.000000000000E+00
 Annihilation of the first spin contaminant:
 S**2 before annihilation     8.7512,   after     8.7500
**********************************************************************
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Table S1 Hydration free energies (kcal mol^{-1}) of metal ions M^+ from the FEP/ and BAR/MD simulations[a]

M^+	$\Delta G_{pol}(M^+ \rightarrow M^0)$ FEP / BAR	$\Delta G_{np}(M^0 \rightarrow d)$ FEP / BAR	ΔG_s FEP / BAR	ΔG_s^{ref}
Na^+ [b]	92.0 / 92.0	–3.2 / –3.2	–99.7±0.2 / –99.7±0.3	–98.8±0.8
K^+ [b]	76.4 / 76.4	–5.0 / –5.0	–82.4±0.3 / –82.4±0.3	–81.2±1.0
Fe^+ [c] M=4	112.5 / 112.5	–2.3 / –2.3	–121.2±0.3 / –121.1±0.3	–121.2±3.8
Fe^+ [c] M=6	104.8 / 104.8	–2.7 / –2.7	–113.0±0.3 / –113.0±0.3	–112.9±3.8

[a] MD simulations of ion annihilation in the 15Å TIP3P/SCAAS water sphere, $\Delta G_s(M^+) = -\Delta G_{pol}(M^+ \rightarrow M^0) - \Delta G_{np}(M^0 \rightarrow d) + \Delta G_{Born}$ where ΔG_{Born} is –10.9 kcal mol^{-1}. [b] the (r_I^m, ε_I^m) parameters of Na^+ and K^+ taken from those of Åqvist in Amber: Na^+ – (1.868, 0.00277), K^+ – (2.658, 0.000328), [c] the parameters of Fe^+ taken from Table 1.

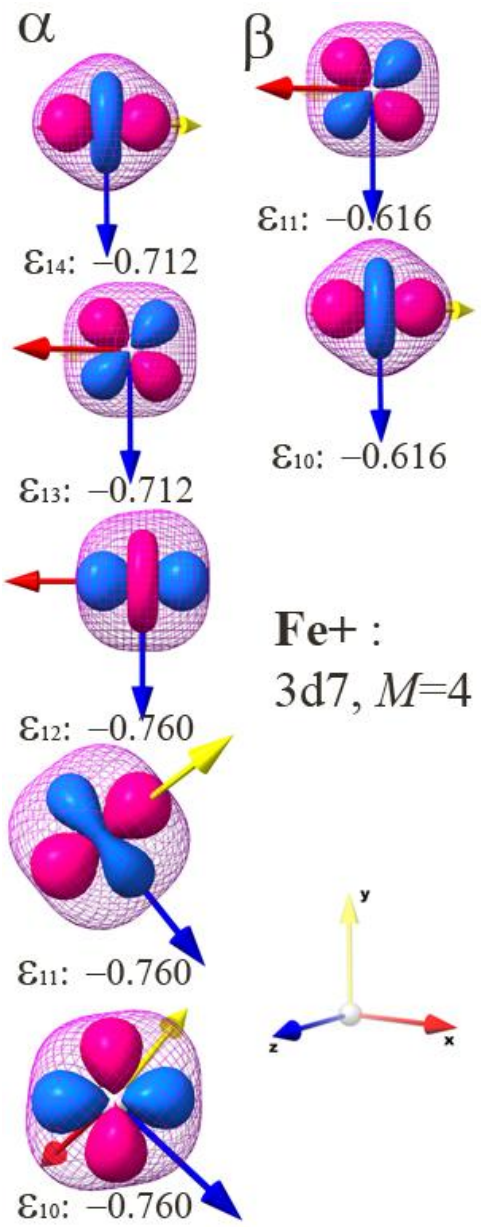
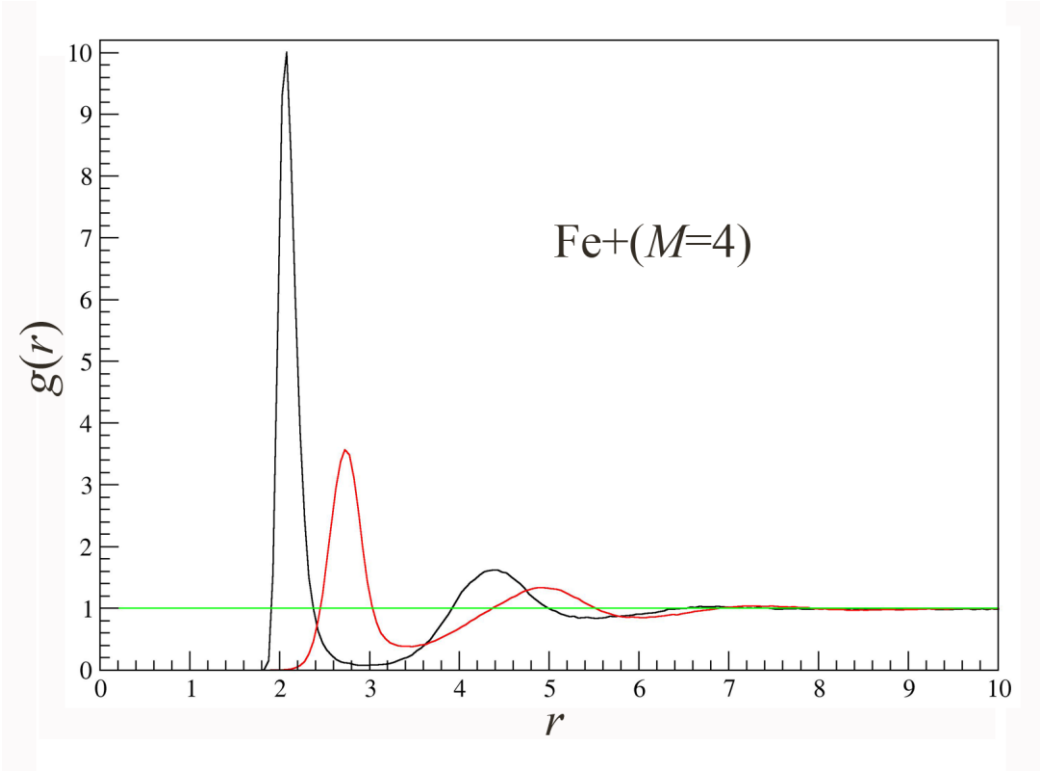


Figure S1 The shapes and energies (in Hartree) of the occupied α and β orbital of Fe^+ in $3d^7$ quartet electronic state. The MP4 electron density surface of Fe^+ is displayed with the magenta mesh style.

(a)



(b)

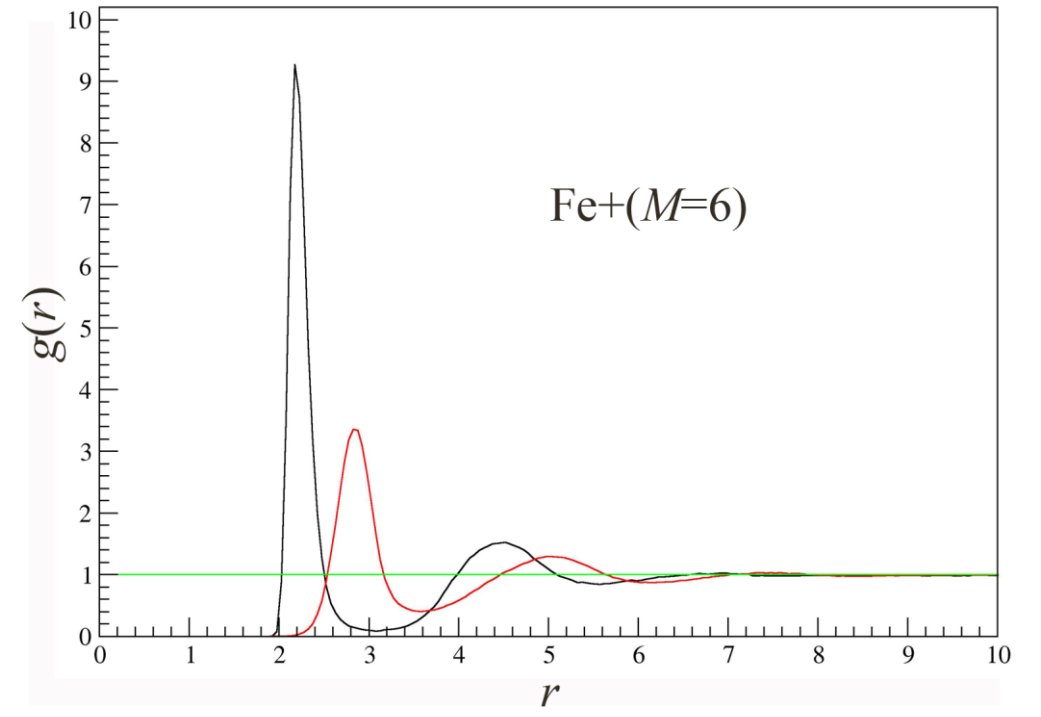


Figure S2 Radial distribution functions of water oxygens, $g_O(r)$, and water hydrogens, $g_H(r)$. $g_O(r)$ is given in black, $g_H(r)$ – in red. (a) plots for the Fe^+ ion with the (r_I^m, ε_I^m) parameters for quartet state, (b) plots with the parameters for sextet state.

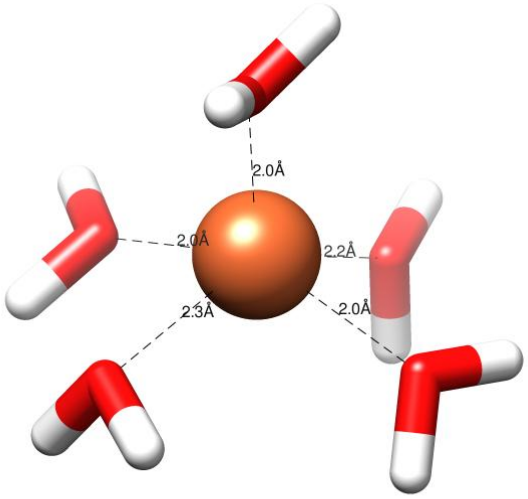


Figure S3 First hydration shell of $^{4}Fe^{+}$ from a snapshot in equilibrated water system.