Supporting Information

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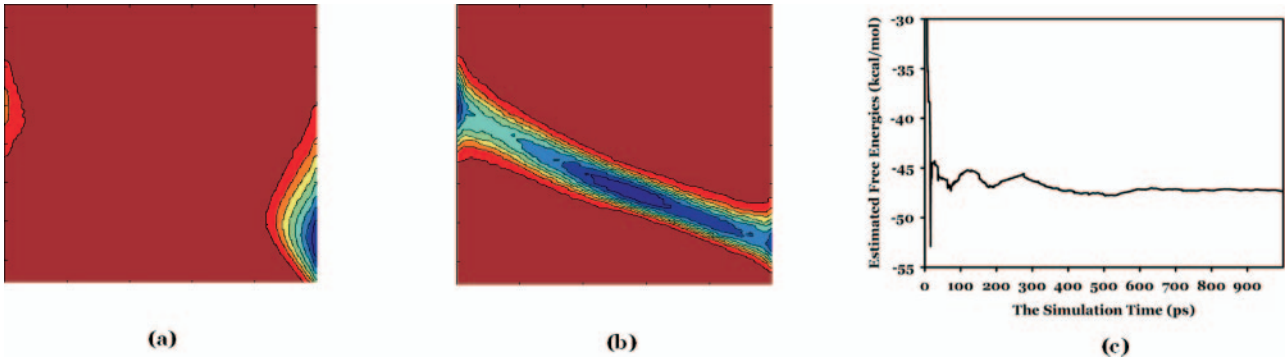

Fig. S1. The OSRW simulation results on model study 1 to illustrate the importance of adding the order parameter space surface flattening term. (*a*) The free-energy surface along the orthogonal space produced by 1-ns simulation based on the OSRW formula without the order parameter space surface flattening term. (*b*) The free-energy surface along the orthogonal space produced by 1-ns simulation based on the OSRW formula with the order parameter space surface flattening term. (*c*) The time-dependent free-energy value changes, which were obtained based on the OSRW formula with the order parameter space surface flattening term.

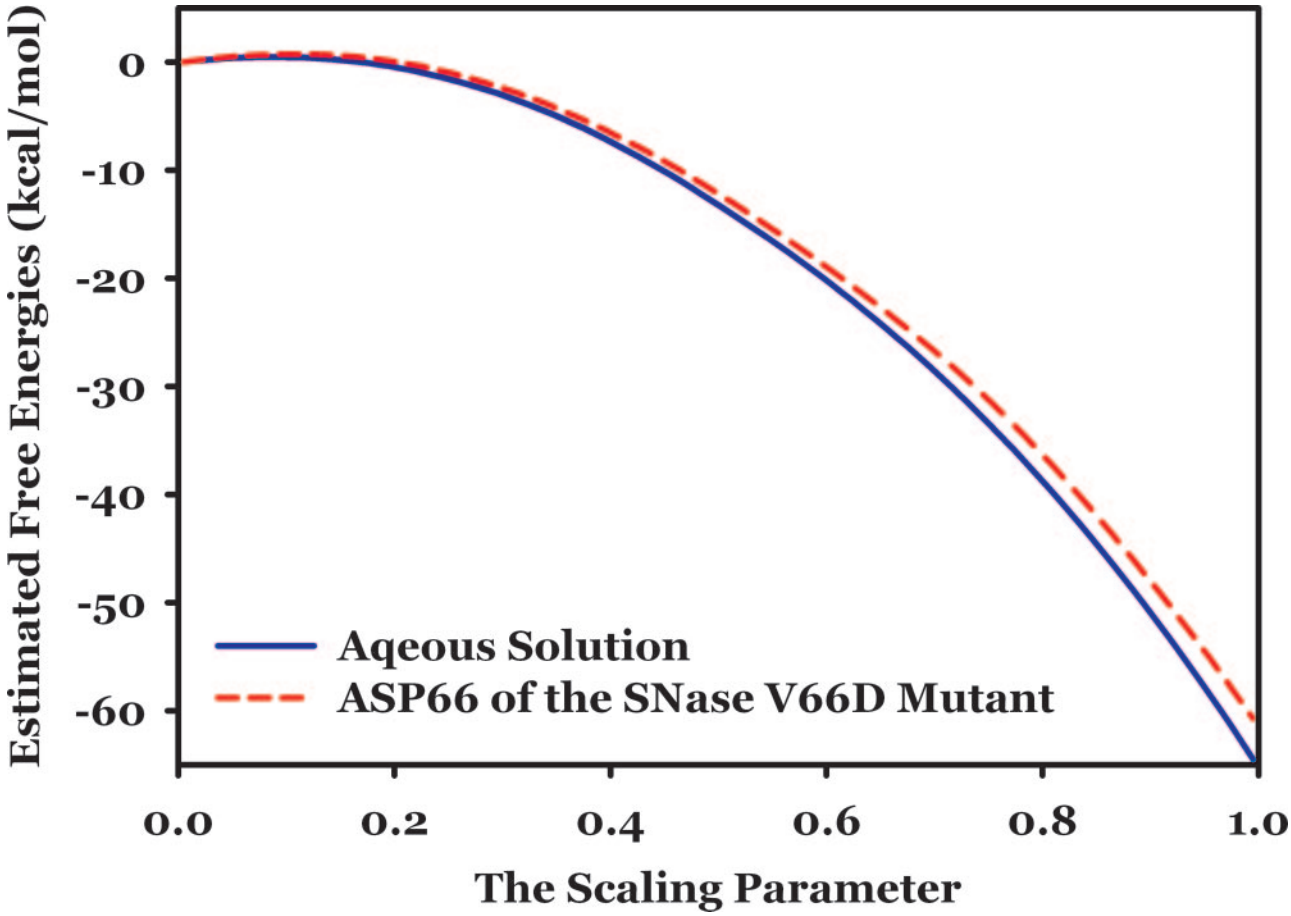

Fig. S2. The free-energy simulation results in model study 2: the scaling parameter-dependent free-energy changes. Dashed lines indicate the results on the protein (the SNase mutant) system; solid lines indicate the results on the solution system.

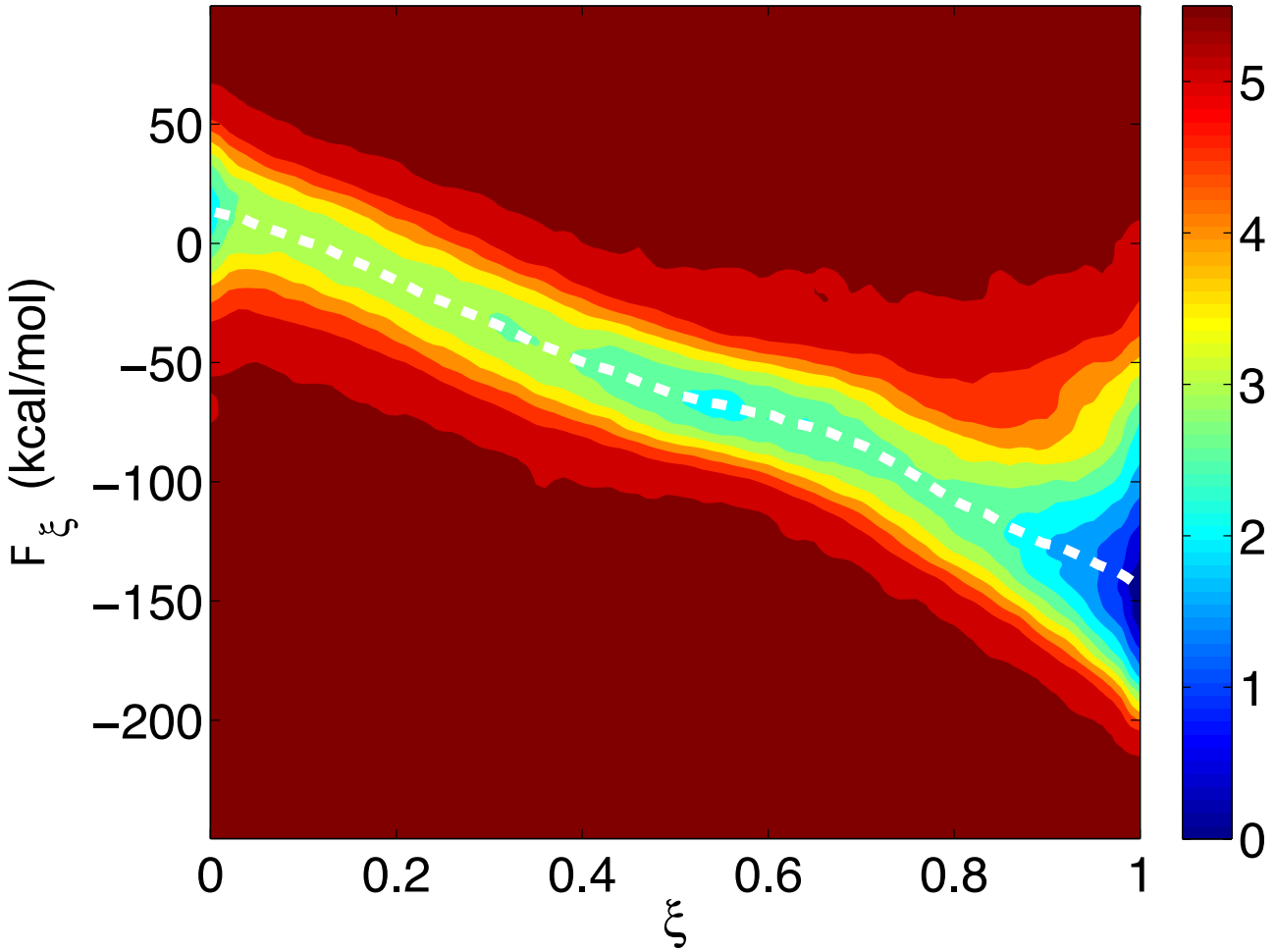

Fig. S3. The free-energy surface along the orthogonal space produced by 600-ps OSRW simulation. In the middle, the white dashed curve shows the estimated free-energy derivatives.

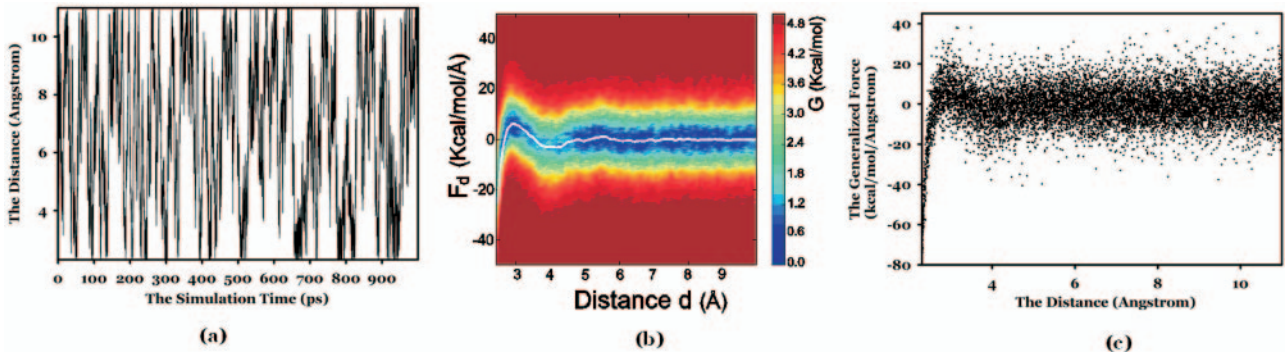

Fig. S4. The behaviors of the OSRW simulation on the separation of the sodium and the chloride ion pair in aqueous solution. (*a*) The time-dependent distance change. (*b*) The free-energy surface along the orthogonal space produced by 250-ps OSRW simulation; in the middle, the white dashed curve shows the estimated generalized forces. (*c*) The distribution of the samples collected during the OSRW simulation in the orthogonal space.