Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting Information for "Comparing Alchemical and Physical Pathway Methods for Computing the Absolute Binding Free Energy of Charged Ligands"

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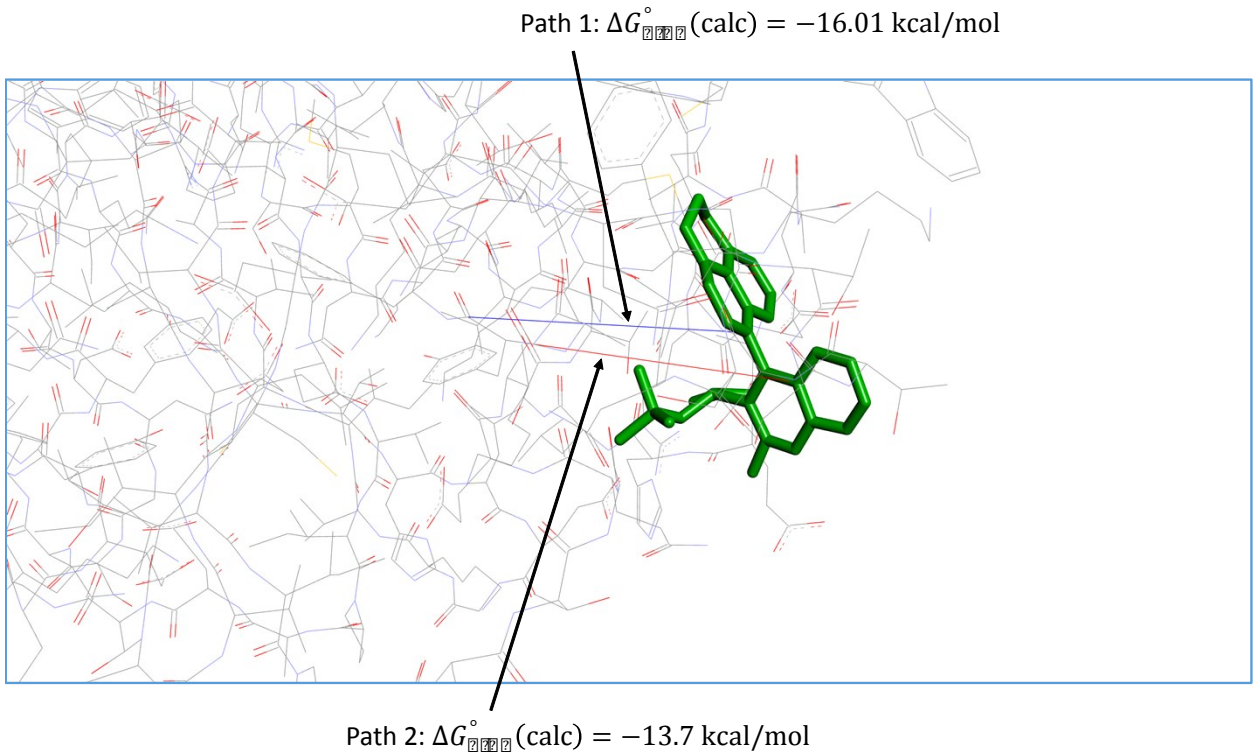

Figure S1. Two low free energy paths used in the PMF calculation of the absolute binding free energy for BI-224436.

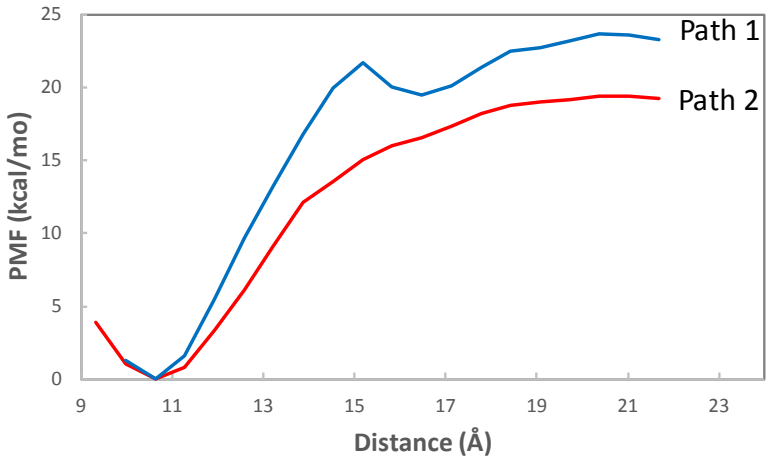

Figure S2. The PMF profiles of the two paths used in the PMF calculation for BI-224436. The error bars in the PMF are omitted for clarity.

Table S1. Meanings of the symbols used in the equations

Symbol	Meaning of the symbol
$Z_{RL,N}$	A system containing one receptor(R)-ligand(L) complex in the complexed state solvated by N water molecules.
$Z_{0,N}$	A system containing N solvent molecules.
$Z_{R,N}$	A system containing one receptor R solvated by N water molecules.
$Z_{L,N}$	A system containing one ligand L solvated by N water molecules.
$Z_{RL,N}^{V_{site}}$	Same as $Z_{RL,N}$, except that the complexed state is defined by those configurations in which the ligand is inside the predefined binding site volume V_{site} enforced by the step function $I(\xi)$, which is implemented by a flat-bottom potential.
$Z_{R\cdots L,N}^{V_{site}}$	A solvated ligand-receptor complex, in which the ligand is coupled with the receptor and solvent, and restrained by the harmonic potential $U_{restr}(\xi)$ and the step function $I(\xi)$.
$Z_{R,N\cdots L_{gas}}^{V_{site}}$	A receptor-ligand complex in which the ligand is restrained by both $I(\xi)$ and $U_{restr}(\xi)$ but its nonbonded interactions with its environment, i.e. receptor plus solvent, are turned off.
$Z_{R,N+L_{gas}}^{V_{site}}$	A receptor-ligand complex in which the ligand is not interacting with its environment but is confined to the binding site V_{site} only by the step function $I(\xi)$.
$Z_{RL(\theta,\phi,\Theta,\Phi,\Psi),N}$	A solvated complex RL in which ligand L's external degrees of freedom, which are defined by the polar angles (θ, ϕ) and three Euler angles (Θ, Φ, Ψ), are restrained to their equilibrium values in the bound state by a set of harmonic restraints $(U_\theta,U_\phi,U_\Theta,U_\Phi,U_\Psi)$.
$Z_{R+L(r^*,\theta,\phi,\Theta,\Phi,\Psi),N}$	A solvated system containing R and L in which L is not only subject to the polar and orientational restraints $(U_\theta,U_\phi,U_\Theta,U_\Phi,U_\Psi)$, but is also subject to the harmonic restraint $U_{r^*}=\frac{1}{2}k_r(r-r^*)^2$, which forces the ligand atom A to be close to a bulk location r^*.
$Z_{P+L,N}$	A system containing the receptor R, an unbound L, and N solvent molecules.