The reorganisation energy of drug compounds upon binding to proteins: some notes about the electrostatics.

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Abstract: The unbound state of drug compounds is important to better understand their binding to proteins, including conformational preorganization and the intramolecular reorganization energy of compounds upon binding (ΔE_{Reorg}). These questions were addressed with molecular dynamics (MD) simulations of diverse compounds, unbound or complexed to their protein target. Analysis of those systems involved observations regarding their electrostatics.

The unbound compounds simulated with MD were compared to conformers generated with implicit generalized Born (*GB*) aqueous solvation models. The notion of conformational pre-organization for binding was investigated by comparing the simulated compounds to their bioactive X-ray structure. The study yielded low to moderate values of ΔE_{Reorg} for most, but not all, compounds. For three particularly polar compounds, ΔE_{Reorg} was substantial (≥ 15 kcal/mol). Those large ΔE_{Reorg} values may be interpreted as a redistribution of electrostatic interactions upon binding.