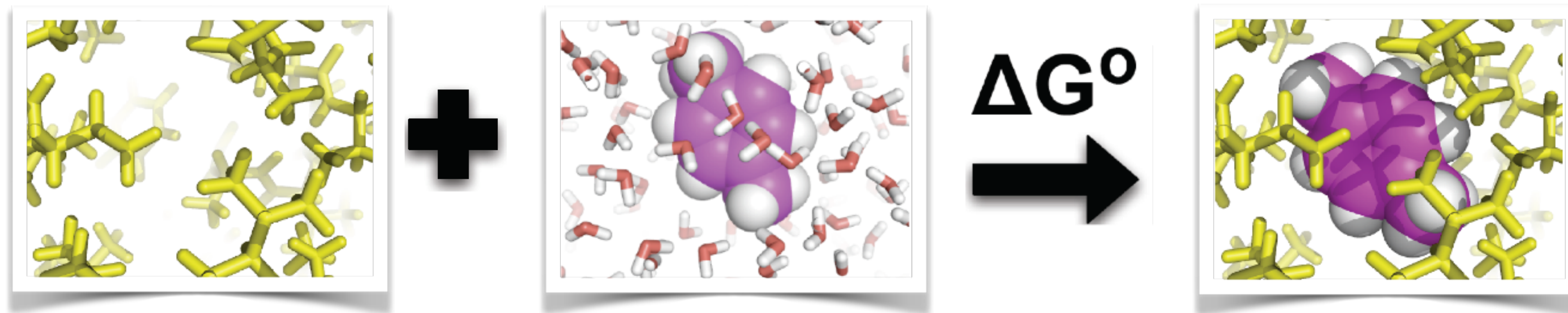


# Why do we use alchemical pathways?

- Adjacent states along an alchemical pathways have high *configuration space overlap*
- Using alchemical pathways is valid because thermodynamic functions like the Gibbs free energy are *state functions*
  - they only depend on the final values, not the path between them
    - height, weight, coordinates are other state functions
  - Hess' law is based on this property of the Gibbs free energy
- Binding free energy calculations usually involve connecting *alchemical pathways* in a *thermodynamic cycle* that joins the end states of interest

# A Thermodynamic Cycle for Absolute $\Delta G$ of Binding



Cycle: Boresch et al., J. Phys. Chem. B  
107:9535 (2003)  
See also Gilson, Biophys J. 1997.  
From [1]