



FIGURE 2.3 Conformational energies of ethylbenzene.

with respect to the phenyl ring (the lowest energy conformation) to a conformation with a coplanar carbon skeleton increases the energy by 6.7 kJ/mol. Thus, even modest changes in the conformation (the shape) of a ligand can result in a significant decrease in the affinity, a fact that should carefully be taken into account in ligand design (for further discussions on ligand conformations, see Section 2.3.2). As mentioned earlier, IC_{50} expresses the concentration of an inhibitor which displaces 50% of the specific binding of a radioactively labeled ligand in a radioligand displacement experiment. The IC_{50} value can be converted to an inhibition constant K_i by the Cheng–Prusoff equation:

$$K_i = \frac{IC_{50}}{\left(1 + \frac{[L]}{K_D}\right)} \quad (2.4)$$

where

[L] is the concentration of the radioligand used in the assay

K_D is the affinity of the radioligand for the receptor

It should be noted that IC_{50} values are dependent on the concentration and the affinity of the radioligand used to determine it. Therefore, care should be taken when comparing IC_{50} values across different experiments unless the same radioligand and assay conditions were used. If not, one needs to convert the IC_{50} value to K_i using Equation 2.4 to get comparable values. K_i is namely independent of radioligand and radioligand concentration and can be compared across assays.

2.3 PARTITIONING OF ΔG

To get a better understanding of the driving forces underlying molecular recognition, it is helpful to express the free energy difference ΔG as a sum of the individual components from which it may be considered to be made up. The main drivers of recognition are

- Electrostatic interactions including ion–ion, ion–dipole, and dipole–dipole interactions
- Lipophilicity/hydrophobicity
- Shape complementarity

Other factors such as entropy and conformational changes also influence the recognition process, and summing up all these contributions leads to Equation 2.5. Several different partitioning