whether there are both "solvent-separated" and "contact" minima for two methane molecules in aqueous solution, there is no question that methane association is quite attractive in aqueous solution compared with the gas phase (38).

One can also apply such approaches to study association of ionic and polar molecules. For example, the association of Na^+ and Cl^- has a free energy of association that is very small in magnitude, in contrast to the gas phase (39). The association of two amides through a C=O . . . H–N hydrogen bond is very favorable in *vacuo* and progressively less favorable in non-polar and aqueous solution (40). Thus, water has a significant "leveling" effect on association, making nonpolar associations more favorable and ionic and polar associations less favorable than their gas phase counterparts.

Let us now summarize the foregoing discussion. Unlike the gas phase association, where AH, and AS, are invariably negative, for the corresponding thermodynamics in solution, AH, and AS, can be of either sign. The enthalpy of association AH, of two molecules in solution will bepositive if the interactions of the solvent with the uncomplexed drug and receptor are sufficiently stronger and more exothermic (AH, – AH, – ΔH_{2R} is more positive than AH, is negative) than are the interactions of the solvent with the drug-receptor complex. Similarly, the entropy of association in solution AS, can be positive if AS, – AS, – ΔS_{2R} is more positive than AS, is negative. This can come about if the entropy gain from release of solvent from its interaction with the isolated drug and receptor is sufficiently larger than the entropy gain from release of solvent from the drug receptor complex.

An additional important point to keep in mind is that the solution phase thermodynamics may be dominated (as in the case of the hydrophobic effect, the association of nonpolar solutes in water) by changes in *solvent–*solvent interactions in the presence of solute.

It is also important to stress that even an analysis of the relative contributions of AH and AS to AG may not give definitive insight into the "nature" of the drug-receptor bond. For example, a large positive AS (and small negative AH) for association might come from either a hydrophobic or an ionic association (35). In either case, the driving force for association is likely "release" of H_2O from "tight" binding to the solute.

One final consideration in determining either gas phase or solution phase association constants of drug-receptor complexes is conformational flexibility. Medicinal chemists have often attempted to synthesize rigid drug of different stereochemistries in the hopes of finding one that fits "perfectly" into the receptor site. If, for example, the drug has three equal energy conformations and only one can fit the receptor site, a price must be paid of $\Delta G = +RT \ln 3$ in binding free energy relative to the drug that is "locked" in the right conformation. If the receptor has to be locked in a conformation to "accept" the drug, one must pay a similar free energy price. A nice example of the latter situation is the difference in binding free energies between "locked" and "unlocked" macrocyclic crown ethers (41) that bind $t\text{-}BuNH_3^+$ cation.

4.3 An Illustrative Example: Protonation of Amines

Before we turn to some examples of drug-receptor interactions, let us present a specific example of the difference between gas phase and solution interactions. We choose the protonation of amines, because of the large literature that attempted to explain the irregular order of p*Ka*'s of the alkyl amines [NH_3 = 9.25; CH_3NH_2 = 10.66; $(CH_3)_2NH$ = 10.73; and $(CH_3)_3N$ = 9.811. This reaction can be represented as

$$\Delta G_1$$

$$R_3N + H^+ \rightarrow R_3N^+H$$

in the gas phase and

$$\Delta G_4$$

$$R_3N(aq) + H^+(aq) \rightarrow R_3NH^+(aq)$$

in aqueous solution. As we noted in connection with Fig. 4.2, the difference between the free energies of protonation in solution and the gas phase is given by