Table 4.4 Free Energies in Cycle (Fig. 4.2) for Protonation of Alkyl Amines (kcal/mol)[a]

R_3N	ΔG_1	$\Delta G_2(H^+)$	$\Delta G_2(R_3N)$	$\Delta G_3(R_3NH^+)$	ΔG_4
NH_3	−198.0	269.8	−2.41	−78.0	−3.79
CH_3NH_2	−210.0	269.8	−2.68	−67.7	−5.22
$(CH_3)_2NH$	−216.6	269.8	−2.41	−61.0	−5.39
$(CH_3)_3N$	−220.8	269.8	−1.34	−54.4	−4.06

"See Aue et al. (42).

$$\Delta G_4 - \Delta G_1 = -\Delta G_2(R_3N) - \Delta G_2(H^+) + \Delta G_3(R_3NH^+)$$

Recall also that the solution $pK_a = -\log K_{as} = \Delta G_4{}^0/2.3$ RT. When the gas phase basicities were measured and showed a regular order, it was clear that the irregular order in solution was caused by a solvation effect. In the gas phase, NH, is a weaker base than $(CH_3)_3$ by about 23 kcal/mol; in solution this difference is only about 1 kcal/mol.

Table 4.4 lists the free energies appropriate to the thermodynamic cycle (Fig. 4.2) for the protonation of the amines. Two points deserve strong emphasis.

1. The magnitude of ΔG_4 is much smaller than that of AG, for protonation, because in aqueous solution, the amines must compete with H_2O for the proton; in the gas phase there is no competition.
2. As clearly analyzed by Aue et al. (42), the smaller the protonated amine, the more effectively solvated it is, and the better base it becomes compared with its relative rank in the gas phase.

5 CALCULATING FREE ENERGIES

Free energy is certainly one of the most important concepts in physical chemistry. The groundwork on calculating free energies was laid by Kirkwood (43) and Zwanzig (43), and the first key "modern" developments and applications came from the work of Postma et al. (44), Jorgensen and Ravimohan (45), Tembe and McCammon (46), and Warshel (47). The fundamentals of computational approaches to calculating free energies are reviewed by Beveridge and Mezei (48), and we attempted to exhaustively review applications up to 1993 (49).

To calculate the relative solvation free energies of molecules A and B in solvent S, we can use a thermodynamic cycle such as in Fig. 4.3. The relative solvation free energy of A and B, determined experimentally, is $\Delta\Delta G_{solv} = \Delta G_{solv}$ (B) − ΔG_{solv} (A), and because the free energy is a state function, AAG is also = AG (S) − AG (g), which are the free energies determined by computational means by "mutating" the molecular mechanical model of A into B in solvent S and in the gas phase (g). Of course, if B consists of all "dummy" (non-interacting) atoms, this approach leads to the calculation of the absolute solvation free energies of A.

Being able to accurately calculate free energies of solvation suggests a reasonable balance in solute–solvent and solvent–solvent interactions. The next key challenge is to calculate $\Delta\Delta G_{bind}$ of guests G and G' to a host H, all in aqueous (or other) solution.

A typical cycle for free energy calculations (45) where H is a host, G is a guest, and HG is the host–guest complex is given in Fig. 4.4.

Now one requires a correct balance of solute (host)–solute (guest), solute (host or guest) -solvent, and solvent–solvent interactions to correctly calculate $\Delta\Delta G_{bind}$, although there clearly can be compensating errors in the calculation of ΔG_{solv} and ΔG_{bind}.

$$\begin{tikzcd}
A(g) \arrow[r, "\Delta G_{mut}(g)"] \arrow[d, "\Delta G_{solv}(A)"] & B(g) \arrow[d, "\Delta G_{solv}(B)"] \\
A(S) \arrow[r, "\Delta G_{mut}(S)"] & B(S)
\end{tikzcd}$$

Figure 4.3. Basic thermodynamic cycle for solvation free energy.