1

Equilibria and thermochemistry

1.1 Introduction

This chapter introduces the quantitative treatment of the energetics of molecules and equilibria and describes how to interpret these quantities. It presents tables of thermochemical data, including standard heats of formation and standard entropies (Tables 1.A.1–1.A.4), Pauling electronegativities (Table 1.A.5), bond lengths (Table 1.A.6), bond dissociation energies (BDEs) or standard homolytic bond dissociation enthalpies (Tables 1.A.7–1.A.11, 1.A.13, 1.A.14), gas-phase heterolytic bond dissociation enthalpies (Tables 1.A.13–1.A.16), gas-phase proton affinities (Tables 1.A.13, 1.A.15, 1.A.18), gas-phase hydride affinities (Tables 1.A.14 and 1.A.16), ionization enthalpies (Tables 1.A.13, 1.A.20, 1.A.21), electron affinities (Tables 1.A.13, 1.A.20, 1.A.22), gas-phase acidities (Table 1.A.17), and substituent effects on the relative stabilities of reactive intermediates in the gas phase such as radicals (Tables 1.A.9 and 1.A.12), carbenium ions (Table 1.A.14) and anions (Tables 1.A.19), and solution acidities (Tables 1.A.23 and 1.A.24) for selected species.

Thermochemistry is "the study of heat produced or required by a chemical reaction" [1]. Thermochemistry is closely associated with calorimetry, an experimental technique that can be used to measure the thermodynamics of chemical reactions. First developed by Black, Lavoisier, and Laplace in the eighteenth century, and further by Berthelot and Thomsen in the nineteenth century [2], the golden years of calorimetry began in the 1930s; Rossini [3] at the National Bureau of Standards determined the thermodynamic quantities for a number of organic compounds. The thermochemical studies of organometallic compounds were pioneered by Skinner and coworkers [4, 5]. Calorimetry has been the main source of thermodynamic quantities, such as the standard enthalpies of selected reactions ($\Delta_r H°$), and, for pure compounds, standard enthalpies of combustion ($\Delta_c H°$), standard enthalpies of hydrogenation ($\Delta_h H°$), standard enthalpies of vaporization ($\Delta_{vap} H°$), standard enthalpies of sublimation ($\Delta_{sub} H°$), standard enthalpies of solubilization ($\Delta_{sol} H°$), standard enthalpies of formation ($\Delta_f H°$), standard entropies ($S°$), and heat capacities ($C_p°$) [6, 7].

1.2 Equilibrium-free enthalpy: reaction-free energy or Gibbs energy

The Le Châtelier principle states "On modifying pressure or temperature of a stable equilibrium, the latter is modified until cancelation of the effects imposed by the external changes; concentrations of reactants and products are modified such as to oppose the effects of the external changes." In other words, an equilibrium (reaction (1.1)) between **A**, **B**, etc., and **P**, **Q**, etc., as reactants and products, respectively, can be written as:

$$\alpha\mathbf{A} + \beta\mathbf{B} + \cdots \underset{}{\overset{K}{\rightleftharpoons}} \pi\mathbf{P} + \theta\mathbf{Q} + \cdots \qquad (1.1)$$

Interestingly, a few months before Le Châtelier, Van't Hoff had announced the same principle [8–10]. At equilibrium, the free energies G^T of the reactants and products are equal. At constant temperature (T) and pressure (p), and for reactants and products in their standard states (that is, 1 M in solution or 1 atm in the gas phase), the second law of thermodynamics gives Eq. (1.2), from which the change in Gibbs energy, $\Delta_r G^T$, between the moment reactants **A**, **B**, … are mixed and the moment equilibrium (1.1) is reached can be determined. $\Delta_r G^T$ is called the Gibbs energy of reaction (free enthalpy or just free energy of reaction).

$$\Delta_r G^T = -RT \ln K \qquad (1.2)$$

where R is the gas constant ($1.987\ \text{cal K}^{-1}\ \text{mol}^{-1} = 1.987$ eu (entropy units) $\cong 8.314\,472\ \text{J K}^{-1}\ \text{mol}^{-1}$), and T is the temperature in K (Kelvin) and

$$K = \frac{a_P^{\pi} a_Q^{\theta} \cdots}{a_A^{\alpha} a_B^{\beta} \cdots} \qquad (1.3)$$

Organic Chemistry: Theory, Reactivity and Mechanisms in Modern Synthesis, First Edition. Pierre Vogel and Kendall N. Houk.

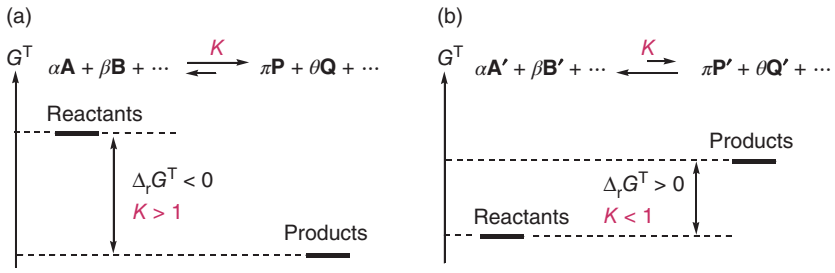


Figure 1.1 Free enthalpy diagrams: variation of Gibbs energy for (a) an exergonic reaction ($K > 1$) and (b) for an endergonic reaction ($K < 1$) (reactants: **A**, **B**, …; products: **P**, **Q**, …).

Here, a_P, a_Q, … and a_A, a_B, … are the activities (or relative activities) of products **P**, **Q**,… and reactants **A**, **B**,..., respectively, at equilibrium, and α, β,… π, θ are the stoichiometric factors of equilibrium (1.1) in solution.

Concentrations are generally used in place of activities; this is equivalent to assuming that the activity coefficients, γ, (e.g. $a_{A=}\gamma_A[\mathbf{A}]$, $a_{B=}\gamma_B[\mathbf{B}]$, $a_{P=}\gamma_P[\mathbf{P}]$, and $a_{Q=}\gamma_Q[\mathbf{Q}]$) are equal to unity.

If $\Delta_r G^T < 0$, the reaction is exergonic: $K > 1$ (e.g. Figure 1.1a)

If $\Delta_r G^T > 0$, the reaction is endergonic: $K < 1$ (e.g. Figure 1.1b).

The terms exergonic and endergonic are related to the more familiar ones exothermic and endothermic that refer to enthalpies (see below).

For a reaction in the gas phase,

$$K = \frac{p_P^{\pi} p_Q^{\theta} \cdots}{p_A^{\alpha} p_B^{\beta} \cdots} \tag{1.4}$$

where p_P, p_Q, p_A, and p_B are the partial pressures of **P**, **Q**, … and **A**, **B**, … respectively.

If equilibrium (1.1) is considered to be an ideal solution, then

$$K = \frac{[\mathbf{P}]^{\pi}[\mathbf{Q}]^{\theta} \cdots}{[\mathbf{A}]^{\alpha}[\mathbf{B}]^{\beta} \cdots} \tag{1.5}$$

where [**P**], [**Q**], … are the concentrations of the products and [**A**], [**B**], … are the concentrations of the reactants. A large number of organic reactions can be treated as ideal solutions, as long as dilute solutions are used under conditions of temperature and pressure that do not differ too greatly from: 298.15 K and 1 atm.

The Gibbs free energy of reaction is directly related to the relative amounts of two or more than two species at equilibrium: at temperature, T. This ratio can be determined from Eq. (1.2),

$$\ln K = -\Delta_r G^T/RT, \quad \text{or}$$
$$K = \exp(-\Delta_r G^T/RT) \tag{1.6}$$

As proposed first by Guldberg and Waage in 1879 [11], the equilibrium constant, K, is a ratio of rate constants (Chapter 3) $k_{forward}$ (k_1) and $k_{reverse}$ (k_{-1}), where $k_{forward}$ is for the forward reaction (pure reactants equilibrating with products) and $k_{reverse}$ is for the reverse reaction (pure products equilibrating with reactants), at the same temperature T: $K = k_{forward}/k_{reverse}$.

We shall show later that a free energy difference can be used to compare not only the forward and reverse reaction rate constants but also any two reaction rate constants k_1 and k_2:

$$\Delta\Delta_r G^T = -RT \ln(k_1/k_2) \tag{1.7}$$

As equilibria are usually discussed as existing at room temperature (25 °C, 298.15 K), it is useful to plot in R, T and to convert ln K to log K to obtain the following relationship (1.8):

$$\Delta_r G^{\circ} = -RT \ln K = (-1.987 \text{ eu}) \times 298.15 \cdot 2.303 \cdot \log K = -1.36 \cdot \log K, \text{ or :}$$
$$\Delta_r G^{\circ} = -1.36 \log K \tag{1.8}$$

In Eq. (1.8), $\Delta_r G°$ is in kcal/mol (IUPAC: kcal mol^{-1}), and the measurement is at room temperature (° for 298.15 K). This is a very useful relationship! Rounding off a bit, this expression shows that a 1.4 kcal mol^{-1} (5.9 kJ mol^{-1}) free energy difference results in a factor of 10 in equilibrium constant at 25 °C. Another way to say this is that $K = 10$ corresponds to a 1.4 kcal mol^{-1} difference in free energy, whereas $\Delta_r G° = -2.8$ kcal mol^{-1} corresponds to $K = 100$ at 25 °C, and so forth.

1.3 Heat of reaction and variation of the entropy of reaction (reaction entropy)

Free energy provides a way to quantify experimental equilibria. Gibbs free energy at temperature T_x is written as $\Delta_r G^T$ (or $\Delta_r G(T_x)$). It can be separated into two other thermodynamic quantities: $\Delta_r H^T$ (or $\mathbf{\Delta}_r H(T_x)$), the change in enthalpy or heat of reaction at temperature T_x, and $\Delta_r S^T$ (or $\mathbf{\Delta}_r S(T_x)$), the change in entropy

or reaction entropy. The heat of reaction is related to the internal energy U ($H = U + RT$) or heat content of a system. The reaction entropy is the variation of entropy between the beginning (when reactants **A**, **B**,… are mixed) and the end of the reaction (when equilibrium (1.1) is reached) at temperature T_x. It gives a quantitative measure of "disorder." The thermodynamic definitions of these quantities are given in the following section. Under constant pressure p, the Gibbs–Helmholtz equation (1.9) provides for equilibrium the relationship between $\Delta_r G^T$ and temperature T,

$$\mathrm{d}(\Delta_r G^T/T)/\mathrm{d}T = \mathrm{d}(\Delta_r H^T/T - \Delta_r S^T)/\mathrm{d}T = -\Delta_r H^T/T^2 \qquad (1.9)$$

The heat of reaction, $\Delta_r H^T$, is the heat produced (exothermic) or absorbed (endothermic) between the beginning of the reaction (time t_0, the moment of mixing the reactants) and the end of the reaction (time t_∞, when the equilibrium **reactants** ⇄ **products** is reached, see Figure 1.2). The reaction entropy, $\Delta_r S^T$, expresses the change of order, or disorder, between products and reactants. This thermodynamic quantity will be discussed further in Section 1.4.

The Van't Hoff equation provides the relationship between the equilibrium constant, K, or rate constant ratio, $K = k\text{forward}/k\text{reverse}$, and the heat of reaction:

$$\ln K = -\Delta_r H^T/RT + \text{constant} \qquad (1.10)$$

The slope of the plot of ln K vs. $1/T$ provides the value of $-\Delta_r H^T/R$. By measuring the equilibrium constant of a given equilibrium at two different temperatures, the average heat of reaction $\overline{\Delta_r H}$ can be determined roughly using Eq. (1.11):

$$\log \frac{(K)_2}{(K)_1} = -\frac{\overline{\Delta_r H}}{2.303\,R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \qquad (1.11)$$

This method is one of the most widely used methods to determine thermochemical parameters of reactions evolving to equilibria. It is not absolutely rigorous because it assumes a constant heat of reaction for the whole temperature range of investigation. However, in reality, the heat content of a substance changes with temperature, and this variation of heat content with temperature is given by Kirchhoff law (1.12):

$$H(T_2) - H(T_1) = \int_{T_1}^{T_2} C_p\,\mathrm{d}T \qquad (1.12)$$

where $C_p = \left(\frac{\delta H}{\delta T}\right)_p$ is the molar heat capacity at a constant pressure.

The second law of thermodynamics states that the difference in free energy, $\Delta_r G^T$, between the initial state of a reaction and the final state at equilibrium depends on these two states only; it does not depend on the path followed to reach the equilibrium. Consequently,

$$\Delta_r H(T_2) - \Delta_r H(T_1) = \int_{T_1}^{T_2} \Delta_r C_p\,\mathrm{d}T \qquad (1.13)$$

where $\Delta_r C_p = \Sigma C_p(\text{products}) - \Sigma C_p(\text{reactants})$

Equation (1.13) is a way to calculate $\Delta_r H(T_2)$ at temperature T_2, as long as $\Delta_r H(T_1)$ is known at temperature T_1, and C_p is known for all reactants and products ($\Delta_r C_p$). Often, it is assumed that $\Delta_r C_p$ has a constant value, leading to the simple approximation (1.14):

$$\Delta_r H(T_2) - \Delta_r H(T_1) = \Delta_r C_p\,(T_2 - T_1) \qquad (1.14)$$

The standard Gibbs free energies for equilibrium (1.1) at T_1 and T_2 are given by Eqs. (1.15) and (1.16), respectively.

$$\Delta_r G(T_1) = \Delta_r H(T_1) - T_1 \Delta_r S(T_1) \qquad (1.15)$$

$$\Delta_r G(T_2) = \Delta_r H(T_2) - T_2 \Delta_r S(T_2) \qquad (1.16)$$

For small temperature differences $T_1 - T_2$, the entropies of reaction $\Delta_r S(T_1)$ and $\Delta_r S(T_2)$ can be

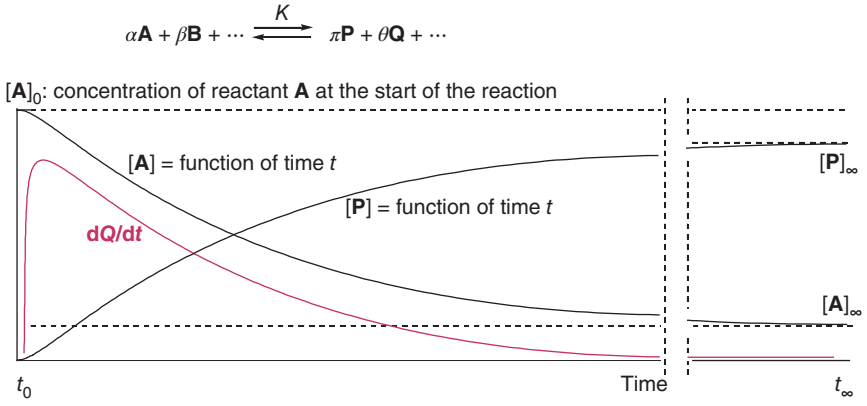


Figure 1.2 Reaction kinetics showing the disappearance of one reactant **A** (rate law d[**A**]/dt) and the appearance of one product **P** (rate law d[**P**]/dt) from the beginning of the reaction (time: t_0) to the end of the reaction (time: t_∞). The red curve is the heat flow (heat produced by time unit: dQ/dt) for an exothermic reaction ($\Delta_r H^T < 0$). $[A]_\infty$, $[M]_\infty$ are the concentrations of reactant **A** and product **P**, respectively, at equilibrium. The integral $\int_0^\infty Q\,\mathrm{d}t = \Delta_r H^T$ = heat of reaction at constant temperature T.

assumed to be identical. Consequently, a measurement of K_1 at T_1 and K_2 at T_2 allows one to estimate the average heat of the reaction $\overline{\Delta_r H}$.

The standard entropies of reaction (in cal K^{-1} mol^{-1} = eu = entropy units) at 298.15 K and under 1 atm (pure compounds that can be considered as ideal gases) can be calculated from Eq. (1.17), applying the third law of thermodynamics:

$$\Delta_r S^o = \Sigma S^o(\text{products}) - \Sigma S^o(\text{reactants}) \quad (1.17)$$

The standard entropy values $S°$ are tabulated for a large number of gaseous compounds in the NIST Webbook of Chemistry (http://webbook.nist.gov) (Table 1.A.2). Alternatively, if the products and reactants are ideal gases (ideal gas law: $pV = NRT$; p = pressure, V = volume, N = number of moles, R = ideal gas constant, and T = temperature in K), the entropies can be calculated from statistical thermodynamics.

1.4 Statistical thermodynamics

Statistical thermodynamics establishes a relationship between the microscopic world of quantum mechanics and the macroscopic world that we readily observe [12, 13]. Thermodynamics has its origin in steam engines, and much of the language used to describe these engines persists to this day and is used to describe chemical processes and chemical themselves. We are able to derive thermodynamic properties of any compound from the structures of molecules. The thermodynamic parameters (internal energy U, enthalpy H ($H = U + pV$), entropy S, and free energy G) of an ensemble of molecules can be determined from spectroscopic data or quantum mechanical treatments of the molecules. The total energy of one molecule is the sum of the nuclear (E_{nucl}), electronic (E_{elec}), vibrational (E_{vib}), rotational (E_{rot}), and translational energies (E_{trans}). All these energies are quantized and only discrete values of energies are available. Only a limited number of discrete energy levels are accessible for the molecules (Figure 1.3). If N_i is defined as the number of molecules occupying the microstate i of energy E_i, and N_o is the number of molecules occupying the microstate o of energy $E_0 = 0$, the Boltzmann relationship (1.18) gives the proportion of molecules in microstate i and microstate o at temperature T (in K) [14, 15]:

$$N_i/N_o = e^{-E_i/k_b T} \quad (1.18)$$

The Boltzmann constant $k_b = 3.30 \times 10^{-24}$ cal K^{-1}, or 1.38×10^{-23} J K^{-1}, is the gas constant for one molecule, i.e. $k_b = R/L$, where L = the Avogadro constant (also named Avogadro's number and also noted as N_A), the number of molecules in 1 mol = 6.02×10^{23} mol^{-1}. If there are several energy levels of the same energy, the proportion N_i/N_o becomes:

$$N_i/N_o = (g_i/g_o)e^{-E_i/k_b T} \quad (1.19)$$

where g_i and g_o are the statistical factors enumerating the number of identical microstates available, for energy levels E_i and E_o, respectively. If N is the total number of molecules of the system under investigation, then:

$$N = \Sigma N_i = \frac{N_o}{g_o} \Sigma g_i e^{-E_i/k_b T} \quad (1.20)$$

The factor N_o/g_o has been taken out of the summation sign as it is a constant. The quantity defined by the sum is the canonical partition function or partition function of the molecule:

$$Z = \Sigma g_i e^{-E_i/k_b T} \quad (1.21)$$

Z is the number of molecules in all microstates i: this function shows how the molecules "partition" among the various available microstates of energy E_i. One assumes that the energies of the molecules are independent of each other, which is the case for an ideal

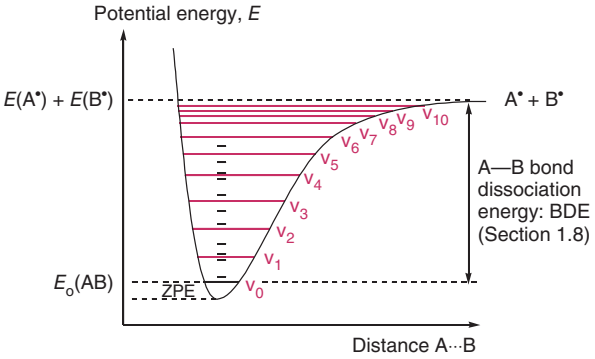


Figure 1.3 Representation of the Morse potential for a diatomic molecule A—B in its electronic ground state. The red full horizontal lines represent the vibrational energy levels (as given by infrared spectroscopy, or calculated by quantum mechanics; the energy difference between the vibrational levels $\Delta E = h\nu$ decreases on increasing E (nonharmonic oscillator). The black horizontal lines represent the rotational levels (as given by microwave spectroscopy or by quantum mechanical calculations, the energy difference between the rotational levels increases on increasing energy E). The translational levels are not shown; they are separated by very small energy differences. E_o(AB) = energy of molecule A–B at 0 K; ZPE = zero-point energy (or quantum vacuum zero-point energy) = $h\nu/2$ with ν = the vibrational frequency of oscillator A—B and h = Planck's constant; E(A•) and E(B•) energies of atoms A• and B•. Similar Morse potentials can be represented for doubly bonded diatomic molecules A=B and triply bonded diatomic molecules A≡B.

gas. From the partition function Z, the thermodynamic parameters U, H, S, and G of the macroscopic system can be calculated. For most chemical systems, $U°$, the lowest internal energy, is the sum of electronic (E_{el}) and nuclear energies (E_{nucl}) at $T = 0$ K for all the molecules of the system. Generally, there are very large differences between the energies of different nuclear and electronic quantum states, so that the accessible energy levels E_i of microstates i for a molecule correspond to quantized translation (E_{trans}), rotation (E_{rot}), and vibration (E_{vib}) energies, all for a single electronic state of energy.

To determine the internal energy change $\Delta U^T = \Sigma N_i E_i$ from 0 K to some finite temperature, T, the partition function can be used to obtain Eq. (1.22).

$$\Delta U^T = \left(\frac{N_o}{g_o}\right) \Sigma g_i E_i e^{-E_i/k_b T} \tag{1.22}$$

Differentiation of the partition function (Eq. (1.21)) with respect to temperature, at a constant volume, followed by rearrangement of the resulting expression yields Eq. (1.23) for one mole of ideal gas:

$$\Delta U^T = RT^2 \left(\frac{\delta \ln Z}{\delta T}\right)_V \tag{1.23}$$

The derivative of this Eq. (1.23) with respect to T, at a constant volume V, is the heat capacity of an ideal gas:

$$C_v = \left(\frac{\delta U}{\delta T}\right)_V = \frac{\delta}{\delta T}\left[RT^2 \left(\frac{\delta \ln Z}{\delta T}\right)\right]_V \tag{1.24}$$

The entropy varies with temperature according to Eq. (1.25):

$$S^T - S^\circ = \Delta S = \int_0^T \frac{C_v}{T}\, dT \tag{1.25}$$

Therefore:

$$S^T - S^\circ = RT\left(\frac{\delta \ln Z}{\delta T}\right)_V + R \ln Z - R \ln Z_o \tag{1.26}$$

At $T = 0$ K, all N molecules occupy microstates of energy level E_o. The partition function $Z_o = g_o$. For an ideal gas, $S° = k_b \cdot \ln[(g_o)^N/N!] = R \cdot \ln(g_o) - k_b \cdot \ln(N!)$ (applying Boltzmann–Planck equation: $S^T = k_b \cdot \ln \Omega$, with Ω the number of microstates available; for N distinguishable molecules, Ω would be $(g_o)^N$, but as the molecules in a gas are not distinguishable, this probability must be divided by N!. At a higher temperature, the entropy S^T of one mole of an ideal gas is

$$S^T = RT\left(\frac{\delta \ln Z}{\delta T}\right)_V + R \ln Z - k_b \ln N! \tag{1.27}$$

(Note the entropy $S°$ of a perfectly ordered crystal at 0 K is 0 eu, which is defined below.)

The internal energy ΔU^T can be calculated from relationship (1.23), the C_V from Eq. (1.24), and the entropy S^T from Eq. (1.27). Quantum mechanical calculations give estimates of the partition functions of isolated molecules in the gas phase; the accuracy can be very high when state-of-the-art quantum mechanical methods are used. The relationships between computed properties of an ideal gas molecule and the partition function are described below.

1.4.1 Contributions from translation energy levels

For translational energy levels, the partition function is given by:

$$Z_{trans} = \frac{(2\pi m k_b T)^{3/2}}{Lh^3} V \tag{1.28}$$

where m = mass of the molecule and h = Planck's constant (=6.626 068 96 × 10^{-34} J s). Combining Eqs. (1.23) and (1.24) gives:

$$\Delta U^T{}_{trans} = 1.5RT \text{ and } C_v = 1.5R$$

The translational entropy at temperature T ($S = S^T$ here below) becomes (using the Sterling approximation for large numbers: $\ln N! = N \cdot \ln N - N$):

$$S_{trans} = R \cdot \left\{ \frac{(2\pi m k_b T)^{3/2}}{Lh^3} V + 5/2 \right\} \tag{1.29}$$

where L is the Avogadro constant.

Using the mass of one molecule $m = M_r$(molecular mass)/L, volume $V = RT/p$ (ideal gas), and the values given for the constants h, R, L at pressure $p = 1$ atm, and using molecular mass in g units:

$$S_{trans} = 2.98 \cdot \ln M_r(g) + 4.97 \cdot \ln T - 2.31 \text{ eu} \tag{1.30}$$

or, converting to base 10 logs:

$$S_{trans} = 6.86 \cdot \log M_r(g) + 11.44 \cdot \log T - 2.31 \text{ eu} \tag{1.31}$$

S_{trans} is the entropy of a gas made of monoatomics (e.g. He, Ne, and Ar). Monoatomics have neither rotational energy levels nor vibrational levels, so that the calculation of entropy requires only the mass and temperature.

1.4.2 Contributions from rotational energy levels

A diatomic molecule can be assumed to be a rigid molecule that does not change its interatomic distance (bond length) with its frequency of rotation.

The partition function for the rotational energy levels in this rigid rotor is given by:

$$Z_{rot} = \frac{8\pi^2 I k_b T}{\sigma h^2} \quad (1.32)$$

where I = the inertia moment of the molecule. The moment of inertia $I = m_i r_i^2$, where m_i = mass of the atom i at distance r_i from the rotation axis. The symbol σ = symmetry number of the molecule, that is $\sigma = 1$, for diatomic molecules made of two different atoms or isotopes, or $\sigma = 2$ for symmetrical molecules made of two identical atoms or isotopes.

Combining Eqs. (1.27) and (1.32), the rotational entropy at temperature T for a rigid diatomic molecule becomes:

$$S_{rot} = 1.987 \cdot (\ln I + \ln T - \ln \sigma + 89.4)\ \text{eu} \quad (1.33)$$

or, in $\log_{10}$ units,

$$S_{rot} = 4.576 \cdot (\log I + \log T - \log \sigma + 32.82)\ \text{eu}$$

Values of I can be determined by rotational spectroscopy or by quantum mechanical calculations.

For a nonlinear polyatomic molecule, the partition function for its rotational energy levels is more complicated, as there are three moments of inertia.

$$Z_{rot} = \frac{(8\pi^2 k_b T)^{3/2}}{\sigma h^3}(\pi ABC)^{1/2} \quad (1.34)$$

The rotational entropy at temperature T becomes:

$$S_{rot} = 1.987 \cdot (0.5 \cdot \ln ABC + 1.5 \cdot \ln T - \ln \sigma + 134.68)\ \text{eu} \quad (1.35)$$

or, converting in $\log_{10}$ units,

$$S_{rot} = 2.288 \cdot \log ABC + 6.864 \cdot \log T - 4.576 \cdot \log \sigma + 267.74\ \text{eu}$$

A, B, and C are the three moments of inertia of the molecule in cgs units, and σ is the symmetry number. σ is the number of times the molecule is superposed upon itself rotating about each rotation axis of symmetry (e.g. $\sigma = 3 \times 2 = 6$ for cyclohexane in a chair conformation, $\sigma = 3$ for $CHCl_3$, $\sigma = 2$ for CH_2Cl_2, $\sigma = 6 \times 2 \times 2 = 24$ for benzene, and $\sigma = 2$ for toluene). According to Eq. (1.35), the entropy is reduced as the symmetry of the molecule increases. If two chemical systems with the same heat of reaction can evolve toward two different types of products, the lower symmetry products will be preferred, as $\Delta_r S$ (higher symmetry) $< \Delta_r S$ (lower symmetry). Nature dislikes symmetry, at least where entropy is concerned.

1.4.3 Contributions from vibrational energy levels

For a real diatomic molecule, vibrations are also present and make a contribution to entropy. For an idealized diatomic system vibrating as a perfectly elastic harmonic oscillator, the partition function for the vibrational energy levels is:

$$Z_{vib} = (1 - e^{-x})^{-1}, \quad \text{with} \quad x = hc\omega/k_b T = h\nu/k_b T \quad (1.36)$$

where $x = hc\omega/k_b T = 1.439 \cdot \omega/T$, with c = light velocity in a vacuum and ω (in cm^{-1} units) is the vibrational frequency of the molecule determined by infrared (IR) absorption spectroscopy or by quantum mechanics calculations. Alternatively, the equation is written in terms of the frequency, ν, of vibration in units of s^{-1}. Combining Eqs. (1.27) and (1.36), the vibrational entropy of a harmonic diatomic molecule is:

$$S_{vib} = 1.987 \cdot x/(e^x - 1) - 4.576 \cdot \log(1 - e^{-x})\ \text{eu} \quad (1.37)$$

For small and rigid molecules of molecular mass < 500, the relative importance of the partition functions is $Z_{trans} > Z_{rot} > Z_{vib}$ because the energy differences between the translational levels are much smaller than those between rotational levels and because the energy differences between rotational levels are smaller than those between vibrational levels. At any given temperature T, more excited translational and rotational states are occupied than higher energy vibrational states. For small and rigid molecules of molecular mass < 500, Hooke's law is the spring equation $F = -kx$. It relates the force F exerted by a spring to the distance x it is stretched by a spring constant k. The negative sign indicates that F is a "restoring force" as it tends to restore the system to equilibrium. The potential energy (PE) stored in the spring is given by $PE = 0.5kx^2$. If a mass m is attached to the end of the spring, the system might be seen as a harmonic oscillator that vibrates with an angular frequency $\omega = \sqrt{k}/\sqrt{m}$, or with a natural frequency $\nu = \omega/2\pi$. The solution to the Schrödinger equation for such system gives the eigenvalues $E_i = (i + 1/2) \cdot h\nu$, where $h\nu$ is the energy difference between two vibrational levels, and ν is the frequency of the vibration. The larger the spring constant k, the "stiffer the spring," the larger the vibrational frequency and the greater the energy difference between two vibrational levels. Molecules that can be deformed easily have small force constants for vibrational deformation. When the spring constant k is small, the energy

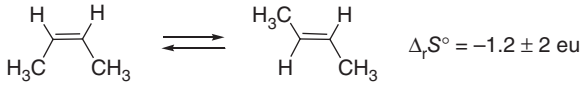
difference between the corresponding vibrational is relatively small, and this mode of deformation can contribute significantly to the partition function Z_{vib}, and to the entropy of the molecule.

The entropy of an ideal gas can be measured "macroscopically" from the relationship:

$$\Delta S = S_2 - S_1 = C_v \int_{T_1}^{T_2} \frac{dT}{T} + R \int_{V_1}^{V_2} \frac{dV}{V}$$
$$= C_v \ln \frac{T_2}{T_1} + R \ln \frac{V_2}{V_1}$$
$$\Delta S = \int_{T_1}^{T_2} C_p \frac{dT}{T} = \int_{T_1}^{T_2} C_p \, d(\ln T) \qquad (1.38)$$

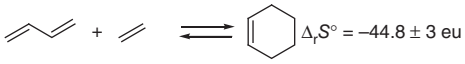
1.4.4 Entropy of reaction depends above all on the change of the number of molecules between products and reactants

For reactions occurring in the gas phase or in ideal solutions and for rigid reactants equilibrating with rigid products (Z_{rot} and Z_{vib} contributions to the entropy are roughly identical for products and reactants), $\Delta_r S^T \cong 0$ when the number of molecules does not change between products and reactants. When this number decreases as in addition reactions, $\Delta_r S^T \ll 0$. In the case of fragmentations, $\Delta_r S^T \gg 0$ (Section 2.6). For instance, the isomerization of (*Z*)-but-2-ene into (*E*)-but-2-ene, a reaction that does not change the number of molecules between the product and the reactant, and using experimental standard entropies for these compounds (Table 1.A.2), one finds $\Delta_r S° = -1.2 \pm 2$ eu at 298 K. As the reactant and the product maintain the same type of σ(C—H), σ(C—C), and π(C=C) bonds and the same number of symmetry ($\sigma = 2$, C_2 axis of symmetry, see Eq. (1.34)), the partition functions Z_{rot} and Z_{vib} are expected to be nearly the same for both the reactant and the product.



S°(Table 1.2): 72.1 ± 1 eu 70.9 ± 1 eu

In the case of Diels–Alder reaction that condenses a diene with an alkene (dienophile) into a cyclohexene derivative (Section 5.3.8), a negative entropy of reaction is expected. In the case of prototype reaction, involving conversion butadiene with ethylene into cyclohexene, experimental standard entropies (Table 1.A.2) permit to calculate $\Delta_r S° = -44.8 \pm 3$ eu for this reaction. If one considers only the contributions from the translation degrees of freedom (Z_{trans}), Eq. (1.31) gives $\Delta_r S°_{trans} = -34.67$ eu. This confirms that Z_{rot} and Z_{vib} contributions to the entropy (c. −10 eu) of this condensation are less important than the Z_{trans} contribution (c. −35 eu).

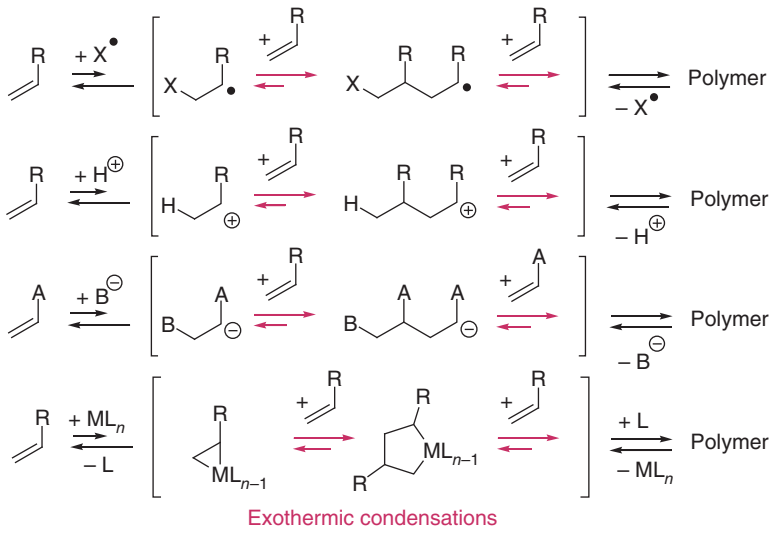


S°(Table 1.2): 66.6 ± 1 eu 52.5 ± 1 eu 74.3 ± 1 eu

1.4.5 Additions are favored thermodynamically on cooling, fragmentations on heating

As condensations have negative $\Delta_r S^T$ values, the $-T\Delta_r S^T$ term in Eq. (1.15) ($\Delta_r G^T = \Delta_r H^T - T\Delta_r S^T$) is positive. For exergonic reactions ($\Delta_r G^T < 0$, $K > 1$), their $\Delta_r H^T$ must be smaller than $T\Delta_r S^T$. Exothermicity is "the glue" that permits the reactants to remain attached in the product, as long as the temperature in not too high. On lowering the reaction temperature, additions have higher equilibrium constants, K, because the $-T\Delta_r S^T$ term becomes less positive. Fragmentations feature a positive $\Delta_r S^T$, yielding a negative $-T\Delta_r S^T$ term favored thermodynamically on heating, and for reactions in the gas phase, on lowering the pressure (Le Châtelier's principle, for examples of reactions of preparative interest, see Section 2.11).

Most addition reactions are exothermic ($\Delta_r H^T < 0$); thus, care must be taken when running them in the laboratory or in a factory. Reactants should never be mixed at once because of the risk of explosion. The danger is real if the heat generated by the reaction cannot be extracted efficiently. Safe practice is to add slowly one of the reactants into the stirred mixture of the other reactants + catalyst (if any). The addition must be stopped if the temperature increases. A simple way to avoid overheating is to carry out the reaction in a boiling solvent under reflux, adapting the addition rate of the reactant with the rate of boiling. Unsaturated compounds such as alkenes, alkynes, dienes, etc., can undergo polymerizations under storage. Reactions involving transformation of a π(C=C) bond into a σ(C—C) bond are typically exothermic by −20 to −24 kcal mol^{-1} (see reaction (1.48)). Polymerization of unsaturated compounds is induced by initiators such as oxy and peroxy radicals resulting from exposure to air (Section 6.9.1). In order to avoid "accidental" polymerization (that



Scheme 1.1 Possible mechanisms for the polymerization of alkenes.

can lead to sudden explosion), one "stabilizes" the unsaturated compounds by radical scavenging agents or one keeps them below room temperature under inert atmosphere (vacuum, Ar, and N_2). Polymerization (Scheme 1.1) can also be induced by protic or Lewis acids, by bases, or by metallic complexes (Section 7.7) or by thermal self-initiation via the formation of 1,4-diradical ↔ zwitterion intermediates (Section 5.5). Storage and shipping of unsaturated compounds such as acetylene (HC≡CH), propyne ($CH_3C{\equiv}CH$), butadiene ($CH_2{=}CH{-}CH{=}CH_2$), styrene ($PhCH{=}CH_2$), acrolein ($CH_2{=}CH{-}CHO$), acrylonitrile ($CH_2{=}CH{-}CN$), acrylic esters ($CH_2{=}CH{-}COOR$), methacrylates ($CH_2{=}CMe{-}COOR$), methyl vinyl ketone ($CH_2{=}CH{-}COMe$), etc., all important industrial chemicals, are risky operations. In this textbook, we teach how one can evaluate the heat of any organic reactions and predict their rates under given conditions.

Problem 1.1 A hydrocarbon, RH, can be reversibly isomerized into two isomeric compounds $\mathbf{P_1}$ and $\mathbf{P_2}$ with the same heat of reaction. Both have C_1 symmetry. $\mathbf{P_1}$ is a rigid compound and $\mathbf{P_2}$ is a flexible one adopting several conformations of similar enthalpies. Which product will be preferred at equilibrium?

Problem 1.2 Define the symmetry numbers, σ, of methane, ethane, propane, cyclopropane, cyclobutane, cyclohexanone, ferrocene, bicyclo[2.2.1]hepta-2,5-diene (norbornadiene), 1,4-difluorobenzene, *meso*-tartaric acid, and (*R,R*)-tartaric acid (see Figure 1.24 for structure of the two latter compounds).

Problem 1.3 What is the Gibbs energy of the racemization of an enantiomerically pure α-amino acid at 25 °C?

1.5 Standard heats of formation

The standard heat of formation, $\Delta_f H°$, of a pure compound is the change in enthalpy for the conversion of the elements into the chosen compound in the standard state, i.e. 1 mol, at 298.15 K, under 1 atm. By convention, the standard heats of formation of the pure elements are set equal to zero. Thus, $\Delta_f H°(\text{graphite, solid}) = 0$, $\Delta_f H°(Cl_2, \text{gas}) = 0$, $\Delta_f H°(H_2, \text{gas}) = 0$, $\Delta_f H°(O_2, \text{gas}) = 0$, etc.

The standard heat of formation of H_2O corresponds to the heat of combustion of H_2:

$$H_2(\text{gas}) + \tfrac{1}{2}O_2(\text{gas}) \rightarrow H_2O(\text{liquid}) \qquad (1.39)$$

For this reaction, the standard heat of reaction can be computed from the standard heats of formation:

$$\begin{aligned}\Delta_r H^\circ(1.39) &= \Delta_f H^\circ(H_2O, \text{liquid}) \\ &\quad -\Delta_f H^\circ(H_2) - \tfrac{1}{2}\Delta_f H^\circ(O_2) \\ &= -68.3 \text{ kcal mol}^{-1}\end{aligned}$$

Similarly, $\Delta_f H°(CO_2)$ corresponds to the heat of combustion of graphite, $\Delta_c H°(C)$:

$$C(\text{graphite}) + O_2(\text{gas}) \rightarrow CO_2(\text{gas}) \qquad (1.40)$$

$$\begin{aligned}\Delta_r H^\circ(1.40) &= \Delta_f H^\circ(CO_2) - \Delta_f H^\circ(\text{graphite}) \\ &\quad -\Delta_f H^\circ(O_2) \\ &= \Delta_f H^\circ(CO_2) = \Delta_c H^\circ(C) \\ &= -94.05 \text{ kcal mol}^{-1}\end{aligned}$$

At 298.15 K and under 1 atm, water and carbon dioxide are more stable than the elements from which they are composed. By contrast, HI in the gas phase has a positive heat of formation, $\Delta_f H°(HI,$

gas)) = 6.2 kcal mol^{-1}, so this compound is unstable thermodynamically ($\Delta_r G^\circ(1.41) \cong \Delta_r H^\circ(1.41) > 0$ as $\Delta_r S^\circ \sim 0$, two molecules in the reactants and two molecules in the products). This compound does not decompose instantaneously, as the activation barrier ($\Delta^\ddagger G$, see Section 3.3) for its decomposition is relatively high. HI is a metastable compound in the gas phase, whereas in water, HI ionizes to give stable ion pair H_3O^+/I^- that is strongly solvated.

$$H_2(\text{gas}) + I_2(\text{solid}) \rightleftarrows 2HI(\text{gas}) \qquad (1.41)$$

$$2 \cdot \Delta_f H^\circ(\text{HI}) = 12.4 \text{ kcal mol}^{-1} \quad (25^\circ\text{C}, 1 \text{ atm})$$

The heat for reaction (1.41) is 12.4 kcal mol^{-1}, so the heat of formation of HI is half of that, or 6.2 kcal mol^{-1}.

The heats of formation of most organic and organometallic compounds cannot be measured directly by calorimetry, which measures $\Delta_r H^T$, or by measuring the equilibrium constants K of the formation reactions at different temperatures (Van't Hoff plot). It is also very rare that the rate constant for the conversion of the elements into the pure substance of interest, or that of the reverse reaction, the decomposition of the substance into its pure elements, can be measured directly. Instead, thermodynamic cycles (Born–Haber cycles) are used to determine the heats of formation (see Figure 1.4 and Eq. (1.42)) for the determination of the standard heats of formation of the hydrocarbons C_nH_m. The heat of combustion of n moles of graphite to produce n moles of CO_2 plus the heat of combustion of $m/2$ moles of H_2 to produce $m/2$ moles of water can be compared to the heat of combustion of hydrocarbon C_nH_m to give the same amount of CO_2 and H_2O (Figure 1.4).

$$\Delta_f H^\circ(C_nH_m) = n \cdot \Delta_c H^\circ(C) + m/2 \cdot \Delta_c H^\circ(H_2) - \Delta_c H^\circ(C_nH_m) \qquad (1.42)$$

In some cases, reactions other than combustions can be used in Born–Haber cycles. Calorimetry can be applied, for instance, to hydrogenations of unsaturated compounds or to catalyzed isomerizations. A major difficulty encountered in calorimetry is the formation of secondary products (isomers, polymers, and products of fragmentation) in addition to the desired products of a given reaction under investigation. If the reaction is not perfectly clean (when it competes with other reactions), deviations of the measured heats from the quantity of evaluation become large. This problem is less serious when applying the Van't Hoff method, i.e. measuring equilibrium constants at various temperatures. Despite this, very accurate heats of formation are now available for a large number of organic and organometallic compounds. With high-pressure mass spectrometry (MS) and ion cyclotron resonance, the thermochemistry of ionized species as well as of transient neutral species such as radicals, diradicals, and carbenes is now possible (Sections 1.10–1.12). Today, accurate heats of formation for almost any kinds of chemical species of relatively small molecular weight ($M_r < 500$) can be reliably determined. To estimate the standard heat of reaction, $\Delta_r H^\circ$, of a given reaction (1.1) from standard heats of formation, Hess's law (Eq. (1.43)) can be used (reactants **A**, **B**, …; products **P**, **Q**, …):

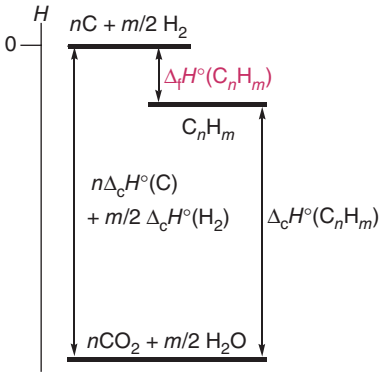


Figure 1.4 A thermodynamic cycle from which the heat of formation of a hydrocarbon can be determined by combustion calorimetry.

$$\Delta_r H^\circ(1.1) = \pi\Delta_f H^\circ(\mathbf{P}) + \theta\Delta_f H^\circ(\mathbf{Q}) + \cdots - \alpha\Delta_f H^\circ(\mathbf{A}) - \beta\Delta_f H^\circ(\mathbf{B}) - \cdots \qquad (1.43)$$

If a value for a given compound is not available from the NIST Webbook of Chemistry or from another source, the Benson's group additivity method proposed in 1958 [16, 17] (Section 2.2) can be used instead to estimate these quantities [18]. Other additivity methods for the calculations of thermochemical parameters have been proposed such as Laidler's bond enthalpy method presented in 1956 [19]. The use of high-level accuracy quantum mechanical methods has also become increasingly important, as well.

1.6 What do standard heats of formation tell us about chemical bonding and ground-state properties of organic compounds?

Table 1.A.1 gives a compilation of the standard heats of formation for a selected number of inorganic compounds in the gas phase under standard conditions. Tables 1.A.2–1.A.4 give standard heats of

formation and standard entropies of selected organic compounds in the gas phase (for more values, see [6, 7, 20–24]). These values can be used for calculating the heats and entropies of reactions or equilibria in ideal solutions. This simplification leads to satisfactory predictions for the thermodynamic parameters of a large number of organic reactions involving nonpolar reagents in nonpolar solvents. Some illustrative examples of the use of these methods are given in the next chapters.

Problem 1.4 What products do you expect to be formed combining HO• with organic compounds? What happens to NO in the air and to SO_2 in the air?

Problem 1.5 Propose a reaction for diimide (diazene: HN=NH) + cyclohexene and calculate its heat of reaction.

1.6.1 Effect of electronegativity on bond strength

The reactions of hydrogen (dihydrogen: H_2) with fluorine (F_2), chlorine (Cl_2), bromine (Br_2), and iodine (I_2) generate the corresponding hydrogen halides HF, HCl, HBr, and HI (called hydrohalic acids when dissolved in water). Although HI has a positive gas-phase standard heat of formation, the other hydrogen halides have negative standard heats of formation in the gas phase (equilibria (1.44)). As already mentioned above, HI in the gas phase is a metastable compound with respect to its decomposition into its elements, whereas HF, HCl, and HBr are stable with respect to their decomposition into their respective elements. On heating in the gas phase, HI will equilibrate with H_2 and I_2, whereas the same type of decomposition will not occur with the other hydrogen halides. The entropies of reaction, $\Delta_r S^T$, are estimated to be small for all of these reactions, as the number of molecules does not change between products and reactants.

$$\tfrac{1}{2}\,H_2 + \tfrac{1}{2}\,X_2 \underset{\text{Gas}}{\rightleftharpoons} HX \qquad (1.44)$$

X =	F	Cl	Br	I
$\Delta_r H°(1.44) = \Delta_f H°(HX)$:	−65.1	−22.1	−8.6	6.2 kcal mol^{-1}

The relatively large variations in the $\Delta_r H°$ (1.44) values are the result of the difference in electronegativity between atoms H and X (Table 1.A.5). HF is more stable than HI because it combines two different atoms with the highest possible (Pauling) electronegativity difference and gives the shortest and strongest bond as a result [25]. Similar observations can be made about the standard heats of formation of the other derivatives of hydrogen of Table 1.A.1. For instance, water is more stable than H_2S, and NH_3 is more stable than PH_3, for the same reasons.

Fluorination, chlorination, and bromination of (1.45) of propane ($CH_3CH_2CH_3$) into the corresponding *n*-propyl halides ($CH_3CH_2CH_2$—X: *n*-Pr—X) are all exothermic. However, direct iodination of propane is endothermic. In fact, the fluorination reaction is an explosive transformation because of the very high exothermicity of −108.4 kcal mol^{-1} (as a comparison, the standard heat of combustion of hydrogen [H_2] amounts to −57.8 kcal mol^{-1} only). These results illustrate the role of electronegativity on bond strength and therefore on the stabilities of organic compounds. In both examples described above, the polarities (electronegativity difference) of the bonds (C—F or H—F) formed in the products are much larger than the polarities of the bonds (F—F or C—H) cleaved in the reactants.

$$Pr{-}H_2 + X_2 \underset{\text{Gas}}{\rightleftharpoons} \textit{n}\text{-}Pr{-}X + HX \qquad (1.45)$$

X =	F	Cl	Br	I
$\Delta_r H°(1.45)$:	−108.4	−28.6	−4.8	21.7 kcal mol^{-1}

Similar observations are made for the direct monohalogenations (1.46) of benzene (C_6H_6 = Ph—H)

$$Ph{-}H + X_2 \underset{\text{Gas}}{\rightleftharpoons} Ph{-}X + HX \qquad (1.46)$$

X =	F	Cl	Br	I
$\Delta_r H°(1.46)$:	−112.5	−29.4	−3.1	26.0 kcal mol^{-1}

The effect of the electronegativity differences between the C—X bonds and the H—X bonds also explains the different standard heats of acid-catalyzed additions (1.47) to propene, giving isopropyl derivatives *i*-Pr—X:

$$\text{Propene} + HX \underset{\text{Gas}}{\rightleftharpoons} \textit{i}\text{-}Pr{-}X \qquad (1.47)$$

X =	F	Cl	Br	I	CN
$\Delta_r H°(1.47)$:	−10.0	−17.4	−20.1	−20.7	−31.8 kcal mol^{-1}

The exothermicity of the additions (1.48) of water, ammonia, and hydrogen sulfide to propene to give isopropanol (propan-2-ol), isopropylamine (2-aminopropane), and isopropylmercaptan (propane-2-thiol), respectively, is the highest for Y = SH and the lowest for Y = OH because the "preference" for hydrogen (more electropositive than carbon) to

be bonded to an oxygen atom (more electronegative) is greater than hydrogen's "preference" to be bonded to sulfur. The exothermicities of hydrocyanation (reaction (1.47), X = CN), of hydrocarbation (reaction (1.48), Y = CH_2—CH_3: hydroethylation; Y = CH=CH_2: hydrovinylation; Y = Ph: hydrophenylation; Y = C≡CH: hydroethynylation; Y = CHO: hydroformylation), and of hydrogenation (Y = H) of alkenes (more precisely, dihydrogenation, as the reaction involves the addition of two hydrogen atoms) are higher than for the heteropolar additions (reaction (1.47), for X = F, Cl, Br, I, and reaction (1.48) for Y = OH, NH_2, SH):

$$\text{Propene} + \text{HY} \underset{}{\overset{\text{Gas}}{\rightleftharpoons}} i\text{-Pr–Y} \qquad (1.48)$$

Y =	OH	NH_2	SH	CH_2CH_3	CH=CH_2
$\Delta_r H°$ (1.48):	−12.2	−13.8	−18.1	−21.5	−23.8

Y =	PH	C≡CH	CHO	H
$\Delta_r H°$ (1.48):	−23.5	−26.7	−28.7	−29.8 kcal mol^{-1}

Under thermodynamic control, substitutions of alkyl halides (1.49) and of alkenyl halides (1.50) by other halides generally favor the formation of HF:

$$\text{Pr–F} + \text{HBr} \underset{}{\overset{\text{Gas}}{\rightleftharpoons}} \text{Pr–Br} + \text{HF} \qquad (1.49)$$

$\Delta_r H°$(1.49): −9.0 kcal mol^{-1}

$$\text{vinyl–F} + \text{HBr} \underset{}{\overset{\text{Gas}}{\rightleftharpoons}} \text{vinyl–Br} + \text{HF} \qquad (1.50)$$

$\Delta_r H°$(1.50): −4.4 kcal mol^{-1}

Problem 1.6 Among the amino acids serine and cysteine, which of these give stable adducts with cyclohex-2-enone at 37 °C when they are part of a protein?

1.6.2 Effects of electronegativity and of hyperconjugation

In contrast with equilibria (1.49) and (1.50) that favor the formation of HF, equilibria (1.51) that exchange the fluoride of acetyl fluoride by chloride, bromide, or iodide with the corresponding hydrogen halide HX disfavor the formation of HF, meaning that fluorine prefers to be bonded to an acyl carbon rather than a hydrogen atom. In contrast, equilibria (1.52) of acetyl chloride with the corresponding bromide and iodide are nearly thermoneutral.

$$\text{AcF} + \text{HX} \underset{}{\overset{\text{Gas}}{\rightleftharpoons}} \text{AcX} + \text{HF} \qquad (1.51)$$

X =	Cl	Br	I
$\Delta_r H°$(1.51):	4.6	4.0	4.0 kcal mol^{-1}

$$\text{AcCl} + \text{HX} \underset{}{\overset{\text{Gas}}{\rightleftharpoons}} \text{AcX} + \text{HCl} \qquad (1.52)$$

X =	Br	I
$\Delta_r H°$(1.52):	−0.6	−0.6 kcal mol^{-1}

Why does fluorine prefer the right side of the equilibrium shown in equilibrium (1.51)? Donation of nonbonding electrons of the oxygen atom of the carbonyl group stabilizes the polar form of the acetyl–halide bond. This hyperconjugation effect (n(C=O:)/σ interaction) involves the interaction of the nonbonding, or lone pair, orbitals n(CO:) of the carbonyl group and the antibonding, empty orbital σ^*(C—F) of the C—F bond (molecular orbital theory, Sections 4.5.15 and 4.8.1). This interaction is not possible in alkyl, alkenyl, and hydrogen halides, which do not possess lone pair electrons. Of all acyl halides, this hyperconjugative interaction is strongest in acyl fluorides where the difference in electronegativity between carbon and fluorine is larger than in other acyl halides. Thus, because of the large electronegativity difference between F and C, σ^*(C—F) is the best sigma acceptor of all C—X bonds. Furthermore, the conjugation n(X:) → π^*(C=O) (donation from the nonbonded electron pairs of X: to the carbonyl double bond), which stabilizes the reactant, is the weakest for X = F and the strongest for amino groups (Figure 1.6). The infrared carbonyl stretching frequencies of acyl derivatives ($\nu_{C=O}$) increase with the C=O bond strength as shown in Figure 1.5.

Quantum mechanical calculations give an indication of the differences between halogen atoms attached to alkyl and acyl groups. Quantum calculations predict a C—F bond length of 1.383 Å for methyl fluoride and a C—Cl bond length of 1.804 Å for methyl chloride [26] (experimentally, these are 1.385 ± 0.004 and 1.66 ± 0.05 Å [27–30], respectively, Å = 10^{-10} m). In the cases of formyl fluoride and formyl chloride, the C—F and C—Cl bond lengths are calculated to be 1.345 and 1.797 Å, respectively [31, 32]. These represent lengthening of the bond lengths of 0.04 and 0.01 Å, respectively. The carbonyl bond length is predicted to be shorter in formyl fluoride (1.186 Å) than in formyl chloride (1.200 Å), consistently with the interpretation given above (Figure 1.5) [33].

Problem 1.7 Explain the difference in C=O bond stretching frequencies between ethyl (*Z*)-3-fluorocinnamate (1736 cm^{-1}) and ethyl cinnamate ((*E*)-PhCH=CHCOOEt: 1715 cm^{-1}) [34].

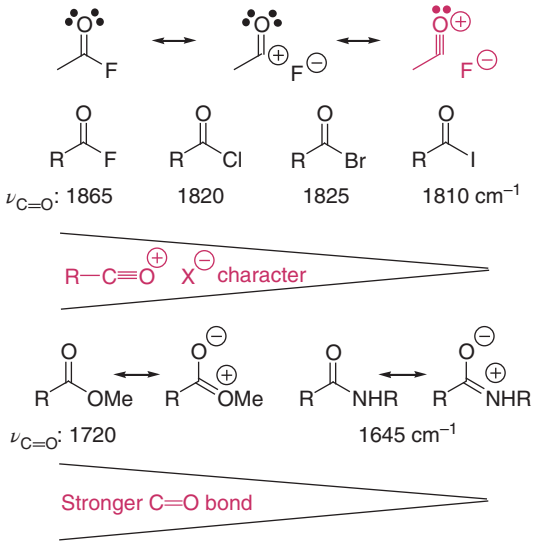


Figure 1.5 Hyperconjugation in acetyl halides (donation from the carbonyl group n(CO:) nonbonded electron-pairs to the σ(C—X) bond) competes with the n(X:)/π(C=O) conjugation. This competition also exists in carboxylic esters and carboxamides.

1.6.3 π-Conjugation and hyperconjugation in carboxylic functions

Esterification equilibrium (1.53) and amidification equilibrium (1.54) are exothermic. In contrast, the formation of ethyl thioacetate from ethanethiol and acetic acid (equilibrium (1.55)) is endothermic by 2.1 kcal mol^{-1}. Anhydride formation (equilibrium (1.56)) is even more endothermic (c. 12 kcal mol^{-1}).

$$\mathrm{AcOH + ROH \overset{Gas}{\rightleftharpoons} AcOR + H_2O} \quad (1.53)$$

R =	Me	*i*-Pr
$\Delta_r H°$(1.53):	−5.0	−5.3 kcal mol^{-1}

$$\mathrm{AcOH + RR'NH \overset{Gas}{\rightleftharpoons} AcNR'R + H_2O} \quad (1.54)$$

RR′NH =	Me_2NH	$PhNH_2$
$\Delta_r H°$(1.54):	−4.4	−6.0 kcal mol^{-1}

$$\mathrm{AcOH + EtSH \overset{Gas}{\rightleftharpoons} AcSEt + H_2O} \quad (1.55)$$

$\Delta_r H°$(1.55): 2.1 kcal mol^{-1}

$$\mathrm{2\ AcOH \overset{Gas}{\rightleftharpoons} Ac_2O + H_2O} \quad (1.56)$$

$\Delta_r H°$(1.56): 12.2 kcal mol^{-1}

These data can be explained by invoking both electronegativity differences between the atom pairs that are exchanged in these reactions and by differential conjugation effects involving the nonbonding electron pair of the nucleophile (O of esters, N of amides, S of thioesters, and O of the carboxylic anhydride) and the carbonyl groups depicted in Figure 1.6. In a classical view, n/π conjugation is proposed to involve some electron transfer from the nucleophilic center Y: to the electrophilic carbonyl group, noted by n(Y:) → π^*(CO) or n(Y:)/π^*(CO) (Section 4.5.15). The charge and geometry analysis by Wiberg and coworkers (Section 2.7.6) show that the carbonyl C=O bond length and oxygen charges are about the same in an aldehyde and an amide, whereas an aldehyde can be represented by resonance structures **A** and **B** and an amide has an additional limiting structure **E**, which represents interactions between donor Y: and the carbonyl group.

The relative importance of resonance structure **E** depends on the ionization energy (IE(Y:) = $\Delta_f H°(Y^{\bullet+}) - \Delta_f H°(Y:)$, Section 1.8) of the nucleophilic center Y: and the overlap of n(Y:) orbitals with the empty 2p orbital at the carbon center (theory of perturbation molecular orbitals, PMO theory, Section 4.4.2). The ionization energy of Y: is another expression of the electronegativity of center Y: (Table 1.A.5). The less Y: is electronegative, the lower its ionization energy, and the easier it can release electrons to the neighboring carbonyl group. In terms of molecular orbital theory (Section 4.5.15), this is expressed by the energy difference between the LUMO (lowest unoccupied molecular orbital) of the carbonyl group and the HOMO (highest occupied molecular orbital) of center Y:. In acetic anhydride (Ac_2O), the Y: center is an oxygen atom stabilized by the acyl group of the carboxylate moiety; the HOMO of AcO moiety is lying lower than that of the alkoxy group in the corresponding ester. The n(alkoxy) → π^*(C=O) interaction is more stabilizing than the n(acyloxy) → π^*(C=O) interaction, rendering esters more stable than the corresponding carboxylic anhydrides, as shown by the standard heats of equilibria (1.53) and (1.56).

Since the electronegativity decreases from oxygen to nitrogen, and then from nitrogen to sulfur (Table 1.A.5), this factor would cause the n(Y:) → π^*(C=O) stabilizing interaction to increase from esters to amides and then from amides to thioesters. The thermochemical data given for equilibria (1.53)–(1.55) are inconsistent with this hypothesis. The increased stabilization of esters and amides (equilibria (1.53) and (1.54)) can be attributed, in part, to the energy necessary to planarize the amine group that maximizes the n(Y:)/π_{CO} overlap. The

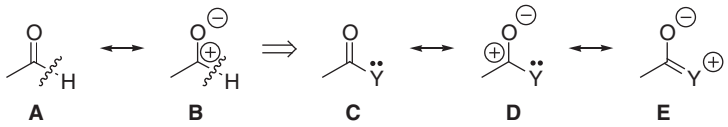
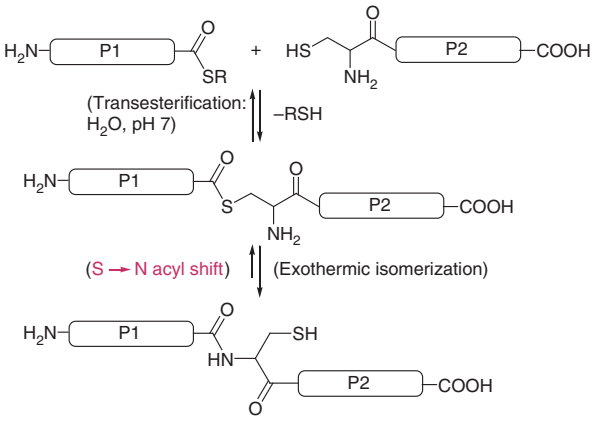


Figure 1.6 Classical limiting structures of aldehydes (**A**, **B**), esters, and amides (**C**, **D**, **E**).



Scheme 1.2 Native chemical ligation: a tool for chemical protein synthesis.

lower stabilization of thioesters compared with esters and amides arises from the poorer overlap and mixing of the high-lying 3p sulfur orbital with the 2p orbital of the vicinal carbon center (see the shape of the 3p(S) orbital and compare it with that of a 2p(O) orbital: the 3p(S) orbital occupies a much larger space than the 2p(O) orbital; as a consequence, the C—S bond is longer than the C—O bond [Table 1.A.6]). The lower stabilities of thioesters compared with amides have been exploited in "native chemical ligations," transformations used, for example, to construct large peptides from two or more unprotected peptides (Scheme 1.2) [35–37].

The relative importance of n(Y:)/π conjugation as a function of the heteroatom will be discussed again in Section 2.7.6 when comparing the heats of hydrogenation of enol ethers, and enamines with the heats of hydrogenation of alkenes, and also in Section 2.7.8 when comparing the stabilizations by the aromaticity of furan, pyrrole (azole), thiophene, and phosphole (for molecular orbital theory applications, see Section 4.6).

Problem 1.8 Estimate the standard heat of esterification of methanol with acetic acid. Estimate the variation of entropy of this reaction at 298.15 K and calculate the equilibrium constant at the same temperature and under 1 atm in tetrahydrofuran (THF) solution. Is the equilibrium constant the same under the same conditions for the esterification of anthracene-2-carboxylic acid with 2-hydroxynaphthacene?

Problem 1.9 The Newman–Kwart rearrangement is a valuable synthetic technique for converting phenols to thiophenols via their *O*- and *S*-thiocarbamates [38–40]. Explain why the *S*-thiocarbamates are more stable than their isomeric *O*-thionocarbamates.

1.6.4 Degree of chain branching and Markovnikov's rule

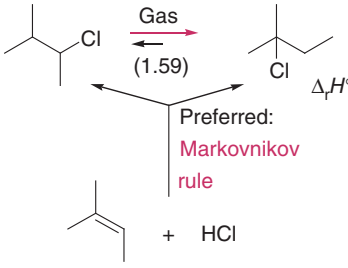
The stability of alkanes increases with the their degree of chain branching [41, 42]. Electron correlation is largely responsible for this observation. Branched alkanes have greater number of attractive 1,3-alkyl/alkyl group interactions; there are three such stabilizing 1,3-"protobranching" dispositions in isobutane (2-methylpropane), but only two in *n*-butane. Neopentane (2,2-dimethylpropane) has six protobranches, but *n*-pentane has only three [43]. In the cases of functional systems such as alcohols, amines, thiols, and alkyl halides, secondary derivatives are more stable than their primary isomers. The same trend is found for the isomerization equilibria (1.58) and (1.59): tertiary systems are more stable than their secondary isomers.

(1.57)

X =	Me	Et	*n*-Pr	OH	SH	NH_2	F	Cl	Br	I
$\Delta_r H°$ (1.57):	−2.0	−1.6	−1.8	−4.2	−4.0	−3.2	−1.8	−3.1	−3.0	−2.4 kcal mol^{-1}

(1.58)

X =	Me	OH	SH	NH_2	Cl	Br	I
$\Delta_r H°$(1.58):	−3.5	−4.8	−3.0	−3.8	−5.0	−5.0	−2.2 kcal mol^{-1}



$\Delta_r H°$(1.59) : −4.1 kcal mol^{-1}

(1.59)

In solution, the additions of hydrogen halides HX (or hydrohalic acids, HX in water) to alkenes give in preference secondary and tertiary alkyl halides instead of the isomeric primary and secondary isomers, respectively. This is Markovnikov's rule, which is often explained in terms of a kinetic control (product selectivity given by the ratio of rate constants of product formation [parallel reactions, Section 3.2.5], no equilibration of products with reactants) rather than in terms of thermodynamic control (the product selectivity is governed by their relative stability) [44–47]. The same rule applies to the additions of water, alcohols, and carboxylic acids to alkenes. The versatility of Markovnikov's rule can be attributed to the large stability difference between primary, secondary, and tertiary carbenium ion intermediates (c. −15 kcal mol^{-1} for acyclic alkyl cations in strongly ionizing media; for the gas phase, Table 1.A.14 gives $\Delta_r H°(n\text{-Pr}^+ \rightarrow i\text{-Pr}^+) = -20$ kcal mol^{-1}, $\Delta_r H°(n\text{-Bu}^+ \rightarrow i\text{-Bu}^+) = -17$ kcal mol^{-1}, and $\Delta_r H°(i\text{-Bu}^+ \rightarrow t\text{-Bu}^+) = -16$ kcal mol^{-1}) [48–50] that are generally considered to be formed in the rate-determining steps of these reactions (protonation of the alkenes). The formulation of Markovnikov's rule as a kinetic effect is not always valid. Additions to alkenes are exothermic but have negative entropies (condensations) that can cause the reactions to be reversible (with $\Delta_r G^T = \pm 1$ kcal mol^{-1}). For example, addition of water to unstrained alkenes are exothermic by c. −12 kcal mol^{-1}. A value very similar to the entropy cost of the addition. For instance, $\Delta_r H°$ (2-methylpropene + $H_2O \rightleftarrows$ *t*-butanol) ≅ −12.6 kcal mol^{-1} and $\Delta_r S°$(2-methylpropene + $H_2O \rightleftarrows$ *t*-butanol) ≅ −37 eu.: at 25 °C, the entropy cost $-T\Delta_r S°$ amounts to −298(−37 cal mol^{-1} K^{-1}) ≅ 11.0 kcal mol^{-1}. Only additions that give rise to highly stable carbenium ion intermediates such as tertiary alkyl cations, cyclopropylmethyl cations, allylic, and benzylic cations proceed via a "cationic mechanism." Additions of HX to 1,2-dialkylethenes, instead, avoid the generation of secondary carbenium intermediates and follow other mechanisms that do not involve carbenium ion intermediates. The reverse reactions, eliminations, may also follow concerted mechanisms avoiding carbenium ion intermediates (Section 3.9.3). Even for such reactions, Markovnikov's rule is generally followed. This is because of the Dimroth principle enounced in 1933 [51]. If one or a set of reactants can undergo two competitive one-step reactions that follow the same mechanism and produce two different isomers, the favored product formed under conditions of kinetic control is the most stable one. The energy barrier is the lowest for the most exothermic reaction (Bell–Evans–Polanyi theory established in 1936–1938 for radical exchange reactions such as $R{-}X + Y^\bullet \rightarrow R^\bullet + X{-}Y$ and proton transfers $\Delta^\ddagger H = \alpha\Delta_r H + \beta$) [52, 53]. In 1928 already, Brønsted had found a linear relationship between the rate of proton transfer of an acid and its acidity constant [54].

Problem 1.10 A mixture of 1 mmol cyclohex-2-enone, 1 mmol of thiophenol, and 5 mg of Et_3N is kept at 25 °C in 1 ml of CH_2Cl_2. After 30 minutes at 25 °C, the ^{1}H-NMR spectra of the reaction mixture shows that the corresponding 1,4-adduct is formed almost completely. Attempted purification of the adduct by column chromatography on silica gel gives, however, only a low yield of adduct (10–20%) and recovered cyclohex-2-enone (80%) and thiophenol (80%). Why?

1.7 Standard heats of typical organic reactions

Alkanes are reference compounds (basis set) for organic chemists (Chapter 2). Their didehydrogenation (elimination of H_2) generates alkenes, and their tetradehydrogenation produces alkynes, allenes, 1,3-dienes or *n*,*n*+2-dienes (if the two double bonds of 1,3-dienes are coplanar, they are said conjugated dienes), 1,4-dienes or *n*,*n*+3-dienes (are often said homoconjugated dienes), and *n*,*n*+*ω*-dienes (*ω* > 3, are usually said nonconjugated dienes). Hydrogenation (addition of H_2) converts unsaturated hydrocarbons into alkanes. Formally, cycloalkanes can be hydrogenated into ring-opened alkanes (Section 1.7.1). These reactions are reference reactions and the corresponding standard heats of hydrogenation ($\Delta_h H°$) are part of a thermochemical basis set. The same can be said for compounds containing heteroatoms. For instance, the hydrogenation of aldehydes and ketones convert them into alcohols that are related to alkanes through C—H oxidations (Section 1.7.2). Thus, the standard heats of these reactions have become reference thermochemical data.

1.7.1 Standard heats of hydrogenation and hydrocarbation

The standard heats of hydrogenation (addition of H—H across a double bond), $\Delta_h H°$, of ethylene, acyclic terminal alkenes, and unstrained (*E*)-1,2-dialkylalkenes are about −32, −30, and −28 kcal mol^{-1} (Table 1.A.2), respectively, consistently with c. 2 kcal mol^{-1} stabilization of an alkene by each alkyl substituent. The standard heats of hydrogenation of acetylene, terminal alkynes, and dialkylethynes to give the corresponding alkenes amount to about −42, −40, and −37 kcal mol^{-1}, respectively. They indicate that alkyl substitution of alkenes increases relative stabilities of these