3

Structural Effects on Stability and Reactivity

Introduction

The concepts of *stability* and *reactivity* are fundamental to understanding chemistry. In this chapter we consider first the *thermodynamic* definition of chemical stability. We then consider *chemical kinetics* (Section 3.2) and how it can provide information about reactivity. We also explore how structure influences stability and reactivity. We want to learn how to make predictions about reactivity based on the structure of the reactants and intermediates. We begin by reviewing the principles of thermodynamics and kinetics, which provide the basis for understanding the relationship of structure to stability and reactivity.

Reactions are usefully described in terms of potential energy diagrams such as shown in Figure 3.1, which identify the potential energy changes associated with the reacting molecules as they proceed to products. The diagram plots the free energy of the system as a function of the progress of the reaction. For each individual step in the reaction there is a *transition state* representing the highest energy arrangement of the molecules for that step. The successive *intermediates* are the molecules that are formed and then react further in the course of the overall reaction. The energies of the transition states relative to the reactants determine the rate of reaction. The energy difference between the reactants and products is ΔG, the free-energy change associated with the reaction. The free energy of a chemical reaction is defined by the equation

$$\Delta G = \Delta H - T\Delta S \qquad (3.1)$$

where ΔH is the *enthalpy change* and ΔS is the *entropy change* for the reaction. The enthalpy term is a measure of the stability of the molecule and is determined by the strength of the chemical bonds in the structure. The entropy term specifies the change
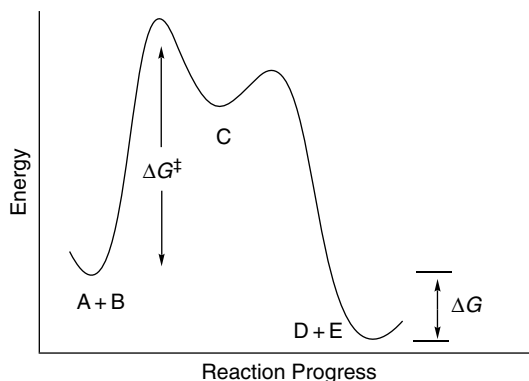
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Fig. 3.1. Reaction potential energy profile showing transition
states and intermediate for a reaction $A + B \rightarrow C \rightarrow D + E$.

in the order (probability) associated with the reaction. The *free energy* of the reaction,
ΔG, determines the position of the equilibrium for the reaction:

$$\Delta G = -RT \ln K \tag{3.2}$$

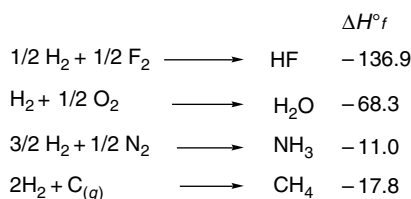where K is the equilibrium constant for the reaction:

$$K = \frac{[D][E]}{[A][B]}$$

The energy required to proceed from reactants to products is $\Delta G^{\ddagger}$, *the free energy
of activation*, which is the energy at the transition state relative to the reactants. We
develop the theoretical foundation for these ideas about reaction rates in Section 3.2.
We first focus attention on the methods for evaluating the inherent thermodynamic
stability of representative molecules. In Section 3.3, we consider general concepts
that interrelate the thermodynamic and kinetic aspects of reactivity. In Section 3.4,
we consider how substituents affect the stability of important intermediates, such as
carbocations, carbanions, radicals, and carbonyl addition (tetrahedral) intermediates.
In Section 3.5, we examine quantitative treatments of substituent effects. In the final
sections of the chapter we consider catalysis and the effect of the solvent medium on
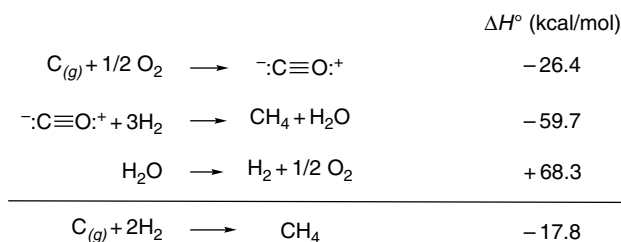reaction rates and mechanisms.

3.1. Thermodynamic Stability

Thermodynamic data provide an unambiguous measure of the stability of a
particular compound under specified conditions. The thermodynamic measure of
molecular stability is ΔH_f°, the *standard enthalpy of formation*, which gives the
enthalpy of the compound relative to the reference state of its constituent elements
under standard conditions of 1 atm and 298 K. For each element a particular form
is assigned an enthalpy (potential energy content) of 0. For example, for hydrogen,
nitrogen, oxygen, and fluorine, the gaseous diatomic molecules are the reference states.
For carbon, 0 energy is assigned to graphite ($C_{(g)}$), which consists entirely of sp^2

carbon atoms. The ΔH_f° of compounds can be measured directly or indirectly. The ΔH_f° in kcal/mol of HF, H_2O, NH_3, and CH_4 are found to be as follows:

			$\Delta H^\circ f$
$1/2\ H_2 + 1/2\ F_2$	$\longrightarrow$	HF	-136.9
$H_2 + 1/2\ O_2$	$\longrightarrow$	H_2O	-68.3
$3/2\ H_2 + 1/2\ N_2$	$\longrightarrow$	NH_3	-11.0
$2H_2 + C_{(g)}$	$\longrightarrow$	CH_4	-17.8

The ΔH_f° of a given compound is a physical constant and is independent of the process by which the compound is formed. Therefore, ΔH_f° values are additive and can be calculated precisely for balanced chemical equations if all the necessary data are available. For example, it might be experimentally impossible to measure the ΔH_f° of methane directly by calorimetry, but it can be calculated as the sum of the enthalpy for an equivalent reaction sequence, e.g:

			ΔH° (kcal/mol)
$C_{(g)} + 1/2\ O_2$	$\longrightarrow$	$^-{:}C{\equiv}O{:}^+$	-26.4
$^-{:}C{\equiv}O{:}^+ + 3H_2$	$\longrightarrow$	$CH_4 + H_2O$	-59.7
H_2O	$\longrightarrow$	$H_2 + 1/2\ O_2$	$+68.3$
$C_{(g)} + 2H_2$	$\longrightarrow$	CH_4	-17.8

The ΔH_f° for many compounds has been determined experimentally and the data tabulated.[1] In the sections that follow, we discuss approaches to computing ΔH_f° when the experimental data are not available. It is important to note that direct comparison of the ΔH_f° values for nonisomeric compounds is not meaningful. The ΔH_f° for methane through hydrogen fluoride, for example, gives us no comparative information on stability, because the reference points are the individual elements. Other information is needed to examine relative stability. For example, as is discussed in the next section, it is possible to assign *bond energies* to the bonds in CH_4, NH_3, H_2O, and HF. This is the energy required to break a C$-$H, N$-$H, O$-$H, or H$-$F bond. These numbers do begin to provide some basis for comparison of the properties of nonisomeric compounds, as we now see that the X$-$H bonds become stronger as we go from C to F in the second-row compounds with hydrogen.

Compound	X$-$H bond energy (kcal/mol)
CH_4	105.0
NH_3	108.2
H_2O	119.3
HF	136.4

[1.] J. B. Pedley, R. D. Naylor, and S. P. Kirby, *Thermochemical Data of Organic Compounds*, 2nd Edition, Chapman and Hall, London, 1986; H. Y. Afeefy, J. F. Liebman, and S. E. Stein, in *NIST Chemistry Webbook*, NIST Standard Reference Database Number 69, P. J. Linstrom and W. G. Mallard, eds., 2001 (http://webbook.nist.gov).

3.1.1. Relationship between Structure and Thermodynamic Stability for Hydrocarbons
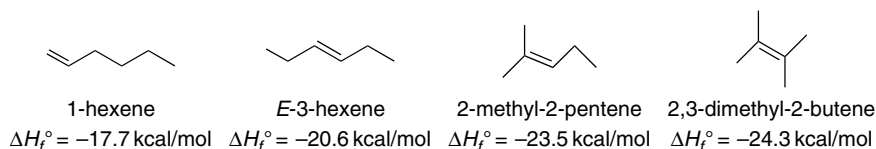
Extensive thermodynamic data are available for the major classes of hydro-carbons. Table 3.1 gives data for the C_4-C_6 and C_8 alkanes and the C_4-C_6 alkenes, and several general relationships become apparent. One is that *chain branching increases the stability of alkanes*. This relationship is clear, for example, in the data for the C_6 alkanes, with a total enthalpy difference of nearly 4 kcal/mol between the straight-chain hexane and the tetra-substituted 2,2-dimethylbutane. There is a similar range of 4.5 kcal/mol between the least stable (octane) and most stable

Table 3.1. Standard Enthalpy of Formation of Some Hydrocarbons (in kcal/mol)[a]

Alkanes (liquid)			
C$_4$		C$_8$	
Butane	−35.0	Octane	−59.8
2-Methylpropane	−36.7	2-Methylheptane	−60.9
		3-Methylheptane	−60.3
C$_5$		4-Methylheptane	−60.1
Pentane	−41.5	2,2-Dimethylhexane	−62.6
2-Methylbutane	−42.7	2,3-Dimethylhexane	−60.4
2,2-Dimethylpropane	−45.5	2,4-Dimethylhexane	−61.4
		2,5-Dimethylhexane	−62.2
C$_6$		3,4-Dimethylhexane	−60.2
Hexane	−47.5	3,3-Dimethyhexane	−61.5
2-Methylpentane	−48.9	2,2,3-Trimethylpentane	−61.4
3-Methylpentane	−48.4	2,2,4-Trimethylpentane	−62.0
2,3-Dimethylbutane	−49.6	2,3,4-Trimethylpentane	−60.9
2,2-Dimethylbutane	−51.1	2,3,3-Trimethylpentane	−60.6
		3-Ethyl-2-methylpentane	−59.7
		3-Ethyl-3-methylpentane	−60.4
		2,2,3,3-Tetramethylbutane	−64.3
B. Alkenes (liquid)			
C$_4$		C$_6$	
1-Butene	−4.90	1-Hexene	−17.7
E-2-Butene	−7.89	*E*-2-Hexene	−20.4
Z-2-Butene	−7.10	*Z*-2-Hexene	−20.1
2-Methylpropene	−8.96	*E*-3-Hexene	−20.6
		Z-3-Hexene	−18.9
C$_5$		2-Methyl-1-pentene	−21.5
1-Pentene	−11.2	3-Methyl-1-pentene	−18.7
E-2-Pentene	−13.9	4-Methyl-1-pentene	−19.1
Z-2-Pentene	−12.8	2-Methyl-2-pentene	−23.5
2-Methyl-1-butene	−12.3	3-Methyl-2-pentene	−22.6
3-Methyl-1-butene	−16.4	*E*-3-Methyl-2-pentene	−22.6
		Z-3-Methyl-2-pentene	−22.6
		E-4-Methyl-2-pentene	−21.9
		Z-4-Methyl-2-pentene	−20.8
		2,3-Dimethyl-1-butene	−22.3
		3,3-Dimethyl-1-butene	−20.9
		2-Ethyl-1-butene	−20.8
		3,3-Dimethyl-1-butene	−20.9
		2,3-Dimethyl-2-butene	−24.3

a. From *Thermochemical Data of Organic Compounds*, 2nd Edition, J. B. Pedley, R. O. Naylor, and S. P. Kirby, Chapman and Hall, London, 1986.

(2,2,3,3-tetramethylbutane) of the C_8 isomers. For alkenes, substitution on the double bond is stabilizing. There is a range of nearly 7 kcal/mol for the C_6H_{12} isomers. The data for C_6 alkenes, for example show:

1-hexene	*E*-3-hexene	2-methyl-2-pentene	2,3-dimethyl-2-butene
$\Delta H_f^\circ = -17.7$ kcal/mol	$\Delta H_f^\circ = -20.6$ kcal/mol	$\Delta H_f^\circ = -23.5$ kcal/mol	$\Delta H_f^\circ = -24.3$ kcal/mol

These relationships are a result of the stabilizing effect of branching and double-bond substitution and hold quite generally, except when branching or substitution results in van der Waals repulsions (see Section 2.3), which have a destabilizing effect.

3.1.2. Calculation of Enthalpy of Formation and Enthalpy of Reaction

In Chapter 1, we introduced various concepts of structure and the idea that the properties of molecules are derived from the combination of the properties of the atoms. One of the qualitative conclusions from these considerations is that the properties of CH_3, CH_2, CH, and C groups in hydrocarbons are expected to be similar from molecule to molecule, as long as they are not perturbed by a nearby functional group. Several methods for the calculation of thermodynamic data based on summation of group properties have been developed and are discussed in the next two sections.

3.1.2.1. Calculations of Enthalpy of Reaction Based on Summation of Bond Energies. The computation of molecular energy by MO or DFT methods gives the *total binding energy* of a molecule. This is a very large number, since it includes all the electron-nuclei forces in the atoms, not just the additional attractive forces of the bonding electrons. The total energy can be converted to an energy representing all bonding between atoms by subtracting the energy of the individual atoms. This difference in energy is called the *energy of atomization*. This quantity still represents an energy that is far larger then the change involved in chemical reactions, which is of primary interest to chemists. The focus of chemical reactivity is on the bonds that are being formed and broken in the reaction. Useful relationships between structure and reactivity can be developed by focusing on *bond dissociation energies* (BDE). The most completely developed information pertains to *homolytic bond dissociation*,[2] which is the energy required to break a specific bond in a molecule with one electron going to each of the atoms. From the general bond energies in Part A of Table 3.2 we can discern several trends. One is that C−C bonds are considerably stronger than the other homonuclear bonds for the second-row elements (compare with O−O and N−N bonds). We can also note that the bonds in the dihalogens are relatively weak, with a somewhat irregular trend with respect to position in the periodic table: $F_2 < Cl_2 > Br_2 > I_2$. The bonds to hydrogen are also slightly irregular: $N < C < O < F$. For the hydrogen halides, there is a sharp drop going down the periodic table.

It is known that the immediate molecular environment significantly affects the bond energy, as is illustrated by the data in Part B of Table 3.2. For hydrocarbons the C−H bond dissociation energy depends on the degree of substitution and hybridization

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[2.] For a discussion of the measurement and application of bond dissociation energies, sec S. J. Blanksby and G. B. Ellison, *Acc. Chem. Res.*, **36**, 255 (2003).

Table 3.2. Bond Energies (in kcal/mol)

A. Some Generalized Bond Energies[a]					
C–C	81	C–H	98	C=C	145
N–N	65	N–H	92	C≡C	198
O–O	34	O–H	105	N≡N	225
F–F	38	F–H	136	C=O	173
Cl–Cl	57	Cl–H	102	C–O	79
Br–Br	45	Br–H	87	C–N	66
I–I	36	I–H	71		

B. Some Specific Bond Dissociation Energies[b]					
CH_3-H	105.0	H_3C-CH_3	90.2	H_3C-F	110.0
CH_3CH_2-H	100.5	$H_5C_2-CH_3$	88.5	H_3C-Cl	83.7
$(CH_3)_2CH-H$	98.1	$(CH_3)_2CH-CH_3$	88.2	H_3C-Br	70.3
$(CH_3)_3C-H$	95.7	$H_5C_2-C_2H_5$	86.8	H_3C-I	57.1
$H_2C=CH-H$	111.2	$(CH_3)_2CH-CH(CH_3)_2$	84.1	CH_3CH_2-F	113.1
$HC\equiv C-H$	132.8	$H_2C=CHCH_2-CH_3$	75.9	CH_3CH_2-Cl	84.2
$H_2C=CHCH_2-H$	88.2	$H_2C=CH-CH=CH_2$	116.9	CH_3CH_2-Br	70.0
Ph-H	112.9	$H_2C=CH_2$	174.1	CH_3CH_2-I	55.8
$PhCH_2-H$	88.5	$HC\equiv CH$	229.5	$(CH_3)_2CH-F$	115.4
$HC\equiv CHCH_2-H$	88.9	$Ph-CH_3$	102.0	$(CH_3)_2CH-Cl$	84.6
H_2N-H	108.2	$PhCH_2-CH_3$	76.4	$(CH_3)_2CH-Br$	71.5
CH_3NH-H	101.6			$(CH_3)_2CH-I$	56.1
CH_3O-H	104.2			H_3C-OH	92.0

a. From Table 1, G. J. Janz, *Thermodynamic Properties of Organic Compounds*, Academic Press, New York, 1967.
b. Y. R. Luo, *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press, Boca Raton, FL, 2002

of the carbon atom. Primary, secondary, and tertiary sp^3 C–H, sp^2 C–H, and sp C–H bonds have characteristic values that are significantly different from one another. The variation in bond strengths is related to the stability of the resulting radicals. For C–H bonds, for example, the decrease in bond strength methane $> pri > sec > tert$ reflects the increasing stability of the more highly substituted carbon radicals. The extra strength of the C–H bond to sp^2 and sp carbons, as reflected by ethene, ethyne, and benzene, is due in part to the poor stability of ethenyl, ethynyl, and phenyl radicals. The relatively weak primary C–H bonds in propene and methylbenzene reflect conjugative stabilization of the resulting allyl and benzyl radicals (see Section 3.4.3).
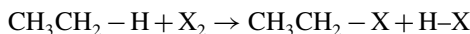
A direct approach to estimation of the ΔH for a reaction is to apply the fundamental thermodynamic relationship,

$$\Delta H = \Delta H_{f\ \text{reactants}}^{\text{o}} - \Delta H_{f\ \text{products}}^{\text{o}} \tag{3.3}$$

This equation is exact, but can be applied only if the thermodynamic data pertaining to the actual reaction conditions are available. Thermodynamic manipulations can be used to account for changes in temperature or pressure, but solvation energies are often uncertain (see Section 3.8). The relationship in Equation (3.3) can be approximated by

$$\Delta H = \text{BDE}_{\text{bonds formed}} - \text{BDE}_{\text{bonds broken}} \tag{3.4}$$

For example, data from Table 3.2 can be used to calculate the ΔH for reaction of each of the halogens with ethane. The strong trend in exothermicity of $F_2 > Cl_2 > Br_2 > I_2$ is evident:

$$CH_3CH_2 - H + X_2 \rightarrow CH_3CH_2 - X + H-X$$

X	Break		Form		
	CH_3CH_2-H	X_2	CH_3CH_2-X	H−X	ΔH
F	100.5	38	113.1	109	−83.6
Cl	100.5	57	84.2	102	−28.7
Br	100.5	45	70.0	87	−11.5
I	100.5	36	55.8	71	+9.7

While bonds of similar type, e.g., C−C, C−O, C−Cl, are of approximately the same strength, the precise value depends on both hybridization and the degree of substitution. For instance, as can be seen in Table 3.2, there is a range from 105.0 to 95.7 kcal/mol for the C−H bonds in methane, ethane, propane (C(2)−H), and isobutane (C(2)−H). The differences between C−H bonds for sp^3, sp^2, and sp carbon is even greater, as can be seen from the significantly different C−H BDE values for ethane, ethene, ethyne, and benzene. Similarly, C−C bonds between sp^2 carbons are considerably stronger than those between two sp^3 carbons, as is indicated by the C(2)−C(3) BDE of 116.9 kcal/mol for 1,3-butadiene. For estimation of reaction enthalpy using Equation (3.4), the most appropriate BDE must be chosen.

3.1.2.2. Relationships between Bond Energies and Electronegativity and Hardness. In his efforts to correlate important chemical properties, Pauling recognized that the difference in electronegativity between two bonded atoms contributes to bond strength. He proposed the empirical relationship

$$BDE_{AB} = 1/2(BDE_{AA} + BDE_{BB}) + 23(\Delta\chi)^2 \tag{3.5}$$

where $\Delta\chi$ is the difference in electronegativity of the two atoms. A related expression is

$$BDE_{AB} = (BDE_{AA} \times BDE_{BB})^{1/2} + 30(\Delta\chi)^2 \tag{3.6}$$

Both relationships propose that BDE is a function of the strength of the two homonuclear bonds and an increment for electronegativity differences.[3] Although the quantitative reliability of the relationships in Equations (3.5) and (3.6) is limited, the equations do indicate that there is an increment to bond strength that is related to electronegativity differences. Subsequently, many investigators have probed the accuracy, scope, and theoretical foundation of these relationships and have suggested other formulations that improve the accuracy.[4] A refinement of the empirical relationship that includes a term for polarizability gives the equation

$$BDE_{AB} = [BDE_{AA} \times BDE_{BB}]^{1/2} + |2.883(\Delta\chi)|^{[\alpha(A)+\alpha(B)]} \tag{3.7}$$

where α are polarizability parameters for each element.[5] The polarizability parameters particularly improve the relationship for third-row atoms and other highly polarizable groups.

3. L. Pauling, *J. Am. Chem. Soc.*, **54**, 3570 (1932); L. Pauling, *The Nature of the Chemical Bond*, 3rd Edition, Cornell University Press, Ithaca, NY, 1960, Chap. 3.
4. R. R. Reddy, T. V. R. Rao, and R. Viswanath, *J. Am. Chem. Soc.*, **111**, 2914 (1989).
5. J. W. Ochterski, G. A. Petersson, and K. B. Wiberg, *J. Am. Chem. Soc.*, **117**, 11299 (1995).

The original Pauling equation was reexamined recently by Zavitsas and co-workers.[6] The equation was shown to give quite good agreement with thermochemical data. Furthermore, it permitted assignment of electronegativity and *stabilization energy* to important radicals. The stabilization energy SE is assigned as

$$SE = 1/2(BDE_{[CH3-CH3]} - BDE_{[X-X]}) \qquad (3.8)$$

Some values are given in Table 3.3. For future reference, note the order of radical stabilization: alkyl > alkenyl > alkynyl and allyl > benzyl > tertiary > secondary > primary. In Section 3.4.3, we discuss the structural basis of these relationships.

Another idea underlying the nature of bond formation is the concept of *electronegativity equalization*[7] or *electronegativity equilibration*[8] (see Section 1.1.4). This concept states that electron density flows from the less electronegative partner in a bond (making it more positive and therefore more electronegative) to the more electronegative atom (making it more negative and therefore less electronegative) until both atoms have the same effective electronegativity. At that point, there is no net attractive force on the electrons in the bond. This intuitively compelling idea has a theoretical foundation in DFT, which states that the chemical potential μ is uniform throughout a molecule. It is observed that the apparent bond strength for several series of compounds increases in the order $CH_3 - X < pri - X < sec - X, tert - X$.[9] The differences *increase* with the electronegativity of the substituent X. These electronegativity relationships lead to some qualitative trends. For alkyl groups with electronegative substituents, such as halogens, oxygen, or nitrogen, the trend is $tert > sec > pri > CH_3$. On the other hand, for organometallics, alanes, and boranes, the order is reversed. Compounds that can readily interconvert can isomerize in response to these stability relationships.[10]

**Table 3.3. Group Electronegativity and Stabilization Energies (in kcal/mol)
Based on the Pauling Equation[a]**

Group	χ	SE	Group	χ	SE
CH_3	2.525	0.0	HO	3.500	
C_2H_5	2.462	1.2	CH_3O	3.439	26.0
$i-C_3H_7$	2.411	1.4	PhO	3.376	43.1
$t-C_4H_9$	2.378	3.7	CH_3NH	3.018	13.5
$CH_2=CHCH_2$	2.488	14.3	$(CH_3)_3Si$	1.838	5.9
$PhCH_2$	2.506	11.7	F	3.938	25.9
Ph		−13.1	Cl	3.174	15.9
$CH_2=CH$		−11.6			
$HC\equiv C$		−32.1			
$CH_3C=O$		7.9			

a. N. Matsunaga, D. W. Rogers, and A. A. Zavitsas, *J. Org. Chem.*, **68**, 3158 (2003).
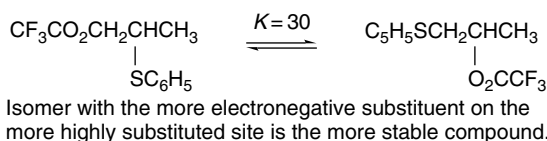
6. N. Matsunaga, D. W. Rogers, and A. A. Zavitsas, *J. Org. Chem.*, **68**, 3158 (2003).
7. S. G. Bratsch, *J. Chem. Educ.*, **61**, 588 (1984); R. T. Sanderson, *Polar Covalence*, Academic Press, New York, 1983.
8. D. W. Smith, *J. Chem. Educ.*, **67**, 559 (1990).
9. Y. R. Luo and S. W. Benson, *J. Phys. Chem.*, **92**, 5255 (1988); Y. R. Luo and S. W. Benson, *Acc. Chem. Res.*, **25**, 375 (1992); N. Laurencelle and P. D. Pacey, *J. Am. Chem. Soc.*, **115**, 625 (1993).
10. J. N. Harvey and H. G. Viehe, *J. Prakt. Chem. Chem. Zeitung*, **337**, 253 (1995).

$$CF_3CO_2CH_2CHCH_3 \quad \xrightleftharpoons{K=30} \quad C_5H_5SCH_2CHCH_3$$

<div align="center">

$CF_3CO_2CH_2CHCH_3$ $\underset{}{\overset{K=30}{\rightleftharpoons}}$ $C_5H_5SCH_2CHCH_3$

|

SC_6H_5 O_2CCF_3

Isomer with the more electronegative substituent on the
more highly substituted site is the more stable compound.

</div>

These treatments of bond energies illustrate that there are fundamental relationships between bond strengths and atomic properties such as electronegativity and polarizability. The crucial point is that bond strength *is increased by electronegativity differences in a given row of the periodic table* as a result of an increment that is due to electrostatic attraction.

3.1.2.3. Calculation of ΔH_f Using Transferable Group Equivalents. The idea that the properties of molecules are the sum of its component atoms and groups has led to the development of schemes by which thermodynamic properties can be calculated as the sum of contributions from all structural units.[11] The most highly developed is that of S. W. Benson and co-workers.[12] The molecule is divided into its component groups. For example, isooctane (which incidentally is the standard for 100 in octane ratings) consists of five $C–(C)(H)_3$ (a), one $C–(C)_2(H)_2$ (b), one $C–(C)_3(H)$ (c), and one $C–(C)_4$ (d), as labeled on the structure.

<div align="center">

$(CH_3)_a$

|

$(CH_3)_a–(C)_d–(CH_2)_b–(CH)_c–(CH_3)_a$

| |

$(CH_3)_a$ $(CH_3)_a$

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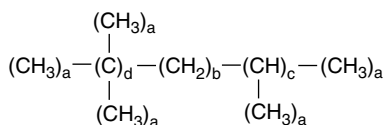
The four groups designated above are sufficient to describe all alkanes. Finer distinctions can be made if these groups are subdivided further, depending on the number of hydrogens on the adjacent carbon. For example, a CH_3 group might be found in four different environments:

<div align="center">

$(CH_3)–CH_3$ $(CH_3)–CH_2CH_3$ $(CH_3)_3–CH$ $(CH_3)_4C$

$n = 3$ $n = 2$ $n = 1$ $n = 0$

</div>
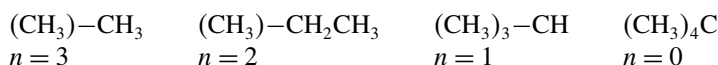
Modified increments are also assigned to carbons adjacent to double or triple bonds or benzene rings. The enthalpy of formation of a molecule can then be calculated as the sum of the contributions of the component groups. The main limitation of this method is that it does not explicitly consider long-range nonbonded interactions. The group equivalents refer to *strain-free molecules*. Further refinement can be incorporated by taking account of nonbonded interactions. For example, *gauche* interactions can be counted and applied as a correction to the sum of group equivalents.[13]

[11] For a discussion of the pioneering efforts in this field, see J. D. Cox and G. Pilcher, *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, New York, 1970, Chap. 7.

[12] N. Cohen and S. W. Benson, *Chem. Rev.*, **93**, 2419 (1993).

[13] N. Cohen and S. W. Benson, *The Chemistry of Alkanes and Cycloalkanes*, S Patai and Z. Rappoport, eds., Wiley, 1992, Chap. 6; S. W. Benson and N. Cohen, in *Computational Thermodynamics*, K. K. Irikura and D. J. Frurip, eds., *ACS Symposium Series*, **677**, 20 (1996).

Example. Calculation of ΔH_f° for Isooctane (2,2,4-trimethylpentane)

5 C-(C)(H$_3$)$_a$	-10.00	-50.00
1 C(C)$_2$(H$_2$)$_b$	-5.00	-5.00
1 C(C)$_3$(H)$_c$	-2.40	-2.40
1 3C(C)$_4$	-0.10	-0.10
3 *gauche* correction	-0.80	$+2.40$
Calculated value		-55.10

Group equivalent methods can be extended to functionalized compounds by assigning the enthalpy components of the substituent groups.[14]

Various other methods for making calculations based on bond dissociation energies more precise have been developed. A method developed by G. Leroy and co-workers is based on extensive thermochemical data, as well as energies calculated by MO methods.[15] The heat of atomization of unstrained hydrocarbons is equated to the number of C−C and primary, secondary and tertiary C−H bonds. The heat of atomization is given by

$$\Delta H_{\text{atom}} = N_{\text{cc}}(E_{\text{cc}}) + N_{\text{pri}}(E_{\text{C}-\text{H}_{\text{pri}}}) + N_{\text{sec}}(E_{\text{C}-\text{H}_{\text{sec}}}) + N_{\text{tert}}(E_{\text{CH}_{\text{tert}}}) \tag{3.9}$$

For stable compounds with known ΔH_{atom} the stabilization (or destabilization) is then the difference between ΔH_{atom} and the calculated sum of standard bond energies:

$$\text{SE} = \Delta H_{\text{atom}} - \Sigma \text{BE}_{\text{standard}} \tag{3.10}$$

Leroy and co-workers developed an extensive series of standard bond energy terms. Terms for specific substituent effects were also assigned, e.g., the $\Delta(C_d-C)$ and $\Delta(C-H)^O$ terms are adjustments for bonds between double bonds and having oxygen substituents, respectively. Comparison of the sum of the standard BE with the actual ΔH_{atom} gives the extra stabilization present in the compound. Calculations for butadiene stabilization (conjugation) and dimethyoxymethane (anomeric effect) are given below.

	Butadiene			Dimethoxymethane	
Bond energies:	2E(C=C)	2(137.23)	Bond energies	4E(C−O)	4(91.66)
	4E(C$_d$−H)$_2$	4(100.30)		2E(C−H)$_s$	2(97.53)
	2E(C$_d$−H)$_1$	2(99.78)		4Δ(C−H)$_s^O$	4(−2.05)
	E(C−C)	85.44		6E(C−H)$_p^O$	6(95.87)
	2Δ(C$_d^c$−C)	2(3.88)			
	$\Sigma N_{\text{AB}} B_{\text{AB}=}$	968.42 kcal/mol^{-1}		$\Sigma N_{\text{AB}} B_{\text{AB}=}$	1128.72 kcal/mol^{-1}
ΔH_{atom}		971.5	ΔH_{atom}		1133.06
	SE	3.08 kcal/mol		SE	4.34 kcal/mol

The enthalpy change of a homolytic bond dissociation is expressed as the difference in stabilization of the products and reactants. A virtue of this approach is

14. J. B. Pedley, R. D. Naylor, and S. P. Kirby, *Thermochemical Data of Organic Compounds*, 2nd Edition, Chapman and Hall, London, 1986, Chap. 2.

15. G. Leroy, M. Sana, and C. Wilante, *J. Mol. Structure: Theochem.*, **234**, 303 (1991).

that it recognizes that there may be special stabilization, e.g., conjugation and anomeric effects, in the reactants as well as in the dissociated radicals.

$$\text{BDE} = \sum_{\text{R–Z}} \cdot \text{BE}_{\text{standard}} - \sum_{\text{R}\cdot} \text{BE}_{\text{standard}} - \sum_{\text{Z}\cdot} \text{BE} + \text{SE}_{\text{R-Z}} - \text{SE}_{\text{R}\cdot} - \text{SE}_{\text{Z}\cdot} \qquad (3.11)$$

Table 3.4 gives some representative results.

According to this analysis, the weakening of the C−H bonds in isobutane and toluene is largely due to the stabilization of the resulting radicals. However, even though trichloromethyl radicals are quite stable, there is also considerable stabilization in the starting material chloroform, and the C−H bond in chloroform is not weakened as much as that in isobutane. More is said about separating structural effects in reactant and intermediate radicals in Topic 11.1.

The calculation of ΔH_f° is now usually done by computational chemistry, but the success of the group equivalent approaches makes an important point. The properties of groups are very similar from molecule to molecule, similar enough to make additivity schemes workable. However, *specific interactions*, e.g., nonbonded interactions, that depend on the detailed structure of the molecule are not accounted for. Whenever interactions that are not accounted for by the group equivalents exist, there will be a discrepancy between the calculated and actual properties of the molecule. Analyses such as that of Leroy can provide valuable insights and concepts. In particular, they provide a means for recognizing stabilization effects present in reactants, as demonstrated by the calculations for 1,3-butadiene and dimethoxymethane.

3.1.2.4. Calculation of Enthalpy of Formation by Molecular Mechanics. Molecular mechanics (MM) is a systematic approach to the calculation of molecular energy based on the summation of bond properties and nonbonding (e.g., van der Waals) interactions (review Section 2.4). MM provides a means for analyzing the energy differences between molecules and among various geometries of a particular molecule.[16] Several systems of parameters and equations for carrying out the calculations have been developed. The method most frequently used in organic chemistry is the one developed by N. L. Allinger and co-workers.[17] In the most recent version of MM calculations

Table 3.4. Calculation of the C−X Bond Dissociation Energies (in kcal/mol; 298.15 K)

R−X	$\Delta\Sigma N_{\text{AB}}E_{\text{AB}}$	$\text{SE}_0(\text{R}-\text{X})$	$\text{SE}_0(\text{R}\cdot)$	BDE(R−X)
Et−H	99.8	0	0	100.3
t-Bu−H	96.8	0.8	3.7	93.9
Et−Cl	83.3	0	−0.5	83.8
t-Bu−Cl	85.6	0	3.7	81.9
$C_6H_5CH_2$−H	99.8	−1.0	11.6	87.1
$(t\text{-Bu})_2$CH−H	98.2	−6.0	−5.9	98.2
Cl_3C−H	93.9	−16.3	−18.0	95.7

16. F. H. Westheimer, in *Steric Effects in Organic Chemistry*, M. S. Newman, ed., Wiley, New York, 1956, Chap. 12; J. E. Williams, P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.*, **19**, 531 (1968); D. B. Boyd and K. P. Lipkowitz, *J. Chem. Educ.*, **59**, 269 (1982); P. J. Cox, *J. Chem. Ed.*, **59**, 275 (1982); N. L. Allinger, *Adv. Phys. Org. Chem.*, **13**, 1 (1976); E. Osawa and H. Musso, *Top. Stereochem.*, **13,** 117 (1982); U. Burkett and N. L. Allinger, *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washington, DC, 1982.
17. N. L. Allinger, Y. H. Yuh, and J. -H. Li, *J. Am. Chem. Soc.*, **111**, 8551 (1989).

for organic molecules, known as MM4,[18] the computations involve iterations to locate an energy minimum. Precautions must be taken to establish that a true ("global") minimum, as opposed to a local minimum energy, is found. This can be accomplished by using a number of different initial geometries and comparing the structures of the minima that are located. As with the group equivalent approach, MM calculations of ΔH_f° are grounded in experimental measurements of a limited number of molecules that were used to optimize the parameters. The original parameters pertained to hydrocarbons, but as the method has developed, the parameters have been extended to many functional groups. MM calculations specifically take molecular geometry into account, including nonbonded and dipolar interactions. Van der Waals interactions are described in terms of energy functions and parameters that describe the interaction of the approaching atoms. Polar interactions are modeled as electrostatic interactions.

Heats of formation are calculated as a sum of the bond energies and other stabilizing and destabilizing (e.g., strain) increments for the structure. MM4 calculations include terms for contributions of higher-energy conformations.[19] For a set of hydrocarbons ranging from methane and ethane to adamantane and bicyclo[2.2.2]octane, the heats of formation are calculated with a standard deviation of 0.353 kcal/mol. The MM4 system has also been applied to alkenes,[20] aldehydes,[21] and ketones.[22]

3.1.2.5. Thermodynamic Data from MO and DFT Computations. MO and DFT calculations provide another approach to obtaining thermodynamic data. The accuracy with which the various computational methods reproduce molecular energies varies. Of the semiempirical methods only MINDO,[23] MNDO,[24] AM1,[25] and PM3[26] provide reliable estimates of energies and the range of applicability is open to some discussion.[27] Among the ab initio methods the level of accuracy generally increases with larger basis sets and treatment of correlation effects. G1, G2, and G3 computations can achieve a level of accuracy that permits comparison of energy data among related molecules. DFT calculations have also been applied to various compounds.[28] Users of computational thermochemical data must critically assess the reliability of the method being applied in the *particular case* under study.

A large series of compounds, including hydrocarbon derivatives, was studied at the G2 and G2(MP2,SVP) levels and compared with results from the B3LYP method.[29] Another group carried out a similar comparison on a smaller set of molecules.[30]

18. N. L. Allinger, K. Chen, and J. -H. Lii, *J. Comput. Chem.*, **17**, 642 (1996).

19. N. L. Allinger, L. R. Schmitz, I. Motoc, C. Bender, and J. Labanowski, *J. Phys. Org. Chem.*, **3**, 732 (1990); N. L. Allinger, L. R. Schmitz, I. Motoc, C. Bender, and J. Labanowski, *J. Am. Chem. Soc.*, **114**, 2880 (1992).

20. N. Nevins, K. Chen, and N. L. Allinger, *J. Comput. Chem.*, **17**, 695 (1996).

21. C. H. Langley, J. H. Lii, and N. L. Allinger, *J. Comput. Chem.*, **22**, 1396 (2001).

22. C. H. Langley, J. H. Lii, and N. L. Allinger, *J. Comput. Chem.*, **22**, 1426, 1451, 1476 (2001).

23. R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, **97**, 1294 (1975).

24. M. J. S. Dewar and G. P. Ford, *J. Am. Chem. Soc.*, **101**, 5558 (1979).

25. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).

26. J. J. P. Stewart, *J. Comput. Chem.*, **10**, 221 (1989).

27. J. A. Pople, *J. Am. Chem. Soc.*, **97**, 5307 (1975); T. A. Halgren, D. A. Kleier, J. H. Hall, Jr., L. D. Brown, and W. L. Lipscomb, *J. Am Chem. Soc.*, **100**, 6595 (1978); M. J. S. Dewar and D. M. Storch, *J. Am. Chem. Soc.*, **107**, 3898 (1985).

28. K. Raghavachari, B. B. Stefanov, and L. A. Curtiss, *Molec. Phys.*, **91**, 555 (1997); B. S. Jursic, *Theochem*, **391**, 75 (1997); B. S. Jursic, *Theochem*, **417**, 99 (1997); J. Andzelm, J. Baker, A. Scheiner, and M. Wrinn, *Int. J. Quantum Chem.*, **56**, 733 (1995).

29. L. A. Curtiss, K. Raghavachari, P. C. Redfern, and J. A. Pople, *J. Chem. Phys.*, **106**, 1063 (1997).

30. J.-W. Pan, D. W. Rogers, and F. J. McLafferty, *Theochem.*, **468**, 59 (1999).

Table 3.5 includes the B3LYP/$6-311+$G$(3df,2p)$ results for some small hydrocarbons. MO and DFT calculations pertain to molecules at 0 K without any molecular motion. In order to make comparisons with thermodynamic data at 298 K, corrections for both zero-point energy (ZPE) and the difference in thermal energy must be made. The corrections are normally incorporated into calculations intended for thermochemical comparisons. The corrections are based on calculation of the vibrations and rotations that contribute to ZPE and thermal energy. Table 3.5 gives a comparison of some calculated ΔH_f with experimental values for some simple hydrocarbons. The absolute errors are small for methods such as G2, CBS-Q, and CBS-QB. There are some indications that B3LYP calculations tend to underestimate the stability of hydrocarbons as the size of the molecule increases. For example, using the $6\text{-}311++$G$(3df,2p)$ basis set, the error increased systematically from propane (-1.5 kcal/mol) to hexane (-9.3) and octane (-14.0).[31] Similarly, the effect of successively adding methyl groups to ethane resulted in an error of 21.1 kcal/mol for 2,2,3,3-tetramethylbutane.[32]

MO methods can also be used to calculate *heats of reaction* by comparing the heats of formation of reactants and products. The *total energy* calculated for even a small hydrocarbon, relative to the separate nuclei and electrons, is enormous (typically 50,000 and 100,000 kcal/mol for C_2 and C_4 compounds, respectively) relative to the energy of reaction. Sometimes the energy is tabulated as the *energy of atomization*, corresponding to the difference in total energy of the molecule and that of the separate atom, which is the energy required to break all the bonds. These values, too, are very large in comparison with the heat of reaction. The energy differences that are of principal chemical interest, such as ΔH for a reaction, are likely to be in the range of 0–30 kcal/mol. A very small error relative to the total energy in an MO calculation becomes a very large error in a calculated ΔH. Fortunately, the absolute errors for compounds of similar structure are likely to be comparable and tend to cancel in calculation of the *energy differences* between related molecules. Calculation of heats of formation and heats of reaction is frequently done on the basis of *isodesmic reactions*,[33] in order to provide for maximum cancellation of errors in total binding energies. An isodesmic reaction is defined as a process in which the number of formal bonds of each type is kept constant; that is, there are the same number of C$-$H, C$=$C, C$=$O, etc., bonds on each side of the equation.[34] For example, an isodesmic reaction to evaluate the stability of benzene would be:

$$3\,H_2C{=}CH_2 + 3\,H_3C{-}CH_3 \longrightarrow \bigcirc\!\!\!\!\!\!\bigcirc + 6\,CH_4$$

3 C$=$C	3 C$=$C
3 C$-$C	3 C$-$C
30 C$-$H	30 C$-$H
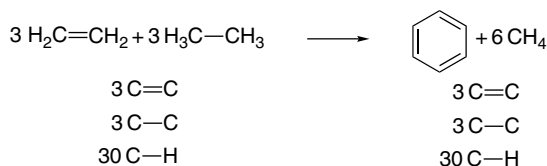
The comparison can be further refined by use of *homodesmotic reactions* in which there is matching not only of bond types, but also of hybridization. Thus in the reaction

[31.] L. A. Curtiss, K. Raghavachari, P. C. Redfern, and J. A. Pople, *J. Chem. Phys.*, **112**, 7374 (2000).

[32.] C. E. Check and T. M. Gilbert, *J. Org. Chem.*, **70**, 9828 (2005).

[33.] W. J. Hehre, R. Ditchfield, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **92**, 4796 (1970).

[34.] D. A. Ponomarev and V. V. Takhistov, *J. Chem. Ed.*, **74**, 201 (1997).