

From Atkins and Paula, Physical Chemistry Chapter 18, Molecular Interactions

(Material in sec.18.4 is the most important section; this is how macromolecules and aggregates stay together, and why things are sticky!)

18.1 Electric dipole moments

Polar molecules
Polarization

18.2 Polarizabilities (omitted--used in a couple of sections of 18.4; don't worry about it)

18.3 Relative permittivities (just skim--18.3 is only important to see how electrostatic interactions are "muted" in water or other substances.)

18.4. Interactions between dipoles (8 parts)

Follow the math on the subsections with stars only if you think you have the background--it might be rewarding for future use; read the rest in detail.

***a. The potential energy of interaction, p.13**

***b. The electric field, p.18**

***c. Dipole-dipole interactions (Keesom interaction, p. 19)**

d. Dipole-induced-dipole interactions (p.24)

e. Induced-dipole-induced-dipole interactions (dispersion or London forces, p.26) [I may give you longer derivation and discussion of this.]

f. Hydrogen bonding [p.28. I definitely will give you a separate reading oriented toward biological macromolecules and water.]

g. Hydrophobic interaction [p.30. Important for lipid bilayer structure of cell membrane as well as many properties of proteins (e.g. notice which amino acids are hydrophobic, hydrophilic), etc.]

h. Total attractive interactions (p.31)

18.5. Repulsive and total interactions (p.31)

Molecular recognition and drug design (I 18.1, p.35)

Questions and exercises (p.39).

Molecular interactions

18

Molecular interactions are responsible for the unique properties of substances as simple as water and as complex as [polymers](#). We begin our examination of molecular interactions by describing the electric properties of molecules, which may be interpreted in terms of concepts in electronic structure. We shall see that small imbalances of charge distributions in molecules allow them to interact with one another and with externally applied fields. One result of this interaction is the cohesion of molecules to form the bulk [phases](#) of matter. These ***noncovalent molecular interactions*** are also important for understanding the shapes adopted by biological and synthetic [macromolecules](#), as we shall see in [Chapter 19](#). (I will distribute an edited version of that chapter, applying (easy) equilibrium statistical mechanics to biological polymers, separately).

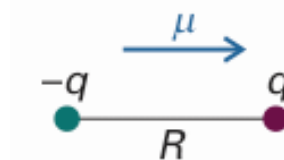
Electric properties of molecules

Many of the electric properties of molecules can be traced to the competing influences of nuclei with different charges or the competition between the control exercised by a nucleus and the influence of an externally applied field. The former competition may result in an electric dipole moment. The latter may result in properties such as refractive index and optical [activity](#). [We don't care about the latter, only that you can induce a dipole moment, for the calculation of London forces.]

18.1 Electric dipole moments

An **electric dipole** consists of two electric charges $+q$ and $-q$ separated by a distance R .

This arrangement of charges is represented by a vector \mathbf{m} (**1**). The magnitude of \mathbf{m} is $\mu = qR$ and, although the SI unit of dipole moment is coulomb metre (C m), it is still commonly reported in the non-SI unit debye, D, named after Peter Debye, a pioneer in the study of dipole moments of molecules, where



1 Electric dipole

$$1 \text{ D} = 3.335\,64 \times 10^{-30} \text{ C m} \quad (18.1)$$

The dipole moment of a pair of charges $+e$ and $-e$ separated by 100 pm is $1.6 \times 10^{-29} \text{ C m}$, corresponding to 4.8 D. Dipole moments of small molecules are typically about 1 D. The conversion factor in **eqn 18.1** stems from the original definition of the debye in terms of c.g.s. units: 1 D is the dipole moment of two equal and opposite charges of magnitude 1 e.s.u. separated by 1 Å.

(a) Polar molecules

Synoptic table 18.1* Dipole moments (μ) and polarizability volumes (α')

	μ/D	$\alpha'/(10^{-30} \text{ m}^3)$
CCl_4	0	10.5
H_2	0	0.819
H_2O	1.85	1.48
HCl	1.08	2.63
HI	0.42	5.45

* More values are given in the *Data section*.

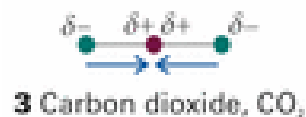
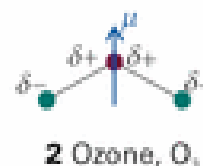
A **polar molecule** is a molecule with a permanent electric dipole moment. The permanent dipole moment stems from the partial charges on the atoms in the molecule that arise from differences in **electronegativity** or other features of bonding (**Section 11-6**). Nonpolar molecules acquire an induced dipole moment in an electric field on account of the distortion the field causes in their electronic distributions and nuclear positions; however, this induced moment is only temporary, and disappears as soon as the perturbing field is removed.

Polar molecules also have their existing dipole moments temporarily modified by an applied field.

In elementary chemistry, an electric dipole moment is represented by the arrow added to the Lewis structure for the molecule, with the + marking the

positive end. Note that the direction of the arrow is opposite to that of μ .

The Stark effect ([Section 13-5](#)) is used to measure the electric dipole moments of molecules for which a rotational spectrum can be observed. In many cases microwave spectroscopy cannot be used because the sample is not volatile, decomposes on vaporization, or consists of molecules that are so complex that their rotational spectra cannot be interpreted. In such cases the dipole moment may be obtained by measurements on a liquid or solid bulk sample using a method explained later. Computational software is now widely available, and typically computes electric dipole moments by assessing the electron density at each point in the molecule and its coordinates relative to the centroid of the molecule; however, it is still important to be able to formulate simple models of the origin of these moments and to understand how they arise. The following paragraphs focus on this aspect.



All heteronuclear diatomic molecules are **polar**, and typical values of μ include 1.08 D for HCl and 0.42 D for HI ([Table 18-1](#)). Molecular symmetry is of the greatest importance in deciding whether a polyatomic molecule is **polar** or not. Indeed, molecular symmetry is more important than the question of whether or not the atoms in the molecule belong to the same element. Homonuclear polyatomic molecules may be **polar** if they have low symmetry and the atoms are in inequivalent positions. For instance, the angular molecule ozone, O_3 (**2**), is homonuclear; however, it is **polar** because the central O atom is different from the outer two (it is bonded to two atoms, they are bonded only to one); moreover, the dipole moments associated with each bond make an angle to each other and do not cancel. Heteronuclear polyatomic molecules may be nonpolar if they have high symmetry, because individual bond dipoles may then cancel. The heteronuclear linear triatomic molecule CO_2 , for example, is nonpolar because, although there are partial charges on all three atoms, the dipole moment associated with the OC bond points in the opposite direction to the dipole moment associated with the CO bond, and the two cancel (**3**).

To a first approximation, it is possible to resolve the dipole moment of a polyatomic molecule into contributions from various groups of atoms in the molecule and the directions in which these individual contributions lie ([Fig. 18.1](#)).

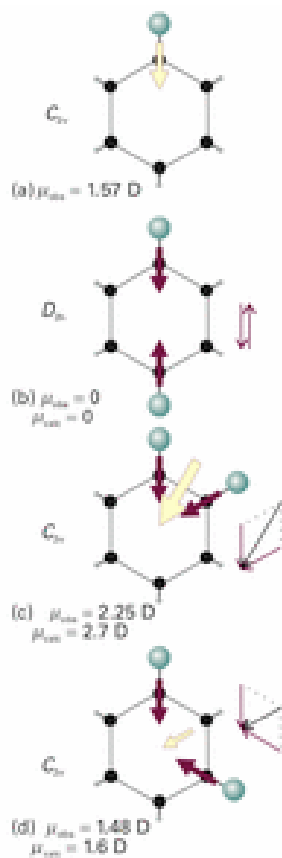
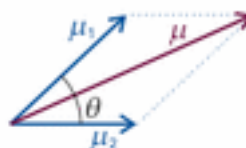


Fig. 18.1 The resultant dipole moments (pale yellow) of the dichlorobenzene isomers (b to d) can be obtained approximately by vectorial addition of two chlorobenzene dipole moments (1.57 D), purple.

Thus, 1,4-dichlorobenzene is nonpolar by symmetry on account of the cancellation of two equal but opposing C—Cl moments (exactly as in carbon dioxide). 1,2-Dichlorobenzene, however, has a dipole moment which is approximately the resultant of two chlorobenzene dipole moments arranged at 60° to each other. This technique of 'vector addition' can be applied with fair success to other series of related molecules, and the resultant μ_{res} of two dipole moments μ_1 and μ_2 that make an angle θ to each other (4)



4 Addition of dipole moments

is approximately

$$\mu_{res} \approx (\mu_1^2 + \mu_2^2 + 2\mu_1\mu_2 \cos \theta)^{1/2} \quad (18.2a)$$

When the two dipole moments have the same magnitude (as in the dichlorobenzenes), this equation simplifies to

$$\mu_{res} \approx 2\mu_1 \cos \frac{1}{2}\theta \quad (18.2b)$$

Self Test 18.1 Estimate the ratio of the electric dipole moments of *ortho* (1,2-) and *meta* (1,3-) disubstituted benzenes.

Correct Answer

$$\mu(\text{ortho})/\mu(\text{meta}) = 1.7$$

A better approach to the calculation of dipole moments is to take into account the locations and magnitudes of the partial charges on all the atoms. These partial charges are included in the output of many molecular structure software packages. To calculate the x-component, for instance, we need to know the partial charge on each atom and the atom's x-coordinate relative to a point in the molecule and form the sum

$$\mu_x = \sum_J q_J x_J \quad (18.3a)$$

Here q_J is the partial charge of atom J , x_J is the x -coordinate of atom J , and the sum is over all the atoms in the molecule. Analogous expressions are used for the y - and z -components. For an electrically neutral molecule, the origin of the coordinates is arbitrary, so it is best chosen to simplify the measurements. In common with all vectors, the magnitude of \mathbf{m} is related to the three components μ_x, μ_y , and μ_z by

$$\mu = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2} \quad (18.3b)$$

Example 18.1 Calculating a molecular dipole moment

Estimate the electric dipole moment of the amide group shown in (5) by using the partial charges (as multiples of e) in **Table 18-2** and the locations of the atoms shown.

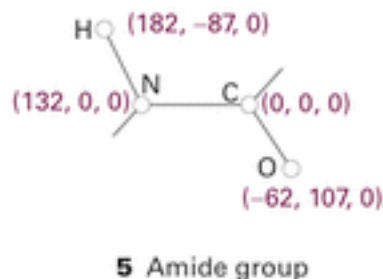


Table 18.2 Partial charges in polypeptides

Atom	Partial charge/ e
C(=O)	+0.45
C(-CO)	+0.06
H(-C)	+0.02
H(-N)	+0.18
H(-O)	+0.42
N	-0.36
O	-0.38

Method We use **eqn 18.3a** to calculate each of the components of the dipole moment and then **eqn 18.3b** to assemble the three components into the magnitude of the dipole moment. Note that the partial charges are multiples of the fundamental charge, $e = 1.609 \times 10^{-19}$ C.

Answer The expression for μ_x is

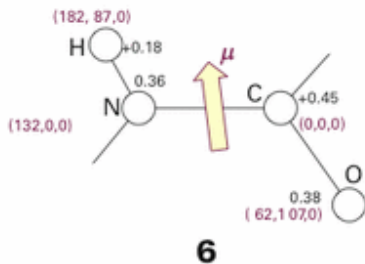
$$\begin{aligned} \mu_x &= (-0.36e) \times (132 \text{ pm}) + (0.45e) \times (0 \text{ pm}) + (0.18e) \times (182 \text{ pm}) \\ &\quad + (-0.38e) \times (-62.0 \text{ pm}) \\ &= 8.8e \text{ pm} \\ &= 8.8 \times (1.609 \times 10^{-19} \text{ C}) \times (10^{-12} \text{ m}) = 1.4 \times 10^{-30} \text{ C m} \end{aligned}$$

corresponding to $\mu_x = 0.42$ D. The expression for μ_y is:

$$\begin{aligned}\mu_y &= (-0.36e) \times (0 \text{ pm}) + (0.45e) \times (0 \text{ pm}) + (0.18e) \times (-86.6 \text{ pm}) \\ &\quad + (-0.38e) \times (107 \text{ pm}) \\ &= -56e \text{ pm} = -9.1 \times 10^{-30} \text{ C m}\end{aligned}$$

It follows that $\mu_y = -2.7$ D. Therefore, because $\mu_z = 0$,

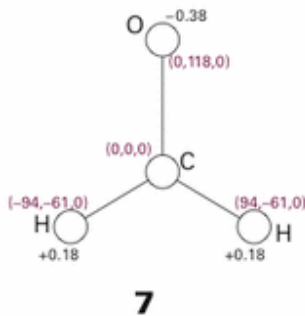
$$\mu = \{(0.42 \text{ D})^2 + (-2.7 \text{ D})^2\}^{1/2} = 2.7 \text{ D}$$



We can find the orientation of the dipole moment by arranging an arrow of length 2.7 units of length to have x, y, and z components of 0.42, -2.7, and 0 units; the orientation is superimposed on (6).

Self Test 18.2 Calculate the electric dipole moment of formaldehyde, using the information in (7).

Correct Answer: - 3.2D.



(b) Polarization

The **polarization**, P , of a sample is the electric dipole moment density, the mean electric dipole moment of the molecules, μ , multiplied by the number density, :

$$P = \langle \mu \rangle \mathcal{N} \quad (18.4)$$

In the following pages we refer to the sample as a **dielectric**, by which is meant a polarizable, nonconducting medium.

The **polarization** of an isotropic fluid sample is zero in the absence of an applied field because the molecules adopt random orientations, so $\mu = 0$. In the presence of a field, the dipoles become partially aligned because some orientations have lower **energies** than others. As a result, the electric dipole moment density is nonzero. We show in the *Justification* below that, at a **temperature** T

$$\langle \mu_z \rangle = \frac{\mu^2 \mathcal{E}}{3kT} \quad (18.5)$$

where z is the direction of the applied field. Moreover, as we shall see, there

is an additional contribution from the dipole moment induced by the field.

Justification 18.1 *The thermally averaged dipole moment*

The probability dp that a dipole has an orientation in the range θ to $\theta + d\theta$ is given by the Boltzmann distribution (**Section 16-1b**), which in this case is

$$dp = \frac{e^{-E(\theta)/kT} \sin \theta d\theta}{\int_0^\pi e^{-E(\theta)/kT} \sin \theta d\theta}$$

where $E(\theta)$ is the energy of the dipole in the field: $E(\theta) = -\mu \cos \theta$, with $0 \leq \theta \leq \pi$. The average value of the component of the dipole moment parallel to the applied electric field is therefore

$$\langle \mu_z \rangle = \int \mu \cos \theta dp = \mu \int \cos \theta dp = \frac{\mu \int_0^\pi e^{x \cos \theta} \cos \theta \sin \theta d\theta}{\int_0^\pi e^{x \cos \theta} \sin \theta d\theta}$$

with $x = \mu/kT$. The integral takes on a simpler appearance when we write $y = \cos \theta$ and note that $dy = -\sin \theta d\theta$.

$$\langle \mu_z \rangle = \frac{\mu \int_{-1}^1 ye^{xy} dy}{\int_{-1}^1 e^{xy} dy}$$

At this point we use

$$\int_{-1}^1 e^{xy} dy = \frac{e^x - e^{-x}}{x} \quad \int_{-1}^1 ye^{xy} dy = \frac{e^x + e^{-x}}{x} - \frac{e^x - e^{-x}}{x^2}$$

It is now straightforward algebra to combine these two results and to obtain

$$\langle \mu_z \rangle = \mu L(x) \quad L(x) = \frac{e^x + e^{-x}}{e^x - e^{-x}} - \frac{1}{x} \quad x = \frac{\mu E}{kT} \quad (18.6)$$

$L(x)$ is called the **Langevin function**.

Under most circumstances, x is very small (for example, if $\mu = 1 \text{ D}$ and $T = 300 \text{ K}$, then x exceeds 0.01 only if the field strength exceeds 100 kV cm^{-1} , and most measurements are done at much lower strengths). When $x \ll 1$, the exponentials in the Langevin function can be expanded, and the largest term that survives is

When x is small, it is possible to simplify expressions by using the expansion $e^x = 1 + x + \frac{1}{2}x^2 + \frac{1}{6}x^3 + \dots$; it is important when developing approximations that all terms of the same order are retained because low-order terms might cancel.

$$L(x) = \frac{1}{3}x + \dots \quad (18.7)$$

Therefore, the average molecular dipole moment is given by **eqn 18.6**.

$$dp = \frac{e^{-E(\theta)/kT} \sin \theta d\theta}{\int_0^\pi e^{-E(\theta)/kT} \sin \theta d\theta}$$

18-3 Relative permittivities

When two charges q_1 and q_2 are separated by a distance r in a vacuum, the potential **energy** of their interaction is (see *Appendix 3*):

$$V = \frac{q_1 q_2}{4\pi\epsilon_0 r} \quad (18.12a)$$

When the same two charges are immersed in a medium (such as air or a liquid), their potential **energy** is reduced to

$$V = \frac{q_1 q_2}{4\pi\epsilon r} \quad (18.12b)$$

where ϵ is the **permittivity** of the medium. The **permittivity** is normally expressed in terms of the dimensionless **relative permittivity**, ϵ_r , (formerly and still widely called the dielectric constant) of the medium:

$$\epsilon_r = \frac{\epsilon}{\epsilon_0} \quad (18.13)$$

The **relative permittivity** can have a very significant effect on the strength of the interactions between ions in solution. For instance, water has a **relative permittivity** of 78 at 25°C, so the interionic Coulombic interaction **energy** is reduced by nearly two orders of magnitude from its vacuum value. Some of the consequences of this reduction for electrolyte solutions were explored in **Chapter 5**.

The **relative permittivity** of a substance is large if its molecules are **polar** or highly polarizable. The quantitative relation between the **relative permittivity** and the electric properties of the molecules is obtained by considering the **polarization** of a medium, and is expressed by the **Debye equation** (for the derivation of this and the following equations, see *Further reading*):

$$\frac{\epsilon_r - 1}{\epsilon_r + 2} = \frac{\rho P_m}{M} \quad (18.14)$$

where ρ is the mass density of the sample, M is the molar mass of the molecules, and P_m is the **molar polarization**, which is defined as

$$P_m = \frac{N_A}{3\epsilon_0} \left(\alpha + \frac{\mu^2}{3kT} \right) \quad (18.15)$$

The term $\mu^2/3kT$ stems from the thermal averaging of the electric dipole moment in the presence of the applied field (**eqn 18.5**). The corresponding

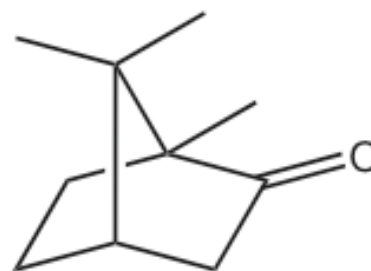
expression without the contribution from the permanent dipole moment is called the **Clausius–Mossotti equation**:

$$\frac{\epsilon_r - 1}{\epsilon_r + 2} = \frac{\rho N_A \alpha}{3M\epsilon_0} \quad (18.16)$$

The Clausius–Mossotti equation is used when there is no contribution from permanent electric dipole moments to the **polarization**, either because the molecules are nonpolar or because the frequency of the applied field is so high that the molecules cannot orientate quickly enough to follow the change in direction of the field.

Example 18.2 *Determining dipole moment and polarizability*

$\theta/^\circ\text{C}$	$\rho/(\text{g cm}^{-3})$	ϵ_r
0	0.99	12.5
20	0.99	11.4
40	0.99	10.8
60	0.99	10.0
80	0.99	9.50
100	0.99	8.90
120	0.97	8.10
140	0.96	7.60
160	0.95	7.11
200	0.91	6.21



8 Camphor

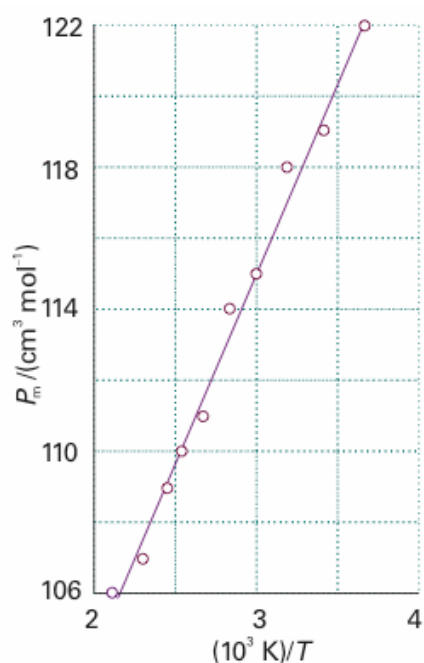
The **relative permittivity** of a substance is measured by comparing the capacitance of a capacitor with and without the sample present (C and C_0 , respectively) and using $\epsilon_r = C/C_0$. The **relative permittivity** of camphor (**8**) was measured at a series of **temperatures** with the results given below. Determine the dipole moment and the **polarizability** volume of the molecule.

Method Equation 18.14 implies that the **polarizability** and permanent electric dipole moment of the molecules in a sample can be determined by measuring ϵ_r at a series of **temperatures**, calculating P_m , and plotting it against $1/T$. The slope of the graph is $N_A \mu^2 / 9 \epsilon_0 k$ and its intercept at $1/T = 0$ is $N_A / 3 \epsilon_0$. We need to calculate $(\epsilon_r - 1) / (\epsilon_r + 2)$ at each **temperature**, and

then multiply by M/ρ to form P_m .

Answer For camphor, $M = 152.23 \text{ g mol}^{-1}$. We can therefore use the data to draw up the following table:

$\theta/^\circ\text{C}$	$(10^3 \text{ K})/T$	ϵ_r	$(\epsilon_r - 1)/(\epsilon_r + 2)$	$P_m/(\text{cm}^3 \text{ mol}^{-1})$
0	3.66	12.5	0.793	122
20	3.41	11.4	0.776	119
40	3.19	10.8	0.766	118
60	3.00	10.0	0.750	115
80	2.83	9.50	0.739	114
100	2.68	8.90	0.725	111
120	2.54	8.10	0.703	110
140	2.42	7.60	0.688	109
160	2.31	7.11	0.670	107
200	2.11	6.21	0.634	106



The points are plotted in **Fig. 18.2**. The intercept lies at 82.7, so $\rho = 3.3 \times 10^{-23} \text{ cm}^3$. The slope is 10.9, so $\mu = 4.46 \times 10^{-30} \text{ C m}$, corresponding to 1.34 D. Because the Debye equation describes molecules that are free to rotate, the data show that camphor, which does not melt until 175°C , is rotating even in the solid. It is an approximately spherical molecule

The Maxwell equations that describe the properties of electromagnetic radiation (see **Further reading**) relate the refractive index at a (visible or ultraviolet) specified wavelength to the relative permittivity at that frequency:

$$n_r = \epsilon_r^{1/2} \quad (18.17)$$

Therefore, the molar polarization, P_m , and the molecular polarizability, ρ , can be measured at frequencies typical of visible light (about 10^{15} to 10^{16} Hz) by measuring the refractive index of the sample and using the Clausius–Mossotti equation.

Interactions between molecules

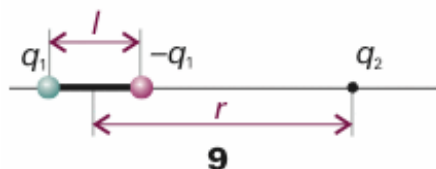
A **van der Waals interaction** is the attractive interaction between closed-shell molecules that depends on the distance between the molecules as $1/r^6$. In addition, there are interactions between ions and the partial charges of **polar molecules** and repulsive interactions that prevent the complete collapse of matter to nuclear densities. The repulsive interactions arise from Coulombic repulsions and, indirectly, from the **Pauli principle** and the exclusion of electrons from regions of space where the orbitals of neighbouring species overlap.

18-4 Interactions between dipoles (eight subsections)

Most of the discussion in this section is based on the Coulombic potential energy of interaction between two charges (**eqn 18.12a**). We can easily adapt this expression to find the potential energy of a point charge and a dipole and to extend it to the interaction between two dipoles.

(a) The potential energy of interaction

We show in the *Justification* below that the potential energy of interaction between a point dipole $\mu_1 = q_1 l$ and the point charge q_2 in the arrangement shown in (9)



is

$$V = -\frac{\mu_1 q_2}{4\pi\epsilon_0 r^2} \quad (18.18)$$

With μ in coulomb metres, q_2 in coulombs, and r in metres, V is obtained in joules. A **point dipole** is a dipole in which the separation between the charges is much smaller than the distance at which the dipole is being observed, $l \ll r$. The potential energy rises towards zero (the value at infinite separation of the charge and the dipole) more rapidly (as $1/r^2$) than that between two point charges (which varies as $1/r$) because, from the viewpoint of the point charge, the partial charges of the dipole seem to

merge and cancel as the distance r increases (**Fig. 18.3**).

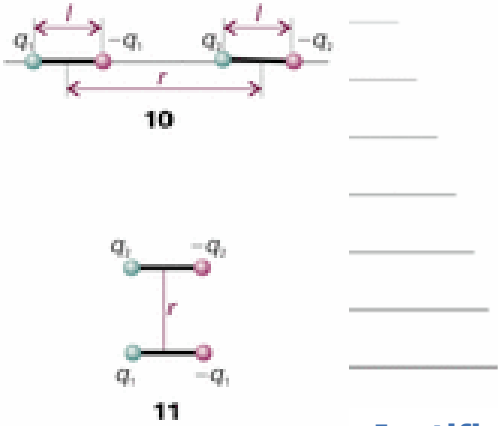


Fig. 18.3 There are two contributions to the diminishing field of an electric dipole with distance (here seen from the side). The potentials of the charges decrease (shown here by a fading intensity) and the two charges appear to merge, so their combined effect approaches zero more rapidly than by the distance effect alone.

Justification 18.4 *The interaction between a point charge and a point dipole*

The sum of the potential energies of repulsion between like charges and attraction between opposite charges in the orientation shown in (9) is

$$V = \frac{1}{4\pi\epsilon_0} \left(-\frac{q_1q_2}{r - \frac{1}{2}l} + \frac{q_1q_2}{r + \frac{1}{2}l} \right) = \frac{q_1q_2}{4\pi\epsilon_0 r} \left(-\frac{1}{1 - x} + \frac{1}{1 + x} \right)$$

where $x = l/2r$. Because $l \ll r$ for a point dipole, this expression can be simplified by expanding the terms in x and retaining only the leading term:

$$V = \frac{q_1q_2}{4\pi\epsilon_0 r} \{ -(1 + x + \dots) + (1 - x + \dots) \} \approx -\frac{2xq_1q_2}{4\pi\epsilon_0 r} = -\frac{q_1q_2l}{4\pi\epsilon_0 r^2}$$

With $\mu_1 = q_1l$, this expression becomes **eqn 18.18**. This expression should be multiplied by $\cos \theta$ when the point charge lies at an angle θ to the axis of the dipole.

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The following expansions are often useful:

$$\frac{1}{1+x} = 1 - x + x^2 - \dots$$

$$\frac{1}{1-x} = 1 + x + x^2 + \dots$$

Example 18.3 *Calculating the interaction energy of two dipoles*
Calculate the potential energy of interaction of two dipoles in the arrangement shown in (10) when their separation is r .

Method We proceed in exactly the same way as in *Justification 18.4*, but now the total interaction **energy** is the sum of four pairwise terms, two attractions between opposite charges, which contribute negative terms to the potential **energy**, and two repulsions between like charges, which contribute positive terms.

Answer The sum of the four contributions is

$$V = \frac{1}{4\pi\epsilon_0} \left(-\frac{q_1q_2}{r+l} + \frac{q_1q_2}{r} + \frac{q_1q_2}{r} - \frac{q_1q_2}{r-l} \right) = -\frac{q_1q_2}{4\pi\epsilon_0 r} \left(\frac{1}{1+x} - 2 + \frac{1}{1-x} \right)$$

with $x = l/r$. As before, provided $l \ll r$ we can expand the two terms in x and retain only the first surviving term, which is equal to $2x^2$. This step results in the expression

$$V = -\frac{2xq_1q_2}{4\pi\epsilon_0 r}$$

Therefore, because $\mu_1 = q_1l$ and $\mu_2 = q_2l$, the potential **energy** of interaction in the alignment shown in the illustration is

$$V = -\frac{\mu_1\mu_2}{2\pi\epsilon_0 r^3}$$

This interaction **energy** approaches zero more rapidly (as $1/r^3$) than for the previous case: now both interacting entities appear neutral to each other at large separations. See *Further information 18.1* for the general expression.

Self Test 18.4 Derive an expression for the potential **energy** when the dipoles are in the arrangement shown in **(11)**.

Correct Answer

$$V = \mu_1\mu_2/4\pi\epsilon_0 r^3$$

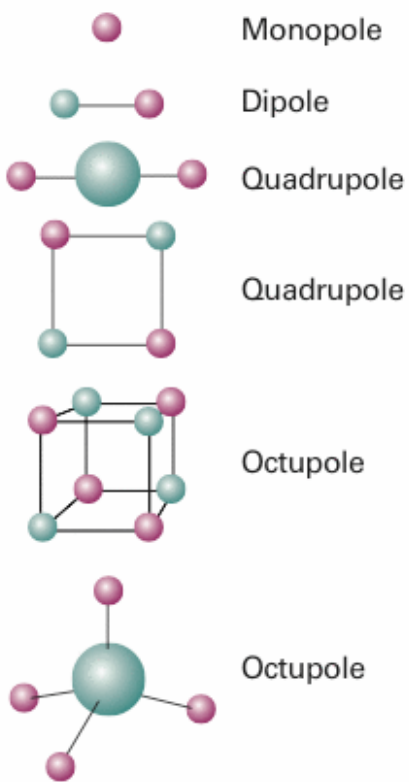
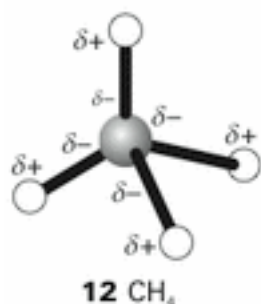
Table 18-3 summarizes the various expressions for the interaction of charges and dipoles.

Table 18.3 Multipole interaction potential energies

Interaction type	Distance dependence of potential energy	Typical energy/ (kJ mol ⁻¹)	Comment
Ion-ion	$1/r$	250	Only between ions*
Ion-dipole	$1/r^2$	15	
Dipole-dipole	$1/r^3$	2	Between stationary polar molecules
	$1/r^6$	0.6	Between rotating polar molecules
London (dispersion)	$1/r^6$	2	Between all types of molecules

The energy of a hydrogen bond A-H...B is typically 20 kJ mol⁻¹ and occurs on contact for A, B = O, N, or F.

* Electrolyte solutions are treated in Chapter 5, ionic solids in Chapter 20.



It is quite easy to extend the formulas given there to obtain expressions for the *energy* of interaction of higher **multipoles**, or arrays of point charges (**Fig. 18.4**).

Fig. 18.4 Typical charge arrays corresponding to electric multipoles. The field arising from an arbitrary finite charge distribution can be expressed as the superposition of the fields arising from a superposition of multipoles.

Specifically, an **n-pole** is an array of point charges with an *n*-pole moment but no lower moment. Thus, a **monopole** ($n = 1$) is a point charge, and the monopole moment is what we normally call the overall charge. A dipole ($n = 2$), as we have seen, is an array of charges that has no monopole moment (no net charge). A **quadrupole** ($n = 3$) consists of an array of point charges that has neither net charge nor dipole moment (as for CO₂ molecules, **3**). An

octupole ($n = 4$) consists of an array of point charges that sum to zero and which has neither a dipole moment nor a quadrupole moment (as for CH_4 molecules, **12**). The feature to remember is that the interaction *energy* falls off more rapidly the higher the order of the multipole. For the interaction of an n -pole with an m -pole, the potential *energy* varies with distance as

$$V \propto \frac{1}{r^{n+m-1}} \quad (18.19)$$

Comment 18.8

The reason for the even steeper decrease with distance is the same as before: the array of charges appears to blend together into neutrality more rapidly with distance the higher the number of individual charges that contribute to the multipole. Note that a given molecule may have a charge distribution that corresponds to a superposition of several different multipoles.

(b) The electric field

The same kind of argument as that used to derive expressions for the potential [energy](#) can be used to establish the distance dependence of the strength of the electric field generated by a dipole. We shall need this expression when we calculate the dipole moment induced in one molecule by another.

The starting point for the calculation is the strength of the electric field generated by a point electric charge:

$$\mathcal{E} = \frac{q}{4\pi\epsilon_0 r^2} \quad (18.20)$$

The field generated by a dipole is the sum of the fields generated by each partial charge. For the point-dipole arrangement shown in [Fig. 18.5](#),



Fig. 18.5 The electric field of a dipole is the sum of the opposing fields from the positive and negative charges, each of which is proportional to $1/r^2$. The difference, the net field, is proportional to $1/r^3$.

The same procedure that was used to derive the potential [energy](#) gives

$$\mathcal{E} = \frac{\mu}{2\pi\epsilon_0 r^3} \quad (18.21)$$

The electric field of a multipole (in this case a dipole) decreases more rapidly with distance (as $1/r^3$ for a dipole) than a monopole (a point charge).

(c) Dipole–dipole interactions

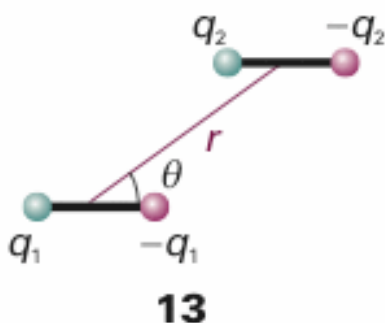
Comment 18.9

[The average (or mean value) of a function $f(x)$ over the range from $x = a$ to $x = b$ is

$$\langle f \rangle = \frac{1}{b-a} \int_a^b f(x) dx$$

The volume element in polar coordinates is proportional to $\sin^2 \theta d\theta$, and θ ranges from 0 to π . Therefore the average value of $(1 - 3 \cos^2 \theta)$ is

$$(1/\pi) \int_0^\pi (1 - 3 \cos^2 \theta) \sin \theta d\theta = 0.$$



The potential energy of interaction between two polar molecules is a complicated function of their relative orientation. When the two dipoles are parallel (as in **13**), the potential energy is simply (see *Further information* 18.1, derivation given below)

$$V = \frac{\mu_1 \mu_2 f(\theta)}{4\pi\epsilon_0 r^3} \quad f(\theta) = 1 - 3 \cos^2 \theta \quad (18.22)$$

This expression applies to polar molecules in a fixed, parallel, orientation in a solid.

Further Information 18.1 The dipole–dipole interaction

An important problem in physical chemistry is the calculation of the potential energy of interaction between two point dipoles with moments μ_1 and μ_2 , separated by a vector \mathbf{r} . From classical electromagnetic theory, the potential energy of μ_2 in the electric field \mathcal{E}_1 generated by μ_1 is given by the dot (scalar) product

$$V = -\mathcal{E}_1 \cdot \mu_2 \quad (18.46)$$

To calculate \mathcal{E}_1 , we consider a distribution of point charges q_i located at $x_i, y_i,$

and z_i from the origin. The Coulomb potential ϕ due to this distribution at a point with coordinates x , y , and z is:

$$\phi = \sum_i \frac{q_i}{4\pi\epsilon_0} \frac{1}{\{(x-x_i)^2 + (y-y_i)^2 + (z-z_i)^2\}^{1/2}} \quad (18.47)$$

Comment 18.10

The potential energy of a charge q_1 in the presence of another charge q_2 may be written as $V = q_1\phi$, where $\phi = q_2/4\pi\epsilon_0 r$ is the Coulomb potential. If there are several charges q_2, q_3, \dots present in the system, then the total potential experienced by the charge q_1 is the sum of the potential generated by each charge: $\phi = \phi_2 + \phi_3 + \dots$. The electric field strength is the negative gradient of the electric potential: $\mathbf{E} = -\nabla\phi$. See *Appendix 3* for more details.

$$\begin{aligned} \phi(r) &= \sum_i \frac{q_i}{4\pi\epsilon_0} \left\{ \frac{1}{r} + \left(\frac{\partial\{(x-x_i)^2 + (y-y_i)^2 + (z-z_i)^2\}^{1/2}}{\partial x_i} \right)_{x_i=0} x_i + \dots \right\} \\ &= \sum_i \frac{q_i}{4\pi\epsilon_0} \left\{ \frac{1}{r} + \frac{xx_i}{r^3} + \dots \right\} \end{aligned} \quad (18.48)$$

where r is the location of the point of interest and the r_i are the locations of the charges q_i . If we suppose that all the charges are close to the origin (in the sense that $r_i \ll r$), we can use a Taylor expansion to write where the ellipses include the terms arising from derivatives with respect to y_i and z_i and higher derivatives. If the charge distribution is electrically neutral, the first term disappears because $\sum_i q_i = 0$. Next we note that $\sum_i q_i x_i = \mu_x$, and likewise for the y - and z -components. That is,

$$\phi = \frac{1}{4\pi\epsilon_0 r^3} (\mu_x x + \mu_y y + \mu_z z) = \frac{1}{4\pi\epsilon_0 r^3} \boldsymbol{\mu}_1 \cdot \mathbf{r} \quad (18.49)$$

The electric field strength is (see [Comment 18.10](#))

$$\mathbf{E}_1 = \frac{1}{4\pi\epsilon_0} \nabla \frac{\boldsymbol{\mu}_1 \cdot \mathbf{r}}{r^3} = -\frac{\boldsymbol{\mu}_1}{4\pi\epsilon_0 r^3} - \frac{\boldsymbol{\mu}_1 \cdot \mathbf{r}}{4\pi\epsilon_0} \nabla \frac{1}{r^3} \quad (18.50)$$

It follows from [eqn 18.46](#) and [eqn 18.50](#) that

$$V = \frac{\boldsymbol{\mu}_1 \cdot \boldsymbol{\mu}_2}{4\pi\epsilon_0 r^3} - 3 \frac{(\boldsymbol{\mu}_1 \cdot \mathbf{r})(\boldsymbol{\mu}_2 \cdot \mathbf{r})}{4\pi\epsilon_0 r^5} \quad (18.51)$$

For the arrangement shown in (13), in which $\mu_1 \cdot r = \mu_1 r \cos \theta$ and $\mu_2 \cdot r = \mu_2 r \cos \theta$, eqn 18.51 becomes:

$$V = \frac{\mu_1 \mu_2 f(\theta)}{4\pi\epsilon_0 r^3} \quad f(\theta) = 1 - 3 \cos^2 \theta \quad (18.52)$$

which is eqn 18.22.

In a fluid of freely rotating molecules, the interaction between dipoles averages to zero because $f(\theta)$ changes sign as the orientation changes, and its average value is zero. Physically, the like partial charges of two freely rotating molecules are close together as much as the two opposite charges, and the repulsion of the former is cancelled by the attraction of the latter.

The interaction energy of two freely rotating dipoles is zero. However, because their mutual potential energy depends on their relative orientation, the molecules do not in fact rotate completely freely, even in a gas. In fact, the lower energy orientations are marginally favoured, so there is a nonzero average interaction between polar molecules. We show in the following *Justification* that the average potential energy of two rotating molecules that are separated by a distance r is

$$\langle V \rangle = -\frac{C}{r^6} \quad C = \frac{2\mu_1^2 \mu_2^2}{3(4\pi\epsilon_0)^2 kT} \quad (18.23)$$

This expression describes the **Keesom interaction**, and is the first of the contributions to the van der Waals interaction.

Justification 18.5 The Keesom interaction

The detailed calculation of the Keesom interaction energy is quite complicated, but the form of the final answer can be constructed quite simply. First, we note that the average interaction energy of two polar molecules rotating at a fixed separation r is given by

$$\langle V \rangle = \frac{\mu_1 \mu_2 \langle f \rangle}{4\pi\epsilon_0 r^3}$$

where f now includes a weighting factor in the averaging that is equal to the probability that a particular orientation will be adopted. This probability is given by the Boltzmann distribution $p \propto e^{-E/kT}$, with E interpreted as the potential energy of interaction of the two dipoles in that orientation. That is,

$$p \propto e^{-V/kT} \quad V = \frac{\mu_1 \mu_2 f}{4\pi\epsilon_0 r^3}$$

When the potential **energy** of interaction of the two dipoles is very small compared with the **energy** of thermal motion, we can use $V \ll kT$, expand the exponential function in p , and retain only the first two terms:

$$p \propto 1 - V/kT + \dots$$

The weighted average of f is therefore

$$\langle f \rangle = \langle f \rangle_0 - \frac{\mu_1 \mu_2}{4\pi\epsilon_0 kT r^3} \langle f^2 \rangle_0 + \dots$$

where \dots_0 denotes an unweighted spherical average. The spherical average of f is zero, so the first term vanishes. However, the average value of f^2 is nonzero because f^2 is positive at all orientations, so we can write

$$\langle V \rangle = - \frac{\mu_1^2 \mu_2^2 \langle f^2 \rangle_0}{(4\pi\epsilon_0)^2 kT r^6}$$

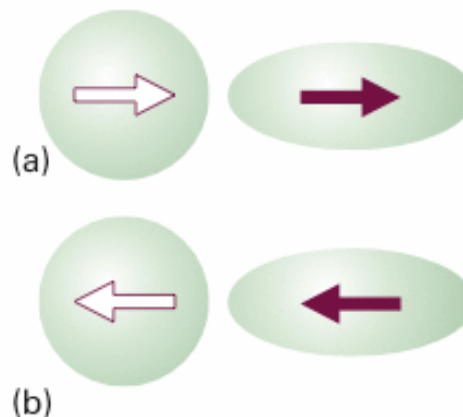
The average value $\langle f^2 \rangle_0$ turns out to be $2/3$ when the calculation is carried through in detail. The final result is that quoted in **eqn 18.23**.

The important features of **eqn 18.23** are its negative sign (the average interaction is attractive), the dependence of the average interaction **energy** on the inverse sixth power of the separation (which identifies it as a van der Waals interaction), and its inverse dependence on the **temperature**. The last feature reflects the way that the greater thermal motion overcomes the mutual orientating effects of the dipoles at higher **temperatures**. The inverse sixth power arises from the inverse third power of the interaction potential **energy** that is weighted by the **energy** in the Boltzmann term, which is also proportional to the inverse third power of the separation.

At 25°C the average interaction **energy** for pairs of molecules with $\mu = 1$ D is about $-0.07 \text{ kJ mol}^{-1}$ when the separation is 0.5 nm. This **energy** should be compared with the average molar kinetic **energy** of $3/2 RT = 3.7 \text{ kJ mol}^{-1}$ at the same **temperature**. The interaction **energy** is also much smaller than the **energies** involved in the making and breaking of chemical bonds.

(d) Dipole–induced-dipole interactions

Fig. 18.6 (a) A polar molecule (purple arrow) can induce a dipole (white arrow) in a nonpolar molecule, and (b) the latter's orientation follows the former's, so the interaction does not average to zero.



A polar molecule with dipole moment μ_1 can induce a dipole μ_2^* in a neighbouring polarizable molecule (**Fig. 18.6**). The induced dipole interacts with the permanent dipole of the first molecule, and the two are attracted together. The average interaction energy when the separation of the molecules is r is (for a derivation, see **Further reading**)

$$V = -\frac{C}{r^6} \quad C = \frac{\mu_1^2 \alpha'_2}{4\pi\epsilon_0} \quad (18.24)$$

where α'_2 is the polarizability volume of molecule 2 and μ_1 is the permanent dipole moment of molecule 1. Note that the C in this expression is different from the C in **eqn 18.23** and other expressions below: we are using the same symbol in C/r^6 to emphasize the similarity of form of each expression.

The dipole–induced-dipole interaction energy is independent of the temperature because thermal motion has no effect on the averaging process. Moreover, like the dipole–dipole interaction, the potential energy depends on $1/r^6$: this distance dependence stems from the $1/r^3$ dependence of the field (and hence the magnitude of the induced dipole) and the $1/r^3$ dependence of the potential energy of interaction between the permanent and induced dipoles. For a molecule with $\mu = 1$ D (such as HCl) near a molecule of polarizability volume $\alpha'_2 = 10 \times 10^{-30} \text{ m}^3$ (such as benzene, **Table 18-1**), the average interaction energy is about -0.8 kJ mol^{-1} when the separation is 0.3 nm.

(e) Induced-dipole–induced-dipole interactions

Nonpolar molecules (including closed-shell atoms, such as Ar) attract one another even though neither has a permanent dipole moment. The abundant evidence for the existence of interactions between them is the formation of condensed **phases** of nonpolar substances, such as the condensation of hydrogen or argon to a liquid at low **temperatures** and the fact that benzene is a liquid at normal **temperatures**.

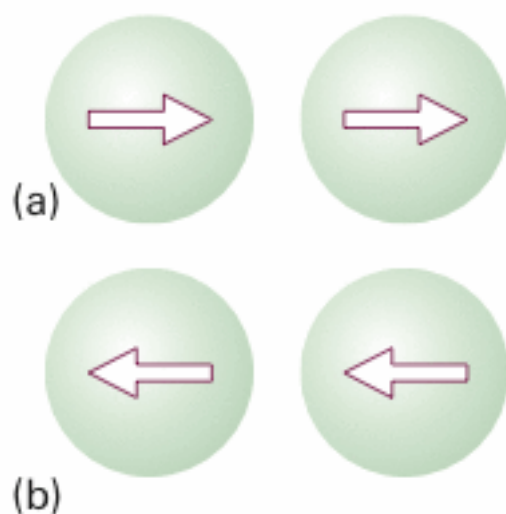


Fig. 18.7 (a) In the dispersion interaction, an instantaneous dipole on one molecule induces a dipole on another molecule, and the two dipoles then interact to lower the **energy**. (b) The two instantaneous dipoles are correlated and, although they occur in different orientations at different instants, the interaction does not average to zero.

The interaction between nonpolar molecules arises from the transient dipoles that all molecules possess as a result of fluctuations in the instantaneous positions of electrons. To appreciate the origin of the interaction, suppose that the electrons in one molecule flicker into an arrangement that gives the molecule an instantaneous dipole moment μ_1^* . This dipole generates an electric field that polarizes the other molecule, and induces in that molecule an instantaneous dipole moment μ_2^* . The two dipoles attract each other and the potential **energy** of the pair is lowered. Although the first molecule will go on to change the size and direction of its instantaneous dipole, the electron distribution of the second molecule will follow; that is, the two dipoles are correlated in direction (**Fig. 18.7**). Because of this correlation, the attraction between the two instantaneous dipoles does not average to zero, and gives rise to an induced-dipole–induced-dipole interaction. This interaction is called either the **dispersion interaction** or the **London interaction** (for Fritz London, who first described it).

Polar molecules also interact by a dispersion interaction: such molecules also possess instantaneous dipoles, the only difference being that the time average of each fluctuating dipole does not vanish, but corresponds to the permanent dipole. Such molecules therefore interact both through their

permanent dipoles and through the correlated, instantaneous fluctuations in these dipoles.

The strength of the dispersion interaction depends on the **polarizability** of the first molecule because the instantaneous dipole moment μ_1^* depends on the looseness of the control that the nuclear charge exercises over the outer electrons. The strength of the interaction also depends on the **polarizability** of the second molecule, for that **polarizability** determines how readily a dipole can be induced by another molecule. The actual calculation of the dispersion interaction is quite involved, but a reasonable approximation to the interaction **energy** is given by the **London formula**:

$$V = -\frac{C}{r^6} \quad C = \frac{3}{2} \alpha'_1 \alpha'_2 \frac{I_1 I_2}{I_1 + I_2} \quad (18.25)$$

where I_1 and I_2 are the **ionization energies** of the two molecules (**Table 10-4**). This interaction **energy** is also proportional to the inverse sixth power of the separation of the molecules, which identifies it as a third contribution to the van der Waals interaction. The dispersion interaction generally dominates all the interactions between molecules other than **hydrogen bonds**.

Illustration 18.1 *Calculating the strength of the dispersion interaction*

For two CH_4 molecules, we can substitute $\alpha = 2.6 \times 10^{-30} \text{ m}^3$ and $I \approx 700 \text{ kJ mol}^{-1}$ to obtain $V = -2 \text{ kJ mol}^{-1}$ for $r = 0.3 \text{ nm}$. A very rough check on this figure is the **enthalpy** of vaporization of methane, which is 8.2 kJ mol^{-1} . However, this comparison is insecure, partly because the **enthalpy** of vaporization is a many-body quantity and partly because the long-distance assumption breaks down.

(f) Hydrogen bonding

The interactions described so far are universal in the sense that they are possessed by all molecules independent of their specific identity. However, there is a type of interaction possessed by molecules that have a particular constitution. A **hydrogen bond** is an attractive interaction between two species that arises from a link of the form A-H...B, where A and B are highly electronegative elements and B possesses a lone pair of electrons. Hydrogen bonding is conventionally regarded as being limited to N, O, and F but, if B is an anionic species (such as Cl⁻), it may also participate in hydrogen bonding. There is no strict cutoff for an ability to participate in hydrogen bonding, but N, O, and F participate most effectively.

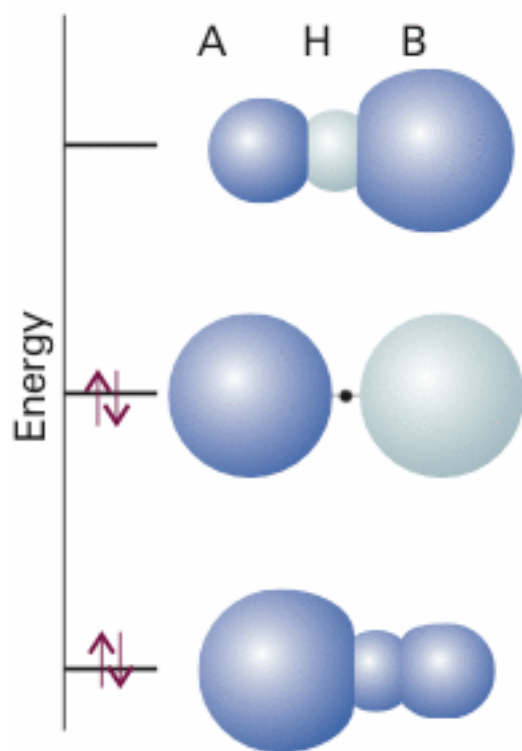


Fig. 18.8 The molecular orbital interpretation of the formation of an A—H...B hydrogen bond. From the three A, H, and B orbitals, three molecular orbitals can be formed (their relative contributions are represented by the sizes of the spheres). Only the two lower energy orbitals are occupied, and there may therefore be a net lowering of energy compared with the separate AH and B species.

The formation of a hydrogen bond can be regarded either as the approach between a partial positive charge of H and a partial negative charge of B or as a particular example of delocalized molecular orbital formation in which A, H, and B each supply one atomic orbital from which three molecular orbitals are constructed (**Fig. 18.8**). Thus, if the A-H bond is

regarded as formed from the overlap of an orbital on A, ψ_A , and a hydrogen 1s orbital, ψ_H , and the lone pair on B occupies an orbital on B, ψ_B , then, when the two molecules are close together, we can build three molecular orbitals from the three basis orbitals:

$$\psi = c_1 \psi_A + c_2 \psi_H + c_3 \psi_B$$

One of the molecular orbitals is bonding, one almost nonbonding, and the third antibonding. These three orbitals need to accommodate four electrons

(two from the original A-H bond and two from the lone pair of B), so two enter the **bonding orbital** and two enter the nonbonding orbital. Because the antibonding orbital remains empty, the net effect—depending on the precise location of the almost nonbonding orbital—may be a lowering of **energy**.

In practice, the strength of the bond is found to be about 20 kJ mol^{-1} . Because the bonding depends on orbital overlap, it is virtually a contact-like interaction that is turned on when AH touches B and is zero as soon as the contact is broken. If hydrogen bonding is present, it dominates the other intermolecular interactions. The properties of liquid and solid water, for example, are dominated by the hydrogen bonding between H_2O molecules. The structure of DNA and hence the transmission of genetic information is crucially dependent on the strength of **hydrogen bonds** between base pairs. The structural evidence for hydrogen bonding comes from noting that the internuclear distance between formally non-bonded atoms is less than their van der Waals contact distance, which suggests that a dominating attractive interaction is present. For example, the O-O distance in $\text{O-H}\cdots\text{O}$ is expected to be 280 pm on the **basis** of van der Waals radii, but is found to be 270 pm in typical compounds. Moreover, the $\text{H}\cdots\text{O}$ distance is expected to be 260 pm but is found to be only 170 pm.

Hydrogen bonds may be either symmetric or unsymmetric. In a symmetric **hydrogen bond**, the H atom lies midway between the two other atoms. This arrangement is rare, but occurs in $\text{F-H}\cdots\text{F}^-$, where both bond lengths are 120 pm. More common is the unsymmetrical arrangement, where the A-H bond is shorter than the $\text{H}\cdots\text{B}$ bond. Simple electrostatic arguments, treating $\text{A-H}\cdots\text{B}$ as an array of point charges (partial negative charges on A and B, partial positive on H) suggest that the lowest **energy** is achieved when the bond is linear, because then the two partial negative charges are furthest apart. The experimental evidence from structural studies support a linear or near-linear arrangement.

(g) The hydrophobic interaction

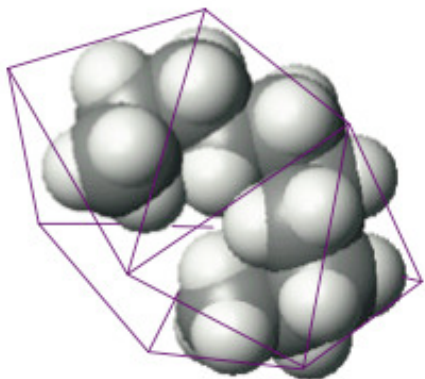
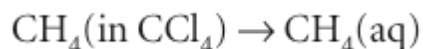


Fig. 18.9 When a hydrocarbon molecule is surrounded by water, the H₂O molecules form a clathrate cage. As a result of this acquisition of structure, the entropy of the water decreases, so the dispersal of the hydrocarbon into the water is entropy-opposed; its coalescence is entropy-favoured.

Nonpolar molecules do dissolve slightly in **polar** solvents, but strong interactions between solute and solvent are not possible and as a result it is found that each individual solute molecule is surrounded by a solvent cage (**Fig. 18.9**). To understand the consequences of this effect, consider the **thermodynamics** of transfer of a nonpolar hydrocarbon solute from a nonpolar solvent to water, a **polar** solvent. Experiments indicate that the process is endergonic ($\Delta_{\text{transfer}}G > 0$), as expected on the **basis** of the increase in polarity of the solvent, but exothermic ($\Delta_{\text{transfer}}H < 0$). Therefore, it is a large decrease in the entropy of the **system** ($\Delta_{\text{transfer}}S < 0$) that accounts for the positive **Gibbs energy** of transfer. For example, the process



has $\Delta_{\text{transfer}}G = +12 \text{ kJ mol}^{-1}$, $\Delta_{\text{transfer}}H = -10 \text{ kJ mol}^{-1}$, and $\Delta_{\text{transfer}}S = -75 \text{ J K}^{-1} \text{ mol}^{-1}$ at 298 K. Substances characterized by a positive **Gibbs energy** of transfer from a nonpolar to a **polar** solvent are called **hydrophobic**.

It is possible to quantify the hydrophobicity of a small molecular group R by defining the **hydrophobicity constant**, π , as

$$\pi = \log \frac{S}{S_0} \quad (18.26)$$

where S is the ratio of the molar solubility of the compound R-A in octanol, a nonpolar solvent, to that in water, and S_0 is the ratio of the molar solubility of the compound H-A in octanol to that in water. Therefore, positive values of

π indicate hydrophobicity and negative values of π indicate hydrophilicity, the thermodynamic preference for water as a solvent. It is observed experimentally that the π values of most groups do not depend on the nature of A. However, measurements do suggest group additivity of π values. For example, π for R = CH₃, CH₂CH₃, (CH₂)₂CH₃, (CH₂)₃CH₃, and (CH₂)₄CH₃ is, respectively, 0.5, 1.0, 1.5, 2.0, and 2.5 and we conclude that acyclic saturated hydrocarbons become more hydrophobic as the carbon chain length increases. This trend can be rationalized by $\Delta_{\text{transfer}}H$ becoming more positive and $\Delta_{\text{transfer}}S$ more negative as the number of carbon atoms in the chain increases.

At the molecular level, formation of a solvent cage around a hydrophobic molecule involves the formation of new **hydrogen bonds** among solvent molecules. This is an **exothermic process** and accounts for the negative values of $\Delta_{\text{transfer}}H$. On the other hand, the increase in order associated with formation of a very large number of small solvent cages decreases the entropy of the **system** and accounts for the negative values of $\Delta_{\text{transfer}}S$. However, when many solute molecules cluster together, fewer (albeit larger) cages are required and more solvent molecules are free to move. The net effect of formation of large clusters of hydrophobic molecules is then a decrease in the organization of the solvent and therefore a net *increase* in entropy of the **system**. This increase in entropy of the solvent is large enough to render spontaneous the association of hydrophobic molecules in a **polar** solvent.

The increase in entropy that results from fewer structural demands on the solvent placed by the clustering of nonpolar molecules is the origin of the **hydrophobic interaction**, which tends to stabilize groupings of hydrophobic groups in **micelles** and biopolymers (**Chapter 19**). The **hydrophobic interaction** is an example of an ordering process that is stabilized by a tendency toward greater disorder of the solvent.

(h) The total attractive interaction

We shall consider molecules that are unable to participate in hydrogen bond formation. The total attractive interaction energy between rotating molecules is then the sum of the three van der Waals contributions discussed above. (Only the dispersion interaction contributes if both molecules are nonpolar.) In a fluid phase, all three contributions to the potential energy vary as the inverse sixth power of the separation of the molecules, so we may write

$$V = -\frac{C_6}{r^6} \quad (18.27)$$

where C_6 is a coefficient that depends on the identity of the molecules.

Although attractive interactions between molecules are often expressed as in eqn 18.27, we must remember that this equation has only limited validity. First, we have taken into account only dipolar interactions of various kinds, for they have the longest range and are dominant if the average separation of the molecules is large. However, in a complete treatment we should also consider quadrupolar and higher-order multipole interactions, particularly if the molecules do not have permanent electric dipole moments. Secondly, the expressions have been derived by assuming that the molecules can rotate reasonably freely. That is not the case in most solids, and in rigid media the dipole-dipole interaction is proportional to $1/r^3$ because the Boltzmann averaging procedure is irrelevant when the molecules are trapped into a fixed orientation.

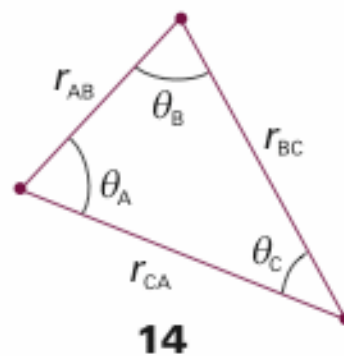
A different kind of limitation is that eqn 18.27 relates to the interactions of pairs of molecules. There is no reason to suppose that the energy of interaction of three (or more) molecules is the sum of the pairwise interaction energies alone. The total dispersion energy of three closed-shell atoms, for instance, is given approximately by the **Axilrod-Teller formula**:

$$V = -\frac{C_6}{r_{AB}^6} - \frac{C_6}{r_{BC}^6} - \frac{C_6}{r_{CA}^6} + \frac{C'}{(r_{AB}r_{BC}r_{CA})^3} \quad (18.28a)$$

where

$$C' = a(3 \cos \theta_A \cos \theta_B \cos \theta_C + 1) \quad (18.28b)$$

The parameter a is approximately equal to $\frac{3}{4} \alpha C_6$; the angles θ are the internal angles of the triangle formed by the three atoms (**14**). The term in C_6 (which represents the non-additivity of the pairwise interactions) is negative for a linear arrangement of atoms (so that arrangement is stabilized) and positive for an equilateral triangular cluster. It is found that the three-body term contributes about 10 per cent of the total interaction energy in liquid argon.



18.5 Repulsive and total interactions

When molecules are squeezed together, the nuclear and electronic repulsions and the rising electronic kinetic energy begin to dominate the attractive forces. The repulsions increase steeply with decreasing separation in a way that can be deduced only by very extensive, complicated molecular structure calculations of the kind described in **Chapter 11 (Fig. 18.10)**.

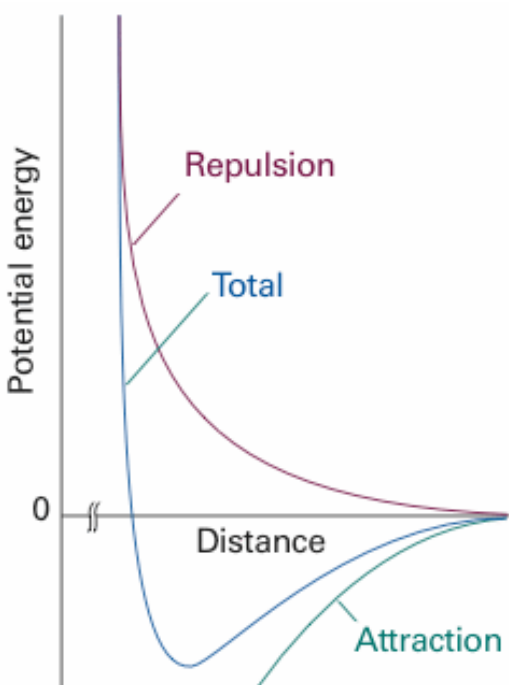


Fig. 18.10 The general form of an intermolecular potential energy curve. At long range the interaction is attractive, but at close range the repulsions dominate.

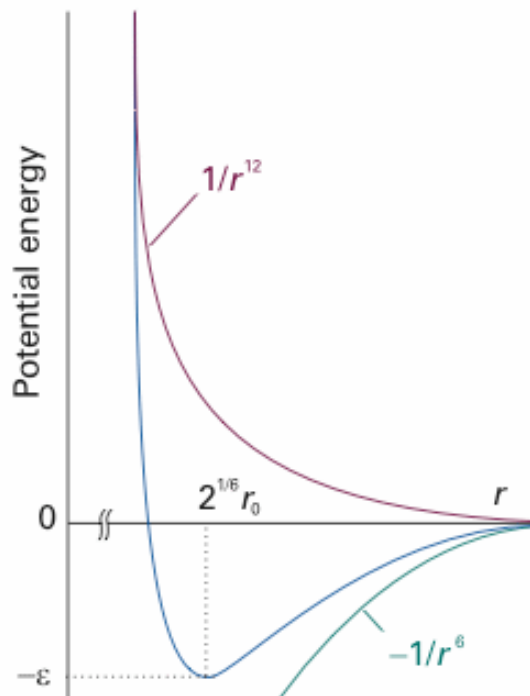


Fig. 18.11 The Lennard-Jones potential, and the relation of the parameters to the features of the curve. The green and purple lines are the two contributions.

In many cases, however, progress can be made by using a greatly simplified representation of the potential energy, where the details are ignored and the general features expressed by a few adjustable parameters. One such approximation is the **hard-sphere potential**, in which it is assumed that the potential energy rises abruptly to infinity as soon as the particles come within a separation d :

$$V = \infty \quad \text{for } r \leq d \quad V = 0 \quad \text{for } r > d \quad (18.29)$$

This very simple potential is surprisingly useful for assessing a number of properties. Another widely used approximation is the **Mie potential**:

$$V = \frac{C_n}{r^n} - \frac{C_m}{r^m} \quad (18.30)$$

with $n > m$. The first term represents repulsions and the second term attractions. The **Lennard-Jones potential** is a special case of the Mie potential with $n = 12$ and $m = 6$ (**Fig. 18.11**); it is often written in the form

$$V = 4\epsilon \left\{ \left(\frac{r_0}{r} \right)^{12} - \left(\frac{r_0}{r} \right)^6 \right\} \quad (18.31)$$

The two parameters are ϵ , the depth of the well (not to be confused with the symbol of the **permittivity** of a medium used in **Section 18-3**), and r_0 , the separation at which $V = 0$ (**Table 18-4**). The well minimum occurs at $r_e = 2^{1/6} r_0$. Although the Lennard-Jones potential has been used in many calculations, there is plenty of evidence to show that $1/r^{12}$ is a very poor representation of the repulsive potential, and that an exponential form, e^{-r/r_0} is greatly superior. An exponential function is more faithful to the exponential decay of atomic **wavefunctions** at large distances, and hence to the overlap that is responsible for repulsion. The potential with an exponential repulsive term and a $1/r^6$ attractive term is known as an **exp-6 potential**. These potentials can be used to calculate the virial coefficients of **gases**, as explained in **Section 17-5**, and through them various properties of real **gases**, such as the Joule–Thompson coefficient. The potentials are also used to model the structures of condensed fluids.

Synoptic table 18.4* Lennard-Jones
(12,6) parameters

	$(\epsilon/k)/\text{K}$	r_0/pm
Ar	111.84	362.3
CCl_4	376.86	624.1
N_2	91.85	391.9
Xe	213.96	426.0

* More values are given in the *Data section*.

With the advent of **atomic force microscopy** (AFM), in which the force between a molecular sized probe and a surface is monitored (see **Impact 19.1**), it has become possible to measure directly the forces acting between molecules. The force, F , is the negative slope of potential, so for a Lennard-Jones potential between individual molecules we write

$$F = -\frac{dV}{dr} = \frac{24\epsilon}{r_0} \left\{ 2 \left(\frac{r_0}{r} \right)^{13} - \left(\frac{r_0}{r} \right)^7 \right\} \quad (18.32)$$

The net attractive force is greatest (from $dF/dr = 0$) at $r = \left(\frac{26}{7} \right)^{1/6} r_0$, or $1.244r_0$, and at that distance is equal to $-\frac{144}{13} \left(\frac{7}{26} \right)^{7/6} \epsilon / r_0$, or $-2.397 \epsilon / r_0$. For typical parameters, the magnitude of this force is about 10 pN.

IMPACT ON MEDICINE_I.18.1

Molecular recognition and drug design

A drug is a small molecule or protein that binds to a specific receptor site of a target molecule, such as a larger protein or nucleic acid, and inhibits the progress of disease. To devise efficient therapies, we need to know how to characterize and optimize molecular interactions between drug and target.

Molecular interactions are responsible for the assembly of many biological structures. Hydrogen bonding and **hydrophobic interactions** are primarily responsible for the three-dimensional structures of biopolymers, such as proteins, nucleic acids, and cell membranes. The binding of a ligand, or *guest*, to a biopolymer, or *host*, is also governed by molecular interactions. Examples of biological *host-guest complexes* include enzyme-substrate complexes, antigen-antibody complexes, and drug-receptor complexes. In all these cases, a site on the guest contains functional groups that can interact with complementary functional groups of the host. For example, a **hydrogen bond** donor group of the guest must be positioned near a **hydrogen bond** acceptor group of the host for tight binding to occur. It is generally true that many specific intermolecular contacts must be made in a biological host-guest complex and, as a result, a guest binds only hosts that are chemically similar. The strict rules governing molecular recognition of a guest by a host control every biological process, from metabolism to immunological response, and provide important clues for the design of effective drugs for the treatment of disease.

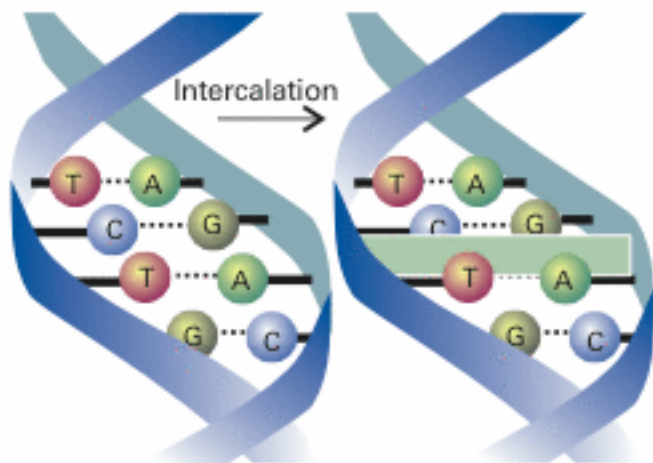


Fig. 18.12 Some drugs with planar π systems, shown as a green rectangle, intercalate between base pairs of DNA.

Interactions between nonpolar groups can be important in the binding of a guest to a host. For example, many enzyme active sites have hydrophobic pockets that bind nonpolar groups of a

substrate. In addition to dispersion, repulsive, and **hydrophobic interactions**, π stacking interactions are also possible, in which the planar π systems of aromatic macrocycles lie one on top of the other, in a nearly parallel

orientation. Such interactions are responsible for the stacking of hydrogen-bonded base pairs in DNA (**Fig. 18.12**). Some drugs with planar π systems, shown as a green rectangle in **Fig. 18.12**, are effective because they intercalate between base pairs through π stacking interactions, causing the helix to unwind slightly and altering the function of DNA.

Coulombic interactions can be important in the interior of a biopolymer host, where the **relative permittivity** can be much lower than that of the aqueous exterior. For example, at physiological pH, amino acid side chains containing carboxylic acid or amine groups are negatively and positively charged, respectively, and can attract each other. Dipole–dipole interactions are also possible because many of the building blocks of biopolymers are **polar**, including the peptide link, $-\text{CONH}-$ (see *Example 18.1*). However, hydrogen bonding interactions are by far the most prevalent in a biological host–guest complexes. Many effective drugs bind tightly and inhibit the action of enzymes that are associated with the progress of a disease. In many cases, a successful inhibitor will be able to form the same **hydrogen bonds** with the binding site that the normal substrate of the enzyme can form, except that the drug is chemically inert toward the enzyme.

There are two main strategies for the discovery of a drug. In *structure-based design*, new drugs are developed on the **basis** of the known structure of the receptor site of a known target. However, in many cases a number of so-called *lead compounds* are known to have some biological **activity** but little information is available about the target. To design a molecule with improved pharmacological efficacy, **quantitative structure–activity relationships** (QSAR) are often established by correlating data on **activity** of lead compounds with molecular properties, also called *molecular descriptors*, which can be determined either experimentally or computationally.

In broad terms, the first stage of the QSAR method consists of compiling molecular descriptors for a very large number of lead compounds. Descriptors such as molar mass, molecular dimensions and volume, and relative solubility in water and nonpolar solvents are available from routine experimental procedures. Quantum mechanical descriptors determined by semi-empirical and *ab initio* calculations include bond orders and HOMO and LUMO **energies**.

In the second stage of the process, biological **activity** is expressed as a function of the molecular descriptors. An example of a QSAR equation is:

$$\text{Activity} = c_0 + c_1 d_1 + c_2 d_1^2 + c_3 d_2 + c_4 d_2^2 + \dots \quad (18.33)$$

where d_i is the value of the descriptor and c_i is a coefficient calculated by fitting the data by regression analysis. The quadratic terms account for the fact that biological **activity** can have a maximum or minimum value at a specific descriptor value. For example, a molecule might not cross a biological membrane and become available for binding to targets in the interior of the cell if it is too hydrophilic (water-loving), in which case it will not partition into the hydrophobic layer of the cell membrane (see **Section 19-14** for details of membrane structure), or too hydrophobic (water-repelling), for then it may bind too tightly to the membrane. It follows that the **activity** will peak at some intermediate value of a parameter that measures the relative solubility of the drug in water and organic solvents.

In the final stage of the QSAR process, the **activity** of a drug candidate can be estimated from its molecular descriptors and the QSAR equation either by interpolation or extrapolation of the data. The predictions are more reliable when a large number of lead compounds and molecular descriptors are used to generate the QSAR equation.

The traditional QSAR technique has been refined into 3D QSAR, in which sophisticated computational methods are used to gain further insight into the three-dimensional features of drug candidates that lead to tight binding to the receptor site of a target. The process begins by using a computer to superimpose three-dimensional structural models of lead compounds and looking for common features, such as similarities in shape, location of functional groups, and electrostatic potential plots, which can be obtained from molecular orbital calculations. The key assumption of the method is that common structural features are indicative of molecular properties that enhance binding of the drug to the receptor. The collection of superimposed molecules is then placed inside a three-dimensional grid of points. An atomic probe, typically an sp^3 -hybridized carbon atom, visits each grid point and two **energies** of interaction are calculated: E_{steric} , the steric **energy** reflecting interactions between the probe and electrons in uncharged regions of the drug, and E_{elec} , the electrostatic **energy** arising from interactions between the probe and a region of the molecule carrying a partial charge. The measured **equilibrium constant** for binding of the drug to the target, K_{bind} , is then assumed to be related to the interaction **energies** at each point r by the 3D QSAR equation

$$\log K_{\text{bind}} = c_0 + \sum_r \{c_S(\mathbf{r})E_{\text{steric}}(\mathbf{r}) + c_E(\mathbf{r})E_{\text{elec}}(\mathbf{r})\} \quad (18.34)$$

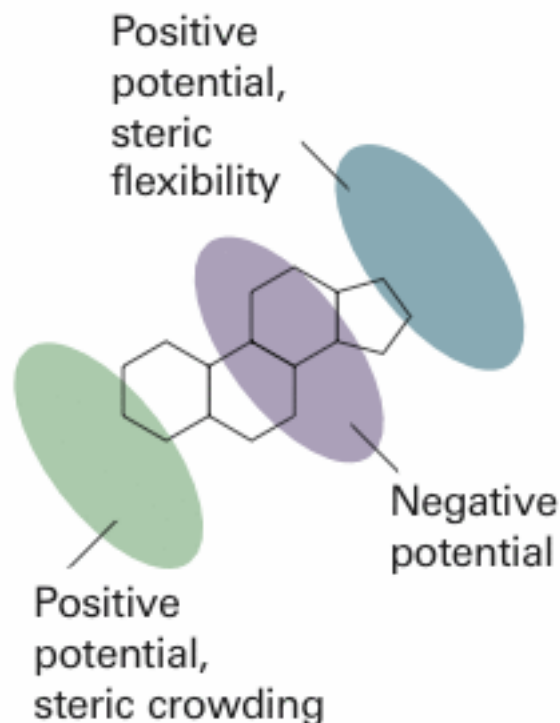


Fig. 18.13 A 3D QSAR analysis of the binding of steroids, molecules with the carbon skeleton shown, to human corticosteroid-binding globulin (CBG). The ellipses indicate areas in the protein's binding site with positive or negative electrostatic potentials and with little or much steric crowding. It follows from the calculations that addition of large substituents near the left-hand side of the molecule (as it is drawn on the page) leads to poor affinity of the drug to the binding site. Also, substituents that lead to the accumulation of negative electrostatic potential at either end of the drug are likely to show enhanced affinity for the binding site. (Adapted from P. Krosgaard-Larsen, T. Liljefors, U. Madsen (ed.), *Textbook of drug design and discovery*, Taylor &

Francis, London (2002).)

where the $c(\mathbf{r})$ are coefficients calculated by regression analysis, with the coefficients c_S and c_E reflecting the relative importance of steric and electrostatic interactions, respectively, at the grid point \mathbf{r} . Visualization of the regression analysis is facilitated by colouring each grid point according to the magnitude of the coefficients. **Figure 18.13** shows results of a 3D QSAR analysis of the binding of steroids, molecules with the carbon skeleton shown, to human corticosteroid-binding globulin (CBG). Indeed, we see that the technique lives up to the promise of opening a window into the chemical nature of the binding site even when its structure is not known.

The QSAR and 3D QSAR methods, though powerful, have limited power: the predictions are only as good as the data used in the correlations are both reliable and abundant. However, the techniques have been used successfully to identify compounds that deserve further synthetic elaboration, such as addition or removal of functional groups, and testing.

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Further Reading

Articles and texts

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M.A.D. Fluendy and K.P. Lawley, *Chemical applications of molecular beam scattering*. Chapman and Hall, London (1973).

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-->**G.A. Jeffrey, *An introduction to hydrogen bonding*. Oxford University Press (1997).**

H.-J. Schneider and A. Yatsimirsky, *Principles and methods in supramolecular chemistry*. Wiley, Chichester (1999).

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J.J. Jasper, The surface tension of pure liquid compounds. *J. Phys. Chem. Ref. Data* **1**, 841 (1972).

D.R. Lide (ed.), *CRC Handbook of Chemistry and Physics*, Sections 3, 4, 6, 9, 10, 12, and 13. CRC Press, Boca Raton (2000).

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Discussion Questions

18.4 Account for the theoretical conclusion that many attractive interactions between molecules vary with their separation as $1/r^6$.

18.5 Describe the formation of a **hydrogen bond** in terms of molecular orbitals.

18.6 Account for the **hydrophobic interaction** and discuss its manifestations.

Exercises

18.1a Which of the following molecules may be **polar**: ClF_3 , O_3 , H_2O_2 ?

18.2a The electric dipole moment of toluene (methylbenzene) is 0.4 D. Estimate the dipole moments of the three xylenes (dimethylbenzene). Which answer can you be sure about?

18.2b Calculate the resultant of two dipole moments of magnitude 1.5 D and 0.80 D that make an angle of 109.5° to each other.

Correct Answer $\mu = 1.4$ D.

18.3a Calculate the magnitude and direction of the dipole moment of the following arrangement of charges in the xy -plane: $3e$ at $(0,0)$, $-e$ at $(0.32 \text{ nm}, 0)$, and $-2e$ at an angle of 20° from the x -axis and a distance of 0.23

nm from the origin.

18.3b Calculate the magnitude and direction of the dipole moment of the following arrangement of charges in the xy -plane: $4e$ at $(0, 0)$, $-2e$ at $(162 \text{ pm}, 0)$, and $-2e$ at an angle of 30° from the x -axis and a distance of 143 pm from the origin.

Correct Answer $\mu = 9.45 \times 10^{-29} \text{ C m}$, $\theta = 194.0^\circ$.

Numerical problems

18.1 Suppose an H_2O molecule ($\mu = 1.85 \text{ D}$) approaches an anion. What is the favourable orientation of the molecule? Calculate the electric field (in volts per metre) experienced by the anion when the water dipole is (a) 1.0 nm , (b) 0.3 nm , (c) 30 nm from the ion.

Correct Answer SF_4 .

18.2 An H_2O molecule is aligned by an external electric field of strength 1.0 kV m^{-1} and an Ar atom ($\alpha = 1.66 \times 10^{-24} \text{ cm}^3$) is brought up slowly from one side. At what separation is it energetically favourable for the H_2O molecule to flip over and point towards the approaching Ar atom?

Correct Answer $\mu = 1.4 \text{ D}$.

18.3 The [relative permittivity](#) of chloroform was measured over a range of [temperatures](#) with the following results:

The freezing point of chloroform is -64°C . Account for these results and calculate the dipole moment and [polarizability](#) volume of the molecule.

Correct Answer $\mu = 9.45 \times 10^{-29} \text{ C m}$, $\theta = 194.0^\circ$.

18.4 The [relative permittivities](#) of methanol (m.p. -95°C) corrected for density variation are given below. What molecular information can be deduced from these values? Take $\rho = 0.791 \text{ g cm}^{-3}$ at 20°C .

Correct Answer $\mu = 3.23 \times 10^{-30} \text{ C m}$, $\alpha = 2.55 \times 10^{-39} \text{ C}^2 \text{ m}^2 \text{ J}^{-1}$.

18.5 In his classic book *Polar molecules*, Debye reports some early measurements of the [polarizability](#) of ammonia. From the selection below, determine the dipole moment and the [polarizability](#) volume of the molecule.

The refractive index of ammonia at 273 K and 100 kPa is 1.000379 (for yellow sodium light). Calculate the molar [polarizability](#) of the gas at this [temperature](#) and at 292.2 K . Combine the value calculated with the static molar [polarizability](#) at 292.2 K and deduce from this information alone the molecular dipole moment.

Correct Answer $\epsilon_r = 8.97$.

18.13 Show that the mean interaction [energy](#) of N atoms of diameter d

interacting with a potential energy of the form C_6/R^6 is given by $U = -2N^2 C_6/3Vd^3$, where V is the volume in which the molecules are confined and all effects of clustering are ignored. Hence, find a connection between the van der Waals parameter a and C_6 , from $n^2 a/V^2 = (\partial U/\partial V)T$.

Correct Answer (a) CH_2Cl_2 ; (b) CH_3CH_3 ; (d) N_2O .

18.14 Suppose the repulsive term in a Lennard-Jones (12,6)-potential is replaced by an exponential function of the form $e^{-r/d}$. Sketch the form of the potential energy and locate the distance at which it is a minimum.

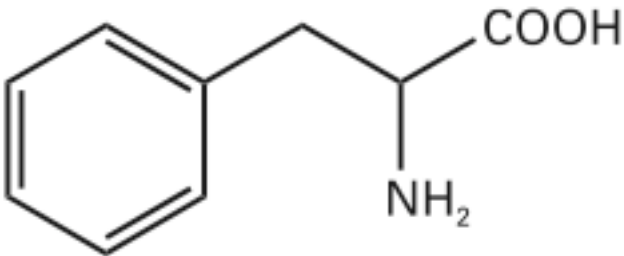
Correct Answer $K \approx 0.25$.

18.15 The cohesive energy density, u_c , is defined as U/V , where U is the mean potential energy of attraction within the sample and V its volume. Show that $u_c = \frac{1}{2} \int V(R) d\rho$, where ρ is the number density of the molecules and $V(R)$ is their attractive potential energy and where the integration ranges from d to infinity and over all angles. Go on to show that the cohesive energy density of a uniform distribution of molecules that interact by a van der Waals attraction of the form $-C_6/R^6$ is equal to $(2\pi/3)(N_A^2/d^3 M^2) \rho^2 C_6$, where ρ is the mass density of the solid sample and M is the molar mass of the molecules.

Correct Answer $B_1 = 9.40 \times 10^{-4} \text{ T}$, $6.25 \mu\text{s}$.

Applications: to biochemistry

18.18 Phenylalanine (Phe, **15**) is a naturally occurring amino acid. What is the energy of interaction between its phenyl group and the electric dipole moment of a neighbouring peptide group?



15

Take the distance between the groups as 4.0 nm and treat the phenyl group as a benzene molecule. The dipole moment of the peptide group is $\mu = 2.7 \text{ D}$ and the polarizability volume of benzene is $\alpha = 1.04 \times 10^{-29} \text{ m}^3$.

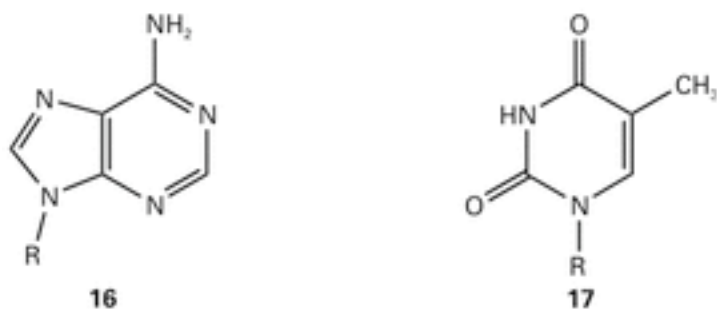
Correct Answer 2.2 mT , $g = 1.992$.

18.19 Now consider the London interaction between the phenyl groups of two Phe residues (see **Problem 18.18**). (a) Estimate the potential energy of

interaction between two such rings (treated as benzene molecules) separated by 4.0 nm. For the **ionization energy**, use $I = 5.0$ eV. (b) Given that force is the negative slope of the potential, calculate the distance dependence of the force acting between two nonbonded groups of atoms, such as the phenyl groups of Phe, in a polypeptide chain that can have a London dispersion interaction with each other. What is the separation at which the force between the phenyl groups (treated as benzene molecules) of two Phe residues is zero? *Hint.* Calculate the slope by considering the potential **energy** at r and $r + \Delta r$, with $\Delta r \ll r$, and evaluating $\{V(r + \Delta r) - V(r)\} / \Delta r$. At the end of the calculation, let Δr become vanishingly small. Correct Answer

Eight equal parts at $\pm 1.445 \pm 1.435 \pm 1.055$ mT from the centre, namely: 328.865, 330.975, 331.735, 331.755, 333.845, 333.865, 334.625 and 336.735 mT.

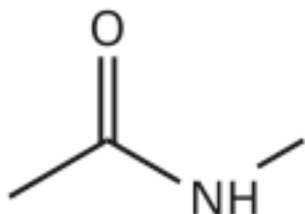
18.20 Molecular orbital calculations may be used to predict structures of intermolecular complexes. **Hydrogen bonds** between purine and pyrimidine bases are responsible for the double helix structure of DNA (see **Chapter 19**). Consider methyl-adenine (**16**, with $R = \text{CH}_3$) and methyl-thymine (**17**, with $R = \text{CH}_3$) as models of two bases that can form **hydrogen bonds** in DNA.



(a) Using molecular modelling software and the computational method of your choice, calculate the atomic charges of all atoms in methyl-adenine and methyl-thymine. (b) Based on your tabulation of atomic charges, identify the atoms in methyl-adenine and methyl-thymine that are likely to participate in **hydrogen bonds**. (c) Draw all possible adenine–thymine pairs that can be linked by **hydrogen bonds**, keeping in mind that linear arrangements of the A–H \cdots B fragments are preferred in DNA. For this step, you may want to use your molecular modelling software to align the molecules properly. (d) Consult **Chapter 19** and determine which of the pairs that you drew in part (c) occur naturally in DNA molecules. (e) Repeat parts (a)–(d) for cytosine and guanine, which also form base pairs in DNA (see **Chapter 19** for the structures of these bases).

Correct Answer $D_0 = 3.235 \times 10^4 \text{ cm}^{-1} = 4.01 \text{ eV}$.

18.21 Molecular orbital calculations may be used to predict the dipole moments of molecules. (a) Using molecular modelling software and the computational method of your choice, calculate the dipole moment of the peptide link, modelled as a *trans*-*N*-methylacetamide (**18**).



18

Plot the **energy** of interaction between these dipoles against the angle θ for $r = 3.0$ nm (see **eqn 18.22**). (b) Compare the maximum value of the dipole-dipole interaction **energy** from part (a) to 20 kJ mol^{-1} , a typical value for the **energy** of a hydrogen-bonding interaction in biological **systems**.
Correct Answer (a) 332.3 mT; (b) 1209 mT.