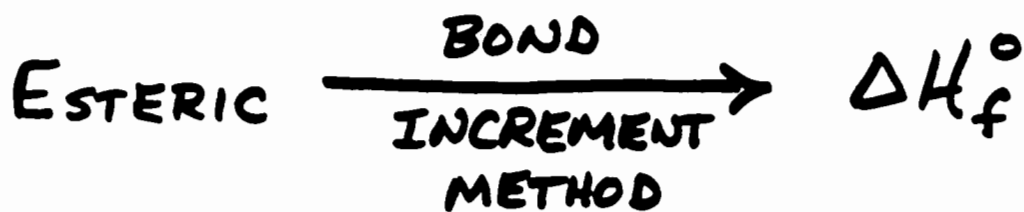


"STERIC" ENERGY

$$\begin{aligned} E_{\text{STERIC}} &= E_{\text{BOND}} + E_{\text{ANGLE}} \\ &+ E_{\text{STR/BEND}} + E_{\text{TORSION}} \\ &+ E_{\text{VDW}} + E_{\text{CH}_6\text{-CH}_6} \\ &+ E_{\text{CH}_6\text{-DPL}} + E_{\text{DPL-DPL}} + E_{\text{HBOND}} \\ &+ E_{\text{SOLVENT}} + \dots \end{aligned}$$



ACCURACY -

HYDROCARBONS	0.42 KCAL
ETHERS	0.50 KCAL
BIOPOLYMERS	???

VAN DER WAALS POTENTIAL

LENNARD - JONES

$$E(R) = \epsilon \left\{ \left(\frac{R_0}{R} \right)^{12} - \left(\frac{R_0}{R} \right)^6 \cdot 2 \right\}$$

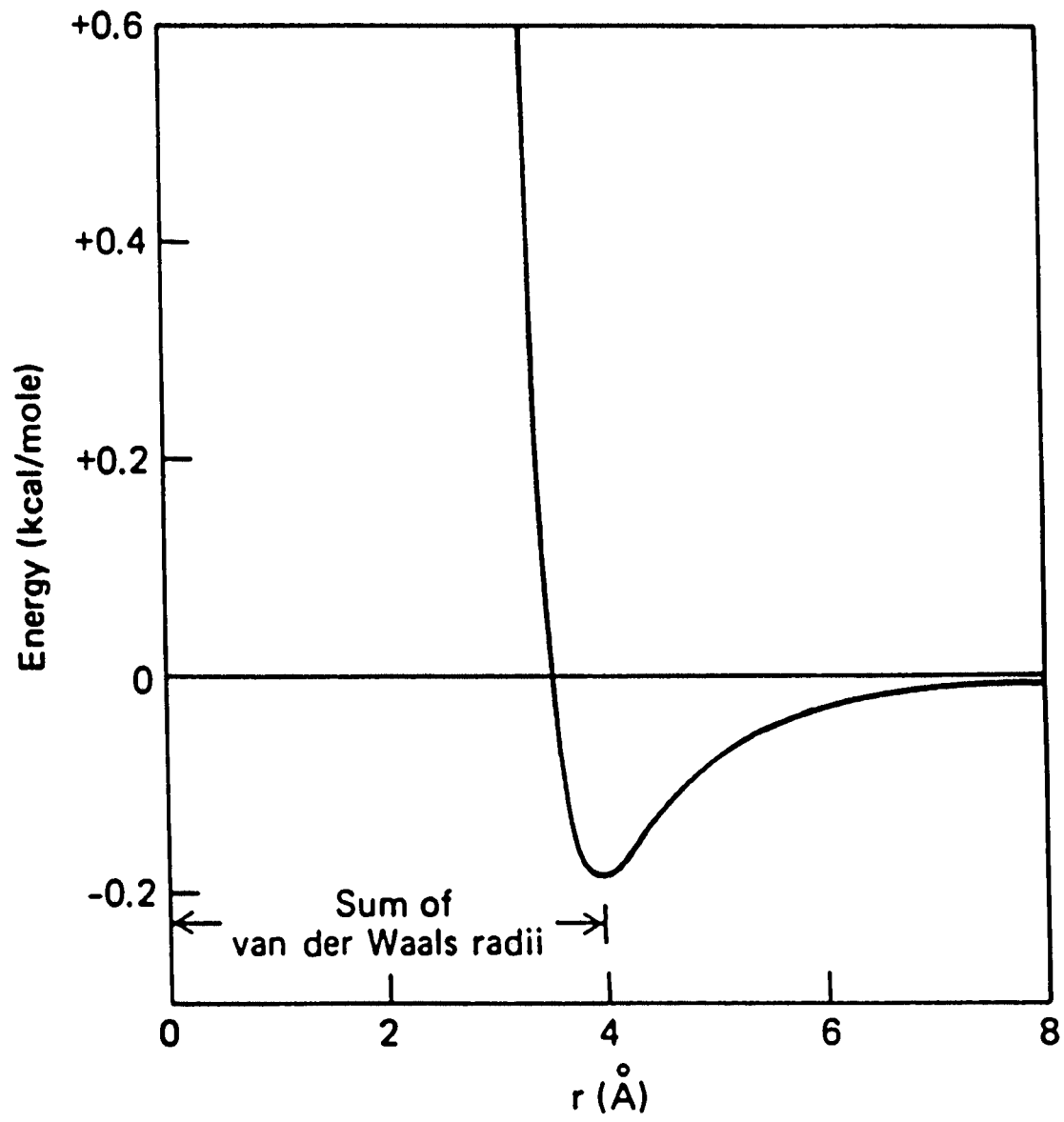
BUCKINGHAM

$$E(R) = 2.9 \cdot 10^5 \epsilon e^{-12.5 (R_0/R)} - 2.25 \epsilon (R_0/R)^6$$

PROBLEM -

MANY BODY EFFECTS SUCH
AS POLARIZABILITY AND
SHIELDING

ANISOTROPY, ESPECIALLY
FOR HYDROGENS



ELECTROSTATIC POTENTIALS

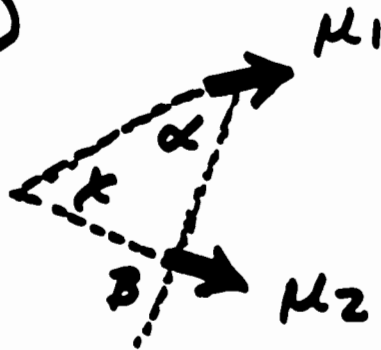
CHARGE-CHARGE

$$E(R) = 332 q_1 q_2 / DR$$

DIPOLE-DIPOLE

$$E(\mu_1, \mu_2) = (\cos \kappa - 3 \cos \alpha \cos \beta) \cdot \mu_1 \mu_2 / DR^3$$

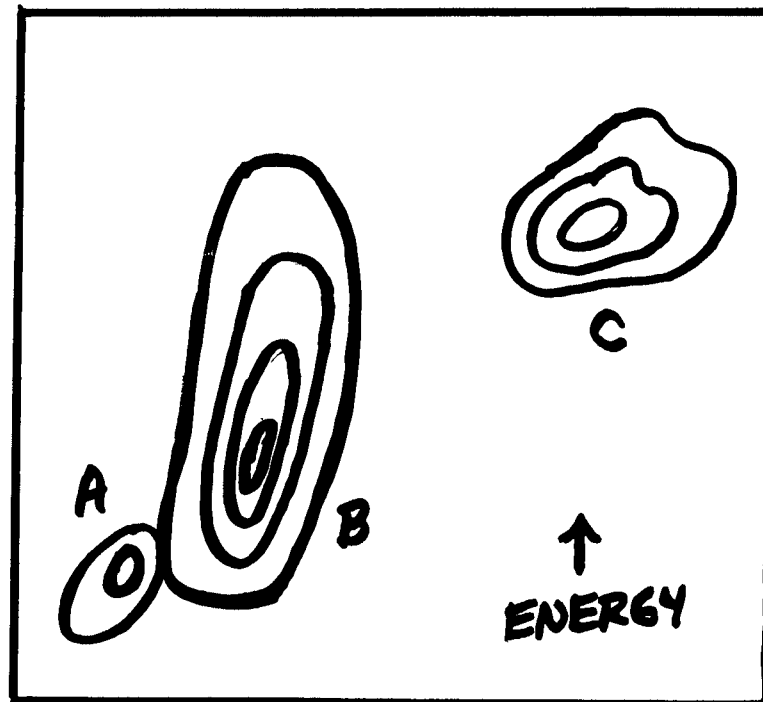
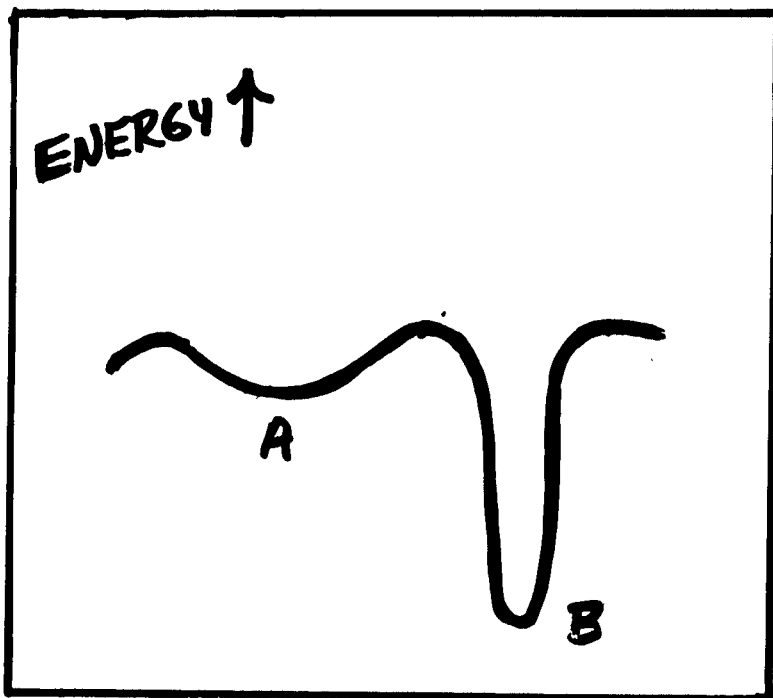
(JEANS' FORMULA)



SIMILARLY, CHARGE-DIPOLE $\propto 1/R^2$

PROBLEMS - VALUE OF D?
H-BONDING POTENTIALS?

CONFORMATIONAL FREE ENERGY



$$Z_{\text{CONF}} = \sum_{\tau_1, \tau_2} \exp[-E(\tau_1, \tau_2)/kT]$$

$$\Delta G^\circ = -kT \ln(Z_{\text{CONF}}^A / Z_{\text{CONF}}^B)$$

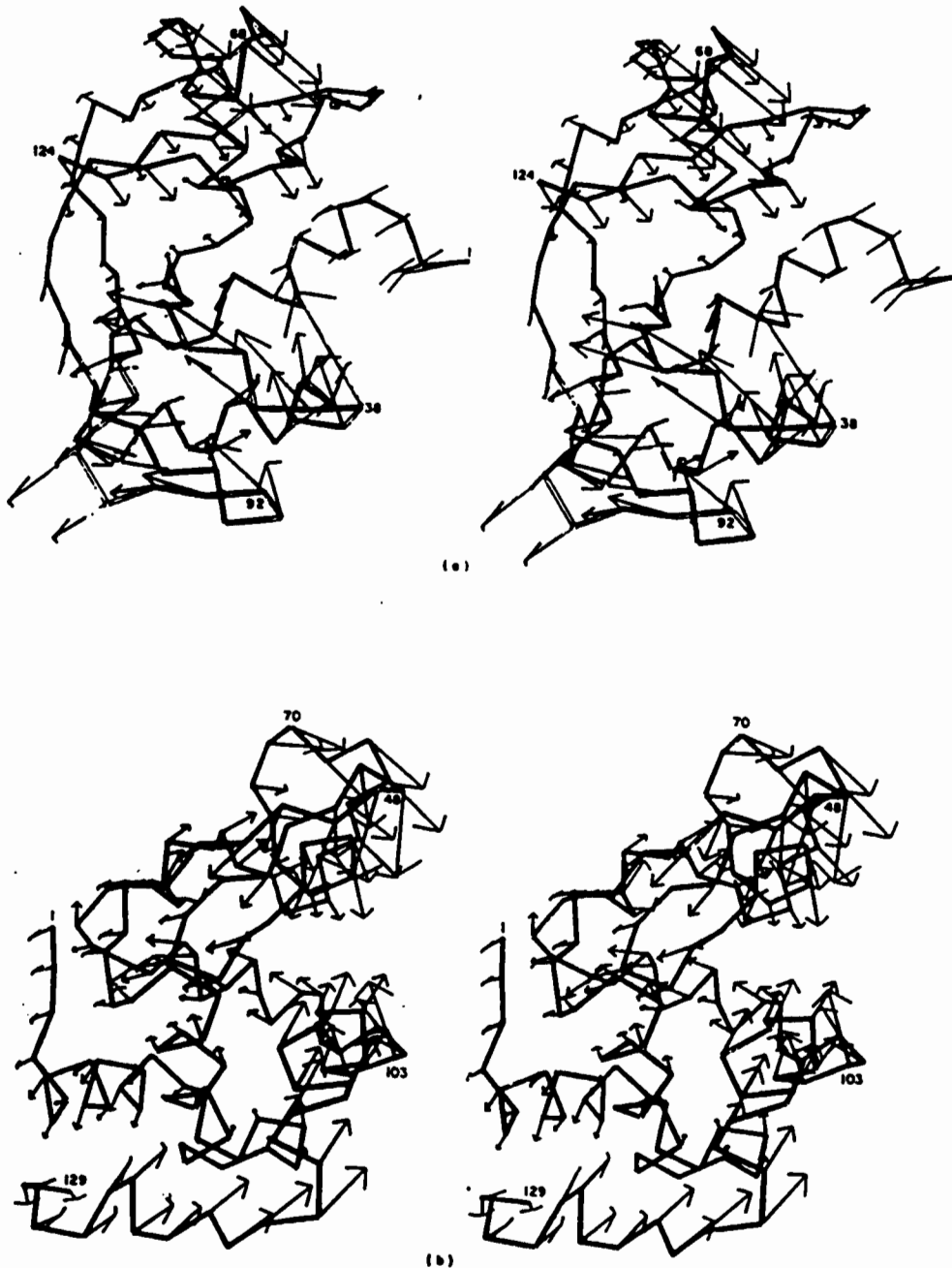


Figure 9. Showing the domain motion due to the lowest frequency modes in ribonuclease and lysozyme. The arrows on the α -carbon backbone are drawn as described in the legend to Fig. 8. (a) Ribonuclease, $\nu_1 = 2.43 \text{ cm}^{-1}$, period = 13.7 ps. (b) Lysozyme, $\nu_1 = 2.98 \text{ cm}^{-1}$, period = 11.2 ps.

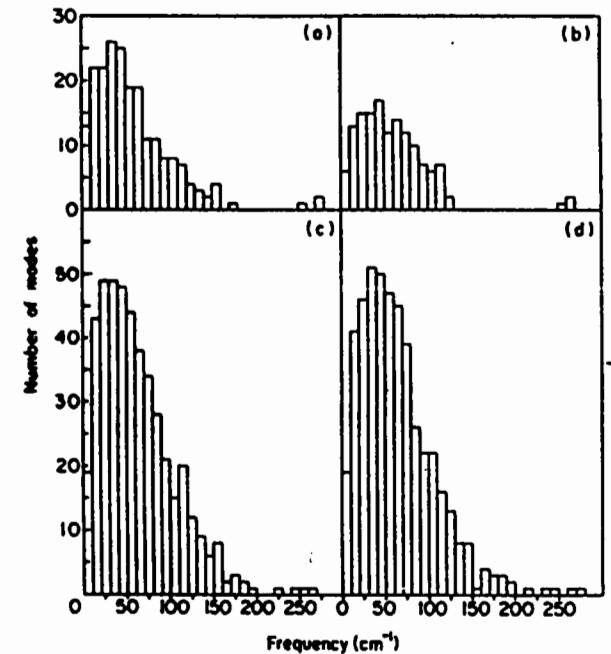
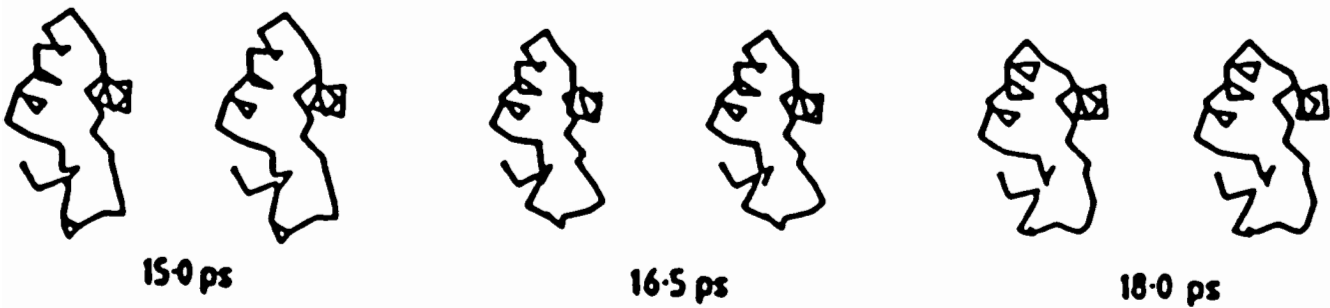
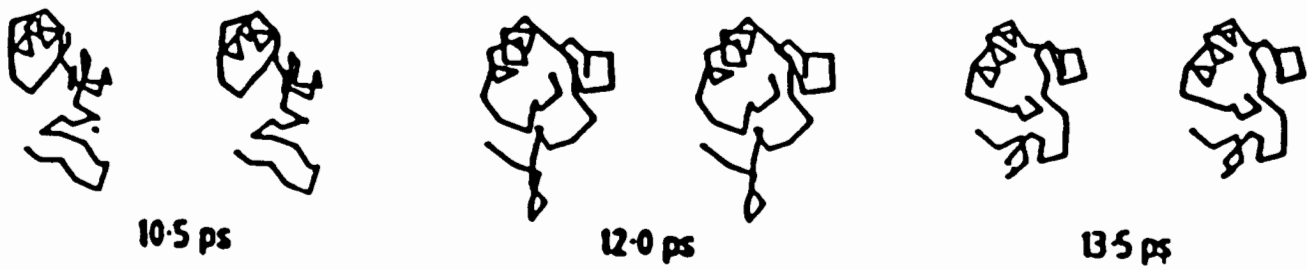
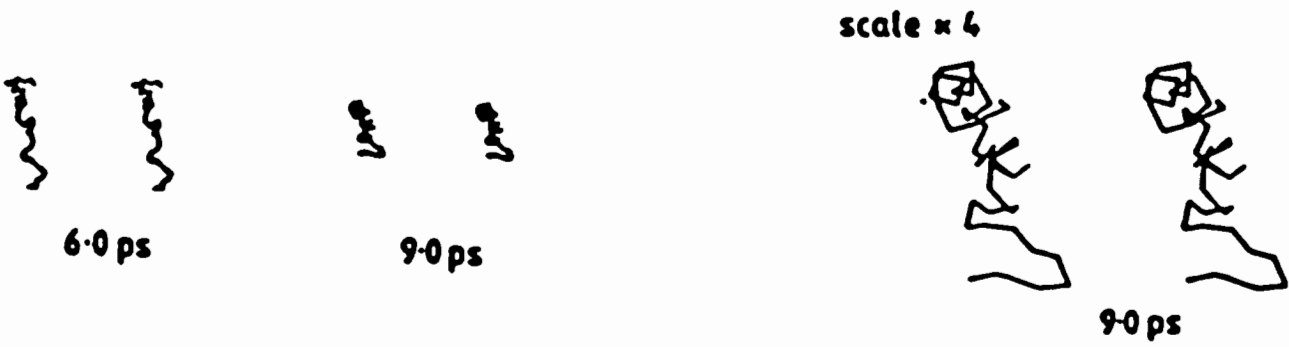
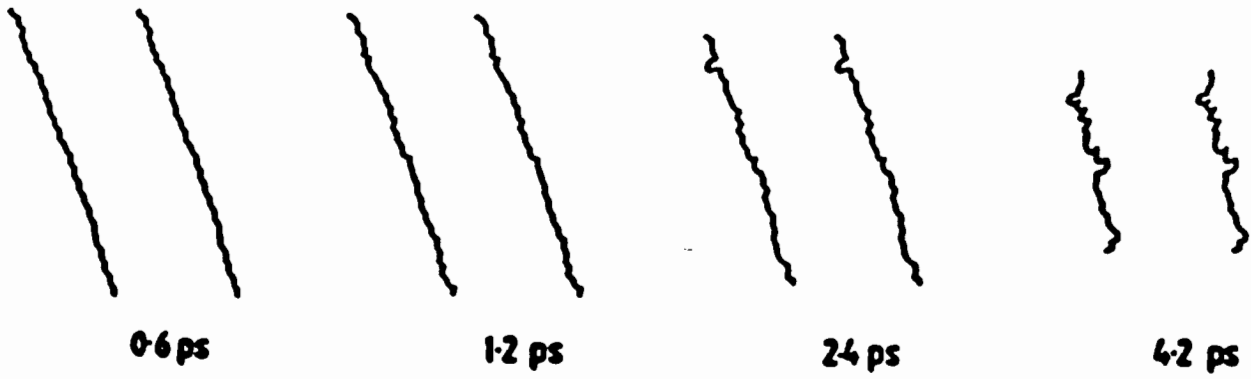


Figure 1. Showing the vibrational spectra calculated here with single-bond torsion angle variables. The number of modes with frequencies in a 10 cm^{-1} interval is plotted against frequency to give a density of states distribution. If each mode had the same intensity and a half line-width of 5 cm^{-1} the intensity envelope would be like the distribution shown. The spectra shown are for: (a) BPTI, (b) crambin, (c) ribonuclease and (d) lysozyme.

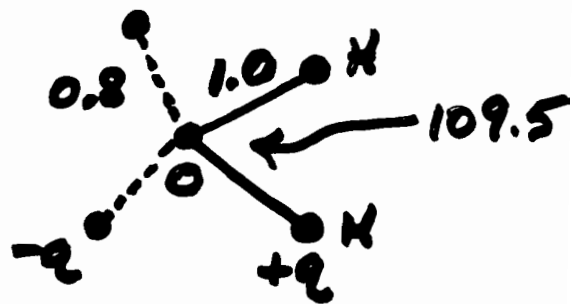


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EXAMPLE: WATER

STILLINGER (ST2)

$$q = 0.2357$$



$$E_{LT} = 0.31 \cdot (\sigma/R)^{12}$$

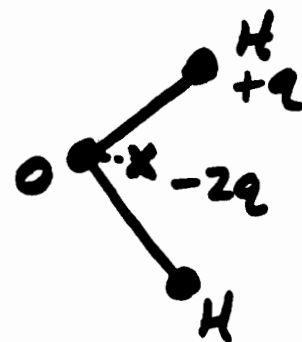
$$- 0.31 \cdot (\sigma/R)^6, \quad \sigma = 3.10 \text{ \AA}$$

JORGENSEN (TIP4P)

$$O-X = 0.15 \text{ \AA}$$

$$q = 0.52$$

$$R = 0.9572 \quad \theta = 104.52$$



$$E_{LT} = 600/R^{12} - 610/R^6$$

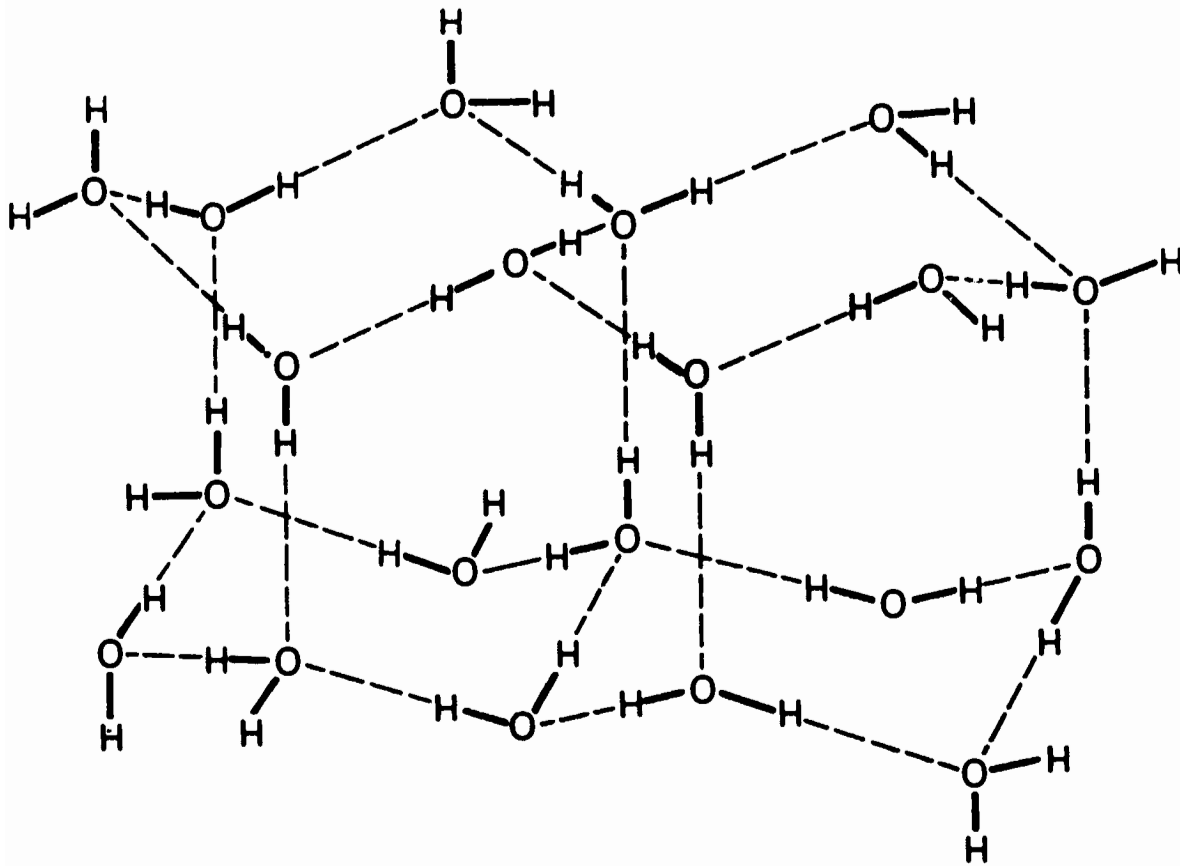
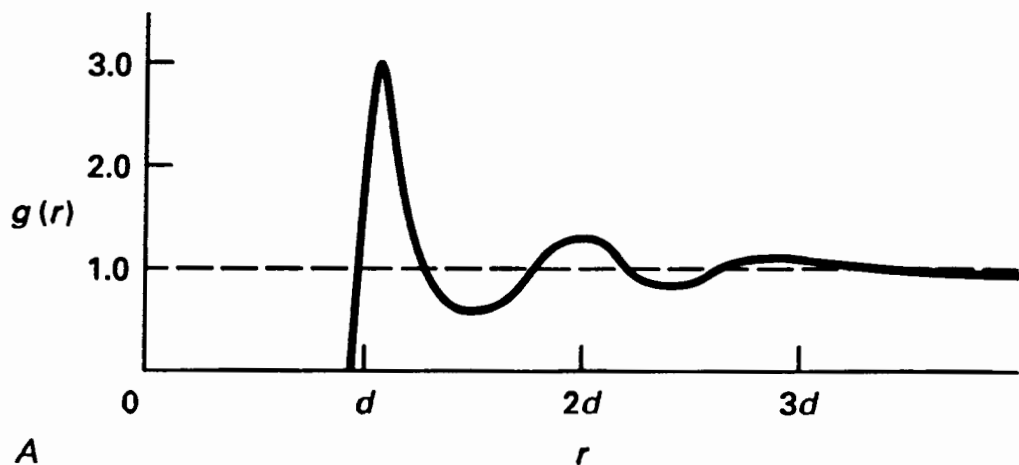
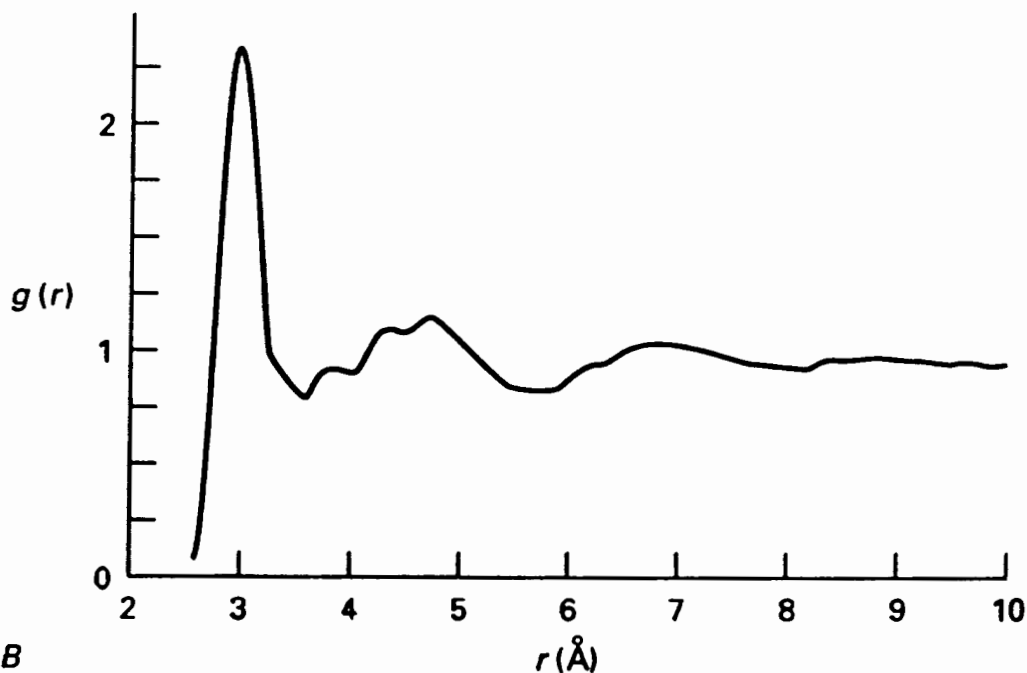


Figure 4-3

*The structure of normal ice. Each H_2O molecule is involved in four hydrogen bonds, each 2.76 Å long, two as hydrogen donor and two as acceptor. As a consequence, substantial empty channels run between the molecules. (Adapted from F. H. Stillinger, *Science* 209:451-457, 1981.)*



A



B

FIGURE 4.5

Radial distribution function of a normal liquid (A) and of water at 4°C (B). The probability of finding other atoms at radial distance r from a central molecule is given by $g(r)$ times the density of the liquid. The distance r is expressed in A in terms of the van der Waals diameter of the molecule, d . The experimental curve for water measured using X rays is given in B; X rays are scattered primarily by the oxygen atom of the water molecule. (From A. H. Narten and H. A. Levy, *J. Chem. Phys.* 55:2263–2269, 1971.)

TABLE 4.2 Hydrated radii and hydration numbers of ions in water (approximate)

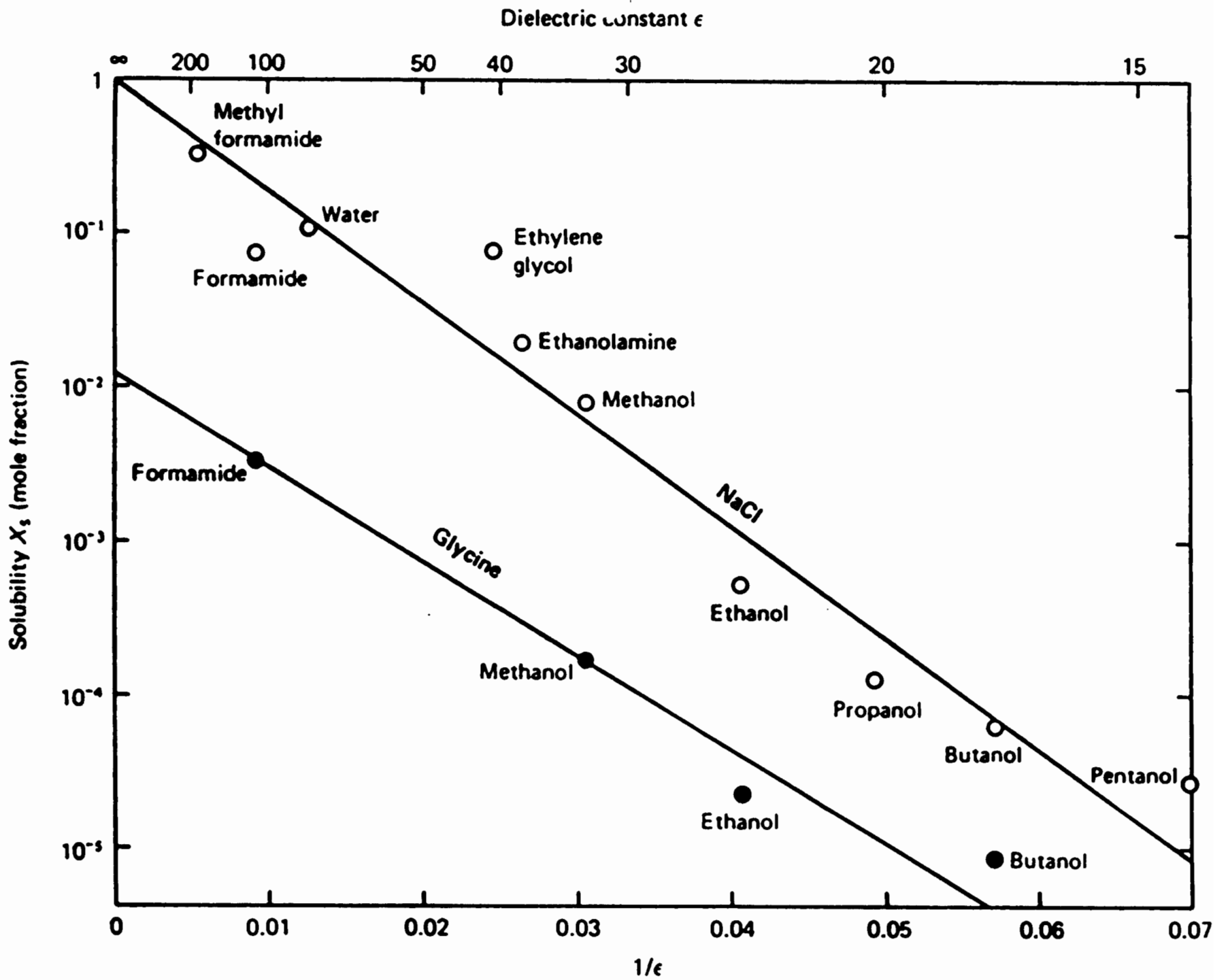
Ion	Bare ion radius (nm)	Hydrated radius (nm)	Hydration number (± 1)	Lifetime (exchange rate) (s)
H ₃ O ⁺	—	0.28	3	—
Li ⁺	0.068	0.38	5–6	10 ⁻⁹ –10 ⁻⁸
Na ⁺	0.095	0.36	4–5	10 ⁻⁹
K ⁺	0.133	0.33	3–4	10 ⁻⁹
Cs ⁺	0.169	0.33	1–2	10 ⁻¹⁰ –10 ⁻⁹
Be ²⁺	0.031	0.46	4 ^a	10 ⁻³ –10 ⁻²
Mg ²⁺	0.065	0.43	6 ^a	10 ⁻⁶ –10 ⁻⁵
Ca ²⁺	0.099	0.41	6	10 ⁻⁸
Al ³⁺	0.050	0.48	6 ^a	10 ⁻¹ –1
OH ⁻	0.176	0.30	3	
F ⁻	0.136	0.35	2	
Cl ⁻	0.181	0.33	1	
Br ⁻	0.195	0.33	1	
I ⁻	0.216	0.33	0	
NO ₃ ⁻	0.264	0.34	0	
N(CH ₃) ₄ ⁺	0.347	0.37	0	

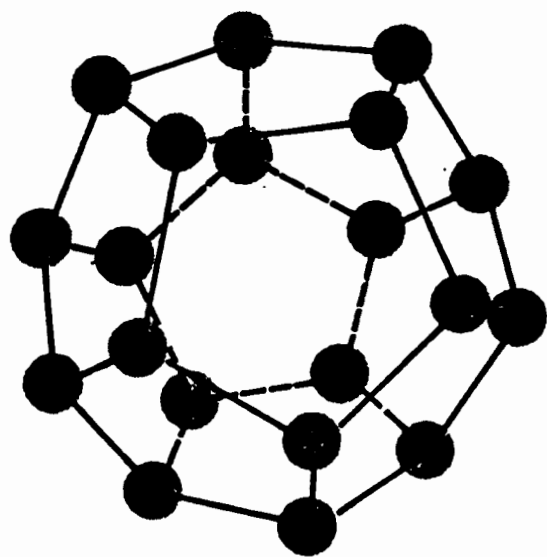
^a Number of water molecules forming a stoichiometric complex with the ion (e.g., [Be(H₂O)₄]²⁺). The hydration number gives the number of water molecules in the primary shell, though the total number of water molecules affected can be much larger and depends on the method of measurement. Similarly, the hydrated radius depends on how it is measured. Different methods can yield radii that can be as much as 0.1 nm smaller or larger than those shown. Table compiled from data given by Nightingale (1959), Amis (1975), Saluja (1976), Bockris and Reddy (1970), Cotton and Wilkinson (1980).

TABLE 3.2 Static dielectric constants^a ϵ of some common liquids and solids at 25°C

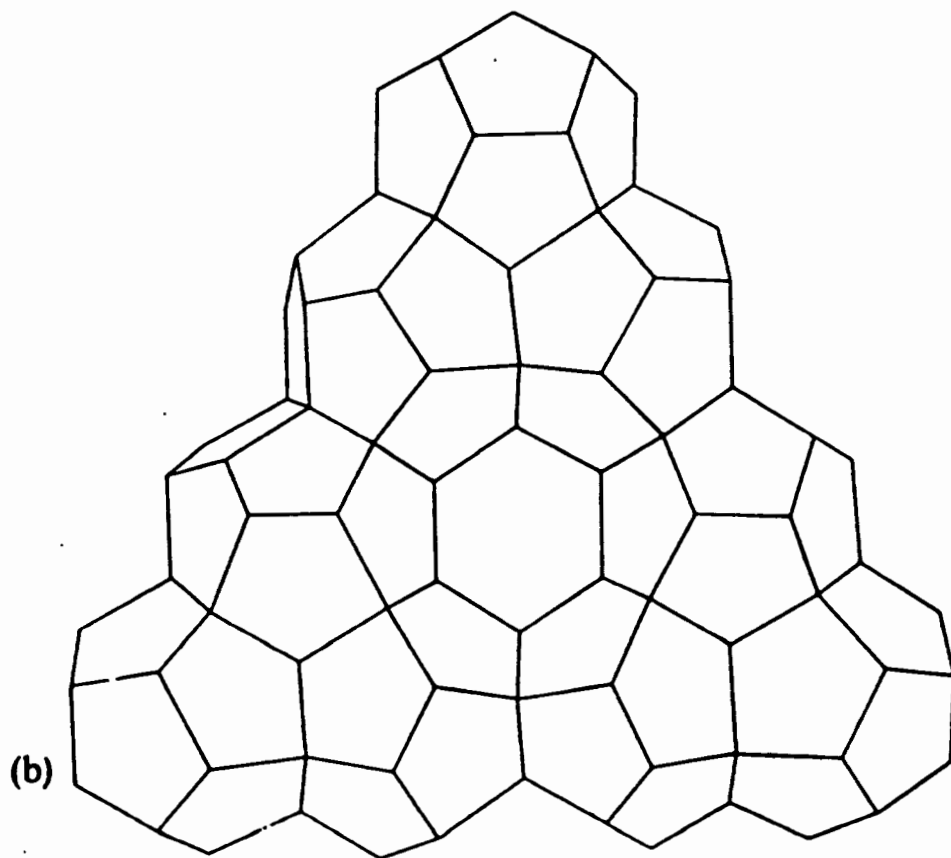
Compound		ϵ	Compound	ϵ
<i>Hydrogen bonding</i>			<i>Polymers</i>	
Methyl formamide	HCONHCH ₃	182.4	Nylon	3.7–4.2
Formamide	HCONH ₂	109.5	Fluorocarbons	2.1–3.6
Hydrogen fluoride	HF (at 0°C)	84	Polycarbonate	3.0
Water	H ₂ O	78.5	Polystyrene	2.4
	D ₂ O	77.9	PTFE	2.0
Formic acid	HCOOH (at 16°C)	58.5	<i>Glasses</i>	
Ethylene glycol	C ₂ H ₄ (OH) ₂	40.7	Fused quartz SiO ₂	3.8
Methanol	CH ₃ OH	32.6	Soda glass	7.0
Ethanol	C ₂ H ₅ OH	24.3	Borosilicate glass	4.5
<i>n</i> -Propanol	C ₃ H ₇ OH	20.2	<i>Crystalline solids</i>	
Ammonia	NH ₃	16.9	Diamond (carbon)	5.7
Acetic acid	CH ₃ COOH	6.2	Quartz SiO ₂	4.5
<i>Non-hydrogen bonding</i>			Micas	5.4–7.0
Acetone	(CH ₃) ₂ CO	20.7	Sodium chloride NaCl	6.0
Chloroform	CHCl ₃	4.8	Alumina Al ₂ O ₃	8.5
Benzene	C ₆ H ₆	2.3	<i>Miscellaneous</i>	
Carbon tetrachloride	CCl ₄	2.2	Paraffin (liquid)	2.2
Cyclohexane	C ₆ H ₁₂	2.0	Paraffin wax (solid)	2.2
Dodecane	C ₁₂ H ₂₆	2.0	Silicone oil	2.8
Hexane	C ₆ H ₁₄	1.9	Liquid helium (2–3 K)	1.055
			Water (liquid at 0°C)	87.9
			Water (ice at 0°C)	91.6–106.4
			Air (dry)	1.00054

^a The dielectric constant is a measure of the extent of reduction of electric fields and consequently of the reduced strengths of electrostatic interactions in a medium.





(a)



(b)

Figure 5-15

Pentagonal dodecahedrons. (a) Pentagonal dodecahedron formed by water molecules (balls) enclosing a cavity of $\sim 5\text{\AA}$ diameter.

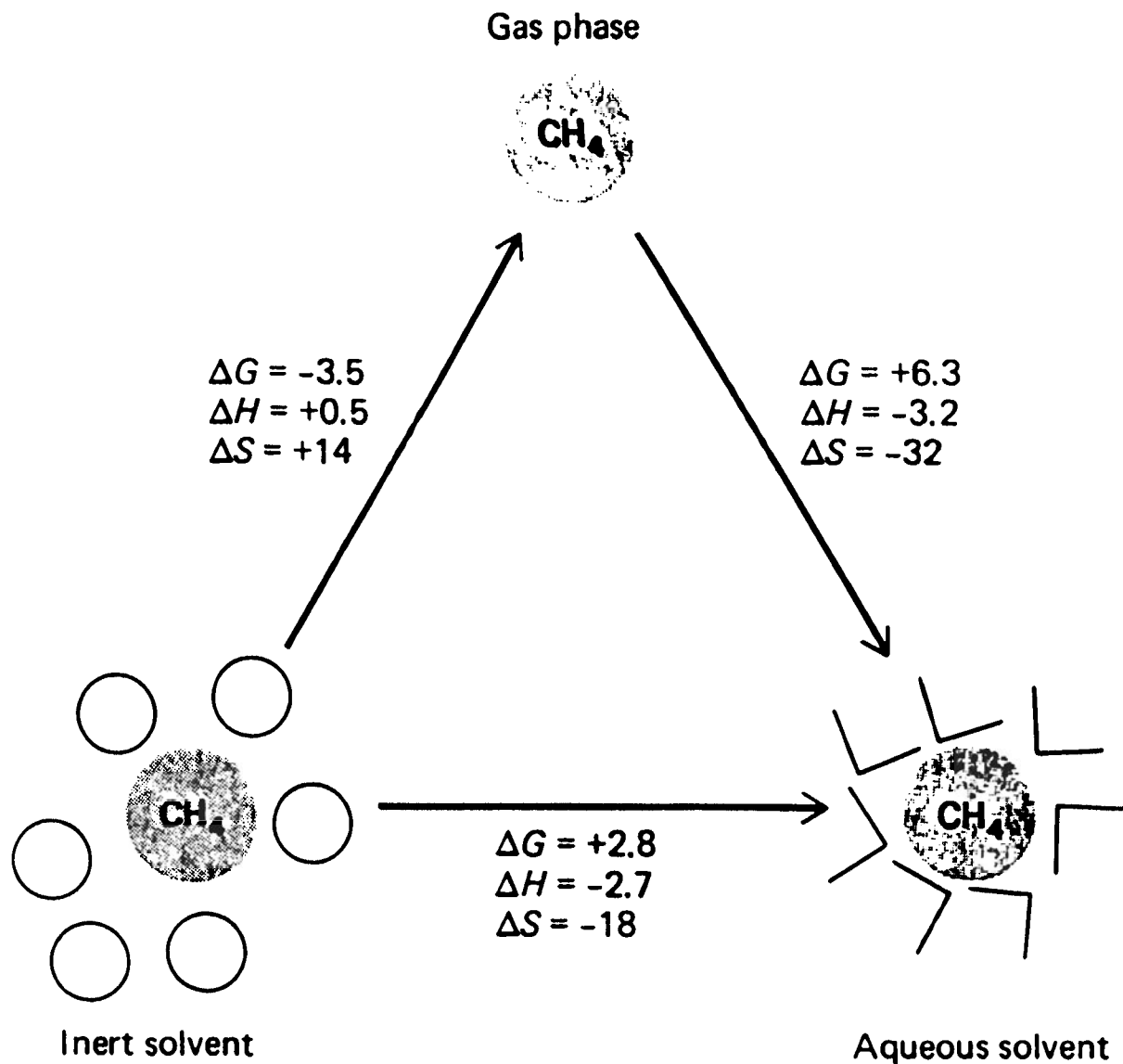


Figure 4-4

*Thermodynamics of the hydrophobic effect. The transfer of one molecule of methane to water from an inert, nonpolar solvent, such as carbon tetrachloride, is illustrated both directly and through the gas phase. The changes in Gibbs free energy, ΔG , and in enthalpy, ΔH , are expressed in kcal/mole; those of entropy, ΔS , in entropy units, kcal/mole/°K. (Adapted from W. P. Jencks, *Catalysis in Chemistry and Enzymology*. New York, McGraw-Hill, 1969.)*

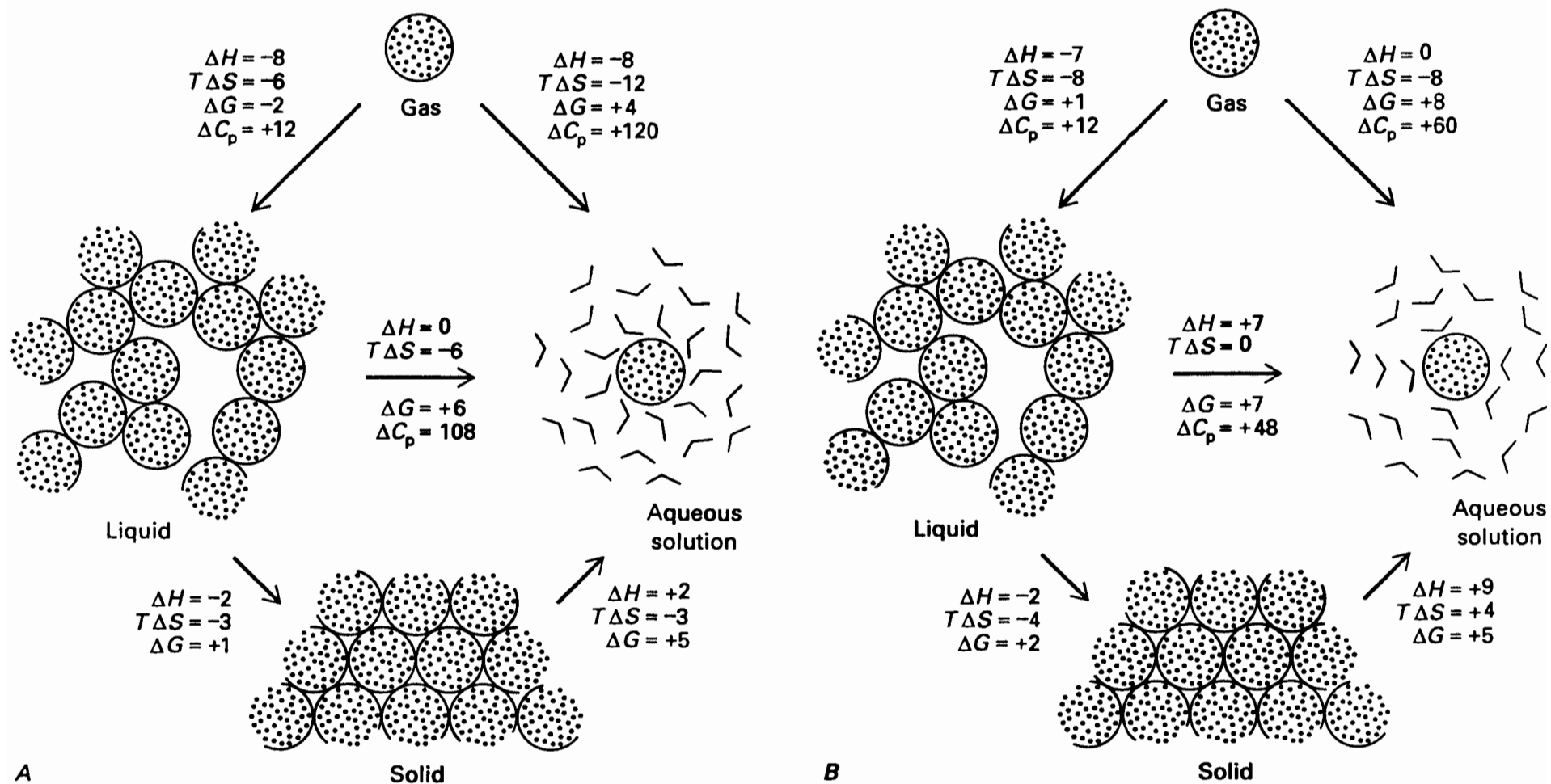


FIGURE 4.9

Typical thermodynamics of transfer of a nonpolar molecule the size of cyclohexane between the gas, liquid, and solid phases and aqueous solution at two temperatures: (A) T_H , approximately 20°C, where $\Delta H_{tr} = 0$ for transfer between liquid and water; and (B) T_S , approximately 140°C, where $\Delta S_{tr} = 0$. The values of ΔH , $T\Delta S$, and ΔG are in units of kcal/mol, that of ΔC_p in units of cal/(K·mol).

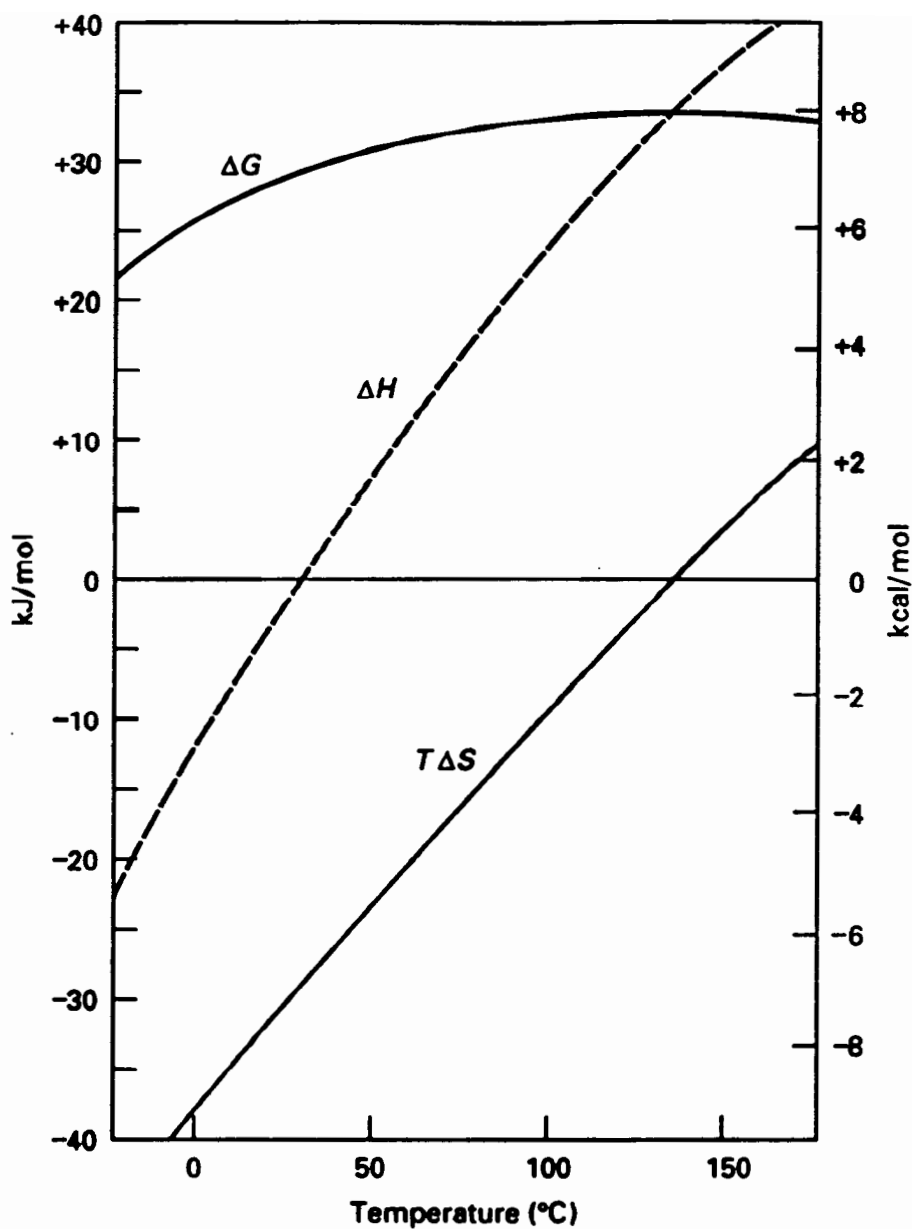


FIGURE 4.10

Typical thermodynamics of the free energy of transfer of a hydrocarbon from the liquid to aqueous solution, using pentane as an example. The strong temperature dependence of both the enthalpy and entropy difference between the two phases is a result of the different heat capacities of the two phases. The free-energy difference is the net difference between the enthalpic (ΔH) and entropic ($T \Delta S$) contributions. It reaches a maximum where $\Delta S = 0$, whereas the equilibrium constant (which is proportional to $-\Delta G/T$) reaches a maximum where $\Delta H = 0$. (Adapted from P. L. Privalov and S. J. Gill, *Adv. Protein Chem.* 39:191–234, 1988.)

TABLE 4-3 *Thermodynamic Changes for the Transfer of Hydrophobic Hydrocarbons from a Nonpolar Solvent to Water*¹

PROCESS	TEMP/K	$\Delta S^\circ/\text{CAL MOL}^{-1}$	$\Delta H^\circ/\text{CAL MOL}^{-1}$	$\Delta G^\circ/\text{CAL MOL}^{-1}$
CH ₄ in benzene → CH ₄ in H ₂ O	298	-18	-2800	+2600
CH ₄ in ether → CH ₄ in H ₂ O	298	-19	-2400	+3300
CH ₄ in CCl ₄ → CH ₄ in H ₂ O	298	-18	-2500	+2900
C ₂ H ₆ in benzene → C ₂ H ₆ in H ₂ O	298	-20	-2200	+3800
Liquid benzene → C ₆ H ₆ in H ₂ O	291	-14 ²	0	+4070 ²
Liquid toluene → C ₇ H ₈ in H ₂ O	291	-16 ²	0	+4650 ²

TABLE 4-4 *Free-Energy Changes for Transfer of Amino Acids to Water at 25°C*¹

AMINO ACID	$\Delta G^\circ/\text{CAL MOL}^{-1}$ FOR TRANSFER	$\Delta G^\circ/\text{CAL MOL}^{-1}$ FOR TRANSFER OF SIDE CHAIN
Glycine	-4630	(0)
Alanine	-3900	730
Valine	-2940	1690
Leucine	-2210	2420
Isoleucine	-1690	2970
Phenylalanine	-1980	2650
Proline	-2060	2600

TABLE 4-5 *Changes in Thermodynamic Quantities for Proteins During Denaturation*¹

PROTEIN	CONDITIONS FOR DENATURATION	$\Delta G/\text{KCAL MOL}^{-1}$	$\Delta H/\text{KCAL MOL}^{-1}$	$\Delta S/\text{CAL MOL}^{-1} \text{ } ^\circ\text{C}^{-1}$	$\Delta C_p/\text{CAL MOL}^{-1} \text{ } ^\circ\text{C}^{-1}$
Ribonuclease	pH 2.5, 30°C	0.9	57	185	2000
Chymotrypsinogen	pH 3, 0.01M Cl ⁻ , 25°C	7.3	39	105	2600
Myoglobin	pH 9, 25°C	13.6	42	95	1900
β -lactoglobulin	5M urea, pH 3, 25°C	0.6	-21	-72	2150

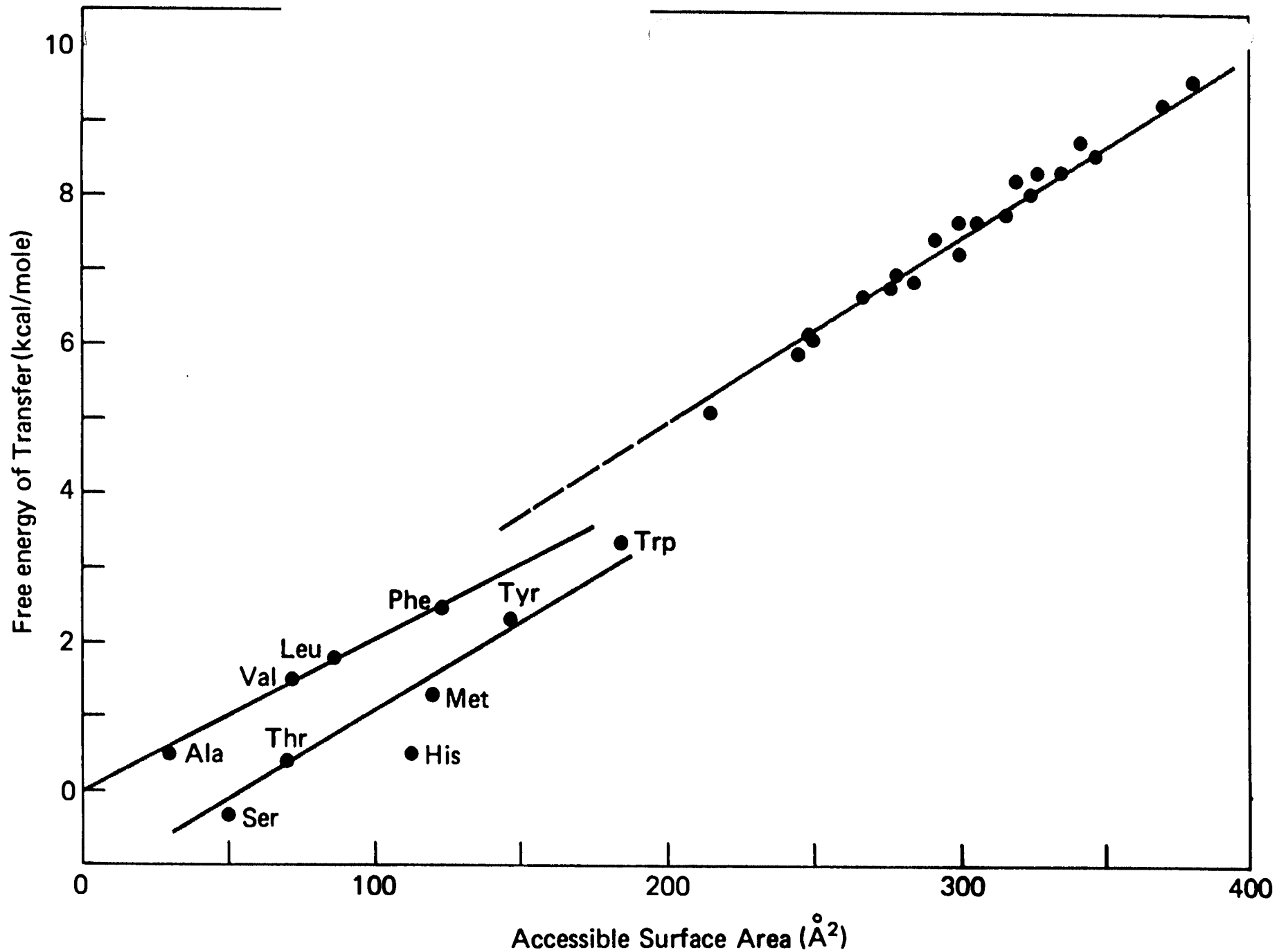


Figure 4-5

Correlation between hydrophobicity and accessible surface area. The unlabeled dots are for various hydrocarbons; the line extrapolates back to the origin and has a slope of 25 cal/Å².

Atomic solvation parameters of proteins in solution

Table 3. *Atomic solvation parameters, $\Delta\sigma$, and their standard deviations derived from Wolfenden et al. (1981) free energies of transfer (Table 2), as modified by Kyte and Doolittle (1982) and by Sharp et al. (1991), in units of $\text{cal mol}^{-1} \text{\AA}^{-2}$*

Parameter	Kyte and Doolittle adjustment	Sharp et al. adjustment
$\Delta\sigma(\text{C})$	4 ± 3	12 ± 3
$\Delta\sigma(\text{O/N})$	-113 ± 14	-116 ± 13
$\Delta\sigma(\text{S})$	-17 ± 22	-18 ± 21
$\Delta\sigma(\text{O}^-)$	-166 ± 38	-175 ± 36
$\Delta\sigma(\text{N}^+)$	-169 ± 31	-186 ± 22

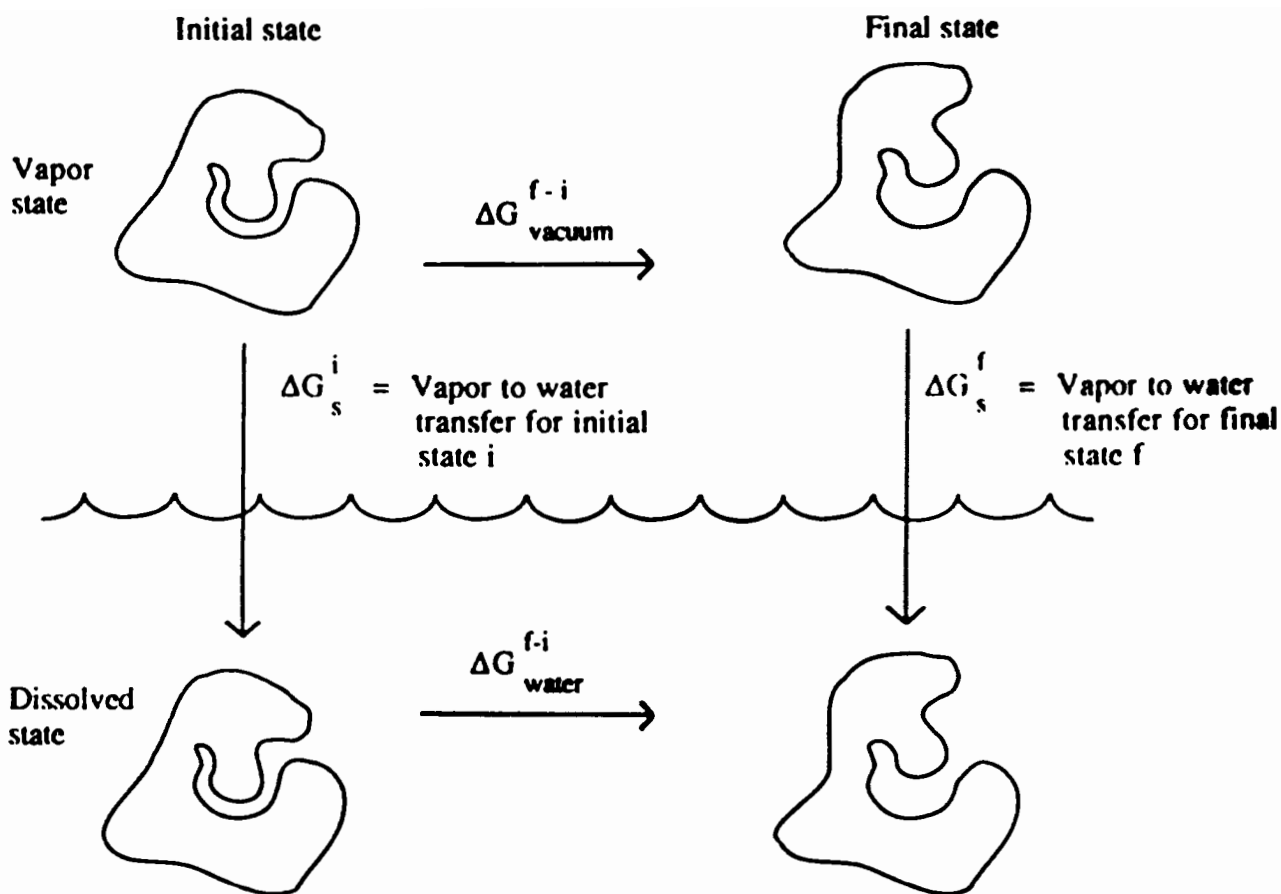


Fig. 1. Thermodynamic cycle that shows how vapor-to-water free energies of transfer may be used to compute protein free energy changes in solution. $\Delta G_{\text{vacuum}}^{f-i}$ is the free energy difference between two conformational states in vacuum, available in principle by molecular simulation. ΔG_s^i and ΔG_s^f are the vapor-to-water free energies of transfer for the protein in the initial and final conformational states. The free energy difference between the two conformational states in water, $\Delta G_{\text{water}}^{f-i}$, may be calculated from the thermodynamic cycle.

Simple treatment of ionic interactions

It is rather difficult to assess the magnitude of the contribution made by ionic interactions to the stability of the native structure. Let us consider the free energy change involved in bringing into contact two oppositely charged ions (see Kauzmann, 1959). We will calculate the difference in free energy ΔG between a final state, in which the charges have approached each other to within the sum of their ionic radii (when they make contact), and an initial state, in which the charges are far enough separated that their interaction energy is negligible. This free energy change is merely the work done on the system in bringing the charges together. For opposite charges this work is negative and is given by

$$\Delta G = - \int_{\infty}^a (z_1 z_2 e^2 / \epsilon r^2) dr \quad (5-15)$$

$$z_1 z_2 e^2 / \epsilon a \quad (5-16)$$

where r is the variable distance of separation, z_1 and z_2 are the ionic valencies of the two ions, e is the electronic charge, and ϵ is the dielectric constant. The parameter a is the contact distance and is equal to the sum of the ionic radii.

Equation 5-16 is only an approximate expression, of course. One shortcoming, among others, is that it was derived on the assumption of constant ϵ , but it is very probable that ϵ varies considerably with r , because the microscopic environment between the two charges changes as they approach each other. If we assume $z_1 = -z_2 = 1$, and $\epsilon = 80$ (which is the dielectric constant of water), then ΔG is approximately -1 kcal mole⁻¹ for $a = 4$ Å. As the charges approach each other near the surface of a protein, however, some lines of force will pass through the protein itself rather than through the solvent. This will tend to lower the effective dielectric constant and will thus increase the magnitude of the net free energy change. On the other hand, the initial separation of charges in a protein in an unfolded state might not be so great as to give rise to even a negligible electrostatic interaction energy. The change in free energy for forming the salt bridge starting from this unfolded state would therefore be correspondingly reduced.

The enthalpy change associated with ion-pair formation can be calculated from Equation 5-16, assuming that a is temperature insensitive.

$$\begin{aligned} \Delta H &= -T^2 [d(\Delta G/T)/dT] = (z_1 z_2 e^2 / \epsilon a) + T(z_1 z_2 e^2 / \epsilon^2 a) (d\epsilon/dT) \\ &= (\Delta G/\epsilon) [d(\epsilon T)/dT] \end{aligned} \quad (5-17)$$

The entropy change is given by

$$\begin{aligned} \Delta S &= -d\Delta G/dT = (z_1 z_2 e^2 / \epsilon^2 a) (d\epsilon/dT) \\ &= (\Delta G/\epsilon) (d\epsilon/dT) \end{aligned} \quad (5-18)$$

Semianalytical Treatment of Solvation for Molecular Mechanics and Dynamics

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Received February 12, 1990

Dealing with solvent has been a perpetual problem for molecular modeling. While using explicit solvent molecules provides one solution to the problem, such calculations require a major computational effort if converged energies are required. Here we describe a more practical alternative in which solvent is treated as a statistical continuum.¹ The treatment provides both energies and derivatives analytically and thus may be used in a molecular mechanics force field. As we will show, it gives small-molecule hydration energies of comparable accuracy to those obtained from contemporary free energy perturbation methods but at only a fraction of the computational expense.

Method. We consider solvation free energy (G_{sol}) traditionally as consisting of a solvent–solvent cavity term (G_{cav}), a solute–solvent van der Waals term (G_{vdW}), and a solute–solvent electrostatic polarization term (G_{pol}):

$$G_{\text{sol}} = G_{\text{cav}} + G_{\text{vdW}} + G_{\text{pol}} \quad (1)$$

Noting that G_{sol} for the saturated hydrocarbons in water is linearly related² to solvent-accessible surface area (SA), we follow precedent^{1a,b} by setting

$$G_{\text{cav}} + G_{\text{vdW}} = \sum \sigma_k \text{SA}_k \quad (2)$$

where SA_k is the total solvent-accessible surface area of atoms of type k and σ_k is an empirical atomic solvation parameter. As a preliminary value for σ_k , we use $+7.2 \text{ cal}/(\text{mol } \text{Å}^2)$ for all atom types to reproduce hydration energies of simple hydrocarbons using our recently described analytical surface area calculation.³

For G_{pol} , the total electrostatic free energy (G_{es} , kcal/mol) of a system of widely separated particles (separations r (Å), charges q (electrons), radii α (Å)) in a medium of dielectric constant ϵ is given (eq 3) by the sum of Coulomb's law in a dielectric (term 1) and the Born equation (term 2). Term 1 can be expanded algebraically (eq 4) to give Coulomb's law in vacuo and a new second term which accounts for the effect of the dielectric medium on the pairwise interactions of charged particles. The sum of terms 2 and 3 in eq 4 is equal to G_{pol} and has been termed the generalized Born (GB) equation.⁴ The similar form of terms 2 and 3 in eq

$$G_{\text{es}} = 332 \sum_{i=1}^{n-1} \sum_{j=i+1}^n \frac{q_i q_j}{r_{ij} \epsilon} - 166 \left(1 - \frac{1}{\epsilon}\right) \sum_i^n \frac{q_i^2}{\alpha_i} \quad (3)$$

$$= 332 \sum_{i=1}^{n-1} \sum_{j=i+1}^n \frac{q_i q_j}{r_{ij}} - 332 \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^{n-1} \sum_{j=i+1}^n \frac{q_i q_j}{r_{ij}} - 166 \left(1 - \frac{1}{\epsilon}\right) \sum_i^n \frac{q_i^2}{\alpha_i} \quad (4)$$

$$G_{\text{pol}} = -166 \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^n \sum_{j=1}^n \frac{q_i q_j}{f_{\text{GB}}} \quad (5)$$

4 prompts us to combine them into a single expression (eq 5) where we define f_{GB} as a function of r_{ij} and α_i which makes eq 5 mimic the relevant equations of classical electrostatics. While we have not defined f_{GB} uniquely, one simple but effective expression is $f_{\text{GB}} = (r_{ij}^2 + \alpha_{ij}^2 e^{-D})^{0.5}$ where $\alpha_{ij} = (\alpha_i \alpha_j)^{0.5}$ and $D = r_{ij}^2 / (2\alpha_{ij})^2$.

Table I. Comparison of Solvation Free Energies from Eqs 2 and 5 with FEP Calculations and Experiment

solute	G_{pol} , kcal/mol		G_{sol} , kcal/mol	
	FEP ^a	eq 5 ^c	expt ^e	eqs 2 + 5 ^f
methanol	-7.1 ± 0.3	-7.1	-5.1 ^{b,d}	-6.2
ethanol	-7.4 ± 0.2	-6.4	-5.0 ^b	-5.2
2-propanol	-7.1 ± 0.3	-5.7	-4.8 ^b	-4.3
acetone	-4.5 ± 0.2	-4.7	-3.9, ^b -3.8 ^d	-3.2
dimethyl ether			-1.9 ^b	-2.0
methyl acetate	-3.1 ± 0.2	-3.9	-3.3 ^b	-2.2
acetic acid	-6.8 ± 0.3	-7.7	-6.7 ^{b,d}	-6.5
<i>N,N</i> -dimethylacetamide	-7.5 ± 0.5	-7.3		
acetamide	-10.8 ± 0.5	-11.4	-9.7 ^b	-10.6
(<i>Z</i>)- <i>N</i> -methylacetamide	-10.1 ± 0.5	-9.0		
(<i>E</i>)- <i>N</i> -methylacetamide	-7.4 ± 0.6	-7.5		
(<i>E</i>)- <i>N</i> -methylacetamide dimer	-4.6 ± 0.2	-5.3		
alanine dipeptide (C7 _{eq})	-13.1 ± 0.4	-12.2		
alanine dipeptide (C5)	-12.3 ± 0.5	-12.4		
alanine dipeptide (α_R)	-20.9 ± 0.7	-18.9		
acetonitrile			-3.9 ^d	-4.8
methyl mercaptan			-1.2, ^b -1.3 ^d	-3.3
benzene	-1.9 ± 0.3	-2.6	-0.9, ^b 0.8 ^c	-1.0
toluene	-0.7 ± 0.2	-1.9	-0.9, ^b -0.8 ^c	-0.1
phenol	-8.0 ± 0.7	-7.7	-6.6 ^b	-6.3
pyridine			-4.7 ^d	-4.4
imidazole			-5.9 ^{d,h}	-6.5
ammonium ion	-103.9 ^g ± 0.7	-91.2	-79 ^d	-90.8
methylammonium ion			-71, ^b -70 ^d	-80.4
trimethylammonium ion			-59 ^d	-63.1
acetate ion	-91.3 ^g ± 1.4	-83.7	-80, ^b -77 ^d	-82.9
ammonium acetate	-47.7 ± 0.9	-43.1		
ethane		0.0	+1.8, ^c ±2.1 ^d	+1.3
<i>n</i> -butane (anti)		0.0	+2.3 ^c	+1.9
<i>n</i> -hexane (all anti)		0.0	+2.6 ^c	+2.4
cyclohexane (chair)		0.0	+1.2 ^c	+1.8
<i>N</i> -octane (all anti)		0.0	+2.9 ^c	+2.9

^aFree energy of transfer from 1 M ideal gas state to 1 M ideal aqueous solution at 25 °C. ^bCabani, S.; Gianni, P.; Mollica, V.; Lepori, L. *J. Solution Chem.* **1981**, *10*, 563. ^cBen-Naim, A.; Marcus, Y. *J. Chem. Phys.* **1984**, *81*, 2016. ^dPearson, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 6109. ^eGeometries obtained by energy minimization in vacuo. ^fGeometries obtained by energy minimization in eqs 2 + 5 water. ^gValue includes a -19.3 kcal/mol Born correction for the 8.5-Å solute-solvent cutoffs employed (Jorgensen, W. L.; Blake, J. F.; Buckner, J. K. *Chem. Phys.* **1989**, *129*, 193). ^hEstimated energy.