

The Energetics of Neighbouring Group Participation

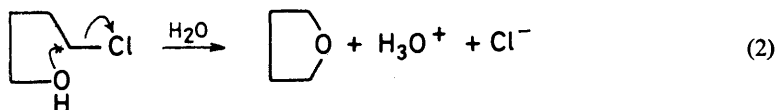
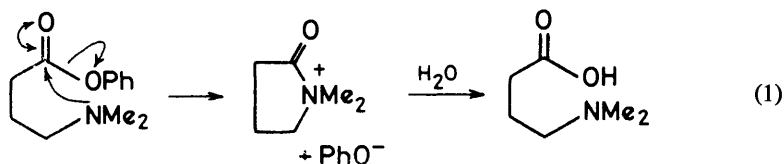
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1 Introduction

Seminal in the development of current chemical thought has been the realization that the rates and the position of equilibria associated with reactions of functional groups are strongly dependent upon the nature of the remainder of the molecule. Such effects of a substituent are usually rationalized in terms of electronic effects transmitted through space or through bonds and steric effects. However, a substituent may exhibit its influence by interacting directly with the reaction centre through partial or complete bonding. In such cases the phenomenon is described as neighbouring group participation.¹

Further classification depends upon how and when participation occurs. If the presence of the neighbouring group increases the rate of the reaction then the term 'anchimeric assistance' is appropriate.² In this case the product may or may not be that expected in the absence of participation [equations (1)³ and (2),⁴



respectively]. In equation (1), the neighbouring group is 'regenerated' in the product and so the phrase 'intramolecular catalysis' is often applied to reactions of this type. If neighbouring group participation occurs after the rate-determining step, *i.e.* in the product-determining step, then the structure of the product is affected but there is no anchimeric assistance.

¹ S. Winstein and R. E. Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2780.

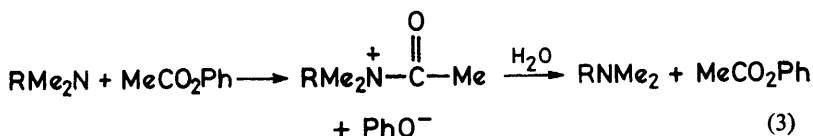
² S. Winstein, C. R. Lindergren, H. Marshall, and L. L. Ingraham, *J. Amer. Chem. Soc.*, 1953, **75**, 147.

³ T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, 1963, **85**, 1.

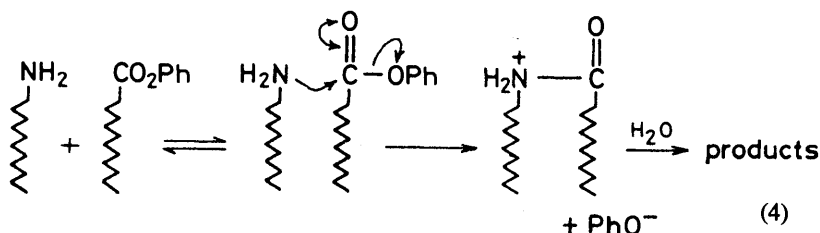
⁴ H. W. Heine, A. D. Miller, W. H. Barton, and R. W. Greiner, *J. Amer. Chem. Soc.*, 1953, **75**, 4778.

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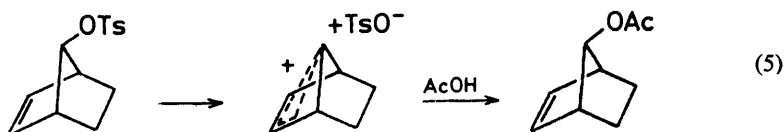
Between the two extremes of an intramolecular reaction, in which the reactants are covalently bound to the same skeleton, and an intermolecular reaction, *e.g.* equation (3),³ lies a vast field of chemistry the classification of which as involving



neighbouring group participation is questionable. These reactions involve the pre-association of catalyst or reactant and substrate through usually weaker forces, often leading to a reversible pre-equilibrium step. This class of reaction includes enzymatic, micellar, and metal-ion catalysis or simply a pre-association step favoured by hydrophobic interactions [equation (4)].⁵



Two approaches are commonly adopted to demonstrate the involvement of neighbouring group participation in a given reaction. Often the magnitude of the anchimeric assistance provided is determined by comparing the rate of the neighbouring group participation reaction with the rate expected in the absence of participation.⁶ For example, the magnitude of homoallylic participation in the acetolysis of *anti*-norborn-2-en-7-yl tosylate, equation (5), is quoted as 10^{11} by



comparison of the first-order rate constant for this reaction with the first-order rate constant for the acetolysis of the analogous saturated compound.⁷ This

³ C. A. Blyth and J. R. Knowles, *J. Amer. Chem. Soc.*, 1971, **93**, 3017; D. G. Oakenfull, *J.C.S. Perkin II*, 1973, 1006.

⁶ B. Capon, *Quart. Rev.*, 1964, **18**, 45.

⁷ S. Winstein and M. Shatavsky, *J. Amer. Chem. Soc.*, 1956, **78**, 592.

approach is similar to that used in estimating the effect of substituents upon the reaction rate. The assumption is made that the rate-determining step of the reaction is the same in the absence and presence of participation or of the substituent group, and therefore it may be said that the substituent or neighbouring group stabilizes the transition state by so many kJ mol⁻¹. It can thus be seen that a classification of some reactions in terms of either normal substituent effects or neighbouring group participation may become artificial in some circumstances.

The second approach is to compare the rate constant for the intramolecular reaction with that of the analogous intermolecular one. This is obviously limited to those systems which have observable analogous intermolecular reactions (although in their absence a lower limit to the magnitude of anchimeric assistance may be obtained). For example, the intermolecular reaction (3) is analogous to the intramolecular reaction (1), the respective rate constants at 25 °C being $1.33 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and $1.67 \times 10^{-1} \text{ s}^{-1}$. The ratio of these rate constants, 1260, has the units of mol dm⁻³ or molarity, M, and is known as the effective molarity or effective concentration. In this particular example, this ratio represents the concentration of trimethylamine required to cause phenyl acetate to undergo reaction (3) with a pseudo first-order rate constant equal to that at which the intramolecular reaction (1) occurs. Such large concentrations as 1260 M are, of course, physically unattainable. It should be noted that the numerical value of this ratio depends upon the units employed to express the second-order rate constant and reactions of type (1) and (3) cannot be rigorously directly compared using thermodynamics because of this units problem. The use of mole fractions would remove this criticism⁸ but it would not affect the relative degree of anchimeric assistance of various intramolecular reactions. This review will therefore adopt the literature practice of using effective concentrations as a measure of the magnitude of anchimeric assistance.

The differences in these two approaches may be seen by considering reaction (1) again. The spontaneous or water-catalysed hydrolysis of phenyl acetate has a first-order rate constant of $1.8 \times 10^{-8} \text{ s}^{-1}$,^{9,10} therefore by the first method described the magnitude of anchimeric assistance is 10⁷. From the comparison of reactions (1) and (3) it has already been mentioned that the effective concentration is 1260 M. These two measurements of neighbouring group participation indicate the effectiveness of an intramolecular amino-group compared with intermolecular 55 M water and an intermolecular amino-group, respectively, in bringing about the hydrolysis of the ester group. In the first method not only is the molecularity different but also the nucleophilicity of the attacking group. The effective concentration provides a measure of just the effect of intramolecularity.

Although so far only rates of reactions have been considered, the effect of intramolecularity is also manifested in equilibria. For example, the equilibrium

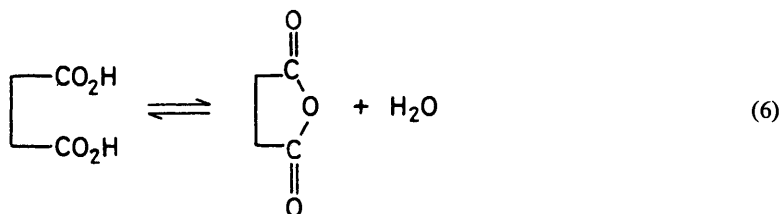
⁸ W. Kauzmann, *Adv. Protein Chem.*, 1959, 14, 1.

⁹ W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, 90, 2622.

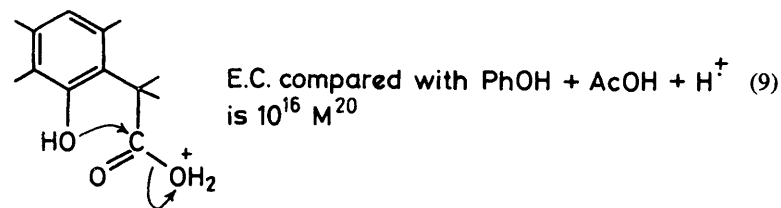
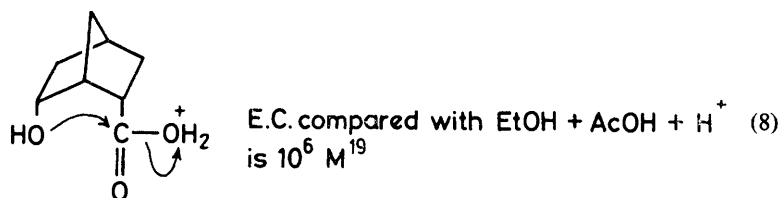
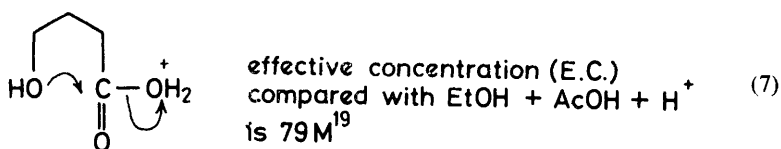
¹⁰ J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, 1964, 86, 837.

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constant for succinic anhydride formation, equation (6), is 3×10^5 M larger than that for acetic anhydride formation.^{11,12}



Since the extensive review by Capon⁶ on neighbouring group participation and intramolecular catalysis, there have been numerous reviews on the subject which have mainly confined themselves to citing examples.¹³⁻¹⁸ Wide variations in the magnitude of anchimeric assistance have been observed, e.g. reactions (7)–(9),



¹¹ W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *J. Amer. Chem. Soc.*, 1966, **88**, 4464.

¹² T. Higuchi, L. Ebersson, and J. D. McRae, *J. Amer. Chem. Soc.*, 1967, **89**, 3001.

¹³ T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms', W. A. Benjamin, New York, 1966, Vol. 1.

¹⁴ W. P. Jencks, 'Catalysis in Chemistry and Enzymology', McGraw-Hill, New York, 1969.

¹⁵ T. C. Bruice, in 'The Enzymes', ed. P. D. Boyer, Academic Press, New York and London, 3rd edn, 1970, Vol. 2, p. 217.

¹⁶ A. J. Kirby and A. R. Fersht, *Progr. Bioorg. Chem.*, 1971, **1**, 1.

¹⁷ B. Capon, *Essays in Chemistry* 1972, **3**, 127.

¹⁸ B. Capon and C. W. Rees, 'Organic Reaction Mechanisms', Wiley-Interscience, London, 1965–1972.

and have led to the suggestion of new concepts and descriptive phraseology.^{19,20} However, the purpose of this Review will be to attempt to present an overall rationalization of neighbouring group participation reactions in terms of presently known and accepted theories.

2 Energetics

Sometimes there is a linear relationship between the rates of a series of related intramolecular reactions and their equilibrium constants.²¹ In such cases a special explanation for the rate differences which is peculiar to the activated complex is not required. Furthermore, the favourable reactions of intramolecular systems over their intermolecular counterparts are manifested in both rates and equilibria. A rationalization of this phenomenon may thus be sought by examining the thermodynamic free-energy differences between reactants and products or between reactants and activated complex. The latter is possible by using the transition-state theory²² for reaction rates. This approach has the advantage of enabling one to examine the thermodynamic state of the molecules, and so with neither rates nor equilibria is it then necessary to be concerned with the probability, kinds, or frequency of collisions between molecules. According to the transition-state theory²² all activated complexes decompose with the same frequency (kT/h), the rate is therefore determined entirely by the free-energy difference between reactants and activated complex, and it is irrelevant to the rate how that complex was reached.

The free-energy difference between two states is given by equation (10),²³ where ΔE_0^0 is the standard temperature-independent potential energy change and comprises all electrical, quantum mechanical, and steric effects, *i.e.* it

$$\Delta G^0 = \Delta E_0^0 - \Delta RT \ln Q \quad (10)$$

includes polar, resonance, and solvation effects, van der Waals interaction, bond angle, bond length, and torsional strain. The second term represents the difference in the partition functions (Q) of the two states and is a measure of the temperature-dependent kinetic energies of motion. The value of the function depends on the motion or degrees of freedom of the molecule as a whole and of the atoms in that molecule. To a useful approximation the partition function may be represented as a product of factors, one for each of the normal modes in terms of which classical mechanics analyses the motions involved. Typically these are translation, rotation, vibration, and internal rotation. As the partition function contribution to the free energy can often be estimated quantitatively in the gas-phase²⁴ this will be considered first, followed by an extrapolation of the conclu-

¹⁹ D. R. Storm and D. E. Koshland, jun. *J. Amer. Chem. Soc.*, 1972, **94**, 5805.

²⁰ S. Milstein and L. A. Cohen, *Proc. Nat. Acad. Sci. U.S.A.*, 1970, **67**, 1143.

²¹ See, for example, refs. 17 and 19.

²² S. Glasstone, K. J. Laidler, and H. Eyring, 'The Theory of Rate Processes', McGraw-Hill, New York, 1941; H. S. Johnston, 'Gas Phase Reaction Rate Theory', Ronald Press Co., New York, 1966.

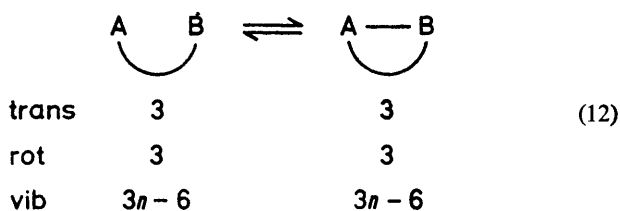
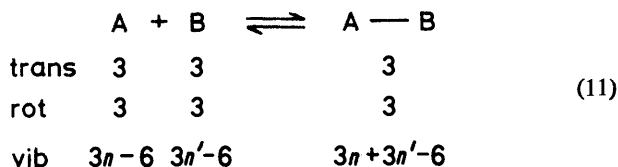
²³ R. W. Taft, in 'Steric Effects in Organic Chemistry', ed. M. S. Newman, Wiley, 1956, Chap. 13.

²⁴ K. S. Pitzer and L. Brewer, 'Thermodynamics', McGraw-Hill, New York, 1961.

sions obtained to the liquid phase. Finally, the contribution of potential energy changes to intra- and inter-molecular reactions will be considered.

3 Entropy Differences

There are different degrees of freedom lost in intramolecular and analogous intermolecular reactions giving rise to large differences in the entropy change between the two systems. Consider a bimolecular reaction (11) and a comparable intra- and uni-molecular reaction (12) in which the product on the right-hand



side of these equations may represent a stable molecule or a transition state. For a non-linear molecule containing n atoms there are three degrees of translational freedom, three degrees of rotational freedom, and $(3n - 6)$ degrees of vibrational freedom. Reaching the transition state or monomolecular product of a bimolecular reaction thus reduces the number of independent species in the system with a consequent loss of three translational and three rotational degrees of freedom. There is a gain of six new vibrational modes in the product of equation (11). However, in the unimolecular reaction (12) there is no net change in the number of degrees of freedom of translation, rotation, and vibration. The differences in energy between these two systems, in the gas phase, may be estimated by calculating the partition functions and thence the related thermodynamic quantities²⁴ e.g.:

$$S = R \ln Q + RT \frac{d \ln Q}{dT} \quad (13)$$

Some typical values of these quantities are shown in Table 1.²⁵

The magnitude of the entropy associated with translational motion (S^0_{trans}) is the only entropy term which depends on the space available to the molecule, hence it is necessary to specify some standard state for a reaction which involves

²⁵ M. I. Page and W. P. Jencks, *Proc. Nat. Acad. Sci. U.S.A.*, 1971, **68**, 1678.

Table 1 Typical entropy and free-energy contributions from translational, rotational, and vibrational motions at 298 K^a

Motion	S^0 J K ⁻¹ mol ⁻¹	$H^0-H_0^0$ kJ mol ⁻¹	$G^0-H_0^0$ kJ mol ⁻¹
Three degrees of translational freedom for mol. wts. 20—200 standard state 1 M	120—148	6.2	-29.6 to -37.9
Three degrees of rotational freedom			
water	43.9 ^b	3.7	-9.4
n-propane	90.0 ^b	3.7	-23.1
endo-dicyclopentadiene	113.8 ^b	3.7	-30.2
Internal rotation ^c	13—21	1.5 ^d	-2.4 to -4.8
Vibrations ω/cm^{-1}			
1000	0.4	0.13	0.0
800	0.8	0.21	-0.04
400	4.2	0.84	-0.42
200	9.2	1.46	-1.30
100	14.2	1.92	-2.33

^a From ref. 25. ^b Symmetry corrected. ^c See text. ^d Typical value; this quantity is a function of the barrier to rotation and the partition function.

a change in the number of molecules present in the system. This review will adopt a standard state of 1 mol dm⁻³ (1 M). The translational entropy of a molecule is proportional to its mass, the temperature, and the volume of space available to it. For a standard state of 1 M and at 298 K, physical constants make up the bulk of the contribution to S^0_{trans} , which varies as $3/2R \ln M$, where M is the molecular weight:*

$$S^0_{\text{trans}} = 82.22 + 28.72 \log M \quad (14)$$

The translational entropy of most molecules therefore has only a small dependence upon mass; *e.g.* if the molecular weight is increased ten times the value of the translational entropy is increased by 28.7 J K⁻¹ mol⁻¹.

A molecule rotates about its centre of gravity and the rotational entropy (S^0_{rot}) is proportional to the moment of inertia, the temperature, and the symmetry of the molecule (σ). S^0_{rot} varies as $\frac{1}{2} R \ln (I_A I_B I_C)$ where I_A , I_B , and I_C are the three principal moments of inertia of the molecule. At 298 K S^0_{rot} is given by equation (15) where D is the product of the three principal moments of inertia. So again for average size molecules the rotational entropy has a relat-

$$S^0_{\text{rot}} = 70.96 + 9.573 \log (D \times 10^{11}) - 19.15 \log \sigma \quad (15)$$

*All entropies are in J K⁻¹mol⁻¹; 4.184 J K⁻¹ mol⁻¹ = 1 cal deg mol⁻¹.

ively small dependence upon the structure of the molecule, *e.g.* a doubling of all three principal moments of inertia increases S^0_{rot} by only $8.8 \text{ J K}^{-1} \text{ mol}^{-1}$.

The vibrational entropy (S^0_{vib}) of a molecule depends upon the frequency of vibration and the temperature, as shown in equation (16) where $u = hc\omega/kT$ and ω is the frequency in cm^{-1} . For frequencies less than 200 cm^{-1} and at 298 K equation (16) may be approximated by equation (17). Vibrational frequencies greater than 1000 cm^{-1} make a negligible contribution to the entropy of the

$$S^0_{\text{vib}} = \frac{Ru}{e^u - 1} - R \ln(1 - e^{-u}) \quad (16)$$

$$S^0_{\text{vib}} \approx 8.33 + 19.15 \log \frac{207.2}{\omega} \quad (17)$$

molecule at 298 K . Although S^0_{vib} for each vibrational mode is generally small (Table 1), the total entropy contribution resulting from vibrational motion within the molecule can be significant because of several low-frequency vibrations.

If groups of atoms within a molecule are connected by a single electron-pair bond then there is an internal rotational motion of these groups against each other and an associated entropy. Some typical values for the entropy of internal rotation ($S^0_{\text{i.r.}}$) are given in Table 1, and are dealt with in more detail below.

For an association reaction such as (11), three translational and three rotational degrees of freedom are converted into vibrational modes and possibly internal rotations. If these new modes are of high frequency ($> 1000 \text{ cm}^{-1}$), and there are no other changes in the contribution of internal motions to the entropy upon conversion of reactants into product or transition state, then association will be accompanied by a large increase in free energy. This is due to the loss of translational and rotational entropy which, for average size molecules, causes an entropy change of *ca.* -210 to $-250 \text{ J K}^{-1} \text{ mol}^{-1}$, equivalent to 63 – 75 kJ mol^{-1} at 298 K . This negative entropy change makes the equilibrium or rate constant for a bimolecular reaction unfavourable by a factor of 10^{11} – 10^{13} . There may be a small compensation of the loss of translational and rotational entropy due to the increased size and mass of the product of transition state, but this total loss represents the *maximum* change upon association. (In the rare situation of the reaction being accompanied by a stiffening of low-frequency vibrations upon conversion of reactants into product, then the reaction may be slightly more unfavourable than this 'maximum'.) Indeed, a few bimolecular associations have entropy changes which are due almost entirely to the loss of translational and rotational entropy. Examples of this are the low-temperature hydrogenation of ethylene,²⁶ some gas-phase radical molecule reactions with 'tight' transition states^{27,28} and the dimerization of propene to cyclohexane. The entropy changes accompanying the latter reaction²⁹ are given in Table 2 for a

²⁶ E. A. Guggenheim, *Trans. Faraday Soc.*, 1941, **37**, 97.




²⁷ S. Bywater and R. Roberts, *Canad. J. Chem.*, 1952, **30**, 773.

²⁸ S. W. Benson, 'Thermochemical Kinetics', Wiley, New York, 1968, Chap. 3.

²⁹ L. S. Kassel, *J. Chem. Phys.*, 1936, **4**, 435; K. S. Pitzer, *ibid.*, 1937, **5**, 473; C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488.




standard state of 1 M and 298 K where S^0_{int} is the entropy due to internal motions (vibrations and internal rotations).

Table 2

		+		→		
S^0_{trans}	128.8		128.8		137.4	$\Delta S^0_{\text{trans}} = -120.2$
S^0_{rot}	89.2		89.2		95.3	$\Delta S^0_{\text{rot}} = -83.1$
S^0_{int}	22.3		22.3		38.9	$\Delta S^0_{\text{int}} = -5.7$
S^0_{total}	240.3		240.3		271.6	$\Delta S^0_{\text{total}} = -209.0$

However, a more common situation is that the product has several new internal rotations or low-frequency vibrations which compensate for the loss of translational and rotational entropy. For example, the gas-phase dimerization of cyclopentadiene (Table 3) gives a product containing low-frequency internal motions³⁰ which causes the entropy change to be $44 \text{ J K}^{-1} \text{ mol}^{-1}$ less negative than that from just considering^{25,31,32} changes in rotational and translational entropy.

Table 3

		+		→		
S^0_{trans}	134.5		134.5		143.1	$\Delta S^0_{\text{trans}} = -125.9$
S^0_{rot}	99.6		99.6		113.8	$\Delta S^0_{\text{rot}} = -85.4$
S^0_{int}	13.9		13.9		71.8	$\Delta S^0_{\text{int}} = +44.0$
S^0_{total}	248.0		248.0		328.7	$\Delta S^0_{\text{total}} = -167.3$

The overall calculated entropy change may be compared with experimental values of from -130 to $-167 \text{ J K}^{-1} \text{ mol}^{-1}$.³³ This appears to be quite a general phenomenon since nearly all gas-phase Diels–Alder reactions have activation and equilibrium entropies of *ca.* -125 to $-170 \text{ J K}^{-1} \text{ mol}^{-1}$.³⁴

In the limit of a very 'loose' transition state or product the low-frequency motions can make the overall entropy change for a bimolecular reaction relatively small. For example, the association of two radicals is generally considered

³⁰ G. B. Kistiakowsky and J. R. Lacher, *J. Amer. Chem. Soc.*, 1936, **58**, 123.

³¹ A. Wassermann, *Proc. Roy. Soc.*, 1941, **A178**, 370; H. E. O'Neal and S. W. Benson, *Internat. J. Chem. Kinetics*, 1970, **2**, 423.

³² H. E. O'Neal and S. W. Benson, *J. Chem. Eng. Data*, 1970, **15**, 266.

³³ W. C. Herndon, C. R. Grayson, and J. M. Manion, *J. Org. Chem.*, 1967, **32**, 526; G. R. Schultze, *Oel Kohle*, 1938, **6**, 113; G. A. Benford and A. Wassermann, *J. Chem. Soc.*, 1939, 362; J. B. Harkness, G. B. Kistiakowsky, and W. H. Mears, *J. Chem. Phys.*, 1937, **5**, 682.

³⁴ A. Wasserman, 'Diels–Alder Reactions', Elsevier, Amsterdam, 1965.

to be encounter controlled³⁵ and thus the transition state is very 'loose'. Typically, the standard entropy change for the combination of two methyl radicals is $-128.9 \text{ J K}^{-1} \text{ mol}^{-1}$, but the entropy of activation is only about $-55 \text{ J K}^{-1} \text{ mol}^{-1}$.²⁸ The difference of about $74 \text{ J K}^{-1} \text{ mol}^{-1}$ may be rationalized by postulating a 'loose' activated complex with four low-frequency rocking modes of the methyl groups, a free internal rotation and an increased rotational entropy (Table 4).^{28,36}

Table 4

	$\text{CH}_3\cdot + \text{CH}_3\cdot \rightarrow [\text{H}_3\text{C} \cdots \text{CH}_3]^\ddagger$		
S^0_{trans}	115.9	115.9	$\Delta S^0_{\text{trans}} = -107.1$
S^0_{rot}	44.8	44.8	$\Delta S^0_{\text{rot}} = -7.6$
S^0_{int}	2.1	2.1	$\Delta S^0_{\text{int}} = +53.5$
$S^0_{\text{total}}^c$	162.8	162.8	$\Delta S^0_{\text{total}} = -61.2$

^aAssuming a C—C distance of 3.5 Å. ^bIncluding free internal rotation and 4 rocking modes of 150 cm^{-1} each. ^cExcluding electronic contributions.

Alternatively, the reaction may be viewed as the collision of two species which are freely rotating within the collision complex as if they were separated from each other.³⁷ The formation of the transition state thus involves the conversion of translational into rotational degrees of freedom.³⁸ This treatment, of course, gives the hard-sphere collision theory approximation of transition-state theory,³⁹ and for average size spheres this corresponds to an entropy change of about $-40 \text{ J K}^{-1} \text{ mol}^{-1}$, corresponding to a collision frequency of $10^{10.5} \text{ M}^{-1} \text{ s}^{-1}$.

In summary, it may be stated that in the gas phase for a standard state of 1 M and 298 K, the entropy change accompanying bimolecular associations may vary from *ca.* -45 to $-210 \text{ J K}^{-1} \text{ mol}^{-1}$ depending on the 'tightness' or 'looseness' of the transition state or product. However, for reactions which are not collision-controlled, the entropy change will generally be *ca.* -125 to $-170 \text{ J K}^{-1} \text{ mol}^{-1}$, making bimolecular associations unfavourable by factors of 10^7 — 10^9 .

Unimolecular reactions.—For intra- and uni-molecular reactions of the type indicated in reaction (12) the translational contribution to the thermodynamic functions is the same for reactant and product or transition state, and hence changes in these functions are independent of the standard state. An examination of the entropy changes accompanying an intramolecular reaction which proceeds *via* a cyclization step suggests that they may be divided into the following categories: (i) ΔS_{rot} : there is a decrease in the moment of inertia associated with the cyclization of an extended chain. However, this effect will generally be small and

³⁵ See, however, R. M. Marshall and J. H. Purnell, *J.C.S. Chem. Comm.*, 1972, 764; R. Hiatt and S. W. Benson, *J. Amer. Chem. Soc.*, 1972, **94**, 6886.

³⁶ S. W. Benson, *Adv. Photochem.*, 1964, **2**, 1; J. H. Purnell and C. P. Quinn, *J. Chem. Soc.*, 1964, 4049; H. E. O'Neal and S. W. Benson, *Internat. J. Chem. Kinetics*, 1969, **1**, 221.

³⁷ T. S. Ree, T. Ree, H. Eyring, and T. Fueno, *J. Chem. Phys.*, 1962, **36**, 281.

³⁸ M. I. Page, *Biophys. Biochem. Res. Comm.*, 1972, **99**, 990.

³⁹ S. W. Benson, 'Foundations of Chemical Kinetics', McGraw-Hill, New York, 1960, p. 273.

decrease the rotational entropy by less than $8 \text{ J K}^{-1} \text{ mol}^{-1}$; (ii) $\Delta S_{1,r}$: cyclization is accompanied by the conversion of restricted internal rotations into torsional modes and this will generally represent a negative entropy change; (iii) ΔS_{vib} : represents the change due to changes in bond stretching and bending vibrations upon cyclization. This will also generally be small and for most cyclizations be between -8 and $+8 \text{ J K}^{-1} \text{ mol}^{-1}$,⁴⁰ (iv) ΔS_{sym} : allowance must be made for the different symmetry properties of the cyclic and acyclic species. $S_{\text{sym}} = R \ln(\sigma/n)$ where σ is the total symmetry number of the molecule and n is the number of optical isomers.²⁴ This will also generally be small.

The loss of internal rotation is usually the largest contribution to changes in entropy upon cyclization. The magnitude of the thermodynamic functions for internal rotations has been estimated theoretically and is in good agreement with experiment. The value depends markedly upon the barrier to rotation.⁴¹ For example, the entropy of free internal rotation in ethane is $12.38 \text{ J K}^{-1} \text{ mol}^{-1}$ at 298 K, but the barrier to rotation of 12.6 kJ mol^{-1} reduces this to $6.95 \text{ J K}^{-1} \text{ mol}^{-1}$.⁴² For the more complex hydrocarbons the entropy of internal rotation increases owing to the increased moments of inertia but this is offset by an increased barrier to rotation. It has been calculated⁴³ that the entropy contribution per internal rotation in an aliphatic hydrocarbon is $18.4 \text{ J K}^{-1} \text{ mol}^{-1}$ at 298 K. This may also be seen by examining the entropy changes accompanying ring closure of aliphatic hydrocarbons shown in Table 5.²⁵ The entropy changes are primarily a consequence of losses of internal rotation, cyclization of C_n linear hydrocarbon transforming $(n - 1)$ internal rotations into ring vibrations. If the small changes in overall rotational entropy, symmetry, stretching and bending vibrations, and the loss of two hydrogen atoms upon cyclization are ignored, the entropy differences between linear and cyclic compounds gives an entropy loss per internal rotation of 11.3 – $18 \text{ J K}^{-1} \text{ mol}^{-1}$ (column 3). The variation is due to differing low-frequency motions in the cyclic product. For example, the pseudorotation of cyclopentane contributes $24.3 \text{ J K}^{-1} \text{ mol}^{-1}$ to the entropy of the molecule,⁴⁴ and the out-of-plane vibration of cyclobutane is associated with an entropy of $15.9 \text{ J K}^{-1} \text{ mol}^{-1}$.⁴⁵ After correction for such low-frequency motions in the C_4 , C_6 , C_7 , and C_8 rings the entropy loss per internal rotation (column 4) is 15.5 to $20.5 \text{ J K}^{-1} \text{ mol}^{-1}$. Entropies of activation for ring-closure reactions are similar or smaller (Table 5). Benson and O'Neal have used an entropy of internal rotation of $20 \text{ J K}^{-1} \text{ mol}^{-1}$ to calculate the entropies of cyclic and polycyclic hydrocarbons,³² and similar values to rationalize the entropies of activation of unimolecular reactions.⁴⁰ A value of 17 – $21 \text{ J K}^{-1} \text{ mol}^{-1}$ for the

⁴⁰ H. E. O'Neal and S. W. Benson, *J. Phys. Chem.*, 1967, **71**, 2903.

⁴¹ K. S. Pitzer, *J. Chem. Phys.*, 1937, **5**, 469; 1946, **14**, 239; K. S. Pitzer and W. D. Gunn, *ibid.*, 1943, **10**, 428; K. S. Pitzer and J. C. M. Li, *J. Phys. Chem.*, 1956, **60**, 466.

⁴² E. A. Guggenheim, *Trans. Faraday Soc.*, 1941, **37**, 97.

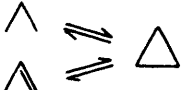

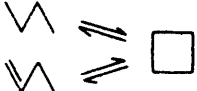

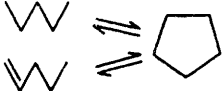

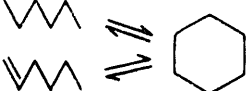
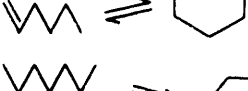
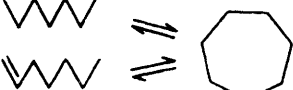

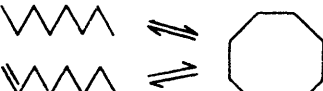
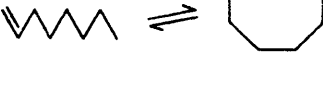
⁴³ K. S. Pitzer, *J. Chem. Phys.*, 1940, **8**, 711, 718; W. B. Person and G. C. Pimentel, *J. Amer. Chem. Soc.*, 1953, **75**, 532.

⁴⁴ C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488; F. A. Miller and R. G. Inskeep, *J. Chem. Phys.*, 1950, **18**, 1519.

⁴⁵ G. W. Rathjens, N. K. Freeman, W. D. Gwinn, and K. S. Pitzer, *J. Amer. Chem. Soc.*, 1953, **75**, 5634.

The Energetics of Neighbouring Group Participation

Table 5 Entropy changes accompanying cyclization at 298 K in $\text{J K}^{-1} \text{mol}^{-1}$

System ^a	ΔS°	$\frac{-\Delta S^{\circ}}{\text{no. int. rot.}}$	$\frac{-\Delta S^{\circ} \text{ corr}}{\text{no. int. rot.}}$
	32.2	16.1	16.1
	29.3	29.3	
	45.6	15.2	20.5
	43.1	21.5	
	55.6	13.9	20.0
	54.8	18.3	
	88.7	17.8	17.8
	87.9	22.0	
	82.8	13.8	15.6
	82.0	16.4	
	79.5	11.3	16.4
	78.6	13.1	
Transition State	ΔS^{\ddagger}	$\frac{-\Delta S^{\ddagger}}{\text{no. int. rot.}}$	
Six-membered			
Claisen rearrangement ^b	- 8 to - 59	2.9 to 19.7	
Cope rearrangement ^c	- 33 to - 50	11.3 to 16.7	
Ester pyrolyses ^d	+ 17 to - 33	- 5.4 to + 11.3	
Five-membered			
$\text{EtNO}_2 \rightarrow \text{C}_2\text{H}_4 + \text{HNO}_2^e$	- 38	18.8	
Four-membered			
Elimination of HX from alkyl halides ^d	+ 20 to - 13	- 20 to + 13	

^a From ref. 25; data from refs. 32, 61, and 140. ^b H. Goering and R. R. Jacobson, *J. Amer. Chem. Soc.*, 1958, **80**, 3277; W. N. White and C. D. Slater, *J. Org. Chem.*, 1962, **27**, 2908. ^c E. G. Foster, A. C. Cope, and F. Daniels, *J. Amer. Chem. Soc.*, 1947, **69**, 1893. ^d Ref. 40. ^e M. C. Fréjacques, *Compt. rend.*, 1950, **231**, 1061.

entropy per internal rotation in an aliphatic hydrocarbon may therefore be accepted with confidence. The loss of entropy upon freezing an internal rotation is partially compensated by a favourable enthalpy function change of about 2 kJ mol^{-1} , so that the increase in free energy upon cyclization is about 4 kJ mol^{-1} per internal rotation,^{25,43} which corresponds to a rate factor of about 5 at 298 K.

It is worth noting that the entropy change accompanying ring closure to seven- and eight-membered rings is less than that for the six-membered ring (Table 5). This is presumably due to low-frequency torsional motions of the methylene groups compensating for the loss of entropy associated with internal rotation. The generally observed higher free energies of formation of seven- and eight-membered rings must thus be due to an enthalpy and not an entropy effect.

Also shown in Table 5 are the entropy changes accompanying ring closure of the corresponding alkenes, which are not significantly different from those of the saturated system which initially has one more internal rotation. This is a consequence of the reduced barrier to rotation of a group adjacent to a double bond and of changes in the symmetry axis in the acyclic compound,⁴⁶ and brings into question the common assumption that ring-closure reactions of unsaturated systems are favourable entropically compared with those of saturated systems.

Gas-phase Examples.—Unfortunately, there are few suitable gas-phase data available to test the predictions made above. For reactions proceeding *via* 'loose' transition states the advantage of intramolecularity should be less marked. The association of radicals is unlikely to have an activation energy,^{47,35} and the frequency factors for the intramolecular ring closure of biradicals are estimated⁴⁸ to be only 10–100 times greater than the corresponding intermolecular reaction of about $10^{10} \text{ M}^{-1} \text{ s}^{-1}$.³⁵ These reactions proceed through loosely structured activated complexes since the transition state closely resembles the initial state, the free radical or biradical.²⁸ The entropy change accompanying the bimolecular reaction is thus not as great as it would be for a more common tighter transition state. For example, the entropy of activation for the gas-phase thermal disrotatory ring closure of hexa-*cis,cis*-1,3,5-triene, reaction (18), which might be



regarded as an intramolecular analogue of the Diels–Alder reaction, is $-20 \text{ J K}^{-1} \text{ mol}^{-1}$.⁴⁹ The difference between this value and that for bimolecular Diels–Alder reactions, such as cyclopentadiene dimerization ($\Delta S^\ddagger = -160 \text{ JK}^{-1} \text{ mol}^{-1}$,^{32,33} see Table 3), corresponds to an entropy advantage of 10^7 M at 25°C for the intramolecular reaction.

⁴⁶ K. S. Pitzer, *J. Chem. Phys.*, 1937, 5, 473, L. S. Kassel, *J. Chem. Phys.*, 1936, 4, 435.

⁴⁷ J. A. Kerr and A. F. Trotman-Dickenson, *Progr. Reaction Kinetics*, 1961, 1, 108.

⁴⁸ H. E. O'Neal and S. W. Benson, *J. Phys. Chem.*, 1968, 72, 1866.

⁴⁹ K. E. Lewis and H. Steiner, *J. Chem. Soc.*, 1964, 3080.

Solution Reactions.—The previous considerations showed that, in the gas phase, intramolecular reactions may have a large entropic advantage over bimolecular associations. It has recently been suggested that this is also true for reactions carried out in solution.²⁵ Entropy is an anthropomorphic concept even at the purely phenomenological level,⁵⁰ and in the absence of a satisfactory theory of liquids^{51,52} it is difficult to assign entropy changes to particular molecular motions in the condensed phase.⁵³ The application of statistical mechanics to liquids is difficult because translational and rotational motions may not be separable⁵⁴ and a suitable model and potential field is required to evaluate the partition functions of such motions.⁵³ Furthermore, observed entropy changes in solution are seldom easy to interpret because of solvation effects.

The entropy of vaporization of a liquid is primarily determined by the increase in volume accompanying the process of vaporization, the acquisition of rotational degrees of freedom frozen or restricted in the liquid and any other changes arising from loss of order in going from the liquid to the gas. Trouton's rule states that the molar entropy of vaporization for all non-associated liquids is about $85 \text{ J K}^{-1} \text{ mol}^{-1}$ at a vapour pressure of 1 atm.⁵⁵ However, approximately half of this quantity is simply the entropy of dilution from a pure liquid to a standard state of 1 atm, 0.045 M. For example, if the pure liquid is 10 M, then only $40 \text{ J K}^{-1} \text{ mol}^{-1}$ of the entropy change is due to effects other than dilution.²⁵ The interpretation of this difference between liquids and gases has been rationalized on a molecular level⁵⁶ although the models used have been criticized.^{53,57} It is questionable whether the partition function in the condensed phase can be separated into various 'contributions', but it is a useful model to ascribe the bulk of this difference to the loss of translational entropy with little loss of entropy that is attributable to rotation in the gas phase.^{25,56,58} Vibrational motions, as determined by i.r. and Raman bands, are not greatly perturbed on transfer from the vapour to the liquid.⁵⁹ Empirical rules for vaporization entropies are valid for solutions to the same extent as for pure liquids.^{59,60}

The difference in the entropy change accompanying a reaction upon transfer

⁵⁰ E. T. Jaynes, *Amer. J. Phys.*, 1965, **33**, 391.

⁵¹ J. A. Barker and D. Henderson, *Ann. Rev. Phys. Chem.*, 1972, **23**, 439, and references therein.

⁵² J. H. Hildebrand and R. L. Scott, 'The Solubility of Non-Electrolytes', Dover, New York, 1964, and references therein.

⁵³ J. H. Hildebrand and E. B. Smith, *J. Chem. Phys.*, 1959, **31**, 1423.

⁵⁴ G. W. Ewing, *Accounts Chem. Res.*, 1969, **2**, 168; H. Welsh and R. Kreigler, *J. Chem. Phys.*, 1969, **50**, 1043; G. W. Ewing and H. Chen, *J. Chem. Phys.*, 1969, **50**, 1044.

⁵⁵ F. Trouton, *Phil. Mag.*, 1884, **18**, 54.

⁵⁶ D. H. Everett, *J. Chem. Soc.*, 1960, 2566; H. S. Frank, *J. Chem. Phys.*, 1945, **13**, 478, 493; J. G. Kirkwood, *J. Chem. Phys.*, 1950, **19**, 380; H. Eyring, D. Henderson, and W. Jost, 'Physical Chemistry—An Advanced Treatise', Academic, New York, 1971, Vols 8A-B Chap. 5.

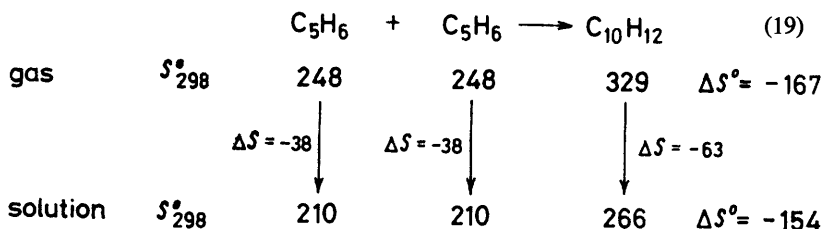
⁵⁷ J. S. Rowlinson, *Trans. Faraday Soc.*, 1971, **67**, 576.

⁵⁸ L. A. K. Staveley and W. I. Tupman, *J. Chem. Soc.*, 1950, 3597; A. Bondi, *J. Phys. Chem.*, 1954, **58**, 929; L. H. Thomas, *J. Chem. Soc. (A)*, 1968, 2609; L. A. K. Staveley, *Ann. Rev. Phys. Chem.*, 1962, **13**, 351.

⁵⁹ H. S. Frank and M. W. Evans, *J. Chem. Phys.*, 1945, **13**, 507.

⁶⁰ I. M. Barclay and J. A. V. Butler, *Trans. Faraday Soc.*, 1938, **34**, 1445.

from the gas to the liquid phase may be deduced from an empirical relationship between the entropies of vaporization at any temperature and the normal boiling point,⁶² or from tabulated values.⁶¹ For example, the dimerization of cyclopentadiene, reaction (19), has an entropy change of $-167 \text{ J K}^{-1} \text{ mol}^{-1}$ at 25°C in the gas phase at a standard state of 1 M. Upon transfer to solution, also at a



standard state of 1 M, it is estimated that cyclopentadiene has an entropy of condensation of $-38 \text{ J K}^{-1} \text{ mol}^{-1}$ and the higher boiling dicyclopentadiene one of $-63 \text{ J K}^{-1} \text{ mol}^{-1}$.²⁵ Thus the entropy change in solution is predicted to be $-154 \text{ J K}^{-1} \text{ mol}^{-1}$, only $13 \text{ J K}^{-1} \text{ mol}^{-1}$ different from the gas phase. The experimental difference is $21 \text{ J K}^{-1} \text{ mol}^{-1}$.⁶² This is in accord with the well-known experimental fact that equilibrium and activation entropies for Diels–Alder reactions of -125 to $-170 \text{ J K}^{-1} \text{ mol}^{-1}$ are very similar in the gas and liquid phases.^{34,63} This is presumably due to the product or transition state having a larger entropy of vaporization than the reactants because of its higher boiling point.²⁵ An extreme example of this effect may be the *negative* difference in the entropy change accompanying NO_2 dimerization from $-151 \text{ J K}^{-1} \text{ mol}^{-1}$ in the gas phase to between -188 and $-226 \text{ J K}^{-1} \text{ mol}^{-1}$ in various solvents.⁶³ When there is no change in the number of molecules in a reaction there appears also to be little difference between the entropy changes in the gas and liquid phases.⁶⁴

Many other bimolecular association reactions, which are apparently free of solvation effects, also have large negative entropy changes in solution. 1,3-Dipolar addition reactions generally have entropies of activation of from -100 to $-170 \text{ J K}^{-1} \text{ mol}^{-1}$,⁶⁵ the morpholine–borane reduction of ketones has $\Delta S^\ddagger = -167 \text{ J K}^{-1} \text{ mol}^{-1}$ and is almost solvent independent,⁶⁶ and the dimerization of dimethyl keten has $\Delta S^\ddagger = -176 \text{ J K}^{-1} \text{ mol}^{-1}$.⁶⁷ With smaller molecules

⁶¹ F. D. Rossini, D. D. Wagman, W. H. Evans, S. Levine, and I. Jaffe, 'Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds', Carnegie Press, Pittsburgh, 1953.

⁶² G. A. Benford and A. Wassermann, *J. Chem. Soc.*, 1939, 367.

⁶³ E. A. Moelwyn-Hughes, 'Physical Chemistry', MacMillan Co., New York 2nd edn., 1961, p. 1026.

⁶⁴ C. M. Blair and D. M. Yost, *J. Amer. Chem. Soc.*, 1933, **55**, 4489.

⁶⁵ R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 633; R. Huisgen *J. Org. Chem.*, 1968, **33**, 2291.

⁶⁶ S. S. White and H. C. Kelly, *J. Amer. Chem. Soc.*, 1970, **92**, 4203.

⁶⁷ R. Huisgen and P. Otto, *J. Amer. Chem. Soc.*, 1968, **90**, 5342.

the entropy changes are expected to be smaller but the values are still highly negative and similar in the gas and liquid phases. The addition of $\text{CF}_3\cdot$ to ethylene has $\Delta S^\ddagger = -100 \text{ J K}^{-1} \text{ mol}^{-1}$ in the gas phase⁶⁸ and $-88 \text{ J K}^{-1} \text{ mol}^{-1}$ in heptane⁶⁹ and the addition of HCN to acetone is solvent-independent and has $\Delta S^\circ \text{ ca. } -112 \text{ J K}^{-1} \text{ mol}^{-1}$,⁷⁰ whereas the calculated value for the gas phase is $-121 \text{ J K}^{-1} \text{ mol}^{-1}$.⁷¹

It is commonly stated that the entropy change in an association reaction is much less negative in solution than it is in the gas phase.⁷² However, there is little evidence to support this claim, as seen above. Small entropy changes are often observed for bimolecular reactions in solution and these may result from (i) a loose transition state or product²⁵ (*cf.* p. 303), this is probably the reason for $\Delta S^\circ \text{ ca. } -40$ to $-80 \text{ J K}^{-1} \text{ mol}^{-1}$ for hydrogen-bonded and charge-transfer complexes, especially since the latter often have similar values in the gas phase;⁷³ (ii) differences in the solvation of polar and hydrophobic groups of reactants, transition states, and products may make large and unpredictable contributions to observed equilibrium and activation entropies, especially in aqueous solution;²⁵ (iii) there may be an intrinsic negative entropy of cavity formation in water⁷⁴ and since two cavities are required for reactants and only one for transition state or product this would have the effect of adding a positive contribution to observed entropies in water.

To summarize, entropy changes of from -125 to $-170 \text{ J K}^{-1} \text{ mol}^{-1}$ are to be expected for many bimolecular reactions in solution, at 25°C this corresponds to a *maximum* entropic rate acceleration of about 10^8 M for a comparable intramolecular reaction.²⁵ Reactions showing effective molarities greater than this are probably the result of additional contributions from potential energy differences. Smaller rate enhancements may result from unfavourable entropy and/or potential energy changes in the intramolecular reaction or a loose product or transition state making the bimolecular reactions entropically less unfavourable.

4 Potential Energy Differences

Differences in potential energy changes between intra- and inter-molecular reactions can either decrease or increase the effective molarity. The forces responsible for this difference may be partitioned into the following, formally independent, contributions: (i) bond stretching; (ii) bond angle bending;

⁶⁸ J. M. Sangster and J. C. J. Thynne, *J. Phys. Chem.*, 1969, **73**, 2746.

⁶⁹ A. A. Weir, P. P. Infecta, and R. H. Schuler, *J. Phys. Chem.*, 1970, **74**, 2596.

⁷⁰ T. Stewart and B. Fontana, *J. Amer. Chem. Soc.*, 1940, **62**, 3281; the ΔS° values quoted in L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1, Table 7 should read ΔH° and *vice versa*.

⁷¹ M. I. Page, unpublished data.

⁷² L. P. Hammett, 'Physical-Organic Chemistry', McGraw-Hill, New York, 1970, 2nd Edn., p. 47.

⁷³ J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions', Wiley, New York 1963, p. 52; R. Foster, 'Organic Charge Transfer Complexes', Academic Press, London, 1969, Chap. 7.

⁷⁴ R. A. Pierotti, *J. Phys. Chem.*, 1963, **67**, 1840; *ibid.*, 1965, **69**, 281; G. Nemethy and H. A. Scheraga, *J. Chem. Phys.*, 1962, **36**, 3382, 3401; O. Sinanoğlu and S. Abdunur, *Fed. Proc.*, 1965, **24**, S-12.

(iii) torsional effects; (iv) attractive and repulsive non-bonded interactions; (v) zero-point energies; (vi) electrostatic interactions such as dipole-dipole and polar effects; (vii) delocalization or resonance energies; (viii) hydrogen-bonding; (ix) solvation. Before discussing these contributions, it is worth emphasizing two points. Firstly, although it is conceivable that all of the above forces may be important, their large number makes it easy to produce *ad hoc* explanations for differences in effective molarities. Secondly, there is by no means universal agreement upon the values of the parameters to be used in the quantitative estimation of the various effects, and although they all have a physical reality (probably containing some areas of overlap), there is a tendency to treat them as adjustable parameters. The assignment of a potential energy difference to a particular contribution is therefore not always as clear-cut as it may seem, and its physical reality may be questionable since it may be an artifact of the computational method. Calculations involving contributions (i)–(v) form the basis of the procedure known as ‘molecular mechanics’, and the models used now are modest modifications of those formulated nearly thirty years ago by Hill,⁷⁵ Ingold,⁷⁶ and Westheimer.⁷⁷ The method has been used successfully to determine ‘strain energies’ and conformations of many molecules,⁷⁸ and even the dynamics of conformational changes⁷⁹ by various minimization techniques,^{78,80,81} and also to reproduce spectra.⁸²

Bond Stretching.—Small deformations in bond lengths are usually assumed to have harmonic restoring forces and thus obey Hooke’s Law. The energy is proportional to the square of the deformation, equation (20), where k_r is the

$$E_r = k_r (r - r_0)^2 \quad (20)$$

force constant and r_0 is the ‘strain-free’ or normal bond length. Using the standard bond lengths found in n-alkanes^{83,84} and the corresponding force constants,⁸⁵ typical equations, with r in Å, are:

$$\begin{aligned} E_{C-C} &= 1369 (r - 1.53)^2 \text{ kJ mol}^{-1} \\ E_{C-H} &= 1333 (r - 1.09)^2 \text{ kJ mol}^{-1} \end{aligned}$$

Deformation of bond lengths is thus very difficult and rarely occurs,^{83,84} and is unlikely to be a factor responsible for differences between intra- and inter-molecular reactions.

⁷⁵ T. L. Hill, *J. Chem. Phys.*, 1946, **14**, 465.

⁷⁶ I. Dostrovsky, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1946, 173.

⁷⁷ F. H. Westheimer and J. E. Mayer, *J. Chem. Phys.*, 1946, **14**, 733.

⁷⁸ J. E. Williams, P. J. Stang, and P. von R. Schleyer, *Ann. Rev. Phys. Chem.*, 1968, **19**, 531.

⁷⁹ K. B. Wiberg and R. H. Boyd, *J. Amer. Chem. Soc.*, 1972, **94**, 8426.

⁸⁰ R. Fletcher and C. M. Reeves, *Computer J.*, 1964, **7**, 149.

⁸¹ K. D. Gibson and H. A. Scheraga, *Comput. Biomed. Res.*, 1970, **3**, 375.

⁸² S. Karplus and S. Lifson, *Biopolymers*, 1971, **10**, 1973.

⁸³ L. S. Bartell and D. A. Kohl, *J. Chem. Phys.*, 1963, **39**, 3097.

⁸⁴ D. R. Lide, jun., *Tetrahedron*, 1962, **17**, 125.

⁸⁵ J. H. Schachtschneider and R. G. Snyder, *Spectrochim. Acta*, 1963, **19**, 117.

Bond Angle Bending.—The deformation of bond angles from their 'normal' value is also usually assumed to be controlled by a harmonic potential, equation (21). The necessary force constants, k_θ , are usually obtained from spectroscopic

$$E_\theta = k_\theta (\theta - \theta_0)^2 \quad (21)$$

measurements and the values of the normal bond angle, θ_0 , are those found experimentally in supposedly 'strain-free' molecules.⁸⁶ For the n-alkanes,^{83,87} typical equations, using the valence force-field analysis of saturated hydrocarbons,⁸⁸ for methylene groups are $E_{\widehat{CCC}} = 0.104 (\theta - 111)^2$ kJ mol⁻¹, $E_{\widehat{CCH}} = 0.0602 (\theta - 109.5)^2$ kJ mol⁻¹, and $E_{\widehat{HCH}} = 0.0504 (\theta - 108)^2$ kJ mol⁻¹. It is sometimes assumed that changes in these angles are linearly related to one another, and hence only one effective methylene group force constant is required to give the total angle strain at a given carbon atom.^{89,90} The above equations could then be replaced by equation (22), which is only applicable

$$E_\theta = 0.113 (\theta - 111)^2 \text{ kJ mol}^{-1} \quad (22)$$

if the methylene groups are constrained to a local C_{2v} symmetry.⁷⁸ Bond angle deformation is fairly easy: *e.g.*, from equation (22), a 10° change costs 11.3 kJ mol⁻¹, and this is the pathway commonly used to relieve non-bonded interaction strain in a molecule.

The extensive analysis of the spectra of hydrocarbons by Snyder and Schachtschneider^{86,88} has provided support for the basic assumption in 'molecular mechanics' that force constants are truly transferable, *i.e.* to a large extent they are independent of the intramolecular environment. However, it is questionable whether the spectroscopic force constants are the ones required to determine strain effects.^{90,91} The value of the force constant depends on the force field employed,⁹² and they are effective or apparent force constants rather than true harmonic ones.⁸⁸ They and the quadratic function also usually *overestimate* the bending energy, especially for large angle deformations.⁹³ Because of these objections, purely empirical force constants are sometimes used⁹³⁻⁹⁵ (although criticized⁹⁶), cubic terms are added,^{95,97} and allowance is made for interaction (stretch-bend *etc.*) force constants.⁹⁵

Torsion.—A clear understanding of the origin of the barrier to internal rotation

⁸⁶ I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332.

⁸⁷ D. R. Lide, jun. *J. Chem. Phys.*, 1960, **33**, 1514, 1519.

⁸⁸ R. G. Snyder and J. H. Schachtschneider, *Spectrochim. Acta*, 1965, **21**, 169.

⁸⁹ J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83**, 4537; *ibid.*, 1967, **89**, 7036.

⁹⁰ M. Bixon and S. Lifson, *Tetrahedron*, 1967, **23**, 769.

⁹¹ K. B. Wiberg, *J. Amer. Chem. Soc.*, 1965, **87**, 1070.

⁹² T. Shimanouchi and I. Nakagawa, *Ann. Rev. Phys. Chem.*, 1972, **23**, 217.

⁹³ K. B. Wiberg and G. M. Lampman, *J. Amer. Chem. Soc.*, 1966, **88**, 4429.

⁹⁴ N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *J. Amer. Chem. Soc.*, 1968, **90**, 1199.

⁹⁵ N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, 1971, **93**, 1637.

in ethane is a long-standing problem in quantum chemistry.⁹⁸ Except when non-bonded interactions are chosen simply to fit this barrier,⁹⁹ it is generally agreed that van der Waals forces alone cannot account for the effect. Therefore the torsional potential is considered to be a separate contribution to the total energy and is usually assumed to be represented by a cosine function:^{100,101}

$$E_{(\phi)} = E_{\phi} (1 \pm \cos n\phi) \quad (23)$$

E_{ϕ} is one half of the barrier height, n depends on the symmetry of rotation, ϕ is the dihedral angle between bonds, and the plus and the minus signs are taken depending on whether $E_{(\phi)}$ has a maximum or a minimum, respectively, at $\phi = 0^{\circ}$. Although the experimental barrier to rotation in ethane is often used as a measure of E_{ϕ} for rotation about C—C single bonds, this leads to an over-estimation of the torsional energy since it includes a contribution from 1,4-nonbonded interactions. The correct value to use for E_{ϕ} depends on the non-bonded interaction functions used. If, for example, this interaction accounts for 10% of the barrier to rotation in ethane, it may be subtracted from the barrier height,^{96,102,103} and the torsional energy about C—C single bonds would be given by:

$$E_{(\phi)} = 5.65 (1 + \cos 3\phi) \text{ kJ mol}^{-1} \quad (24)$$

For dihedral angles up to about 20° , equation (24) may be replaced by a quadratic function (25).^{103,104} Torsional energy is the 'softest' of all the potential energy

$$E_{(\phi)} = 11.30 - 0.00769 (\phi)^2 \quad (25)$$

terms, and hence distortion of dihedral angles is relatively easy. Instead of using the same E_{ϕ} for all types of X—C—C—Y, for which there is some justification,¹⁰⁵ a value dependent on the nature of X and Y is sometimes used.⁹⁷ Separate values are, of course, needed when rotation occurs around a bond which is adjacent to a

⁹⁸ S. Chang, D. McNally, S. S. Tehrani, M. J. Hickey, and R. H. Boyd, *J. Amer. Chem. Soc.* 1970, **92**, 3109.

⁹⁷ J. L. Fry, E. M. Engler, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, 1972, **94**, 4628.

⁹⁶ L. C. Allen and H. Basch, *J. Amer. Chem. Soc.*, 1972, **94**, 2699; W. England and M. S. Gordon, *J. Amer. Chem. Soc.*, 1971, **93**, 4649; O. J. Sovers, G. W. Kern, R. M. Pitzer, and M. Karplus, *J. Chem. Phys.*, 1968, **49**, 2593; L. Radom, A. Latham, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, 1973, **95**, 693.

⁹⁹ E. A. Mason and M. M. Kreevoy, *J. Amer. Chem. Soc.*, 1955, **77**, 5808; H. E. Simmons and J. K. Williams, *J. Amer. Chem. Soc.*, 1964, **86**, 3222.

¹⁰⁰ E. B. Wilson, *Chem. Soc. Rev.*, 1972, **1**, 293.

¹⁰¹ L. Radom and J. A. Pople, *J. Amer. Chem. Soc.*, 1970, **92**, 4786.

¹⁰² R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, 1965, **42**, 2209.

¹⁰³ E. J. Jacob, H. B. Thompson, and L. S. Bartell, *J. Chem. Phys.*, 1967, **47**, 3736.

¹⁰⁴ A. J. Kalls, A. L. H. Chung, and T. L. Allen, *J. Amer. Chem. Soc.*, 1965, **88**, 631.

¹⁰⁵ E. B. Wilson, *Adv. Chem. Phys.*, 1959, **2**, 367; J. Dale, *Tetrahedron*, 1966, **22**, 3373; J. P. Lowe, *Progr. Phys. Org. Chem.*, 1968, **6**, 1.

C=C¹⁰⁶ or a C=O¹⁰⁷ bond and some other environments.^{82, 86, 102, 108-110} Lone pairs of electrons may not affect eclipsing energies¹⁰⁵ and it appears that only the number of opposed bonds is important.¹¹¹

Non-bonded Interaction.—Unfortunately, probably the most important but the least understood energy function is that describing non-bonded interaction.^{78, 108, 112} As a consequence not only is there a variety of functional forms used to describe this interaction, but there is a range of values reported for the parameters of the same functions. Most of the functions in the literature are evaluated empirically from data on gas viscosity, molecular scattering, and other data relating to *inter-molecular* forces. By analogy with intermolecular concepts, the intramolecular interaction energy is assumed to be the sum of short-range repulsive forces and long-range attractive dispersion or London forces. Most treatments have made use of the Buckingham exp-6 (26) or the Lennard-Jones 12-6 (27) potential

$$E_{n.b.} = A \exp(-Br) - Cr^{-6} \quad (26)$$

$$E_{n.b.} = Dr^{-12} - Er^{-6} \quad (27)$$

functions. The attractive potential is taken as the inverse sixth power of the internuclear distance, r , and values of C or E may be derived from atomic polarizabilities¹¹³ using the Slater-Kirkwood equation.¹¹⁴ The parameters used in equations (26) and (27) have been reviewed,^{78, 89, 108, 112, 115} and other recent values may be found in references 79, 82, 95, 97, 106, 107, and 109 and references cited therein.

By the use of an empirical relationship the three parameters in equation (26) may be reduced to two.^{95, 116} The variation in the parameters used for CC and HH non-bonded interaction is exemplified by equations (28)⁹⁵ and (29),⁹⁷ with E in kJ mol⁻¹ and r in Å. The calculation of meaningful non-bonded interaction

$$\left. \begin{aligned} E_{C \dots C} &= 4.018 \times 10^5 \exp(-4.53 r) - 795.8 r^{-6} \\ E_{H \dots H} &= 2.079 \times 10^5 \exp(-4.53 r) - 411.8 r^{-6} \end{aligned} \right\} \quad (28)$$

$$\left. \begin{aligned} E_{C \dots C} &= 6.263 \times 10^4 \exp(-3.15 r) - 2690 r^{-6} \\ E_{H \dots H} &= 1.108 \times 10^4 \exp(-3.74 r) - 114.4 r^{-6} \end{aligned} \right\} \quad (29)$$

¹⁰⁶ N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, 1972, 94, 5734.

¹⁰⁷ N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, 1972, 1173.

¹⁰⁸ H. A. Scheraga, *Adv. Phys. Org. Chem.*, 1968, 6, 103.

¹⁰⁹ J. F. Yan, G. Vanderkooi, and H. A. Scheraga, *J. Chem. Phys.*, 1968, 49, 2713.

¹¹⁰ F. A. Momany, R. F. McGuire, J. F. Yan, and H. A. Scheraga, *J. Phys. Chem.*, 1971, 75, 2286; A. Warshel, M. Levitt, and S. Lifson, *J. Mol. Spectroscopy*, 1970, 33, 84; D. E. Brant and P. J. Flory, *J. Amer. Chem. Soc.*, 1965, 87, 2791.

¹¹¹ S. Wolfe, *Accounts Chem. Res.*, 1972, 5, 102; L. Phillips and V. Wray, *J.C.S. Chem. Comm.* 1973, 90; M. A. Robb and W. J. Haines, *J. Amer. Chem. Soc.*, 1973, 95, 42.

¹¹² F. H. Westheimer, in 'Steric Effects in Organic Chemistry', ed. M. S. Newman, Wiley, New York, 1956, Chap. 12.

¹¹³ J. Ketelaar, 'Chemical Constitution', Elsevier, New York, 1953, p. 91.

¹¹⁴ K. S. Pitzer, *Adv. Chem. Phys.*, 1959, 2, 59.

¹¹⁵ M. Cignitti and T. L. Allen, *J. Chem. Phys.*, 1965, 43, 4472.

¹¹⁶ T. L. Hill, *J. Chem. Phys.*, 1948, 16, 399.

energies is beset by a number of complications. Unlike the free atoms, those in molecules do not possess spherical symmetry. To allow for this anisotropic character of non-bonded interactions it has been suggested that, say, the centre of a hydrogen atom should be shifted along the C—H bond, but still treated as spherical.^{95,117,118} Another problem is that the effective dielectric constant of the molecule may influence the transmission of the forces involved. Finally, the calculations apply to the gas phase and in solution the attractive part of the non-bonded interaction would be decreased by the solvent.¹¹⁹

Non-bonded interactions are normally only considered to operate between atoms separated by three or more bonds; 1,3 interactions are presumed to be incorporated into angle-bending,^{91,120} unless they are treated explicitly as, say, in a Urey-Bradley force field.^{118,121}

It is difficult to make meaningful comparisons between the many different non-bonded force laws since they cannot really be isolated from the other terms in the total potential energy expression. Most of the methods give very similar 'strain-energies' and molecular geometries although, as mentioned earlier as a cautionary note, the origin of the 'strain' may be attributed to different physical terms.

Zero-point Energies.—It is usually assumed that zero-point energy differences are not important, although they may affect the strain energy.¹²² Little work has been done on this contribution.

Electrostatic Interactions.—Differences in dipole-dipole electrostatic interactions may affect the effective molarity. These are sometimes treated in a classical way, as originally suggested by Jeans,^{123,124} which does not allow for induction or mutual polarization effects. A simplified approach is to use partial charges on the individual atoms, obtained from group dipole moments,¹²⁵ and to calculate the electrostatic interaction by Coulomb's law (30) as a function of the distance, r Å, between the partial charges, q expressed in terms of the electronic charge, in a

$$E_{\text{el}} = \frac{q_1 q_2}{Dr} \times 1389 \text{ kJ mol}^{-1} \quad (30)$$

medium of dielectric constant D .^{108,126} On a qualitative basis, a system of alternate positive and negative partial charges imparts stability to a molecule, while destabilization is associated with adjacent like charges. The use of Coulomb's law

¹¹⁷ D. E. Williams, *J. Chem. Phys.*, 1966, **45**, 3770.

¹¹⁸ A. Warshel and S. Lifson, *J. Chem. Phys.*, 1970, **53**, 582.

¹¹⁹ N. R. Kestner and O. Sinanoğlu, *J. Chem. Phys.*, 1963, **38**, 1730.

¹²⁰ L. S. Bartell, *J. Chem. Phys.*, 1960, **32**, 827.

¹²¹ L. S. Bartell, *J. Chem. Educ.*, 1968, **45**, 754.

¹²² B. Nelander and S. Sunner, *J. Chem. Phys.*, 1966, **44**, 2476.

¹²³ J. H. Jeans, 'Mathematical Theory of Electricity and Magnetism', Cambridge University Press, 5th Edn. 1933, p. 377.

¹²⁴ N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. Tyminski, *J. Amer. Chem. Soc.*, 1969, **91**, 337.

¹²⁵ C. J. F. Bottcher, 'Theory of Electric Polarisation', Elsevier, Amsterdam, 1952.

¹²⁶ R. K. Solly, D. M. Golden, and S. W. Benson, *J. Amer. Chem. Soc.*, 1970, **92**, 4653.

should be regarded as a purely empirical procedure since, when two partial charges are not well separated, the solvent molecules and the rest of the solute between and around the two charges do not behave like a continuous medium of constant dielectric constant,¹²⁷ and it is also difficult to know where the point dipoles should be located.¹⁰⁰ For two partial charges separated by greater than one width of water layer it has been suggested¹²⁸ that the effective dielectric constant approaches that of bulk water, 80; hence electrostatic interactions would be negligible at these distances.

Delocalization Energies.—The relief of steric strain may cause loss of some delocalization energy in both intermolecular and intramolecular systems and this may be an important factor contributing to the magnitude of the effective molarity.¹⁷ For example, the effective molarity of anhydride formation, equation (6), may in part be due to the fact that succinic anhydride is a planar molecule¹²⁹ with presumably greater delocalization energy than acetic anhydride which is non-planar by about 45°, as indicated by dipole moment studies.¹³⁰ The energy change may sometimes be calculated, to a first approximation, using the cosine potential for torsion and the barrier to rotation around the bond concerned. In studying 1,2-disubstituted benzene derivatives one has to ensure that the resonance energies are the same in the intramolecular and analogous intermolecular reactions before ascribing rate differences to other effects.¹³¹

Hydrogen Bonding.—Differences in entropy favour intramolecular hydrogen bonds over their intermolecular counterparts.¹³² However, they will be less important in aqueous solution,¹⁴ and also the rates of reactions are normally less affected by hydrogen bonding than by the actual proton transfer itself.¹³³ Intramolecular hydrogen bonding may be important in determining the rates of some reactions, especially in non-aqueous solvents, but it may sometimes be better to attribute rate differences to 'solvent sorting'.¹³⁴ It has been suggested that hydrogen bonding may be treated quantitatively by combining a non-bonded potential with an electrostatic part.¹³⁵

Solvation.—Bimolecular substitution reactions between anions and neutral molecules are faster in dipolar aprotic than protic solvents because in the ground state the anion is much more solvated by the latter and this outweighs any effects due to transition state solvation.¹³⁶ This suggests that an intramolecular substitu-

¹²⁷ M. Gö, N. Gö, and H. A. Scheraga, *J. Chem. Phys.*, 1970, **52**, 2060.

¹²⁸ H. A. Scheraga, *Ann. New York Acad. Sci.*, 1965, **125**, 273.

¹²⁹ R. J. W. LeFèvre and A. Sundaram, *J. Chem. Soc.*, 1962, 4009.

¹³⁰ P. A. Hopkins and R. J. W. LeFèvre, *J. Chem. Soc. (B)*, 1971, 338; O. Exner and V. Jehlicka, *Coll. Czech. Chem. Comm.*, 1970, **35**, 1514; cf. A. Boogaard, H. J. Geise, and F. C. Mijlhoff, *J. Mol. Structure*, 1972, **13**, 53.

¹³¹ J. E. C. Hutchins and T. H. Fife, *J. Amer. Chem. Soc.*, 1973, **95**, 2282.

¹³² H. H. Jaffe, *J. Amer. Chem. Soc.*, 1957, **79**, 2373.

¹³³ W. P. Jencks, *Chem. Rev.*, 1972, **72**, 705.

¹³⁴ B. Capon and M. I. Page, *J. Chem. Soc. (B)*, 1971, 741.

¹³⁵ D. Poland and H. A. Scheraga, *Biochemistry*, 1967, **6**, 3791.

¹³⁶ A. J. Parker, *Chem. Rev.*, 1969, **69**, 1.

tion reaction may be facilitated if solvation of the nucleophile is inhibited in any way,¹⁴ e.g. by steric hindrance. However, it has been concluded that solvation is not important in determining the magnitude of the effective molarity of carboxylate ion attack on an ester.¹³⁷ Furthermore, it has been suggested^{108,138} that the first hydration shell of ions and non-polar solutes contributes very much more to the free energy of solvation than all other solvent molecules. In view of the small size of water molecules¹³⁹ it thus appears that solvation differences will only rarely be important in contributing to the effective molarity of reactions in aqueous solution, providing that the reacting atoms are solvated by at least one layer of solvent molecules.

5 Strain

The strain energy of molecules has to be defined relative to some standard and is often taken as the difference between that calculated from group increment schemes and the observed energy.^{140,141} The calculations described previously are not always possible and it is convenient to have a compilation of strain energies of various molecules for analogy.^{106,140,141} In Table 6 are shown the strain energies of a few cyclic systems relative to their 'strain-free' acyclic analogues.¹⁴⁰ With the exception of sulphur derivatives, the strain is, to a crude approximation, characteristic of the ring size and not of its constituent parts. The strain in the hydrocarbons has been used as a model for the substituted derivatives and a remarkable correlation is obtained between accelerated and decelerated rates of solvolysis and the strain energy difference between the hydrocarbon and carbonium ion.^{97,142}

Intramolecular reactions involve cyclization and the combination of data given in Tables 5 and 6 should permit a rationalization of the relative rates of closure of various ring sizes. The ratio of rate or equilibrium constants involving three-, four-, five-, six-, seven-, and eight-membered rings is thus predicted to be *ca.* 10^{-14} : 10^{-14} : 1 : 10 : 10^{-2} : 10^{-4} , respectively. Although this order is sometimes observed there are many exceptions.^{6,143,143a} Three-membered ring closure is subject to electronic effects peculiar to this ring size, and is therefore not directly comparable with the other rings.^{6,144} This is especially true when there is the possibility of conjugation between the ring and a substituent.¹⁴³ The strain energy of rings containing S atoms is less than O and N derivatives and this favours their relative rates of ring closure. The *ca.* 1—100-fold slower rate of closure of six- compared with five-membered rings in certain S_N2 displace-

¹³⁷ T. C. Bruice and A. Turner, *J. Amer. Chem. Soc.*, 1970, **92**, 3422.

¹³⁸ K. D. Gibson and H. A. Scheraga, *Proc. Nat. Acad. Sci. U.S.A.*, 1967, **58**, 420.

¹³⁹ E. Grunwald, R. L. Lipnick and E. K. Ralph, *J. Amer. Chem. Soc.*, 1969, **91**, 4333.

¹⁴⁰ S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.* 1969, **69**, 279.

¹⁴¹ P. von R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.* 1970, **92**, 2377.

¹⁴² G. J. Gleicher and P. von R. Schleyer, *J. Amer. Chem. Soc.*, 1967, **89**, 582.

¹⁴³ A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. (B)* 1968, 67.

^{143a} J. Dale and J. Krane, *Acta Chem. Scand.* 1972, **26**, 4049.

¹⁴⁴ J. W. Larsen and A. V. Metzner, *J. Amer. Chem. Soc.*, 1972, **94**, 1614.

Table 6 Strain energies of various molecules^a

Molecule	Strain kJ mol ⁻¹	Molecule	Strain kJ mol ⁻¹
Cyclopropane	115.5	Cyclohexane	0
Oxiran	115.5	Tetrahydropyran	9.2
Aziridine	115.9	Piperidine	4.2
Thiiran	74.1	Tetrahydrothiopyran	0
		Cyclohexanone	14.2
Cyclobutane	109.6	Glutaric anhydride	5.9
Oxetan	110.5		
Azetidine	109.6	Cycloheptane	26.8
Thietan	81.0	Cyclo-octane	41.4
Cyclopentane	26.4	2,6- <i>endo</i> -Dimethyl	
Tetrahydrofuran	28.0	bicyclo[2,2,1]heptane	98.7 ^c
Tetrahydropyrrole	28.5		
Tetrahydrothiophen	7.2	Tricyclo[4,2,1,0 ^{3,7}]nonane	94.6 ^c
Cyclopentanone	25.1		
Succinic anhydride ^b	18.8		
Maleic anhydride	19.2		
Succinimide	35.6		

^a Ref. 140. ^b Revised value, S. W. Benson, personal communication. ^c P. von R. Schleyer, personal communication.

ments^{8,143} presumably reflects the unfavourable geometry brought about by a 90° bond angle in the transition state,²⁵ which is also largely responsible for the relative instability of most six-membered compared with five-membered chelate rings.¹⁴⁵ Torsional strain may also favour *sp*³ centres in five- relative to six-membered rings.^{108,146}

The strain energies in Table 6 are not directly applicable to rates, although there may be a correlation between these values and the relative rates, since the estimation of the strain of the transition state depends on the length of the forming bond.¹⁴⁷

6 Stereochemical Requirements

In reactions with severe stereoelectronic demands, intramolecular reactions may be *less* favourable than the analogous intermolecular reaction if the geometry between the interacting groups does not correspond to the favoured configuration. (Indeed, in such cases an alternative reaction path may be followed.) The rate differences within a series of intramolecular reactions may sometimes be rationalized in terms of rate deceleration in the slower reacting substrates rather than in

¹⁴⁵ E. J. Corey and J. C. Bailar, Jr., *J. Amer. Chem. Soc.*, 1959, **81**, 2620.

¹⁴⁶ H. C. Brown and K. Ichikawa, *Tetrahedron*, 1967, **1**, 221.

¹⁴⁷ B. Capon, *J. Chem. Soc. (B)*, 1971, 1207.

terms of special effects leading to rate acceleration in the faster reacting substrates.

The most favourable configuration for reactions proceeding *via* four-electron three-centred bonds, such as S_N2 displacements and proton transfers, is a linear one.¹⁴⁸ The bonding consists of two electrons in a bonding and two in a non-bonding orbital.¹⁴⁹ However, as the system is constrained into an intramolecular cyclic case the interaction between the terminal orbitals increases and moves up in energy and, in the limit, becomes antibonding.¹⁵⁰ Non-linear transition states for these reactions are thus unfavourable. Experimentally, 1,2-proton shifts are very rare.¹⁵¹ For example, the aminolysis of acetylimidazole by several diamines is facilitated by the second amino-group acting as a general base; such is not the case when the diamine is hydrazine.¹⁵² Intramolecular *endocyclic* nucleophilic substitutions are unfavourable and rarely found because of the non-linear transition state involved, but intramolecular *exocyclic* displacements occur readily where a linear configuration is readily attainable.¹⁵³ The importance of the correct geometry for intramolecular reactions of carbonium ions has also been emphasized.¹⁵⁴

7 Participation and Stability

The effect of substituents upon both the equilibria and rates of ionization reactions is not cumulative but appears to be a function of the demand made upon it.¹⁵⁵ Similarly, anchimeric assistance occurs where it is needed and the degree of participation depends upon the stability of the system in the absence of participation.¹⁵⁶ For example, the ability of the double bond, in the solvolysis of 7-aryl-7-*anti*-norbornenyl *p*-nitrobenzoates,¹⁵⁷ and of the cyclopropyl ring, in the solvolysis of 1-aryl-1-cyclopropyl-1-ethyl *p*-nitrobenzoates,¹⁵⁸ to stabilize the incipient carbonium ion centre *increases* as the latter becomes more electron-deficient and *less stable*.

The rate increase brought about by homoallylic participation is 10^{11} in reaction (5)⁷ but is totally absent in the solvolysis of the comparable tosylate of but-4-en-1-ol,¹⁵⁹ and an analogous situation holds for cyclopropane participa-

¹⁴⁸ G. C. Pimentel and A. L. McClellan, *Ann. Rev. Phys. Chem.*, 1971, **22**, 347; P. A. Kollman and L. C. Allen, *Chem. Rev.*, 1972, **72**, 283; H. Fujimoto, S. Yamabe, and K. Fukui, *Tetrahedron Letters*, 1971, 439, 443; J. P. Lowe, *J. Amer. Chem. Soc.*, 1971, **93**, 301; N. L. Allinger, J. C. Tai, and F. T. Wu, *ibid.*, 1970, **92**, 579.

¹⁴⁹ R. Gleiter and R. Hoffmann, *Tetrahedron*, 1968, **24**, 5899.

¹⁵⁰ R. Hoffmann, personal communication.

¹⁵¹ D. S. Kemp, *J. Org. Chem.*, 1971, **36**, 202.

¹⁵² M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, 1972, **94**, 8818.

¹⁵³ L. Tenuid, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta.*, 1971, **53**, 2059.

¹⁵⁴ D. M. Brouwer and H. Hogeveen, *Rec. Trav. chim.*, 1970, **89**, 212.

¹⁵⁵ J. Hine, 'Physical Organic Chemistry', McGraw-Hill, New York, 1962, p. 101; L. D. McKeever and R. W. Taft, *J. Amer. Chem. Soc.*, 1966, **88**, 4544; H. G. Richey and N. C. Buckley, *ibid.*, 1963, **85**, 3057; S. V. McKinley, J. W. Rakskys, A. E. Young, and H. H. Freedman, *ibid.*, 1971, **93**, 4715; E. H. Cordes, *Progr. Phys. Org. Chem.*, 1967, **4**, 1.

¹⁵⁶ S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Amer. Chem. Soc.*, 1952, **74**, 1113.

¹⁵⁷ P. G. Gassman and A. F. Fentiman, *J. Amer. Chem. Soc.*, 1970, **92**, 2549, 2551.

¹⁵⁸ E. N. Peters and H. C. Brown, *J. Amer. Chem. Soc.*, 1973, **95**, 2397.

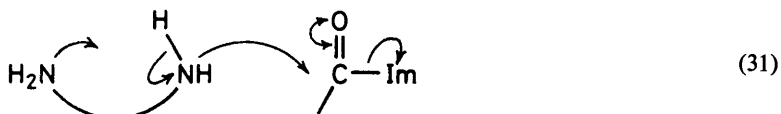
¹⁵⁹ K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, 1964, **86**, 3773.

tion.¹⁶⁰ The absence of participation in the acyclic systems may be due more to the very unstable carbonium ion formed in 7-norbornyl derivatives¹⁶¹ than to correct alignment of the neighbouring group.¹⁶² However, in such comparisons the rate-determining steps may be different and, for example, the 'standard' may or may not involve solvent assistance.¹⁶³

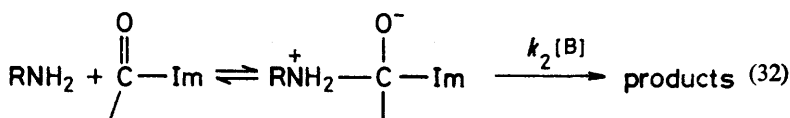
8 Examples

In Table 7 is shown a number of comparisons of inter- and intra-molecular reactions which, except for example 17, proceed *via* the formation of five-membered rings. When comparing rate or equilibrium constants at 25 °C a difference of 10^n is equivalent to a free-energy difference of $5.70n$ kJ mol⁻¹.

Examples 1 and 2 in Table 7 involve proton transfer and, in general, other intramolecular general acid- and base-catalysed reactions show small effective molarities. This could be caused by (i) an unfavourable potential energy effect in the intramolecular reaction such as non-bonded interactions, bond angle, and torsional strain or the non-linear transition state involved (see p. 319), or (ii) a very loose transition state making the intermolecular reaction entropically less unfavourable (see p. 303). The general base-catalysed aminolysis of acetyl-imidazole by several diamines, reaction (31), shows a small sensitivity to the



structure of the diamine indicating that the potential energy effect is not predominant.¹⁵² Furthermore, the intermolecular reaction probably has a diffusion-controlled rate-determining step, k_2 in reaction (32).¹⁶⁴ The transition state is thus very loose and the bimolecular step, k_2 , will be associated with a small entropy change giving rise to the low effective molarities of about 1 M.¹⁵²



Molecules containing the function —CO—XY prefer the *trans* conformation *i.e.* with the XY bond eclipsing the C=O bond. For example, the difference in

¹⁶⁰ H. Tanida, T. Tsuji, and T. Irie, *J. Amer. Chem. Soc.*, 1967, **89**, 1953; Y. E. Rhodes and T. Takino, *ibid.*, 1968, **90**, 4469.

¹⁶¹ J. D. Roberts, F. O. Johnson, and R. A. Carboni, *J. Amer. Chem. Soc.*, 1954, **76**, 5692; R. C. Bingham and P. von R. Schleyer, *ibid.*, 1971, **93**, 3189.

¹⁶² M. Hanack and H. J. Schneider, *Angew. Chem. Internat. Edn.*, 1967, **6**, 666.

¹⁶³ Y. E. Rhodes and T. Takino, *J. Amer. Chem. Soc.*, 1970, **92**, 5270; P. von R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *ibid.*, 1970, **92**, 2542; H. C. Brown and C. J. Kim, *ibid.*, 1971, **93**, 5765; D. J. Raber and J. M. Harris, *J. Chem. Educ.*, 1972, **49**, 60.

¹⁶⁴ M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, 1972, **94**, 8828.

free energy between this conformation, found in esters, and the *cis* conformation in lactones is about 15 kJ mol⁻¹.¹⁶⁵ Combined with the torsional and bending strain found in five-membered rings⁹⁵ and the possibility of strain in some of the acyclic analogues due to loss of resonance in a non-planar conformation (see p. 316) this makes the average strain in five-membered rings about 21 kJ mol⁻¹ (Table 6).¹⁶⁶ The loss of 3 internal rotations accompanying cyclization costs about 12 kJ mol⁻¹. Therefore the effective molarities of such cyclizations as examples 3 to 11 in Table 7 are expected to be less than the maximum predicted from entropy considerations alone and to be *ca.* 10⁸/10^(33/5.7), 10^{2.2}M: since the strain energy of the incipient cyclic system is normally less in the transition state than in the fully formed cyclic product,¹⁴⁷ this prediction is in reasonable agreement with the experimental results (Table 7). Such generalizations are obviously very crude but show that observed effective molarities may be rationalized to within an order of magnitude.

If torsional strain and non-bonded interactions are already present in the initial state of the intramolecular reaction causing it to be as strained as the cyclic product (*cf.* the last two entries in Table 6) then the maximum entropic advantage is expected. Examples 13 to 15 in Table 7 presumably fall into this category, and the effective molarities are about 10⁹ M.

Examples 16 and 17 in Table 7 have effective molarities greater than 10⁸ M and therefore must involve a potential energy effect in addition to the entropic advantage. X-Ray crystallographic studies indicate that the C—C—H angle is 118° in maleic acid¹⁶⁷ but is 128.5° in maleic anhydride.¹⁶⁸ If the methyl groups in dimethylmaleic acid adopt the same conformation as in *cis*-but-2-ene¹⁶⁹ and the same angle change occurred upon cyclization, then the H ··· H distance would increase from 1.53 to 1.98 Å. Even using a 'soft' potential (equation 29)⁹⁷ this relief of non-bonded interaction upon cyclization corresponds to about 22 kJ mol⁻¹ and an advantage of 10⁴ in the equilibrium constant.

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¹⁶⁵ R. Huisgen and H. Ott, *Tetrahedron*, 1969, 6, 253.

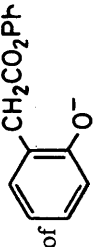
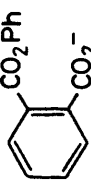
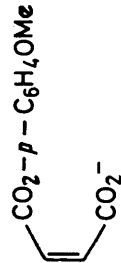
¹⁶⁶ Excluding thiophen and succinimide.

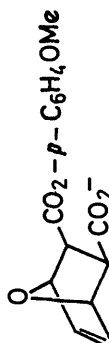
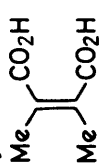
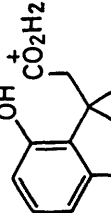
¹⁶⁷ M. Shahat, *Acta Cryst.*, 1952, 5, 763.

¹⁶⁸ R. E. Marsh, E. Ubell, and H. E. Wilcox, *Acta Cryst.*, 1962, 15, 35.

¹⁶⁹ A. Almendinger, I. M. Afinsen, and A. Haaland, *Acta Chem. Scand.*, 1970, 24, 43.

Table 7 A comparison of some inter- and intramolecularly catalysed reactions in water

Intramolecular reaction	Intermolecular reaction	Temp/°C	Effective molarity/ mol.dm ⁻³	Ref.
1. Enolization of MeCOCH ₂ CH ₂ CO ₂ ⁻	AcO ⁻ + MeCOCH ₂ CH ₂ CO ₂ Et	25	0.5	a
2. Aminolysis of AcIm by H ₂ NCH ₂ CH ₂ NH ₂	RNH ₂ + RNH ₂ + AcIm	25	0.6	b
3. Hydrolysis of PhO ₂ CCH ₂ CH ₂ CO ₂ ⁻	AcO ⁻ + MeCO ₂ Ph ^c	25	5.1 × 10 ⁴	d,e
4. Lactonization of PhO ₂ CCH ₂ CH ₂ CH ₂ O ⁻ f	MeO ⁻ + MeCO ₂ Ph	25	5.0 × 10 ³	g,h
5. Hydrolysis of PhO ₂ CCH ₂ CH ₂ CH ₂ NMe ₂	NMe ₃ + MeCO ₂ Ph	20	1.3 × 10 ³	i
6. Lactonization of H ₂ O ₂ CCH ₂ CH ₂ CH ₂ OH	EtOH + MeCO ₂ H ₃	25	80	j,k
7. Cyclization of ⁻ O(CH ₂) ₄ Cl/	EtO ⁻ + EtCl ^{l,m}	30	8.1 × 10 ⁴	n,o
8. Hydrolysis of HO(CH ₂) ₄ Cl	H ₂ O + C ₂ H ₅ Cl ^{l,p}	55	2.4 × 10 ⁴	q,r
9. Hydrolysis of ⁻ O ₂ C(CH ₂) ₃ Cl	AcO ⁻ + C ₂ H ₅ Cl ^{l,s}	37.5	8.5 × 10 ²	n,t
10. Cyclization of H ₂ N(CH ₂) ₄ Br	NEt ₃ + C ₂ H ₅ Br ^u	25	1.4 × 10 ⁴	v,t
11. Cyclization of (EtO ₂ C) ₂ C(CH ₂) ₄ Br ^w	HC(CO ₂ Et) ₂ + C ₂ H ₅ Br ^m	25	4.6 × 10 ³	x,y
12. Lactonization of 	PhO ⁻ + CH ₃ CO ₂ Ph	25	2.5 × 10 ⁵	g,z
13. Hydrolysis of 	AcO ⁻ + CH ₃ CO ₂ Ph ^c	30	1.8 × 10 ⁶	aa,e
	RCO ₂ ⁻ + PhCO ₂ Ph	30	~ 1.0 × 10 ⁶	bb,cc
14. Hydrolysis of 	AcO ⁻ + MeCO ₂ -p-C ₆ H ₄ OMe ^c	25	1.8 × 10 ⁶	d,e
	RCO ₂ ⁻ + MeCH=CHCO ₂ -p-C ₆ H ₄ OMe	25	~ 2.8 × 10 ⁶	dd,cc

15. Hydrolysis of  $\text{CO}_2\text{-}p\text{-C}_6\text{H}_4\text{OMe}$ CO_2^- 25 9.1×10^7 *d,e*
25 $\sim 1.1 \times 10^9$ *ee*
16. Equilibrium anhydride formation of  $\text{Me-CO}_2\text{H}$ CO_2H 25 2×10^{13} *ff,gg*
17. Lactonization of  $\text{OH} + \text{CO}_2\text{H}_2$ 30 3×10^{15} *hh*

^a R. P. Bell and M. A. D. Fluently, *Trans. Faraday Soc.*, 1963, 59, 1623; R. P. Bell and P. DeMaria, *ibid.*, 1970, 66, 930. ^b M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, 1972, 94, 8818. ^c Based on estimated nucleophilic catalysis from Bronsted plot. ^d T. C. Bruice and U. K. Pandit, *J. Amer. Chem. Soc.*, 1960, 82, 5858. ^e V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc. (B)*, 1968, 515. ^f pK_a of ROH taken as 15.9. ^g B. Capon, S. T. McDowell, and W. V. Raftery, *Chem. Comm.*, 1971, 389. ^h W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, 90, 2622. ⁱ T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, 1963, 85, 1. ^j Ref. 19, 20% v/v ethanol. ^k J. Gerstein and W. P. Jencks, *J. Amer. Chem. Soc.*, 1964, 86, 4655. ^l $k_{\text{RCI}}/k_{\text{RBR}}$ taken as 0.02. ^m Solvent ethanol. ⁿ Ref. 6. ^o M. L. Dhar, E. D. Hughes, C. K. Ingold, and S. Masterman, *J. Chem. Soc.*, 1948, 2055. ^p Solvent 4:1 EtOH:H₂O molarity of water taken as 11 M. ^q H. H. Heine, A. D. Miller, W. H. Barton and R. W. Greiner, *J. Amer. Chem. Soc.*, 1953, 75, 4778. ^r L. C. Bateman, K. A. Cooper, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1940, 925. ^s $k_{\text{RCI}}/k_{\text{RBR}}$ taken as 2. ^t S. Eagle and J. C. Warner, *J. Amer. Chem. Soc.*, 1939, 61, 488. ^u Extrapolated data to 100% water by plotting $\log k$ vs. $(\epsilon - 1)/(2\epsilon + 1)$. ^v H. Freundlich and H. Kroepelin, *Z. Phys. Chem.*, 1926, 122, 39. ^w M. L. Bender and W. A. Glasson, *J. Amer. Chem. Soc.*, 1959, 81, 1590. ^{aa} J. W. Thanassi and T. C. Bruice, *J. Amer. Chem. Soc.*, 1966, 88, 747. ^{ab} Solvent t-butyl alcohol. ^{ac} A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. (B)*, 1968, 67. ^{ad} R. G. Pearson, *J. Amer. Chem. Soc.*, 1949, 71, 2212. ^{ae} For RCO_2H of pK_a 2.9, estimated assuming $\beta = 1.0$ and $k_{\text{RCO}_2\text{H}}/k_{\text{MeCO}_2\text{H}} = 8.7 \times 10^{-4}$. ^{af} R. W. Taft, jun., in ref. 23, p. 556. ^{ag} For RCO_2H of pK_a 2.7, estimated assuming $\beta = 1.0$ and $k_{\text{MeCH}=\text{CHCO}_2\text{H}}/k_{\text{MeCO}_2\text{H}} = 6.3 \times 10^{-4}$. ^{ah} For RCO_2H of pK_a 3.5, estimated assuming $\beta = 1.0$. ^{ai} L. E. Ebersohn and H. Weifelder, *J. Amer. Chem. Soc.*, 1971, 93, 5821. ^{aj} W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *J. Amer. Chem. Soc.*, 1966, 88, 4464. ^{ak} S. Milstein and L. A. Cohen, *J. Amer. Chem. Soc.*, 1972, 94, 9158 in 20% dioxan-water.