

Kinetics of Reactions in Aqueous Mixtures

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1 Introduction

The dependences of kinetic parameters for reactions on the composition of mixed aqueous solvents often afford complicated patterns. Several examples, involving organic and inorganic substrates and a variety of kinetic parameters such as enthalpies, entropies, volumes, and heat capacities of activation, are shown in Figures 1—3. Such patterns cannot but arouse interest and enquiry.

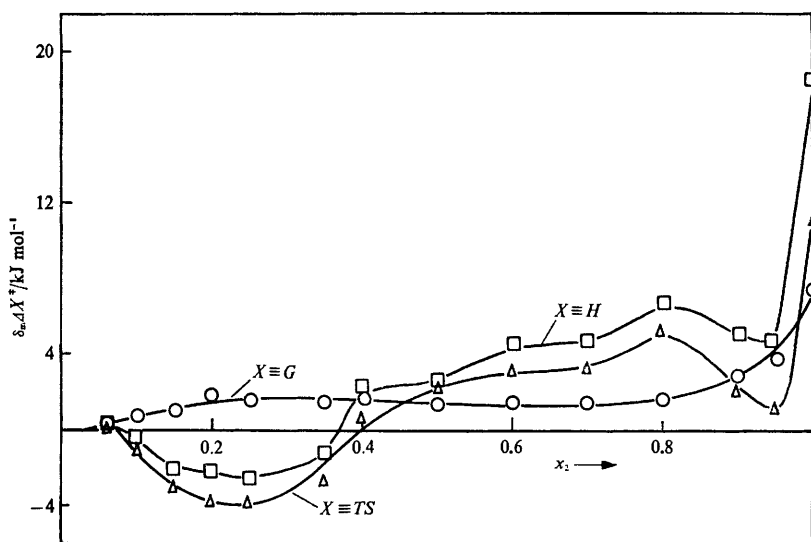


Figure 1 Dependence of activation parameters on solvent composition: $\delta_m \Delta G^\ddagger$ (\circ), $\delta_m \Delta H^\ddagger$ (\square), and $T\delta_m \Delta S^\ddagger$ (\triangle) for reaction between nickel(II) and 2,2'-bipyridyl in methanol + water mixtures at 298 K (values taken from references cited in text)

In aqueous solutions, at least, it has become clear that an important aspect of the activation process is the reorganization of the solvent surrounding the reacting solute(s).¹⁻³ Not surprisingly, such reorganizations will be profoundly

¹ E. A. Moelwyn-Hughes, 'The Chemical Statics and Kinetics of Solutions,' Academic Press, London, 1971.

² R. E. Robertson, *Progr. Phys. Org. Chem.*, 1967, 4, 213.

³ E. F. Caldin and H. P. Benetto, *J. Solution Chem.*, 1973, 2, 217.

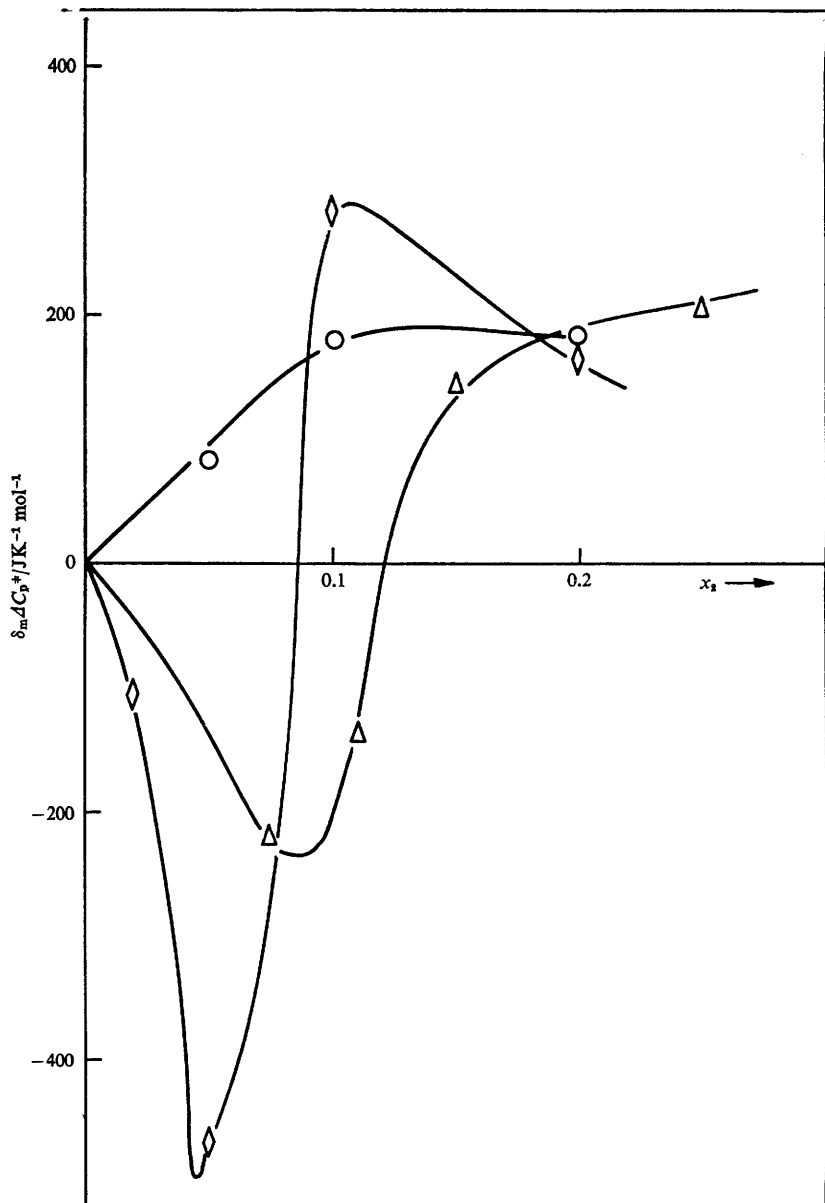


Figure 2 Dependence of activation parameters on solvent composition: $\delta_m \Delta C_p^\ddagger$ for the solvolysis of *t*-butyl chloride in binary aqueous mixtures containing *t*-butyl alcohol (\diamond), ethanol (\triangle), and acetonitrile (\circ) (values taken from references cited in text)

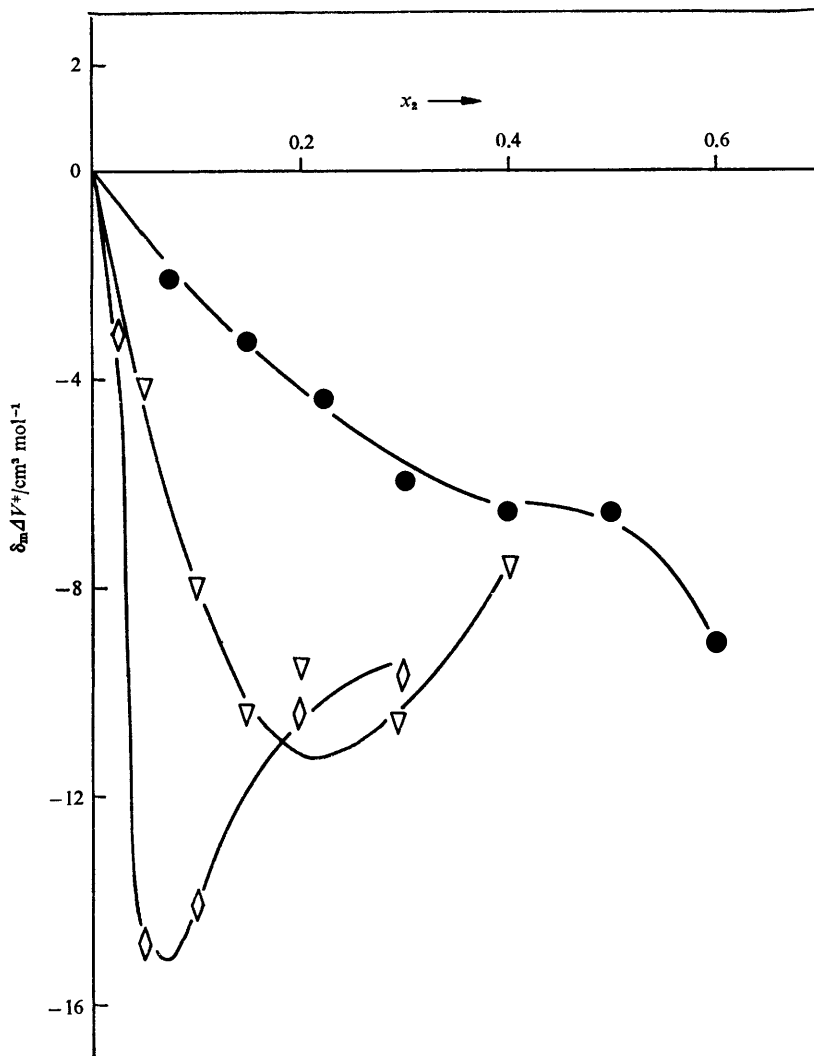


Figure 3 Dependence of activation parameters on solvent composition: $\delta_m \Delta V^\ddagger$ ($p = 0$, 323 K) for the solvolysis of benzyl chloride in binary aqueous mixtures containing *t*-butyl alcohol (◇), acetone (△), and DMSO (●) (values taken from references cited in text)

affected by addition of a co-solvent to these aqueous solutions. Indeed it is now clearly recognized that the action of the non-aqueous component of a mixture is more than as a simple diluent of water or modifier of its dielectric properties. To understand the complex patterns of the type shown in Figures 1—3, it is

necessary to investigate how reactants and transition states are affected when a co-solvent is added to the reacting system in water.

In this present Review we shall firstly deal with such properties of binary aqueous mixtures and solute-solvent interactions as are relevant to our main topic. We shall then define and discuss the thermodynamic transfer functions used as the basis of our discussion of the kinetic patterns observed in binary aqueous mixtures. Having established these foundations we shall describe and discuss variations in reactivity (in terms of free energies, enthalpies, entropies, heat capacities, and volumes of activation) with solvent composition. Throughout we shall attempt to correlate the kinetic patterns with other property trends established for these solvent mixtures. We shall also examine how far the variations in thermodynamic properties of the solvent mixtures (the various thermodynamic functions of mixing) are reflected in the reactivities of the substrates dissolved in these mixtures.

We restrict our attention to substitution reactions where certain key features of the mechanism are established, ranging from dissociative reactions such as the solvolysis of *t*-butyl chloride and complex formation from hexa-aquanickel(II) to associative processes such as the alkaline hydrolysis of organic halides and carboxylic esters. We do not deal with the complementary area where the dependence of rate constants on solvent composition is used in the diagnosis of reaction mechanism. In view of the complexities of kinetic behaviour in mixed aqueous solvents, exercises of the latter type should be embarked on, and any conclusions treated, with great caution.⁴

2 Water and Aqueous Solutions

Water.—The properties of water have been reviewed in considerable detail.⁵ A simple but attractive model describes^{5a} liquid water in terms of a dynamic two-state system, $(\text{H}_2\text{O})_b \rightleftharpoons (\text{H}_2\text{O})_d$, comprising hydrogen-bonded (bulky) and non-hydrogen-bonded (dense) states; $\Delta H^\circ > 0$ and $\Delta V^\circ < 0$. The latter state is formed by water molecules that occupy voids formed by intermolecularly hydrogen-bonded water molecules. The lifetime of the bulky state is between 10^{-10} and 10^{-11} s, just long enough for this state to be chemically meaningful, and very much shorter than the half-lives of the chemical reactions discussed in this review.

Binary Aqueous Mixtures.—These can be conveniently classified⁶ on the basis of their thermodynamic properties, particularly their molar excess functions, X^E (where X is a thermodynamic function of state, *e.g.* the Gibbs function G , enthalpy H , entropy S , volume V , and heat capacity at constant pressure C_p).

⁴ E. Grunwald and A. Effio, *J. Amer. Chem. Soc.*, 1974, 96, 423.

⁵ 'Water - A Comprehensive Treatise', ed. F. Franks, Plenum Press, 1973; (a) H. Frank, Vol. 1, Chapter 14; (b) G. M. Schneider, Vol. 2, Chapter 6; (c) F. Franks, Vol. 2, Chapter 1; (d) M. J. Blandamer and M. F. Fox, Vol. 2, Chapter 8; (e) M. J. Blandamer, Vol. 2, Chapter 9; (f) M. D. Zeidler, Vol. 2, p. 564; (g) F. Franks and D. S. Reid, Vol. 2, Chapter 3; (h) H. Friedman and C. V. Krishnan, Vol. 3, Chapter 1.

⁶ 'Hydrogen-Bonded Solvent Systems', ed. A. Covington and P. Jones, Taylor and Francis, London 1968; (a) F. Franks, p. 31; (b) J. B. Hyne, p. 99.

Excess functions express the extent to which the properties of a given mixture differ from those of the corresponding ideal mixture at the same temperature and pressure. Those aqueous mixtures for which G^E is positive and $|TS^E| > |H^E|$, (*i.e.* dominant entropy of mixing) are called typically aqueous, TA; acetone + water and ethyl alcohol + water mixtures are examples of this class. These mixtures may separate at a lower critical solution temperature, LCST, *e.g.* triethylamine + water. Critical solution temperatures of aqueous mixtures are very sensitive to added solutes, and the tendency should be borne in mind for a given mixture to undergo phase separation (appear cloudy) when reactants are added. Some TA mixtures, while completely miscible at ambient pressure, will undergo phase separation if the pressure is changed.^{5b} The properties of TA mixtures are particularly sensitive to the mole fraction of the non-aqueous co-solvent, x_2 , but within this group, some clear-cut patterns have emerged.^{5c-5e} At low mole fractions, a TA solvent exerts a water 'structure-forming' action, the solvent co-spheres around each solute overlapping and mutually enhancing water-water interactions. As more co-solvent is added, the mole fraction exceeds a particular mole fraction, x_2^* , where there is insufficient water to maintain a three-dimensional hydrogen-bonded network of water molecules. Localized attempts to regain this arrangement produce concentration fluctuations (*i.e.* an overall water 'structure-breaking' action), the effect being maximal at a mole fraction x_2^{**} . At this mole fraction, the system has the largest tendency to undergo phase separation. Indeed, it would be interesting to know if the kinetics in aqueous systems close to phase separation at a critical point [*i.e.* near an upper critical solution temperature (UCST) or lower critical solution temperature (LCST)] are in any way anomalous.⁷ The two mole fractions x_2^* and x_2^{**} depend both on co-solvent and temperature. Further, their precise values depend on the property of the mixture under examination. Nevertheless, these values do provide a useful signpost for effects in kinetic data. At 298 K approximate values of x_2^* and x_2^{**} are ^{5e} 0.09 and 0.2 (ethanol), 0.06 and 0.18 (isopropyl alcohol), 0.04 and 0.1 (t-butyl alcohol), and 0.06 and 0.35 (acetone), respectively. For tetrahydrofuran (THF), $x_2^{**} \simeq 0.3$. Dioxan is often used as an organic co-solvent because the relative permittivity of this aqueous mixture can be varied over a wide range, $2 < \epsilon_r < 78$. However, the properties of this mixture sometimes conflict with, for example, the generalizations discussed above. Thus dioxan-water is a TA system but some authors⁸ suggest that dioxan is a water structure-breaker. The latter conclusion may be consistent with the observation⁹ that the kinetic solvent isotope effect, $k(D_2O)/k(H_2O)$, for the solvolysis of t-butyl chloride tends to unity when dioxan is added, although this behaviour is not observed¹⁰ for methanesulphonyl chloride.

Aqueous mixtures where $|H^E| > |TS^E|$, *i.e.* enthalpy-controlled mixing,

⁷ J. C. Wheeler, *Ber. Bunsengesellschaft phys. Chem.*, 1972, 76, 308.

⁸ R. K. Mohanty and J. C. Ahluwalia, *J. Solution Chem.*, 1972, 1, 531.

⁹ W. C. Craig, L. Hakka, P. M. Laughton, and R. E. Robertson, *Canad. J. Chem.*, 1969, 41, 2118.

¹⁰ M. L. Tennen and A. N. Hambly, *Austral. J. Chem.*, 1970, 23, 2427, 2435.

are called typically non-aqueous,^{6a} TNA. In some TNA mixtures, G^E is positive, TNAP, *e.g.* acetonitrile + water.¹¹ However, for some TNA mixtures, G^E is negative, TNAN, *e.g.* hydrogen peroxide + water¹² and dimethyl sulphoxide (DMSO) + water.¹³ In the TNAP mixtures, the co-solvent exerts a depolymerizing effect on water (*cf.* the effect of carbon tetrachloride on methyl alcohol) and in this sense is a structure breaker. Such mixtures may undergo phase separation at a UCST. In the TNAN mixtures, intercomponent association occurs (*cf.* the effect of chloroform on acetone). This intermolecular association in, for example, DMSO + water^{5f} leads to a breakdown of water-water interactions. (See also hydrogen peroxide + water¹⁴). Indeed, analysis of the kinetics of hydrolysis of acetals in DMSO + water mixtures prompted the conclusion¹⁵ that these mixtures can be divided into three regions, $0 \leq x_2 \lesssim 0.3$, $0.3 \lesssim x_2 \lesssim 0.45$, $0.45 \lesssim x_2 \leq 1$. In the second region, the properties of the system are dominated by 2:1 H₂O : DMSO associated species (*cf.* solubility and thermodynamic data¹⁶).

The volumetric properties of aqueous mixtures¹⁷ are important in the analysis of volumes of activation. Generally, the relative partial molar volume of a TA co-solvent has a minimum close to x_2^* , but that for a TNA co-solvent shows no minimum at low mole fractions.^{6a}

Solute-Water Interactions.—The low solubility of non-polar solutes [*i.e.* ΔG° (gas \rightarrow aqueous solution) > 0] in water is a consequence of a large negative value for $T\Delta S^\circ$ even though ΔH° is negative (*i.e.* exothermic). The current view is that in water these solutes enhance water-water interactions and so are structure formers.^{5e} The organization of the water molecules around a non-polar solute may resemble that found in clathrate hydrates, the enhancement of water-water interactions being responsible for the positive partial molar heat capacity of the solute, which increases as the hydrophobic content of the solute increases.¹⁸

A similar structure-forming action is attributed to large hydrophobic ions, *e.g.* tetra-alkylammonium ions where R is larger than ethyl. However, ions, in general, by virtue of intense ion-solvent interactions, exert a structure-breaking

¹¹ A. L. Vierk, *Z. anorg. Chem.*, 1950, **201**, 283; K. W. Morcom and R. W. Smith, *J. Chem. Thermodynamics*, 1969, **1**, 503.

¹² G. Scatchard, G. M. Kavanagh, and L. B. Ticknor, *J. Amer. Chem. Soc.*, 1952, **74**, 3715; A. G. Mitchell and W. F. K. Wynne-Jones, *Discuss. Faraday Soc.*, 1953, **15**, 161; P. A. Giguère, O. Knop, and M. Falk, *Canad. J. Chem.*, 1958, **36**, 883.

¹³ H. L. Clever and S. P. Pigott, *J. Chem. Thermodynamics*, 1971, **3**, 221; J. Kentamaa and J. J. Lindberg, *Suomen Kem.*, 1960, **33B**, 98.

¹⁴ J. H. Stern and W. R. Bottenberg, *J. Phys. Chem.*, 1971, **75**, 2229.

¹⁵ R. K. Wolford, *J. Phys. Chem.*, 1964, **68**, 3392.

¹⁶ E. A. Symons, *Canad. J. Chem.*, 1971, **49**, 3940; D. D. MacDonald and J. B. Hyne, *Canad. J. Chem.*, 1971, **49**, 611.

¹⁷ R. Battino, *Chem. Rev.*, 1971, **71**, 5.

¹⁸ D. M. Alexander and D. J. T. Hill, *Austral. J. Chem.*, 1969, **22**, 347; E. M. Arnett, W. B. Kover, and J. V. Carter, *J. Amer. Chem. Soc.*, 1969, **91**, 4028; R. D. Wauchope and R. Haque, *Canad. J. Chem.*, 1972, **50**, 133.

influence on water beyond a nearest neighbour layer of electrostricted water molecules.¹⁹

3 Analysis of Kinetic Data

According to transition-state theory,²⁰ the rate constant at fixed temperature and pressure is related to ΔG^\ddagger , the difference between chemical potentials of transition state, μ^\ddagger , and reactant(s), μ° , in their solution standard states; thus for a first-order reaction, $\Delta G^\ddagger = \mu^\ddagger - \mu^\circ$, where species 3 is the reactant. Standard thermodynamic operations on ΔG^\ddagger lead to the definition of isobaric (ΔH^\ddagger and ΔS^\ddagger from the temperature variation) and isothermal (ΔV^\ddagger from pressure variation) parameters. Further operations lead to the definition of a heat capacity of activation ΔC_p^\ddagger (differentiation of ΔH^\ddagger with respect to temperature), the isothermal compressibility coefficients of activation $\Delta \kappa_T^\ddagger$ (calculated from the dependence of ΔV^\ddagger on pressure), and the isochoric quantity ΔU_v^\ddagger . Obviously, more caution is required in the derivation of the latter three quantities than the former three.²¹ The various Maxwell equations provide additional links between the activation parameters.²²

The experimental data comprise values of the rate constants k for a given reaction at discrete values of temperature, pressure, and co-solvent mole fraction, x_2 . The dependence of k on T at fixed p and x_2 and on p at fixed T and x_2 is analysed using a similar methodology to that used in the analysis of equilibrium constants, K . Many methods have been proposed, including expressing the dependence of k (or K) on T using equations which are polynomials in T , polynomials in $T - \theta$, where θ is a reference temperature,^{23a} and using orthogonal polynomials^{23b} or spline functions.^{23c} Various empirical expressions have been used to represent the dependence of rate constant on pressure. When the dependence of rate constant on either T or p has been described satisfactorily, the activation parameters can be calculated at selected values of either T or p , respectively.

4 Thermodynamic Transfer Functions

The calculated activation parameters ΔX^\ddagger for a given reaction depend on x_2 and are assumed to be continuous functions of x_2 . The change in ΔX^\ddagger on going from a solution in water to one in a binary solvent mixture can be represented by $\delta_m \Delta X^\ddagger [= \Delta X^\ddagger(x_2) - \Delta X^\ddagger(x_2 = 0)]$, where δ_m is the solvent operator.²⁴

¹⁹ M. J. Blandamer, *Quart. Rev.*, 1970, **24**, 169; W.-Y. Wen, *J. Solution Chem.*, 1973, **2**, 253; T. S. Sarma and J. C. Ahluwalia, *Chem. Soc. Rev.*, 1973, **2**, 203.

²⁰ S. Glasstone, K. J. Laidler, and H. Eyring, 'The Theory of Rate Processes', McGraw-Hill, New York, 1941.

²¹ G. Kohnstam, *Adv. Phys. Org. Chem.*, 1967, **5**, 121.

²² (a) K. J. Laidler, *Discuss. Faraday Soc.*, 1956, **22**, 88; (b) S. J. Dickson and J. B. Hyne, *Canad. J. Chem.*, 1971, **49**, 2394.

²³ (a) E. C. W. Clarke and D. N. Glew, *Trans. Faraday Soc.*, 1966, **62**, 539; (b) D. J. G. Ives and P. D. Marsden, *J. Chem. Soc.*, 1965, 649; (c) S. Wold, *Acta Chem. Scand.*, 1970, **24**, 2321; *J. Phys. Chem.*, 1972, **76**, 369.

²⁴ J. A. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions', Wiley, New York, 1963.

Because ΔX^\ddagger depends on x_2 , the corresponding properties of transition and initial states must differ in regard to their own dependence on x_2 . If the measured rate constant is first-order, then $\delta_m X^\ddagger \neq \delta_m X_3^\circ$, although either $\delta_m X^\ddagger$ or $\delta_m X_3^\circ$ may be zero. The co-solvent may change the properties of a solute (reactant or transition state) in water by direct co-solvent-solute interaction. For example, the dependence of activation enthalpies on composition for the solvolysis of benzyl chloride and derivatives in water + ethyl alcohol mixtures can be attributed to changes in specific solvent-reactant and solvent-transition state interactions.²⁵ However, equally striking changes in the properties of a solute may result from modifications of water-water interactions produced by the co-solvent, *i.e.* an indirect effect. In addition, where the reactant and co-solvent are, to a large degree, hydrophobic, they may associate by hydrophobic bonding.²⁶

If the measured rate constant is second-order, and the reaction mechanism simple bimolecular, the dependence of $\delta_m \Delta X^\ddagger$ on x_2 must be considered with reference to the three quantities $\delta_m X^\ddagger$, $\delta_m X_3^\circ$, and $\delta_m X_4^\circ$, where $\Delta X^\ddagger = X^\ddagger - (X_3^\circ + X_4^\circ)$, species 3 and 4 being the two reactants.

The quantities $\delta_m X^\ddagger$ and $\delta_m X^\circ$ are thermodynamic transfer functions, representing the effect of co-solvent on a particular partial molar property. Clearly, analysis of the factors contributing towards a given $\delta_m \Delta X^\ddagger$ requires information concerning the individual transfer functions. By definition, it is not possible to measure independently $\delta_m X^\ddagger$. Indeed, as the composition of the solvent mixture changes, both the energy and the nature of the transition state (*e.g.* position along reaction co-ordinate) may change. Such changes may produce a change in the nature of the products. Thus in the solvolysis of *t*-butyl chloride at 298 K, the percentages of alkene produced are 6.2 and 52 when $x(\text{DMSO}) = 0.134$ and 0.512, respectively.²⁷ However, these observations do not necessarily require a gross change in the transition state because the product may be determined in another stage of the reaction after the transition state has been passed, *i.e.* in a product-determining step. It is an unfortunate aspect of this subject that so much of the discussion must necessarily centre around the nature and energy of an elusive and ephemeral entity called the transition state/activated complex. However, attempts have been made to estimate $\delta_m X^\ddagger$ by measuring $\delta_m X^\circ$ for a solute which is thought to resemble the transition state. Thus value of $\delta_m V^\circ$ for various salts have been measured in order to estimate $\delta_m V^\ddagger$ for the transition states involved in the hydrolysis of alkyl and substituted-benzyl chlorides.²⁸

Where reactants are concerned, these conceptual difficulties do not, of course, arise. Even where a reactant is labile, measurements of certain $\delta_m X_3^\circ$ quantities have been made, although special techniques must be used. Thus, using a specially designed calorimeter, $\delta_m H^\circ$ values for *t*-butyl chloride in water + ethyl

²⁵ J. B. Hyne, *J. Amer. Chem. Soc.*, 1960, **82**, 5129; J. B. Hyne, R. Wills, and R. E. Wonkka, *ibid.*, 1962, **84**, 2914; J. B. Hyne and R. Wills, *ibid.*, 1963, **85**, 3650.

²⁶ W. Kauzmann, *Adv. Protein Chem.*, 1959, **14**, 1.

²⁷ K. Heinonen and E. Tommila, *Suomen Kem.*, 1965, **38B**, 9.

²⁸ I. Lee and J. B. Hyne, *Canad. J. Chem.*, 1968, **46**, 2333; 1969, **47**, 1437.

alcohol mixtures were determined before significant hydrolysis had occurred.^{29,30a} A method for estimating instantaneous values of $\delta_m V^\circ$ for reactants in aqueous mixtures has been described.³¹ In other cases, the properties of the reactants can be conveniently measured because the conditions (*e.g.* pH, temperature) have been so adjusted that no or negligible reactions occur. Where measurements either cannot or have not been made, it is often possible to draw tentative conclusions concerning the trends in $\delta_m X^\circ$ for a reactant from the behaviour of solutes which resemble the reactants. Thus in the analysis of solvent effects on alkyl halides, which are generally hydrophobic solutes, information concerning the solubilities of hydrocarbons and other gases in pure solvents^{32,33} and in aqueous mixtures^{33,34} can be most useful. Hydrophobic solutes are more soluble in an organic co-solvent than in water. Consider the case of ethane in ethanol + water mixtures.³³ The change in chemical potential for ethane, $\delta_m \mu^\circ$, on going from pure water to pure ethanol is negative, although the transfer is endothermic, $\delta_m H^\circ > 0$. Nevertheless, $\delta_m S^\circ$ is > 0 , the change in entropy being more dramatic, *i.e.* $T\delta_m S^\circ > \delta_m H^\circ$. The data show another important feature. Thus in the aqueous mixtures, $\delta_m \mu^\circ$ changes almost regularly with increase in x_2 , with only small deviation from a linear interdependence. However, $\delta_m H^\circ$ and $\delta_m S^\circ$ for ethane deviate considerably from such a simple pattern, *e.g.* $\delta_m H^\circ$ is much larger in the water-rich aqueous mixtures than might otherwise be predicted. At this stage it is possibly unwise to advance a firm prediction. However, we might tentatively conclude that when an organic co-solvent is added to a hydrophobic reactant in water, there will be a tendency for $\delta_m \Delta G^\ddagger$ to increase (*i.e.* rate constant to decrease) because this reactant will be stabilized, *i.e.* $\delta_m \mu_3^\circ < 0$. Further, this behaviour will contribute to a more marked change in $T\delta_m \Delta S^\ddagger$ than in $\delta_m \Delta H^\ddagger$. We will return to these considerations in Sections 7 and 8.

Thermodynamic transfer functions for salts from water to other pure solvents have been calculated for a wide range of systems. Unfortunately, in the analysis of kinetic data, transfer functions for single ions are usually required, and some assumption must be made before these can be obtained from the values for salts.^{5b} Single ion transfer functions have been calculated³⁵ for seven pure co-solvents (using as a reference the tetramethylammonium ion) and so provide some indication of the change expected in the properties of ionic reactants and transition states between the extremes $x_2 = 0$ to $x_2 = 1$. For the large hydro-

²⁹ E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. M. Duggleby, *J. Amer. Chem. Soc.*, 1965, **87**, 1541; E. M. Arnett, P. M. Duggleby, and J. J. Burke, *ibid.*, 1963, **85**, 1350; E. M. Arnett and D. R. McKelvey, *ibid.*, 1965, **87**, 1393; 1966, **88**, 5031.

³⁰ 'Physico-Chemical Processes in Mixed Aqueous Solvents', ed. F. Franks, Heinemann, London, 1967; (a) E. M. Arnett, p. 105; (b) D. Feakins, p. 71.

³¹ H. S. Golinkin, I. Lee, and J. B. Hyne, *J. Amer. Chem. Soc.*, 1967, **89**, 1309.

³² R. Battino and H. L. Clever, *Chem. Rev.*, 1966, **66**, 395; E. Wilhelm and R. Battino, *ibid.*, 1973, **73**, 1.

³³ M. Yaacobi and A. Ben-Naim, *J. Solution Chem.*, 1973, **2**, 425; *J. Phys. Chem.*, 1974, **78**, 175.

³⁴ A. Ben-Naim and S. Baer, *Trans. Faraday Soc.*, 1964, **60**, 1736; A. Ben-Naim, *J. Phys. Chem.*, 1965, **69**, 3245.

³⁵ M. H. Abraham, *J.C.S. Faraday I*, 1973, **69**, 1375.

phobic ions, *e.g.* Bu^n_4N^+ and Ph_4B^- , $\delta_m\mu^\circ$ is negative for transfer from water into *N*-methylformamide, methanol, ethanol, DMSO, acetonitrile, DMF, and acetone. Transfer of small anions, *e.g.* chloride, bromide, and iodide, is distinctly unfavourable, $\delta_m\mu^\circ > 0$, but $\delta_m\mu^\circ$ for small cations depends on solvent and ion, being nevertheless much smaller in magnitude. The entropies of transfer for small ions, *e.g.* K^+ and Cl^- , are generally negative, but those for large hydrophobic ions, *e.g.* Bu^n_4N^+ and Ph_4B^- , are positive. Of course, in the present context, it is preferable to consider the transfer function for ions as a function of co-solvent mole fraction. These have been measured for certain salts in selected aqueous mixtures, and different methods of calculating single ion values have been examined.^{30b} In methyl alcohol and water mixtures, $\delta_m\mu^\circ$ is positive for small anions, *e.g.* Cl^- and OH^- ,³⁶ and negative for small cations,^{30b} *e.g.* H^+ , although there is some disagreement between reported values for alkali-metal ions.³⁷ Similar trends are reported for ions in dioxan, acetone, and ethyl alcohol aqueous mixtures.³⁸ Plots of $\delta_m\mu^\circ$ for salts against x_2 do not show, in general, marked extrema (for one example of an exception see hydrogen iodide in methanol + water^{30b}). However, these are clearly seen in the plots of the corresponding enthalpy and entropy quantities (*e.g.* hydrogen chloride in aqueous methanol and aqueous ethanol³⁹). The corresponding plots of $\delta_m\mu^\circ$ for ions against x_2 again show no marked extrema as a general rule, although there are exceptions, *e.g.* H^+ in methanol + water³⁷ and Ph_4B^- in acetone + water.^{38a}

The partial molar entropies of small ions (*e.g.* Li^+ , Na^+ , Cl^- , Br^-) increase when small amounts of methanol are added to aqueous solutions of these ions, but then decrease steadily, to values more negative than in water, as the mole fraction of methanol increases. These deviations from a simple linear interdependence between entropy and mole fraction are largest when S^E for the solvent mixture is most negative.⁴⁰ The possibility of linking the properties of a solute in a binary aqueous mixture with the thermodynamic excess function will be mentioned again in Section 7. Information concerning thermodynamic transfer functions for alkali-metal and halide ions can be obtained from n.m.r. shift measurements on the respective nuclei; this technique may prove important in the present context.⁴¹

Again it is probably too simplistic to draw general conclusions from the pattern identified here for ions. Nevertheless some predictions can be made. For example, in alkaline hydrolysis reactions, addition of an organic co-solvent would appear to destabilize OH^- ion, and this will contribute to a decrease in $\delta_m\Delta G^\ddagger$ and thus an increase in rate constant. In contrast, the rate of a reaction involving

³⁰ C. H. Rochester, *J.C.S. Dalton*, 1972, 5.

³⁷ C. F. Wells, *J.C.S. Faraday I*, 1973, 69, 684; D. Feakins and P. J. Voice, *ibid.*, 1972, 68, 1390; A. L. Andrews, H. P. Bennetto, D. Feakins, K. G. Lawrence, and R. P. T. Tomkins, *J. Chem. Soc. (A)*, 1968, 1486.

³⁸ (a) H. P. Bennetto, D. Feakins, and K. G. Lawrence, *J. Chem. Soc. (A)*, 1968, 1493; (b) D. Bax, C. L. de Ligny, and A. G. Remijnse, *Rec. Trav. chim.*, 1972, 91, 965, 1225.

³⁹ J. H. Stern and S. L. Hansen, *J. Chem. and Eng. Data*, 1971, 16, 360.

⁴⁰ C. M. Criss, R. P. Held, and E. Kuksha, *J. Phys. Chem.*, 1968, 72, 2970; F. Franks and D. S. Reid, *ibid.*, 1969, 73, 3153.

⁴¹ A. K. Covington, K. E. Newman, and T. H. Lilley, *J.C.S. Faraday I*, 1973, 69, 973.

a complex ion where the ligands are hydrophobic will tend to fall because the co-solvent stabilizes such ions. Such conclusions must be drawn carefully. It is noteworthy, for example, that $\delta_m H^\ominus$ for a given solute in a particular mixture often bears little relation to the sign and magnitude for $\delta_m \mu^\ominus$ of the same solute, so that $\delta_m H^\ominus$ alone is of little value in predicting trends in the rate constants.⁴² Finally, it is important when using these thermodynamic transfer functions in the analysis of kinetic data to pay close attention to the definition of the solution standard states.

5 Analysis of Solvent Effects in Kinetics

So far we have attempted to establish that in coming to an understanding of the patterns shown by $\delta_m \Delta X^\ddagger$ quantities for reactions in aqueous mixtures, the often unique properties of both aqueous solutions and aqueous mixtures should be borne in mind. For example, in aqueous systems, we have seen that the entropy changes are extremely important, controlling in some cases the sign and magnitude of the change in Gibbs function. We have also noted that in interpreting a given $\delta_m \Delta X^\ddagger$, some information is required concerning the corresponding changes in the initial and transition states.^{8b} These generalizations are now illustrated by reference to examples taken from quite an extensive literature. We start our discussion with an examination of trends in ΔG^\ddagger because this is directly calculated from the primary observable, the rate constant, and because interpretation of $\delta_m \Delta G^\ddagger$ illustrates most of the points made above.

6 Rate Constants and $\delta_m \Delta G^\ddagger$

ΔG^\ddagger is generally a 'well-behaved' function – it usually changes smoothly and gradually as the solvent composition changes. This behaviour contrasts with those of ΔH^\ddagger and ΔS^\ddagger ; these quantities often vary in, at first sight, an erratic manner but usually in such a way as to minimize changes in ΔG^\ddagger . The dependence of ΔG^\ddagger on solvent composition has been reported for a wide range of organic and inorganic reactions in a variety of mixed aqueous solvents. However, the distribution of such mixed solvent systems between the classes discussed in Section 2 is highly biased towards TA mixtures; only one TNAN co-solvent (DMSO), and only one TNAP co-solvent (acetonitrile) have been extensively used in kinetic studies.

The lack of any real success in correlating rate constants with dielectric properties of solvent mixtures prompted the development of the more generalized concept of solvent polarity.⁴³ Thus solvent Y values,⁴⁴ defined in terms of solvent effects on rates of S_N1 solvolysis of *t*-butyl chloride, have been used to correlate effects of solvents on rate constants for other more or less related reactions. Such correlations have also been used to probe the mechanisms of a

⁴² E. M. Arnett and D. R. McKelvey, *J. Amer. Chem. Soc.*, 1966, **88**, 2598.

⁴³ C. Reichardt, *Angew. Chem. Internat. Edn.*, 1965, **4**, 29.

⁴⁴ E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 846.

variety of reactions, in inorganic (e.g. solvolysis of halides of phosphorus,^{45a} sulphur,^{45b} and boron^{45c}) and organometallic⁴⁶ as well as in organic chemistry. These correlations involving Y values are examples from the many linear free-energy relationships in chemistry. Underlying the Y value concept is the requirement that solvent and solute interact through a single mechanism.²⁴

Although the use of solvent Y values has permitted the correlation of kinetic results in certain areas of chemistry, further generalization and codification of reactivities in mixed aqueous media are difficult. Nonetheless some regular patterns can be discerned. Thus rates of S_N1 solvolysis of organic halides⁴⁴ and of I_d aquations of cobalt(III)-ammine or -amine halide complexes⁴⁷ always decrease as the proportion of a TA non-aqueous component increases. The same is true for the TNAP co-solvent acetonitrile,^{48,49} and even for the TNAN co-solvent DMSO.²⁷ Only for the inorganic TNAN co-solvent hydrogen peroxide is there an increase in rate (for Bu^4Cl solvolysis) with increasing amount of non-aqueous co-solvent.⁵⁰ The aquations of chromium(III) and of rhodium(III)^{47b} chloride complexes, arguably at least partly associative in character, follow the same pattern in TA and TNAP solvents (their behaviour in TNAN solvents remains to be investigated). Examples of reactions whose rates increase with increasing proportion of non-aqueous component are much rarer;⁵¹ they include S_N1 decarboxylation of some cyanoacetates^{51a} (in mixtures containing the TA co-solvents ethanol or dioxan), and the S_N2 aquation of Me_3NSO_3 [aqueous acetone (TA) and DMSO (TNAN)].^{51b} Patterns of kinetic behaviour for the solvolysis and base hydrolysis of esters and related compounds are varied – most of the (few) examples of maxima or minima in k vs. x_2 plots come from this type of reaction.⁵²

There is surprising variation in kinetic pattern with the nature of the leaving group for the aquation of the iron(II) complexes of various substituted 1,10-phenanthrolines.^{48,53} In aqueous *t*-butyl alcohol and in aqueous ethyl alcohol mixtures (TA co-solvents), the rate of aquation of the 5-nitro-complex increases markedly with increasing x_2 , in aqueous acetonitrile (TNAP) the rate increases less markedly, whilst in aqueous formic acid the rate decreases with increasing

⁴⁵ (a) E. W. Crunden and R. H. Hudson, *J. Chem. Soc.*, 1962, 3591; (b) O. Rogne, *J. Chem. Soc. (B)*, 1969, 663; (c) J. R. Lowe, S. S. Appal, C. Weidig, and H. C. Kelly, *Inorg. Chem.*, 1970, 9, 1423.

⁴⁶ See e.g. F. E. Smith and I. S. Butler, *Canad. J. Chem.*, 1969, 47, 1311; W. J. Bland, J. Burgess, and R. D. W. Kemmitt, *J. Organometallic Chem.*, 1965, 15, 217; 1969, 18, 199.

⁴⁷ (a) C. H. Langford, *Inorg. Chem.*, 1964, 3, 225; (b) J. Burgess and M. G. Price, *J. Chem. Soc. (A)*, 1971, 3108.

⁴⁸ J. Burgess, *J. Chem. Soc. (A)*, 1970, 2351.

⁴⁹ R. E. Robertson and S. E. Sugamori, *J. Amer. Chem. Soc.*, 1969, 91, 7254; *Canad. J. Chem.*, 1972, 50, 1353.

⁵⁰ M. J. Blandamer and J. R. Membrey, *J.C.S. Chem. Comm.*, 1973, 514.

⁵¹ (a) A. Thomson, *J. Chem. Soc. (B)*, 1970, 1798; (b) J. H. Krueger and M. A. Johnson, *Inorg. Chem.*, 1968, 7, 679.

⁵² See e.g. (a) E. Tommila, A. Koivosto, J. P. Lyrre, K. Antell, and S. Heimo, *Ann. Acad. Sci. Fennicae, AII*, 1952, 47, 3; (b) E. Tommila, *Suomen Kem.*, 1964, 37B, 117; (c) R. K. Wolford, *J. Phys. Chem.*, 1963, 67, 632; (d) R. L. Foon and A. N. Hamby, *Austral J. Chem.*, 1970, 23, 2427, 2435.

⁵³ J. Burgess, *J. Chem. Soc. (A)*, 1968, 1085; 1969, 1899.

x_2 . In contrast, the rate of aquation of the 4,7-dimethyl complex [like aquation rates for, *e.g.*, cobalt(III) or chromium(III) halide complexes] decreases with increasing x_2 no matter what co-solvent. It is interesting that in *t*-butyl alcohol + water mixtures, the effects of ligand substitution and counter ion on reactivities are small below x_2^* but rapidly become more marked beyond that composition.⁵³

Having established these rough generalizations, we now wish to review how these variations can be accounted for. For the most part our analysis must be qualitative because much of the information required for a quantitative analysis is not available.

The increase in $\delta_m \Delta G^\ddagger$ with x_2 for hydrolysis of alkyl halides when organic co-solvents are added (*e.g.* ethyl alcohol, *t*-butyl alcohol, THF, or acetonitrile to *t*-butyl chloride in water,^{44,49,54} ethyl alcohol to benzyl chloride or derivatives in water,²⁵ dioxan to alkyl esters of benzenesulphonic acids,⁵⁵ and acetone to alkyl halides in water⁵⁶) can be attributed in part to the increased solubility of these hydrophobic solutes in the mixture, *i.e.* $\delta_m \mu_3^\circ < 0$. Indeed, solubility data show that for *t*-butyl chloride in ethanol-rich mixtures, $\delta_m \mu^\circ$ is negative and accounts for more than one-half of the increase in ΔG^\ddagger .⁵⁴ Similarly, in the bimolecular (S_E2) reaction between tin tetra-alkyls and mercuric chloride in methanol-rich aqueous mixtures, the larger part of the increase in ΔG^\ddagger with increase in x_2 can be attributed^{57a} to a stabilization of both reactants. A similar conclusion^{57b} was reached for the Menshutkin reaction of trimethylamine with methyl iodide, but in the case of the reaction between lead tetra-alkyls and iodine, changes in the chemical potential of the transition state are important.^{57c} However, here interpretation is not straightforward because there is some ambiguity over the structure, *i.e.* open or cyclic, of the transition state.

In some cases, the chemical potentials of the reactants may change in quite different ways when the co-solvent is added. The chemical potential of OH^- in water is dramatically increased when DMSO is added⁵⁸ so that, despite an expected stabilization of benzyl chloride (see below), the rate constant for alkaline hydrolysis of benzyl chloride increases when DMSO is added.⁵⁹ A similar explanation may account for the increase observed in the rates of alkaline hydrolysis of methyl iodide^{60a} or of fluorobenzene and derivatives,^{60b} and in the reaction between thiosulphate and benzyl chloride,^{60c} anions being generally destabilized by added DMSO.⁶¹ In other cases the effect of added co-solvent is determined by the change in the chemical potential of the transition state. Thus

⁵⁴ S. Winstein and A. H. Fainberg, *J. Amer. Chem. Soc.*, 1957, **79**, 5937.

⁵⁵ E. Tommila and E. Merikallio, *Suomen Kem.*, 1953, **12B**, 79.

⁵⁶ E. Tommila, M. Tiilikainen, and A. Voipo, *Ann. Acad. Sci. Fennicae AII*, 1955, **65**, 3.

⁵⁷ M. H. Abraham, (a) *J. Chem. Soc. (A)*, 1971, 1067; (b) *J.C.S. Chem. Comm.*, 1969, 1307; (c) *J.C.S. Perkin II*, 1972, 1343.

⁵⁸ A. K. Das and K. K. Kandu, *J.C.S. Faraday I*, 1973, **69**, 730.

⁵⁹ E. Tommila and I. P. Pitkainen, *Acta Chem. Scand.*, 1966, **20**, 937.

⁶⁰ (a) J. Murto, *Suomen Kem.*, 1961, **B34**, 92; (b) J. M. Murto and A. M. Hirro, *ibid.*, 1964, **B37**, 177; (c) K. Kalliorinne and E. Tommila, *Acta Chem. Scand.*, 1969, **23**, 2567.

⁶¹ J. Courtot-Coupez, M. L. Démézet, A. Laauenan, and C. Madoc, *J. Electroanalyt. Chem.*, 1971, **29**, 21.

the addition of DMSO, acetonitrile, or dioxan to ethyl acetate in water produces a stabilization of the ester,⁶² *i.e.* $\delta_m\mu^\ominus < 0$. In dioxan + water, $\delta_m\mu^\ominus$ (ester) is approximately -1.5 kJ mol^{-1} at $x_2 = 0.5$. However, $\delta_m\mu^\ominus$ for the hydroxide ion is positive,^{38a} approximately $+5.54 \text{ kJ mol}^{-1}$ when $x_2 = 0.5$. Thus, taken together, these require that the rate constant should increase. However, the reverse trend is observed, $\delta_m\Delta G^\ddagger = +0.19 \text{ kJ mol}^{-1}$, and so $\delta_m\mu^\ddagger$ for the transition state is approximately $+4.2 \text{ kJ mol}^{-1}$. It appears that while $\delta_m\mu^\ominus$ (OH^-) is usually positive when a co-solvent is added, it is not sufficiently large (except in the case of added DMSO) to determine the change in rate constant except in co-solvent-rich mixtures. Thus the complicated pattern referred to above emerges,⁵² depending on whether the trends in initial or transition states are dominant. For example, in contrast to the effect of DMSO, added acetone⁵⁹ or dioxan^{63a} result in a fall in the rate constant for the alkaline hydrolysis of benzyl chloride. Similarly, the rate constant for the alkaline hydrolysis of methyl acetate decreases when methanol is added^{63b} even though $\delta_m\mu^\ominus(\text{OH}^-)$ is again positive in this mixture.³⁶ The marked enhancement of the rate of alkaline hydrolysis of esters by added DMSO has attracted considerable attention.^{51b, 52b, 64}

Thermodynamic results indicate that $\delta_m\mu^\ominus(\text{H}^+)$ is generally negative when organic solvents are added to H^+ in water. However, the use of this information in rationalizing reactivity patterns for the acid-catalysed hydrolysis of esters,^{52b, 65} is complicated by the two-stage nature (rapid equilibrium of ester and proton followed by rate-determining dissociative or associative solvolysis of the protonated ester) of the reaction mechanism.

Another pattern which emerges from the available data concerns a possible link between G^\ddagger for the binary mixture and the trend in $\delta_m\Delta G^\ddagger$. It is noteworthy, for example, that in the hydrolysis of *t*-butyl chloride, $\delta_m\Delta G^\ddagger$ at a fixed mole fraction in the TA aqueous-rich mixtures increases as G^\ddagger increases at that mole fraction. Results for solvent mixtures containing the TNAP solvent acetonitrile can be included in this pattern but those for mixtures containing DMSO, a TNAN system, cannot. If for this reactant the increase in $\delta_m\Delta G^\ddagger$ can be solely attributed to a stabilization of the initial state, a clear-cut correspondence between $\delta_m\Delta G^\ddagger$ and G^\ddagger would only be expected if the solubilities of *t*-butyl chloride in the co-solvents were the same. If the mixture were ideal (*i.e.* $G^\ddagger = 0$), then $\delta_m\mu^\ominus$ (Bu^tCl) and thus $\delta_m\Delta G^\ddagger$ would be linear functions of x_2 . In fact the solubilities of hydrocarbons, *e.g.* ethane and methane, in alcohols, whilst markedly different from those in water, are, within themselves, very close. Further, an extra-thermodynamic analysis indicates that, at least qualitatively, deviations from this ideal behaviour can be related to G^\ddagger for the binary mixture.⁶⁶ Thus if

⁶² B. G. Cox, *J.C.S. Perkin II*, 1970, 607.

⁶³ (a) H. Sadek, F. M. A. Halim, and E. Y. Khalid, *Suomen Kem.*, 1963, **36B**, 141; (b) E. Tommila and S. Maltamo, *ibid.*, 1956, **28B**, 73.

⁶⁴ (a) E. Tommila and M. L. Murto, *Acta Chem. Scand.*, 1963, **17**, 1947; (b) E. Tommila and I. Polenius, *ibid.*, 1963, **17**, 1980.

⁶⁵ (a) P. T. McTigue and P. V. Renowden, *Austral. J. Chem.*, 1970, **23**, 297; (b) E. Tommila and A. Hella, *Ann. Acad. Sci. Fennicae AII*, 1954, **53**, 3.

⁶⁶ J. P. O'Connell and J. M. Prausnitz, *Ind. and Eng. Chem. (Fundamentals)*, 1964, **3**, 347.

G^E is positive the solute should be more soluble in the mixture than predicted from the solubilities in the two pure solvents, and several examples for aqueous mixtures bear this out.⁶⁷ This simple analysis, by being applied to a hydrophobic initial state, may account in part for the fact that the increase in ΔG^\ddagger when a monohydric alcohol is added to t-butyl chloride has the order $\text{Bu}^i\text{OH} > \text{Pr}^i\text{OH} > \text{EtOH}$ and also why, when H_2O_2 is added, ΔG^\ddagger decreases. Similarly, ΔG^\ddagger for the hydrolysis of methyl trifluoroacetate and of chloromethyltrichloroacetate increases more rapidly when either acetone (TA) or acetonitrile (TNAP) are added than when DMSO (TNAN) is added.⁶⁸ Again ΔG^\ddagger for the hydrolysis of benzyl chloride increases more markedly when acetone, ethyl alcohol, or dioxan are added than when DMSO is added.⁶⁹ There are insufficient results for other reactions and other solvent systems to press this point further. However, the reactions of aquonickel(II) with 2,2-bipyridyl in methanol,^{70a} ethanol,^{70b} and t-butyl alcohol^{70b} mixtures seem to show a similar correlation between $\delta_m \Delta G^\ddagger$ and G^E (though we have too few values at present to be certain). Current work in our laboratories indicates that rate constants for the dissociative aquation of the $\text{Fe}(\text{5-NO}_2\text{-phen})_3^{2+}$ cation in a wide range of aqueous mixtures conform to this pattern. This is an interesting aquation reaction because when TA co-solvents are added, $\delta_m \Delta G^\ddagger$ decreases as G^E increases. The quite different behaviour from t-butyl chloride hydrolysis can nevertheless be explained in a very similar fashion. For the iron complex, however, the transition state is more hydrophobic than the initial state,⁷¹ so that here the transition state is stabilized by added co-solvent in the same way that the initial state of t-butyl chloride is stabilized.

These qualitative links between $\delta_m \Delta G^\ddagger$ and G^E , indeed between $\delta_m \Delta X^\ddagger$ and X^E in general, have received support from a more quantitative analysis.⁴ Underlying the difficulties of relating kinetic data, e.g. $\delta_m \Delta X$, to the properties of the binary aqueous mixture, e.g. X^E , is the awareness that the properties of the two components and, consequently, of the mixture will be modified where reactants are added. A quantitative method has been suggested,⁴ therefore, of transforming the derived activation parameter ΔG^\ddagger for reaction in the binary mixture to an endostatic quantity ΔG_α^\ddagger . The latter is calculated for a system (binary mixture + reactants + transition state) in which the ratio of the thermodynamic activities of the two components, a_1/a_2 , remains the same as in the binary mixture. Further expressions are obtained for related endostatic activation quantities, e.g. ΔH_α^\ddagger and ΔV_α^\ddagger , which involve the appropriate partial molar properties of the two components of the binary aqueous mixture. This analysis has only been applied to one system so far,⁴ namely the hydrolysis of t-butyl chloride in ethanol-water, so it is too early to judge the efficacy of this analytical method. It is not clear, for example, why or what significance can be read into the observation that the

⁶⁷ (a) T. T. Herskovits and J. P. Harrington, *Biochemistry*, 1972, **11**, 4800; (b) C. L. de Ligny and N. G. van Deer Keen, *Rec. Trav. chim.*, 1971, **90**, 984.

⁶⁸ N. J. Cleve, *Suomen Kem.*, 1972, **45B**, 235, 285.

⁶⁹ E. Tommila, *Acta Chem. Scand.*, 1966, **20**, 923.

⁷⁰ (a) H. P. Bennetto and E. F. Caldin, *J. Chem. Soc. (A)*, 1971, 2207; (b) P. K. Chattopadhyay and J. F. Coetzee, *Inorg. Chem.*, 1973, **12**, 113.

⁷¹ M. J. Blandamer, J. Burgess, and S. H. Morris, *J.C.S. Dalton*, 1974, 1717.

dependence of $\Delta G_{\alpha}^{\ddagger}$ on mixture composition is more complicated than that for ΔG^{\ddagger} but that of $\Delta H_{\alpha}^{\ddagger}$ is less complex than ΔH^{\ddagger} . Nevertheless the proposals warrant serious attention in the context of both organic and inorganic reactants.

7 Trends in $\delta_m \Delta H^{\ddagger}$ and $\delta_m \Delta S^{\ddagger}$

As noted above, the quantities $\delta_m \Delta H$ and $T \delta_m \Delta S^{\ddagger}$ often have similar sign and magnitude. Of course, they are rarely equal, otherwise the rate constant would be independent of x_2 . Again, this type of behaviour is not confined to kinetics.⁷²

In the hydrolysis of neutral organic halides, the increase in ΔG^{\ddagger} with increase in x_2 generally stems from a dominant change in $T \delta_m \Delta S^{\ddagger}$, the latter decreasing with increase in x_2 ,⁴⁹ e.g. alkyl halides in acetone + water mixtures.⁵⁶ Indeed, if the rate constant were a function of ΔH^{\ddagger} only, then, for example, the rate constant for the hydrolysis of t-butyl chloride would increase when t-butyl alcohol was initially added. This dominant role of entropy changes is often a characteristic of aqueous solutions. In fact, following on from the importance of the changes in the properties of initial states in determining $\delta_m \Delta G^{\ddagger}$, the quantity $\delta_m S^{\circ}$ for such states is expected to play an important part. For neutral solutes in water $T \Delta S^{\circ}$ (gas phase \rightarrow water) is large and negative whereas in non-aqueous solvents, ΔH° is usually the important term. Thus as x_2 increases, $T \delta_m S_3^{\circ}$ should increase more rapidly than $\delta_m H_3^{\circ}$ for the initial state, so contributing to an increase in $\delta_m \Delta G^{\ddagger}$. However, for the decarboxylation of carboxylic acid derivatives, both ΔH^{\ddagger} and ΔS^{\ddagger} decrease as x_2 increases when either ethyl alcohol or dioxan are added, but now ΔH^{\ddagger} decreases more rapidly so ΔG^{\ddagger} decreases.^{51a} In contrast, ΔH^{\ddagger} increases as x_2 increases for the hydrolysis of t-butyl dimethylsulphonium ions in ethyl alcohol + water mixtures, with a maximum at $x_2 = 0.2$, but no maximum is observed in t-butyl alcohol + water mixtures.²⁵ However, $\delta_m \Delta H^{\ddagger}$ shows a minimum for the hydrolysis of arylsulphonic esters in water containing methyl alcohol, ethyl alcohol, or isopropyl alcohol.⁷³

A convenient summary of the data is obtained by plotting ΔH^{\ddagger} against ΔS^{\ddagger} .^{54,70a} Where the points fall on a single straight line, the slope is called the isokinetic temperature, but this behaviour is rarely observed over a wide range of x_2 values. Often the points for the aqueous-rich mixtures fall close to a single straight line when $x_2 < x_2^*$, e.g. t-butyl chloride in alcohol + water mixtures.⁴⁹ Similarly, ΔV^{\ddagger} appears to be a linear function of ΔS^{\ddagger} for the hydrolysis of benzyl chloride in aqueous alcohols over this range.⁷⁴ A linear dependence of ΔH^{\ddagger} on ΔS^{\ddagger} is observed on either side of the mole fraction at which ΔH^{\ddagger} is a minimum in the alkaline hydrolysis of ethyl acetate.^{52a} Nevertheless a statistical

⁷² See e.g. W. Van der Poel and P. J. Sloopmaekers, *Bull. Soc. chim., belges*, 1970, 79, 223; 1971, 80, 401.

⁷³ J. B. Hyne and R. E. Robertson, *Canad. J. Chem.*, 1956, 34, 931.

⁷⁴ H. S. Golinkin and J. B. Hyne, *Canad. J. Chem.*, 1968, 46, 125.

analysis of trends in $\delta_m\Delta H^\ddagger$ and $\delta_m\Delta S^\ddagger$ is still required to ensure that these trends are not illusory.⁷⁵

As noted above, entropy quantities are important in aqueous solutions, so attention should be concentrated on $\delta_m\Delta S^\ddagger$, $\delta_mS_3^\circ$, and δ_mS^\ddagger . By their very nature, entropies are not directly measurable but are calculated from two other properties, the appropriate Gibbs and enthalpy functions. However, enthalpy data are often more readily obtained, so it is often more convenient to analyse trends in $\delta_m\Delta H^\ddagger$. In most systems, an extremum in $\delta_m\Delta S^\ddagger$ occurs close to the mole fraction where $\delta_m\Delta H^\ddagger$ is an extremum. However, this is not always the case. Extrema in activation parameters, $\delta_m\Delta X^\ddagger$, do not always occur at the same mole fraction for a given reaction in a particular mixture. Thus an explanation for an extremum in $\delta_m\Delta H^\ddagger$ cannot be immediately used to account for extrema in $\delta_m\Delta V^\ddagger$, $\delta_m\Delta C_p^\ddagger$, $\delta_m\Delta U_v^\ddagger$, although the causes are often related because these usually stem from the same source, the properties of the solvent mixture.

8 Activation Enthalpies and $\delta_m\Delta H^\ddagger$

We have so far stressed that, in the analysis of activation parameters, the changes in the initial state cannot be overlooked, and that information concerning such changes can often be gained from other non-kinetic experiments. A striking example of both points concerns the analysis of $\delta_m\Delta H^\ddagger$ for t-butyl chloride in ethyl alcohol + water mixtures.^{29,30a} In this mixture, δ_mH° for neutral solutes and salts increases when ethyl alcohol is added to a solution in water, passing through a maximum when $x_2 \simeq 0.1$ (cf. x_2^*) and then decreasing when $x_2 > x_2^*$. The sharpness of the maximum and the extent of the endothermic shift depend on the solute. When t-butyl alcohol is used instead of ethyl alcohol, the trend is more dramatic, the endothermic maximum coming near $x_2 \simeq 0.04$ (cf. x_2^*). Indeed, extrema in $\delta_m\Delta H^\ddagger$ (and $\delta_m\Delta C_p^\ddagger$) are especially marked in this mixture.⁴⁹ With reference to t-butyl chloride in ethyl alcohol + water, at least 95% of the minimum in $\delta_m\Delta H^\ddagger$ near $x_2 = 0.1$ stems from a maximum in δ_mH° for t-butyl chloride. Indeed the calculated δ_mH^\ddagger ($= \delta_m\Delta H^\ddagger + \delta_mH_3^\circ$) is close to zero over the range $0 < x_2 < 0.4$. The fact that δ_mH^\ddagger is zero for this transition state is itself largely fortuitous. In another case, $\delta_m\Delta H^\ddagger$ might be zero because $\delta_mH_3^\circ \simeq \delta_mH^\ddagger$, and this is thought to be the case in the hydrolysis of butyl-dimethylsulphonium ion in water + ethyl alcohol. Clearly a small change in $\delta_m\Delta H^\ddagger$ can mask quite marked changes in the enthalpies of initial and transition states. This behaviour is also observed following analysis of volumes of activation (see below).

Similar positive extrema in δ_mH° for ethyl acetate in aqueous mixtures (cf. the behaviour of carboxylic acids⁷⁶) may contribute to the negative extrema in $\delta_m\Delta H^\ddagger$ for the alkaline hydrolysis of ethyl acetate.^{52a} In the latter system, the intensity of the extremum decreases through the series t-butyl alcohol, isopropyl alcohol, acetone \simeq ethyl alcohol, methyl alcohol, ethylene glycol, and increases

⁷⁵ O. Exner, *Progr. Phys. Org. Chem.*, 1972, **10**, 411; *Coll. Czech. Chem. Comm.*, 1972, **37**, 1425; O. Exner and V. Beránek, *ibid.*, 1973, **38**, 781; S. Wold and O. Exner, *Chemica Scripta*, 1973, **3**, 5.

⁷⁶ L. Avedikian, J. Juillard, J.-P. Morel, and M. Ducros, *Thermochim. Acta*, 1973, **6**, 283.

as the hydrophobic nature of the ester increases.⁷⁷ However, a detailed analysis requires information concerning $\delta_m H^\circ$ (OH^-), which is unlikely to be zero.³⁷ The extent of the extrema in $\delta_m \Delta H^\ddagger$ for the reaction of nickel(II) with 2,2'-bipyridyl in aqueous alcohols also decreases along the series t-butyl alcohol, ethyl alcohol, methyl alcohol; in each case the extremum occurs when $x_2 \simeq x_2^*$.⁷⁰ (Parallel behaviour is shown by $\delta_m \Delta S^\ddagger$.)

Extrema in $\delta_m \Delta H^\ddagger$ are often much smaller in TNA than in TA mixtures. For example, extrema in $\delta_m \Delta H^\ddagger$ and $\delta_m \Delta S^\ddagger$ for hydrolysis of benzyl chloride in acetone + water mixtures are almost lost when acetone is replaced by DMSO.⁶⁹ Similarly, the minimum in $\delta_m \Delta H^\ddagger$ for the hydrolysis of methyl trifluoroacetate becomes less marked through the series of co-solvents acetone, acetonitrile, DMSO; in the latter case only a very shallow minimum is observed, near $x_2 = 0.3$. However, a minimum in $\delta_m \Delta H^\ddagger$ for the hydrolysis of t-butyl chloride in acetonitrile + water mixtures is still clear-cut, although slightly smaller than when ethyl alcohol, THF, or t-butyl alcohol are co-solvents. The distinction between TA and TNA co-solvents is more obvious in $\delta_m \Delta C_p^\ddagger$ (see below).

It is noteworthy that the extrema in $\delta_m H^\circ$ for solutes in ethanol + water do not occur at the mole fraction where H^E is a minimum⁷⁷ nor where the relative partial molar enthalpy of ethanol is a maximum. Similarly, extrema in $\delta_m \Delta S^\ddagger$ occur at a lower mole fraction than indicated by the minimum in S^E .⁷⁴

Although the reality of the endothermic maxima for solutes in ethanol + water is well established, its explanation is not obvious in view of the observation that nearly all solutes are affected in the same way. It appears that when a hydrophobic structure-former is the solute, the amount of water structure which can be enhanced by this solute decreases as more ethanol is added, so $\delta_m H^\circ$ for the solute is positive. Alternatively, the amount of water structure which can be broken by a structure-breaker increases with increase in x_2 , and so $\delta_m H_3^\circ$ is again positive. Only in the limit that the solute exerts little effect on the structure of the system (*cf.* $\text{Me}_4\text{N}^+ \text{Cl}^-$), then $\delta_m H^\circ \rightarrow 0$. In all cases, this unique behaviour of the aqueous mixture disappears when $x_2 \gg x_2^*$.

9 Heat Capacity of Activation and $\delta_m \Delta C_p^\ddagger$

Although the dependence of ΔC_p^\ddagger on x_2 has been measured for only relatively few systems, quite marked extrema have been observed (compare Figure 2). For example,⁴⁹ when t-butyl alcohol, isopropyl alcohol, ethanol, or THF (which form TA mixtures) are added to t-butyl chloride in water, $\delta_m \Delta C_p^\ddagger$ decreases initially with increase in x_2 , reaches a minimum when $x_2 \simeq x_2^*$, and then increases. In contrast, when acetonitrile (TNAP) is added, $\delta_m \Delta C_p^\ddagger$ increases for the hydrolysis of t-butyl chloride⁴⁹ and a series of sulphamoyl chlorides.⁷⁸ A fairly clear-cut pattern emerges in the hydrolysis of methyl trifluoroacetate,⁶⁸ where the addition of acetone (TA) produces an initial decrease in ΔC_p^\ddagger ,

⁷⁷ R. F. Lama and B. C. Lu, *J. Chem. and Eng. Data*, 1965, **10**, 216; J. A. Boyne and A. G. Williamson, *ibid.*, 1967, **12**, 216.

⁷⁸ E. C. F. Ko and R. E. Robertson, *Canad. J. Chem.*, 1972, **50**, 946; *J. Amer. Chem. Soc.*, 1972, **94**, 573.

addition of acetonitrile produces an initial increase (extremum near $x_2 = 0.2$), whereas addition of DMSO (TNAN) results in a more gradual increase in ΔC_p^\ddagger (see also hydrolysis of chloromethyl dichloroacetate^{68,79}).

The complexity of ΔC_p^\ddagger quantities makes the interpretation difficult. It is noteworthy, however, that C_p^E values for alcohol + water mixtures show positive extrema⁸⁰ near $x_2 \simeq x_2^*$, these becoming more marked and at lower mole fractions along the series methanol, ethanol, isopropyl alcohol, t-butyl alcohol, (but C_p^E is much smaller for DMSO + water¹³). A large negative ΔC_p^\ddagger for the hydrolysis of t-butyl chloride in water is attributed² to the S_N1 mechanism, which requires significant breakdown of water-water interaction around the solute in order to stabilize the developing cation. Thus with $\Delta C_p^\ddagger = C_p^\ddagger - C_p^\circ$, in this case $C_p^\ddagger \simeq 0$ and $C_p^\circ > 0$. This is consistent with the idea concerning ΔH^\ddagger , where it is argued that an important contribution to the activation process is the need to break down water-water interactions. This contribution will decrease with increase in temperature. Addition of a structure-forming co-solvent will produce a more thermally labile initial state, so that $\delta_m C_p^\circ > 0$, and then $\delta_m \Delta C_p^\ddagger < 0$ until $x_2 \geq x_2^*$. Addition of a structure breaker (*cf.* acetonitrile) produces the opposite effect, namely $\delta_m \Delta C_p^\ddagger > 0$. This interpretation places a great deal of emphasis on the initial state and, as in the analysis of $\delta_m \Delta H^\ddagger$ for t-butyl chloride, may also rely on the particular properties of the ionic transition state for this reaction. If indeed $\delta_m C_p^\ddagger \simeq 0$, the trend is for $\delta_m C_p^\circ$ of a hydrophobic solute over the range $0 < x_2 < 1$ to decrease because ΔC_p° (gas \rightarrow water) for organic solutes > 0 but ΔC_p° (gas \rightarrow organic solvent) $\simeq 0$. Consequently, $\delta_m \Delta C_p^\ddagger$ should increase (*i.e.* ΔC_p^\ddagger change from negative to zero) and then the negative extrema in the aqueous systems reflect the unique character of these solvent mixtures. There is little information concerning the dependence on x_2 of partial molar heat capacities of neutral hydrophobic solutes in aqueous mixtures. However, the partial molar heat capacities of large alkylammonium ions in water increase to a positive extremum at $x_2 \simeq 0.4$ when t-butyl alcohol is added⁸¹ (see also behaviour for sodium tetraphenylboronate²⁹). This trend is a consequence of the hydrophobic character of these ions⁸² and promotion of water-water interactions by the added alcohol. By way of contrast, heat-capacity data for these salts show that dioxan,⁸ ethylene glycol, and urea, break water-water interactions.⁸¹ In view of the extensive information available concerning aqueous solutions of urea,⁸³ kinetic information for reaction in these solutions should prove interesting, although specific solute-urea interactions⁸⁴ may add new complications.

⁷⁹ N. J. Cleve and E. K. Euranto, *Suomen Kem.*, 1964, 37B, 126.

⁸⁰ R. Arnaud, L. Avedikian, and J. P. Morel, *J. Chim. phys.*, 1972, 45.

⁸¹ R. K. Mohanty, S. Sunder, and J. C. Ahluwalia, *J. Phys. Chem.*, 1972, 76, 2577; B. Chaula and J. C. Ahluwalia, *ibid.*, p. 2582; *J.C.S. Faraday I*, 1973, 69, 434.

⁸² Compare heat capacity of alkylammonium ions in non-aqueous solvents; C. de Visser and G. Somsen, *J.C.S. Faraday I*, 1973, 69, 1440.

⁸³ H. S. Frank and F. Franks, *J. Chem. Phys.*, 1968, 48, 4746; E. G. Finer, F. Franks, and M. J. Tait, *J. Amer. Chem. Soc.*, 1972, 94, 4424.

⁸⁴ W.-Y. Wen and C. L. Chen, *J. Phys. Chem.*, 1969, 73, 2895.

10 Volumes of Activation and $\delta_m \Delta V^\ddagger$

The extrema in V^E and, more particularly, in the partial molar volumes of the co-solvent in a TA mixture indicate that extrema are to be expected in $\delta_m \Delta V^\ddagger$ quantities. Indeed in ethanol + water mixtures, ΔV^\ddagger for the hydrolysis of benzyl chloride, which is negative over the range $0 \leq x_2 < 0.4$, has a minimum at $x_2 = 0.3$ (323.4 K).⁸⁵ Through the series of TA co-solvents methanol, ethanol, isopropyl alcohol, and t-butyl alcohol, the minimum in ΔV^\ddagger becomes more marked and at lower mole fractions, *e.g.* at $x_2 = 0.1$ for t-butyl alcohol.⁸⁵ The latter minimum is, for the most part, determined by a maximum in $\delta_m V^\circ$ for the initial state. A similar conclusion is drawn from direct measurements of solution densities for the extrema shown by $\delta_m \Delta V^\ddagger$ in the other alcohol + water mixtures. A comparison of the $\delta_m \Delta V^\ddagger$ and $\delta_m V^\circ$ values for solvolysis of *p*-chlorobenzyl chloride, benzyl chloride, and t-butyl chloride shows that the pattern shown by $\delta_m \Delta V^\ddagger$ depends considerably on both $\delta_m V^\circ$ and $\delta_m V^\ddagger$, which in turn depend on the mechanism of the reaction.⁸⁵ For example, a minimum in $\delta_m \Delta V^\ddagger$ for *p*-chlorobenzyl chloride in ethanol-water at $x_2 \simeq 0.2$ is a consequence of maxima in $\delta_m V^\ddagger$ and $\delta_m V^\circ$, the latter being more marked. Maxima in $\delta_m V^\ddagger$ and $\delta_m V^\circ$ appear to be characteristic of non-ionic solutes and minima of ionic states. The minimum in $\delta_m V^\ddagger$ for t-butyl chloride is similar to that observed for $\text{Me}_4\text{N}^+ \text{Cl}^-$.

The extrema in these volume parameters correspond closely to the mole fraction x_2^{**} . Thus for benzyl chloride, $V_2^\circ - V_2^*$ is negative (V_2^* = molar volume of pure benzyl chloride) in ethanol-water when $x_2 < x_2^{**}$, indicating that the solute is accommodated to some extent in the clathrate-like cavities in the aqueous solution. But when $x_2 > x_2^{**}$, $V_2^\circ > V_2^*$, and indeed a sharp positive extremum in $d\Delta V^\ddagger/dp$ is observed at $x_2 \simeq 0.04$ for benzyl chloride in t-butyl alcohol-water system,^{22a} although when $x_2 = 0$, $d\Delta V^\ddagger/dp = 0$, which means that the compressibilities of transition state and hydrophobic initial state are equal. When acetone is added to benzyl chloride in water, $\delta_m \Delta V^\ddagger$ has an extremum near $x_2 = 0.2$, but when DMSO is added, $\delta_m \Delta V^\ddagger$, $\delta_m V^\ddagger$, and $\delta_m V_3^\circ$ are much smaller.

We are unable to extend this discussion of $\delta_m \Delta V^\ddagger$ to include inorganic reactions because relevant results are singularly rare.

11 Isochoric Activation Parameters: ΔU_v^\ddagger

The dependence of these quantities on the composition of an aqueous mixture has not been investigated in any great detail.⁸⁶ The quantity ΔU_v^\ddagger for the hydrolysis of t-butyl chloride increases when ethanol is added to water, then decreases, and eventually increases at higher alcohol mole fractions. A similar

⁸⁵ J. B. Hyne, H. S. Golinkin, and W. G. Laidlaw, *J. Amer. Chem. Soc.*, 1966, **88**, 2104; H. S. Golinkin, I. Lee, and J. B. Hyne, *ibid.*, 1967, **89**, 1307; M. J. Mackinnon, A. B. Lateef, and J. B. Hyne, *Canad. J. Chem.*, 1970, **48**, 2025; D. D. MacDonald and J. B. Hyne, *ibid.*, 1970, **48**, 2494.

⁸⁶ B. T. Baliga and E. Whalley, *Canad. J. Chem.*, 1970, **48**, 528; B. T. Baliga, R. J. Withey, D. Poulton, and E. Whalley, *Trans. Faraday Soc.*, 1965, **61**, 517; B. T. Baliga and E. Whalley, *J. Phys. Chem.*, 1967, **71**, 1166.

pattern is shown by $\delta_m \Delta S_v^\ddagger$. The extrema here are roughly one-half those observed in the isobaric activation parameters ΔH^\ddagger and ΔS^\ddagger , and do not occur at the same mole fraction. However, in two other cases, *viz.* acid-catalysed hydrolysis of methyl acetate in acetone + water and hydrolysis of benzyl chloride in ethanol + water, less striking extrema relative to those in isobaric quantities are observed in the isochoric quantities.

At this time there seems to be no simple way in which the behaviour of isochoric quantities can be explained. Thus the concept of activation at constant total volume is simple to understand, but the implications on molecular processes accompanying the conversion of initial state into transition state are not.

12 Conclusions

We have attempted to highlight a number of themes in this review. First, the complex patterns in activation parameters often reflect the sometimes unique features of aqueous systems. Second, that in explaining the observed trends, the changes in activation parameters reflect changes in both transition and initial states, the latter being dangerous to ignore. Finally, it is possible to analyse the kinetic data by using thermodynamic properties of solutes in aqueous and non-aqueous systems. We hope that this review will encourage chemists to measure kinetics of reaction in a wide range of aqueous mixtures as functions of x_2 , temperature, and pressure.