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Understanding organic reactions in water: from hydrophobic encounters to surfactant aggregates

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A crucial factor in realising a green chemical process in solution involves the choice of a safe, non-toxic and cheap solvent. Water is the obvious choice. Despite solubility problems, considerable interest has developed recently in organic chemistry in water. This interest also results from the fact that association and chemical reactions often benefit noticeably from the special properties of water, resulting mainly from its small molecular size, its three-dimensional hydrogen-bond network and hydrophobic interactions which are so unique for liquid water. Here we discuss organic reactions and assembly processes in water, largely taken from experiments performed in the authors' laboratories. We show that non-covalent interactions in water can be utilised for fine tuning organic reactions in aqueous media.

Introduction

For a very long time, water has been recognised as essential for all life processes and indeed life support on planet Earth. For example, at the dawn of western scientific thought, Thales (from Milete, B.C. 640–548) said: '*All things are produced from water*'. This statement was one of the first attempts to formulate a generalisation; *i.e.* referring all things to a common origin. In ancient Chinese thought, water was frequently used as a root metaphor for natural and civilised behaviour.[1] K'ung Tzu said: '*Water, which extends everywhere and gives everything life without acting (wuwei) is like virtue (de) . . . That is the reason that when a gentleman (junzi) sees a great river, he will always look upon it . . .*'

In all major religions and philosophies, water plays an important role. In chemical research, a long-standing interest exists in the properties of water[2,3] and in chemical reactions between solutes taking place in this fascinating liquid. However, water is rarely seen as the solvent of choice in which to carry out synthetic chemistry. In this review we illustrate some of the key features involved in understanding the role of solvent water for chemical reactions involving small molecules and then for processes involving larger molecules and large molecular assemblies including micelles and vesicles. We emphasise that water is not just a 'green' solvent, but that the special properties of the liquid give rise to intra- and intermolecular non-covalent interactions leading to novel solvation behaviour and assembly processes.

Professor Jan B. F. N. Engberts graduated with a PhD degree from the University of Groningen, The Netherlands (1967). After a stay at the University of Amsterdam with Prof. Th. J. de Boer (ESR spectroscopy) Jan returned to Groningen and was appointed as a Professor of General Chemistry in 1978 and as a Professor of Physical Organic Chemistry in 1991. Fascinated by the peculiar properties of water as a medium for organic reactions and aggregation processes, much emphasis has been placed on hydrolysis reactions in water in the presence of hydrophobic addenda, surfactant aggregation, vesicle fusion, and, most recently, development of DNA carrier systems for application in gene therapy. In these studies, thermodynamics always played an important role, and these interests brought Mike and Jan together, more years ago than both care to remember.

Professor Mike Blandamer is an Emeritus Professor at the University of Leicester, having retired in 1999. Mike graduated with BSc and PhD degrees from the University of Southampton who awarded Mike the degree of DSc in 1984. Following post-doctoral research at NRC in Ottawa (Canada), Mike joined the staff at the University of Leicester. Mike and Jan share a common interest in aqueous solution chemistry, good food, good wine and New Orleans jazz music. They were coauthors on a paper published in 1985 followed over 26 years by 50 joint papers and reviews. For part of their period of cooperation, Mike was a Visiting Professor at the University of Groningen.

Aqueous solutions: general features

Introductory chemistry textbooks reviewing the properties of water stress the importance of intermolecular hydrogen bonding, leading to the conclusion that water is an associated liquid. The high relative permittivity is consistent with the idea that water is a polar liquid and therefore a good solvent for salts such as sodium chloride. $E(T)$30-values, as defined by Reichardt, which are particularly useful microscopic solvent micropolarity reporter values, confirm that water is a polar solvent.[4] The absence of strong ion-pairing in aqueous solution allows unambiguous mechanistic studies of reactions that proceed *via* highly polar or ionic intermediates. We also note that water has one of the highest heat capacities per unit volume for a liquid; *e.g.* for water, C_p = 4.18 J K^{-1} cm^{-3}; for ethanol C_p = 1.92 J K^{-1} cm^{-3}. This high heat capacity is important in moderating possible extremes of temperature on planet Earth.

This emphasis on molecular association should be set against the fact that water has a modest (shear) viscosity; the liquid pours easily, quite different from, say, glycerol.

Granted the properties of water, including its volumetric properties (*e.g.* a temperature of maximum density near 277 K) are complicated, the expectation is that the properties of aqueous solutions are also complicated. This is indeed the case. Nevertheless important features of water and aqueous solutions can be understood in the following general terms.[2]

A cluster of non-intermolecularly hydrogen bonded, but closely packed water molecules has high density–low molar volume coupled with weak cohesion. A cluster of inter-

molecularly hydrogen-bonded water molecules has low density–large molar volume with strong cohesion. In other words, strong cohesion is coupled with large molar volume. The latter is a consequence of the structural requirements of hydrogen bond formation which for a simple dimer has a *trans*-near linear configuration. To an important extent hydrogen bonding is both cohesive and repulsive, the latter reflecting the tendency to hold apart the centres of mass of water molecules. This situation is reflected in the low internal pressure of water.[5] In the context of describing the properties of aqueous solutions, we might speculate that any process (*e.g.* chemical reaction) which enhances water–water hydrogen bonding leads to an increase in molar volume. This rather unusual situation (compared to organic solvents) accounts in part for the complexity of the properties of aqueous solutions.

Experimental

This review focuses on the results obtained in the laboratories of the two authors using two major experimental techniques: (i) chemical kinetics, and (ii) titration microcalorimetry.

Determination of rate constants for chemical reactions in aqueous solutions using spectrophotometric techniques is considerably helped by computer-based data capture and data analysis programs, coupled with good thermostatting of solutions. In recently published kinetic studies from Groningen we routinely monitor chemical reactions for up to six half-lives leading to rate constants having standard errors of better than 1%. This precision is important in the determination of standard enthalpies ($\Delta^{\ddagger}H^0$) and entropies ($\Delta^{\ddagger}S^0$) of activation as defined by Eyring transition-state theory.

Titration microcalorimetry[6] has proved an extremely important technique particularly in the context of our investigations into the properties of surfactants in aqueous solutions. In this technique (see Fig. 1 of ref. 7) a micro-syringe under computer control injects at pre-selected time intervals a small volume (*e.g.* 5×10^{-6} dm^3) of an aqueous solution into another aqueous solution held in the sample cell, volume *ca.* 1.5 cm^3. A reference cell for the systems discussed here contains water. The reference cell is heated, raising the temperature very slowly. The computer-based control system monitors the temperature of reference and sample cells, adjusting the power to heaters of both sample and reference cells in order to hold the two cells at the same temperature. The recorded quantity is the rate of heating of the sample cell over the time required to bring both sample and reference cells on to the same temperature ramp. In effect the outcome is a plot of the ratio $(q/\delta n_j^0)$ {where heat q results from adding δn_j^0 moles of chemical substance j to the solution in the sample cell} against either injection number or concentration of chemical substance j in the sample cell.

The thermodynamic analysis is based on the following set of equations. The extensive state variable enthalpy H for a closed system is defined by the three independent variables, T, p, ξ where ξ describes the composition of the system. Thus,

$$H = H[T,p,\xi] \tag{1}$$

The complete differential of eqn. (1) yields an equation for the change in enthalpy; eqn. (2)

$$\mathrm{d}H = \left(\frac{\partial H}{\partial T}\right)_{p,\xi} \cdot \mathrm{d}T + \left(\frac{\partial H}{\partial p}\right)_{T,\xi} \cdot \mathrm{d}p + \left(\frac{\partial H}{\partial \xi}\right)_{T,p} \cdot \mathrm{d}\xi \tag{2}$$

Then at constant temperature and pressure the heat q recorded by the calorimeter between injection numbers I and $(I+1)$ following injection of δn_j^0 moles of chemical substance j at injection number I is given by eqn. (3).

$$\left[\frac{q}{\delta n_j^0}\right]_I^{I+1} = \left[\left(\frac{\partial H}{\partial \xi}\right)_{T,p} \cdot \frac{\delta \xi}{\delta n_j^0}\right]_I^{I+1} \tag{3}$$

The left-hand side of eqn. (3) is the measured quantity recorded as a function of injection number. Eqn. (3) shows that the measured ratio $(q/\delta n_j^0)$ is given by the product of two terms which are not known *a priori*. We indicate below some important cases where analysis of the thermodynamic properties of the solutions in the sample cells and injected aliquots yields important information concerning a given system, *e.g.* micelle formation.[7] The thermodynamic properties commented on in this review are Gibbsian[8] in that they are generated by differentials of Gibbs energies with respect to the variables T and p.

Aqueous solutions: general properties

Enderby and coworkers[9] using neutron inelastic scattering techniques have published detailed information for the structures of hydrated metal cations and halide ions in aqueous solutions. For cations, the results are in line with the structures predicted on the basis of secondary evidence; *e.g.* ionic mobilities. Thus for Ni^{2+}, the oxygen atom is adjacent to the cation but the $Ni^{2+}\cdots$O–D(H) angle is less than 2π; the water molecules undergo a wagging motion.

For many years there was intense speculation concerning the arrangement of water molecules around, for example, chloride ions. Two models were often proposed; (i) a bifurcated structure such that the water dipole moment is co-linear with the centre of the anion, and (ii) a linear structure for $Cl^-\cdots$H–O(H). The latter turns out to be the favoured structure. However, the systems are quite dynamic in that water molecules in the primary hydration sheath exchange with water molecules in the bulk solvent although the hydrogen-bond dynamics of water molecules in the hydration shell are slow compared to those for pure water.[10]

Again the fact that water is a polar liquid is often stated to account for the fact that apolar molecules such as rare gases and hydrocarbons are sparingly soluble in water. Even here complexities emerge. The solubilities of argon, methane, ethane and butane in cold water are higher than predicted on the basis of the cohesive energy density of water.[11] For almost 50 years the low solubilities of apolar solutes in water were attributed to the loss of entropy by the solvent accompanying enhancement of water–water hydrogen bonding.[12] The structures of solid clathrate hydrates were taken as models for the H-bond structure of water around apolar solutes.

In general terms the standard enthalpy of solution for neutral solute j (*i.e.* gas phase to solution) $\Delta_{\mathrm{sln}}H^0$ is negative (*i.e.* exothermic). But the solution process is dominated by a negative $\Delta_{\mathrm{sln}}S^0$ such that $\Delta_{\mathrm{sln}}G^0 > 0$ where $\left|T\Delta_{\mathrm{sln}}S^0\right| > \left|\Delta_{\mathrm{sln}}H^0\right|$. Interestingly, thermodynamic parameters such as limiting isobaric heat capacities C_{pj}^{∞}(aq) and limiting partial molar volumes V_j^{∞}(aq) for neutral solute j in aqueous solution can be expressed in terms of group contributions, a form of analysis which seemed to support the clathrate hydrate model.[13] A similar clathrate model[14] was advanced for the hydration of alkylammonium salts, $R_4N^+X^-$.

Serious doubt was thrown on the clathrate model (and the general concept of structure making) for hydration of apolar solutes (including alkylammonium salts) by the results of neutron inelastic experiments. Neutron diffraction data for $(CH_3)_4N^+Cl^-$ in aqueous solution show no evidence for enhancement of water–water interactions over that in pure water.[15] The negative entropy change for dissolution of apolar gases apparently arises largely from a pronounced preference for tangentially oriented water O–H groups with respect to the apolar solute rather than from more or stronger H-bonds in the hydrophobic hydration shell. Apart from neutron scattering, supporting evidence comes from MD computer simulations,[16] thermodynamic analyses,[17a] and quantum chemical calculations.[17b] However, 'whether or not the H-bond structure in the

hydrophobic hydration shell is significantly different from that in water?' is a question still not fully answered.[18]

Analysis of the properties of polyfunctional solutes in aqueous solution is not straightforward. In the case of, for example, monosaccharides account must be taken of the possible multitude of conformations for these solutes. Such is the complexity that it is difficult to formulate general rules although we return in a later section to these systems. Similar complexities emerge in the case of aqueous solutions containing proteins.[19]

Intermolecular interactions in water

The properties of aqueous solutions reflect both (i) solute–water interactions, and (ii) solute–solute interactions. Certainly for concentrated solutions the two sets of interactions cannot be considered independent.

In the context of understanding solute–solute interactions the simple calculation described by Robinson and Stokes[20] has considerable merit leading to intermolecular solute–solute centre-to-centre distances d as a function of solute concentration, c_j; eqns. (4) and (5), where c_j is expressed in mol dm^{-3} and N_A is the Avogadro constant.

$$\text{neutral solutes: } d = (10^3 N_A c_j)^{1/3} \quad (4)$$

$$1:1 \text{ salts: } \quad d = (2 \times 10^3 N_A c_j)^{1/3} \quad (5)$$

The results are summarised in Table 1 for solutions prepared

Table 1 Inter-solute distances[a]

c_j/mol dm^{-3}	10^{-4}	10^{-3}	10^{-2}	0.1	1.0	10.0
Neutral solutes (*e.g.* urea) d/nm	26	12	5.4	2.6	1.2	0.55
1:1 Salts (*e.g.* NaCl) d/nm	20	9.4	4.4	2.0	0.94	0.44

[a] The distances are calculated on the basis that each solute molecule (ion) is at the centre of a cube, volume d^3. The difference between calculated distances for a neutral solute and a 1:1 salt is a consequence of the fact that each mole of a 1:1 salt yields, with complete dissociation, 2 moles of ions.

using a simple solute (*e.g.* urea) and using a 1:1 salt. Distance d provides an indication of the number of solvent molecules between solute molecules, a number which dramatically decreases with increase in solute concentration.

A useful concept was introduced by Gurney[21] who identified a cosphere of water around each solute molecule (ion). The organisation of water in the cosphere differs from that in bulk water. Then the properties of real aqueous solutions of neutral molecules (*e.g.* urea) differ from the properties of the corresponding ideal solutions as a consequence of 'communication' through the intervening water molecules between solute molecules plus their cospheres. Quantitatively this communication is described by the Gibbs–Duhem equation which requires that (at fixed T and p) for an aqueous solution containing water (1) and solute (j), the chemical potentials μ_1(aq) and μ_j(aq) are not independent but closely linked.

$$n_1 \mathrm{d}\mu_1(\text{aq}) + n_j \mathrm{d}\mu_j(\text{aq}) = 0 \quad (6)$$

In these terms the extent and nature of the differences between the properties of real and ideal aqueous solutions (at fixed T and p) are a function of the organisation of water in the cospheres. Then for a given solution, molality m_j, the differences between Gibbs energies of real and ideal solutions can be expressed in terms of an excess Gibbs energy G^E. Moreover the latter property for dilute solutions can also be expressed in terms of pairwise solute–solute interaction parameters[22] g_{jj} as shown in eqn. (7) where $m^o = 1$ mol kg^{-1}.

$$G^E = RTg_{jj}(m_j/m^o)^2 \quad (7)$$

Interaction parameter g_{jj} is a member of a family of such parameters which includes volumetric v_{jj}, enthalpic h_{jj} and entropic s_{jj} pairwise interaction parameters. For ideal solutions h_{jj} is zero and so the enthalpy of dilution of a given aqueous ideal solution is zero. This is not the case for real solutions as is readily demonstrated using a titration microcalorimeter. We can compare the recorded traces for two experiments. In both cases the sample cell at the start of the experiment contained water. In one experiment the syringe contained urea(aq); in a second experiment the syringe contained *N*-ethylurea(aq) at the same molality, 0.8 mol kg^{-1}. The point to note is that in terms of the model discussed above (*cf.* Table 1) dilution simply means that the inter-solute distance increases. We find that for urea(aq), separation is *endothermic* whereas for monoethylurea(aq) separation is *exothermic*, showing a dramatic impact on the properties of the solutions by replacing a hydrogen atom in urea by an ethyl group.[23] The latter comments signal the possibility that these pairwise solute–solute interaction parameters can be decomposed into pairwise group–group interaction parameters. Wood and coworkers[24] developed this method of analysis leading to a significant increase in the understanding of the properties of aqueous solutions containing neutral solutes (Savage–Wood Additivity of Group Interactions, SWAG, approach).

Kinetics of organic reactions in water containing inert cosolutes

If a substrate X undergoes spontaneous hydrolysis in very dilute aqueous solutions at fixed temperature and pressure, the (first-order) rate constant k(aq;id) (id = ideal, *i.e.* in the absence of a cosolute) is determined by the standard Gibbs energy of activation, $\Delta^{\ddagger}G^0$.

When an inert cosolute j is added, the rate constant changes reflecting the impact of solute j on the chemical potentials of X in both initial and transition states. The rate constant k(aq) is sensitive to the molality of added solute m_j as determined by the impact of solute j on the hydration properties of solute X in both initial and transition states. The changes in the latter two states depend on the hydration properties of solute j. In addition, account must be taken of the fact that in real solutions properties of the solvent are not ideal. The final equation[25] takes the following form where ϕ is the practical osmotic coefficient for the solvent, molar mass M_1.

$$\ln[k(\text{aq})/k(\text{aq;id})] = (2/RT)[1/m^o]^2 G_c m_j - \phi M_1 m_j \quad (8)$$

Here G_c is a compact representation of the effect of added solute j on the chemical potentials of initial and transition states for reacting solute X. For most dilute aqueous solutions it can be assumed that ϕ is unity. Then $\{\ln[k(\text{aq})/k(\text{aq;id})]\}$ is a linear function of the solute molality m_j such that if added solute lowers the rate constant, G_c is negative. This model was originally tested using kinetic data describing the effects of added monohydric alcohols on the water-catalysed hydrolysis of 1-acyl-1,2,4-triazoles[26] and the effects of added ureas on the neutral hydrolysis of *p*-methoxyphenyl dichloroethanoate,[25] Fig. 1 and 2, respectively.

In both cases kinetic data at low concentrations of cosolute followed patterns in which G_c parameters can be understood in terms of pairwise interactions describing added solute–substrate interactions. With increase in hydrophobicity of both added cosolute and reacting substrate, G_c decreases. Hence in terms of the substrate, the hydration characteristics of the initial state rather than the transition state are important. In the context of the model, interaction between added cosolvent and initial state is envisaged as taking place *via* the cooperative hydrogen-bonding interactions within the solvent; that is *via* cosphere–cosphere communication.

This kinetic analysis of the effects of added solutes is illustrated by kinetic data for the following reactions:

(i) Hydrolysis of [(*p*-nitrophenyl)sulfonyl]methyl perchlorate;[27] Fig. 3.

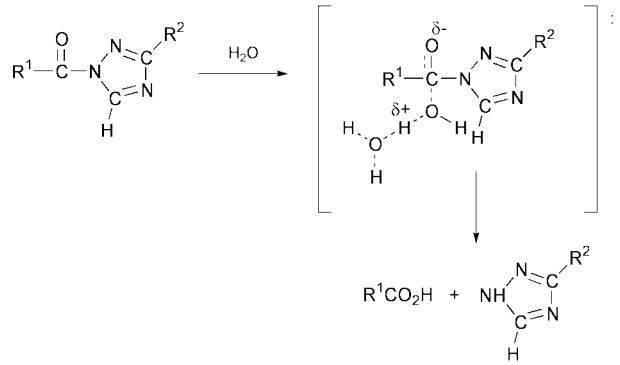

Fig. 1 Neutral hydrolysis of 1-acyl-3-substituted-1,2,4-triazoles.

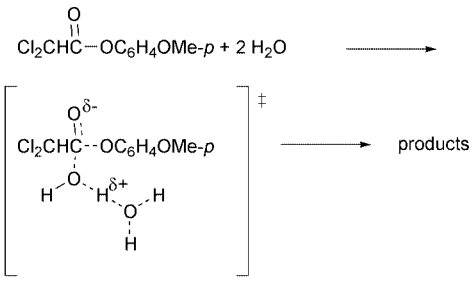

Fig. 2 Mechanism of the water-catalysed hydrolysis of acyl-activated esters.

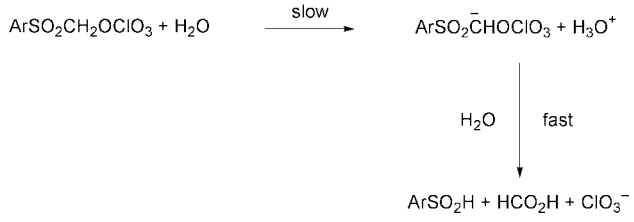

Fig. 3 Water-catalysed hydrolysis of covalent arylsulfonylmethyl perchlorates.

(ii) Hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole in aqueous solution containing monohydric alcohols. No alcoholysis of the kinetic probes occurs under the reaction conditions. Group interaction parameters for polyhydric alcohols are strongly dependent on the positions of the hydroxyl groups in the alcohols.[28]

(iii) Hydrolysis of eighteen 1-acyl-(3-substituted)-1,2,4-triazoles in aqueous solutions containing ethanol and propan-1-ol. Although the SWAG analysis is reasonably satisfactory, stereochemical effects also play an important role.[29] The latter feature is also shown by the effects of added monosaccharides on rate constants for hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazoles.[30]

(iv) For the hydrolysis of *p*-methoxyphenyl dichloroethanoate in aqueous solutions, the elegance of the SWAG approach is shown by the additivity of G_c for carboxamides, ureas, sulfonamides and sulfoxides.[31]

(v) The kinetics of hydrolysis of 1-benzoyl-1,2,4-triazole in aqueous solutions is accounted for in terms of pairwise solute interactions in solution containing amphiphilic solutes below their critical micellar concentrations.[32]

The additivity pattern does break down if salts are added to the solutions in solvents comprising alcohol + water mixtures.

There are interesting and important exceptions to the SWAG additivity concept as shown in the dramatic retardation by added α-phenylalanine of the hydrolysis of activated amides in contrast to the rate acceleration induced by alanine.[33] Similar non-additivity is observed for the effects of isomeric aliphatic α-amino acids on the kinetics of hydrolysis of 2-(4-nitrophenoxy)tetrahydropyran and of alkylammonium salts on the hydrolysis of 1-benzoyl-1,2,4-triazole.[34]

Camouflage effects

Quite generally solutes in aqueous solutions can be classified as either hydrophilic or hydrophobic. However, we noted above that the properties of hydrophilic solutes in aqueous solutions are quite complicated. Indeed the properties of mono- and polyhydroxylated solutes point to key influences of the structure and stereochemistry of the functional groups. This conclusion is confirmed by limiting partial molar volumes and apparent molar isentropic compressions $\phi(K_{Sj};\ \mathrm{def})^{\infty}$ of carbohydrates in aqueous solutions.[35] However we note that $\phi(K_{Sj};\ \mathrm{def})^{\infty}$ is a complicated property[8,36] being for the most part based on an extrathermodynamic assumption.[37]

Hydration of carbohydrates is crucially governed by the relative positions of OH groups in a given carbohydrate. Their hydration characteristics depend on the matching fit between OH-groups in a given carbohydrate and either nearest neighbour (*e.g.* D-talose) or next nearest-neighbour oxygen; Table 2. A

Table 2 Kinetic medium effects and related properties of D-galactose and D-talose in aqueous solutions at 298.15 K

Property	D-galactose	D-talose
$G_c{}^a$/J kg mol^{-2}	−142	−280
$\phi(K_{Sj};\mathrm{def})^{\infty b}$/cm^3 mol^{-1} bar^{-1}	−20.14	−11.9
$n_S{}^c$	8.7	7.7

[a] G_c; see eqn. (6). [b] $\phi(K_{Sj};\mathrm{def})^{\infty}$; defined limiting apparent molar isentropic compression for solute *j* in aqueous solution; see ref. 37. [c] n_h; hydration number.

further feature emerges from analysis of isobaric heat capacity data which can be understood in terms of solute–solute interactions. For a 'probe' solute *j* in an aqueous solution containing a carbohydrate, we might ask how solute *j* 'reacts' to the presence of the carbohydrate. The evidence suggests that if the OH groups of a carbohydrate match into the three-dimensional hydrogen-bond structure of water, solute *j* is unaware of their presence—they have been camouflaged by the solvent. Indeed solute *j* may characterise the carbohydrate solute as hydrophobic.[38] The dependence of the hydration of monosaccharides on the detailed stereochemistry of the OH moieties has also been noted for single-tailed nonionic surfactants with sugar head groups.[39]

Hydrophobic inhibition

The thermodynamic properties of solute X in real solutions containing neutral solute *j* can be described in terms of the activity coefficient of solute X which can in turn be expressed in terms of Gibbs energy interaction parameters. This analysis leads to the description of the effects of added neutral solutes (*e.g.* alcohols) on rate constants for ester hydrolysis in terms of $G(c)$ parameters. This line of argument envisages that the chemical potential of a given solute X in aqueous solution is sensitive to the nature and hydration properties of other solutes by virtue of the communication through intervening water molecules; *i.e.* cosphere–cosphere interactions. This type of explanation is based on the proposal that the properties of a given solute molecule X in solution are perturbed by the sum of individual effects of all other solute molecules in solution.

In an alternative explanation the properties of a given solute molecule X are strongly influenced by intense interaction with a single neighbouring solute molecule *j* in a specific solute–solute interaction. The possibility that the latter model could account for the effects of added solute on the rate of ester hydrolysis was raised by a molecular dynamics simulation.[40]

The latter indicated that an encounter complex[41] involving ester and added solute could be formed. Moreover the cosolute *j* blocks the reaction centre from attack by water in the hydrolysis reaction. In these terms the first-order rate constant for ester hydrolysis $k(m_j)$ in the presence of solute *j*, molality m_j, is related to the equilibrium constant K_{ec} using eqn. (9); (ec = encounter complex).

$$k(m_j) = k(m_j = 0) / [1 + K_{ec}m_j] \quad (9)$$

In the limit that $K_{ec}m_j < 1$, $\ln[k(m_j)]$ is predicted to be a linear function of molality m_j, with slope K_{ec}. Kinetic data for the hydrolysis of three activated esters show that the model accounts satisfactorily for the observed patterns.[42]

Diels–Alder reactions in water

Relatively apolar solutes in aqueous solutions can form encounter complexes which are stabilised by hydrophobic interactions. This can occur for two solutes that can react to form a product if the orientation of both reactions in the encounter complex is suitable for bond making/bond breaking processes. An important example is provided by the formation of an encounter complex that consists of a diene/dienophile pair. The relative stability of the encounter complex in aqueous solution then leads to a rate acceleration compared to the reaction in organic solvents, primarily because the larger number of intermolecular collisions in the complex will favour the cycloaddition reaction. If, in addition to this effect, the activated complex is also stabilised by increased hydrogen-bond interaction relative to the initial state, substantial rate enhancements in water can be realised.[43]

Even in 1931 Diels and Alder used water as a solvent for their famous reaction. However it was the communication by Rideout and Breslow[44] that aroused particular interest in Diels–Alder (DA) reactions and other organic reactions in water. It was reported that the DA reaction of methyl vinyl ketone with cyclopentadiene (CP) was 290 times faster in water than in cyanomethane and that the preference for the *endo* adduct was significantly increased, Fig. 4. Later we found that the second-order rate constant for the DA reaction of 5-methoxy-naphthoquinone with CP was about 1.3×10^4 times higher in water than in *n*-hexane.[43] Detailed examination of aqueous solvent effects on the otherwise solvent-insensitive DA reactions showed that *enforced hydrophobic interactions* between diene and dienophile and *hydrogen bonding* of water to the polarised carbonyl moieties in the activated complex play a major role in the large aqueous rate acceleration.[45] The enhanced preference for the *endo* reaction product (mentioned above) is understood in terms of the smaller solvent accessible surface area for the activated complex leading to this stereoisomer. Computational studies support the interpretation of the beneficial effect of water on these electrocyclic reactions.[46] Aqueous rate acceleration for DA reactions is quite general and has been employed in many synthetic applications. Of course, the magnitude of the effect depends on the contribution of both hydrophobic and hydrogen-bonding interactions.The hydrogen-bonding effect of water can be replaced by Lewis-acid catalysts such as Cu(II) ions with particularly successful applications for bidentate dienophiles,[47] Fig. 5. Relative to the uncatalysed cycloaddition with CP, 0.01 mol dm^{-3} $Cu(NO_3)_2$ in water leads to a rate enhancement of *ca.* 8×10^4. Lewis-acids Ni^{2+}, Co^{2+} and Zn^{2+} are less effective. Water does not enhance the *endo*-selectivity for these reactions, consistent with the view that the stereochemistry is influenced by enforced hydrophobic interactions.

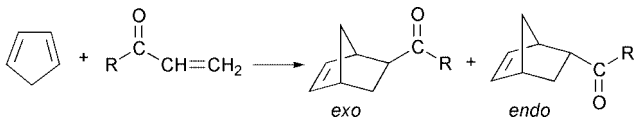

Fig. 4 Diels–Alder reaction of cyclopentadiene with alkyl vinyl ketones.

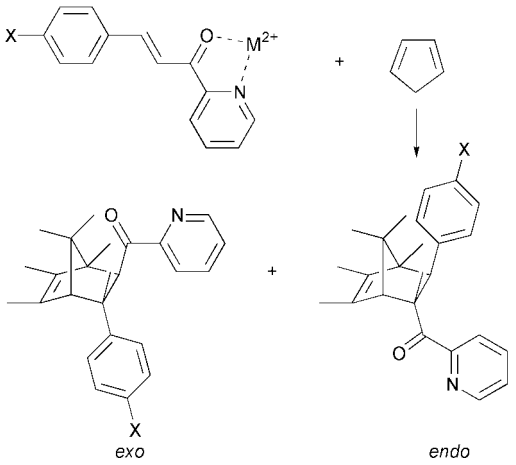

Fig. 5 Lewis-acid catalysed Diels–Alder reaction of 3-*para*-substituted-phenyl-1-(2-pyridyl)-2-propen-1-ones with cyclopentadiene to provide the *endo* (major product) and *exo* (minor product) cycloadducts. (a) X = NO_2, (b) X = Cl, (c) X = H, (d) X = CH_3, (e) X = OCH_3, (f) X = $CH_2SO_3^-$ Na^+, (g) X = $CH_2N^+(CH_3)_3Br^-$.

The same DA reactions have also been performed in the presence of diamine and α-amino acid ligands. Interestingly, ligand-accelerated catalysis of the reaction in the presence of Cu^{2+} ions was observed for a series of (chiral) aromatic α-amino acid ligands. In the case of N^{α}-methyl-L-tryptophan, 74% enantioselectivity was found. Smaller selectivities were found when organic solvents were used. The enhanced catalytic effect and the enantioselectivity are consistent with arene–arene interactions between the pyridine ring[48] of the dienophile and the aromatic ring of the α-amino acid ligand bound to Cu^{2+}, Fig. 6.

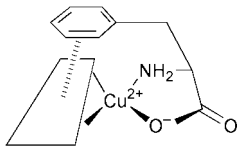

Fig. 6 Ligand-induced hydrophobic bonding of the Lewis acid to the dienophile.

Combination of Lewis-acid catalysis with micellar catalysis leads to exceptionally efficient catalysis.[49] For example, the DA reaction with copper didodecyl sulfate micelles shows a rate acceleration of 1.8×10^6, again compared to the uncatalysed cycloaddition in cyanomethane. The major factor responsible for this huge catalytic effect is the essentially complete complexation of the dienophile to the Cu^{2+} ions at the surface of the micelles. A similar vesicular-catalysed reaction is somewhat less effective (rate acceleration *ca.* 10^6), but the maximum catalytic effect is obtained at significantly lower surfactant concentration, which is important from the view point of 'green chemistry'.[50] Lewis-acid–surfactant-combined catalysts have a definite potential for green organic synthesis in aqueous media as demonstrated by Kobayashi *et al.* for several carbon–carbon bond-forming reactions.[51] The detailed studies of the aqueous rate accelerations of DA reactions have set the stage for extensive application of organic synthesis in water.[50]

Surfactant aggregation

Micelles

The story is told[52] how McBain's original proposal[53] concerning the possibility that surfactants might aggregate in water above a critical micellar concentration was met with the reply, 'Nonsense, McBain'. Of course it is now recognised that in

aqueous solutions up to 100 monomer surfactant monomers may associate to form micelles. Nevertheless the actual structure of micelles is still a matter for debate.

Interest in these systems not only stems from their use in detergent formulations but also for their general ability to solubilise chemical substances in aqueous systems and to act as catalysts for their chemical reactions. Thermodynamic description of the equilibrium between micelles and monomers in solutions is generally based on one of two models, both recognising that micelle formation is a strongly cooperative process, with hydrophobic interactions as the major driving force.[54]

According to the closed association model, a chemical equilibrium exists between monomers and micelles. This is the mass action model.[55] Thus if N is the aggregation number for surfactant S,

$$N\mathrm{S(aq)} \rightleftharpoons \mathrm{S}_N\mathrm{(aq)} \quad (10)$$

Hence, the equilibrium constant is,

$$K = [\mathrm{S}_N\mathrm{(aq)}]/[\mathrm{S(aq)}]^N \quad (11)$$

Numerical analysis shows that with an increase in aggregation number N and with increase in concentration of surfactant, the change in composition of the solution at the critical micellar concentration becomes sharper.

According to the phase separation model,[54] micelles form a separate phase in the aqueous system with surfactant in the micellar phase in equilibrium with surfactant in aqueous solution at the critical micellar concentration. Thus the equilibrium for surfactant j is described as follows; c_r = 1 mol dm^{-3}.

$$\mu^*(\mathrm{micelle};N\mathrm{S}) = N[\mu^0(\mathrm{aq}) + RT\ln(\mathrm{cmc}/c_r)] \quad (12)$$

Then the standard Gibbs energy for micelle formation $\Delta_{mic}G^o$(aq) is given by the following equation.

$$\Delta_{mic}G^o(\mathrm{aq}) = \mu^*(\mathrm{micelle};\ N\mathrm{S}) - N\mu^0(\mathrm{aq}) = NRT\ln(\mathrm{cmc}/c_r) \quad (13)$$

The right-hand site of eqn. (13) contains two important quantities, N and cmc of which only the cmc is readily determined. This point signals that there are complications in the thermodynamic analysis of micellar systems.[56] The way ahead defines a standard Gibbs energy of micelle formation per monomer, $\Delta_{mic}G^o$(aq;mon) [$= \Delta_{mic}G^o(\mathrm{aq})/N$].

Then,

$$\Delta_{mic}G^o(\mathrm{aq;mon}) = RT\ln(\mathrm{cmc}/c_r) \quad (14)$$

If the monomer surfactant is a 1:1 salt (*e.g.* hexadecyltrimethylammonium bromide; CTAB) then the standard Gibbs energy of micelle formation per monomer is given by the following equation.

$$\Delta_{mic}G^o(\mathrm{aq;mon}) = \Delta_{mic}H^o(\mathrm{aq;mon}) - T\Delta_{mic}S^o(\mathrm{aq;mon}) = 2RT\ln(\mathrm{cmc}/c_r) \quad (15)$$

Here $\Delta_{mic}H^o$(aq;mon) is the standard enthalpy of micelle formation per monomer. We have used the latter two equations in an extensive study of the thermodynamics of micelle formation using a titration microcalorimeter. In these experiments the syringe contains an aqueous solution of, for example, CTAB, at a concentration above the cmc whereas the sample cell contains, initially, water. Over the first set of injections of aliquots, the calorimeter records the heat associated with the break up (*i.e.* deaggregation) of the injected micelles to form monomers.[57] However gradually the concentration of surfactant in the sample cell increases, eventually approaching the cmc. At this stage the recorded heat is close to zero in that a micellar solution is being injected into a micellar solution. The resulting plot, an enthalpogram, of the ratio $[q/\delta n_j^0]$ against injection number I is step-shaped such that the ratio $[q/\delta n_j^0]$ effectively yields the enthalpy of micelle formation because $[q/\delta n_j^0]$ at high injection numbers is close to zero. A more detailed analysis takes account of the fact that CTAB is a 1:1 salt. The cmc is calculated using the van Os method[58] in which $\sum_{I=1}^{I=N}[q/\delta n_j^0]$ is plotted against the concentration of CTAB in the sample cell at injection number N. The points generate two straight lines which intersect at a point corresponding to the cmc.

With decreasing alkyl chain length (*e.g.* C_{16} to C_{10} trimethylammonium bromide) the enthalpograms become more complicated indicating that account has to be taken of the thermodynamic properties of the monomer salt and ionic micelles together with the extent of counter ion binding.[59]

An interesting study exploited the structural variations in the cation using 1-alkyl-4-pyridinium surfactants in aqueous solutions.[60] For 1-alkyl-4-methylpyridinium halides, the standard enthalpy of micelle formation becomes more exothermic with an increase in alkyl chain length by -2.6 ± 0.2 kJ mol^{-1} per CH_2 group at 303 K. For 1-methyl-4-*n*-dodecylpyridinium surfactants prepared using aromatic counter ions, the enthalpograms point to different degrees of penetration of the counter anions into the cationic micelles.[61]

Interpretation of the enthalpograms generated by different surfactants is often complicated by the fact that enthalpies of micelle formation are strongly temperature dependent leading in some cases to a change in sign of the standard enthalpy of micelle formation.

In fact there are further complications as shown by the change in sign of the enthalpy of micelle deaggregation of CTAB(aq) when pentanol is added.[62] Titration calorimetric data for non-ionic carbohydrate-derived surfactants[63] show interesting but complicated patterns in the contributions to standard Gibbs energies and enthalpies of micelle formation. A similar comment applies to aqueous solutions containing alkylpolyoxyethylene glycol ethers.[64] The enthalpograms are complicated by the presence of two processes when aliquots are injected into the sample cell, namely micelle deaggregation and declustering of micellar aggregates. The impact of additional methylene groups in the alkyl chain on going from CTAB to octadecyltrimethylammonium bromide is dramatic. The enthalpograms show that the sign of deaggregation changes with a change in concentration of surfactant in the injected aliquots, again pointing to the influence of micellar aggregation.

Analysis of the enthalpograms for mixed alkyltrimethylammonium bromide surfactants turns out not to be straightforward.[65] The effective cmc of a given mixture, as signalled by an enthalpogram, is a function of the mixture concentration. The mixed micellar phase is treated as resembling a binary liquid mixture characterised by rational activity coefficients for both components together with enthalpic interaction parameters treated along the lines used in the treatment of binary liquid mixtures.[66] Monomer–monomer surfactant interaction in both aqueous solution and mixed micellar phase are important in determining the properties of a mixed surfactant. For solutions containing high concentrations of surfactants, the presence of large aggregates is confirmed by a DSC scan for concentrated aqueous solutions of hexadecyltrimethylammonium bromide and chloride.[67]

Vesicles

Whether a surfactant molecule preferentially undergoes molecular assembly to form a micelle or a (closed) bilayer, depends, in a first approximation, on the architecture of the amphiphilic molecule.[68] This shape-dependent association signals a tendency for the most efficient intermolecular overlap of hydrophobic hydration shells with a maximum release of these water molecules to the bulk aqueous solution. The thermodynamics of vesicle formation have also been examined using a titration microcalorimeter.[69] The results emphasise the importance of the nature of the counter ion and reveal a large temperature dependence of the enthalpy of vesiculation as anticipated for a

process involving hydration shell overlap.Gel-to-liquid crystalline phase transitions in vesicular bilayers can be studied using a differential scanning microcalorimeter.[70] The design of the latter is similar to that for a titration microcalorimeter except that the syringe system is absent and the sample cell sealed under nitrogen gas. Both cells are gradually heated from 5 to 90 °C under computer control. The system records the differential amounts of heat required to raise together the temperatures of sample and reference cells. A plot is obtained of the relative isobaric heat capacity of a given vesicular aqueous system as a function of temperature. These scans are extremely informative concerning the factors controlling the thermal characteristics of vesicular bilayers. We have concentrated attention on two classes of vesicular systems, dialkyldimethylammonium bromides[71] (*e.g.* DOAB = di-*n*-octadecyldimethylammonium bromide) and sodium dialkylphosphates[72] (*e.g.* DDP = sodium di-*n*-dodecyl phosphate).

The DSC experiments show that the transitions responsible for extrema in isobaric heat capacities involve patches of between 100 and 200 monomers which melt cooperatively. The extent of cooperative melting in each patch involves but a small fraction of the total number of monomers in each vesicle. The melting temperature (as revealed by the maximum in isobaric heat capacity) depends on the vesicle both in terms of the dialkyl component and the counter ion.[72] The melting has a dynamic feature. For some vesicular systems no extremum in isobaric heat capacity is detected in the second scan if the latter is recorded shortly after the first. In other words there is an element of kinetic control to the repacking of the dialkyl chains forming the gel state from the liquid crystal state.[73]

DSC scans for mixed vesicular systems indicate that when the differences in alkyl chain lengths are small, the chains can assemble in reasonably ordered fashion leading to well defined features in the DSC scans. When the lengths of the dialkyl chains differ considerably, the DSC scans are complicated indicative of domains having different compositions; *cf.* partial miscibility.[74]

For vesicles formed by a series of three sodium dialkylphosphates having identical chain lengths, their thermal stability is strongly dependent on the degree of unsaturation in the alkyl chains. In general, vesicles are stabilised by alkyl–alkyl group cohesion and destablised by charge–charge interactions in the ionic head groups. The thermal stability of the bilayers is very sensitive to added salt,[75a] and other cosolutes including surfactants,[75b] α-amino acids,[75c] sodium dipicolinate[75d] and poly(sodium acrylate)s.[75e]

Conclusion and outlook

Chemical reactions and aggregation processes in water are strongly determined by the properties of the aqueous medium, *i.e.* by the three-dimensional hydrogen-bond network that combines strongly intermolecular interactions with low density. Because water molecules are small and each molecule can form up to four hydrogen bonds (twice as a donor and twice as an acceptor), changes in the H-bond network are associated with large entropy changes (often largely compensated by changes in enthalpy) and with large temperature effects. There appears to be little doubt that in the coming years the unique solvent properties of water will be frequently employed for tuning of desired chemical processes. In particular hydrophobic interactions provide rich possibilities for this purpose. Mother Nature was the first to recognise the potential of such medium-induced control of chemical reactivity.

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