

Review Commentary

Reactant–solute encounters in aqueous solutions studied by kinetic methods: hydration cosphere overlap and camouflage effects

Jan B. F. N. Engberts^{1*} and Michael J. Blandamer²

¹Laboratory of Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

²Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK

Received 19 April 1998; accepted 5 May 1998

ABSTRACT: Rates of chemical reactions in aqueous solutions are often sensitive to low concentrations of added solutes such as ureas, alcohols, α -amino acids and carbohydrates. In this work, several simple chemical reactions were used to probe this sensitivity, which arises from interactions between added solute and the reacting solute. It was found that derived interaction parameters provide a novel insight into interactions between solute molecules in aqueous solution. For example, it was possible to identify two interesting effects, which are termed (i) 'destructive overlap' of hydration cospheres and (ii) 'camouflage effects' by water–solute interactions. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: reactant–solute encounters; aqueous solutions; water; kinetic methods; hydration cosphere destructive overlap; camouflage effects

INTRODUCTION

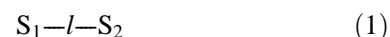
The structure of liquid water¹ is dominated by strong intermolecular hydrogen bonding, yet liquid water has a modest (shear) viscosity, considerably lower than that of glycerol. Furthermore, the volume of 1 mol of liquid water is higher than expected if the water molecules are otherwise close-packed. Clearly, cohesion increases intermolecular separation, in contrast to the usual higher density/lower volume found for strongly interacting molecules. These properties of water contribute to the complexity of processes occurring in aqueous solutions.¹ We know that life processes nearly always occur in water-rich systems. Therefore, there is a continuing challenge to understand the role of water in these processes. In many cases, these reactions involve complicated and large organic molecules. However, we have found that our understanding of these phenomena can be improved by studying in depth the rates of relatively simple organic reactions in aqueous solutions.

The role of solvents in determining the rates of reactions involving organic solutes has been, and still forms, an important challenge in physical-organic chemistry with its origins in the classic monograph

written by Ingold.² The subject has made enormous strides^{3–5} but the complexity of even the simplest reactions in aqueous solutions is significantly greater than that for reactions in organic solvents.^{6,7} The task of understanding this complexity is further complicated when the aqueous solutions contain, in addition to the organic substance undergoing chemical reaction, other solutes in low concentrations such as alcohols, carbohydrates and α -amino acids. We have approached this problem by studying water-catalysed hydrolysis reactions of activated amides and esters for which the reaction mechanisms are well understood.

PAIRWISE INTERACTIONS

Consider two solute molecules in solution S_1 and S_2 , a distance l apart:



In aqueous solution, the two solutes signal their presence to each other ('molecular recognition'). This 'pairwise interaction' involves a potential of average force, $G(l)$, between the solutes that is given by

$$G(l) = U_{S_1S_2}(l) + G^w(l) \quad (2)$$

where $U_{S_1S_2}(l)$ is the solute–solute interaction potential (work required to bring S_1 and S_2 together in vacuum)

*Correspondence to: J. B. F. N. Engberts, Laboratory of Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands.

and $G^w(l)$ is the contribution of water to the intermolecular interaction. The latter term is particularly difficult to quantify both experimentally and computationally and depends crucially on the hydration properties of S_1 and S_2 .

We have found a method, based on chemical kinetics, which starts to answer relevant questions related to such pairwise interactions in aqueous solutions. We briefly describe the hydrolysis reactions that we used for the kinetic analysis.

NEUTRAL HYDROLYSIS OF ESTERS AND AMIDES

Activated amides (1-acyl-3-substituted-1,2,4-triazoles) and esters (aryl α,α -dichloroalkanoates) undergo water-catalysed (*i.e.* pH-independent) hydrolyses in aqueous solutions (Fig. 1). In a fairly extensive pH range, roughly between 2 and 5, the reaction mechanism involves water-catalysed, rate-determining nucleophilic attack of water at the carbonyl moiety *via* an activated complex, incorporating two water molecules with three protons in flight⁸ (Fig. 2). During the activation process, the hydrophobic substrate is transformed into a polar activated complex. For our purposes, these types of reactions have definite advantages: (i) the reactions occur in the absence of perturbing buffer systems; (ii) the extent of the large change in polarity of the substrate during activation can be subtly varied by changing the substituents; and (iii) the reactions have biological significance with the medium effects providing important pointers for those occurring at the active sites of proteolytic enzymes.

The neutral hydrolysis of *p*-methoxyphenyl dichloroacetate (**4**) has been simulated by Lensink *et al.*⁹ Embedding semi-empirical quantum mechanics and quantum dynamics in a classical molecular dynamics simulation, the calculated rate constant and primary kinetic deuterium isotope effect are in close agreement with experiment. The computational results confirm that proton transfer between the two water molecules in the

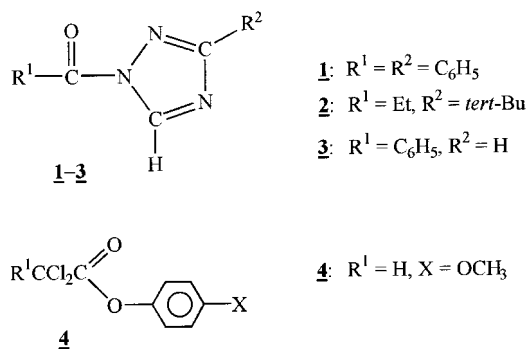


Figure 1. The activated amides **1-3** and the activated ester **4**.

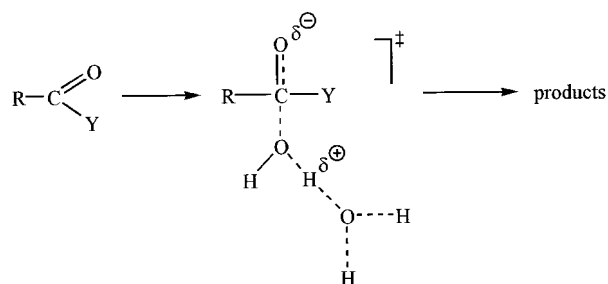


Figure 2. Reaction mechanism for water-catalysed hydrolysis.

activated complex is concerted with the formation of the new C—O bond. The proton transfer has an essential quantum character and is driven by a fluctuating potential in the aqueous environment. The low probability that a water molecule occupies the required position for proton transfer accounts for the large and negative entropy of activation for the hydrolytic process.⁸

REACTION ENERGETICS

Here we turn our attention to understanding how the rate of a chemical reaction is modified by adding different solutes to the aqueous solutions containing the substance undergoing chemical reaction. There are, in fact, two themes to this subject.

The first theme concerns the description of chemical reactions.¹⁰ Within the framework of transition state theory, each molecule of reactant in solution is the initial state, IS. The process of reaction requires that a reacting molecule proceeds from this IS over a Gibbs energy barrier, the maximum corresponding to the activated complex, AC.¹¹ The difference in Gibbs energies (correctly the reference chemical potentials) of the two states is the Gibbs energy of activation, $\Delta^\ddagger G^\circ$. The change in rate constant resulting from the addition of another solute (*e.g.* a monohydric alcohol) can be expressed as a change in this Gibbs energy of activation.

Broadly, two classes of solutes are identified: (i) hydrophilic solutes where water–solute interactions are stronger than water–water interactions in the bulk and (ii) hydrophobic solutes where the water–solute interactions are weaker than water–water interactions in bulk water. Controversy still surrounds the nature of hydrophobic hydration.¹² There is evidence that for hydrophobic solutes the tangential orientation of water molecules around an apolar group possibly results in an enhancement of dispersion forces between the solute and water.¹² In any event, the concept developed by Gurney¹³ is extended to describe solute–solute interactions in aqueous solution in terms of, for neutral solutes, overlap of the water cospheres. The overlap may either raise or lower the chemical potential of a given solute in aqueous

solution above the chemical potential in the corresponding ideal solution.¹⁴

In the second theme we are concerned with the properties of a trace amount of ester or amide (*e.g.* $\leq 10^{-5}$ mol dm⁻³) undergoing chemical reaction via an activated complex in an aqueous solution containing an added solute of molality m_{CS} . In these experiments the molality of added solute, CS, is of the order 0.1–2 mol kg⁻¹. Under these circumstances, the activity coefficient of (neutral) solute j (either IS or AC) is related to m_{CS} by a characteristic pairwise Gibbs energy interaction parameter g_{jcs} according to

$$\ln(\gamma_j^T) = (2/RT)g_{j,cs} \cdot m_{cs}(m^0)^{-1} \quad (3)$$

where $m^0 = 1$ mol kg⁻¹. Equation (3) is applied to both IS and AC where, by definition, $\lim(m_{cs} \rightarrow 0)\gamma_j^T = 1$ at all temperatures and pressures. These equations are combined¹⁵ in the context of the formalism of transition state theory to account for the dependence of rate constants for a given reaction on m_{cs} .

Solute–solute interactions determine how the Gibbs energy of activation, $\Delta^\ddagger G^\circ(m_{cs})$, in a real solution with molality m_{cs} differs from the standard Gibbs energy of activation (that is, in the absence of added solutes), $\Delta^\ddagger G^\circ(m_{cs} = 0)$ for the same reaction in an ideal aqueous solution.

$$\Delta\Delta^\ddagger G^\circ = \Delta^\ddagger G^\circ(m_{cs}) - \Delta^\ddagger G^\circ(m_{cs} = 0) \quad (4)$$

A quantitative analysis of kinetic medium effects is based on the following relationship:^{16–18}

$$\ln[k(m_{cs})/k(m_{cs} = 0)] = (1/RT)G(c)m_{cs} - n\phi M_1 m_{cs} \quad (5)$$

where m_{cs} is the molality of added solute, n is the number of water molecules incorporated into the AC, ϕ is the practical osmotic coefficient of the water ($\phi = 1$ for ideal solutions and is also effectively unity for the dilute aqueous solutions considered here), M_1 is the molar mass of water and $G(c)$ is the difference between the Gibbs energy of interaction between (a) the added solute and the IS and (b) the added solute and the AC. This parameter is a combination of contributions of different functional group interactions involving both IS and AC with added solute and is calculated from the slope of the linear plot of $\ln[k(m_{cs})/k(m_{cs} = 0)]$ versus m_{cs} . Non-linearity of such a plot is indicative of higher order (*e.g.* triplet solute–solute) interactions. The second term in Eqn (5) signifies the fact that water is both a reactant and a solvent and provides a correction for the effect of the added solute on the reactivity of water.

The approach outlined here differs considerably from previous analyses of kinetic solvent effects.^{19,20} Traditionally, rate constants are plotted as a function of microscopic or macroscopic solvent parameters, recently with emphasis placed on solvatochromic micropolarity scales.⁵ Our theory is uniquely focused on pairwise

interactions with the added solute and provides a direct link between transition state theory and thermodynamics. The $G(c)$ parameters for added solutes are determined by hydrophobic–hydrophobic, hydrophobic–hydrophilic and hydrophilic–hydrophilic solute–solute interactions. Generally, negative $G(c)$ parameters, signalling rate retardation by the added solute, are observed for hydrophobic cosolutes which stabilize²¹ the IS relative to the AC. By contrast, positive $G(c)$ parameters associated with induced rate accelerations by added solute are indicative of stabilization of the AC relative to the IS through polar interactions with the added solute. Further insight into these $G(c)$ parameters is important for understanding non-covalent interactions in aqueous solutions.

ADDITIVITY OF FUNCTIONAL GROUP INTERACTIONS

The quantity $g_{j,cs}$ in Eqn (3) is re-expressed in terms of pairwise group interaction parameters.²² For example, the solute pairwise interaction parameter g_{jj} (where $j =$ methanol) is re-expressed²² in terms of parameters describing CH₂ ⋯ CH₂, CH₂ ⋯ OH and OH ⋯ OH pairwise group interaction parameters; the latter set can be briefly described in turn as hydrophobic–hydrophobic, hydrophobic–hydrophilic and hydrophilic–hydrophilic interaction parameters. Moreover, across a related group of solutes these group parameters turn out to be characteristic of the groups. A similar pattern emerges from our analysis of the kinetic data for a wide range of chemical reactions in aqueous solutions,^{16–18} allowing us to identify important underlying common features describing the functional groups which are involved in reactions and which control rates of reactions. For example, the difference between $G(c)$ parameters recorded for the effect of added ethanol and added propanol can be expressed as

$$G(\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}) - G(\text{CH}_3\text{CH}_2\text{OH}) = G(\text{CH}_2) = 2G(\text{CH}) \quad (6)$$

and

$$G(\text{CH}_3\text{CH}_2\text{OH}) - 5G(\text{CH}) = G(\text{OH}) \quad (7)$$

This SWAG (Savage–Wood Additivity of Group interactions) approach²² predicts a unique value for $G(\text{CH})$ for all isomers of a particular alkanol. This prediction is often confirmed in practice, but there are important exceptions as we describe below.

MONOHYDRIC ALCOHOLS

The kinetic medium effects of an extensive series of monohydric alcohols¹⁶ with branched and unbranched

Table 1. $G(c)$ parameters for the neutral hydrolysis of **1** in aqueous solutions containing 0–2 mol dm⁻³ of mono- and polyhydric alcohols

| Alcohol | $G(c)$ (exp.) (J kg mol ⁻²) | $G(c)$ (calc.) ^a (J kg mol ⁻²) |
|----------------------------|--|--|
| Methanol | 27 ± 2 | 22 |
| Ethanol ^{b,c} | -120 ± 6 | -114 |
| Propan-1-ol ^{c,d} | -258 ± 6 | -250 |
| Propan-2-ol | -231 ± 6 | -250 |
| Butan-1-ol ^e | -474 ± 39 | -386 |
| Butan-2-ol ^e | -405 ± 12 | -386 |
| 2-Methyl-propan-1-ol | -425 ± 24 | -386 |
| 2-Methyl-propan-2-ol | -392 ± 14 | -386 |
| Cyclopentanol | -379 ± 18 | -386 |
| Glycol | -40 ± 6 | |
| Butane-1,2-diol | -214 ± 14 | |
| Butane-1,3-diol | -172 ± 6 | |
| Butane-1,4-diol | -108 ± 6 | |
| Pentane-1,5-diol | -216 ± 6 | |
| Hexane-1,6-diol | -410 ± 4 | |

^a Calculated using $G(\text{CH}) = -68 \text{ J kg mol}^{-2}$ and $G(\text{OH}) = +226 \text{ J kg mol}^{-2}$.

^b $H(c) = 290 \pm 39 \text{ J kg mol}^{-2}$, $TS(c) = 339 \text{ J kg mol}^{-2}$.

^c $H(\text{CH}) = 345 \pm 52 \text{ J kg mol}^{-2}$, $TS(\text{CH}) = 410 \text{ J kg mol}^{-2}$; $H(\text{OH}) = -1440 \pm 300 \text{ J kg mol}^{-2}$, $TS(\text{OH}) = 1532 \text{ J kg mol}^{-2}$.

^d $H(c) = 980 \pm 66 \text{ J kg mol}^{-2}$, $TS(c) = 1202 \text{ J kg mol}^{-2}$.

^e Concentration range 0–1 mol dm⁻³.

alkyl chains on the neutral hydrolysis of **1** were analysed in terms of $G(c)$ parameters obtained from linear plots of $\ln[k(m_{\text{cs}})/k(m_{\text{cs}}=0)]$ against m_{c} at 298 K. No evidence was obtained for alcoholysis under the reaction conditions used. Low solubilities place an upper limit on the length of the alkyl chains. $G(c)$ parameters vary from $27 \pm 2 \text{ J kg mol}^{-2}$ for methanol to $-392 \pm 14 \text{ J kg mol}^{-2}$ for 2-methyl propan-2-ol and exhibit additivity upon increasing the number of methylene groups in the alcohol. The parameters can be analysed in terms of a rate-enhancing contribution from the OH groups [pairwise Gibbs energy group interaction parameter $G(\text{OH}) = 226 \text{ J kg mol}^{-2}$] and a rate-decreasing contribution of CH groups [$G(\text{CH}) = -68 \text{ J kg mol}^{-2}$]. For all alcohols except methanol the hydrophobic effects of the alkyl group dominate the kinetic medium effects (Table 1). Stabilization of the apolar initial state accounts for this behaviour. This conclusion is supported²³ by kinetic data for **1** in water-rich ethanol and water-rich propan-1-ol mixtures in the temperature range 288–333 K.

BIFUNCTIONAL SOLUTES

Significantly, we have found that kinetic data and derived $G(c)$ parameters signal how groups within the same molecule interact and affect how the molecules interact with water molecules in their cospheres.

A simple diagram makes the point. We imagine that to

a solution containing reacting molecule Z we have added a molecule having the following general formula:



The two groups X and Y are separated by a chain of n methylene groups. In solution, the reactant molecule Z 'sees' this molecule *via* the cosphere–cosphere interactions noted above and so its reactivity is modified in terms of effects on both IS and AC. An obvious question centres on the extent to which the impact of groups X and Y depends on the number n .

The overwhelming influences of such hydration effects on $G(c)$ parameters is dramatically demonstrated by rate constants for the pH-independent hydrolysis of **1** in aqueous solutions in the presence of low concentrations of dihydric alcohols.¹⁸ The $G(c)$ parameters now depend strongly on the relative position of the OH groups in the cosolute. Only for 1,4-, 1,5- and 1,6-diols can the $G(c)$ values be reasonably reproduced using the $G(\text{CH})$ and $G(\text{OH})$ parameters obtained for monohydric alcohols. If the two OH groups are in closer proximity, their hydration shells overlap intramolecularly and the $G(\text{OH})$ parameters are reduced below those of well separated OH groups. No additivity of group interaction parameters is found. For polyhydric alcohols, these effects are even more pronounced, and [$G(\text{OH}) + G(\text{CH})$] can actually become negative. Glycerol, for example, exerts a rate-decreasing effect on the hydrolysis of **1** [$G(c) = -91 \pm 6 \text{ J kg mol}^{-2}$] because mutual destructive overlap of the OH hydration spheres within the molecule opposes the otherwise rate increasing effect of the individual OH groups. Similar intermolecular hydration shell overlap effects are revealed by kinetic medium effects in solvents comprising ternary aqueous mixtures containing both propan-1-ol and urea.¹⁸

Whereas urea itself has a negligible effect on the rate constants for the hydrolysis of esters shown in Figs 1 and 2 its presence disturbs the hydrophobic hydration shell of the propyl group and drastically reduces the rate decreasing effect of the alcohol.

THE CAMOUFLAGE EFFECT

We have shown that the impact of groups X and Y when both are OH groups significantly depends on the stereochemistry of the linking alkyl chain.

Kinetic data for chemical reactions in the presence of carbohydrates have shown in a simple but dramatic way the role of the stereochemistry in determining solute–solute interactions. We have identified a camouflage effect.^{24,25} The latter emerges if the hydrophilic OH groups can fit into the three-dimensional hydrogen-bonded network of water molecules.¹ Consequently, these OH groups are camouflaged by the solvent water from the reactant molecules in both their IS and AC. On the other hand, the reactant molecules still 'see' the

Table 2. Some representative $G(c)$ parameters for the neutral hydrolysis of **1** in aqueous carbohydrate solutions (298 K)

| Carbohydrate ^a | $G(c)$ (J kg mol ⁻²) |
|---------------------------|----------------------------------|
| D-Arabinose | -98 ± 8 |
| D-Ribose | -223 ± 10 |
| D-Galactose | -142 ± 11 |
| D-Glucose | -201 ± 12 |
| D-Mannose | -227 ± 12 |
| D-Talose | -280 ± 10 |
| D-Idose | -330 ± 40 |
| D-Fructose | -222 ± 12 |
| Maltose | -659 ± 49 |
| Sucrose | -541 ± 25 |
| Lactose | -472 ± 37 |

^a Concentration 0–1 mol dm⁻³.

hydrophobic C—H groups and respond as if the hydration properties of the added carbohydrate solute molecules are dominated by their hydrophobic properties, although the high solubility is determined by the dominant hydrophilic character of the carbohydrate.

All the carbohydrates that we examined decreased the rate constants for hydrolysis [$G(c)$ between -98 and -330 J kg mol⁻²]. All data are in accord with hydration shell overlap effects, which depend crucially on the relative position of the OH groups in the carbohydrate molecule. As the fit of the OH groups into the three-dimensional hydrogen-bonded structure of water improves, the properties of a given carbohydrate resemble those of a 'hydrophobic' cosolute (Table 2). Two contrasting examples are D-talose [good fit; $G(c) = -280$ J kg mol⁻²] and D-galactose [bad fit; $G(c) = -142$ J kg mol⁻²]. Of particular importance for the fit of the solute into the water organization is the relative position of the OH(2) and OH(4) groups. This interpretation is supported by isentropic partial molar compressions²⁴ and by chromatographic retention times.²⁶ A molecular dynamics (MD) simulation of β -D-galactopyranose and α,β -D-talopyranose in aqueous solution substantiates the importance of next-nearest neighbour oxygen distances in the carbohydrates relative to average oxygen–oxygen distances in water.²⁷ We suggest that the concept of camouflage by OH groups in carbohydrates dissolved in aqueous solutions will prove generally useful.

That this phenomenon can be identified by measuring the rates of chemical reactions in aqueous systems shows the merit of the approach which we have exploited in these studies. We are developing this approach to examine the impact of more complicated solutions containing, for example, mixtures of added solutes. Not unexpectedly, the data analysis is not as straightforward as in the cases discussed here, but preliminary analyses show that the methodology has considerable merit in probing what are very complicated systems.

ALKYL SULPHATES AND ALKYLAMMONIUM SALTS

Kinetic medium effects also throw light on a particularly important issue of molecular recognition processes in aqueous solution. This issue involves the notion that almost all solutes have an 'amphibious' nature since they contain both apolar groups (which can engage in hydrophobic interactions) and polar or ionic groups (providing water solubility and which participate in polar and/or hydrogen bonding interactions). A simple case is represented by a solute of type **5**:



5

where X = a polar or ionic group. Unavoidably, the hydrophobic hydration shell of the alkyl group and the hydrophilic hydration shell of group X interact intramolecularly, leading to destructive overlap effects in their contact zone.²⁸ In view of the previous discussion, these overlap effects influence the respective $G(\text{CH})$ and $G(\text{X})$ parameters for the apolar groups in **5**. Extensive studies have been made^{29,30} for several added solutes **5** with X = —OSO₃⁻ and X = —N⁺R₃ using the kinetic probe **3** and carefully avoiding micellization for longer alkyl chains. A plot of $G(c)$ for ionic cosolutes against the number of CH groups clearly shows that the first three methylene units attached to the X functionality are largely deprived from exerting a rate-decreasing kinetic medium effect through stabilization of the substrate. This deviation from additivity demonstrates the delicacy of the hydrophilic/hydrophobic nature of solutes such as alkyl sulphates and alkylammonium salts. Similar phenomena occur in all biomolecules and allow accurate fine-tuning of non-covalent intermolecular interactions.³¹

α -AMINO ACIDS

Zwitterionic α -amino acids are a particularly important class of compounds for examining the implications of intramolecular hydration shell overlap effects for intermolecular interactions in aqueous solutions. The hydration shells of the —NH₃⁺ and —CO₂⁻ moieties greatly influence the hydration of the substituent at the α -carbon atom. Using **1** as a kinetic probe, $G(c)$ parameters for a series of α -amino acids and some derivatives have been determined.^{32,33} Most of the α -amino acids induce rate enhancements as quantified by the positive $G(c)$ values. These effects are accounted for in terms of stabilization of the activated complex through favourable interactions with the carboxylate moiety. General base catalysis is not involved. Even for valine and leucine, the hydrophobic effects of the isopropyl and isobutyl groups, respectively, are countered by the hydration shells of both ionic groups in close proximity. Only in the case of phenylalanine and

3-phenylserine are the hydrophobic benzyl substituents sufficiently remote from the ionic moieties and able to exert their hydrophobic effects. Neutron scattering experiments reveal the altered water organization (compared with bulk water) in the hydration spheres of hydrophobic α -amino acid analogues.³⁴ These α -amino acids now *retard* the rate of hydrolysis as a result of initial state stabilization. Aromatic stacking cannot explain these results because similar rate retardations are observed for substrate **2**, lacking the benzoyl substituent. As expected, phenylalaninamide, in which the $-\text{CO}_2^-$ group is replaced by an uncharged $-\text{CONH}_2$ moiety, exhibits a much stronger hydrophobic character, as indicated by the strongly negative $G(c)$ parameter³³ ($-1870 \pm 25 \text{ J kg mol}^{-2}$). A similar but less marked difference exists between glycine [$G(c) = +875 \pm 21 \text{ J kg mol}^{-2}$] and glycinamide [$G(c) = -148 \pm 2.5 \text{ J kg mol}^{-2}$]. We contend that intramolecular destructive hydration shell overlap effects are also highly relevant for a quantitative understanding of intermolecular interactions and conformational preferences of more complicated biomolecules such as proteins³⁵ and oligosaccharides.³⁶

In sum, the kinetic analysis outlined in terms of a direct link between thermodynamics and transition state theory offers a precise indicator for non-covalent interactions in aqueous solutions. The required rate constants can be obtained with high precision and the conditions can be selected for analysing 1:1 intermolecular interactions. However, the fact that the approach is based on the application of transition state theory necessitates that only chemical reactions can be used for which the transition state structures are relatively well defined.

REFERENCES

1. F. Franks (Ed.). *Water—A Comprehensive Treatise*, Vols 1–7. Plenum Press, New York (1972–82).
2. C. K. Ingold. *Structure and Mechanism in Organic Chemistry*, G. Bell, London (1953).
3. See also H. Maskill. *The Physical Basis of Organic Chemistry*, Oxford University Press, 1993.
4. See also J. E. Leffler and E. Grunwald. *Rates and Equilibria of Organic Reactions*. Wiley, New York (1963).
5. C. Reichardt. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed. VCH, Weinheim (1988).
6. R. E. Robertson. *Phys. Org. Chem.* **4**, 213 (1969).
7. J. B. F. N. Engberts. in *Water—A Comprehensive Treatise*, edited by F. Franks, Vol. VI, Chapt. 4. Plenum Press, New York (1979).
8. W. Karzijn and J. B. F. N. Engberts. *Tetrahedron Lett.* 1787 (1978).
9. M. F. Lensink, J. Mavri and H. Berendsen. *J. Compt. Chem.*, submitted for publication.
10. L. P. Hammett. *Physical Organic Chemistry*, 2nd. ed. McGraw-Hill, New York (1970).
11. S. Glasstone, K. J. Laidler and H. Eyring. *The Theory of Rate Processes*, McGraw-Hill, New York (1941).
12. W. Blokzijl and J. B. F. N. Engberts. *Angew. Chem., Int. Ed. Engl.* **32**, 1545 (1993).
13. R. W. Gurney. *Ionic Processes in Solution*. McGraw-Hill, New York (1953).
14. J. J. Kozak, W. S. Knight and W. Kauzmann. *J. Chem. Phys.* **48**, 675 (1968).
15. M. J. Blandamer, J. Burgess, J. B. F. N. Engberts and W. Blokzijl. *Annu. Rep. R. Soc. Chem., Sect. C* 45 (1968).
16. W. Blokzijl, J. Jager, J. B. F. N. Engberts and M. J. Blandamer. *J. Am. Chem. Soc.* **108**, 6411 (1986).
17. W. Blokzijl, J. Jager, J. B. F. N. Engberts and M. J. Blandamer. *J. Phys. Chem.* **91**, 6022 (1987). The analysis described here for hydrolytic processes has also been applied to keto–enol equilibria [W. Blokzijl, J. B. F. N. Engberts and M. J. Blandamer. *J. Chem. Soc. Perkin. Trans.* 2 455 (1994)], reactions of iron(II) complexes [M. J. Blandamer, J. Burgess, H. J. Cowles, A. J. De Young, J. B. F. N. Engberts, S. A. Galema, S. J. Hill and I. Horn, *J. Chem. Soc., Chem. Commun.* 1141 (1988)] and outer-sphere electron transfer reactions [M. Biatti, E. Baciocchi and J. B. F. N. Engberts, *J. Chem. Soc., Chem. Commun.* 1307 (1996)].
18. W. Blokzijl, J. B. F. N. Engberts and M. J. Blandamer. *J. Am. Chem. Soc.* **112**, 1197 (1990).
19. E. S. Amis and J. F. Hinton. *Solvent Effects on Chemical Phenomena*. Academic Press, New York (1973).
20. M. H. Abraham, P. L. Grellier, J. L. M. Abboud, R. M. Doherty and R. W. Taft. *Can. J. Chem.* **66**, 2673 (1988).
21. R. P. V. Kerstholt, J. B. F. N. Engberts and M. J. Blandamer. *J. Chem. Soc., Perkin Trans.* **2**, 49 (1993).
22. J. J. Savage and R. H. Wood. *J. Solution Chem.* **5**, 733 (1976).
23. H. Benak, J. B. F. N. Engberts and M. J. Blandamer. *J. Chem. Soc., Perkin Trans.* **2**, 2035 (1992).
24. S. A. Galema, M. J. Blandamer and J. B. F. N. Engberts. *J. Am. Chem. Soc.* **112**, 9665 (1990).
25. S. A. Galema, M. J. Blandamer and J. B. F. N. Engberts. *J. Org. Chem.* **57**, 1995 (1992).
26. N. W. H. Cheetham and K. Lam. *Carbohydr. Lett.* **1**, 69 (1994).
27. S. A. Galema, E. Howard, J. B. F. N. Engberts and J. R. Grigera. *Carbohydr. Res.* **265**, 215 (1994).
28. These effects have also been assessed by molecular dynamics simulations: E. C. Meng and P. A. Kollman. *J. Phys. Chem.* **100**, 11460 (1996).
29. W. Noordman, W. Blokzijl, J. Jager, J. B. F. N. Engberts and M. J. Blandamer. *J. Org. Chem.* **58**, 7111 (1993).
30. P. Hol, L. Streefland, M. J. Blandamer and J. B. F. N. Engberts. *J. Chem. Soc., Perkin Trans.* 2 485 (1997).
31. For a recent, thoughtful discussion of the solvation of organic solutes, see E. Grunwald, *Thermodynamics of Molecular Species*, Chapt. 11. Wiley, New York (1997).
32. L. Streefland, M. J. Blandamer and J. B. F. N. Engberts. *J. Phys. Chem.* **99**, 5769 (1995).
33. L. Streefland, M. J. Blandamer and J. B. F. N. Engberts. *J. Am. Chem. Soc.* **118**, 9539 (1996).
34. A. Pertsemliadis, A. M. Saxena, A. K. Soper, T. Head-Gordon and R. M. Glaeser. *Proc. Natl. Acad. Sci. USA* **93**, 10769 (1996).
35. See for example G. I. Makhatadze and P. L. Privalov. *Adv. Protein Chem.* **47**, 30 (1998).
36. R. U. Lemieux. *Chem. Soc. Rev.* **18**, 347 (1989).