Kinetics of Neutral Hydrolysis of 1-Benzoyl-3-phenyl-1,2,4-triazole in Highly Aqueous Media: Analysis of Effects of Added Ethanol and Propan-1-ol in terms of Pairwise Group Interaction Parameters

Harm Benak,[a] Jan B. F. N. Engberts[*,a] and Michael J. Blandamer[b]
[a] *Department of Organic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG GRONINGEN, Groningen, The Netherlands*
[b] *Department of Chemistry, The University, Leicester LE1 7RH, UK*

Over the range 288.15 ≤ T/K ≤ 333.15, the first-order rate constant for the neutral hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole in aqueous solutions (pH *ca.* 4) decreases when either ethanol or propan-1-ol is added. The kinetic data are analysed in terms of (*a*) the dependence of rate constant on temperature at fixed molality of added alcohol, and (*b*) the dependence of rate constant on molality of added alcohol at fixed temperature. In the latter case, the analysis leads to Gibbs energy interaction parameters which are assigned to group interaction parameters G(CH) and G(OH) for methine and hydroxy groups respectively. G(CH) is negative and G(OH) is positive, the corresponding enthalpic pairwise group interaction parameters having the opposite sign. This pattern is consistent with a more dramatic effect of added alcohol on the initial than on the transition state for the water-catalysed hydrolysis of the activated amide.

An interesting and important treatment of the properties of neutral solutes in aqueous solutions re-expresses the excess Gibbs energy in terms of pairwise solute–solute interaction parameters (for details and references, see refs. 1 and 2). A further interesting development identified pairwise Gibbs energy group interaction parameters based on the SWAG model[3] (Savage–Wood Additivity of Group Interactions). In fact, the analysis can be extended to pairwise group enthalpic and entropic parameters.[4] Despite criticisms,[5] the approach has been quite successful.[6] Certainly, no obvious alternative to this method of data analysis has emerged which encompasses so many different solutes. In fact, we have shown[1,2,7–10] that the SWAG procedure has considerable merit in the context of analysing kinetic data for chemical reactions in aqueous solutions containing small amounts of added co-solutes such as alcohols, carbohydrates,[11] sulfonamides,[12] sulfones,[12] sulfoxides,[12] ureas[1] and carboxamides.[10] The approach also offers interesting possibilities for probing details of reaction mechanisms.[11]

In a conventional approach,[13] the dependence of rate constant on temperature at fixed solvent composition is analysed to yield the enthalpy of activation $\Delta^{\ddagger}H^{0}$(sln; m_2) in an aqueous solution where the molality of added solute is m_2 mol kg^{-1}. If $\Delta^{\ddagger}H^{\infty}$(aq; m_2) is independent of temperature, then so is the entropy of activation $\Delta^{\ddagger}S^{0}$(aq; m_2). Hence at temperature T, we may examine the dependence of $\Delta^{\ddagger}G^{0}$(aq; m_2), $\Delta^{\ddagger}H^{\infty}$(aq; m_2) and $\Delta^{\ddagger}S^{0}$(aq; m_2) on m_2.

In terms of the SWAG model,[1,2] the dependence of rate constant on molality m_2 of added solute at fixed temperature is examined to yield the related pairwise Gibbs energy interaction quantity $G_{\rm C}(T)$ at temperature T. We express[3] $G_{\rm C}(T)$ as a function of pairwise Gibbs energy group interaction parameters G(OH; T) and G(CH: T) for the hydroxy and methine groups respectively. Therefore, the dependence on temperature of these group parameters yields the corresponding enthalpy and entropy group interaction parameters; *e.g.* H(CH; T), H(OH; T), S(CH; T) and S(OH; T) at temperature T. Here we report these parameters where temperature T equals 298.2 K.

In the study reported here, we start out with two sets of data presented in matrix form which summarise the dependence of first-order rate constants k as a function of temperature and molality of added alcohol m_2. The data describe the effects

of added ethanol and propan-1-ol. Significantly, these alcohols differ by one methylene group. We show how these data can be analysed to yield the pairwise Gibbs energy interaction parameters for these two alcohols. These interaction parameters are used to calculate pairwise interaction parameters for methine and OH groups, *i.e.* G(CH) and G(OH). The dependence of these parameters on temperature yields the related enthalpic and entropic parameters, *i.e.* H(CH) and S(CH) together with H(OH) and S(OH). In the present study we used the water-catalysed hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole as a model reaction. In aqueous solutions having pH *ca.* 4, the hydrolysis of this substrate proceeds *via* a rate-determining water-catalysed nucleophilic attack of water at the amide carbonyl moiety[14] (Scheme 1). For this reaction we
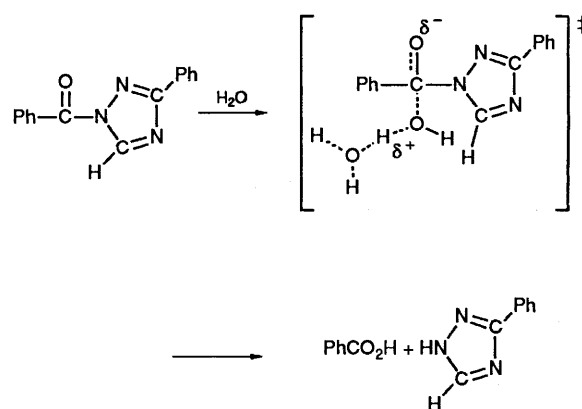
Scheme 1

generally find that the pairwise interaction parameter G(CH) is negative although the enthalpy parameter, H(CH), is positive. We show how these and related parameters can be used to comment in detail on the changes in kinetic parameters when the two alcohols, ethanol and propan-1-ol, are added.

Experimental

Materials.—1-Benzoyl-3-phenyl-1,2,4-triazole was prepared according to a standard procedure.[14] The alcohols (fresh p.a. grade from Merck Chemicals) were used as supplied.

Table 1 First-order rate constants $(k/10^{-3}\ \mathrm{s}^{-1})$ for the spontaneous hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole in aqueous solution as a function of both temperature and molality of added alcohol

| Added solute, m/mol kg^{-1} | $T/°C$ | | | | |
	15	25	36	47	60
Ethanol					
0.0	0.57	1.18	2.42	4.50	8.51
0.25	0.55	1.15	2.33	4.34	8.08
0.75	0.52	1.08	2.19	4.05	7.50
1.25	0.49	1.02	2.06	3.78	6.93
1.75	0.47	0.96	1.93	3.52	6.53
Propan-1-ol					
0.25	0.54	1.13	2.29	4.25	7.95
0.75	0.49	1.02	2.05	3.76	6.92
1.25	0.45	0.92	1.81	3.32	5.98
1.75	0.42	0.81	1.56	2.83	5.08

Kinetic Measurements.—First-order rate constants were measured as described previously.[1,8] In all cases, a Perkin-Elmer $\lambda 5$ spectrophotometer was used, equipped with a thermostatted cell compartment. Rate constants (Table 1) were calculated using a data station PE $\lambda 5$, connected to the spectrophotometer, and were reproducible to within 2%. Isobaric activation parameters were obtained from rate constants measured at 15.00, 25.00, 36.00, 47.00 and 60.00 °C. Plots of log (k/T) vs. T^{-1} were perfectly linear.

Analysis.—At fixed molality of added alcohol and at fixed ambient pressure, the dependence of rate constant for amide hydrolysis on temperature was described[13,15] using eqn. (1) where reference temperature θ was set at 298.15 K.

$$\ln (k/T) = a_1 + a_2\cdot[(1/T) - (1/\theta)] \qquad (1)$$

Here a_1 and a_2 are the calculated least squares parameters describing the dependence of ln (k/T) on temperature. Thus a_1 is ln (k/θ) at temperature θ; a_2 yields the required enthalpy term.

The standard enthalpy of activation $\Delta^{\ddagger}H^{\circ}(m_2)$ for reaction in a solution of molality m_2 is given by eqn. (2). The data did not

$$\Delta^{\ddagger}H^{\circ}(m_2) = -R\cdot a_2 \qquad (2)$$

warrant further terms for eqn. (1) which include the heat capacity quantity $\Delta^{\ddagger}C_p^{\circ}(m_2)$. At temperature T, the standard Gibbs energy of activation $\Delta^{\ddagger}G^{\circ}(T; m_2)$ is given by eqn. (3)

$$\Delta^{\ddagger}G^{\circ}(m_2; T) = -R\cdot T\cdot\ln (k\cdot h/k_B\cdot T) \qquad (3)$$

leading to the standard entropy of activation, eqn. (4). Here k is

$$T\cdot\Delta^{\ddagger}S^{\circ}(m_2; T) = \Delta^{\ddagger}H^{\circ}(m_2) - \Delta^{\ddagger}G^{\circ}(T; m_2) \qquad (4)$$

the rate constant at temperature T and k_B is Boltzmann's constant. Eqns. (1)–(4) conform to a traditional method of analysis of kinetic data.[13,15]

Previously,[1,2,7–12] we expressed the dependence of rate constant on molality m_2 at fixed temperature using eqn. (5).

$$\ln [k(m_2)/k(m_2 = 0)] =$$
$$(2/R\cdot T)\cdot G(C)\cdot(m_2/m^{\circ}) - n\cdot\varphi\cdot M_1\cdot R\cdot T \qquad (5)$$

$G(C)$ is the pairwise Gibbs energy interaction parameter characteristic of the substrate (initial and transition states) and of the added solute. M_1 is the molar mass of water; φ is the

practical osmotic coefficient; n is the number of water molecules incorporated into the substrate on forming the transition state. For dilute solutions a satisfactory approximation sets φ equal to unity. For the amide hydrolysis discussed here,[14] n is 2. Hence eqn. (5) can be rewritten as eqn. (6). The dependence of

$$\ln [k(m_2)/k(m_2 = 0)] + (2\cdot M_1\cdot R\cdot T) =$$
$$(2/R\cdot T)\cdot G(C)\cdot m_2/(m^{\circ})^2 \qquad (6)$$

$G(C)$ on temperature can be expressed using eqn. (7). Here a_3

$$G(C)/T = a_3 + a_4\cdot[(1/T) - (1/\theta)] \qquad (7)$$

is the least-squares-calculated estimate for $[G(C)/\theta]$ at temperature θ. The enthalpic pairwise interaction parameter $H(C)$ equals a_4 where $T\cdot S(C)$ equals $H(C) - G(C)$, at temperature T.

The interaction parameter $G(C)$ was subdivided following the SWAG procedure[1,2] to yield pairwise group interaction parameters, *i.e.* $G(CH)$ for the CH-group and $G(OH)$ for the hydroxy group [eqns. (8) and (9)]. The dependence of $G(OH)$

$$G(C: \text{ethanol}) = 5\cdot G(CH) + G(OH) \qquad (8)$$

$$G(C: \text{propan-1-ol}) = 7\cdot G(CH) + G(OH) \qquad (9)$$

and $G(CH)$ on temperature at fixed m_2 was expressed using the analogues of eqn. (7) yielding the group enthalpic parameters $H(OH)$ and $H(CH)$ respectively. Hence the kinetic data yield for the hydrolysis reaction at a given temperature the six parameters including the entropic parameters; *i.e.* $G(OH)$, $G(CH)$, $H(OH)$, $H(CH)$, $S(OH)$ and $S(CH)$.

Results

The dependence on temperature of rate constants k for neutral hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole were fitted to eqn. (1) yielding the parameters summarised in Table 2 for reaction as a function of temperature and molality of added alcohol, m_2. With increase in molality m_2, the rate constant decreases, the effectiveness of propan-1-ol being more dramatic than that of ethanol. The enthalpy of activation $\Delta^{\ddagger}H^{\circ}(m_2)$ decreases with increase in m_2 so that the decrease in rate constant [increase in $\Delta^{\ddagger}G^{\circ}(m_2)$] arises from a dominant decrease in $\Delta^{\ddagger}S^{\circ}(m_2)$. The trends are more striking in the propan-1-ol solutions than in the ethanol solutions. Nevertheless, the contributions from $\Delta^{\ddagger}H^{\circ}(m_2)$ and $\Delta^{\ddagger}S^{\circ}(m_2)$ largely compensate to minimise the dependence of rate constant on m_2. This pattern is unexceptional.[16,17]

For hydrolysis at fixed temperature, each plot of the left-hand side of eqn. (6) against molality m_2 was linear yielding the solute interaction parameters summarised in Table 3. These $G(C)$ estimates decrease with increase in temperature for a given alcohol and decrease on going from solute ethanol to solute propan-1-ol at fixed temperature. The $G(C)$ parameters were used to calculate [eqns. (8) and (9)] the related group parameters $G(OH)$ and $G(CH)$ at each temperature. Interestingly, the calculated $G(CH)$ and $G(OH)$ parameters are in reasonable agreement with those obtained previously,[8] namely -68 and $+226$ J kg^{-1} mol^{-2} respectively. Plots of both $[G(OH)/T]$ and $[G(CH)/T]$ against $(1/T)$ were linear yielding the related enthalpy terms $H(OH)$ and $H(CH)$. These quantities were used to calculate the related group entropy terms, $S(OH)$ and $S(CH)$; Table 4.

Discussion

In the course of the spontaneous hydrolysis in aqueous

Table 2 Derived parameters describing the dependence of rate constant on temperature about reference temperature $\theta = 298.2$ K

Alcohol molality, m_2/mol kg^{-1}	$-a_1$	$-a_2/10^3$	k_1 (298.2 K)/10^{-3} s^{-1}	$\Delta^{\ddagger}H^{\infty}$(sln)/kJ mol^{-1}	$-T \cdot \Delta^{\ddagger}S^0$(sln)/kJ mol^{-1}
0	36.20 ± 0.02	5.44 ± 0.12	1.18	45.21 ± 0.97	45.37
Ethanol					
0.25	36.24 ± 0.02	5.40 ± 0.13	1.15	44.90 ± 1.08	44.94
0.75	36.30 ± 0.03	5.37 ± 0.14	1.08	44.61 ± 1.14	45.37
1.25	36.36 ± 0.03	5.33 ± 0.15	1.02	44.30 ± 1.22	45.84
1.75	36.43 ± 0.03	5.31 ± 0.13	0.956	44.17 ± 1.07	46.12
Propan-1-ol					
0.25	36.26 ± 0.03	5.42 ± 0.14	1.13	45.09 ± 1.17	44.79
0.75	36.37 ± 0.03	5.34 ± 0.15	1.02	44.39 ± 1.26	45.76
1.25	36.47 ± 0.03	5.22 ± 0.15	0.92	43.41 ± 1.22	46.99
1.75	36.59 ± 0.02	5.04 ± 0.10		41.90 ± 0.86	48.79

Table 3 Solute interaction parameters at 298.2 K

Alcohol	G(C)/J kg mol^{-2}	H(C)/J kg mol^{-2}	$T \cdot S$(C)/J kg mol^{-2}
Ethanol	-105.9 ± 1.6	290.3 ± 39	399
Propan-1-ol	-226.7 ± 8.9	980.8 ± 66	1201

Table 4 Pairwise group interaction parameters at 298.2 K

Methine

G(CH)/J kg mol^{-2} = -60.4
H(CH)/J kg mol^{-2} = 345 ± 52
$T \cdot S$(CH)/kJ kg mol^{-2} = 0.41

Hydroxy

G(OH)/kJ kg mol^{-2} = 196
H(OH)/kJ kg mol^{-2} = -1.44 ± 0.30
$T \cdot S$(OH)/kJ kg mol^{-2} = 1.532

Group CH

Group OH
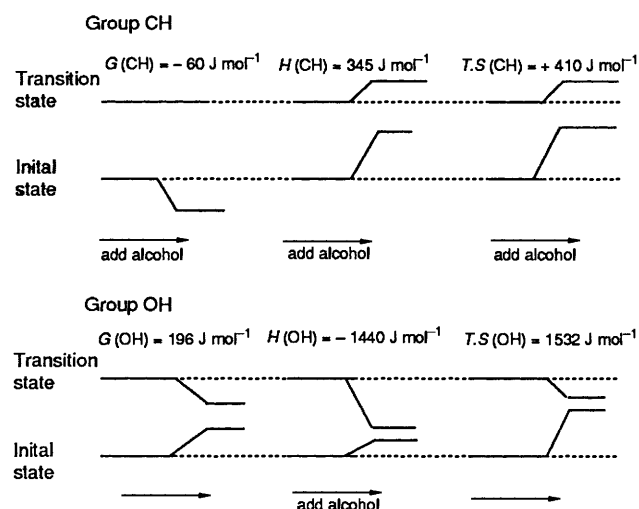
Fig. 1 Molecular orbital energy changes upon addition of alcohol

solutions having pH *ca.* 4, two molecules of water interact with the substrate, 1-benzoyl-3-phenyl-1,2,4-triazole on going from the initial to the transition state; for a mechanistic scheme, see ref. 8. The transition state is therefore less hydrophobic (more hydrophilic) than the initial state. Initially, therefore, we can anticipate that parameters describing interactions between, on the one hand, the initial and transition states, and on the other, the methine group of the alcohol will differ, describing the corresponding interactions involving the hydroxy group. As

shown in Table 3, this is indeed the case. Nevertheless, we can take the argument one step further and attempt to understand the patterns shown by the parameters in Table 4 in terms of the separate initial and transition state contributions. One possible scheme is shown in Fig. 1 based on generalisations concerning the sign and magnitudes of pairwise parameters.

With reference to the methine parameters, it is noteworthy that G(CH) is negative whereas H(CH) is large and positive. This pattern points to an important contribution involving the hydrophobic initial state. The negative G(CH) contributes towards a decrease in rate constant. However, from an enthalpic point of view, there is a strong destabilisation of the initial state resulting from interaction with added alcohol. The latter is associated with a positive $T \cdot S$(CH) value. These trends are also linked with a destabilisation of the hydrophilic transition state relative to the initial state by interaction with the hydrophobic CH-groups.

The positive G(OH) probably reflects a corresponding de-stabilisation of the hydrophobic initial state by the hydrophilic OH group in the alcohol. Since initial state–cosolvent interactions are largely determined by hydration shell overlap effects,[8] the overall positive G(OH) group interaction parameter signals an attenuation of the effects of the hydrophobic alcohol molecules. This attenuation follows interaction between the hydration shells surrounding the hydrophobic alkyl and hydrophilic OH group of the alcohol molecules. The marked negative H(OH) we assign to interactions involving the polarised hydrophilic transition state and the OH group of the added alcohol.

References

1 W. Blokzijl, J. B. F. N. Engberts, J. Jager and M. J. Blandamer, *J. Phys. Chem.*, 1987, **91**, 6022.
2 M. J. Blandamer, J. Burgess, J. B. F. N. Engberts and W. Blokzijl, *Ann. Reports C*, Royal Society of Chemistry, London, 1991, p. 45.
3 J. J. Savage and R. H. Wood, *J. Soln. Chem.*, 1976, **5**, 733.
4 S. K. Suri, J. J. Spitzer, R. H. Wood, E. G. Abel and P. T. Thompson, *J. Soln. Chem.*, 1985, **14**, 781, and references therein.
5 F. Franks, *Pure Appl. Chem.*, 1987, **59**, 1189.
6 S. Cabani, *Portugalia Electrochim. Acta*, 1975, **3**, 5.
7 W. Blokzijl, J. Jager, J. B. F. N. Engberts and M. J. Blandamer, *J. Am. Chem. Soc.*, 1986, **108**, 6411.
8 W. Blokzijl, J. B. F. N. Engberts and M. J. Blandamer, *J. Am. Chem. Soc.*, 1991, **113**, 4241.
9 S. Galema, J. B. F. N. Engberts and M. J. Blandamer, *J. Am. Chem. Soc.*, 1990, **112**, 9665.
10 J. B. F. N. Engberts, R. Kerstholt and M. J. Blandamer, *J. Chem. Soc., Chem. Commun.*, 1991, 1230.

11 S. A. Galema, M. J. Blandamer and J. B. F. N. Engberts, *J. Org. Chem.*, 1992, **57**, 1995.
12 R. Kerstholt, M. J. Blandamer and J. B. F. N. Engberts, to be submitted.
13 M. J. Blandamer, J. Burgess, J. M. W. Scott and R. E. Robertson, *Chem. Rev.*, 1982, **82**, 259.
14 W. Karzyn and J. B. F. N. Engberts, *Tetrahedron Lett.*, 1978, 1787.
15 M. J. Blandamer, *Chemical Equilibria in Solution*, Ellis Horwood, London, 1992.

16 M. J. Blandamer, *Adv. Phys. Org. Chem.*, 1977, **14**, 203.
17 M. J. Blandamer, J. Burgess, J. B. F. N. Engberts and F. Sanchez, *Faraday Disc. Chem. Soc.*, 1988, **85**, 309.