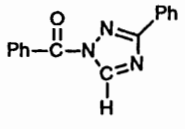
Kinetics of Uncatalysed Hydrolysis of 1-Benzoyl-3-phenyl-1,2,4-triazole and *p*-Methoxyphenyl Dichloroethanoate in Aqueous Solution Containing Ureas, Carboxamides, Sulfonamides, Sulfones and Sulfoxides

René P. V. Kerstholt,[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, The Netherlands*
[b] *Department of Chemistry, University of Leicester, Leicester, UK LE1 7RH*

Rate constants are reported for the hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole and *p*-methoxyphenyl dichloroethanoate in aqueous solutions containing formamide, acetamide, propionamide, isobutyramide, *N*-methylformamide, *N,N*-dimethylformamide, n-butyramide, *N*-methylacetamide, *N,N*-dimethylacetamide, urea, 1,3-dimethylurea, 1,1,3,3-tetramethylurea, methanesulfonamide, *N*-methylmethanesulfonamide, dimethylsulfonamide, dimethyl sulfone, tetramethylene sulfone, diethyl sulfone, DMSO, tetramethylene sulfoxide or diethyl sulfoxide. The data are analysed to yield quantities defined as $G(c)$ which describe Gibbs energies for substrate ⟷ added solute interactions. The $G(c)$ parameters are used to calculate group interaction parameters. Trends in derived $G(c)$ parameters can be understood in terms of additivity of group interactions following the pattern described by Savage and Wood for pairwise solute–solute interactions in aqueous solutions.

Interactions between neutral solutes in dilute aqueous solutions can be described using pairwise interaction parameters;[1] *e.g.* g_{jj}, the pairwise Gibbs energy interaction parameter. Savage and Wood[2] showed how these g_{jj} quantities can be re-expressed in terms of group interaction parameters, the SWAG model. We have shown how this approach can be applied in a quantitative treatment of kinetic data[1,3–5] describing chemical reactions in aqueous solutions. The dependence of rate constants for chemical reactions on molality of added solute-c is accounted for using a quantity $G(c)$ which describes interaction between added solute-c and both transition and initial states. We have shown how trends in $G(c)$ can be understood in terms of group contributions, *e.g.* $G(CH_2)$ for methylene groups in added solute-c. This treatment of kinetic data has been used to quantify the effect of alcohols,[4] ureas[3] and carbohydrates[6] on rate constants for ester and amide hydrolysis and, more recently, to probe rates of Diels–Alder reactions[7] in aqueous solution. A gap in these studies concerned those cases where the added solute contains a sulfur-based functional group. Another important gap concerned substituted ureas $R^1R^2NCONR^3R^4$ and carboxamides, $R^1CONR^2R^3$. We report here the kinetics of hydrolysis of two substrates, 1-benzoyl-3-phenyl-1,2,4-triazole (**I**) and *p*-methoxyphenyl dichloroethanoate (**II**). The added



I

solutes were methanesulfonamide (MSA), *N*-methylmethanesulfonamide (NMMSA), *N,N*-dimethylmethanesulfonamide (DMMSA), dimethyl sulfone ($DMSO_2$), tetramethyl sulfone ($TMSO_2$, sulfolane), diethyl sulfone ($DESO_2$), DMSO, tetramethylene sulfoxide (TMSO) and diethyl sulfoxide (DESO), formamide (F), acetamide (A), propionamide (P), isobutyramide (iB), *N*-methylformamide (NMF), *N,N*-dimethylformamide (DMF), n-butyramide (nB), *N*-methylacetamide (NMA), *N,N*-dimethylacetamide (DMA), urea (U), 1,3-dimethylurea (DMU) and 1,1,3,3-tetramethylurea (TMU). In each case, these solutes do not participate as a general base in the hydrolysis reactions described below. Therefore, this extensive range of solutes provide a critical test of the general approach.[1] We show that the model is very successful in describing medium effects in dilute aqueous solutions.

Experimental

Materials—The substrates, **I** and **II**, were synthesised and purified as described previously.[8,9] All solutions were prepared by weight and contained HCl (3.2×10^{-4} mol dm^{-3}) to suppress catalysis by hydroxide ions. The pH of the solutions were in the range 3.5–4.5, the range over which the kinetics of hydrolysis are pH independent. Most solutes were commercial products with four exceptions. Methanesulfonamide (MSA), *N*-methylmethanesulfonamide (NMMSA) and *N,N*-dimethylmethanesulfonamide (DMMSA) were synthesised from the sulfonyl chloride and the relevant amine. Diethyl sulfoxide was synthesised from diethyl sulfide using $NaIO_4$ as oxidant. All solutes were purified by recrystallisation or vacuum distillation.

Kinetics of Reaction—The progress of chemical reaction was followed by the change in absorbance at 273 nm for **I** and 288 nm for **II**. Approximately $5–8 \times 10^{-3}$ cm^3 of concentrated solution of either **I** or **II** in acetonitrile (*ca.* 3×10^{-2} mol dm^{-3}) was added to the reaction medium (2.5 cm^3) in a quartz cell, path length 1 cm, held in a thermostatted cell compartment. The change in absorbance with time was followed using either a Perkin-Elmer λ5 spectrophotometer equipped with a data station or a Philips PU8700 spectrophotometer linked to a PC desk-top computer. All reactions were followed for four half-lives at 25.00 ± 0.05 Celsius, between 75 and 100 data points being normally logged using the Perkin-Elmer spectrophotometer. Between 300 and 400 data points were recorded using the Philips spectrophotometer. For each system between 2–3 rate constants were measured, the first-order rate plots being linear. Rate constants were reproducible to within ±1%.

Analysis of Data—The dependence of rate constant on molality of added solute was analysed using a least squares procedure.

Table 1 Derived interaction parameters[a] $G(c)$ for hydrolysis of I and II

Compound[b]	$n(CH_2)$	Hydrolysis of I		Hydrolysis of II	
		$G(c)_{exp}$	$G(c)_{calc}$	$G(c)_{exp}$	$G(c)_{calc}$
F	0.5	−152 ± 5	−151	−167 ± 9	−159
A	1.5	−206 ± 10	−202	−289 ± 10	−301
P	2.5	−244 ± 9	−253	−436 ± 15	−444
nB	3.5	−327 ± 15	−304	−597 ± 11	−586
iB	3.5	−254 ± 14	−304	−568 ± 14	−586
NMF	2	−208 ± 6	−227	−357 ± 6	−372
DMF	3.5	−182 ± 4	−304	−631 ± 7	−586
NMA	3	−327 ± 22	−278	−527 ± 12	−515
DMA	4.5	−134 ± 6	−355	−705 ± 31	−729
U	0	−1 ± 2	−1	+97 ± 1	+109
DMU	3	−435 ± 20	−435	−354 ± 17	−379
TMU	6	−178 ± 5	−869	−879 ± 27	−867
MSA	1.5	−508 ± 17	−537	−470 ± 9	−468
NMMSA	3	−810 ± 36	−753	−796 ± 31	−800
DMMSA	4.5	−941 ± 19	−970	−1133 ± 10	−1131
$DMSO_2$	3	−550 ± 11	−550	−659 ± 21	−659
$TMSO_2$	4	−778 ± 2	−677	−1012 ± 38	−876
$DESO_2$	5	−804 ± 20	−804	−1093 ± 6	−1093
DMSO	3	−62 ± 2	−62	−380 ± 6	−380
TMSO	4	+36 ± 14	−104	−574 ± 16	−551
DESO	5	−145 ± 5	−145	−721 ± 10	−721

[a] $G(c)$ expressed in J kg mol^{-2}. [b] For abbreviations used see text.

Previously,[1–5] we showed that the dependence of rate constant $k(m_c)$ on molality of added solute m_c can be expressed using eqn. (1). In the latter equation, k ($m_c = 0$) is the rate constant for

$$\ln [k(m_c)/k(m_c = 0)] = (2/R \cdot T) \cdot G(c) \cdot m_c - n \cdot \varphi \cdot m_c \cdot M_1 \quad (1)$$

solvolysis in solutions which contain no added solute; φ is the practical osmotic coefficient. The integer n is a mechanism-related parameter, described the number of molecules of water incorporated into the transition state. For the two reactions described here, n equals 2. For the dilute solutions used in this study a good approximation sets φ equal to unity. In each case, a plot of $\{\ln [k(m_c)/k(m_c = 0)] + 2 \cdot m_c \cdot M_1\}$ against m_c was found to be a straight line, the slope yielding the Gibbs energy interaction parameter $G(c)$. The latter is a composite term describing interaction of added solute with initial and transition states.

Resuslts

Kinetic data were recorded for solutions containing carboxamides over the range $0 \leqslant m_c/\text{mol kg}^{-1} \leqslant 1.2$. For the ureas, the range was $0 \leqslant m_c/\text{mol kg}^{-1} \leqslant 2.8$. The slopes of the plot discussed above yielded the $G(c)$ parameters recorded in Table 1. [The estimates of $G(c)$ for the ureas and substrate II were taken from reference 10.] For DMU and substrate I, the corresponding plot was not linear; the estimate of $G(c)$ for this system is based on the kinetic data for the two solutions, $m(\text{DMU}) = 0.3$ mol kg^{-1} and for $m(\text{DMU}) =$ zero. Interestingly, the corresponding plot was linear for substrate II. Generally, we found that the data for substrate I showed deviations from a linear dependence at lower concentrations of added solute than for substrate II. This trend points to the importance of interactions of order higher than pairwise in the case of substrate I.

Linear dependences of the same plot were obtained for the sulfonamides and the sulfones over the range, $0 \leqslant m_c/\text{mol kg}^{-1} \leqslant 0.6$. A similar pattern emerged for the sulfoxides over the range $0 \leqslant m_c/\text{mol kg}^{-1} \leqslant 2.4$; Table 1. However, the same plot for solutions containing TMSO and substrate I was not linear. An estimate of $G(c)$ for TMSO was obtained using the rate constant for solutions where $m(\text{TMSO}) = 0.3$ mol kg^{-1} and $m(\text{TMSO}) =$ zero. Again the corresponding plot was linear for substrate II.

Discussion

In terms of the model[1–5] underlying eqn. (1), the changes in rate constants following addition of a solute-c reflect the changes in chemical potentials of initial and transition state brought about by cosphere–cosphere interaction (*i.e.* solvation shell–solvation shell) with the solute. In other words, the changes in reactivity primarily reflect solvent-transmitted solute effects rather than direct (contact) solute-initial and solute-transition state interactions. It is therefore interesting to note the wide variation in $G(c)$ for a given substrate across a range of added solutes and the difference between $G(c)$ for two substrates in the presence of the same solute. For example, the negative $G(c)$ for DMMSA is striking. In fact, it is the most rate retarding functional group that has been examined in our studies.

Following the procedures previously described, the estimates of $G(c)$ are used to calculate the corresponding functional group parameters. In these terms, we assumed that $CH_2 \equiv 2 \times CH \equiv (2/3) \cdot CH_3$ and so constructed a plot of $G(c)$ against $n(CH_2)$. In Fig. 1 we show this plot for substrate I and the carboxamides. The intercept at $n(CH_2) = 0$ yields $G(\text{CONH})$. The data points for DMF and DMA are off the line, pointing up a non-additivity of group contributions for these systems. In a similar plot for the ureas, the data point for TMU is off the line. If these three data points are ignored, the group contributions $G(CH_2)$, $G(\text{CONH})$ and $G(\text{HNCONH})$ are obtained. The same analysis was used in the context of sulfur-containing added solutes. The outcome is summarised in Table 1 for both substrates. For the sulfones and sulfoxides, the data for $TMSO_2$ and TMSO were not used in this calculation.

The derived group interaction parameters were used to recalculate $G(c)$, the pairwise solute interaction parameters; Table 2. The agreement between $G(c)_{calc}$ and $G(c)_{exp}$ is generally good except for DMF, TMU, DMA, $TMSO_2$, TMSO and substrate II. The differences are generally greater for substrate I.

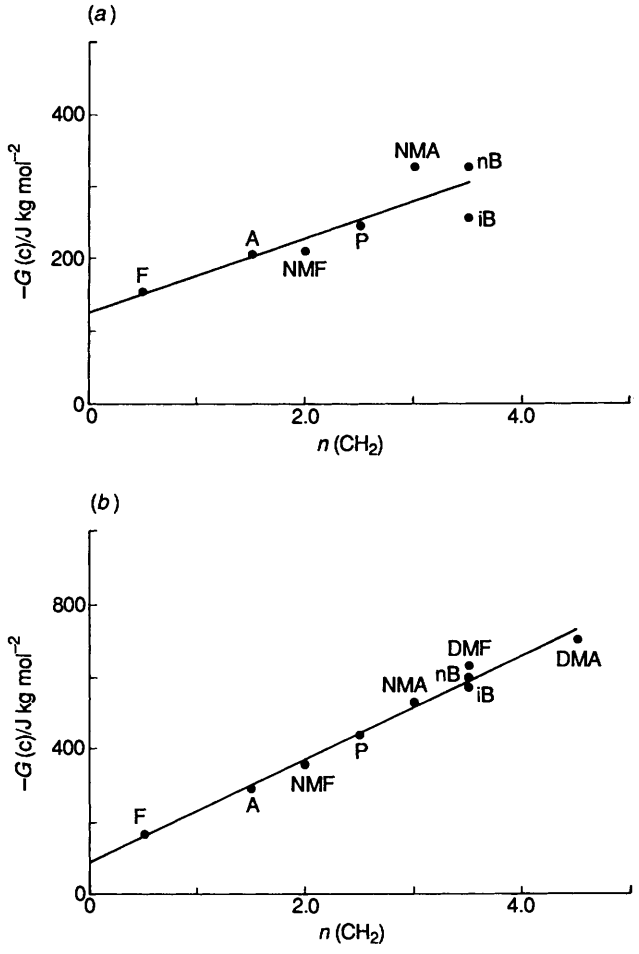


Fig. 1 Dependence of pairwise Gibbs energy interaction parameter G(c) as a function of the number of methylene groups hydrolysis of substrate (*a*) **I** and (*b*) **II**

Table 2 Pairwise Gibbs energy group interaction parameters[a]

	Hydrolysis of I		Hydrolysis of II	
X	$G(CH_2)$	G(X)	$G(CH_2)$	G(X)
CONH	−51	−125	−142	−87
HNCONH	−145	−1	−163	+109
SO_2NH_2	−144	−320	−221	−137
SO_2	−127	−169	−217	−8
SO	−42	+63	−171	+132

[a] G(c) expressed in J kg mol^{-2}.

Nevertheless, $G(c)_{exp}$ for $TMSO_2$ and $DESO_2$ are close indicating that calculation of the number of equivalent methylene groups for a cyclic structure is not straightforward.

Possibly the most surprising result concerns the effect of added urea on substrate **I** where G(c) is negligibly small (Table 1). To conclude that there are no U–substrate interactions seems erroneous. Therefore, the impact of added U on transition and initial states of substrate **I** must cancel.

A most dramatic finding is the contrast in importance of $G(CH_2)$ and $G(SO_2)$ for the two substrates (Table 1). In fact, for the hydrolysis of **II**, $G(SO_2)$ is negligibly small. It was also somewhat surprising to discover that $G(SO_2)$ and $G(SO_2NH)$ are, together with $G(CH_2)$, negative. It had been anticipated that these G(c) estimates would reflect the hydrophobicity/hydrophilicity of the groups. Probably the hydration shells of the sulfonoyl compounds overlap and stabilise the initial states of substrates **I** and **II**. Only G(SO) has a different sign than $G(CH_2)$, dramatically so for substrate **II**; it is one of the rare functional groups that enhance the rate of hydrolysis in aqueous media. For example, in the case of the sulfonamides and sulfones, the $G(CH_2)$ values are very similar for substrate **I** and **II** despite the fact that $G(SO_2NH_2)$ and $G(SO_2)$ are quite different. Furthermore, we consistently find that substrate **II**, as compared to **I**, is most sensitive to hydrophobic effects as quantified in $G(CH_2)$. This is, *inter alia*, demonstrated by the observation that G(c) for substrate **II** is about equal for **nB** and **iB** (Table 1) as required by additivity.

Despite possible critical comments, the broad sweep of the data summarised in Table 1 taken together with the agreement between $G(c)_{exp}$ and $G(c)_{calc}$ is impressive, providing support to the underlying model.[1–5] Certainly, we can think of no other approach to chemical reactivity in solution which has anything like comparable success.

Acknowledgements

We thank the University of Leicester for a travel grant to M. J. B.

References

1 M. J. Blandamer, J. Burgess, J. B. F. N. Engberts and W. Blokzijl, *Annu. Rep. Prog. Chem., Sect C, Phys. Chem.*, 1992, 45.
2 J. J. Savage and R. H. Wood, *J. Solution Chem.*, 1976, **5**, 733.
3 W. Blokzijl, J. Jager, J. B. F. N. Engberts and M. J. Blandamer, *J. Am. Chem. Soc.*, 1986, **108**, 6411.
4 M. J. Blandamer, J. B. F. N. Engberts and W. Blokzijl, *J. Am. Chem. Soc.*, 1990, **112**, 1197.
5 J. B. F. N. Engberts, R. Kerstholt and M. J. Blandamer, *J. Chem. Soc., Chem. Comm.*, 1991, 1230.
6 M. J. Blandamer, S. A. Galema and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1990, **112**, 9665; M. J. Blandamer, S. A. Galema and J. B. F. N. Engberts, *J. Org. Chem.*, 1992, **57**, 1995.
7 M. J. Blandamer, W. Blokzijl and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1991, **113**, 4241.
8 W. Karzijn and J. B. F. N. Engberts, *Tetrahedron Lett.*, 1978, 1787.
9 J. F. J. Engbersen and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1975, **97**, 1563.
10 W. Blokzijl, J. B. F. N. Engberts, J. Jager and M. J. Blandamer, *J. Phys. Chem.*, 1987, **91**, 6022.

Paper 2/04460I
Received 18*th August* 1992
Accepted 2*nd November* 1992