Entropic strain and conformational preference in the hydrolysis of some *N*-alkyl-6-acetylaminotriazinediones

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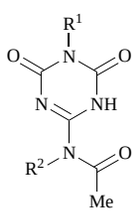
The rate–pH profiles for hydrolysis of the title compounds 1 show four distinct regions: k_A, k_B and k_C for rate plateaux corresponding to cationic, neutral and anionic species, plus k_D for attack of OH^- on the anion. At the ends of the pH scale the reaction is much slower than for model amides of comparable pK_{lg}, due to exceptional charge dispersal in reactant and leaving group. The plateau rates k_B and k_C are due to hydrolysis by water, not to some kinetically equivalent process, and are much faster than model calculations would predict. This is traced to intramolecular general base catalysis *via* solvent bridges, and leads to remarkable rate enhancements in aqueous alcohols. The considerable, and quite independent, variations in k_B, k_C and acid pK_a with only alkyl substitution in the amide moiety points to a dominant effect of conformation which has been explored using a number of techniques, notably octanol–water partitioning, and appears best rationalised in terms of Taft's 'steric hindrance of motions' or Tillett's 'entropic strain'. The overall picture for the effect of pH is of successively increasing C–O bond formation in the transition state along the sequence $k_A \longrightarrow k_B \longrightarrow k_C$ but with C–N bond breaking quite out of line and largely dependent on conformational factors.

Given p$K_{cat} < 0$, the presence of effective intramolecular general base catalysis in k_B is unexpected. We explain this as being due to a unique feature of 1 whereby catalyst and leaving group are part of the same conjugated structure, leading to p$K_{cat} \longrightarrow$ pK_{lg} as C–N bond-breaking proceeds. Further light on k_B comes from the ring-*N*-methylated analogue 3d, which cannot form the intramolecular hydrogen bond found elsewhere and whose otherwise similar rate–pH profile shows an anomalous 'apparent pK_a' that can be explained as a consequence of this.

The title compounds **1**, originally investigated as potential



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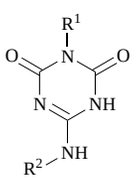

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herbicides,[1] were later found to have analgesic and in some cases anti-inflammatory activity.[2–4] At the same time, they proved to be gastric irritants.[4] This behaviour is reminiscent of aspirin, an irreversible inhibitor of cyclooxygenase[5] whose propensity for irritating the gastric mucosa[6] may depend on the same acetylation process that mediates its analgesic action.[5] As potential acetylating agents, the triazinediones **1** may therefore mimic the behaviour of aspirin in both respects. Hence the present investigation, while designed in part as a check on their chemical stability *in vitro*, was also intended to throw light on their possible mode of action *in vivo*.

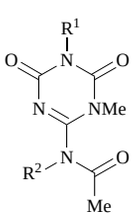
The result of this investigation has been not only to illuminate the above parallelism, but to uncover a mechanistic situation of some complexity. Despite the fact that the substituents R^2 in **1** are simple alkyl groups, variation in this respect produces considerable variation in pK_a and in the rate of the reaction to give **2**, and these variations moreover appear to bear little relation to one another. Furthermore, their hydrolytic behaviour is not that of typical amides. While the expected dependence on $[H^+]$ and $[OH^-]$ both appear, there are rate plateaux in the middle pH region, corresponding formally to the concentrations of neutral and anionic species, that clearly point to the presence of intramolecular catalysis. The nature of that catalysis is the principal subject of this paper.

Our results point to conformation of the reacting species as a major determinant of its reactivity. The rules appear to be different for neutral species and anion, so that the same structural change has different consequences for each. Evidence for conformation has been obtained not only from expected sources such as spectroscopy, but also from less usual sources such as the partition coefficient. On the hypothesis that analgesia and gastric irritation may relate, respectively, to the reactivities of anion and neutral species, we might then hope to elucidate the structural factors that underpin therapeutic ratio. A preliminary account of this work has appeared.[7]

Experimental

Materials and methods

All compounds were supplied by colleagues; the few not explicitly covered by the relevant patents,[1–3] *i.e.* **3d**, **4d** and **5**,



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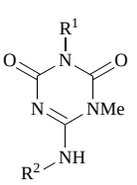

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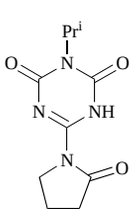

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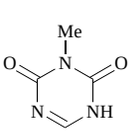

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Table 1 UV, pK_a and log P data for some triazinediones

	R^1	R^2	log P [a,b]	pK_{a1} [b,c]	pK_{a2} [b,d]	λ_{max}/nm (log ε) [e] C_6H_{12}	A	B	C
1a	Pr^i	Me	0.06		5.60	240 (3.79)		244	234
1b	Pr^i	Et	0.49		4.87			246	238
1c	Pr^i	Pr^n	0.96		5.16	233 (3.81)			
1d	Pr^i	Pr^i	0.45	−0.95	4.53	241 (4.05)	248 (4.03)	243 (3.90)	253 (3.94)
1e	Pr^i	Bu^s	0.94	−1.01	4.65	240 (4.00)		247	250
1f	Pr^i	Bu^i	1.11		4.72	243 (4.08)		248	244
1g	Pr^i	$CHEt_2$	1.44		4.76			248 (3.98)	248 (4.01)
1h	Pr^i	CH_2Bu^t	1.78		4.27	243 (4.04)		250	244
1i	Pr^i	$CH(Et)Pr^n$	1.96		4.75				
1j	Pr^i	Cyclohexyl	1.59		4.38				
1k	Pr^i	1-Piperidyl	2.33		5.26				
1l	Pr^i	$CHBu_2$	3.22		4.70				
1m	Pr^n	Pr^n	0.88		5.04				
1n	Bu^n	Bu^n			4.99				
1o	C_6H_4-4-Me	Bu^n			4.46			249	245
1p	C_6H_4-4-Me	Bu^i	1.65	−3.67	4.11		232 (4.29)	248 (4.31)	
1q	C_6H_4-4-Me	CH_2Bu^t			3.61			250	244
1r	C_6H_4-4-OMe	Bu^i	1.16	−3.65	4.18		228 (4.37)	248 (4.31)	
2d	Pr^i	Pr^i	0.52	1.69	7.95		205 (4.34)	229 (4.29)	223 (4.33)
3d	Pr^i	Pr^i	0.18	<0	—			246 (3.83)	
4d	Pr^i	Pr^i	0.53	1.59	13.70		<200 (>4.3)	229 (4.20)	
5					6.91	241 (3.98)			

[a] Octanol–water. [b] At 25 °C. [c] Basic pK_a. [d] Acid pK_a. [e] A = cation, B = neutral species, C = anion (*cf.* Scheme 1); data for aqueous solution at 25 °C.

had been prepared by one of the methodologies described therein. Table 1 lists salient physical properties for the 22 triazinediones here considered. ^{13}C NMR spectra were obtained on a JEOL FX 90Q NMR spectrometer in $CDCl_3$ solution using tetramethylsilane as internal lock, and IR spectra in $CHCl_3$ solution on a Perkin-Elmer 580B IR spectrophotometer. Either a Unicam SP 8000 or a Unicam SP 1800 UV spectrometer was used for UV spectra (Table 1) and for reaction following. Product analysis by reversed-phase HPLC employed a Cecil constant-pressure system using an octadecylsilane column with 90% aqueous acetonitrile as eluent, and with peak monitoring by UV. A Radiometer PHM 28 pH meter was employed for pH measurement at 25 °C using Radiometer type B electrodes, which require correction of only 0.03 pH units even at pH 13. pK_a Values in the range pK_a 4–8 were sometimes measured by potentiometry, elsewhere and more generally by UV spectrophotometry, using standard techniques.[8] Water was glass distilled, while alcohols and all inorganic reagents were of AnalaR grade. Temperatures, except at 100 °C (*i.e.* usually under reflux), were measured to ±0.1 °C.

Kinetics

Because of the high temperatures (>60 °C) mostly employed, sampling at appropriate intervals of time was mainly used for reaction following. Buffer solutions, usually of 99 cm^3 in a 100 cm^3 volumetric flask, were equilibrated in a thermostatted bath at the required temperature and the reaction was initiated by adding 1 cm^3 of a stock reagent solution in acetonitrile, also at the required temperature. The reaction solution would typically contain reagent at *ca.* 10^{-4} mol dm^{-3} and acetate or phosphate buffer at *ca.* 10^{-2} mol dm^{-3} adjusted to $I = 1.0$ mol dm^{-3} with sodium perchlorate. These buffer concentrations were shown by spot checks to have no appreciable effect on the reaction rate. Some experiments at very low or very high pH were conducted in $HClO_4$–$NaClO_4$ or NaOH–$NaClO_4$ mixtures at $I = 5.0$ mol dm^{-3}. Aliquot samples were cooled rapidly to ambient temperature and their UV spectra examined in 1 cm quartz cells. Successive UV traces were overlaid as a check on possible isosbestic drift; this was never detected. The progress of the reaction was then followed by the decline in the absorbance of **1** at some wavelength in the range 220–260 nm; since reactant **1** and product **2** both possess UV spectra, and both ionise, a variety of wavelengths had to be employed. Only for **3d** in NaOH–$NaClO_4$ mixtures at $I = 1.0$ mol dm^{-3} was the reaction followed *in situ*, at 25 and 37 °C in a thermostatted UV cell, as well as at 83 °C by the method outlined above.

With the above exception, all work with **3d** was carried out at 100 °C. Rates for the only other compound for which the full rate–pH profile has been determined, **1d**, were followed at 83 °C at pH ≤ 2 and pH > 11 and at 100 °C between these limits. Temperature coefficients were measured under four conditions: at 83, 90 and 100 °C for pH *ca.* 3.5 and *ca.* 6.5 at $I = 1.0$ mol dm^{-3}; and at 64, 72 and 83 °C for $HClO_4$ and NaOH at 1.0 mol dm^{-3} with $I = 5.0$ mol dm^{-3}. These conditions define either rate plateaux or constant $\{H^+\}$ or $\{OH^-\}$, so could be used for constructing the full rate–pH profile of Fig. 1. In this, pH values are adjusted to 100 °C from their measured values at 25 °C with corrections at pH ≤ 2 according to Day and Wyatt[9] and at pH > 2.5 from the temperature coefficients of Dempsey and Perrin.[10] pH Values at $[H^+]$ and $[OH^-] \geq 1.0$ mol dm^{-3} and $I = 1.0$ or 5.0 mol dm^{-3} are those given by Rochester;[11] the latter incorporate the appropriate correction for pK_w.[8] Temperature coefficients for **1d** and **3d** appear in Table 2 while those for a few other compounds were measured on the plateaux at pH *ca.* 3.5

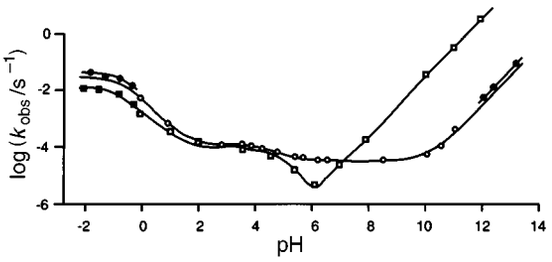


Fig. 1 Rate–pH profiles in water at 100 °C for **1d**, circles, and **3d**, squares; open symbols, at I = 1.0 mol dm^{-3}; full symbols, at I = 5.0 mol dm^{-3}

Table 2 Fitting constants at 100 °C,[a] and activation parameters, for the hydrolysis of **1d** and **3d**

Constant[b]	**1d**	**3d**
k_A/s^{-1}	2.96(0.35) × 10^{-2}	1.14(0.22) × 10^{-2}
E_a/cal mol^{-1}	20 320	
$\Delta S_{25}^{\ddagger}$/cal mol^{-1} K^{-1}	−13.1	
k_B/s^{-1}	1.02(0.09) × 10^{-4}	0.831(0.155) × 10^{-4}
E_a/cal mol^{-1}	22 270	
$\Delta S_{25}^{\ddagger}$/cal mol^{-1} K^{-1}	−19.0	
k_C/s^{-1}	0.285(0.025) × 10^{-4}	—
E_a/cal mol^{-1}	19 810	
$\Delta S_{25}^{\ddagger}$/cal mol^{-1} K^{-1}	−28.2	
k_D/dm^3 mol^{-1} s^{-1}	2.63(0.18) × 10^{-3}	2.66(0.13)
E_a/cal mol^{-1}	16 700	11 250
$\Delta S_{25}^{\ddagger}$/cal mol^{-1} K^{-1}	−27.5	−28.5
pK_I	−0.67(0.80)	−0.74(0.14)
pK_{II}	4.69(0.21)	4.75(0.13)

[a] 1 cal = 4.184 J. [b] Eqn. (1).

and *ca.* 6.5 and appear in the text. Rates were followed for 2–3 half-lives and pseudo-first-order rate constants (k_{obs}) were obtained by a least-squares procedure according to Swain's method.[12]

Data analysis

The full rate–pH profile for **1d** was analysed by ENZFITTER[13] according to eqn. (1). This contains as adjustable parameters

$$k_{obs} = \frac{k_A[H^+]^2 + k_B K_I[H^+] + k_C K_I K_{II}}{[H]^2 + K_I[H^+] + K_I K_{II}} + \frac{k_D K_w}{[H^+]} \qquad (1)$$

the plateau rate constants k_A, k_B and k_C, the second-order constant k_D for attack of hydroxide ion, and the apparent ionisation constants K_I and K_{II}, with pK_w at 100 °C (*cf.* Fig. 1) taken as 12.12. At the extremes of the pH scale, k_{obs} is accelerated by the change in ionic strength from I = 1.0 to I = 5.0 mol dm^{-3}; this was factored out before analysis by applying corrections of Δ log k = −0.16 at low pH and −0.20 at high pH so that the derived fitting constants are all for I = 1.0 mol dm^{-3}. A similar procedure at low pH (Δ log k = −0.05) was used for **3d**, whose analysis employed the same equation except that the term in k_C is missing since **3d** cannot form an anion. These fitting constants, with their error limits, appear in Table 2. Activation parameters were obtained from the temperature coefficients by use of the Eyring equation[14] and are believed accurate to ±300 cal mol^{-1} in $\Delta H^{\ddagger}$ and ±1 cal mol^{-1} K^{-1} in $\Delta S^{\ddagger}$.†

Reaction products

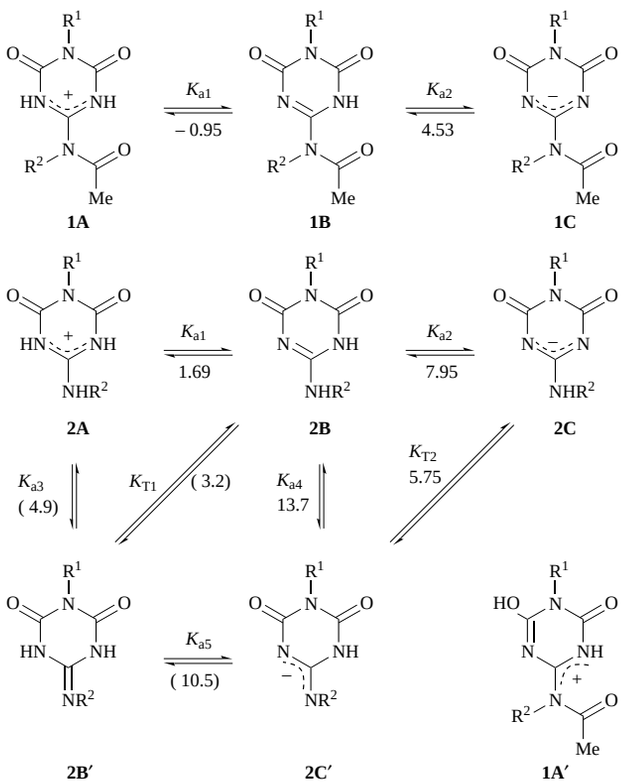
The course of the reaction was followed for **1d** in water by HPLC for several half-lives at pH values corresponding to each of k_A–k_D. Reactant **1d** and hydrolysis product **2d** produced well separated peaks, at 1.6 and 2.8 min under the conditions employed, and only these species were detectable. In this case and others, UV spectroscopy also demonstrated quantitative conversion of **1** to **2**. This demonstration is important, in that the triazinedione **6** is known to hydrolyse to a ring-opened species *via* covalent hydration under mild conditions.[15] No such reaction appears to take place here.

Identification of the reactive sub-species

In most studies of acyl transfer, there is no ambiguity concerning the nature of the reactive species. Here however there are tautomeric and conformational complexities which carry mechanistic implications and so require prior discussion.

Ionisation and tautomeric form

Interrelationships between sub-species are set out in Scheme 1,



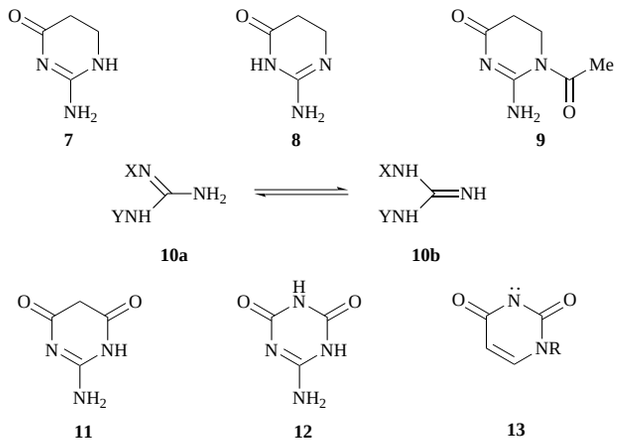
Scheme 1 Measured and estimated values are for **1d**, **2d** and **4d**; K_{T1}, K_{a3} and K_{a5} incorporate statistical factors

whose pK_a and pK_T values relate to compounds **1d**, **2d** and **4d** (*cf.* Table 1); the bracketed values are estimates, as derived below. While the structure of **1** is unambiguous, **2** could exist as **2B** or **2B′** in the neutral form and as **2C** or **2C′** in the anion. Hence there are problems in determining leaving group pK_a and these must be resolved.

We attempt their resolution as follows. We have previously estimated basic pK_a values of 7.05 and 9.9 for the tautomeric acylguanidines **7** and **8**, respectively.[16] Further acylation of **8** to **9** is analogous to that of acetylguanidine (**10a**, X = COMe, Y = H), pK_a 8.20,[17] to diacetylguanidine (**10a**, X = Y = COMe), pK_a 4.93,[18] *i.e.* ΔpK_a *ca.* −3.3; this analogy predicts pK_a *ca.* 3.8 for **9**. However, a closer model for **2** is the hypothetical species **11**,‡ which differs from **9** in the alignment of its added carbonyl group; we have estimated ΔpK_a ≥ −1.2 for this change in geometry,[16] hence pK_a ≤ 2.6 for **11**. This is close enough to pK_a 1.8 for ammelide **12**[20] to suggest the same tautomeric form for the latter, given minor imponderables such as its extra ring NH and the tendency of aromatisation to reduce basicity. Hence pK_{a1} for **2A** represents deprotonation to **2B**, as written (Scheme

† 1 cal = 4.184 J.

‡ The tautomeric form of **11** is likely to be disfavoured, making its pK_a value inaccessible; *cf.* pp. 132–133 (formula **211f**) of ref. 19.



7 **8** **9**

10a **10b**

11 **12** **13**

Table 3 IR and ^{13}C NMR data for triazinediones

			ν/cm^{-1} ($CHCl_3$)			δ/ppm ($CDCl_3$)	
	R^1	R^2	NH	C=O[a]	C=N	C-2	C-4
5			3225	1683			
1a	Pr^i	Me	3180	1677			
1f	Pr^i	Bu^i	3170	1673			
1e	Pr^i	Bu^s	3145	1672	1616		
1h	Pr^i	Bu^t	3180	1672			
1c	Pr^i	Pr^n				148.9	155.1
1d	Pr^i	Pr^i				151.9	
2d	Pr^i	Pr^i			1612		

[a] Ring plus exocyclic carbonyl.

1). Further evidence for **2B** as the dominant species comes from the near-identity of $\nu_{C=N}$ for **1e** and **2d** (Table 3); the switch in structure between compound classes **7** and **8** raises $\nu_{C=N}$ by 50–80 cm^{-1}.[21]

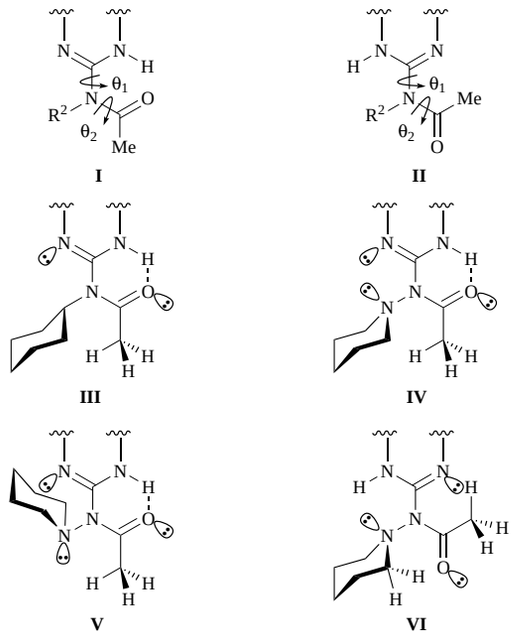
Calculation of pK_{a3} requires an estimate for pK_{T1}. Species **2B** and **2B′** are analogous to **7** and **8** in that C=N is deconjugated from carbonyl in the second of each pair. If this analogy holds, pK_{T1} = *ca.* 2.9, hence pK_{a3} = *ca.* 4.6. In fact there is evidence, for the equilibrium **10a** ⇌ **10b**, that **10a** becomes more dominant as both tautomers become less basic,[17] so that these estimates are probably minima. Statistically corrected, they appear in Scheme 1.

The large reduction in the acidity of **2d** brought about by ring *N*-methylation to **4d** shows that these do not share a common anion. Since **4d** can only give **2C′**, its tautomer **2C** must be formed by **2d**, leading to pK_{T2} = *ca.* 5.75 (Scheme 1). This is large, presumably because the anionic charge in **2C′** is much less well distributed than in **2C**. The unsubstituted triazinedione **6** possesses[22] pK_a 6.58, hence amino-substitution (relative to **2B**) is not greatly acid-weakening. Contrariwise, acylation is more acid-strengthening than base-weakening (Scheme 1). Since twisting out of plane of the whole acetylamino unit will reduce its resonance donor power without much affecting its inductive ability, this is part of the evidence, to be discussed below, that twisting is much more severe in the anion **1C** than in the cation or neutral species.

With basic pK_a values of −3.67 and −3.65 respectively, compounds **1p** and **1r** for which R^1 = aryl do not fit the above pattern. Since pK_{a2} is not much affected, and neither is the hydrolysis rate (*vide infra*), we can only suppose their cations to possess the alternative *O*-protonated structure **1A′**. Though normal for amides, as, *e.g.*, the related uracils **13**,[23] this is highly unusual for guanidines[16,17] and there seems no obvious explanation for it. UV spectroscopy (Table 1) provides little help: while **1d** shows a bathochromic shift on protonation but **1p** and **1r** the reverse, a hypsochromic shift is also shown by **2d** and by compounds of type **7**, which certainly *N*-protonate.[16] Kinetic consequences are considered below.

Conformation in the neutral species

For the acyltriazinediones **1**, the obvious conformation in non-polar solvents is shown as **I** in Scheme 2. This not only contains



I **II** **III** **IV** **V** **VI**

Scheme 2

a stabilising intramolecular hydrogen bond, but also avoids the potentially destabilising clash between NH and R^2 in **II**, its only plausible alternative. The latter is shown in the *E*-conformation so as to avoid the otherwise severe lone pair clash between carbonyl and aza-nitrogen.

While the planarity expected for maximum resonance stabilisation is unlikely to be threatened where R^2 is a linear alkyl group, increasing rotundity might have one of three effects: twisting away from $\theta_1 = 0$, the same for θ_2, or an in-plane compression of the relatively polarisable hydrogen bond. The first two will weaken this bond, whereas the third will strengthen it. While the second is improbable on resonance grounds, there is evidence for both the other phenomena (Table 3). Compounds **1a**, **1f** and **1e** represent R^2 = linear, β-branched and α-branched respectively; here ν_{NH} falls in sequence as the hydrogen bond strengthens. Only for **1h** with its very bulky neopentyl substituent does the effect reverse, pointing to some degree of twisting out of plane. Even so, ν_{NH} is lower in **1h** than in **5**, where bonding is weakened not by steric hindrance but by the different bond angle at amide nitrogen dictated by the five-membered ring. Nevertheless, even though α-branching may forcibly strengthen this hydrogen bond, it also reduces the energy barrier to rotation, as is shown by the collapse of the two ring carbonyl ^{13}C NMR signals for **1c** to a single time-averaged signal in **1d**.

What counts for reactivity is how far this hydrogen bond may survive in aqueous solution. Compounds **1** possess a strong band at *ca.* 240 nm in cyclohexane which typically shows a small bathochromic shift in water (Table 3) where a hypsochromic shift might have resulted through loss of conjugation had twisting been severe; the deacyl reaction products **2d** and **4d** do indeed show a shift to 229 nm. However, this criterion does not distinguish between **I** and **II** if planar or near-planar, and indeed **3d** in which NMe replaces ring NH cannot form an intramolecular hydrogen bond. Nevertheless, it may still prefer some approximation to **I** as its dominant conformer, as affording the best compromise between planarity and steric strain. In terms both of λ_{max} and of reactivity at pH < 5, **1d** and **3d** are almost identical.

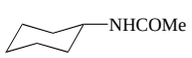
The partition coefficients of Table 1 provide unexpected evidence as to the conformation. For R^1 = Pr^i or Pr^n, and omitting

1j and **1k** where R^2 is cyclic, we obtain eqn. (2) where C, α and β

$$\log P = -0.45(0.06) + 0.46(0.02)C - 0.41(0.09)\alpha - 0.07(0.06)\beta \quad (2)$$
$$(n = 11,\ r^2 = 0.992,\ s = 0.10,\ F = 274)$$

are indicator variables that sum the total number of carbon atoms, and of α- and β-branches, respectively. Here the coefficient of C is close to the expected 0.53 for the value of the methylene increment[24] while those of α and β should be compared with Leo's[24] 'branching factor' F_{cbr} of −0.13. Clearly, the coefficient of α is much greater than expected; it approaches, in the opposite sense, the value of +0.63 estimated by Leo[25] for the effect of an intramolecular hydrogen bond in 1,2-disubstituted benzenes. If α-branching were to restrict solvation of aza-nitrogen (*cf.* **I**), a rise in log P should result; its fall suggests, contrariwise, that this solvation is maintained at the expense of planarity, with some weakening of the intramolecular bond. Allowing for F_{cbr}, this appears equivalent to about half the predicted full effect on log P, though we have no means of knowing whether a full bond has been weakened by one-half, a half-strength bond has wholly disappeared, or the truth lies in between.

Important further evidence comes from log P for **1j** and **1k**. The former could not be included in the regression since elision of two hydrogen atoms necessarily lowers log P. As between hexane and cyclohexane, Δ log $P = -0.44$;[26] Δ log $P = -0.37$ between **1i** and **1j** is in line with this. Calculation for the piperidyl derivative **1k** is more complex. We start from the model amides **14** and **15**, for which log P may be reliably calculated[26]



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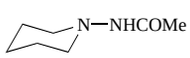
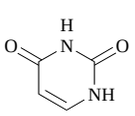


15

as 0.95 for **14**, and has been measured[18] as −0.05 for **15**. Applying the difference to log P for **1j**, that for **1k** calculates as log P *ca.* 0.6; the measured value is 2.33 (Table 1).

We believe the explanation to lie in a major shift in conformation between **1j** and **1k**. For **1j**, the conformation shown in Scheme 2 as **III** is that which best 'tucks away' the cyclohexyl moiety (or any other) in such a way as to maximise the dispersion interaction with methyl while also allowing maximum access of water to the hydrophilic portions of the molecule. However, the same conformation for **1k**, as **IV**, leads to a severe lone pair clash between hydrazine nitrogen and that of the ring. This can be relieved by the reversal in conformation shown as **V**, but only at the cost of shielding both lone pairs. We may calculate this cost in terms of log P. Uracil **16** and 5-azauracil **17** possess[26] log $P = -1.05$ (average) and −1.87 respectively; if



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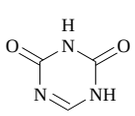


17

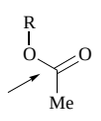
this difference, Δ log P −0.82, is attributed to aza-nitrogen, its subtraction from the above estimate leads to a new calculated value for **1k** of log P *ca.* 1.4. The difference remaining, of Δ log P *ca.* 0.9, is similar to that between **14** and **15** and provides evidence that the hydrazine nitrogen atom is also shielded from the solvent. An alternative possibility which may better accommodate the kinetic results (see later) is the variant on **II** shown as **VI**; with, in each case, one carbonyl and no nitrogen lone pairs accessible to the solvent, a similar effect on log P might be expected. If **V** or **VI** belongs uniquely to **1k**, then it seems probable that **III** or something closely approaching it applies in all other cases, allowing for a variable, but perhaps never very great, departure from planarity.

Leaving aside till later the precise mechanism of hydrolysis for the neutral species, its variation with structure may be considered in this light. Available data are assembled in Table 4. Use of the same three parameters employed for log P leads to eqn. (3) where k_B is expressed in units of 10^5 s^{-1} and the

$$\log k_B = 0.05(0.04) + 0.09(0.02)C - 0.36(0.05)\alpha - 0.29(0.06)\beta \quad (3)$$
$$(n = 6,\ r^2 = 0.964,\ s = 0.04,\ F = 18)$$

above exclusions continue to apply. This is not a very good equation but the best we can find, and far better than that in the single parameter E_s,[27] for which $r^2 = 0.22$. According to eqn. (3), α- and β-branching both slow the rate about twofold, whereas chain length has little effect. We consider k_B for **1k** later.

The steric hindrance parameter E_s was derived from the hydrolysis of esters, and strictly applies only to the acyl group; there is little evidence as to whether it holds even for the alkyl moiety. Tertiary amides are necessarily different. The cases compare as **18** and **19**. Baldwin[28] has pointed out that, in



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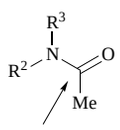
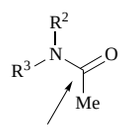


19a



19b

amides, the expected trajectory of the approaching nucleophile lies close to the acyl moiety as shown, and not bisecting the angle, the result of considerable double bond character in the nominal C–N linkage. So less variation in rate might be expected here than for the defining reaction, hence the much below unity coefficients in eqn. (3); and the structural factors behind that variation could also be different.

We believe the variation in rate for k_B (and k_C) depends on 'entropic strain';[29] the 'steric hindrance of motions'[30] term RT ln ($IIQ^{\ddagger}$) described by Taft as the entropic component in E_s. Neither k_B nor k_C in fact correlates with this, any more than with the global term E_s itself, but that is understandable given the stereochemistry of **19**. Any alkyl substituent R^2 sweeps out a volume which in part will be constricted by solvational freezing in the highly structured transition state (*vide infra*). The degree of this constriction will depend on distance from the reaction centre, so that only the first few carbon atoms matter, and branching has more effect than linearity. The equal weight carried by α- and β-branching is just what would be expected if all alkyl groups, not only cyclohexyl, are constrained into roughly the conformation shown as **III**. This will help to explain the very similar rates (Table 4) for R^2 = isopropyl ($E_s = -0.47$) and cyclohexyl ($E_s = -0.79$), and also why no special penalty attaches to the bulky isobutyl substituent ($E_s = -0.93$), since if full rotation is not possible, its γ-carbon atom can restrict attack at only one face. If conformer **V** or **VI** dominates for **1k**, its tenfold faster reaction rate than that of **1j** becomes understandable.

Conformation in the anion

No intramolecular hydrogen bond is possible in the anion, while heavy solvation of the anionic charge, plus the inability of the amide moiety to share it, both militate strongly against planarity. The dominant conformation may not be fully orthogonal (θ_1 *ca.* 90°) but will certainly be such that no special conformation for **1k** is now required. It will be seen (Table 4) that k_C for **1k** (*cf.* k_B) is now quite normal.

On the same lines as eqn. (3), eqn. (4) for k_C may be formu-

Table 4 Values of k_B and k_C of some triazinediones

	R^1	R^2	$-E_s$ [a]	At 72 °C $k_B/10^{-5}$ s^{-1}	At 72 °C $k_C/10^{-5}$ s^{-1}	At 62 °C $k_C/10^{-6}$ s^{-1}
1a	Pr^i	Me	0.00	1.4 [b]	2.0 [b]	8.4 [b]
1c	Pr^i	Pr^n	0.36	1.93	3.05	
1d	Pr^i	Pr^i	0.47	0.89 [b]	0.33 [b]	1.38 [b]
1j	Pr^i	Cyclohexyl	0.79	0.932	0.703	
1k	Pr^i	1-Piperidyl	*c*	9.78	1.01	
1f	Pr^i	Bu^i	0.93	1.28	1.61	
1e	Pr^i	Bu^s	1.13	1.02 [b]	0.407 [b]	1.55 [b]
1g	Pr^i	$CHEt_2$	1.98	1.45 [b]	0.537 [b]	1.88 [b]
1o	C_6H_4-4-Me	Bu^n	0.39			13.0
1p	C_6H_4-4-Me	Bu^i	0.93	2.40	2.04	8.8
1q	C_6H_4-4-Me	CH_2Bu^t	1.74		0.257	0.89

[a] Re-scaled to Me = 0 from the compilation of S. H. Unger and C. Hansch, *Prog. Phys. Org. Chem.*, 1976, **12**, 91. [b] Calculated from results at other temperatures. [c] Unknown; presumably similar to cyclohexyl.

$$\log k_C = 0.20(0.02) + 0.10(0.01)C - 0.97(0.02)\alpha - 0.38(0.02)\beta \quad (4)$$
$$(n = 6, r^2 = 0.999, s = 0.14, F = 1450)$$

lated. This differs from eqn. (3) in showing much greater sensitivity to α-substitution. The reason for this may lie in the much greater 'sweep volume' possible when the amide moiety is twisted out of plane, since relatively free rotation of R^2 is now permitted. This matters most for the α-branched substituents since these are the most rotund. The continued importance of both forms of branching, however, demonstrates that the carbonyl alignment shown for **I** still dominates, not that for **II**. This has important stereochemical implications for intramolecular catalysis (see later). A reversal in the amide conformation—*i.e.* **19b** replacing **19a**—would result in the triazine ring, as R^3, now lying in the path of the nucleophile, in which case the nature of R^2 would scarcely matter. This preference for **I** even when nonplanar is presumably due to solvational factors: the hydrophilic portions of ring and substituent can be serviced by a common solvation shell, while dispersion interactions can mutually stabilise methyl and R^2. There is a sense in which these two hydrophobic moieties form a single giant substituent. In the self-association of peptides in solution, it is known that like attracts like.[31]

$$\log (k_C/k_B) = 0.15 + 0.01C - 0.61\alpha - 0.09\beta \quad (5)$$

Subtraction of eqn. (3) from eqn. (4) gives eqn. (5). This shows what simple inspection of Table 4 will also reveal: that α-branching is the main factor in reducing k_C relative to k_B. These equations may be compared with eqn. (6) for pK_a; a very poor

$$pK_a = 5.17(0.14) - 0.01(0.04)C - 0.42(0.17)\alpha - 0.41(0.12)\beta \quad (6)$$
$$(n = 12, r^2 = 0.72, s = 0.21, F = 6.9)$$

equation, but the only one we can find. Given R^1 = alkyl, variation in pK_a can have nothing to do with electronic factors and, indeed, most closely reflects the same steric factors as k_B. To some extent the resemblance between eqns. (3) and (6) must be fortuitous, since their negative coefficients reflect different factors: steric hindrance to nucleophilic attack for k_B, weakening of the intramolecular hydrogen bond in the case of pK_a. Nevertheless, since pK_a reflects the difference in ΔG between neutral species and anion, this does seem to suggest that structural variation affects the free energy of the former much more. If indeed that of the ionised species is nearly a constant, this may reflect release of steric strain once the amide group is no longer constrained to be planar. Possibly therefore the angle of twist (θ_1) in the anion, whatever it may be, is substantially the same through the series. The kinetic consequences of this and other conclusions are explored below.

Kinetics and mechanism

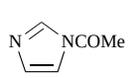
Amide hydrolysis typically shows a V-shaped rate–pH profile with roughly equal sensitivity to acid and alkali ($k_H \approx k_{OH}$).[32] At a pH low enough for full protonation of the substrate, a rate–pH plateau appears for water attack on the amide cation,[32] here designated k_A. Fortuitously, the actual values of k_H, k_A and k_D for **1d** closely resemble k_H,[32,33] k_A[32,33] and k_{OH}[32,34] for acetamide, though k_D differs from k_{OH} in involving hydroxide ion attack on the anion. Only activated amides show a 'water rate', *i.e.* a central rate–pH plateau that appears not to involve H^+ or OH^-, and this is always accompanied by much greater sensitivity to alkali; for acetylimidazole **20**,[35–37] k_{OH} is of the order of 10^7 times greater than for acetamide.

The acetyltriazinediones **1** are possibly unique in showing two such 'water rates', k_B and k_C (Fig. 1), and this despite their evident lack of activation. These rate plateaux correspond to nominal water attack on neutral species and anion respectively; $pK_{II} = 4.69$ at 100 °C for **1d** (Table 2) corresponds closely enough to $pK_{a2} = 4.53$ at 25 °C (Table 1) to demonstrate their identity. However, the large attenuation that might be expected for k_C relative to k_B is absent (Fig. 1 and Table 4). And, while the ring-methylated derivative **3d** behaves similarly to **1d** at pH < **5**, it too shows an apparent $pK_{II} = 4.75$, which here relates to no change in its UV spectrum and no possible ionisation process.

There are, therefore, unexpected features in the kinetics of this reaction that point to mechanistic complexities of an unusual sort. In the following sections we attempt to unravel them. Some data useful for the purpose of cross-comparison are assembled in Table 5.

The rate plateau in acid: k_A

The amino heterocycle **2** bears some structural resemblance to the leaving groups of the acylazoles **20**–**22** studied by Jencks



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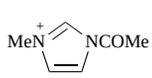

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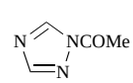


22

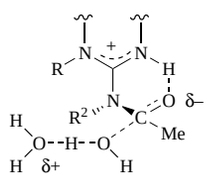
and co-workers,[35–38] so that mechanistic parallels might be anticipated. The near-equivalence in hydrolysis rate of **21**,[36] and of **20** as its cation,[35,37] was used to demonstrate that the observed general base (GB) catalysis involves partial proton

Table 5 Microscopic rate constants ($dm^3\ mol^{-1}\ s^{-1}$) calculated for 25 °C

Constant	Status	**1d**	**3d**	**1e**	**1p**	**20**[a]	**21**[b]	**22**[c]
k_H	$[A][H^+]$	5.5×10^{-6}		4.1×10^{-6}	1.5×10^{-5}			
$k_1 = k_A/[H_2O]$	$[HA^+][H_2O]$	5.3×10^{-7}				6.8×10^{-4}[d]	8.4×10^{-4}	6.8×10^{-3}
$k_2 = k_B/[H_2O]$	$[A][H_2O]$	9.6×10^{-10}		6.3×10^{-10}	2.8×10^{-9}	1.8×10^{-6}[e]		3.1×10^{-5}
$k_2' = k_B K_{a1}/K_w$	$[HA^+][OH^-]$	4.5×10^{7}		3.5×10^{7}	7.4×10^{10}	1.2×10^{6}	1.5×10^{5}	2.6×10^{11}
$k_2' = k_B K_{a1}/K_w$	$[HA^+][OH^-]$[f]	6.3×10^{8}	6.0×10^{8}		1.5×10^{12}[g]			
$k_3 = k_C/[H_2O]$	$[A^-][H_2O]$	6.3×10^{-10}	—	3.8×10^{-10}	3.5×10^{-9}			
$k_3' = k_C K_{a2}/K_w$	$[A][OH^-]$	1×10^{2}		48	1.5×10^{3}			
$k_{OH} = k_D$	$[A][OH^-]$		5.8×10^{-2}			2.7×10^{2}[h]		2.7×10^{3}
k_D	$[A^-][OH^-]$	9.1×10^{-6}			8.1×10^{-4}			

[a] Ref. 37 (I = 1.0 mol dm^{-3}). [b] Ref. 36 (I = 0.2 mol dm^{-3}). [c] Ref. 38 (I = 1.0 mol dm^{-3}). [d] $k = 8.4 \times 10^{-4}$ at I = 0.2 mol dm^{-3} (ref. 35). [e] $k = 1.5 \times 10^{-6}$ at I = 0.2 mol dm^{-3} (ref. 35). [f] At 100 °C. [g] Assumes pK_{a1} unchanged at 100 °C. [h] $k = 3.2 \times 10^{2}$ $dm^3\ mol^{-1}\ s^{-1}$ at I = 0.2 mol dm^{-3} (ref. 35).

removal from water as nucleophile, not from the imidazolium cation.[37b] Values of $\beta_{cat} = 0.34$ for the hydrolysis of **20** cation,[37a] and of β_{lg} *ca.* −0.35 for **20** and **22** as neutral and cationic species,[38] point to an early, nearly symmetrical transition state for addition of nucleophile, with most of the cationic charge still on the leaving group. The equivalent transition state in the present case may be written as **23** and, again, will explain the near-equivalence of k_A (Table 2) for **1d** (**23**, R = H) and **3d** (**23**, R = Me).



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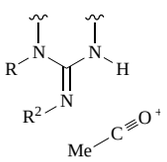

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Jencks and Carriuolo[35] rejected the alternative A1 fission of **20** cation (*cf.* **24**) on a number of grounds which included the very large negative ionic strength effect and $\Delta S^{\ddagger} = -30.2$ cal $mol^{-1}\ K^{-1}$. For **1d**, $\Delta S = -13.1$ kcal $mol^{-1}\ K^{-1}$ while a rate increase of *ca.* 45% between I = 1.0 and I = 5.0 mol dm^{-3} (*ca.* 10% for **3d**) compares with a 16-fold fall for **20** cation between I = 0.2 and I = 4.8 mol dm^{-3}. Nevertheless, we believe that **23** continues to represent the transition state. Most of the charge in **21** or **20** cation will be concentrated on the distal nitrogen atom, whose charge density will then fall sharply in the transition state as the remaining charge spreads itself over both nitrogen atoms. Here, with an extra nitrogen atom to share the charge, an already low charge density will be relatively little affected at the small degree of C–N bond fission likely to be attained.

Second-order rate constants for the attack of water on **1d**, **20**, **22** and their cations (k_1 and k_2 of Table 5) are shown in Fig. 2 as a function of pK_{lg}. Following Fox and Jencks,[38] pK_{lg} for **22** cation is taken as that of the disfavoured tautomer, pK_a *ca.* 3.6, while $pK_a = 4.9$ is similarly adopted for **1d** (*cf.* **2B′** in Scheme 1). As stated,[38] β_{lg} *ca.* −0.35 is found for imidazole and triazole. The results for **1d** fall below this line at a separation of approaching 10^4. Gravitz and Jencks[39] have demonstrated that imidazole is a poorer leaving group by a factor of *ca.* 10^4 relative to a 'point-charge' amine of equal pK_a. This further drop in rate by a similar margin when three nitrogens are available to share the charge reinforces their argument, and explains why the triazinediones are far less susceptible to acid or alkaline hydrolysis than the electronegativity of the ring might have suggested.

A planar conformation with carbonyl locked tightly into an intramolecular hydrogen bond is almost obligatory for the cation **1A** (Scheme 1), and little difference is expected for **23** if, as suggested above, the three nitrogen atoms are well conjugated. Even for **3d** (**23**, R = Me) this state of affairs may not be greatly affected. Intramolecular general acid (GA) catalysis is therefore a possibility. However, while as seen above this hydrogen bond

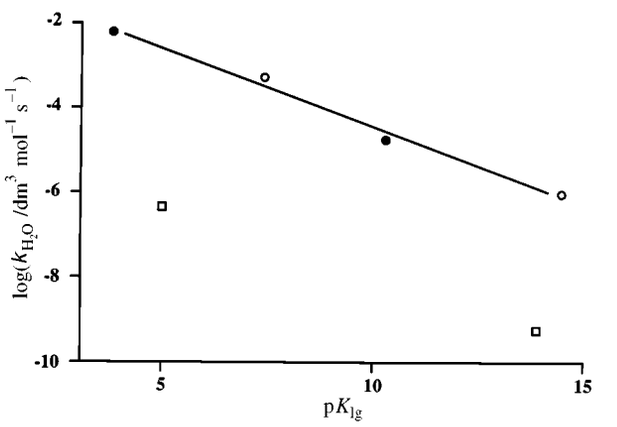
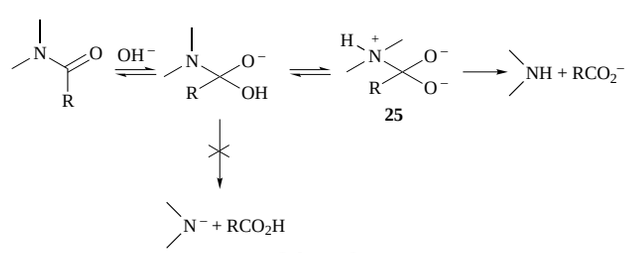


Fig. 2 Hydrolysis rate at 25 °C for the cationic and neutral forms of **20**, open circles; **22**, filled circles; and **1d**, squares

is probably still present in the neutral species **1B**, no such bond is possible for **3d**, yet k_A and k_B are little changed (Fig. 1). So this hydrogen bond has no kinetic consequences. Jencks and co-workers[37] have demonstrated that GA catalysis by partial proton transfer to carbonyl in the hydrolysis of **20** does not occur. Others[40,41] have noted its inefficiency in this context, the reason being that it will tend to stabilise reactant ($\rightharpoonup C{=}O \cdots HN^+$) and transition state ($\geqslant C{-}O^- \cdots HN^+$) to much the same extent. Hence intramolecular GA catalysis in series **1** is likely to be minimal.

The reaction of 1d and 3d with hydroxide ion: k_D

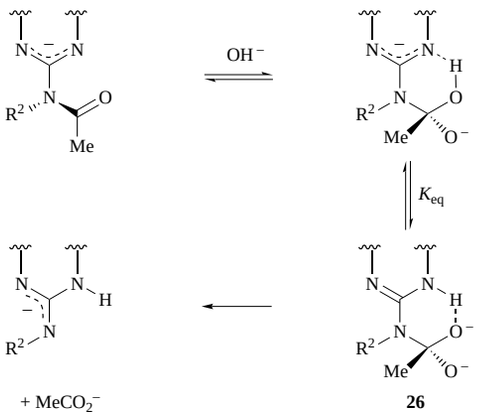
The generally accepted mechanism of alkali-catalysed amide hydrolysis is shown as Scheme 3. The anions of simple amines



Scheme 3

are very poor leaving groups and require prior protonation;[42] a proton switch to give **25** as the crucial intermediate was first suggested by Bender and Thomas.[43] However, since imidazole and 1,2,4-triazole possess acid pK_a values (14.2 and 10.1, respectively)[38] of the same order as alcohols, these are exceptions to the rule, and are able to leave as their anions. The same should be true of series **1** and **3d**, given pK_a *ca.* 13.7 for the disfavoured tautomer **2C′** (Scheme 1) which is the actual leaving group. It is notable that k_{OH} for **3d** is almost 5000 times less than that for **20**[37] (Table 5) despite its very similar pK_{lg}, so that the cationic (see above) and anionic forms of the acyltriazinediones appear to show about the same gain in stability.

A similar mechanism for hydroxide ion attack on the anion of **1** would require that **2** depart as its dianion. This can be avoided by a mechanism (Scheme 4) analogous to that of



Scheme 4

Scheme 3. Evidence of this route for **1d** comes from the slowing of this reaction, by *ca.* 20%, in 50% aqueous methanol; everywhere else in the rate–pH profile, methanol accelerates the rate (see below). Formation of the dianion **26** (or **25**) is specific to water. Relative to **3d**, k_D is lower by *ca.* 6.4×10^3. This margin is much greater than the *ca.* 10^2 that is normal for the effect of a negative charge in otherwise comparable systems[44] and in part reflects the reduced efficiency entailed in the need for an extra reaction step; using our recent methodology,[45] for the proton switch step of Scheme 4 we estimate K_{eq} *ca.* 10^{-5}. Necessarily, the transition state for **1d** is much later than that for **3d**. Nevertheless, despite the unit difference in charge between them, their $\Delta S^{\ddagger}$ values are similar, and not abnormally negative (Table 2); most of the difference in rate is contained in $\Delta H^{\ddagger}$, presumably reflecting the electron deficiency at the carbonyl. Possibly the strong intramolecular hydrogen bond expected for **26** acts as a form of internal solvation. Consistently with this theory, a rise in ionic strength for **1d** from $I = 1.0$ to $I = 5.0$ mol dm^{-3} increases k_D by only *ca.* 60%, an acceleration scarcely more than that found by Jencks and co-workers[35,37] for the monoanionic process involved in the alkaline hydrolysis of **20**.

The 'water rates' k_B and k_C: kinetic ambiguity

Before the question of catalysis in the middle pH region can be addressed, we have to establish the nature of the reactive subspecies. While k_B and k_C nominally represent attack of water on neutral and anionic substrates respectively, each is capable of another interpretation, as attack of OH^- on cation or neutral molecule. These alternatives, as k_2 or k_2' for k_B and as k_3 or k_3' for k_C, are set out in Table 5 for some triazinediones and reference compounds. We shall restrict discussion so far as the data allow to 25 °C and $I = 1.0$ mol dm^{-3}, so as to permit the most level comparison possible.

Wolfenden and Jencks[36] interpret the 'water rate' for the hydrolysis of acetylimidazole **20** in the following way. Recalculated from [A][H_2O] to [AH^+][OH^-], $k_2' = 1.2 \times 10^6$ dm^3 mol^{-1} s^{-1}. This compares with an observed $k_2' = 1.5 \times 10^5$ dm^3 mol^{-1} s^{-1} for the cation **21**. If **21** is a good model for **20** cation, as on a number of criteria it seems to be,[35–37] then hydrolysis of neutral **20** is substantially faster than attack of OH^- on its cation would permit; hence the 'water rate' is largely what it claims to be.

Such a simple and elegant demonstration is not possible for **1d**. However, Bruice and Holmquist[46] have derived eqn. (7) for

$$\log k_{OH} = 0.84 \log k_O + 8.0 \qquad (7)$$

the relation between the second-order rate constants for water (k_O) and hydroxide ion (k_{OH}) attack on esters, which if valid here, allows an alternative approach. Applied to **20** it leads to a predicted $k_2' = 2.2 \times 10^5$ dm^3 mol^{-1} s^{-1}, not far from the value for **21** quoted above. Applied to **1d**, $k_2' = 535$ dm^3 mol^{-1} s^{-1} results. That required to account for k_B is $k_2' = 4.5 \times 10^7$ dm^3 mol^{-1} s^{-1}, which decisively rebuts the cationic rate alternative. Even more decisively, for **1p**, re-interpretation of k_2 as attack by OH^- gives $k_2' = 7.4 \times 10^{10}$ dm^3 mol^{-1} s^{-1} which lies beyond the encounter rate limit, the result of this compound's very low basic pK_a. A similar calculation for the acetyltriazole **22** would give $k_2' = 2.6 \times 10^{11}$ dm^3 mol^{-1} s^{-1}, with similar mechanistic consequences.

The interpretation of k_C for **1d** may be addressed directly. Replacement of k_3 for [A^-][H_2O] by k_3' for [A][OH^-] gives $k_3' = 1.0 \times 10^2$ dm^3 mol^{-1} s^{-1}, but the actual k_{OH} value for **3d**, which cannot ionise, is 5.8×10^{-2} dm^3 mol^{-1} s^{-1}, so falls short of the required rate by a factor of *ca.* 1700. Hence k_C also is what it appears to be. Applied to the calculation of k_{OH} from k_O for **20** and **22**, where intramolecular catalysis is unlikely, eqn. (7) gives results that fall short of the actual value by factors of 5.5 and 5.9, respectively; quite possibly therefore, a small adaptation of this equation would allow its generalisation from esters to activated amides, and perhaps to amides generally.

The extent of intramolecular catalysis

Perhaps the most surprising feature of these rate–pH profiles (*cf.* Fig. 1) is the very small effect of anion formation on k_C relative to k_B (Table 4), bearing in mind the deactivation that might have been anticipated. It is difficult to quantify this discrepancy. One possible approach starts from the use of eqn. (7) in reverse. For **1d**, k_D is not as it stands a reasonable model for k_{OH}, since electrostatic repulsion must depress the rate and perturbations may also be introduced by the special mechanism of Scheme 4. Correcting for the first using the factor of *ca.* 10^2 noted above[44] gives k_{OH} *ca.* 10^{-3} dm^3 mol^{-1} s^{-1}, leading to an 'expected' (uncatalysed) k_3' *ca.* 10^{-13} dm^3 mol^{-1} s^{-1}. This falls short of the observed k_3' (Table 5) by *ca.* 6×10^3. A similar calculation for aspirin, starting from $k_{OH} = 0.11$ dm^3 mol^{-1} s^{-1} at 25 °C,[47] leads to k_O *ca.* 2.2×10^{-11} dm^3 mol^{-1} s^{-1}; given an observed plateau rate of *ca.* 3.7×10^{-6} s^{-1},[47] which translates to k_3' *ca.* 6.7×10^{-8} dm^3 mol^{-1} s^{-1}, a rate enhancement of *ca.* 3×10^3 results. Even if this calculation somewhat exaggerates the true rate enhancement for the triazinediones, their k_C values may still compare with aspirin in the degree of intramolecular GB catalysis they show, a point very relevant to our interest in them.§

From $k_{OH} = 5.8 \times 10^{-2}$ dm^3 mol^{-1} s^{-1} for **3d**, eqn. (7) gives k_O *ca.* 1.0×10^{-11} dm^3 mol^{-1} s^{-1}. Since **1d** and **3d** possess virtually identical k_B values, this prediction for the uncatalysed rate may be transposed to **1d**. Hence the extent of catalysis for $k_B = k_2/k_O \leqslant 10^2$, a notably smaller enhancement than that for k_C. This combination of rate enhancements of $\leqslant 10^2$ for k_B, $\geqslant 10^3$ for k_C, and electrostatic repulsion of the order of 10^2 for the latter, will explain why k_B and k_C are in practice so similar, with $k_B > k_C$ common but not universal (Table 4).

The nature of intramolecular catalysis

Part of the evidence for intramolecular GB catalysis in aspirin hydrolysis comes from the effect of aqueous alcohols on the plateau rate. In 50% aqueous alcohols, Fersht and Kirby[49] found rate accelerations in the order MeOH > EtOH > Pr^iOH > Bu^tOH, and we find similarly for the triazinediones (Table 6). The rationale for this phenomenon lies in the known[50,51] nonlinear relation, for highly basic alkoxides, between basicity and

§ These rate enhancements are not of course EMs, which measure intramolecular *vs.* intermolecular catalytic efficiency; that for aspirin is only *ca.* 13.[48] Nevertheless, they are of interest as very visible evidence of intramolecular catalysis relative to no catalysis at all. The present reaction does not show catalysis by those external buffers studied at concentrations of the order of 10^{-2} mol dm^{-3}.

Table 6 Rate enhancements in 50% aqueous alcohol[a]

	R^1	R^2	pK_a	k	r MeOH	EtOH	Pr^iOH	Bu^tOH	T/°C
1a	Pr^i	Me	5.60	k_C	49	8.5	1.4	0.6	62
1d	Pr^i	Pr^i	−0.95	k_A	3.7				37
	Pr^i	Pr^i	4.53	k_C	53	11.6	1.8		76
	Pr^i	Pr^i		k_D	0.8				37
1f	Pr^i	Bu^i	4.72	k_C	49	8.5	1.4	0.6	76
1j	Pr^i	Cyclohexyl	4.38	k_C	32	10.6	1.2		76
1k	Pr^i	1-Piperidyl	5.26	k_C	20	4.2	1.6	1.2	76
1o	C_6H_4-*p*-Me	Bu^n	4.46	k_C	46	10	1.6		62
1p	C_6H_4-*p*-Me	Bu^i	−3.67	k_H	3.0				37
	C_6H_4-*p*-Me	Bu^i		k_B	12.5	4.3	2.1		62
	C_6H_4-*p*-Me	Bu^i	4.11	k_C	50	8.4	1.4	0.6	62
1q	C_6H_4-*p*-Me	CH_2Bu^t	3.61	k_C	40	8.2	1.3		76
Aspirin[b]			3.59	k_C	10.2	3.5	2.3	0.8	39
p-Nitrobenzoyl chloride[c]				k_B	2.6	1.4			25

[a] Reaction at temperature T/ °C specified; for definition of r, see eqn. (8). [b] Ref. 49. [c] Ref. 52.

nucleophilicity towards carbonyl: the latter, while much greater than for hydroxide, is not far from constant at $pK_{nuc} > 13$,[50a] and this 'break-point' is little affected by pK_{lg}.[50b] Hence, at constant pH (or, as here, at constant catalyst pK_a), reactivity is largely a function of $[OR^-]$ and does not cancel exactly against this as would happen for $\beta_{nuc} = 1.0$. This almost level nucleophilicity has been attributed to the heavy solvation of these very basic, point-charge anions, which will also explain why OH^- is still less reactive.[51] It is not known, however, how Pr^iO^- or Bu^tO^- compare in this respect, and whether steric hindrance or solvational differences come into play.

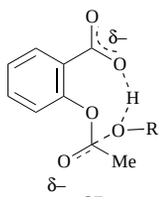
In order to calibrate these results, it would help to be able to quote neutral uncatalysed rates for the attack of aqueous alcohols at carbonyl. Information on this topic is sparse. Bentley and Jones[52] have studied the neutral hydrolysis in aqueous methanol and aqueous ethanol of 4-nitrobenzoyl chloride, whose solvolysis follows exclusively the addition–elimination pathway so is pertinent here. In each solvent, the dominant process is water-catalysed addition of alcohol; overall acceleration in 50% methanol and 50% ethanol is 2.6- and 1.4-fold respectively [r of eqn. (8)]. This compares with corresponding

$$r = k_{50\%\ ROH}/k_{water} \qquad (8)$$

ratios of 10.2 and 3.5 for aspirin,[49] consistent with the incursion there of intramolecular GB catalysis. There are few data for other alcohols, and none in water. In the direct reaction of ROH with $MeCO_2Me$, the reactivity ratio for R = Me, Et and Pr^i is about 3:2:1,[53] while the same three alcohols span a reactivity range of about two in their reaction, as cyclic trimers, with *p*-chloroisocyanate in diethyl ether.[54] Except possibly for *tert*-butyl alcohol, on which there is no information, it therefore seems improbable that steric factors are of compelling importance.

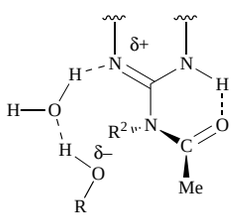
The r-factors of 3.7 on k_A for **1d** in 50% aqueous methanol, and of 3.0 on k_H for **1p** (Table 6), coming close as they do to $r = 2.6$ as reported by Bentley and Jones,[52] provide further evidence for the absence of intramolecular GA catalysis in the cation and, by implication, in the neutral species also. As noted above, the near-identical k_B values for **1d** and **3d** show that the intramolecular hydrogen bond of which series **1** is capable, and which we show above probably persists in water, has no catalytic consequences. (It may have structural consequences; see below.) Hence the rate enhancement shown by k_B for **1p**, and which possesses a sensitivity to aqueous alcohol comparable to aspirin (Table 6), must result from general base catalysis. This is a remarkable achievement for a base of $pK_a < 0$. It is further compounded by the probable stereochemistry of the process.

The stereochemistry of aspirin is almost ideal for incorporating one molecule of solvent in a transition state which may be



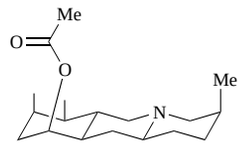
27

approximated as **27**.[49] This is written to imply partial bond formation and little or no bond fission, as is normal for ester hydrolysis.[41,50,55] If r is some guide to the relative extent of C–O bond formation, then k_B for **1p** is comparable in this respect to aspirin, whereas k_C throughout implies considerably more. Yet this result is achieved, as it were, by remote control; at least for k_B, a single solvent molecule cannot be involved. Structure **28**



28

shows the smallest feasible solvent bridge for the neutral species and is drawn just prior to attack, without prejudice to the timing of the transition state. There are precedents of a sort. Neutral ester hydrolysis is thought to involve two water molecules;[41] that of neutral **20** is supposed to go the same way;[37b] while Engberts and co-workers[56] provide evidence for a similar process in the hydrolysis of an acyltriazole related to **22**. However, none of these involve the steric constraints dictated by an intramolecular process. A multiple solvent bridge must cer-



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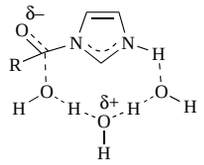

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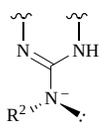

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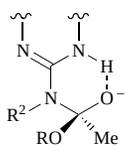


32

tainly be involved in the intramolecular GB catalysed methanolysis, in methanol, of **29**,[57] while the structure shown as **30** is considered by Fife *et al.*[58] to account for the almost zero effect of substituents on acetylimidazole's neutral hydrolysis rate. The concerted solvolysis of *p*-chloroisocyanate by an alcohol trimer[54] takes place in an otherwise aprotic solvent where this is not difficult to envisage.

The purpose of GB catalysis in the addition of water or an alcohol to carbonyl is to avoid the production of an intermediate whose very low pK_a value, of <-2, would make it too unstable to exist.[59] Full or partial removal of a proton by the catalyst converts the nucleophile all or part of the way to a species of p$K_a > 15$ which will give rise to no such problem. Hence the catalyst must possess a pK_a value somewhere between these extremes.[59] The carboxylate group of aspirin, p$K_a = 3.59$,[41] falls in this range, as do the triazinedione anions, pK_a 3.6–5.6, as relevant to k_C. However, it is difficult on the face of it to see how efficient catalysis can result for the neutral species (k_B) given p$K_{cat} < 0$, especially with the stereochemical constraints described above. It is impossible to understand it for **1p**, pK_{cat} −3.67,¶ where proton removal by water should be more efficient than that by the 'catalyst', yet where catalysis seems in practice to be of similar efficiency to that in aspirin.

We believe the explanation, at least for k_B, to lie in a structural feature of the triazinediones for which we are aware of no precedent. Here the catalyst is not merely part of the substrate, as for aspirin, but part of the conjugated unit which comprises the leaving group itself. As the leaving group starts to leave, pK_{cat} also and of necessity changes with it: from a value, for **1d**, of −0.95, towards a limiting value of perhaps *ca.* 5‖ (*cf.* structure **2B**′). Somewhere between these limits, according to the degree of C–N bond breaking in the transition state, lies the effective pK_a value of the catalyst. That is, pK_{cat} will tend to rise towards pK_{lg} as the addition step proceeds; a prime example of the principle that 'catalysis occurs where it is most needed'.[59a] For aspirin, in contrast, p$K_a = 3.69$ becomes p$K_a = 3.02$ in the product salicylic acid, a change actually in the opposite direction. We may possibly represent the transition state for k_B as resembling that for k_A in that C–N bond breaking is more or less in line with C–O bond formation, but differing from it in that both steps are much more advanced, as is necessary if catalysis is to be efficient enough to overcome the stereochemical problems discussed above. A transition state involving a high degree of C–N bond breaking accompanied by an equally high degree of C–O bond formation, the latter but not the former signalled by *r*, might explain why *r* for k_B is so very similar to that for aspirin.

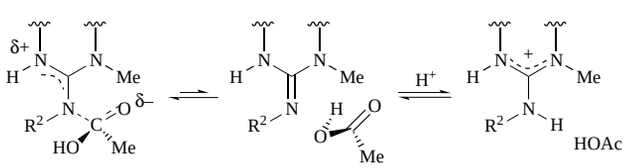
As seen above, the anomalously fast k_B for **1k** may be explained in terms of conformer **VI**; here twisting of the acyl moiety might allow a transition state analogous to **27**. While the alternative conformer **V** would remove the steric hindrance present in **III** or **IV**, it is difficult to see how intramolecular catalysis could survive shielding of the nitrogen lone pair. An alternative explanation in terms of the 'α-effect'[60] is discounted because this does not seem to enhance leaving group ability,[39] and since no such increase in rate is found for k_C.

The anion **1C** (Scheme 1) lacks the intramolecular hydrogen bond of **1A** or **1B**, and in addition, electrostatic repulsion may produce a high degree of twist ($\theta_1 \gg 0$ in Scheme 2); *cf.* above discussion of eqn. (4). If the synchronous mechanism adduced for k_B were to prevail, then by the principle of least motion,[61] the amine anion at its moment of departure would have to adopt a conformation approaching that of **31**. This represents an unconjugated, point-charge anion of high charge density, which probably could not leave at all except *via* the mechanism of Scheme 3; a route ruled out by the accelerating effect on k_C of alcohols, as discussed above in connection with k_D. MO calculation at the 3-21G level of refinement suggests θ_1 *ca.* 78° in the (unsolvated) anion **1C** which, as water adds to carbonyl, falls towards θ_1 *ca.* 26° even for $R^2 = Bu^t$ with concomitant transfer of a proton to ring nitrogen. Exocyclic nitrogen remains almost trigonal, implying minimal C–N bond fission. This progressive collapse in dihedral angle suggests the possibility that, for k_C, only a single water (or alcohol) molecule may be required as a bridge; *i.e.* as for aspirin **27** and *contra* **28** (k_B). If so this helps to explain why, allowing for electrostatic repulsion, catalysis is more efficient in k_C than in k_B, as noted above. While tetrahedral intermediates tend to present as potential minima in calculations of this sort,[62] whether or not the transition state in solution is approximated by T^-, the much increased *r* value for k_C relative to k_B also provides evidence that C–O bond formation is essentially complete. (There is one exception: the appreciably lower value of *r* for **1k** than that found elsewhere may reflect some repulsion between the nitrogen lone pair of the 1-piperidyl substituent and the attacking reagent.) This fully formed T^- can then rotate to give the favourable, near-planar conformation **32**, after which rate-limiting loss of **2C**′ follows. Interestingly, and despite the longer solvent bridge for k_B, $\Delta S^{\ddagger}$ on our limited evidence is always more negative for k_C: −19.0 and −28.2 cal mol^{-1} K^{-1} respectively for **1d**, −26.7 and −31.6 cal mol^{-1} K^{-1} for **1p**. This again implies a late transition state for k_C, in which electrostriction of the solvent by the anionic charge can exert its maximum effect.

The hydrolysis of 3d: further light on k_B

An unexpected feature of this reaction was the discovery of an inflection in the rate–pH profile for **3d** at a position almost identical to that for **1d** (pK_{II} of Table 2). Yet **3d** cannot ionise, so that this must represent some change in rate-determining step. The problem is two-fold: what the nature of this step may be; and whether, or how far, it may affect the interpretation we have placed on the break-point between k_B and k_C for **1d** and its analogues.

Our postulate for **3d**** is sketched in Scheme 5, which starts



33 **34** **35**

Scheme 5

from **33**, the transition state for k_B delineated above. Fission of **33** as shown in **34** will generate the tautomerically disfavoured amine **2B**′ (*cf.* **24**), which if sufficiently nucleophilic, may simply recapture the acyl residue before it can diffuse away. Protonation of **2B**′ may be required for the reaction to proceed—though note that the fission step need not be very disfavoured to account for what is visible on Fig. 1. This process may be represented by eqn. (9), which gives rise to the steady-state eqn. (10). From eqn. (11), pK_{II} is composite of pK_{lg} and the rate constants

$$\mathbf{33} \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} \mathbf{34} \overset{H^+}{\rightleftharpoons} \mathbf{35} \xrightarrow{k_f} \text{Products} \qquad (9)$$

$$k = k_b k_f[H^+]/(k_f[H^+] + k_{-b}K_{lg}) \qquad (10)$$

$$pK_{II} = pK_{lg} + \log k_f/k_{-b} \qquad (11)$$

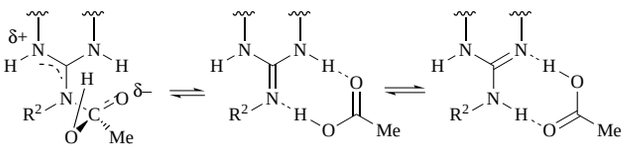
¶ If as postulated above this pK_a value involves *O*-protonation, the *N*-protonated species involved in catalysis must be a still weaker base.

‖ If C–N bond breaking were to precede N–H bond formation, this limit could lie even higher, but we see no reason why the former process should be fast enough for this to happen.

** We thank Professor M. I. Page for the germ of this idea.

k_{-b} and k_f, both of which are expected to be very fast. It is possible that, fortuitously, $pK_{II} \approx pK_{lg}$. There is also the curious circumstance that $pK_{II} \approx pK_a$ of acetic acid, so that at pH < pK_{II}, protonation of the leaving group might be accomplished by the acetic acid moiety of **34**. In view of this and other imponderables, we view it as profitless to extend the analysis. The net effect of Scheme 5 is that, at pH > pK_{II}, the transition state moves from **33** to some point beyond **35**, *i.e.* it now involves diffusion apart of the reagents, a not uncommon situation in reactions of this sort.[63]

The situation for **1d** (Scheme 6) is different in that the departing acyl group of **36** will be tightly bonded to NH. An equivalent conformation for **33** is precluded by the severe steric clash that would result between R^2 and ring N–Me. If this hydrogen bond can persist through the course of the C–N fission process, there is the opportunity for rotation of the acyl moiety to occur inside the solvation shell. This is shown as just beginning in **36** and could lead to the hydrogen bonded complex **37**. An energetically favourable double proton switch to **38** inside this complex could then generate the stable tautomer **2B**, pK_a *ca.* 1.7 and a much poorer nucleophile. This places **37** beyond the transition state and circumvents the problem posed by **34**.



36 **37** **38**

Scheme 6

Lacunae remain, one of them being that the transformations **36** ⟶ **38** cannot take place as shown if the reaction product is an ester, so that a similar phenomenon may exist for series **1** in aqueous alcohols. Our rate measurements were carried out at the centres of the rate–pH plateaux, so shed no light on this possibility. In view of this, our analysis has to be tentative.

Conclusions

The three plateau regions k_A to k_C form an interesting sequence in which T^+ (**23**), T^0 (**36**) and T^- (**32**) appear to involve successively increasing C–O bond formation, a reflection of increasing difficulty in expelling the amine leaving group, accompanied by an apparently irregular pattern of C–N bond fission: small, large, and probably nil, as the pH range is ascended. What this last reflects is conformation, tempered by the special consequences of a situation in which catalyst and leaving group, for k_B, progressively modify one another's behaviour. These conformational peculiarities add complexity to the mechanism but, by a fortunate exercise in serendipity, have helped to elucidate it. Overall, we know of no parallel for the maze of criss-crossing factors that this investigation has unearthed.

Nevertheless, we are left with a paradox. The analgesic behaviour of the triazinediones, and their effects on the gastric mucosa, take place at pH values which, if acyl transfer is involved, correspond to k_C and k_B respectively. Hence structural changes which favour k_C over k_B should increase their therapeutic ratio. Exactly the reverse is found: the α-branching which specifically inhibits k_C [eqn. (5)] has proved therapeutically desirable,[4] and all those compounds that came closest to clinical trial possessed this feature. Either therefore one biological response or both has nothing to do with acyl transfer, or some special feature attaches to one or other site of action that over-rides the behaviour expected in free solution. In the absence of a detailed biochemical picture, we forbear to speculate. 'Whereof one cannot speak, thereof one must be silent.'[64]

Acknowledgements

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