

Covalent Hydrates as Transient Species in Heterocyclic Rearrangements. Part I. The Ring Fission of Some *s*-Triazolopyrazines

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Hydrolysis of the *s*-triazolo[4,3-*a*]pyrazines (1) and (3) gives rise to pH profiles whose apparent pK_a ' values differ markedly from those measured. A steady-state treatment is derived for transient intermediates with a lifetime sufficient for them to exist as an equilibrium mixture of the possible ionic forms. In the general case, these 'apparent pK_a ' values represent no one actual pK_a value but, instead, various combinations of rate and protonation constants. The reaction mechanism is discussed and reasons are given for believing these transient intermediates to be covalent hydrates. In particular, this postulate leads to reasonable predictions concerning relative rate and equilibrium constants and the approximate pK_a values of the covalently hydrated species themselves. Qualitative evidence suggests that the acid-catalysed rearrangement of compound (1) to the imidazo[2,1-*c*]-*s*-triazole (5) is a general reaction of *s*-triazolo[4,3-*a*]pyrazines.

COVALENT hydration is a well recognised phenomenon in heterocyclic chemistry.^{1,2} It generally acts to reduce excessive electronegativity, so that cations are particularly susceptible to the process. However, while qualitative¹ and quantitative² aspects have been thoroughly explored,³ work has been confined entirely to reversible systems. This is even true of the ring-opening reaction which occasionally^{1,2} follows covalent hydration and whose detailed kinetics have been reported^{2,4} in a few cases; in the latter example, ring fission is reversible and kinetic analysis reveals no complications.

Many heterocyclic rearrangements probably involve the intervention of water at some stage. Typically, ring opening is followed by ring closure to an isomeric species, and the intermediate, known or hypothetical, incorporates one molecule of water more than the reactant. Often, if not always, the precursor to this intermediate may most plausibly be written as a covalent hydrate. One example is the rearrangement of the triazolo[4,3-*c*]pyrimidines to their [2,3-*c*]-isomers.⁵ This reaction is typical also in that, although indirect evidence was later⁶ obtained as to the probable nature of the intermediate in certain cases, none could ever be isolated.

¹ A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1.

² D. D. Perrin, *Adv. Heterocyclic Chem.*, 1965, **4**, 43.

³ For a review see A. Albert, *Angew. Chem. Internat. Edn.*, 1967, **6**, 919.

⁴ Y. Inoue and D. D. Perrin, *J. Chem. Soc.*, 1963, 2648.

⁵ G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 1963, 5642.

The recent discovery⁷ of bronchodilator activity in certain *s*-triazolo[4,3-*a*]pyrazines⁸ led us to study these compounds. When compound (1) is treated with acid the product⁹ is not the [2,3-*a*]-isomer as previously¹⁰ supposed, but 3-*n*-butyryl-6-methyl-1*H*-imidazo[2,1-*c*]-*s*-triazole (5), a member of a new class of compound. The intermediate (2) has been isolated and characterised.⁹ A kinetic study of the hydrolysis of compounds (1) and (3) to (2) has revealed complexities in the rate-pH profiles consistent with the intervention of transient charged species. If these species are covalent hydrates, this represents the first kinetic demonstration of their intermediacy in a heterocyclic rearrangement. We report here this kinetic evidence and also provide the experimental evidence missing from the earlier⁹ account. We also comment on the generality of the reaction.

RESULTS AND DISCUSSION

Equilibria.—Relevant pK_a values (Table 1) were obtained by u.v. spectrophotometry, using conventional¹¹ techniques; that of the dication of compound

⁶ J. A. Bee and F. L. Rose, *J. Chem. Soc. (C)*, 1966, 2031.

⁷ G. E. Davies, in preparation; J. Maguire and F. L. Rose, *B.P.* 1,146,770.

⁸ J. Maguire, D. Paton, and F. L. Rose, *J. Chem. Soc. (C)*, 1969, 1593.

⁹ F. L. Rose, G. J. Stacey, P. J. Taylor, and T. W. Thompson, *Chem. Comm.*, 1970, 1524.

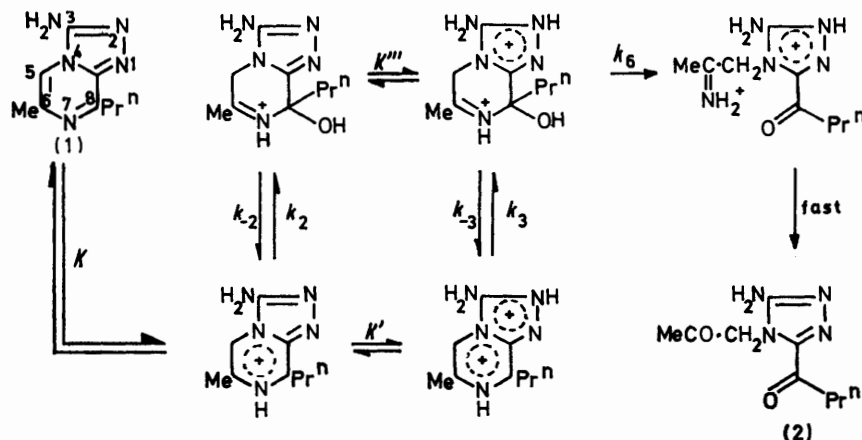
¹⁰ S. E. Mallett and F. L. Rose, *J. Chem. Soc. (C)*, 1966, 2038.

¹¹ A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962.

(1), which is relatively unstable even at 25°, was obtained by extrapolation of each reading to zero time. All values are reasonable and nothing in these or the associated u.v. data suggests covalent hydration as an equilibrium phenomenon. Since compound (1) can be diprotonated, its monocation could be formed by the protonation of either ring. No decision can be reached

related by a pH-independent equilibrium.¹² All that is affected is the precise significance of certain microscopic rate constants (see later), the numerical values of which are, in any case, inaccessible.

Kinetics.—The pH profiles were obtained at 60° in water using perchloric acid–sodium perchlorate at $I = 1.0$; subsidiary experiments at $I = 5.0$ using



SCHEME 1

Representation of the aromatic cations is schematic; all are resonance hybrids involving both rings.

on this on *a priori* grounds, but the u.v. spectrum of the monocation of compound (6) is sufficiently different from that of (1) [in fact it more resembles that of the free

perchloric acid–lithium perchlorate were conducted at high acidity. The H_0 values assumed at $I = 1.0$

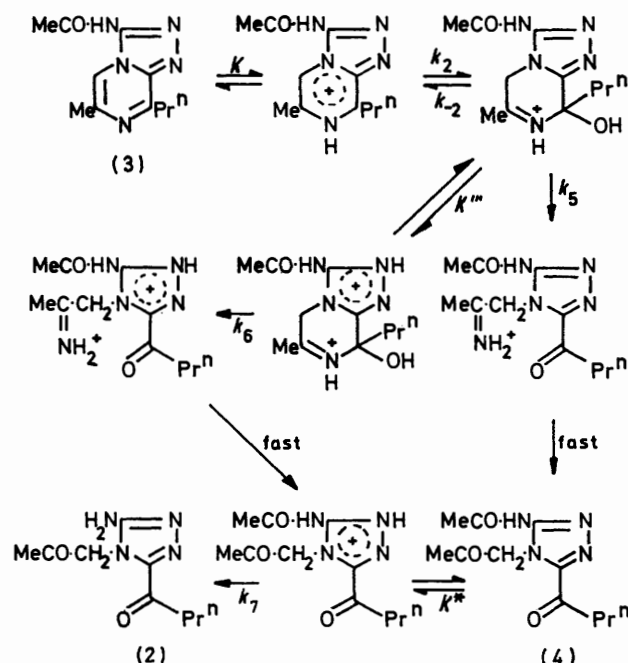
TABLE 1

pK_a and u.v. data (25°, $I = 0.01$) for dications (AH_2^{++}), monocations (AH^+), and neutral species (A)

Compd.	AH_2^{++}		AH^+		A
(1)	pK_a	—0.52		2.93	
	$\lambda_{\max.}$ nm	242, 274, 373	230, 290, 330	230, 265, 330	
	log ϵ	4.08, 3.49, 3.54	4.18, 3.45, 3.46	4.30, 3.43, 3.56	
(2)	pK_a			3.11	
	$\lambda_{\max.}$ nm		262	291	
	log ϵ		3.72	3.91	
(3)	pK_a			1.42	
	$\lambda_{\max.}$ nm		215, 280, 310	220, 305	
	log ϵ		4.40, 3.57, 3.54	4.30, 3.64	
(4)	pK_a			0.59	
	$\lambda_{\max.}$ nm		217, 242	304	
	log ϵ		4.01, 3.98	3.66	
(5)	pK_a			2.28	
	$\lambda_{\max.}$ nm		242, 281	259, 310	
	log ϵ		3.63, 3.68	3.64, 3.98	
(6)	pK_a				
	$\lambda_{\max.}$ nm		229, 254, 324		
	log ϵ		4.34, 3.36, 3.63		

base of (1)] to make a similar structure for the latter cation improbable. Protonation on the pyrazine ring is required by Scheme 1. Kinetically, the argument is irrelevant; all sub-species of the same charge must be

¹² I. Weil and J. C. Morris, *J. Amer. Chem. Soc.*, 1949, **71**, 1664.



SCHEME 2

See footnote to Scheme 1

pertain to perchloric acid alone,¹³ whereas those at $I = 5.0$ use the values of Day and Wyatt¹⁴ for $I = 6.0$. Some slight error will have been introduced this way, as

¹³ M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1.

¹⁴ J. S. Day and P. A. H. Wyatt, *J. Chem. Soc. (B)*, 1966, 343.

also from the difference in temperature, but not enough to affect subsequent arguments. The latter series of values was required to show that the apparent plateaux at low pH are, in fact, genuine; lithium replaced sodium since this has been shown¹⁴ to minimise activity effects. Temperature coefficients were obtained by use of

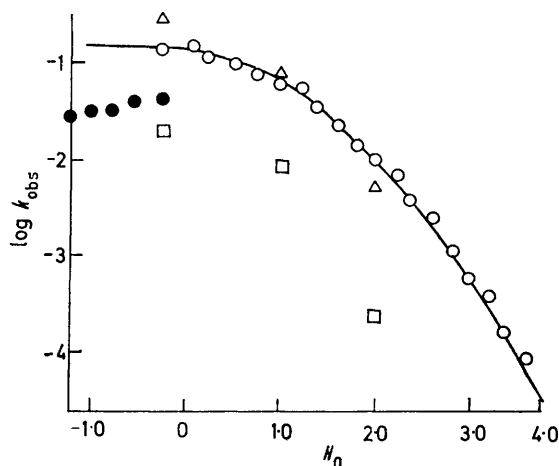


FIGURE 1 Rate-pH profiles in water at 60° for the hydrolysis of (1) at $I = 1.0$, \circ ; (1) at $I = 5.0$, \bullet ; (19) at $I = 1.0$, \square ; and (22) at $I = 1.0$, \triangle

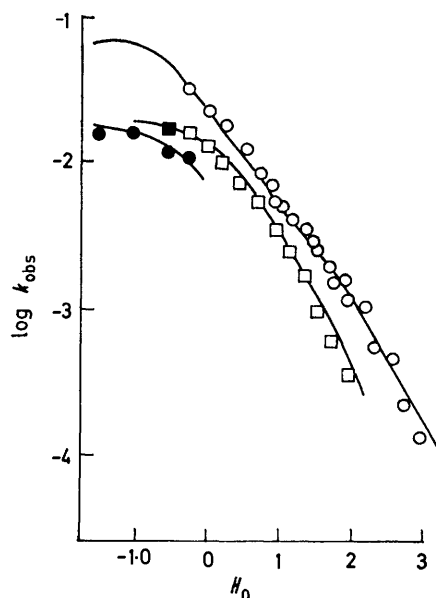


FIGURE 2 Rate-pH profiles in water at 60° for the hydrolysis of (3) at $I = 1.0$, \circ ; (3) at $I = 5.0$, \bullet ; (4) at $I = 1.0$, \square ; and (4) at $I = 5.0$, \blacksquare

solutions of constant molal composition; activation parameters, calculated from the Eyring equation,¹⁵ are in Table 3. With one exception (see later) these are uninterpretable, there being too few relevant published data with which to compare them; in addition, all represent composite quantities.

The pH profile for the hydrolysis of compound (1) is shown in Figure 1. It is a smooth curve changing from dependence on $[H^+]^2$ at high pH to pH-invariance at

high acidity. This is the behaviour expected for a reactant dication both of whose pK_a values lie within the experimental range. By suitable adjustment of the constants in equation (1), the line on Figure 1 can be

$$k_{\text{obs}} = a[H^+]^2/(b + c[H^+] + d[H^+]^2) \quad (1)$$

derived (see Appendix). The upper and lower pK_a values of (1) are given by $-\log(b/c)$ and $-\log(c/d)$, respectively. Exact correspondence is not to be expected; increase in ionic strength should raise the pK_a , while increase in temperature should lower it again. In view of this, the measured and derived upper pK_a values (Table 2) agree well enough. The lower ones do not; a

TABLE 2

Measured (25°, $I = 0.01$) pK_a values and those derived (60°, $I = 1.0$) from the rate-pH profiles

Compound	Measured	Derived
(1)	2.93	3.09
	-0.52	0.87
(2)	1.42	1.70
	Below -4	-0.30
(4)	0.59	0.32

divergence of 1.4 pK units is too great to be explained this way.

Figure 2 displays the pH profiles for the hydrolyses of compounds (3) and (4). That for compound (4) has the simple form [equation (2)] expected for a reactive

$$k_{\text{obs}} = e[H^+]/(f + g[H^+]) \quad (2)$$

monocation ($k_{\text{max}} 1.9 \times 10^{-2} \text{ min}^{-1}$), and the pK_a value so derived (Table 2) agrees reasonably well with that measured. Since compound (3) forms only a monocation, similar behaviour might have been expected. In fact, its pH profile is clearly much more complex. While it starts at high pH with a simple dependence on $[H^+]$, and finishes once again on a rate plateau at low pH, its behaviour in between is anomalous. No simple relation based on equation (2) will fit. However, it can be shown that simultaneously reactive mono- and di-cations result in an equation of the form (3). When the dication is the more reactive, the result is effectively to superimpose two relations of type (2); suitable adjustment of the constants in equation (3) leads to the line for compound

$$k_{\text{obs}} = (h[H^+] + j[H^+]^2)/(l + m[H^+] + n[H^+]^2) \quad (3)$$

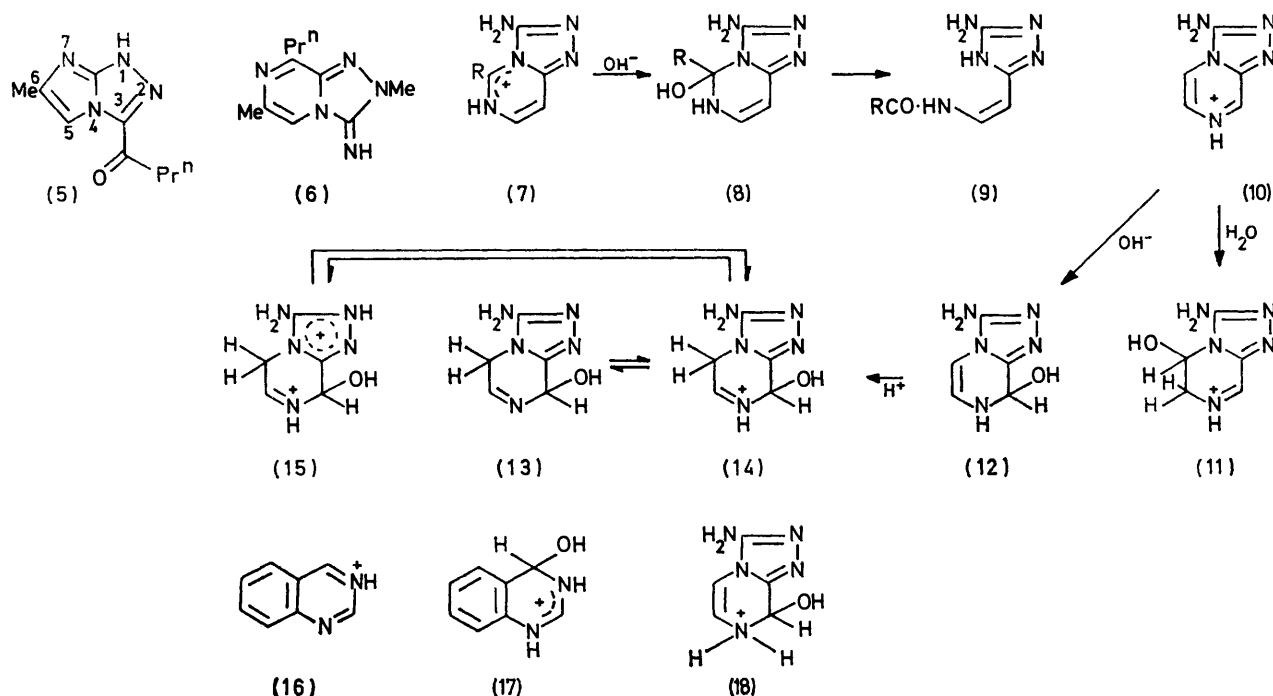
(3) on Figure 2, a double plateau relation with a 'kink' in it. The derived upper and lower pK_a values are $-\log(l/m)$ and $-\log(m/n)$, respectively. Once again (Table 2) the upper pK_a values roughly correspond but the lower ones do not; indeed, in this case there is no detectable lower pK_a value at all.

We were thus led to consider the possible occurrence of transient intermediates. There is nothing new in the postulate that steady-state intermediates may lead to a pH-controlled change in rate-determining step giving rise, independently of ionisation, to a relation of type

¹⁵ K. J. Laidler and H. Eyring, *Ann. New York Acad. Sci.*, 1940, **39**, 303.

(2).¹⁶ However, such intermediates are commonly considered to possess a lifetime little more than that of a transition state. We decided to explore the contrary case, one in which the transient species is sufficiently stable to exist as an equilibrium mixture of its various ionic forms, these corresponding in charge, but not in pK_a , to those of the reactant. The full details of that treatment are presented in the Appendix. Its essential conclusion may be stated simply: relations of type (1) and (3), *etc.*, may readily be derived; but the 'derived pK' ' values turn out to relate, not to any one pK_a , but to various combinations of rate and protonation constants. This result holds for any ionisable transient species of reasonable stability, howsoever formed, and it may have applications far beyond the present context.

compound (8), charge dispersal results. However, even this structure does not satisfy the second of Albert's criteria;^{1,3} there is no way [contrast (16) \rightarrow (17)] in which a cation can be stabilised by resonance in a way not open to the parent molecule. We suspect this to be the 'flaw' in molecular design, as it were, that leads to a further and irreversible reaction where the systems previously investigated give reversible equilibria. We suggest (14) as the corresponding cation, compound (12) behaving as an enamine. This cation has two important properties. As a protonated Schiff's base it is expected to be hydrolysed ultimately to a molecule of type (2), as is actually found. Secondly, as is crucial to the present argument, it can gain or lose a proton to give the dication (15) or the neutral species (13).[†] Since in



Reaction Mechanism.—The rearrangement of the triazolo[4,3-*c*]pyrimidines (7) to their [2,3-*c*]-isomers has been represented⁵ as going through the neutral covalent hydrate (8), fission of the ring following to give the hypothetical intermediate (9). Addition of water at the same point in (10) involves hydration of a C=C bond, a situation almost without precedent in this field.* In addition, one driving force behind covalent hydration is^{1,3} removal of the electronegativity associated with a protonated double bond, an objective achieved in compound (8) but not in compound (11). Starting from compound (10), the most reasonable point for hydroxide ion attack is that resulting in the hydrate (12); as in

both cases rapid¹⁷ proton loss or gain takes place at nitrogen, equilibration is likely to be fast relative to the hydration and fission steps. We have in the process (13) \rightleftharpoons (14) \rightleftharpoons (15) the transient species we have been looking for.

The amine (1) has, in principle, the pH profile expected for a reactive dication. Accordingly we suggest that its covalently hydrated dication is a reactive species, whereas the corresponding monocation is not. Also, the unreactivity of the free base (1) and its negligible degree of covalent hydration enable all steps bar protonation involving this to be eliminated (Scheme 1). Algebraically, elimination of the redundant rate and equilibrium constants from equation (18) leads to equation (4),

* Some tetra-azanaphthalenes can become dihydrated in the pyrazole ring, but the circumstances are different (see ref. 3).

[†] Deprotonation [(14) \rightarrow (12)] is of course feasible, but (13) is likely to be preferred kinetically even if (12) is thermodynamically more stable.

¹⁶ See, *e.g.*, W. P. Jencks, *Progr. Phys. Org. Chem.*, 1964, **2**, 63; S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.

¹⁷ R. P. Bell, 'The Proton in Chemistry,' Methuen, London, 1959.

which on multiplying out is of type (5). This is still too complex; although at high and low pH values it gives

$$k_{\text{obs}} = \left(\frac{k_2 K' + k_3 [\text{H}^+]}{K K' + K' [\text{H}^+] + [\text{H}^+]^2} \right) \left\{ \frac{k_6 [\text{H}^+]^2}{k_{-2} K''' + (k_{-3} + k_6) [\text{H}^+]} \right\} \quad (4)$$

the right relation, it could lead at intermediate values to an alternation between dependence of rate on $[\text{H}^+]^2$ and $[\text{H}^+]$ (five distinct regions in all) which is not observed.

There are various possible explanations for this anomaly. The one we favour is the accidental near-cancellation of various terms. This most readily takes place if $p/q \approx s/t$ [equation (5)]. Given the additional

$$k_{\text{obs}} = (p[\text{H}^+]^2 + q[\text{H}^+]^3) / (r + s[\text{H}^+] + t[\text{H}^+]^2 + u[\text{H}^+]^3) \quad (5)$$

condition that $p \gg q[\text{H}^+]$ at high pH and that the reverse holds at low pH, the three regions of the pH profile are then defined by $p[\text{H}^+]^2/r$, $p[\text{H}^+]/s$, and q/u . It is possible to derive terms of the same general form equating p/q with r/s or t/u , but this is less convincing since the additional condition noted above would have to apply to adjacent sections of the pH profile instead of to its extremes.* Reduction of equation (5) in this way leads to equation (3), which can now be used to analyse the 'derived' pK values whose upper and lower terms are given by equations (6) and (7), respectively. Reduction of these equations depends on making reasonable

$$K_{\text{app}} = k_{-2} K K''' / [k_{-2} K''' + (k_{-3} + k_6) K] \quad (6)$$

$$K_{\text{app}} = [k_{-2} K''' + (k_{-3} + k_6) K] / (k_{-3} + k_6) \quad (7)$$

assumptions as to the relative magnitudes of K , K''' , and the microscopic rate constants. Since the monocation must be less electronegative than the dication it should become hydrated less readily, giving $k_{-2} > k_{-3}$; at the same time steady-state conditions are best satisfied if $k_{-3} > k_6$, so k_{-2} should be the largest rate term. Given that $K''' \ll K$ (see below), equation (6) reduces approximately to $K_{\text{app}} = K$. (Actually, pK_{app} should be a little greater than pK, as is found, but the temperature and ionic strength differences previously discussed mean that too much cannot be read into this.) The lower pK_{app} has no simple meaning; at 0.87 it is a compromise between pK, at -0.52, and pK''' , which must therefore be higher. It is difficult to find a precise model for this dication, but compound (2), which lacks a second positive charge but possesses the electron-withdrawing butyryl function, has pK_a 3.11. Probably pK''' should lie below this.

The case of compound (3) is, paradoxically, the simpler. Scheme 2 describes the mechanism from which equation (8), which this time is already in the correct algebraic

$$k_{\text{obs}} = \left(\frac{k_2 [\text{H}^+]}{K + [\text{H}^+]} \right) \left\{ \frac{k_6 K''' + k_6 [\text{H}^+]}{(k_{-2} + k_5) K''' + k_6 [\text{H}^+]} \right\} \quad (8)$$

form, can be derived [cf. (3)]. We suppose that the electronegativity introduced by acetylation, which

destroys the second basic function of compound (3), also destabilises its covalently hydrated monocation sufficiently to make this, as well as the corresponding dication, a reactive species. Equation (9)

$$K_{\text{app}} = [(k_{-2} + k_5) K K''' / [(k_{-2} + k_5) K''' + k_6 K]] \quad (9)$$

defines the upper 'derived' pK. This takes the same form as equation (6) and may be treated similarly. A rough model for the covalently hydrated dication is compound (4), which has pK_a 0.59; if pK''' is ca. 0 then the second denominator term disappears and K_{app} is $\leq K$ (as before, the derived pK_a value is slightly above that measured). The lower 'derived pK' is defined by equation (10), which a similar simplification reduces to equation (11); i.e., K_{app} is related to K''' but is not,

$$K_{\text{app}} = [(k_{-2} + k_5) K''' + k_6 K] / k_6 \quad (10)$$

$$= (k_{-2} + k_5) K''' / k_6 \quad (11)$$

unless accidentally, identical with it. If pK''' is ca. 0 as suggested above, a rough coincidence does in fact fortuitously hold. In that case k_{-2} approximately equals k_6 [k_{-2} is $> k_5$ necessarily, or the steady-state treatment of equation (8) breaks down].

While nearly all these microscopic rate constants are themselves inaccessible, certain interrelationships can be deduced. From equation (4) at very low pH, and assuming $k_{-3} \gg k_6$, then in the case of compound (1), $k_6 K_3 = 0.16 \text{ min}^{-1}$ (see Appendix for the numerical values here employed). The equation for the initial slope is $k_6 K_2 / K K''' = 1480 \text{ min}^{-1}$; given $pK = 3$ and estimating pK''' as 2, this simplifies to $k_6 K_2 = 0.015 \text{ min}^{-1}$. From this, $K_3 = 10 K_2$ approximately, a reasonable result in that the dication should be hydrated to a greater extent than the monocation. In the case of compound (3), j/h from equation (3) defines $k_6 / k_5 K'''$; if pK''' is ca. 0 as suggested above, use of the computer-derived constants (see Appendix) gives $k_6 = 11 k_5$. Again, this is reasonable since more rapid breakdown of the covalently hydrated dication would be expected. In both cases, therefore, the likely properties of these covalently hydrated species are mirrored in the results.

The only accessible microscopic constant is k_2 for compound (3), which defines the upper plateau rate. The apparent simplicity of this result is, however, deceptive. It is convenient in Schemes 1 and 2, since it makes no mathematical difference to the treatment, to collate several processes under the hydration step, i.e. hydroxide ion attack, reprotonation, and possibly proton transfer from nitrogen to carbon as well. The last possibility is suggested by the work of Stamhuis *et al.*,¹⁸ who have shown this step to be rate-determining in the hydrolysis of certain simple enamines under moderately acid conditions. If so, a nitrogen-protonated species (18) lies between the hydrate (12) and the

* We are grateful to a referee for pointing this out.

¹⁸ E. J. Stamhuis and W. Maas, *J. Org. Chem.*, 1965, **30**, 2156; W. Maas, M. J. Janssen, E. J. Stamhuis, and H. Wynberg, *ibid.*, 1967, **32**, 1111; see E. J. Stamhuis, in 'Enamines,' ed. A. G. Cook, Marcel Dekker, New York and London, 1969, ch. 3.

ion (14), and formation of the latter from the ion (18) should be the rate-limiting step; fission of the ion (14) would then be fast and would yield the acetylonyl function directly, and not precisely as shown in Schemes 1 and 2. We make no attempt to decide between the alternatives since these are not simple enamines and the distinction is immaterial in terms of the kinetic demonstration of the existence of covalently hydrated intermediates. We do not find, down to $H_0 -2$, the ultimate fall in rate detected under these conditions by Stamhuis *et al.*¹⁸ The actual value of k_2 , $7 \times 10^{-2} \text{ min}^{-1}$ at 60° , is vastly less than those discussed by Perrin,² suggesting that hydroxide ion attack is no longer uniquely rate-determining. The activation parameters at $H_0 -1.01$ (Table 3) are similarly ambiguous; ΔH^\ddagger is very much

TABLE 3

Activation parameters^a at $I = 1.0$ and various H_0 values

H_0	Compound (1)		H_0	Compound (3)	
	$\Delta H^\ddagger/\text{cal mol}^{-1}$	$\Delta S^\ddagger/\text{cal mol}^{-1} \text{ K}^{-1}$		$\Delta H^\ddagger/\text{cal mol}^{-1}$	$\Delta S^\ddagger/\text{cal mol}^{-1} \text{ K}^{-1}$
-0.22	15,600	-24.1	-1.01 ^b	21,200	-10.2
1.00	18,100	-17.7	0.55	16,200	-26.9
1.60	12,600	-36.3	1.60	16,300	-29.9
3.22	12,800	-44.0	2.82	19,100	-25.8

^a 1 cal = 4.184 J. ^b At $I = 5.0$.

higher than the value reported¹⁸ for carbon protonation, while a more positive value for ΔS^\ddagger ought to result from

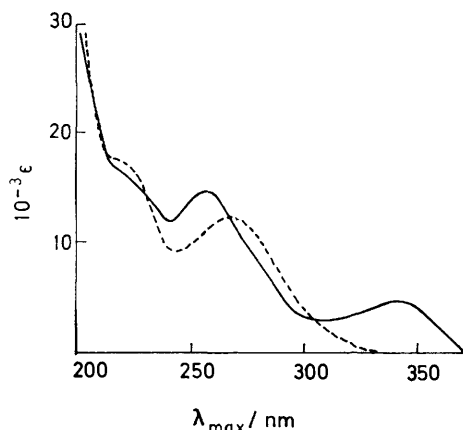
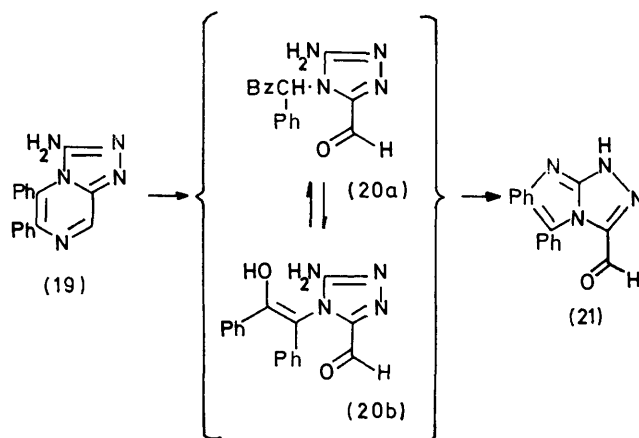


FIGURE 3 U.v. spectra of (19) in water at 60° and pH 1 at zero time, —; and after 24 h, ----. The latter is identical with the spectrum of (21)

rate-determining hydroxide ion attack. If these steps are combined in k_2 , both values, as well as the rate itself make better sense, which to some extent supports the mechanism as written.

Other Reaction Sequences.—Some attention has been paid to the diphenyl- (19) and dimethyl- (22) triazolopyrazines originally¹⁰ investigated. Their hydrolytic rates have not been studied in detail, but the limited data available (see Figure 1) appear to indicate pH profiles similar to that of compound (1). In the case of compound (19) the reaction goes straight through to the aldehyde (21) (see Figure 3) perhaps because (20) exists as the reactive enol (20b) (Scheme 3). Analysis of the

kinetics shows consecutive reactions to occur, and these cannot be separated at any pH. Chemical proof of structure (21) is not therefore readily attainable, but its



SCHEME 3

n.m.r. spectrum¹⁰ and its close i.r.¹⁰ spectral resemblance to (5) leave no reasonable doubt [its u.v. spectrum, like that of compound (19), is too distorted by aryl substitution to be helpful]. The final product of hydrolysis of compound (22) has u.v. end-absorption only (Figure 4). Since this is a characteristic of aminotriazoles,¹⁹ we suggest that the intermediate (23) exists in aqueous solution as (23b) (Scheme 4). This is consistent with the discovery⁹ that (24) readily hydrates to the diol (24b) in the solid state, its carbonyl function reappearing on dissolution in dimethyl sulphoxide, which acts as a dehydrating agent (see Experimental section). Again, the n.m.r. evidence is consistent with structure (24). It

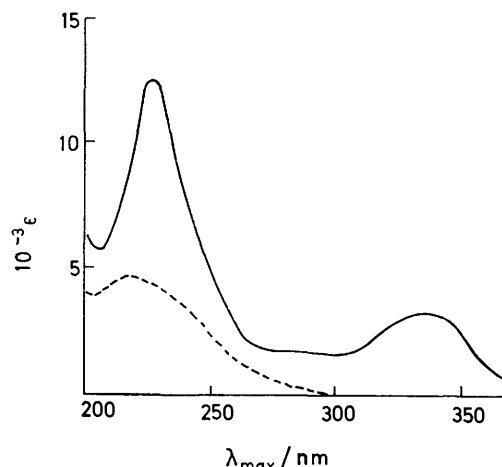


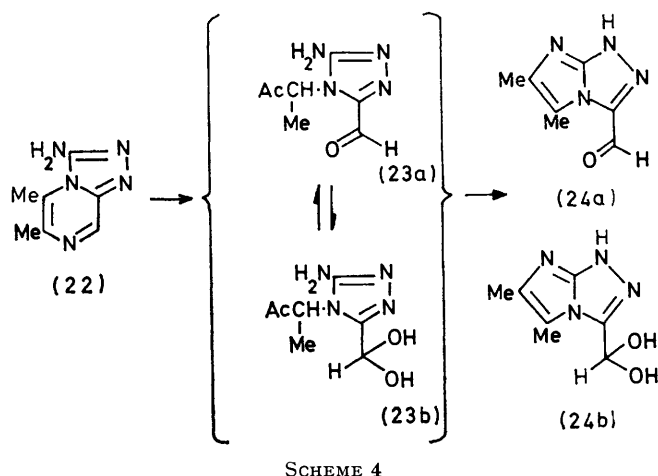
FIGURE 4 U.v. spectra of (22) in water at 60° and pH 1 at zero time, —; and after 24 h, ----

therefore appears probable that this acid-catalysed rearrangement is general for *s*-triazolo[4,3-*a*]pyrazines.

In the rearrangement of the triazolo[4,3-*c*]pyrimidines, ring closure follows closely on ring opening.¹⁹ The

¹⁹ P. J. Taylor, unpublished data.

relative slowness of ring closure here, by leading to the isolation of compound (2), was responsible for unearthing the novel reaction sequence previously⁹ described. Unsaturated amides undergo with heterocyclic NH a notably different type of condensation from saturated



SCHEME 4

ketones with an amino-group. However, this change alone might well accelerate ring closure, not slow it down. We suspect that the crucial factor may be ring strain in the product; 6,5-ring fusions are common; 5,5-fusions are rare.

EXPERIMENTAL

Kinetics.—Rates were measured in water, mostly at 60°, by u.v. spectrometry. A preliminary survey was conducted with a Perkin-Elmer 137 u.v. recording spectrophotometer at unit pH intervals to determine optimum wavelengths and to ensure that the reactions were simple and quantitative. This was so except for the hydrolyses of compounds (3) and (19), where intermediates were detected. Both undergo consecutive first-order reactions. For example, compound (4) is formed from (3) at pH 1 with $t_{\frac{1}{2}}$ ca. 2 h and goes to compound (2) with $t_{\frac{1}{2}}$ ca. 3 h. This problem was circumvented by selecting a convenient isobestic point between compounds (4) and (2), or a wavelength where neither appreciably absorbs, the precise position depending on the pH. A similar technique was employed with compound (19). Accurate results were then obtained at fixed wavelength on a Cary 16 manual u.v. spectrometer. In all cases samples were taken; in the faster runs it was convenient to quench these in acetate buffer (pH ca. 5) before examination. All reactions were followed through at least three half-lives and rates were measured by Swinbourne's method.²⁰

Materials.—Compounds (1), (3), (19), (21), (22), and (24) were supplied by Dr. F. L. Rose. The preparation of compounds not previously reported, and of compound (5) from (2), is described below. N.m.r. and i.r. data were obtained, respectively, on a Varian A60 n.m.r. spectrometer for [²H₆]dimethyl sulphoxide solutions, and on a Perkin-Elmer 457 i.r. spectrophotometer for Nujol mulls. U.v. data for compounds (2), (4), (5), and (6) are in Table 1. Water was distilled deionised; other reagents were of analytical reagent grade.

(3-Amino-5-n-butyryl-4H-1,2,4-triazol-4-yl)acetone (2).—

Compound (1) (9.55 g) was boiled under reflux with 2N-hydrochloric acid (50 ml) for 10 min. A solid was deposited on cooling. The suspension was washed with methylene dichloride and the washings were extracted with 2N-hydrochloric acid. Aqueous solutions were combined and brought to pH 7 by addition of aqueous sodium carbonate. The precipitate was collected, washed with water, and dried. Two crystallisations from ethyl acetate gave the *product* (6.65 g), m.p. 162.5–163.5° (Found: C, 51.1; H, 6.5; N, 26.5. C₉H₁₄N₄O₂ requires C, 51.3; H, 6.7; N, 26.6%); δ 6.48br (2H, s, exchangeable, NH₂), 5.00 (2H, s, acetylonyl CH₂), 2.92 (2H, t, CH₂), 2.17 (3H, s, acetylonyl Me), 1.6 (2H, m, CH₂), and 0.85 p.p.m. (3H, t, Me); ν_{\max} 3150m, 3050ms (NH₂), 1738ms (acetylonyl C=O), 1672s (butyryl C=O), 1650sh (NH₂), and 1567s cm⁻¹ (conjugated C=N).

N-(4-Acetylonyl-5-n-butyryl-4H-1,2,4-triazol-3-yl)acetamide (4).—Compound (2) (1.5 g) was heated with acetic anhydride (4 ml) and acetic acid (3 ml) for 10 min on a steam-bath. On cooling and scratching, a solid slowly separated, which was collected and combined with a second crop obtained by diluting the mother liquor with water. The total solid (0.6 g) was recrystallised from ethyl acetate to give the *product* (4), m.p. 189–190° (Found: C, 52.5; H, 6.2; N, 22.2. C₁₁H₁₆N₄O₃ requires C, 52.3; H, 6.4; N, 22.2%); ν_{\max} 3170m (NH), 1741s, 1720s, 1710s (all C=O), and 1572ms cm⁻¹ (amide II). When acetic anhydride was used alone instead of mixed with acetic acid, further acetylation occurred to give the *diacetylated derivative*, m.p. 132.5–134° (from carbon tetrachloride) (Found: C, 53.3; H, 6.0; N, 19.1. C₁₃H₁₈N₄O₄ requires C, 53.0; H, 6.2; N, 19.0%).

6-Methyl-1H-imidazo[2,1-c]-s-triazol-3-yl Propyl Ketone (5).—Compound (1) (13.4 g) in 2N-hydrochloric acid (65 ml) was boiled under reflux for 30 min. The hot solution was treated with carbon, filtered, and cooled. Sodium hydrogen carbonate was added to the filtrate to give pH 7, and the precipitated solid was collected, washed with water, and dried. On heating in a bath at 170–180° for 10 min, water was driven off and the mixture of (2) and (5) was converted completely into the latter. Crystallisation from methanol gave *material* (4.5 g), m.p. 220.5–221.5° (decomp.) (Found: C, 56.4; H, 6.3; N, 29.2. C₉H₁₂N₄O requires C, 56.2; H, 6.3; N, 29.2%); δ 8.3–7.5 (1H, NH), 7.36 (1H, d, J 2 Hz, HC=CMe), 3.04 (2H, t, CH₂), 2.28 (3H, d, J 2 Hz, MeC=CH), 1.74 (2H, m, CH₂), and 0.94 p.p.m. (3H, t, Me); ν_{\max} 3100–2600ms (NH), 1665s (C=O), 1652sh, and 1615ms cm⁻¹. Identical material was prepared by heating compound (2) in the solid state under the above conditions.

3-Imino-2,6-dimethyl-8-n-propyl-s-triazolo[4,3-a]pyrazine (6).—Compound (1) (11.5 g) in methyl iodide (15 ml), and ethanol (100 ml) was boiled under reflux for 18 h. The resultant solution was evaporated to dryness under reduced pressure and the residue was triturated with water (120 ml). Undissolved material was removed by filtration and recrystallised in turn from water and methanol to give 3-amino-1,6-dimethyl-8-n-propyl-s-triazolo[4,3-a]pyrazinium iodide, m.p. 247–248°, identical with material prepared²¹ by an unambiguous route. Addition of saturated aqueous sodium iodide (70 ml) to the filtrate caused the slow precipitation of a solid (5.4 g) which was collected, washed with acetone, and redissolved in water. To the solution was then added aqueous 10N-potassium hydroxide (25 ml). The yellow precipitate was extracted into ether and the extracts were washed with water, dried (Na₂SO₄),

²⁰ E. S. Swinbourne, *J. Chem. Soc.*, 1960, 2371.

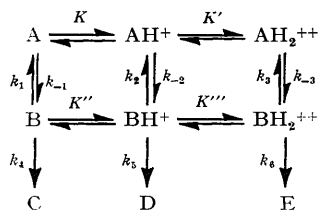
²¹ G. J. Stacey, unpublished data.

and evaporated to leave an oil which solidified on scratching (2.6 g). A further quantity (0.85 g) was obtained by treating the mother liquors with aqueous 10N-potassium hydroxide and isolating as above. The total amount was dissolved in hot cyclohexane (12 ml), treated with decolorising carbon, and filtered. The filtrate was stirred while a trace of water (ca. 0.5 ml) was added to cause the crystallisation of compound (6) as a *monohydrate*, m.p. 82.5–83.5° (Found: C, 53.9; H, 7.2; N, 31.2. C₁₀H₁₅N₅H₂O requires C, 53.8; H, 7.7; N, 31.4%); δ (CDCl₃) 7.28 (1H, d, *J* 2 Hz, CH), 3.64 (3H, s, MeN), 3.27br (3H, NH + H₂O), 2.90 (2H, t, CH₂), 2.34 (3H, d, *J* 2 Hz, Me), 1.86 (2H, m, CH₂), and 1.05 p.p.m. (3H, t, Me); ν_{\max} , 3500–3000 (H₂O), 3260 (NH), and 1640 cm⁻¹ (C=NH); basic pK_a 8.35 (by potentiometry in 50% aqueous acetone).

Spectroscopic Investigation of Compound (24).—A sample of the compound previously believed¹⁰ to be 2-hydroxy-5,6-dimethyl-s-triazolo[2,3-*a*]pyrazine was examined by i.r. spectroscopy (Nujol mull): its strongest band was confirmed¹⁰ as that at 1565, with a weak band at 1596, a shoulder near 1680, and broad absorption at 3500–2500 cm⁻¹. A solution in dimethyl sulphoxide showed a strongest band at 1675, other bands appearing at 1638 and 1592 [cf. (5)] with the band near 1560 cm⁻¹ now weak. Under the same conditions the n.m.r. spectrum showed absorption at δ 9.7 (<1H, s, CH), 2.42 (3H, s, Me), and 2.17 p.p.m. (3H, s, Me); there was also a weak singlet at δ 5.25 p.p.m. This is consistent with structure (24a) contaminated with some (24b) [Found (for undried sample): C, 50.2, 49.9, 50.1; H, 4.9, 4.7, 5.1; N, 32.9, 32.9, 33.1. C₇H₈N₄O_{0.25}H₂O requires C, 49.8; H, 5.05; N, 33.2%]. This much water will not account for the Nujol i.r. spectrum. However, a finely ground sample heated at 100° overnight and used at once to prepare a Nujol mull showed carbonyl absorption at 1680 cm⁻¹.

APPENDIX

The Steady State Treatment.—We derive the master equation (18) based on Scheme 5 assuming that steps



SCHEME 5

involving net protonation (horizontal sequences) are fast with respect to the rest. Species A are reactant, species B are steady-state intermediates, and the products C, D, and E may be the same or different. Relations (12) and (13)

$$[\text{A}_0] = [\text{A}] + [\text{AH}^+] + [\text{AH}_2^{++}] \quad (12)$$

$$[\text{B}_0] = [\text{B}] + [\text{BH}^+] + [\text{BH}_2^{++}] \quad (13)$$

are defined as shown. The steady state equation is given by equation (14). Substituting equations (12) and (13) into

$$\begin{aligned}
 d[\text{B}_0]/dt = & k_1[\text{A}] + k_2[\text{AH}^+] + k_3[\text{AH}_2^{++}] - \\
 & (k_{-1} + k_4)[\text{B}] - (k_{-2} + k_5)[\text{BH}^+] - \\
 & (k_{-3} + k_6)[\text{BH}_2^{++}] = 0 \quad (14)
 \end{aligned}$$

(14) gives equation (15).

$$\begin{aligned}
 & \left(\frac{k_1KK' + k_2K'[\text{H}^+] + k_3[\text{H}^+]^2}{KK' + K'[\text{H}^+] + [\text{H}^+]^2} \right) [\text{A}_0] \\
 & = \left\{ \frac{(k_{-1} + k_4)K''K''' + (k_{-2} + k_5)K'''[\text{H}^+] +}{(k_{-3} + k_6)[\text{H}^+]^2} \right\} [\text{B}_0] \quad (15)
 \end{aligned}$$

The overall rate is given by equation (16), which on

$$\text{Rate} = k_{\text{obs}}[\text{A}_0] = k_4[\text{B}] + k_5[\text{BH}^+] + k_6[\text{BH}_2^{++}] \quad (16)$$

defining species B in terms of [B₀] becomes equation (17).

$$k_{\text{obs}}[\text{A}_0] = \left(\frac{k_4K''K''' + k_5K'''[\text{H}^+] + k_6[\text{H}^+]^2}{K''K''' + K'''[\text{H}^+] + [\text{H}^+]^2} \right) [\text{B}_0] \quad (17)$$

Combining equations (15) and (17) gives equation (18).

$$\begin{aligned}
 k_{\text{obs}} = & \left(\frac{k_1KK' + k_2K'[\text{H}^+] + k_3[\text{H}^+]^2}{KK' + K'[\text{H}^+] + [\text{H}^+]^2} \right) \\
 & \left\{ \frac{k_4K''K''' + k_5K'''[\text{H}^+] + k_6[\text{H}^+]^2}{(k_{-1} + k_4)K''K''' + (k_{-2} + k_5)K'''[\text{H}^+] + (k_{-3} + k_6)[\text{H}^+]^2} \right\} \quad (18)
 \end{aligned}$$

Appropriate simplification of equation (18) can now lead to equations (4), (8), and a variety of other possibilities.

A similar equation has been derived by Dunn *et al.*²² to account for the failure of the decarboxylation of anthranilic acid to show the expected pH profile. However, their treatment concerns zwitterionic species and is cast in a form much more difficult to generalise or simplify. Katritzky *et al.*²³ have invoked covalent hydration to explain an anomalous apparent pK value in a reaction involving deuterium exchange. Schmir and Cunningham²⁴ have shown that, when the products C, D, and E are different, the product- and rate-pH profiles need not correspond; however, nothing in their treatment leads to the expectation of anomalies in the latter. Equation (18) can be manipulated to show that the above result is general; the product profile need correspond neither to the rate-pH profile expected nor to that found. Using the simplified equation (8) as an example, it is readily shown that, had the products D and E been different, the equivalence point in the product profile would have defined the term k_5K'''/k_6 ; contrast (11), the equation for the corresponding 'derived pK'.

The curves shown for compounds (1) and (3) on Figures 1 and 2 were derived iteratively by computer programmes based on equations (1) and (3), respectively. For equation (1), the curve assumes $a/b = 1480$, $a/c = 1.2$, and $a/d = 0.16 \text{ min}^{-1}$. For equation (3), $h/l = 0.16$, $h/m = 0.0032$, $j/m = 0.035$, and $j/n = 0.07 \text{ min}^{-1}$. From the reduced forms of equation (18), these ratios can be given numerical values which relate to combinations of microscopic rate and equilibrium constants. Examples of these procedures are given in the text.

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