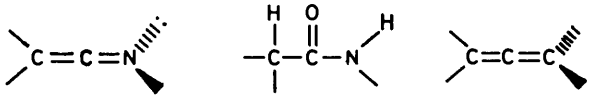
Rapid Acid-catalysed and Uncatalysed Hydration of Ketenimines [1]

By **Daniel G. McCarthy** and **Anthony F. Hegarty,***† Chemistry Department, University College, Cork, Ireland

The rates of hydration of a series of ketenimines (9) have been examined in water (μ 1.0; 25°) over the pH range 2—13. Three mechanisms of hydration to the amides (8) were noted: (a) general acid catalysis by proton transfer from H_3O^+ in the pH range 2—7 (giving $k_{H_3O^+}/k_{D_3O^+}$ 2.65); (b) general acid catalysis by H_2O at pH >7 (where k_{H_2O}/k_{D_2O} = 4.8); (c) rate-determining HO^- attack. The last mechanism was only shown by *N*-arylketenimines, *e.g.* (9e); other *N*-alkylketenimines continue to react by rate-determining proton transfer from water even at pH 13. This result is confirmed by the incorporation of just one deuterium when (9a) reacted in acidic or basic D_2O, while the deuteriated ketenimine (9f) does not loose the label on reaction in water. Substituent effects are parallel for reactions involving H^+ transfer from H_3O^+ or H_2O; the major effects are obtained on changing substituents at carbon (the protonation site). For example, replacement of C–H by C–Me reduces the reactivity by 10—20-fold, while replacement of C–Me by C–Ph reduces the rate of hydration by >100-fold. Ammonium ions also generally react with ketenimines by rate-determining H^+ transfer to the ketenimine followed by trapping of the nitrilium ion formed by the free amine. Only with the strongest amine base studied (piperidine) does direct nucleophilic attack on the ketenimine compete.

ALTHOUGH ketenimines (1) were first reported by Staudinger [2] in the 1920s, significant development in the chemistry of these materials is of relatively recent origin. These compounds, which can be formally regarded as imine derivatives of ketens, are isoelectronic with allenes (3), and indeed some of the reactions of these compounds parallel the reactions of allenes. In recent years keten-



(1) (2) (3)

imines have attracted interest as dehydrating agents for peptide synthesis,[3-5] complexing agents for transition metal ions, as co-reagents for DMSO oxidations,[6] and as substrates for the synthesis of heterocycles through photochemical [7,8] or thermal [2 + 2] cycloadditions.[9]

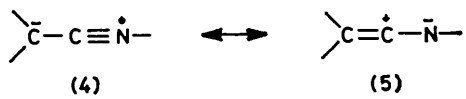
The ketenimine system is potentially axially dissymmetric in an analogous manner to allenes (2) where the two π bonds, and thus the substituents attached to the terminal atoms, are in orthogonal planes. However, the ability to observe asymmetry depends on the configurational stability of the ketenimine system, which can invert its configuration about the imine nitrogen by an inversion or rotation mechanism. The calculated energy barrier for inversion is *ca.* 10 kcal mol^{-1}, a value supported by recent variable temperature n.m.r. studies.[10-12] At room temperature therefore simple ketenimines undergo rapid configurational interconversions.

As the formal dehydration products of amides (2), ketenimines readily add on water to regenerate the amide. In addition, the heterocumelene linkage reacts readily with electrophiles (halogens and hydrogen halides), indicating the importance of resonance structures (4) and (5). In this respect ketenimines should show a similarity in reactivity akin to enamines (6) and ynamines (7).

† Present address: Chemistry Department, University College, Belfield, Dublin 4, Ireland.

Nucleophilic addition to the central carbon of the ketenimine [see (5)] is less well characterised but may occur in the reactions of (1) with amines (to give amidines) or alkoxides (to give imidates).

Little however is known about the mechanism (or indeed the conditions necessary) for these reactions. This partly arises from the difficulty of dealing with such reactive species which undergo reaction under a wide



(4) (5)

(6) (7)

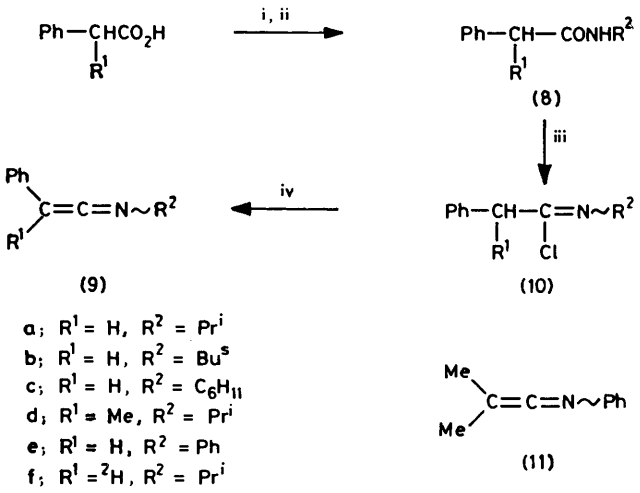
variety of conditions (including dimerisation and polymerisation which makes storage difficult). We have therefore examined the mechanism and catalysis of the reaction of water with (1) to give (2) and also the reaction of (1) with amines.

RESULTS AND DISCUSSION

Synthesis of Ketenimines.—The ketenimines used in this work were obtained by two variations of the base-catalysed dehydrohalogenation route outlined in Scheme 1. Reaction of the secondary amides with PCl_5 (one equivalent) gave the imidoyl chlorides (10) which, on treatment with triethylamine in benzene, at reflux, gave the ketenimines (9) in quantitative yield. Dimethylketen *N*-phenylimine (11) was obtained directly by the addition of isobutyranilide to a solution of dibromotriphenylphosphorane and triethylamine.

A different route was developed for the synthesis of the deuteriated ketenimine (13) (Scheme 2). Phenylmalonic acid was deuteriated at the methine and carboxylic OH positions by stirring the acid in 20 : 80 dioxan–D_2O for 24 h. Removal of the solvent, followed by pyrolytic decarboxylation of the residue at 180° gave

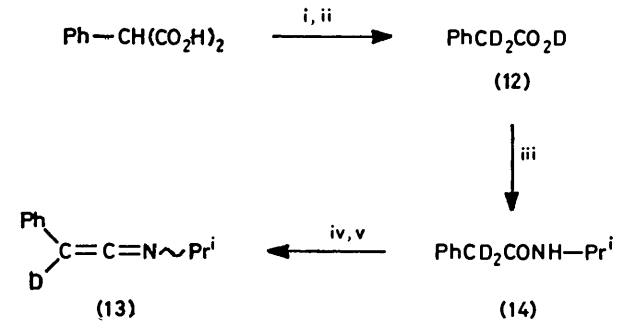
the phenylacetic acid (12) containing 94% deuterium in the benzylic position (determined by n.m.r.). This was converted into the *N*-isopropylamide (14) in 82% yield using the dicyclohexylcarbodi-imide (DCC) method in the presence of 1-hydroxybenzotriazole (HBT) as an additive. In the absence of the latter, the yield of amide was reduced to 22%. The amide (14) contained



SCHEME 1 Reagents: i, $SOCl_2$; ii, R^2NH_2; iii, PCl_5; iv, NEt_3

92% deuterium at the benzylic carbon. Exchange of the N–H proton in D_2O followed by treatment of the amide with PCl_5 and triethylamine gave the deuteriated ketenimine (13) in 35% yield (on distillation) with 88% deuterium. If the N–H proton was not exchanged initially, the % deuterium in the ketenimine (11) obtained reduced to 72%.

The ketenimines prepared here were liquids which were purified by vacuum distillation, which was accompanied

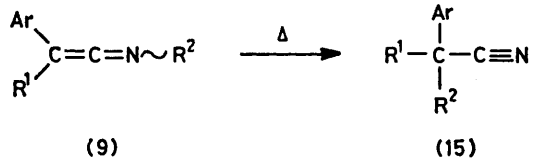


SCHEME 2 Reagents: i, D_2O; ii, Δ; iii, DCC–HBT–Pr^iNH_2; iv, PCl_5; v, NEt_3

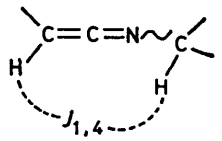
by considerable polymerisation of the ketenimine. However by keeping the distillation temperatures below 60° and using low pressures (*ca.* 0.1 mmHg), it was possible to distill *ca.* 50% of the ketenimine.

In addition, purification of ketenimines by distillation presents the problem that thermal rearrangement to nitriles (15) may occur.[13,14] This rearrangement can be fast when the group attached to nitrogen (R^2) is benzylic and the terminal carbon has at least one aryl group attached to it. However we found that the spectral properties of our ketenimines did not change on distillation and that these gave secondary amides (rather than carboxylic acids) as the only reaction products on hydration on a preparative scale.

The spectroscopic properties of the ketenimines were in agreement with the assigned structures. In particular the i.r. spectra showed absorptions of the cumulated double bonds in the region 2 020—2 050 cm^{-1}. An interesting feature of the ^1H n.m.r. spectra was the



observation of five-bond coupling between the vinylic proton attached to C-2 and the methine proton of the *N*-isopropyl, *N*-s-butyl, or *N*-cyclohexyl group (16). This assignment was confirmed by spin decoupling; the value of this long range coupling constant was $J_{1.4}$ 1.9—2.1 Hz.



Kinetics of Hydration of Ketenimines.—The kinetics of hydration of ketenimines to give the corresponding secondary amides were investigated by spectrophotometric methods in water at 25°; ionic strength was maintained constant by the addition where necessary of sodium perchlorate. Initially the ketenimine (11) was studied. Although this ketenimine hydrolysed readily in aqueous solution, it proved to be unsatisfactory for detailed kinetic study as the spectral change in the u.v. accompanying hydrolysis was very small. The major change was the loss of a weak absorption band at 330 nm (ε *ca.* 50) together with an increasing higher energy shoulder at 250 nm. It was possible to obtain some kinetic data for the hydration of this ketenimine by conducting the reaction in 40 : 60 dioxan–water, which permits the use of higher substrate concentrations.

The problem of poor spectral change accompanying hydration of the ketenimine was overcome by using a *C*-aryl substrate in which the ketenimine chromophore is directly linked to an aromatic ring. Hydration which destroys both the cumulene chromophore and its conjugation with the aromatic ring then gives a marked spectral change in the u.v., as shown in Figure 1. Thus, reaction of phenylketen *N*-isopropylimine (9a) at pH 9.5 in water in the presence of a borax buffer (5×10^{-3}M) was complete in *ca.* 1 h, the absorbance of the ketenimine, $\lambda_{max.}$ (water; pH 9.5) 270 nm, ($\varepsilon_{max.}$ 8 050), being replaced by the weak $n \longrightarrow \pi^*$ transition of the *N*-isopropylphenylacetamide (8a) [$\lambda_{max.}$ 255 nm ($\varepsilon_{max.}$ 340)]. That this amide was the only product was confirmed by

carrying out the reaction under the same conditions, but on a larger scale.

The first-order rate constants for the hydration of this ketenimine were determined as a function of the pH of the aqueous reaction medium (Table 1). These k_{obs} values are plotted (open circles) in the form of a pH–rate profile in Figure 2 (together with other data for the ketenimines). It is clear from this profile that the ketenimine reacts by two routes in aqueous solution. At low pH (pH < 6), k_{obs} is directly proportional to the

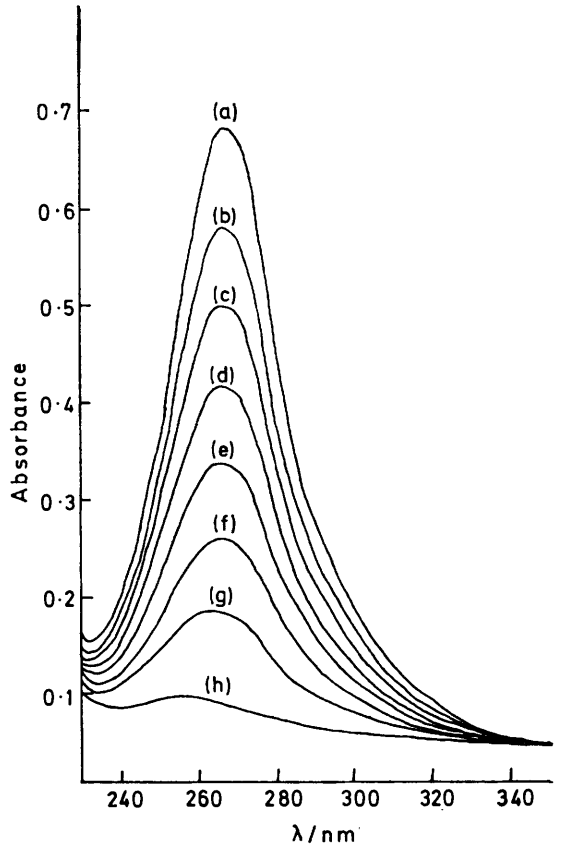


FIGURE 1 Repetitive scans of the u.v. spectrum for the hydration of phenylketen-*N*-isopropylimine (9a) at 25° in water containing 5 × 10^{-2}M-borax buffer at pH 9.5; (a) *t* 0; (b) *t* 3; (c) *t* 6; (d) 10; (e) *t* 15; (f) *t* 22; (g) *t* 32 min; (h) *t* ∞ (*ca.* 70 min)

acidity of the medium while k_{obs} becomes pH independent at higher pH. A significant feature is the absence of any pronounced base-catalysed route for the hydration of the ketenimine. Over the pH range studied the rates of hydration of the ketenimine can be represented by the empirical rate equation (1).

$$k_{obs} = k_0 + k_{H_3O^+}a_{H_3O^+} \quad (1)$$

Table 2 contains a summary of the rate constants for hydration of all the ketenimines used in this study. It is clear that both *N*-cyclohexyl- and *N*-s-butyl-ketenimines (9c and b) react at very similar rates under both neutral and acidic conditions. Substitution of a methyl group for hydrogen at C-2 [as in (9d)] reduces both rates, the pH-independent by *ca.* 17, the acid-catalysed process by *ca.* 10-fold. With the replacement of the *N*-alkyl by an *N*-phenyl substitutent, the rate of the acid-catalysed

TABLE 1

Observed first-order rate constants as a function of pH for the hydration of phenylketen-*N*-isopropylimine (9a) in water at 25°

pH	$10^3k_{obs}/s^{-1}$ [a]	pH	$10^3k_{obs}/s^{-1}$ [a]
4.43	70.20	9.05	1.37
4.68	32.0	9.45	1.40
4.88	29.50	9.80	1.56
5.12	13.14	10.25	1.30
5.46	9.44	10.68	1.47
5.82	4.74	11.19	1.32
6.18	2.58	11.65	1.42
6.68	1.77	12.18	1.56
7.15	1.60	12.66	1.84
7.50	1.33	13.08	2.74
8.50	1.39		

[a] ±3%, determined in the absence of added buffer species using the Cary 14 pH-stat method (see Experimental section).

reaction is reduced more than 20-fold, and the pH-independent reaction is no longer evident. At high pH a specific base catalysed mechanism of hydration [k_{HO^-} 47.9 l mol^{-1} s^{-1} for (9e)] is observed (see Figure 3).

Mechanism of Hydration

(a) *Catalysis by Hydronium Ion.*—Two mechanisms may be considered for the acid (H_3O^+)-catalysed hydration of the ketenimines used in this study.

(*i*) The first involves rapid pre-equilibrium protonation of the substrate to give the nitrilium ion (17) (protonation on C-2) or the keteniminium ion (18)

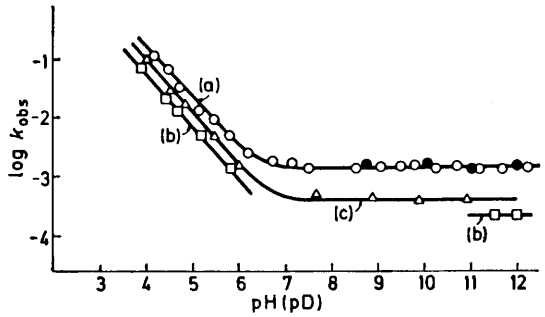


FIGURE 2 pH–Rate profiles for the hydration of phenylketen-*N*-isopropylimine (9a) at 25° (μ 1.0, $NaClO_4$); (a) in H_2O; (b) in D_2O; (c) 1 : 4 dioxan–H_2O (all in absence of buffers). Filled circles refer to rate constants for hydration of (9f) in H_2O

(protonation on nitrogen) followed by *rate-determining addition of water* to the protonated species to give the observed amide product (Scheme 3, specific-acid catalysis).

(ii) This differs from the previous mechanism in that the *proton transfer* from H_3O^+ to C-2 [transition state (19)] or to the imino-nitrogen [transition state (19a)] is the *rate-determining* step (H_3O^+ acting as a general acid). We have distinguished between these two mechanisms and established the site of protonation (C-2 or N) using structural and electronic effects, solvent and substrate isotope effects, and by product analysis from reactions conducted in deuterium oxide.

When the hydration of the ketenimine (9a) was studied in deuterium oxide over the pH range 4—6, a reduction in the rate of the pH dependent reaction was observed. Table 3 contains the first-order rate-constants observed. These taken together with the rate constants in Table 2

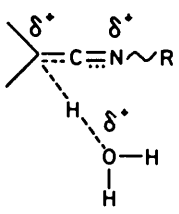
TABLE 2

Second- and first-order rate constants for the acid-catalysed and pH-independent hydration of ketenimines (9) and (11) in water at 25° (μ 1.0; $NaClO_4$)

Ketenimine	$k_{H_3O^+}$/l m^{-1} s^{-1}	k_0/s^{-1}	λ/nm [d]
(11)	8.71 × 10^3 [a]		333
	15.0 × 10^3 [b]		
(9a)	2.2 × 10^3	1.35 × 10^{-3}	268
(9b)	2.88 × 10^3	2.25 × 10^{-3}	268
(9c)	2.75 × 10^3	2.2 × 10^{-3}	270
(9d)	2.0 × 10^2	0.08 × 10^{-3}	274
(9e)	1.0 × 10^2	[c]	265
(9f)	1.80 × 10^3	1.42 × 10^{-3}	270

[a] In 40 : 60 dioxan–water (v/v). [b] From buffer dilutions in 20 : 80 dioxan–water. [c] This compound reacts by a specific base-catalysed route at high pH. [d] Wavelength at which kinetic measurements were carried out.

yield solvent isotope effect (k_{H_2O}/k_{D_2O}) = 2.65 ± 0.15. This clearly indicates that the acid-catalysed reaction involves direct proton transfer from H_3O^+ to the ketenimine in transition state (19). Reactions proceeding by true specific acid catalysis have k_{H_2O}/k_{D_2O} values signi-



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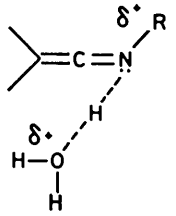
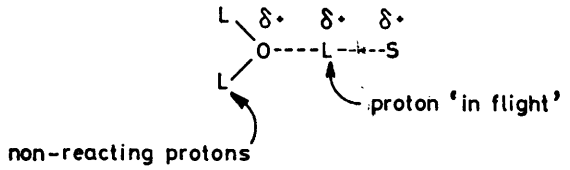


(19a)

ficantly less than unity (for example, acid-catalysed hydrolysis of ethyl diazoacetate, which has been shown to involve initial pre-equilibrium protonation of the substrate gives a solvent isotope effect of 0.35).[16] The limiting solvent isotope effect observed for the hydration of (9a) is a product of the normal primary isotope effect



(20)

for the proton 'in flight' and the inverse secondary isotope effect which is due to the non-reacting but isotopically substituted protons in the hydronium ion (20; L = H or D). Because k_{H_2O}/k_{D_2O} is large in the acid region, the primary isotope effect must also be considerable, but a separation of the two effects awaits a study in H_2O–D_2O solvent mixtures or determination of the product isotope fractionation factors for the hydration of the ketenimine.[17]

Site of protonation. For a number of reasons we believe that protonation takes place on the terminal carbon of the cumulene linkage which is activated

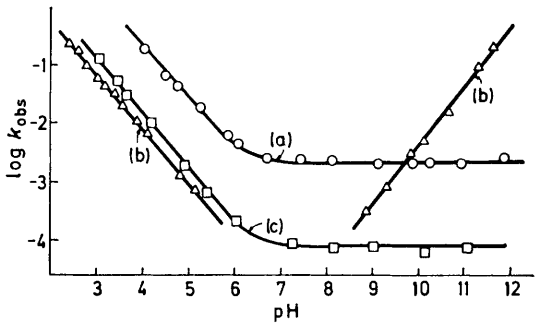
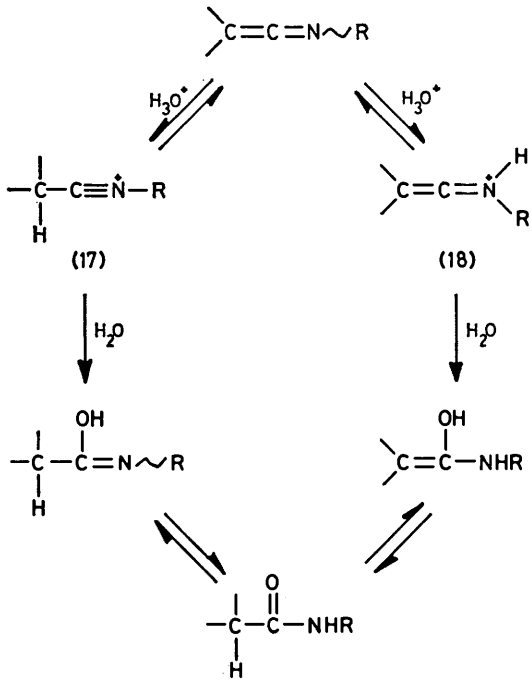


FIGURE 3 pH–Rate profiles for the hydration of ketenimines in water at 25°, in the absence of buffer species: (a) (9b); (b) (9e); (c) (9d)

towards electrophilic attack by the lone pair of electrons on the imino-nitrogen. Recent ^{13}C n.m.r. studies by Firl [18] indicate that there is considerable electron



(17) (18)

SCHEME 3

density on the terminal carbon atom [compare resonance structures (4) and (5)]. Thus, for a range of substituted ketenimines, it was found that only the resonance of this

TABLE 3

Observed first-order rate constants for the hydration of phenylketen-*N*-isopropylimine (9a) in deuterium oxide at 25° (μ 1.0; $NaClO_4$)

pD [a]	10^3k_{obs}/s^{-1}	pD [a]	10^3k_{obs}/s^{-1}
3.95	72.0	5.20	5.48
4.43	23.0	5.55	4.62
4.75	14.8	5.88	1.42

[a] Determined from the measured pH of the solution using the relation [15] pD = pH + 0.4.

carbon (δ 37—75 p.p.m.) was sensitive to substituents and compared with analogously substituted allenes this carbon was shielded by *ca.* 30 p.p.m. This study indicated that bonds to the terminal carbon have the same degree of σ-bond character as those in the corresponding allene (from C–H coupling constants). The shielding of this carbon was suggested to be due to increased π-electron density on the terminal carbon as a result of the conjugative interaction between this atom and the electron pair on the nitrogen. Electrophiles other than H_3O^+ can be shown to add to the C=C rather than the

TABLE 4

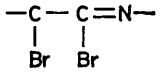
Summary of product deuterium content from hydration of (9f) in 20 : 80 dioxan–water at 20° (μ 1.0; $NaClO_4$)

pH	Reaction time	%D (±3%) [a]
3.5	15 min	45 (40, 43) [b]
	1 h	46
9.5	2 h	42
	4 h	46

[a] At the benzylic position, determined by n.m.r. ($CDCl_3$). [b] Estimated by mass spectrometry (*m/e* 178 and 93, respectively.

C=N bond of the ketenimine; for example [6] addition of bromine gives (21).

The effect of substituents on carbon and nitrogen is not expected to be particularly useful as a tool to distinguish between the two possible sites of protonation



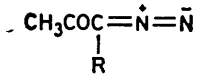
(21)

since *C*- (17) or *N*-protonation (18) gives a species with a broadly similar charge distribution; in both cases the positive charge is expected to be largely located on nitrogen. The situation is similar to that observed for electrophilic attack on hydrazones [equation (2)]; for bromination (attack at carbon) substituents in Ar^1 have a greater effect (ρ −2.2) than those in Ar (ρ −0.62).[19]

$$ArCH{=}N{-}NH{-}Ar^1 \xrightarrow{Br_2} \{ArCHBr{-}N{=}\overset{+}{N}H{-}Ar^1\} \longrightarrow\longrightarrow Ar{-}CBr{=}N{-}NHAr^1 \quad (2)$$

As can be seen from Table 2, the three *N*-alkyl substituents (Pr^i, Bu^s, and cyclohexyl) do not greatly affect the rate of hydration of the ketenimine. This is to be expected in view of the similar electron-releasing abilities of these groups. However, the electron-withdrawing *N*-phenyl substituent (σ* +0.6), by reducing the extent of electron delocalization from nitrogen, decreases the rate of reaction by a factor of 22. Replacement of the hydrogen attached to C-2 of the ketenimine linkage by a methyl group has an unusual effect—the rate of reaction is reduced by a factor of 10.

This effect, which is probably steric in origin, is also inconsistent with rate-determining protonation on nitrogen. In a study of the decomposition of diazoketones (22) catalysed by H_3O^+, Dahn and Bellenegger [20] found that on changing from R = H to R = Me the mechanism of the reaction changed from specific acid

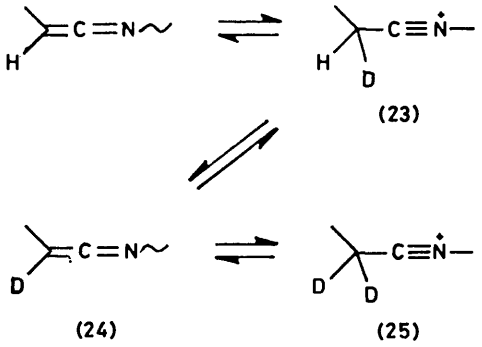


(22)

catalysis to rate-determining protonation on carbon From the data in Table 2 it is clear that the dimethylketenimine (11) reacts *ca.* 100-fold more rapidly with H_3O^+ than does the *C*-phenyl analogue (9e). This very large effect is most likely due to conjugative stabilization of the starting ketenimine by the *C*-phenyl group in (9e) which is lost when *C*-protonation (17) [but significantly not *N*-protonation (18)] occurs.

Isotopic labelling experiments. In order to confirm that proton transfer from H_3O^+ is the slow step at low pH, the ketenimine (9a) was allowed to react on a preparative scale in D_2O at pH 2.4 (at 25° for 30 min). The amide (8a) was formed in quantitative yield, and analysis (by n.m.r. and mass spectra, see Experimental section) showed the incorporation of *one* deuterium at the benzylic position in the product. A control experiment showed that the deuteriated amide did not loose the label under the reaction conditions.

Initial *pre-equilibrium* protonation of the ketenimine by D_3O^+ will give successively the nitrilium ion,[21] containing one deuterium atom at the α-position, the deuteriated ketenimine (24), and ultimately, *via* the nitrilium ion (25), a dideuteriated amide. Rapid pre-equilibrium protonation can therefore be ruled out.



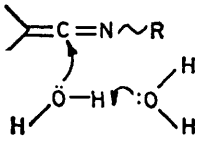
(23) (24) (25)

SCHEME 4

We have also carried out the reverse reactions in which the deuteriated ketenimine (9f) was hydrated at pH 3.5 on a preparative scale in 20 : 80 dioxan–water. As can be seen from Table 4, the ketenimine which originally contained 88% deuterium at C-2 undergoes hydration with no loss of the isotopic label. Furthermore, variation of the reaction time shows that the isotopic label in the reaction product does not exchange with the solvent under the reaction conditions. The results of this experiment are also consistent with the general acid catalysis mechanism proposed (19).

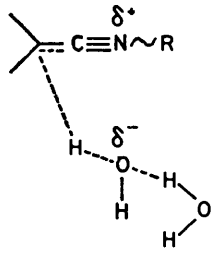
(b) *Spontaneous and Base-catalysed Hydration.*—An unusual feature of the results obtained here is the presence of a substantial pH independent (pH 7—13.5) route for the disappearance of the ketenimine [with the exception of (9c)]. At least four mechanisms can be considered for the disappearance of the ketenimine. The reaction does not involve a bimolecular mechanism ([2 + 2] cycloaddition of the ketenimine with itself) as the rate of reaction was found to be independent of the initial substrate concentration and the only product formed from the reaction was the expected amide.

The second mechanism requires nucleophilic attack by water at the central carbon atom of the ketenimine linkage with a second water molecule acting as a general base to facilitate proton transfer (26). This mechanism

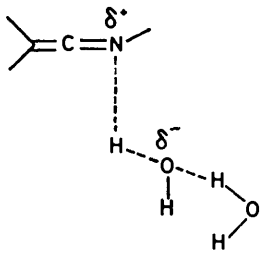


(26)

is unlikely as no significant nucleophilic attack by hydroxide ion (which is a much stronger nucleophile) was observed in the case of the *N*-alkylketenimines. It is also possible that water can act as a general acid, with protonation at carbon (27) or nitrogen (28). The final pH independent mechanism to be considered requires initial pre-equilibrium protonation of the ketenimine at high pH followed by rate-determining attack of hydroxide ion on the nitrilium ion formed in the first step, *i.e.* attack of HO^- on (17).



(27)



(28)

Involvement of the solvent in the transition state is evident from the deuterium solvent isotope effect obtained in the pH-independent region, k_{H_2O}/k_{D_2O} 4.8 ± 0.2 (pD 11.5—12.0) (see Figure 2). Further evidence for participation of the solvent is obtained from the entropies of activation (Table 5) which are of the order of magnitude expected for a transition state in which one or more water molecules are structured. When the reaction was changed to 20 : 80 dioxan–water the rate of the pH-independent reaction was reduced by a factor of 3.5 (k_0 0.4 × 10^{-3} s^{-1}) while the acid catalysed rate was reduced by much less ($k_{H_3O^+}$ 1.32 × 10^3 l mol^{-1} s^{-1}). The decrease in the rate of hydration on decreasing the ionizing power of the solvent indicates that the transition state for the rate-determining step is of greater polarity than the ground state.[22]

At present we favour the general acid catalysis mechanism for the hydration of the *N*-alkylketenimines in basic solution, *i.e.* (27) or (28). Table 2 shows that the three *N*-alkylketenimines react at approximately the same rate. Introduction of a *C*-methyl substituent results in a rate reduction of both the acid-catalysed and pH-independent reaction (by 11- and 17-fold, respectively) over the unsubstituted compound (9a). This

TABLE 5

Activation parameters for the hydration of ketenimines (9a and b) in water at pH 10 (μ 1.0; $NaClO_4$)

Ketenimine	E_a [a,b]	$\Delta H^{\ddagger}$ [a]	$\Delta S^{\ddagger}$ [c]
(9a)	15.8	15.2	−28.4
(9b)	15.2	14.6	−29.2

[a] kcal mol^{-1} (±0.5). [b] Obtained from the slopes of plots of log (k_{obs}/55.5) *versus* T^{-1} over the temperature range 15—50 °C. [c] Entropy units (±0.5), calculated for 298 K using the relation [21] $\Delta S^{\ddagger} = R\ln(k_{obs}/55.5) - R\ln(ek_BT/h) + E_a/T$.

is consistent with the transition states for both reactions having similar steric and electronic requirements, and with the same site of protonation (*i.e.* carbon) in both cases. Furthermore, if the general base mechanism for reaction with H_2O were operative (26), replacement of the *N*-alkyl group by a phenyl ring would be expected to increase the rate of the spontaneous rate, whereas in fact this route is absent and is replaced by a specific base catalysed mechanism.

The solvent isotope effect observed (4.8) rules out a general base catalysed mechanism but is close to that reported [23] (3.3—4.5) for the addition of water to ynamines (29), a reaction which has been suggested to proceed by general acid catalysis at high pH. The

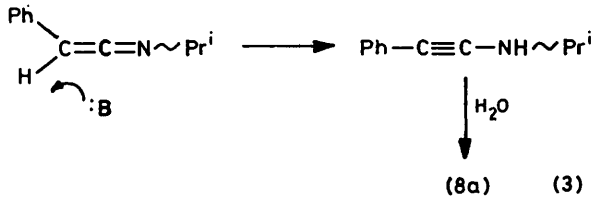
(29) (30)

only other example apart from ours and the ynamine system, comes from the work of Albery [24] who found that 3-diazobutan-2-one (30) decomposes in basic media by a spontaneous (water-catalysed) mechanism (k_{obs} *ca.* 10^{-6} s^{-1} at 25°). This reaction gives a solvent isotope effect (k_{H_3O}/k_{D_3O}) of 1.2 which has been interpreted in terms of rate-determining hydroxide ion attack, in an ion pair, on the initially formed cation.

Further support for the general acid mechanism comes from the small but measurable secondary isotope effect for the hydration of the deuteriated ketenimine (9f) at pH 10.1. This isotope effect, $k_H/k_D = 0.97 \pm 0.1$, is consistent with a mechanism in which the hybridization of the carbon at the reaction site changes from sp^2 to sp^3 in the transition state.

When the hydration of the deuteriated ketenimine was carried out on a synthetic scale at pH 9.5, the amide product recovered had the same percentage deuterium at the benzylic carbon (Table 4) as the starting ketenimine. This result is consistent with, but not definitive

of, the general acid catalysis mechanism. The low substrate isotope effect and the retention of deuterium in the product however precludes a mechanism which involves initial isomerization of the ketenimine to an ynamine [equation (3)] followed by reaction of the latter to give the amide product as this would lead to complete loss of the deuterium label from the product and result in a large rate reduction (if rate determining).



(8a) (3)

Overall, the general acid mechanism also seems reasonable in view of the fact that other weakly acidic species (piperidinium ion, HPO_4^{2-}) were found to act as general acidic catalysts for the hydration reaction (see below).

(c) *General Acid Catalysis of Hydration.*—Reactions which involve rate-determining proton transfer from H_3O^+ to the substrate are usually subject to catalysis by other acidic species. The hydration of ketenimines was found to be catalysed by a wide range of buffers from

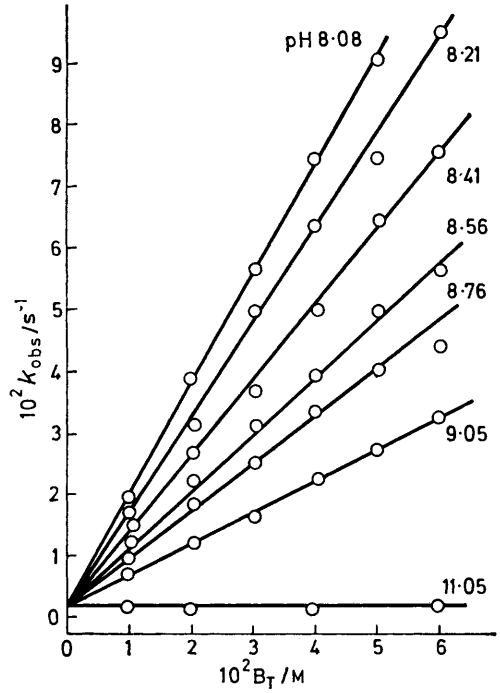


FIGURE 4 Buffer dilution plots of k_{obs} *versus* the total buffer concentration (B_T) for the hydration of (9a) in morpholine buffers at 25°

acetate [for (9d)] to morpholine and the weakly acidic HPO_4^{2-}. Reaction with morpholine buffers was investigated in detail to identify the mode of catalysis. In the presence of morpholine buffers (0.01—0.06M) the pseudo-first-order rate constants for the disappearance of the ketenimine (9a) were proportional to the total buffer concentration at fixed pH. The buffer dilution plots obtained for these buffers over the pH range 8.1—11.0 are shown in Figure 4. As can be seen, the slopes of the plots increase with decreasing pH of the reaction medium. A secondary plot of the apparent second-order rate constants (slopes of lines in Figure 4) *versus* the fraction of free morpholine in the buffer (Figure 5) enables the catalytic contributions of morpho-

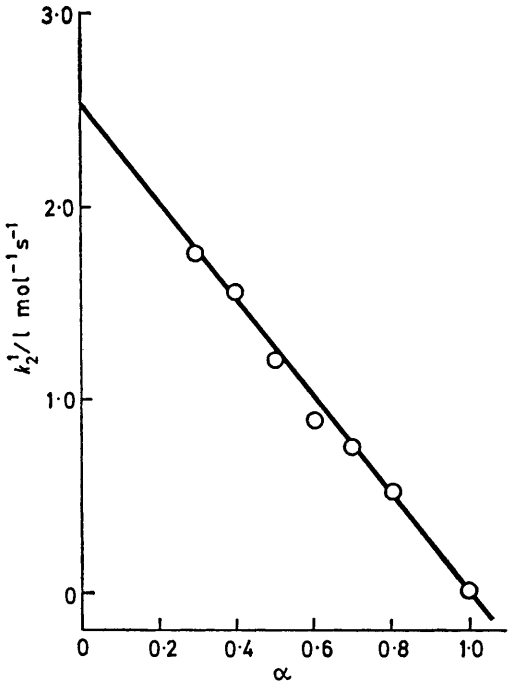


FIGURE 5 Plot of the slopes (k'_2) of the lines (k_{obs} *versus* B_T) in Figure 4 against α, the fraction of free base present

lium ion and free morpholine to be separated. It is obvious from Figure 5 that only the acidic component of the buffer is the active catalytic species. This serves to donate a proton to the ketenimine in the transition state (31).

With the more basic piperidine buffers (Table 6)

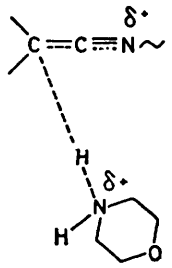
TABLE 6

First-order rate constants for the hydration of (9a) in piperidine buffers at 25° (μ 1.0; $NaClO_4$)

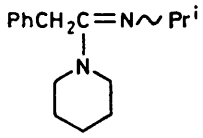
	$10^3 k_{obs}/s^{-1}$	
B_T/M	pH 10.68	pH 11.44
0.06	5.5	4.8
0.12	9.6	8.2
0.18	13.4	11.3
0.24	17.3	14.7
0.30	21.4	17.2

different behaviour was observed in that a significant reaction due to the basic component of the buffer was present. This term (k_n 4.1 × 10^{-2} l mol^{-1} s^{-1}) is approximately half that of the general acid term and most probably represents nucleophilic attack on the ketenimine by piperidine to give the amidine (32). This might seem unreasonable at first, in view of the fact

that hydroxide ion, which is a stronger nucleophile, does not attack the ketenimine. However, it is well known from studies with acyl centres, that hydroxide is a much poorer nucleophile than would be anticipated



(31)



(32)

from the pK_a of its conjugate acid (H_2O). This nucleophile usually shows a substantial negative deviation from Brönsted plots for oxygen and nitrogen nucleophiles.

Catalysis of hydration was also observed with the primary amino-group of hydrazinium ion and by carbonate, phosphate, and acetate buffers, the latter for compound (9d). Table 7 gives the rate constants obtained for hydrazine buffers while Figure 6 gives the buffer dilution plots obtained for carbonate buffers over the pH range 9.6—10.6. Again it can be seen that the acidic component of both buffers is the active catalytic species. Reactions which are subject to general acid catalysis can be generally described by the Brönsted catalysis law [equation (4)] where G_{HA} is a constant,

$$k_{HA}/p = G_{HA}(q\ K_a/p)^{\alpha} \qquad (4)$$

p and q are statistical correction factors and α is, in most cases, a measure of the degree of proton transfer to the substrate in the transition state. The Brönsted plot (covering a ΔpK_a of 8) is shown in Figure 7 while the second-order rate constants are summarised in Table 8. As Figure 7 shows, the hydration of (9a) catalysed by weak oxy-acids obeys the Brönsted equation to a good approximation with a α value of 0.53. The point for H_3O^+ deviates considerably from the plot and the possible reasons for this, including solvation effects and the interpretation of α in terms of the Marcus theory of proton transfer, have been discussed by Albery and by Kresge.[24,25] While the two secondary amines, morpholine and piperidine, show positive deviation from the Brönsted plot they give the same α value as the oxygen acids. This type of deviation is well established in acyl-transfer reactions and has generally been explained in terms of a lower steric requirement for these amines. The incorporation of the *N*-alkyl groups into a cyclic structure reduces the interference from these sub-

TABLE 7

Pseudo-first-order rate constants for the hydration of (9a) in hydrazine buffers at 25° (μ 1.0; $NaClO_4$)

	$10^3k_{obs}/s^{-1}$	
B_T/M	pH 8.12	pH 8.45
0.01	5.9	3.8
0.02	10.3	6.4
0.03	14.2	8.9
0.04	18.1	11.2
0.05	23.0	14.1
0.06	26.3	16.2

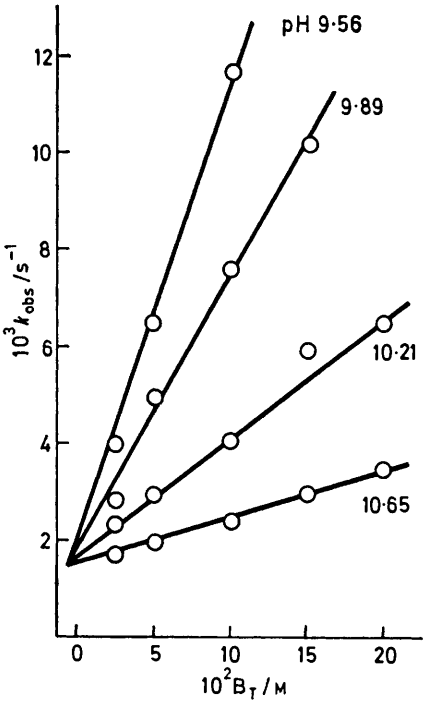


FIGURE 6 Buffer dilution plots for the hydration of (9a) in carbonate–hydrogen carbonate buffers at 25°

TABLE 8

Summary of second-order rate constants (k_{HA}) for the general acid catalysed hydration of phenylketen-*N*-isopropylimine (9a) in water at 25°

Catalyst	pK_a [a]	p [c]	q [c]	Buffer concentration/M	k_{HA}/l mol^{-1} s^{-1}
H_3O^+	−1.5 [b]	3	2	10^{-6}—10^{-4}	2.2×10^3
$NH_2NH_3^+$	8.14	3	2	0.01—0.06	0.82
Morpholine-H$^+$	8.41	2	1	0.01—0.06	2.57
HCO_3^-	10.25	1	3	0.025—0.20	5.3×10^{-2}
HPO_4^{2-}	10.73 [d]	1	4	0.01—0.10	1.25×10^{-2}
Piperidine-H$^+$	11.09	2	1	0.06—0.30	7.66×10^{-2}
H_2O	15.7 [c]	2	1	55.5	2.4×10^{-5}

[a] Calculated from the measured pH of buffer solutions containing different buffer ratios. [b] R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, London, 1973, 2nd edn., p. 92. [c] Ref. 23. [d] Measured for ionic strength of unity ($NaClO_4$); the thermodynamic value (at μ 0) is 12.4. [e] Statistical factors in Brönsted equation.

stituents in the transition state for nucleophilic attack or proton transfer in the present case. Rate-determining proton transfers to carbon sites, activated by conjugation with a lone pair of electrons on a neighbouring heteroatom, are characterised by Brönsted α values in the range 0.5—0.7,[23,24,26-28] so that our observed value of 0.53 is consistent with rate-determining proton transfer to carbon.

The addition of carboxylic acids to ketenimines is of

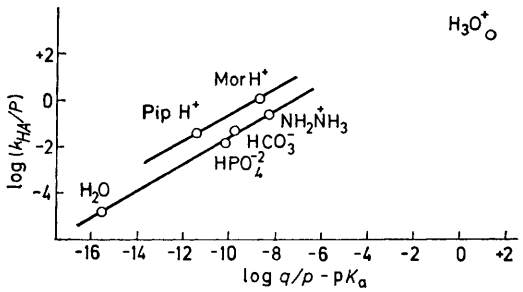


FIGURE 7 Brönsted plots for the general acid catalysed hydration of phenylketen-*N*-isopropylimine (9a) in water at 25°; the lines drawn have slopes α of 0.53

particular interest as the *O*-acyl intermediate [29] generated is similar to the *O*-acylisourea (33) which is suggested to be an intermediate in condensation reactions (*e.g.* peptide bond formation) mediated by carbodi-imides (34). We found that when acetic acid was added to a solution of ketenimine (9a) in ether, the *N*-acyl compound (36) was formed in quantitative yield. This presumably arose by initial addition of the acid to the

(33) (34)

ketenimine to form the *O*-acyl adduct (35) which then rapidly isomerised to the *N*-acyl isomer (36).

When the *N*-isopropylketenimine (9a) was added to a 10^{-2}M-acetate buffer at pH 4.7, the u.v. spectrum showed that the imine had reacted immediately on mixing. Increasing the pH of the reaction did not slow the reaction and the buffer solutions could not be diluted below 10^{-2}M without reducing the buffering capacity of the system. The Brönsted plot in Figure 7 predicts that this

(35) (36)

reaction should be particularly rapid with an approximate second-order rate constant of 30 l mol^{-1} s^{-1}. With the 2-methylketenimine (9d) which reacts slower than (9a) it was possible to observe acetate catalysis. The disappearance of this compound was studied in acetate buffers (0.01—0.1M) over the pH range 5.1—4.35 at 25° (Table 9). At constant pH the pseudo-first-order rate constant for disappearance of the ketenimine was proportional to the total buffer concentration and the slopes of plots of k_{obs} *versus* B_T (Figure 8) increased with increasing pH indicating that acetic acid rather than acetate is the catalytic species (k_{HOAc} 0.6 l mol^{-1} s^{-1}).

TABLE 9

Variation of pseudo-first-order rate constants with the total buffer concentration (B_T) for the reaction of methylphenylketen-*N*-isopropylimine (9d) with acetate buffers in aqueous solution at 25° (μ 1.0; $NaClO_4$)

	10^3k_{obs}/s^{-1}		
B_T/M	pH 4.35	pH 4.75	pH 5.12
0.01	61.4	33.3	14.7
0.02	51.7	27.1	13.0
0.04	41.1	20.9	8.8
0.06	26.4	15.4	7.0
0.08	18.0	8.5	4.75
0.10	12.5	5.5	2.0

Conclusions.—In summary, the mechanism of hydration of *N*-alkylketenimines involves (see Scheme 5) rate-determining proton transfer from H_3O^+, H_2O, or other general acids (37; B = OH_2, ^-OH, AcO^-, R_2NH *etc.*). Proton transfer to carbon might ultimately

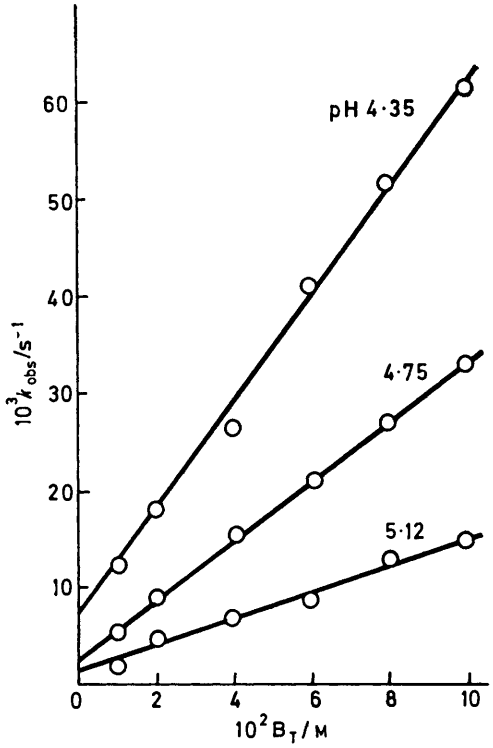
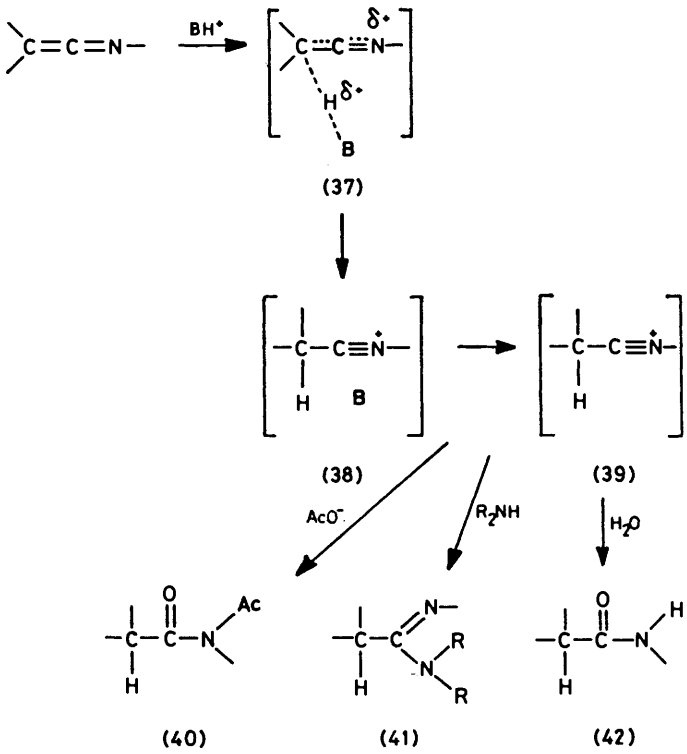


FIGURE 8 Plots of k_{obs} *versus* total buffer concentration for the reaction of (9d) in acetate buffers at 25°

involve the formation of the nitrilium ion intermediate (39), which can be trapped to yield the observed products (40)—(42). Nitrilium ions (39) are known to be highly selective [30,31] (as shown, for example, by large common ion rate depressions on solvolysis of imidoyl halides).[32] We have shown (see Experimental section) that the other nucleophiles compete best with water at

higher pH (when the concentration of the active nucleophile AcO^-, R_2NH, *etc.* is greatest). However there is also the possibility that trapping occurs before nitrilium



SCHEME 5

ion (39) formation, possibly *via* the ion pair (38), or addition of the nucleophile might actually be concerted with proton transfer to the ketenimine (a mechanism indicated by recent theoretical studies on the reaction of 1,3-dipoles with water).[33] However we are unable on the basis of our results to distinguish between these possibilities at this stage.

EXPERIMENTAL

N-Phenylisobutyramide.—Ethyl chloroformate (32.6 g, 0.3 mol) in dry dichloromethane (50 ml) was added dropwise over 15 min to a cooled (−5°) solution of isobutyric acid (26.4 g, 0.3 mol) and dry triethylamine (30.3 g, 0.3 mol) also in dry dichloromethane (200 ml). A precipitate slowly formed. The solution was stirred at −5° for a further 30 min. Aniline (28.9 g) was then added dropwise and during this addition the precipitate slowly disappeared. The mixture was allowed to warm to room temperature and stirred for 24 h. Successive washing of the solution with 2N-HCl (2 × 500 ml), 10% $NaHCO_3$ (2 × 500 ml), and water (2 × 200 ml), followed by evaporation of the dried ($MgSO_4$) solvent gave the amide (38 g) which on recrystallisation from aqueous ethanol had m.p. 103—105° (lit.,[34] 105°).

Dimethylketen-*N*-phenylimine was prepared by the method of Bestmann.[35]

N-Isopropyl-2-phenylacetamide.—Phenylacetyl chloride (prepared by treatment of the acid with thionyl chloride in benzene) (46.5 g, 0.3 mol) in dry ether (200 ml) was added dropwise to a solution of isopropylamine (17.7 g) and dry triethylamine (30.3 g) in ether (200 ml) which had been cooled in an ice–salt bath. A precipitate of triethylammonium chloride slowly formed and the mixture was stirred at ambient temperature for 5 h after the addition of the last of the acid chloride. The solution was then filtered and the solid residue was washed with ether (100 ml). Evaporation of the combined filtrate and washings left a yellow syrup which solidified when mixed with cold light petroleum. This solid was recrystallised twice from chloroform–light petroleum to give the amide as needles, δ($CDCl_3$) 7.21 (5 H, s), 5.6 (1 H, s, br), 4.0 (1 H, septet), 3.46 (2 H, s), and 1.06 (6 H, d). Table 10 gives the other physical details for this compound and the following *N*-substituted phenylacetamides obtained by this procedure: N-*s-butyl*, δ($CDCl_3$) 7.2 (5 H, s), 3.75 (1 H, sextet), 3.38 (2 H, s), 1.2 (2 H, q), 1.0 (3 H, d), and 0.9 (3 H, t); N-*cyclohexyl*, δ([$^2H_6$]acetone) 7.31 (5 H, s), 3.45 (2 H, s), 3.1 (1 H, t), and 1.5 (10 H, m).

N-Isopropyl-2-phenylpropionamide.—This amide was obtained from 2-phenylpropionic acid which was prepared by the following route. Acetophenone and ethyl chloroacetate were condensed in the presence of potassium t-butoxide to give 1-ethoxycarbonyl-2-phenyl-2-methyloxiran (88%), b.p. 84—86° at 0.45 mmHg (lit.,[36] 111—114°

TABLE 10

Physical and analytical data for *N*-substituted 2-phenylacetamides (8)

			Found (%)			Required (%)		
N-Substituent	M.p. (°C)	ν_{max}/cm^{-1}	C	H	N	C	H	N
Isopropyl	103—104 [a]	3 440 [d] 1 648	74.3	8.5	8.1	74.6	8.5	7.9
Cyclohexyl	123—125 [a]	3 280 1 650	77.7	8.9	6.4	77.4	8.75	6.4
s-Butyl	62—63 [b]	3 300 1 655	75.9	8.9	7.3	75.4	8.9	7.3
n-Butyl	49—50.5 [c]	3 280 1 665	75.3	8.6	7.35	75.4	8.9	7.3
Phenyl	116—117 [a] (lit.[e] 118)	3 220 1 650	79.3	6.1	6.4	79.6	6.2	6.6

[a] From chloroform–light petroleum. [b] From cyclohexane–light petroleum. [c] From ether–light petroleum. [d] In chloroform solution. The other spectra were run for KBr discs. [e] H. Staudinger, *Ber.*, 1911, **44**, 537.

at 3 mmHg). The sodium salt of the glycidic acid was converted into 2-phenylpropionaldehyde, $\nu_{max.}$ (film) 2 725, 1 740, and 1 620 cm^{-1}; δ(CCl_4) 9.58 (1 H, d, *J* 2.3 Hz), 7.36 (5 H, m), 3.45 (qd), and 1.3 (3 H, d, *J* 7.4 Hz). Oxidation of the aldehyde with acidic permanganate[37] gave 2-phenylpropionic acid, b.p. 90—92° at 0.2 mmHg (lit.,[38] 144—147° at 11 mmHg), δ(CCl_4) 12.4 (1 H, s, collapses in D_2O), 7.29 (5 H, m), 3.65 (1 H, q), and 1.43 (3 H, d). The acid was converted into the acid chloride with thionyl chlor-

ide which was then treated with isopropylamine to give the amide which had m.p. 84—85° (chloroform–light petroleum), $\bar{\nu}_{max.}$ (KBr) 3 410, 3 310, and 1 655 cm^{-1}; δ($CDCl_3$) 7.31 (5 H, s), 6.25 (1 H, d), 4.0 (1 H, m), 3.5 (1 H, q), 1.45 (3 H, d), and 1.1 (6 H, d) (Found: C, 75.15; H, 8.8; N, 7.3. $C_{12}H_{17}NO$ requires C, 75.6; H, 8.9; N, 7.3%).

Phenylketen-N-isopropylimine.—Finely powdered PCl_5 (15.6 g, 0.075 mol) was added slowly to a solution of *N*-isopropylphenylacetamide (13.3 g, 0.075 mol) in dry benzene (150 ml). The solution was refluxed for 1 h, then cooled, and the benzene was evaporated on a rotary evaporator. The residual $POCl_3$ was removed under high vacuum (*ca.* 0.2 mmHg) and condensed in a liquid nitrogen trap. Distillation of the residue gave *N*-isopropylphenylacetimidoyl chloride as a liquid, b.p. 68—72° at 0.55 mmHg, δ($CDCl_3$) 7.14 (5 H, s), 3.7—3.85 (3 H, overlapping s and septet), and 1.1 (6 H, d, *J* 7.5 Hz).

Dry triethylamine (12 ml) was added dropwise with shaking to a solution of *N*-isopropylphenylacetimidoyl chloride (7.14 g) in dry benzene (75 ml). A precipitate formed immediately. The mixture was protected from moisture ($CaCl_2$ tube) and refluxed for 6 h, then cooled and filtered to remove the insoluble amine hydrochloride which was washed with benzene (50 ml). Evaporation of the combined filtrate and washings left the crude *ketenimine* as a yellow liquid which was purified by vacuum distillation (see Table 11) (Found: C, 82.6; H, 8.3; N, 8.5. $C_{11}H_{13}N$ requires C, 83.0; H, 8.2; N, 8.8%). This ketenimine could only be obtained pure by distilling the liquid immediately before analysis. In general, these ketenimines could be purified by vacuum distillation and are stable for at least six months if stored under a nitrogen atmosphere at −20 °C in the absence of light. On standing in sunlight these materials darken in colour but this does not affect the spectroscopic properties (i.r. and n.m.r.) of the compounds. The *N*-phenyl compound (9e) decomposed on distillation under vacuum. However, this compound could be purified prior to the kinetic experiments by extraction into dry low-boiling light petroleum. Evaporation of the solvent left the pure ketenimine (as judged by n.m.r.). The ketenimine derived from *N*-n-butyl-2-phenylacetamide was extremely unstable. This ketenimine which showed a cumulene absorption at 2 055 cm^{-1} (CCl_4) polymerised within a few hours of preparation and was not investigated further.

TABLE 11

Physical and spectroscopic properties of ketenimines

Ketenimine	B.p. (°C) (*p*/mmHg)	$\bar{\nu}_{C=C=N}/cm^{-1}$	Chemical shift (δ) [b]
(11)	56—58 (0.45) [a]	2 020 [b]	7.1 (5 H, s), 1.7 (6 H, s)
(9a)	69—71 (0.3) [c]	2 050 [d]	7.2 (5 H, m), 4.7 (1 H, d, *J* 2.17 Hz), 3.89 (1 H, septet of d), 1.35 (6 H, d, *J* 7 Hz)
(9b)	58—61 (0.08)	2 045 [b]	7.3 (5 H, m), 4.68 (1 H, d, *J* 1.9 Hz), 3.55 (1 H, sextet), 1.5 (2 H, m), 1.22 (3 H, d), 0.95 (3 H, t)
(9c)	92—94 (0.08)	2 025 [b]	7.31 (5 H, m), 4.7 (1 H, d, *J* 1.9 Hz), 3.4br (1 H, m), 1.4br (10 H, m)
(9d)	50—52 (0.1)	2 030 [b]	7.35 (5 H, m), 3.75 (1 H, septet, *J* 6.4 Hz), 1.95 (3 H, s), 1.25 (6 H, d)
(9e)	*e*	2 040 [d]	7.28 (5 H, s), 7.15 (5 H, s),5.12 (1 H, s)
(9f)	54—56 (0.15)	2 030 [b] 2 250 [f]	7.13 (5 H, m), 3.8 (1 H, septet), 1.25 (6 H, d)

[a] Lit. b.p. 53—55° at 0.6 mmHg (J. K. Crandall and L. C. Crawley, *J. Org. Chem.*, 1974, **39**, 489). [b] CCl_4. [c] Lit. b.p. 53—54° at 0.15 mmHg (J. L. Reilly and G. R. Krow, *J. Org. Chem.*, 1972, **37**, 2364). [d] $CHCl_3$. [e] Compound decomposed on attempted distillation. [f] C–D stretching vibration (weak).

Ketenimines listed in Table 11 were prepared by the general method used for the *N*-isopropyl compound, using the crude imidoyl chlorides which had the following n.m.r. spectra: N-*s-butyl*-, δ(CCl_4) 7.31 (5 H, m), 3.82 (2 H, s), 3.7 (1 H, sextet, overlapped with last signal), 1.5 (2 H, quintet), 1.04 (3 H, d), and 0.85 (3 H, t); N-*cyclohexyl*-, δ(CCl_4) 7.28 (5 H, m), 3.78 (2 H, s), 3.65br (1 H, m), 1.55 (10 H, m); N-*phenyl*-, δ($CDCl_3$) 7.4—7.6 (10 H, m), 4.0 (2 H, s); N-*isopropyl-2-methylphenylacetimidoyl chloride* δ(CCl_4) 7.3 (5 H, m), 4.12—3.65 (2 H, m), 1.47 (3 H, d), and 1.15 (6 H, d).

[2,2-$^2H_2$]*Phenylacetic Acid.*—Phenylmalonic acid (10 g) was dissolved by shaking in a mixture of dioxan (8 ml), previously ' wet ' with D_2O and then distilled from sodium, and D_2O (42 ml) and the resulting solution was stirred at 30° for 24 h. The solvent was removed by distillation under nitrogen and the residue was then heated to 180°. At this temperature brisk effervescence occurred. When decarboxylation was complete, the residue was cooled and dissolved in chloroform. The chloroform solution was dried (Na_2SO_4) and evaporated to leave the crude deuteriated phenylacetic acid as a solid which was purified by sublimation at atmospheric pressure to give the phenylacetic acid (6.45 g, 85%), m.p. 75—76.5°. ^1H N.m.r. ($CDCl_3$) showed that the benzylic carbon contained 94 ± 2% deuterium.

N-*Isopropyl-2-phenyl*[2,2-$^2H_2$]*acetamide.*—[2,2-$^2H_2$]-Phenylacetic acid (6.12 g, 0.045 mol), isopropylamine, (2.7 g, 0.045 mol), and anhydrous 1-hydroxybenzotriazole (6.12 g, 0.045 mol) were dissolved in dry tetrahydrofuran (300 ml). To this solution was added dicyclohexylcarbodi-imide (9.27 g, 0.045 mol) in the same solvent (50 ml). The mixture, which was allowed to stand in a refrigerator for 24 h and then warmed to room temperature, was filtered to remove the insoluble dicyclohexylurea (8.5 g, 84%). Evaporation of the solvent left a yellow syrup which was dissolved in cold chloroform (100 ml) and a further small quantity of the urea was removed by filtration.

The filtrate was washed with 5% $NaHCO_3$ (70 ml) and water (2 × 50 ml) and then dried (Na_2SO_4). Removal of the solvent gave a solid (7.2 g) which was recrystallised from ether–light petroleum to give the amide, m.p. 102—104°, as needles. Analysis of the amide by ^1H n.m.r. ($CDCl_3$) showed that the benzylic position contained 92 ± 2% deuterium.

Note: (1) THF was dried using sodium benzophenone ketyl. (2) Isopropylamine was ' wet ' with D_2O and then distilled from BaO under nitrogen. (3) 1-Hydroxybenzotriazole was shaken (in $CHCl_3$) with D_2O and then dried (Na_2SO_4) before use.

N-*Isopropyl-2-phenyl*[N,2,2-$^2H_3$]*acetamide.*—The deuteriated amide above (1.97 g) was dissolved in ether (50 ml) and dry triethylamine (10 ml) was added together with D_2O (10 ml). The two-phase system was stirred at ambient temperature for 24 h. Evaporation of the dried ($MgSO_4$) ether phase left the *N*-deuteriated amide. N.m.r. ($CDCl_3$) analysis showed that the exchange at nitrogen has gone to completion, δ 5.6 (N–H), and the i.r. spectrum

(KBr) showed an N–D stretch at 2 450 cm^{-1} (2 560 cm^{-1} in $CHCl_3$). In addition, the amide showed a weak C–D stretch at 2 120 cm^{-1} ($CHCl_3$).

[2-^{2}H]*Phenylketen*-N-*isopropylimine*.—Finely powdered PCl_5 (2.02 g, 9.7 mmol) was added in one portion to a solution of the trideuteriated amide (1.75 g, 9.7 mmol) in dry benzene (100 ml). The resulting mixture was heated under reflux for 1 h while a slow stream of dry nitrogen was bubbled through the solution to sweep out any DCl evolved. The solvent was then distilled off under nitrogen and the $POCl_3$ residue was removed by evacuation of the flask at 1 mmHg for 15 min. Dry benzene (100 ml) was then added to the residue followed by dropwise addition of dry triethylamine (6 ml), previously 'wet' with D_2O and distilled from BaO, in the same solvent (20 ml). The mixture was then refluxed under nitrogen for 2 h, cooled, and filtered to remove the amine deuteriochloride which was washed with dry benzene (20 ml). Evaporation of the combined filtrate and washings left the crude ketenimine as a yellow oil (Table 11). The yield of distilled product was 0.53 g (34% from the amide). Examination of the n.m.r. spectrum (CCl_4), using the aromatic protons as an internal standard, showed that the ketenimine contained 88 ± 3% deuterium at the terminal carbon.

N-*Acetyl*-N-*isopropyl*-2-*phenylacetamide*.—Acetic acid (1.2 g, 0.2 mol) was added dropwise to a solution of phenylketen-*N*-isopropylimine (0.8 g, 0.05 mol) in dry ether (50 ml). The solution was refluxed for 1 h, then cooled, washed with 5% $NaHCO_3$ (2 × 50 ml), water (3 × 50 ml), dried (Na_2SO_4), and evaporated to leave a yellow liquid (0.83 g). This was distilled under reduced pressure to give the amide as a clear liquid, b.p. 108—111° at 0.9 mmHg; $\bar{\nu}_{max.}$ (CCl_4) 1 700 and 1 715 cm^{-1}; δ 7.25 (5 H, m), 4.1 (1 H, septet), 3.88 (2 H, s), 2.15 (3 H, s), and 1.25 (6 H, d) (Found: C, 70.7; H, 7.85; N, 6.9. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%).

N-(N-*Isopropylphenylacetimidoyl*)*morpholine*.—A solution of morpholine (2 ml) and phenylketen-*N*-isopropylimine was refluxed in dry toluene (25 ml) for 25 h. Evaporation of the toluene on a rotary evaporator gave a yellow liquid which solidified when it was allowed to stand in a refrigerator. The resulting solid was recrystallised from hexane to give the amidine as yellow needles (0.43 g, 60%), m.p. 54—56°, δ(CCl_4) 7.22 (5 H, m), 3.7—3.12 (11 H, m), and 1.04 (6 H, d) (Found: C, 72.9; H, 8.9; N, 11.2. $C_{15}H_{22}N_2O$ requires C, 73.2; H, 8.9; N, 11.3%).

Product Analysis.—*Hydration of phenylketen*-N-*isopropylimine*. (a) Low pH. The ketenimine (0.1 g) in dioxan (25 ml) was added dropwise over 15 min to a solution containing distilled water (400 ml), dioxan (75 ml), and $NaClO_4$,-$1H_2O$ (70.3 g) maintained at pH 4 with a pH-stat containing 1M-NaOH. The solution was stirred at room temperature for 2 h, then saturated with sodium chloride, and extracted with chloroform (6 × 50 ml). Evaporation of the dried ($MgSO_4$) extracts left a solid (198 mg, 98%). This was identical by t.l.c. [silica; chloroform–ethyl acetate (1 : 1)] with an authentic sample of the amide and on recrystallisation from chloroform–light petroleum had m.p. 104°.

(b) High pH. This procedure was repeated at pH 10 using the same conditions, except that the reaction was allowed to proceed for 4 h before work-up. The yield of amide obtained was 177 mg (85%).

(c) Hydration of (9a) in D_2O at pH 2. The ketenimine (0.1 g) in dioxan (2 ml) was added dropwise over 10 min to a solution containing deuterium oxide (99.8 atom % D; 16 ml), dioxan (2 ml), and anhydrous sodium perchlorate (3.06 g), maintained at pH 2 by the addition of dilute perchloric acid solution (the isotopic dilution under these conditions was <0.02%). The solution slowly became turbid and a precipitate (amide) slowly formed. Stirring was continued for a further 20 min, the mixture was then extracted with chloroform (6 × 10 ml). Evaporation of the dried (Na_2SO_4) extracts left a yellow oil which slowly solidified. N.m.r. examination showed that this product was the expected amide containing 50 ± 3% deuterium at the benzylic position. As a check for deuterium exchange, a sample of undeuteriated amide was stirred in the same D_2O solution at pH 2 for 30 min. The n.m.r. spectrum of the extracted product showed that no incorporation of deuterium had occurred. In a similar experiment, a sample of the dideuteriated amide (prepared above) was stirred under the same conditions in dioxan–water. Again no deuterium loss was found by n.m.r.

The product from the above experiment was recrystallised from chloroform–light petroleum and the deuterium content assessed by mass spectrometry (70 eV; 150°) using the *m/e* 178 (M^+, intensity, 4.5% of base peak at *m/e* 92) and 93 peaks. Correction of the $M + 1$ peak in the deuteriated amide for the intensity of the $M + 1$ peak in the undeuteriated amide (14%) showed that the amide obtained from hydration of the ketenimine in D_2O contained 9.6% undeuteriated amide, 82.3% monodeuteriated product, and 8.2% dideuteriated material. This corresponds to 41% deuterium at the benzylic position (theoretical 50%). Prior to examination of this material exchange of the labile N–D in the product was carried out by stirring the amide in water with triethylamine. This procedure did not affect the deuterium content at the benzylic carbon (by n.m.r.). Use of the mass spectral peak due to the methylenecyclohexadienyl radical cation (*m/e* 92/93) gives a higher (45%) degree of deuteriation at the benzylic position. The difference between the two figures may be due to the $M + 2$ peak representing amide monodeuteriated both at nitrogen and at the benzylic carbon. If this is the case, then the agreement between the two figures would be satisfactory.

(d) Hydration of [2-^{2}H]phenylketen-*N*-isopropylimine (9f). (i) Low pH. This was conducted using the deuteriated ketenimine (0.15 g) in 20 : 80 dioxan–water (1 l) containing 1M-$NaClO_4$ at pH 3.5. The solution was stirred for 15 min at room temperature and then divided into two 500 ml portions. The first was extracted with chloroform [as for the product extraction in (a) above]. The chloroform extract was shaken with charcoal, then filtered through Celite, dried, and evaporated. The deuterium content of the product was estimated by n.m.r. ($CDCl_3$). This product (0.08 g) was then purified by preparative t.l.c. (silica HF_{254}, using chloroform–ethyl acetate as eluant) and analysed for deuterium by mass spectrometry (Table 4). The second 500 ml portion was allowed to stir at ambient temperature for 1 h and extracted as above.

(ii) High pH. This procedure was repeated at pH 9.5 using the same amount of substrate. After 2 h half the product was extracted (0.065 g) while the remainder was allowed to stir for 4 h. The yield of product obtained was 0.085 g.

Trapping Experiments.—(a) *With acetate buffer*. A solution of the ketenimine (0.1 g) in dioxan (20 ml) was added slowly to a 0.5M-sodium acetate in 20 : 80 dioxan–water maintained at pH 9.35. This solution which was slightly turbid initially was stirred at ambient temperature for

4 h and then extracted as above. The crude product obtained (0.15 g) was shown by n.m.r. analysis ($CDCl_3$) to contain 22% of the trapped product by integration of the *N*-acetyl protons (δ 2.3) relative to the benzylic methylene protons (δ 3.52). The identity of the *N*-acyl material was further confirmed by addition of an authentic sample of the *N*-acyl compound to the n.m.r. tube and noting an increase in the integration of the acetyl group resonance while the benzylic resonance of the amide was unchanged.

This procedure was repeated at pH 4.15 and the crude product (0.105 g) was shown to be the amide. No trace of the *N*-acyl compound could be found. Prior to the extraction of the product, the mixture was basified to pH 8 to avoid extracting any acetic acid into the chloroform.

(b) *With morpholine buffer.* This experiment was conducted using the same procedure in a 0.2M-morpholine buffer at pH 11.05 using a reaction time of 4 h. The product was obtained as a yellow oil (0.21 g). T.l.c. analysis [silica, chloroform–ethyl acetate (2 : 1) as eluant] showed that the amide of R_F 0.4 was present together with an immobile spot at the origin. Further elution using 10% ammonia (*d* 0.88) in methanol showed that the expected amidine, R_F 0.63, was also present. The amidine was detected by I_2 staining.

Kinetic Method.—Kinetic studies were carried out by spectrophotometric methods using either a Perkin-Elmer 124 or Unicam SP 800 spectrophotometer for reactions where buffer solutions were used or for initial repetitive scanning of reactions. For reactions which were run in the absence of buffer solutions, a Cary 14 spectrophotometer equipped with a pH-stat was used.[39] Stock solutions of the substrates were prepared in dioxan or acetonitrile.

Deuterium oxide for kinetic studies was used as received (Aldrich Gold Label; 99.8 atom % D). For this solvent the ionic strength was maintained at unity with anhydrous sodium perchlorate. This was obtained by heating the monohydrate (AnalaR) grade) at 200 °C under vacuum (1 mmHg) for 6 h.[23] Solutions of sodium deuterioxide in D_2O were obtained by dissolving the required amount of dry sodium metal in the solvent. Solutions of deuteronium ion in D_2O were obtained by addition of a small amount of $HClO_4$ in D_2O to 1M-$NaClO_4$ in D_2O. The isotopic dilution under these conditions was negligible.[40]

Solvent isotope effects were calculated using rate constants which were determined under exactly the same conditions on the same day using the same spectrophotometer. The secondary isotope effect reported was calculated from the mean value of four rate constants for each of the two compounds and was corrected for the amount of undeuteriated material present in (9f).

Amine Perchlorates.—Morpholinium perchlorate was prepared by mixing 72% perchloric acid (70 g) in ice-cold ethanol (50 ml) with the amine (0.5 mol) in the same solvent. The salt which precipitated was recrystallised from ethanol–ether. Piperidinium perchlorate was prepared by the same method and recrystallised from acetonitrile–ether. Hydrazinium perchlorate was not isolated but prepared *in situ* from hydrazine hydrate and standardised 72% AnalaR perchloric acid solution.

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