Formation of hemiaminals by *N*-protonation of ketenimines (etheneimines) sterically hindered at carbon

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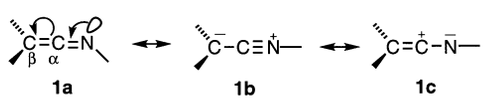
The bis(pentamethylphenyl)-*N*-isopropyl-ketenimine [*N*-isopropyl-2,2-bis(pentamethylphenyl)-ethenimine] 11 undergoes pre-equilibrium *N*-protonation followed by water attack in 1 : 1 acetonitrile–water at 25 °C. This is confirmed by the inverse solvent isotope effect for this acid-catalysed reaction (k_{H_2O}/k_{D_2O} = 0.48) and the observation of the 2,2-bis(pentamethylphenyl)ethene-1,1-diol 23 as an intermediate. This is formed from the ketene 22 on fragmentation of the intermediate hemiaminal 26. At pH 1.15, proton transfer to the hemiaminal 26 (which is formally an enol of an amide) and pH independent fragmentation of 26 proceed at equal rates. This change in protonation site from the normal carbon [observed with the phenyl and diphenyl ketenimines (8, 9)] is ascribed to the steric crowding about carbon in the pentamethylphenyl- and mesityl-ketenimines (11, 10).

Although ketenimines were first reported by Staudinger and Hauser[1] in the 1920s, only significant development in the chemistry of these compounds has only occurred in the last twenty years. Ketenimines **1** are isoelectronic with allenes **2** and ketenes **3** and can be regarded as the nitrogen analogues of ketenes. Ketenimines, like ketenes, can be highly reactive when appropriately substituted; the chemistry of ketenes has recently been reviewed, notably by Tidwell.[2]

The reactivity of ketenimines is dominated by the significant back donation of electron pair density from the formal nitrogen lone pair to the β-carbon. This is particularly significant because of the short α-carbon–nitrogen bond and the spatial positioning of the orbitals involved. The 'carbanion' character of the β-carbon is reflected in the reaction of ketenimines with electrophiles at this β-carbon (rather than at nitrogen), and the very low basicity (pK_a < 0) of the nitrogen.[3]



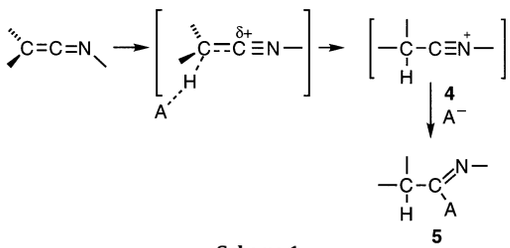
1a **1b** **1c**

2 **3**

The ketenimine system is potentially axially disymmetric in an analogous manner to allenes (**2**) where the two π bonds and thus the substituents attached to the terminal carbon atoms are in orthogonal planes. In principle therefore, it should be possible to obtain chiral ketenimines either by resolution or *via* a synthesis involving chiral substrates or reagents. However, the configurational stability of these compounds is dominated by a low barrier to isomerisation (*ca.* 40 kJ mol^{-1}) as shown by variable temperature NMR.[4] These studies are supported by reported X-ray structures which indicate considerable C–N triple bond character in the ketenimine (see **1b**) and also indicate that the C–N-substituent bond angle was in the region 145–180°, dependent on the substituents present in nitrogen[5–7] and on the β-carbon.

^{13}C NMR studies of a series of ketenimines have also been reported[8,9] and interpreted in a similar manner. The α-carbon of the heterocumulenes exhibited signals between δ 186.55 and δ 195.49 while the β-carbon signals were between δ 33.6 and δ 77.79.

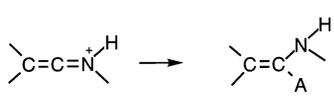
Kinetic studies previously reported[3] show that in aqueous solution the reactions of ketenimines are dominated by rate-determining proton transfer to the β-carbon to give the nitrilium ions **4** as intermediates.



Scheme 1

The driving force for this reaction is such that, for example, water reacts with ketenimines *via* this mechanism (A = OH, Scheme 1) and even amines react, not *via* the expected nucleophilic attack at the C=N bond, but preferentially *via* proton transfer from the protonated amines (which are very weak acids in aqueous solution).

We were interested in whether conditions could be generated where the ketenimine would be induced to undergo *N*-protonation to the elusive keteniminium ions **6** which on trapping by nucleophiles can give rise to **7** which is isomeric to **5**.



6 **7**

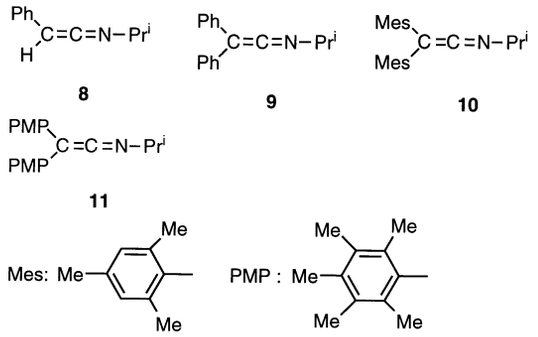
In particular we are interested in the possibility of detecting or isolating ketene hemiaminals (**7**, A = OH) by this route. These are the formal adducts of ketenes and amines or 'enols' of amides and are expected to be highly reactive.

Results and discussion

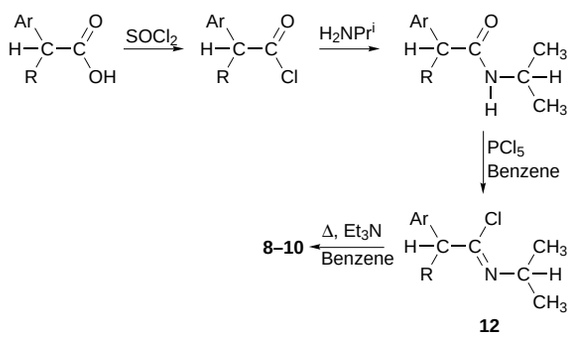
Synthesis of ketenimines

The ketenimines used in this work were obtained by two variations of the route involving the base-catalysed dehydrohalogenation of imidoyl halides. Ketenimines **8** and **9** were prepared by treating *N*-isopropylphenylacetamide and *N*-isopropyldiphenylacetamide, respectively, with phosphorus pentachloride to form the imidoyl chloride. The imidoyl chloride was then refluxed with triethylamine to effect dehydrochlorination (Scheme 2).

During the preparation of *N*-isopropylphenylketenimine **8**

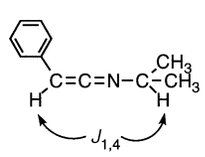


the imidoyl chloride (**12**) was isolated as a yellow liquid, by distillation and characterised by ^{1}H NMR. The ^{1}H NMR shows a doublet at δ 1.1 (6 H) for the isopropyl methyl groups, a septet overlapping a singlet at δ 3.7–4.1 (3 H) for the isopropyl proton on the secondary carbon and the two α hydrogens, and a singlet at δ 7.14 (5 H) for the aromatic hydrogens.



Scheme 2

The ^{1}H NMR of the ketenimine **8** shows a doublet at δ 1.32 (6 H) for the isopropyl methyl groups, a septet of doublets at δ 3.75–3.9 (1 H) for the hydrogen on the isopropyl secondary carbon, a doublet at δ 4.8 (1 H) for the hydrogen on the terminal carbon of the heterocumulene and a multiplet at δ 7.0–7.3 (5 H) for the aromatic hydrogens. An interesting feature of this ^{1}H NMR spectrum is the observation of five bond coupling (J 2 Hz) between the vinyl proton attached to the β-carbon of the heterocumulene and the methine proton of the *N*-isopropyl group **13**. This long range coupling was confirmed by spin-decoupling techniques.



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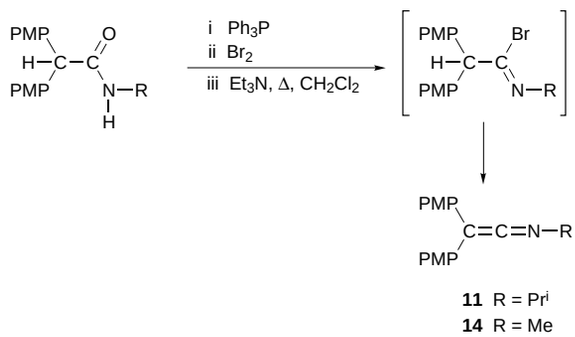
The *N*-isopropyldiphenylketenimine **9** was prepared in a similar manner; since the distillation of **9** required a higher temperature than **8**, the yield was lower due to dissociation of the ketenimine to form diphenylacetonitrile and isopropyl chloride during distillation. The IR spectrum of **9** showed the characteristic heterocumulene absorption ν(C=C=N) at 2009 cm^{-1}. The ^{1}H NMR shows a doublet at δ 1.35 (6 H) for the *N*-isopropyl methyl groups, a septet at δ 3.92 (1 H) for the *N*-isopropyl methine proton and a multiplet at δ 7.26 (10 H) for the aromatic hydrogens.

The *N*-isopropyldimesitylketenimine **10** was prepared in a similar manner except triethylamine was not necessary to effect dehydrochlorination of the imidoyl chloride formed as an intermediate. During chromatographic purification, the yellow band of the ketenimine was followed by a pink band. This band shows an IR spectrum at 2100 cm^{-1} which quickly fades. Hegarty and O'Neill[10] observed this in other bispentamethylphenyl and bispentachlorophenyl systems and showed that the distinct pink colour is due to radical formation. The radical in this case would be dimesitylcyanomethyl and, consistent with this, dimesitylacetonitrile was also isolated as a by-product.

These results are not surprising in view of the fact that the dehydrochlorination of imidoyl chlorides **12** will yield an alkyl chloride and a nitrile as the major reaction products if the substituents on nitrogen are capable of forming stable carbonium ions, such as *tert*-butyl and adamantyl.

The IR spectrum of the dimesitylketenimine **10** shows the characteristic ketenimine heterocumulene absorption ν(C=C=N) at 2015 cm^{-1}. The ^{1}H NMR shows a doublet at δ 1.2 (6 H) for the *N*-isopropyl methyl groups, two singlets at δ 2.18 (12 H) and δ 2.26 (6 H) for the ring methyl groups, a septet at δ 4.0 (1 H) for the *N*-isopropyl methine proton and a singlet at δ 6.17 (4 H) for the aromatic hydrogens.

The *N*-isopropylbis(pentamethylphenyl)ketenimine **11** and *N*-methylbis(pentamethylphenyl)ketenimine **14** were prepared by refluxing the respective amides in dichloromethane with triphenylphosphine dibromide complex in the presence of triethylamine (Scheme 3). Both **11** and **14** were isolated by flash



Scheme 3

chromatography on silica gel. It is interesting to note that **14** was isolated in 53% yield while **11** was isolated in 20.5% yield. This may be related to the ability of the isopropyl group to form a stable carbenium ion, relative to the methyl group, during dehydrobromination of the imidoyl bromide intermediate.

Kinetics and products of hydration of ketenimines

The kinetics for hydration of ketenimines, to give the corresponding amides, were investigated by spectrophotometric methods in acetonitrile–water (1:1) at 25 °C while maintaining the ionic strength constant (μ = 0.05 M, NaCl).

Hegarty and McCarthy[3] have reported the pH profile in water for the hydration of *N*-isopropylketenimine **8** at 25 °C in water (μ = 1.0, $NaClO_4$) in the absence of buffers. This shows a pH independent rate of reaction (pH 7–12) ascribed to water acting as a general acid and acid catalysis (pH < 6), where H_3O^+ acted as a general acid catalyst in rate determining β-carbon protonation; similar reaction pathways are observed for **8** in the 1:1 acetonitrile–water solvent used in the present study.

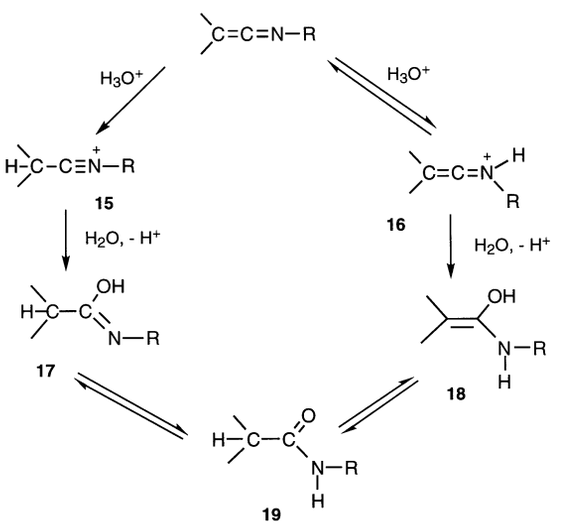
The *N*-isopropyldiphenylketenimine **9** showed lower reactivity (relative to **8**) so its hydrolysis could be studied at lower pH values. The observed first-order rate constants for the hydration are listed in Table 1.

These results (Fig. 1) show a direct dependency of log k_{obs} on the pH of the reaction medium over the pH range studied (slope = 1.0). That *N*-isopropyldiphenylacetamide was the only product of hydration **9** was confirmed by HPLC of the solutions after each kinetic measurement and also by isolation of *N*-isopropyldiphenylacetamide as the only product when hydration was carried out on a preparative scale.

Two mechanisms may be considered for the acid-catalysed hydration of ketenimines (Scheme 4). The first involves rate-determining protonation of the β-carbon of the heterocumulene to give the nitrilium ion **15**; the alternative involves rapid

Table 1 Observed rate constants for the hydration of *N*-isopropyldiphenylketenimine **9** and *N*-isopropyldimesitylketenimine **10** as a function of pH in acetonitrile–water, 1:1

pH	Ketenimine **9** $k_{obs}/10^{-4}$ s^{-1}	Ketenimine **10** $k_{obs}/10^{-4}$ s^{-1}
1.13	1905	100
1.28	—	62
1.32	1023	—
1.64	247	24
1.95	205	12.1
2.15	145	7.59
2.52	60.3	3.63
2.74	36.8	1.95
2.86	28.2	1.70
2.95	23.0	—
3.19	18.3	0.76
3.38	10.6	0.68
3.55	6.76	—
3.78	2.19	—
4.01	1.26	—



Scheme 4

pre-equilibrium protonation of the heterocumulene nitrogen to give the keteniminium ion **16**, followed by rate-determining addition of water to the protonated species to give the observed amide product.

The key difference between the mechanisms is that either proton transfer from H_3O^+ to the β-carbon or the water attack on the protonated heterocumulene α-carbon is the rate-determining step. Reactions which involve rate-determining proton transfer from H_3O^+ to carbon are usually subject to catalysis by other acid species, thus this mechanism represents general acid catalysis of hydration.

The hydration of *N*-isopropyldiphenylketenimine **9** was found to be catalysed by a range of buffers. In the presence of these buffers (0.001–0.005 M) the pseudo-first-order rate constants for the disappearance of ketenimine were proportional to the concentration of the buffer acid species present at fixed pH and the slopes of the plots of observed rate *versus* [H^+] increase with decreasing pH. Although a detailed study of buffer catalysis was not carried out, this observed rate *versus* [H^+] increase with decreasing pH is normal behaviour for ketenimines.[3]

Evidence has already been presented that the β-carbon is the site of protonation of *N*-isopropylphenylketenimine **8** using structural and electronic effects, solvent and substrate isotope effects and by-product analysis from reactions in deuterium oxide.[3] Based on this work and on subsequent theoretical studies[11,12] of the favoured sites for protonation of ketenimines together with the fact that *N*-isopropyldiphenylketenimine undergoes general acid catalysis of hydration, we suggest that **9**

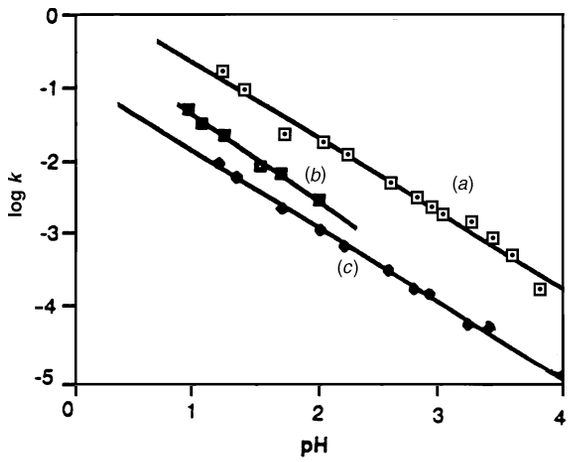


Fig. 1 Plot of the log of the observed rate constants against pH for the hydration of ketenimines: (*a*) **9** (*b*) **11** (*c*) **10** in 1:1 acetonitrile–water at 25 °C

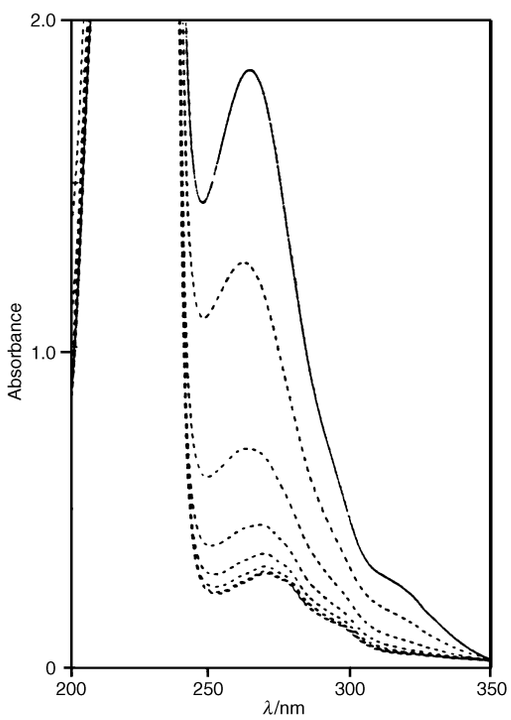


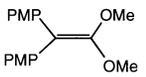
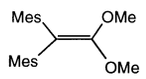
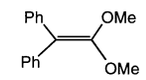
Fig. 2 UV repetitive scans for the hydration of *N*-isopropyldimesitylketenimine **10** in aqueous acetonitrile (1:1) at pH 1.0

also undergoes 'normal' hydration *via* rate-determining protonation of C_β.

The hydration of the sterically hindered dimesitylketenimine **10** was also studied in acetonitrile–water (1:1). Fig. 2 shows the repetitive scans for the hydration of this ketenimine in aqueous acetonitrile. Monitoring the rate of disappearance of ketenimine at 320 or at 260 nm gave the same results. The pseudo-first-order rate constants are given in Table 1 and plotted as a function of pH in Fig. 1.

As can be seen in Fig. 1, log k_{obs} shows a direct dependency on the pH of the reaction medium over the pH range studied. From our results the unsubstituted ketenimine **9** is more reactive towards H_3O^+ than **10** by a factor of 18. On initial consideration one might attribute this difference to the large steric bulk of the aromatic ring substituents, where the *ortho* methyl groups retard protonation of the β-carbon of the heterocumulene. However, this value is very small in comparison with a ratio of $>10^5$, reported by Kelleher[13] for the acid-catalysed hydrolysis of the corresponding diphenyl and bismesityl ketene acetals (Table 2), which involves rate-determining

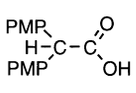
Table 2 Acid-catalysed rate constants, k_{H^+}, for hydrolysis of ketene acetals, $Ar_2C{=}C(OMe)_2$, in MeOH–water (1:1) in 1 M $HClO_4$ at 25 °C

Ketene acetal	k_{H^+}/dm^3 mol^{-1} s^{-1}	k_{rel}[a]
	1.503×10^{-4}	1
	2.215×10^{-4}	1.47
	2.515×10^{1}	1.67×10^{5}

[a] Relative rates.

protonation of the β-carbon. This raises the possibility of an alternative mechanism of reaction for this ketenimine.

The hydration of the more sterically hindered *N*-isopropylbis(pentamethylphenyl)ketenimine **11** was also investigated. The kinetics for hydration of this ketenimine proved more complex. UV repetitive scans for the hydration of **11** at low pH indicate an A ⟶ B ⟶ C type reaction. This is shown by the initial decrease in absorbance for the ketenimine at $\lambda = 320$ nm, while a strong absorbance appears at $\lambda = 260$ nm. HPLC analysis indicated the presence of two products which were identified as bis(pentamethylphenyl)acetic acid **20** and *N*-isopropylbis(pentamethylphenyl)acetamide **21**.



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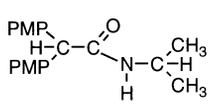

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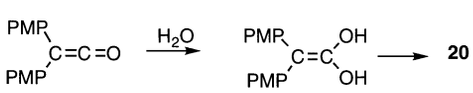
Evidence for the formation of acid **20** during the hydration of *N*-isopropylbis(pentamethylphenyl)ketenimine **11** is also supported by direct comparison of the kinetic data for the species absorbing at $\lambda = 260$ nm, which is formed during the hydration of *N*-isopropylbis(pentamethylphenyl)ketenimine **11** (intermediate B) with that for the hydration of bis(pentamethylphenyl)ketene (**22**) under the same conditions (Table 3). The ene-1,1-diol **23** is formed rapidly from the bispentamethylphenylketene **22** under these conditions.[14]

These results are consistent with the same reaction occurring in the slow step in both cases, *i.e.* ketonisation of the ene-1,1-diol **23** to form bis(pentamethylphenyl)acetic acid **20**.



22 **23**

The relative amounts of acid **20** and amide **21** formed by hydration of *N*-isopropylbis(pentamethylphenyl)ketenimine **11** over the pH range 0.87–2.2 are shown in Table 3. At pH values greater than 2.2 only bis(pentamethylphenyl)acetic acid can be detected.

Scheme 5 outlines a possible mechanism for formation of acid and amide during the reaction of **11**. Route i involves rate-determining protonation on the β-carbon of the heterocumulene to form the nitrilium ion **25** which in turn is hydrated to give amide. The second route (route ii in Scheme 5), which can account for the formation of both acid and amide, involves pre-equilibrium protonation of the heterocumulene nitrogen followed by rate-determing addition of water to the protonated species **24** to form the enol of the amide **26a** which is in equilibrium with the zwitterion species **26b**. This enol of the amide **26** can react in two ways to form either acid or amide, depending on the reaction conditions. Formation of amide requires ketonisation of the enol of the amide **26** which may be achieved

Table 3 Observed rate constants and products for the hydrolysis of the bis(pentamethylphenyl)ketenimine **11** as a function of pH in 1:1 acetonitrile–water at 25 °C

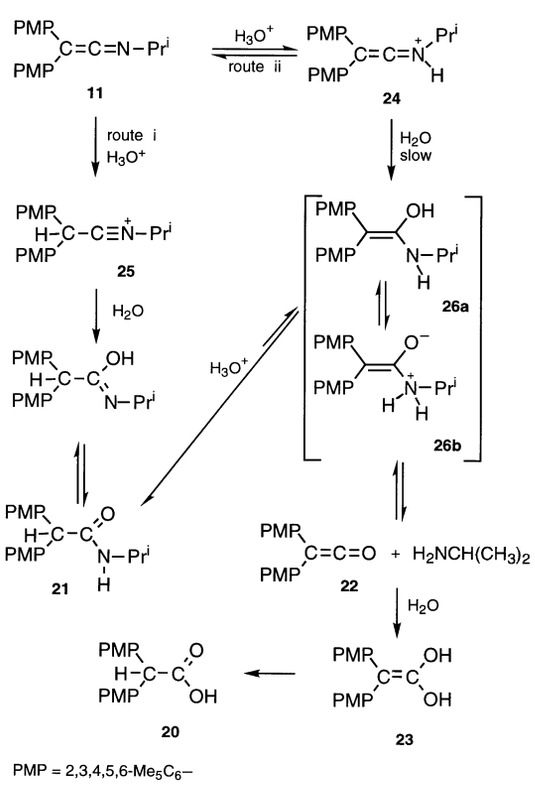
pH	$k_{obs}/10^{-4}$ s^{-1} [a]	$\log(k_{obs}/s^{-1})$ [b]	$\log(k_{obs}/s^{-1})$ [c]	Acid **20** (%)	Amide **21** (%)
0.87	525	−2.10	−2.14	27.5	72.5
0.99	340	−2.39	−2.40	39.1	60.9
1.17	229	−2.62	−2.60	52.9	47.1
1.46	94	−2.89	−2.91	70.6	29.4
1.62	71	−3.08	−3.06	83.7	16.3
1.93	32	−3.30	−3.29	90.8	9.2
2.02	—	−3.44	−3.43	98.2	1.8
2.20	—	—	—	100	—

[a] Rates of hydrolysis of **11**, measured at 320 nm. [b] Values obtained from the species absorbing at 260 nm and formed from **11**. [c] Rate constants for ketonisation of the ene-1,1-diol **23**, to the acid **20** which was formed independently from the ketene **22**.

by proton transfer, from hydronium ions present, to the carbon α to the O–C–N triad giving **21**. The formation of the acid involves dissociation of the enol of the amide to form the ketene **22** which is then rapidly hydrated to form the ene-1,-diol **23**. The ene-1,1-diol subsequently ketonises irreversibly to form bis(pentamethylphenyl)acetic acid **20**. The alternative route to the formation of acid **20** by hydrolysis of the amide **21** can be eliminated since the amide is stable to hydrolysis under the reaction conditions (pH 0–4).

The ketonisation and dissociation of the enol of the amide **26** are competing reactions; the relative amounts of each product formed is dependent on the $[H^+]$ concentration. As can be seen from Table 5 the amount of amide formed (which reflects the rate of ketonisation) decreases with decreasing $[H^+]$. Above pH 2.2 the dissociation reaction is dominant and therefore only acid is formed in this pH range.

Although both reactions (*i.e.* of the ketenimine **11** and of the ene-1,1-diol **23**) occur at similar rates in part of the pH range, measurement of the rate of reaction of *N*-isopropylbis(pentamethylphenyl)ketenimine could be monitored by following the disappearance of the ketenimine absorbance at 320 nm, where the ene-1,1-diol **23** does not have significant absorbance. The



PMP = 2,3,4,5,6-Me_5C_6–

Scheme 5

Table 4 k_{obs} values for the hydration of bis(pentamethylphenyl)ketenimine **11** as a function of pH in acetonitrile–H_2O or acetonitrile–D_2O (1:1) measured at 320 nm

	$k_{obs}/10^{-4}$ s^{-1}	$k_{obs}/10^{-4}$ s^{-1}	
pH (pD)	H_2O/HCl	D_2O/DCl	k_{H_2O}/k_{D_2O}
1.0	238	478	0.50
1.5	90	189	0.48
2.0	37.5	80	0.47

pseudo-first-order rate constants thus obtained for the hydration of **11** are given in Table 3.

At pH 1.17 the acid **20** and *N*-isopropylamide **21** are formed in a 1:1 ratio (Table 3). Therefore, we can conclude that the rate of proton transfer to the enol of the amide **26** (which is present as a short lived intermediate) and the rate of its dissociation to ketene **22** are proceeding at the same rate under these conditions. Estimation of the microscopic rate constant for proton transfer to **26** would therefore allow one to estimate the rate of dissociation of **26** to ketene **22**. Suitable models to make a reliable estimate are not yet available.

Solvent isotope effects were also examined to distinguish between rate-determining proton transfer and pre-equilibrium protonation followed by slower attack of water.

Solvent isotope effects rely on the fact that hydrogens in H_3O^+ are more loosely bound than those in H_2O. If a reaction proceeds by pre-equilibrium protonation an increase in isotopically sensitive zero point energy will result from the production of H_2O resulting and is indicated by an inverse solvent isotope effect, $k_H/k_D < 1$, on this step. The inverse effect will extend to the entire reaction provided there is a smaller isotope effect on the rate-determining step.

In the alternative rate-determining proton transfer (Path i, Scheme 5) a large primary isotope effect is produced by the breaking of the O–H bond during proton transfer. As in the previous case the change from positively charged O–H to uncharged O–H bonds in H_2O results in an inverse isotope effect but it is small as the charge building is incomplete at the transition state. The primary isotope effect dominates and the net result is $k_H/k_D > 1$.

The hydration experiments were carried out in acetonitrile–H_2O or acetonitrile–D_2O (1:1) at various values of pH and monitored spectrophotometrically at 320 nm. Experimental results are listed in Table 4 and show an average inverse isotope effect $k_{H_2O}/k_{D_2O} = 0.48$. This result indicates that the mechanism of hydration of bis(pentamethylphenyl)ketenimine proceeds *via* pre-equilibrium protonation followed by rate-determining attack of water.

The three-fold faster hydrolysis of *N*-isopropylbis-(pentamethylphenyl)ketenimine **11** relative to *N*-isopropyldimesitylketenimine **10** may be attributed to the greater accumulation of electron density on the nitrogen atom of the heterocumulene relative to that of *N*-isopropyldimesitylketenimine, due to the four extra ring-activating methyl groups. This will cause the pre-equilibrium to favour the protonated species **24**; this is clearly the more dominant factor relative to the expected slower rate of water attack on the more stable *N*-protonated ketenimine.

The enhanced elimination from **26** leading to the formation of the acid **20** during the hydrolysis of the *N*-isopropylbis-(pentamethylphenyl)ketenimine relative to that observed for **10** may also be attributed to the extra ring substituents. These *meta* methyl substituents introduce a buttressing effect causing the β-carbon of the enol of the amide **26** to be more sterically hindered (than the dimesityl case), thereby reducing the rate of its protonation and hence reducing amide formation. Elimination to form **22** may also be more rapid than when the mesityl substituents are present; so that while only the amide is formed from **10**, both amide and acid are formed competitively from **11**.

Conclusion

The hydration of the sterically hindered *N*-isopropyldimesitylketenimine **10** and *N*-isopropylbis(pentamethylphenyl)ketenimine **11** proved to be surprisingly fast (18-fold and 6-fold less reactive at pH 2, respectively, than the diphenyl analogue **9**). Such a small rate difference was unexpected on the basis of corresponding rates of proton transfer to the carbon of ketene *O*,*O*-acetals. The mechanism therefore proposed for these hydrations involves pre-equilibrium *N*-protonation (which would be less subject to steric hindrance) followed by rate-determining water attack to form the respective enols of the amides. The enol of dimesitylacetamide once formed ketonises rapidly to give dimesitylacetamide. The enol of bis(pentamethylphenyl)acetamide **26** on the other hand was found to follow two different paths: (*a*) ketonisation at a rate dependent on the pH of the solution to give bis(pentamethylphenyl)-acetamide **21** and (*b*) dissociation to form ketene **22** and amine which is a pH independent reaction; the ketene in turn is hydrated to from the ene-1,1-diol **23** which subsequently ketonises to yield bis(pentamethylphenyl)acetic acid **20**. This latter mechanism is supported by the observation of A ⟶ B ⟶ C type kinetics and the identification of ene-1,1-diol **23** as an intermediate (both spectrally and from the kinetics of its acid-catalysed further reaction). Since these competing reactions can be clearly seen for the *N*-isopropylbis(pentamethylphenyl)-ketenimine, it establishes the formation of the enol of the amide (**26**) as an intermediate. Solvent isotope effects (k_{H_2O}/k_{D_2O} *ca.* 0.48) are consistent with this change-over in normal ketenimine C-protonation as the slow step to pre-equilibrium nitrogen protonation when the carbon centre is hindered by the *ortho*-substituted aryl groups.

Experimental

Melting points were determined on a Gallenkamp melting block or a Buchi 530 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 60 MHz on a Jeol JNM-PMX60 spectrometer and at 270 MHz on a Jeol JNM-GX270 FT spectrometer. Tetramethylsilane (TMS) was used as an internal reference in all cases and deuteriated chloroform was used as a solvent unless otherwise stated; *J* values are in Hz. The IR spectra were recorded on a Perkin-Elmer 1710 FT spectrometer or on a Mattson Instruments Galaxy Series FTIR 3000 spectrometer.

Thin layer chromatography (TLC) was performed on Merck precoated Kieselgel 60F_{254} slides. Merck silica 60 (Art 7748) was used for preparative layer chromatography (PLC), and Merck silica 9385, particle size 0.04–0.063, for flash chromatography.

Reagents and solvents were purified, where stated, by standard techniques. Combustion analyses were carried out by the Microanalytical Laboratory, University College Dublin.

UV–VIS measurements were obtained from a Cary 210 equipped with a thermostatted cell compartment. Temperature control was achieved using a Techne RB12 Refrigerated Bath. UV–VIS spectra were also recorded on a Philips PU8700 series UV spectrophotometer.

HPLC analysis was performed by injection onto a C_{18} Bondapak column. Mobile phase was pumped through the system using a Waters 501 LC pump. Detection was achieved by a Waters LC spectrophotometer model 455. Peak areas were obtained by electronic integration with a Waters 745 Data module or a Shimadzu C-R3A Chromatopac.

Materials

Inorganic materials used for kinetic measurements were

AnalaR grade. The salts employed, *e.g.* sodium acetate and sodium chloride, were finely ground and dried at 120 °C for 2 h before use. Water was doubly distilled using an Exelo Water still. Amines were purified by distillation from KOH followed by distillation from CaH_2. Solutions of sodium hydroxide and hydrochloric acid were prepared by dilution of Rhone Poulenc Volucon ampoules. HPLC organic solvents were used where possible for kinetic solutions.

N-Isopropyldiphenylketenimine 9†

Phosphorus pentachloride (7.8 g, 3.75 mmol) was slowly added, with constant stirring to a solution of *N*-isopropyldiphenylacetamide (9.45 g, 3.75 nmol) in dry benzene (75 ml). The solution was refluxed for 1 h, then cooled, and the benzene removed on a rotary evaporator. The residual phosphorus oxychloride was removed under high vacuum and condensed in a dry ice–acetone trap leaving a green–yellow liquid with a small amount of white solid. NMR of this crude material showed the major compound present was *N*-isopropyldiphenylacetimidoyl chloride with the starting amide as a trace impurity. $\delta_H(CDCl_3)$ 1.21 (d, 6 H); 3.8–4.3 (septet, 1 H); 5.4 (s, 1 H); 7.3 (s, 10 H).

The *N*-isopropyldiphenylacetimidoyl chloride was not purified but used directly in the next step.

The imidoyl chloride was dissolved in dry benzene (45 ml) and dry triethylamine (6 ml) was added slowly to the green–yellow solution to give an instant colour change to orange–red. The solution 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 dry benzene (3 × 15 ml). Evaporation of the combined filtrate and washings left the crude ketenimine as an orange liquid which was purified by vacuum distillation to give a yellow oil, bp 100 °C at 0.07 mmHg. $\delta_H(CDCl_3)$ 1.35 (d, 6 H, *J* 6); 3.92 (septet, 1 H, *J* 6); 7.26 (m, 10 H). ν/cm^{-1} (KBr disc) ν(C=C=N) 2009. $C_{17}H_{17}N$ requires: C, 86.81; H, 7.23; N, 5.96. Found: C, 86.96; H, 7.19; N, 5.85%.

N-Isopropylbis(2,4,6-trimethylphenyl)acetamide

Bis(2,4,6-trimethylphenyl)ketene (6 g, 0.0216 mol) was added to 1.2 equiv. of dry isopropylamine (1.5 g, 0.0258 mol) in light petroleum (bp 40–60 °C) (75 ml) and heated under reflux for 4 h. At this stage a white precipitate had formed, the solvent and residual amine were removed under vacuum to leave an off white solid. The solid was dissolved in dichloromethane (80 ml), washed with aqueous sodium chloride (3 × 30 ml) and dried over anhydrous magnesium sulfate. Removal of the solvent and recrystallisation from light petroleum (60–80 °C) gave the desired *N*-isopropylacetamide as white needle-like crystals (4.9 g, 67% yields) mp 156–157 °C. $\delta_H(CDCl_3)$ 1.06 (d, 6 H, *J* 6.1); 2.09 (s, 12 H); 2.25 (s, 6 H); 4.18 (septet, 1 H, *J* 6.1); 5.2 (s, 1 H); 5.41 (broad s, 1 H); 6.82 (s, 4 H) ν/cm^{1} (KBr disc) ν(C=O) 1640 ν(N–H) 3300. $C_{23}H_{31}NO$ requires: C, 81.85; H, 9.25; N, 4.15. Found: C, 82.00; H, 9.45; N, 3.87%.

N-Isopropylbis(pentamethylphenyl)acetamide

Crude bis(pentamethylphenyl)ketene, prepared by treating bis(pentamethylphenyl)acetic acid (10 g, 2.88 mmol) with thionyl chloride (2.2 ml, 2.98 mmol) in dry toluene (200 ml) at 70 °C for 2 h, was dissolved in dry toluene (200 ml) and 3 equiv. of dry isopropylamine (5 g, 8.52 mmol) was added. The resulting solution was then refluxed for 12 h to give a dark red solution. The mixture was cooled, washed with aqueous sulfuric acid (4 × 50 ml), aqueous sodium hydrogen carbonate (1 × 50 ml), water (2 × 50 ml), saturated brine solution and finally dried over magnesium sulfate. After several treatments with charcoal in refluxing toluene, the solvent was removed under reduced pressure to leave an off white solid which was recrystallised from ethyl acetate–light petroleum (bp 40–60 °C) to yield the amide (7.8 g, 70% yield based on acid) as white plate-like crystals, mp 212–214 °C. $\delta_H(CDCl_3)$ 1.0 (d, 6 H, *J* 6.4); 1.98 (s, 12 H); 2.19 (s, 6 H); 4.12 (septet, 1 H, *J* 6.52); 5.29 (s, 1 H); 5.44 (broad s, 1 H) ν/cm^{-1} (KBr disc) ν(C=O) 1639. $C_{27}H_{39}NO$ requires: C, 82.39; H, 9.99; N, 3.56. Found: C, 82.05; H, 9.89; N, 3.32%.

N-Isopropylbis(2,4,6-trimethylphenyl)ketenimine 10

Phosphorus pentachloride (0.93 g, 4.4 mmol) was added slowly to a warm benzene solution (30 ml) of *N*-isopropyldimesitylacetamide (1.5 g, 4.4 mmol). As this solution was refluxed for 1 h the colour changed from bright yellow to orange and hydrogen chloride was liberated. The solvent was removed to leave an orange-coloured oil which was applied to silica gel (Merck 9385-flash chromatography) and eluted with 1:10 diethyl ether–light petroleum. The bright yellow band ($R_f = 0.75$) was collected and yielded *N*-isopropyldimesitylketenimine as a yellow oil. $\delta_H(CDCl_3)$ 1.2 (d, 6 H); 2.18 (s, 12 H); 2.26 (s, 6 H); 4.0 (septet, 1 H); 6.76 (s, 4 H). ν/cm^{-1} (C=C=N) 2015. $C_{23}H_{29}N$ requires C, 86.52; H, 9.09; N, 4.39. Found: C, 86.52; H, 9.20; N, 4.28%.

N-Isopropylbis(pentamethylphenyl)ketenimine 11

Bromine (0.2 ml, 0.0039 mol), dry triethylamine (2.74 ml, 0.0197 mol) and *N*-isopropylbis(pentamethylphenyl)acetamide (1.544 g, 0.003 93 mol) were added in that order to a solution of triphenylphosphine (1.03 g, 0.009 mol) in dry dichloromethane (50 ml). The reaction mixture was then heated under reflux for 1 h, cooled and silica gel added to the flask until the reaction mixture had caked. Removal of the solvent on a rotary evaporator gave a powder which was then applied to the surface of premoistened (CCl_4) chromatographic column of silica gel (Merck 9385; 2.5 × 35 cm) and eluted with carbon tetrachloride under applied pressure. The elution was monitored by TLC (1:5 diethyl ether–light petroleum) and the fraction with $R_f = 0.8$ was evaporated to dryness to afford 0.3 g (20.5% yield) of *N*-isopropylbis(pentamethylphenyl)ketenimine as an off-white solid. A second fraction R_f 0.28 was also recorded and was identified as *N*-isopropylbis(pentamethylphenyl)acetamide (1 g). The *N*-isopropylbis(pentamethylphenyl)ketenimine was recrystallised from diethyl ether–methanol to give a white crystalline solid, mp 179–180 °C. $\delta_H(CDCl_3)$: 1.19 (d, 6 H, *J* 6.3); 2.14 (s, 12 H); 2.19 (s, 12 H); 2.24 (s, 6 H); 4.02 (septet, 1 H, *J* 6.3) ν/cm^{-1} ν(C=C=N) 2012. $C_{27}H_{37}N$ requires C, 86.34; H, 9.93; N, 3.73. Found: C, 86.56; H, 10.1; N, 3.34%.

N-Methylbis(pentamethylphenyl)acetamide

Thionyl chloride (2 ml, 0.027 23 mol, 1.2 equiv.) was added to a cold suspension of bis(pentamethylphenyl)acetic acid (8 g, 0.0267 mol) in dry toluene (80 ml). The resulting mixture was refluxed for 2 h during which time copious amounts of hydrogen chloride were liberated. The excess thionyl chloride was removed under reduced pressure, dry toluene (50 ml) was added and the hot solution was treated twice with charcoal, filtered and cooled. Methylamine (dried by passing it through two potassium hydroxide columns using dry nitrogen as a carrier gas) was bubbled through the vigorously stirred solution for 3 h. The crude product which had precipitated was then removed by filtration and recrystallised from methanol–light petroleum (2:1) to afford 5.16 g (53% yield based on acid) of *N*-methylbis(pentamethylphenyl)acetamide as a white crystalline solid, mp 158–160 °C. $\delta_H(CDCl_3)$ 2.03 (s, 12 H); 2.17 (s, 12 H); 2.23 (s, 6 H); 2.79 (d, 3 H, *J* 4.8); 5.39 (s, 1 H); 5.73 (broad s, 1 H) ν/cm^{-1} (KBr disc) ν(C=O) 1649. $C_{25}H_{35}NO$ requires: C, 82.19; H, 9.59; N, 3.84. Found: C, 82.61; H, 9.62; N, 3.77%.

N-Methylbis(pentamethylphenyl)ketenimine 14

Bromine (0.4 ml, 0.0078 mol), triethylamine (5.48 ml, 0.0394 mol) and *N*-methylbis(pentamethylphenyl)acetamide (2.78 g, 0.0078 mol) were added, in that order, to triphenylphosphine (2.06 g, 0.0078 mol) in dry dichloromethane (80 ml). After

† IUPAC name: *N*-isopropyl-2,2-diphenylethenimine; related compounds can be named similarly.

heating under reflux for 1 h sufficient silica gel was added to adsorb the products. Removal of the solvent on a rotary evaporator gave a dry powder which was then applied to the surface of a premoistened (CCl_4) chromatographic column of silica gel (Merck 9385) and eluted under applied pressure. The elution was monitored using TLC (1:9 diethyl ether–light petroleum and the fraction with $R_f = 0.55$ was evaporated to dryness to afford 1.85 g (68% yield) of *N*-methylbis(pentamethylphenyl)ketenimine as a pale-yellow solid. Recrystallisation from dry diethyl ether gave white needle-like crystals, mp 180–182 °C. $\delta_H(CDCl_3)$ 2.14 (s, 12 H); 2.2 (s, 12 H); 2.24 (s, 6 H); 3.24 (s, 3 H) ν/cm^{-1} (KBr disc) ν(C=C=N) 2020. $C_{25}H_{33}N$ requires: C, 86.4; H, 9.57; N, 4.03. Found: C, 86.0; H, 9.64; N, 4.36%.

N-Isopropylacetimidoyl chloride 12

Phosphorus pentachloride (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 evaporated on a rotary evaporator. The residual phosphorus oxychloride was removed under high vacuum (*ca.* 0.5 mmHg) and condensed in a dry ice–acetone trap. Distillation of the lemon-yellow residue gave 7.14 g (48.7% yield) of *N*-isopropylphenylacetimidoyl chloride as a colourless liquid of bp 68–70 °C at 0.5 mmHg. $\delta_H(CDCl_3)$ 1.1 (d, 6 H, *J* 6.0); 3.7–4.1 (overlapping singlet and septet, 3 H, *J* 6.0); 7.14 (s, 5 H).

N-Isopropylphenylketenimine 8

Dry triethylamine (12 ml) was added dropwise with vigorous stirring to a solution of *N*-isopropylphenylacetimidoyl chloride (7.14 g, 0.0365 mol) in dry benzene (75 ml). A white 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 (3 × 30 ml). Evaporation of the combined filtrate and washings left the crude ketenimine as a yellow liquid which was purified by vacuum distillation through a 4 mm vigreaux column bp 46 °C at 0.1 mmHg; 38 °C at 0.15 mmHg. $\delta_H(CDCl_3)$ 1.32 (d, 6 H, *J* 6.4); 3.75–3.9 (septet of d, 1 H, *J* 6.4, *J* 2); 4.8 (d, 1 H, *J* 2); ν/cm^{-1} (C=C=N) 2021.5. $C_{11}H_{13}N$ requires: C, 83.02; H, 8.18; N, 8.80. Found: C, 83.15; H, 8.32; N, 8.53%.

Kinetic method

The pH values quoted were measured using a Radiometer model 26 pH meter with a Radiometer combined pH glass electrode. The electrode was first standardised in aqueous buffers (Radiometer pH 4.00, 9.18, 10.00), then allowed to steep in the acetonitrile–water solution for *ca.* 30 min before making a measurement. The pH values quoted are the measured values.

The acetonitrile–water solutions used for the kinetic experiments were made up by mixing the appropriate volumes of solvents. Sodium chloride was added as a solution or in solid form, although the former was found to be more satisfactory. Any aqueous sodium chloride had to be compensated for by adding acetonitrile to maintain the correct ratio. Buffers were made up in wholly aqueous medium initially, by mixing solutions of the acid and its salt or by addition of sodium hydroxide to the acid solution. The buffer was diluted by the appropriate amount of co-solvent and made up to the standard volume using a mixture of the solvents. Buffer dilutions were made from the stock buffer in mixed solvent, by adding a solution of the solvent mixture at the same ionic strength.

All kinetics were followed spectrophotometrically using a Cary 210 at appropriate wavelengths in the UV region. In all cases the rates were studied under pseudo-first-order conditions. For a typical experiment, 2 ml of solution was added to a 3 ml quartz cuvette, with pathlength 1 cm, and the temperature was allowed to equilibrate in the thermostatted cell compartment for about 15 min. The reaction was initiated by adding 20 μl (of 10^{-2} M) or 50 μl (of 5×10^{-3} M) of substrate solution from a microsyringe to the 2 ml of solvent in the cuvette. This gave substrate concentrations in the cuvette of *ca.* 10^{-4} M. Repetitive scans in the UV region established wavelengths at which optical density changed in the course of the reaction. The rates were then measured at a suitable fixed wavelength by initiating the reaction as before and plotting the change in optical density *versus* time.

Table 5 HPLC retention times (R_t) of various compounds; mobile phase is acetonitrile–water (75:25) and a flow rate of 1.5 ml min^{-1} was used

Compound	R_t/min
$(PMP)_2CHCOOH$	4.66
$(Mes)_2CHCOOH$	4.70
$(PMP)_2CHCO(NPr^i)$	8.80
Ph_2CHCO_2H	9.71

Pseudo-first-order rate constants were calculated from data covering several halflives and using experimental infinity values. Plots of log $(A_t - A_\infty)$ *versus* time, where A_t is the absorbance of the solution at any time *t* and A_∞ is the experimental absorbance of the solution under kinetic conditions at t = infinity, gave straight lines of slope $k_{obs}/2.303$. In certain cases where the infinity was not well defined (*e.g.* due to a consecutive slower reaction) the Guggenheim method of calculation was used. Rates were reproducible to within 4% of the mean value. Experiments measuring solvent isotope effects on the hydration of *N*-isopropyl bis(pentamethylphenyl)ketenimine were followed at a wavelength of 320 nm. These experiments involved adding 0.5 ml of solution to a 1 ml quartz cuvette of pathlengths 1 cm and the temperature allowed to equilibrate at 25 °C. The reaction medium was made up using 1 M DCl in D_2O or 1 M HCl in H_2O to give solutions of pH 1, 1.5 and 2 in D_2O/H_2O acetonitrile 1:1. The reaction was initiated by adding 25 μl of substrate in acetonitrile (1×10^{-3} M) to the cuvette to give a substrate concentration of *ca.* 5×10^{-5} M.

The final product spectrum, on completion of a kinetic experiment, was compared with the spectrum of an authentic sample of the product. In most cases the products were also identified by HPLC analysis of the sample from the kinetic run. (Table 5 gives retention times.)

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