Amination of Ketenes: Kinetic and Mechanistic Studies

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The rate constants for reaction of $PhMe_2SiCH{=}C{=}O$ (**6**) with amines to form amides in CH_3CN are best fitted with a mixed second- and third-order dependence on [amine], in stark contrast to previous studies of $Ph_2C{=}C{=}O$ and other reactive ketenes in which only a first-order dependence on [amine] was observed in H_2O or in CH_3CN. Derived third-order rate constants for **6** depend on the amine basicity, with a 1.7×10^7 greater reactivity for *n*-$BuNH_2$ compared to $CF_3CH_2NH_2$. These kinetic results are consistent with recently reported theoretical studies for reaction of $CH_2{=}C{=}O$ with NH_3. For **6** the relative reactivity k(*n*-$BuNH_2$)/$k(H_2O)$ is estimated to be 10^{13} in CH_3CN. The crowded ketene *t*-$Bu_2C{=}C{=}O$ (**10**) is enormously deactivated toward amination and reacts in neat *n*-$BuNH_2$ with rates 10^{12} and 2×10^5 times slower than those for *t*-$BuCH{=}C{=}O$ and *t*-$BuC(i\text{-}Pr){=}C{=}O$ (**11**), respectively. The observed rate constants for **11** also show a higher than first-order dependence on [*n*-$BuNH_2$]. The absence of higher order kinetic terms in [amine] for more reactive ketenes is attributed to irreversibility of addition of an initial amine to the ketene, while with more stable ketenes the initial step is reversible and later steps involving additional amine molecules are kinetically significant. The general acid $CF_3CH_2NH_3^+$ catalyses the addition of $CF_3CH_2NH_2$ to **6** in a process independent of [$CF_3CH_2NH_2$]. The reactivity of **6** with *n*-$BuNH_2$ is 370 times greater in CH_3CN compared to isooctane, a result attributed to the polar nature of the transition state and possible catalysis of the addition by CH_3CN.

The reaction of ketenes with amines was reported in the first publication on ketenes[1a] and usually proceeds rapidly and quantitatively at ambient temperatures to provide amides.[1] The reaction of chiral amines to create amides with high enantiomeric excess at the new chiral center has received particular attention.[2] In early studies of the kinetics of ketene amination, Satchell and co-workers[3] observed dependences of the rate of reaction not only on [amine] but also on [amine]^2. These reactions were interpreted as involving initial addition to the C═C bond of the ketenes, but this viewpoint has been disputed.[1c] Detailed studies of the reactions of dienylketenes with amines by Quinkert and co-workers[4] have included direct observation by UV of intermediates in the reaction assigned as zwitterions and amide enols, and kinetic studies of their formation. Other recent studies of ketene amination[5] include kinetic measurements of the reactions of $Ph_2C{=}C{=}O$ with various amines in H_2O[5a] and of reactions of ketenes with amines in CH_3CN with the observation by IR of transient amide enols (or zwitterions),[5b,c] the observation of a stable amide enol from amination of a crowded diarylketene,[5d] and studies of the reactivity of dienyl-[5e] and acylketenes[5f,g] with alcohols and amines.

As part of our studies of ketene reactivity,[6] we recently[6e] made a theoretical examination of the reaction of $CH_2{=}C{=}O$ with NH_3 and found for the gas phase that reaction with two NH_3 molecules preferentially proceeds through a nonplanar transition state **1** involving in-plane attack by the nucleophilic nitrogen at the carbonyl carbon, with hydrogen-bonding assistance by the second NH_3 molecule leading to an amide enol/ammonia complex **2** (eq 1).[6e] Tautomerization of the amide enol **3** preferentially occurs with catalysis by NH_3 in a subsequent step through the complex **4** to give the amide **5** (eq 2). This initial formation of the amide enol has a lower barrier than alternatives involving addition of only a single NH_3 to

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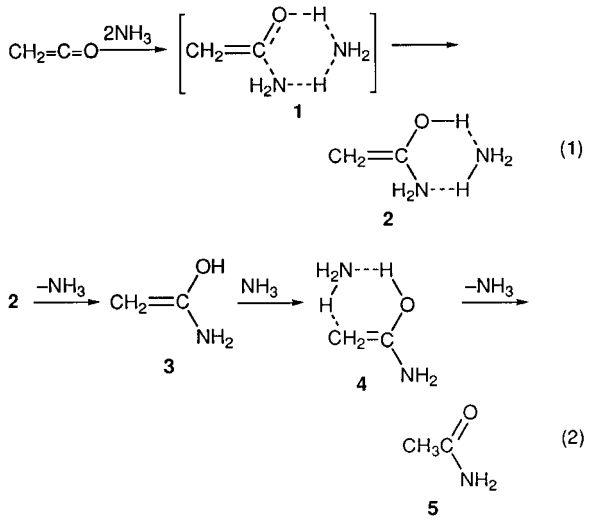


the C=O bond, or addition involving one or two NH_3 molecules to the C=C bond giving the amide directly, even though the latter process is energetically much more favorable than initial formation of an amide enol. The calculated barrier for conversion of **2** via **4** to the product amide **5** is higher than that for the reversion of **2** to reactants, suggesting that the formation of **2** would be reversible.

Recent kinetic studies of the reactions of amines with $Ph_2C{=}C{=}O$ in H_2O,[5a] or of amines with various ketenes in CH_3CN,[5b,c,g] have however shown a first-order dependence of the rates on [amine]. In H_2O the reactivities of various amines showed small differences and no systematic dependence on the pK_a of the amine conjugate acids.[5a] Studies of ketene amination in CH_3CN with time-resolved infrared detection (TRIR) also showed only a first-order rate dependence on [amine] and allowed the detection of amide enol (or zwitterionic) intermediates and the amine-catalyzed conversion of these species to amides.[5b,c]

To elucidate the discrepancy between the theoretical prediction that ketene amination would prefer transition states involving two amine molecules rather than one, and the experimental observations in both H_2O[5a] and CH_3CN[5b] of a first-order dependence on [amine], we have carried out further kinetic studies and now report results for ketene amination that are consistent with the theoretical studies and show both second and third-order terms in [amine]. We have also observed very large kinetic effects due to amine nucleophilicity and substrate steric crowding, general acid catalysis of amination, and a significant solvent effect.

Results and Discussion

The ketene $PhMe_2SiCH{=}C{=}O$ (**6**)[6d] is a long-lived species that reacts with amines at convenient rates at ambient temperatures. In previous studies[6f] the analogous silylketene $Me_3SiCH{=}C{=}O$ was found to be less reactive than *t*-BuCH=C=O toward H_2O by a factor of 60, a result attributed to ground-state stabilization of the ketene by Me_3Si.[6f] By contrast the acid-catalyzed hydration is accelerated, as k_{H^+}/k_{H_2O} (M^{-1}) is 100 times greater for $Me_3SiCH{=}C{=}O$ than for *t*-BuCH=C=O, an effect attributed to hyperconjugative stabilization by silicon of the developing $Me_3SiCH_2C^+{=}O$ ion in the transition state.[6f]

Reaction of the ketene **6** with *n*-$BuNH_2$ and with $CF_3CH_2NH_2$ in CH_3CN at room temperature cleanly formed the corresponding amides **7a** and **7b** as the only detectable products. The rates of the reaction of **6** in CH_3CN with excess amine were followed using either stopped-flow or conventional UV spectroscopic detection by the disappearance of the ketene UV absorption and give good pseudo-first-order kinetics, with rate constants that are much smaller than those of any of the ketenes studied in a previous survey of ketene reactivities with amines in CH_3CN.[5b] However, in contrast to previous studies, the measured rate constants for **6** are not linear in [amine], and so a total of 10 rate expressions were tested to fit the data, as reported in the Supporting Information (Table 7 and plots 1−23). The best fit was found using eq 3, with values of $k_a = (2.26 \pm 0.08) \times 10^5\ M^{-2}\ s^{-1}$ and $k_b = (3.80 \pm 0.22) \times 10^6\ M^{-3}\ s^{-1}$ for *n*-$BuNH_2$ (Figure 1a). Similar results were found for the reaction of **6** with

$$k_{obs} = k_a[\text{amine}]^2 + k_b[\text{amine}]^3 \qquad (3)$$

morpholine and with $CF_3CH_2NH_2$, for which the data were also fit best by eq 3 (Figure 1b,c). The derived values of k_a and k_b are collected in Table 1, and the measured rate constants are given in Table 2 (Supporting Information). Rate expressions such as $k_{obs} = k_a[\text{amine}]^2$ showed significant deviations of experimental points from the correlation in some regions of the data.

A simplified reaction scheme for ketene amination is shown in eqs 4 and 5, where the amide enol complex **8** corresponds to structure **2** previously calculated for the reaction of $CH_2{=}C{=}O$ with NH_3 (eqs 1 and 2).[6e] In this process two amine molecules participate in the reversible formation of the amide enol/amine complex **8**, which undergoes conversion to the amide **7** by two competitive processes, one of which involves catalysis by another amine molecule. The resulting rate expression in eq 6 and the steady state eq 7 lead to eq 10, which has the form of eq 3, with $k_c[\text{amine}] \ll 1$, and $k_a = k_1k_2/(k_{-1} + k_2)$, $k_b = k_1k_3/(k_{-1} + k_2)$, and $k_c = k_3/(k_{-1} + k_2)$. Fitting the data to eq 10 gave a poorer fit of the data, with $k_c[\text{amine}] \ll 1$ over almost the entire range of [amine] (see Supporting Information, Table 7).

$$\text{ketene} + 2\ \text{amine} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{complex (}\mathbf{8}\text{)} \xrightarrow{k_2} \text{amine (}\mathbf{7}\text{)} \qquad (4)$$

$$\text{complex (}\mathbf{8}\text{)} + \text{amine} \xrightarrow{k_3} \text{amine (}\mathbf{7}\text{)} \qquad (5)$$

$$-\text{d[ketene]}/\text{d}t = k_1[\text{ketene}][\text{amine}]^2 - k_{-1}[\mathbf{8}] \qquad (6)$$

$$\text{d}[\mathbf{8}]/\text{d}t = k_1[\text{ketene}][\text{amine}]^2 - (k_{-1} + k_2 + k_3[\text{amine}])[\mathbf{8}] = 0 \qquad (7)$$

$$-\text{d[ketene]}/\text{d}t = k_1[\text{ketene}][\text{amine}]^2 - k_1k_{-1}[\text{ketene}][\text{amine}]^2/(k_{-1} + k_2 + k_3[\text{amine}]) \qquad (8)$$

$$-\text{d[ketene]}/\text{d}t = [(k_1k_2[\text{amine}]^2 + k_1k_3[\text{amine}]^3)/(k_{-1} + k_2 + k_3[\text{amine}])][\text{ketene}] \qquad (9)$$

$$-\text{d[ketene]}/\text{d}t = [(k_a[\text{amine}]^2 + k_b[\text{amine}]^3)/(1 + k_c[\text{amine}])][\text{ketene}] \qquad (10)$$

The rate expression for eq 3 is also obtained from eq 11 and the equilibrium expression eq 12.

Table 1. Derived Rate Constants for Amination of $PhMe_2SiCH{=}C{=}O$

amine	solvent	k_a (M^{-2} s^{-1})	k_a^{rel}	k_b (M^{-3} s^{-1})	k_b^{rel}	pK_{BH^+}
n-$BuNH_2$	CH_3CN[a]	$(2.26 \pm 0.08) \times 10^5$	1.0	$(3.80 \pm 0.22) \times 10^6$	1.0	10.6
	isooctane[b]			$(2.01 \pm 0.04) \times 10^4$		
morpholine	CH_3CN[c]	$(4.20 \pm 0.28) \times 10^4$	1/5.4	$(2.63 \pm 0.53) \times 10^5$	1/14.4	8.49
$CF_3CH_2NH_2$	CH_3CN[d]	0.292 ± 0.010	$1/7.7 \times 10^5$	0.220 ± 0.013	$1/1.7 \times 10^7$	5.59
$CF_3CH_2NH_3^+/CF_3CH_2NH_2$	CH_3CN[e]					

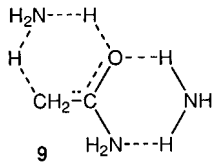
[a] [*n*-$BuNH_2$] 4.98×10^{-2} to 4.03×10^{-4} M, [ketene] = 6.8×10^{-5} M. [b] [*n*-$BuNH_2$] 6.10×10^{-2} to 9.74×10^{-3} M. [c] [morpholine] 6.28×10^{-2} to 4.04×10^{-4} M. [d] [$CF_3CH_2NH_2$] = 1.051 to 1.471 $\times 10^{-2}$ M. [e] $k_{BH^+} = 3.91 \pm 0.05$ [$CF_3CH_2NH_3^+{-}O_2CCF_3$] s^{-1} M^{-1}.

$$-\mathrm{d[ketene]}/\mathrm{d}t = \mathrm{d[amide]}/\mathrm{d}t = (k_2 + k_3[\mathrm{amine}])[\mathbf{8}] \quad (11)$$

$$k_1/k_{-1} = [\mathbf{8}]/[\mathrm{ketene}][\mathrm{amine}]^2 \quad (12)$$

$$-\mathrm{d[ketene]}/\mathrm{d}t = [(k_1k_2/k_{-1})[\mathrm{amine}]^2 + (k_1k_3/k_{-1})[\mathrm{amine}]^3][\mathrm{ketene}] \quad (13)$$

The rate law for this process (eq 10) agrees with the experimental data for the measured pseudo-first-order rate constants in the presence of excess amine (eq 3). In the previous theoretical calculations,[6e] no attempt was made to calculate a reaction pathway involving a third amine molecule. A model (**9**) is shown for an NH_3 catalyzed isomerization of the amide enol/NH_3 complex **2** which leads to the amide product **5**. In the alternative path not involving a third amine molecule isomerization of **2** to **4** (eq 2) may occur, or the catalytic role may be taken by the CH_3CN solvent.



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The reactivity of **6** in CH_3CN with morpholine and with $CF_3CH_2NH_2$ was also fit best by eq 3 (Figure 1b,c), with rate ratios $k_{n\text{-}BuNH_2}/k_{morpholine}$ of 5.4 and 14.4, and $k_{n\text{-}BuNH_2}/k_{CF_3CH_2NH_2}$ of 7.7×10^5 and 1.7×10^7, for k_a and k_b, respectively. The correlations of log k_a or log k_b with pK_{BH^+} of the amines are only fair, with slopes of 1.18 and 1.45, respectively; however, because of the various roles of several amine molecules in this multistep mechanism the absence of a good correlation is not unexpected. The absence of a strong dependence of k_2 on amine basicity for reaction of $Ph_2C{=}C{=}O$ with amines in H_2O[5a] may be attributed to hydrogen bonding of H_2O to the amine lone pair, as demonstrated by McClelland et al., for the amination of carbocations.[7a]

The reactivity of **6** with *n*-$BuNH_2$ in isooctane was also examined, and the observed first-order rate constants at different [*n*-$BuNH_2$] are given in Table 3 (Supporting Information). The data were correlated by eq 3, but with an insignificant value for k_a for the second-order term, and the best correlation (Figure 3, Supporting Information) was with a third-order term only, $k_{obs} = (2.01 \pm 0.04) \times 10^4$ M^{-3} s^{-1} [*n*-$BuNH_2$]^3. Calculated values of k_{obs} for **6** in CH_3CN at [*n*-$BuNH_2$] of 6.10×10^{-2} and 0.974×10^{-2} M of 1700 and 24.9 s^{-1} give rate ratios for **6** $k_{CH_3CN}/k_{isooctane}$ of 370 and 375, respectively. The data set for *n*-$BuNH_2$ in isooctane solvent is not as large as in CH_3CN, and the possibility that a larger data set would favor a somewhat different rate law cannot be excluded. However, the observed rate difference with solvent is secure.

The second- and third-order dependences of the rate of **6** on [*n*-$BuNH_2$] in CH_3CN are consistent with the process outlined in eqs 4−10, and the much greater observed reactivity with the more basic *n*-$BuNH_2$ shows the strong nucleophilic component in the reaction. The significantly greater reactivity in CH_3CN compared to isooctane may arise from stabilization of a polar transition state and from hydrogen-bond acceptor interactions by CH_3CN, and the absence of the second-order term in [*n*-$BuNH_2$] for **6** in isooctane suggests that this poorly coordinating solvent cannot substitute for a third amine molecule.

The reactivity of *t*-$BuCH{=}C{=}O$ showed[5b] a linear dependence of k_{obs} on [*n*-$BuNH_2$] in CH_3CN, and so because $PhMe_2SiCH{=}C{=}O$ (**6**) shows a higher order dependence on [*n*-$BuNH_2$] (eq 3), the rate ratio k_{obs} (*t*-$BuCH{=}C{=}O$)/k_{obs} (**6**) varies from 1.1×10^4 to 80 over the measured range of [*n*-$BuNH_2$] (4.03×10^{-4} to 4.98×10^{-2} M). Over this range of concentrations the fraction of the reaction of **6** due to the term in [*n*-$BuNH_2$]^2 changes from 0.995 to 0.544.

A recent analogy to the third-order rate dependences found here is the observed dependence on $[H_2O]^3$ of quenching of fluorescence of excited *m*-hydroxy-1,1-diarylalkenes, which was attributed to proton transfer via a water trimer.[7b]

Previously[6d] the rate constant for hydration of $PhMe_2SiCH{=}C{=}O$ (**6**) in 11.1 M H_2O in CH_3CN at 25 °C was reported as 8.24×10^{-4} s^{-1}, and the calculated rate constant from eq 3 for reaction of **6** with 11.1 M *n*-$BuNH_2$ is 5.2×10^9 s^{-1}, giving an enormous rate ratio k(*n*-$BuNH_2$)/k(H_2O) for **6** of 10^{13}. Even at 0.0498 M *n*-$BuNH_2$, the highest concentration used in these studies, the observed rate constant for **6** of 990 s^{-1} is 10^6 greater than the hydration rate constant measured with a 220-fold greater concentration of nucleophile.

For comparison the reported[6h] rate constant of 0.0873 s^{-1} for hydration of *t*-$BuCHC{=}C{=}O$ in 11.1 M H_2O in CH_3CN gives an estimated k_2 of 7.9×10^{-3} s^{-1} M^{-1}, which combined with the reported[5b] k_2 for *t*-$BuCH{=}C{=}O$ with *n*-$BuNH_2$ in CH_3CN gives k(*n*-$BuNH_2$)/k(H_2O) of 2.0×10^9.

To test the generality of this behavior the amination of other unreactive ketenes was studied. The sterically protected *t*-$Bu_2C{=}C{=}O$ (**10**)[8a,b] proved to be enormously deactivated toward amination, and gave the amide *t*-$Bu_2CHCONHBu$-*n* after reaction with neat *n*-$BuNH_2$ for 8

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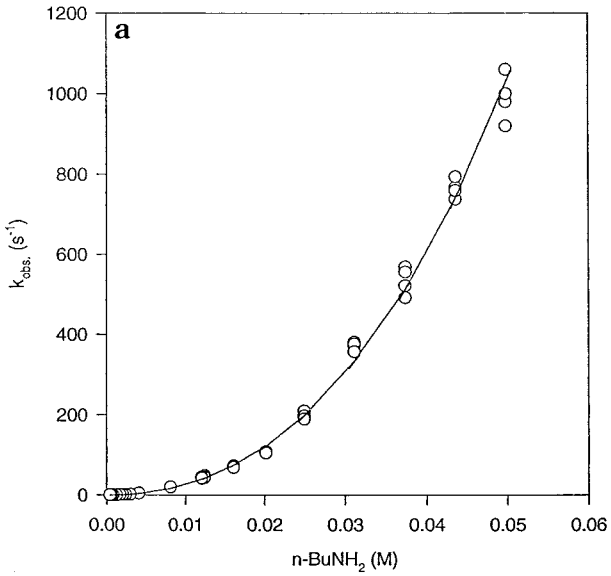
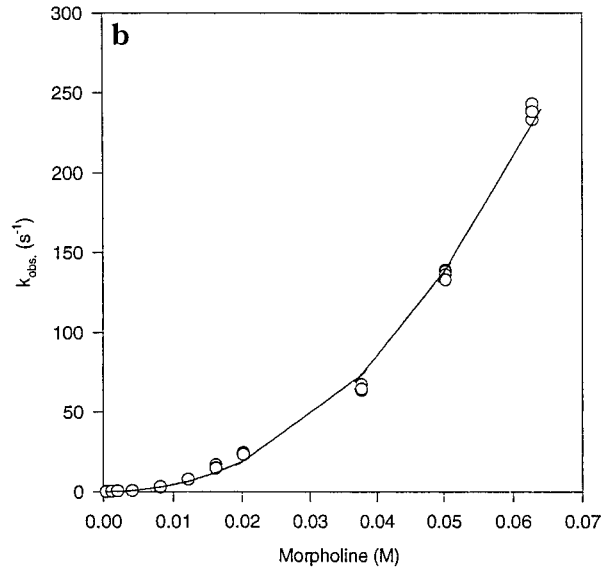




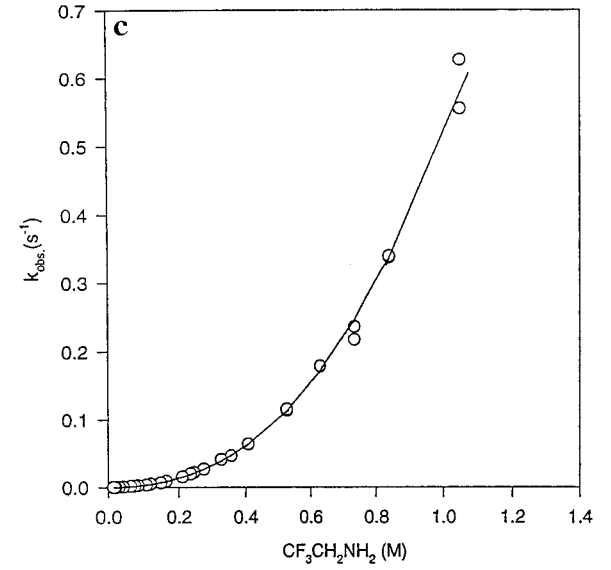


Figure 1. Rate constants for reaction of $PhMe_2SiCH{=}C{=}O$ (**6**) versus [amine] in CH_3CN and fit by eq 3: (a) *n*-$BuNH_2$, (b) morpholine, (c) $CF_3CH_2NH_2$.

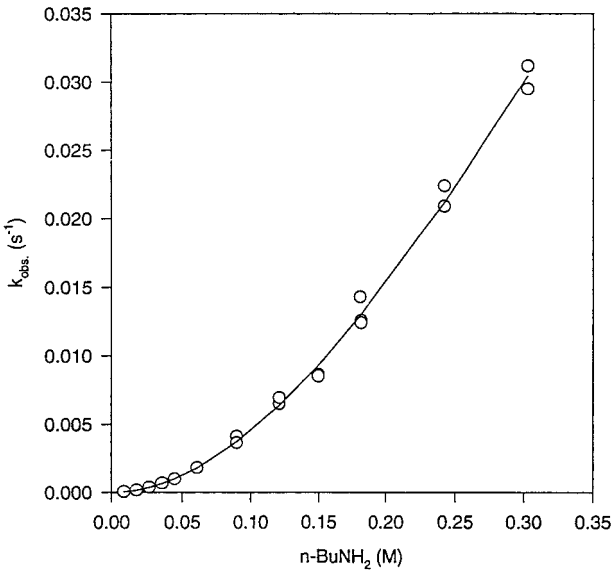


Figure 2. Rate constants for reaction of *t*-BuC(*i*-Pr)=C=O (**11**) versus [*n*-$BuNH_2$] in CH_3CN and fit by eq 14.

days at room temperature. Measured rate constants are reported in Table 4 (Supporting Information), with k_{obs} of 1.35×10^{-5} s^{-1} at 25 °C in neat *n*-$BuNH_2$, $\Delta H^{\ddagger} = 6.96 \pm 0.49$ kcal/mol, and $\Delta S^{\ddagger}$ of -57.3 ± 8.7 eu. The large negative value of the latter resembles the gas-phase value calculated for amination of $CH_2{=}C{=}O$ to give **2** (eq 1) of −45.2 eu.[6e] The reported[5b] second-order rate constant for the reaction of *t*-BuCH=C=O with *n*-$BuNH_2$ in CH_3CN of $k_2 = 1.6 \times 10^6$ M^{-1} s^{-1} gives a calculated k_{obs} for neat (10.1 M) *n*-$BuNH_2$ of 1.6×10^7 s^{-1}, indicating a rate ratio for this reaction of k(*t*-BuCH=C=O)/k(*t*-Bu_2C=C=O) of 10^{12}.

The less-crowded homologue *t*-BuC(*i*-Pr)=C=O (**11**)[8c,d] proved to be much more reactive toward *n*-$BuNH_2$ than is *t*-Bu_2C=C=O (**10**), and rate constants measured in CH_3CN (Table 5, Supporting Information) also showed a higher than first-order dependence of k_{obs} on [*n*-$BuNH_2$]. These rates gave a good fit (Figure 2) with eq 14, with $k_d = (0.552 \pm 0.023)$ M^{-2} s^{-1} and $k_e = (2.19 \pm 0.28)$ M^{-1}. For neat *n*-$BuNH_2$ (10.1 M), the predicted rate constant for **11** is 2.4 s^{-1}, leading to a rate ratio k(**11**)/k(**10**) of 1.8×10^5.

$$k_{obs} = k_d[\text{amine}]^2/(k_e[\text{amine}] + 1) \qquad (14)$$

The reaction scheme of eq 15 leads to the rate expression in eq 16 which with the steady-state eq 17 leads to eq 18, which has the form of eq 14, with $k_d = k_2k_1/k_{-1}$ and $k_e = k_2/k_{-1}$, and from the observed fit $k_2/k_{-1} = 2.19$ and $k_1 = 0.252$ M^{-1} s^{-1}.

$$\text{ketene} + \text{amine} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{complex} \xrightarrow[\text{amine}]{k_2} \text{amide} \qquad (15)$$

$$-\text{d[ketene]}/\text{d}t = k_1[\text{ketene}][\text{amine}] - k_{-1}[\text{complex}] \qquad (16)$$

$$\text{d[complex]}/\text{d}t = k_1[\text{ketene}][\text{amine}] - (k_{-1} + k_2[\text{amine}])[\text{complex}] = 0 \qquad (17)$$

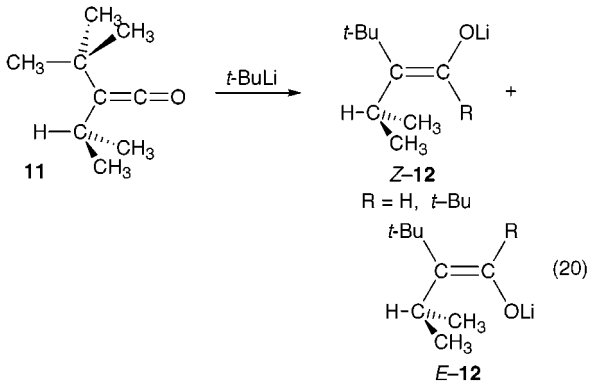
$$-\text{d[ketene]}/\text{d}t = [k_d[\text{amine}]^2/(k_e[\text{amine}] + 1)][\text{ketene}] \qquad (18)$$

This result shows that the occurrence of higher order terms in [amine] in ketene amination is not a feature only of silylated ketenes. The appearance of this behavior depends on the ketene structure in that for less reactive ketenes initial attack of a single amine molecule is not rate limiting but is reversible, and further steps involving one or more additional amine molecules are kinetically significant. In the reported[5a−c,g] studies where a first-order dependence of k_{obs} on [amine] for ketene amination is observed the initial reaction of these more reactive ketenes with a single amine molecule is irreversible. Additional amine molecules are, however, involved in the subsequent product forming steps, as the formation of intermediate amide enols and their amine-catalyzed conversion to amides was observed.[5b] For PhCH=C=O, the rate constant for the amine-catalyzed conversion of the initially formed amide enol to the amide was 24 times less than that for formation of the amide enol.[5b]

In the case of **6** studied here, direct reaction of the ketene with amine dimers or trimers may be unimportant, as the degree of association of amines in CH_3CN at the concentrations used has been found to be low.[9] The amination may proceed by two successive reversible reactions with individual amine molecules (eq 19), leading to complex **8** shown in eq 4.

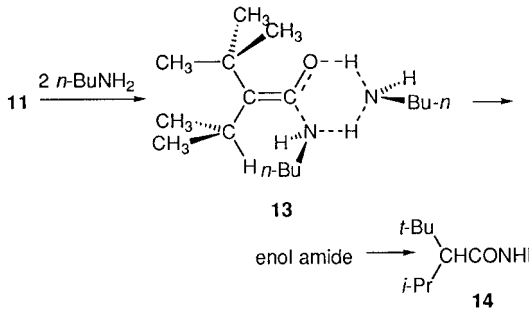
$$\text{ketene} + \text{amine} \rightleftharpoons \text{ketene}\cdot\text{amine} \overset{\text{amine}}{\rightleftharpoons} (\text{ketene})\cdot 2\text{amine} \quad (19)$$

In a previous study[8d] it was found that **11** reacted with *t*-BuLi to give reduction by hydride transfer with an 83/17 preference for delivery syn to the isopropyl group, and also addition of the *tert*-butyl exclusively from the syn side. Molecular mechanics calculations of the stabilities of the *E*/*Z* isomers of these products indicated a slight (0.2 kcal/mol) preference for the *E* isomer **12** in the product of hydride attack, whereas for *t*-Bu attack there was a calculated 10.8 kcal/mol preference for the *Z* isomer from addition syn to *i*-Pr (eq 20).



(20)

A model **13** for the rate-limiting transition state for *n*-$BuNH_2$ addition to **11** (step 2, eq 15) involving two molecules of *n*-$BuNH_2$ is based on the calculated transition structure **1**[6e] and involves in-plane attack by the amine nitrogen on the carbonyl carbon syn to the isopropyl group to give an unobserved amide enol which forms the amide **14** (eq 21). The large rate acceleration relative to *t*-Bu_2C=C=O (**10**) could arise from the conformation shown which greatly reduces the steric interaction over that for amination of **10**.



(21)

The enormous steric retardation expressed in the *k*(*t*-BuCH=C=O)/*k*(*t*-Bu_2C=C=O) rate ratio of 10^{12} for reaction with *n*-$BuNH_2$ may be compared with the corresponding rate ratio of 9.3×10^4 for reaction with H_2O[6h] and indicates a much larger effect in the former process. The model transition structure **13** indicates the bulky ketene substituents would not only interact with nucleophilic nitrogen but also suggests there would be a severe interaction involving the *n*-butyl group on this nitrogen, which would be directed toward one of the *tert*-butyl groups on C_β of the ketene **10**. The rate constant for hydration of **11** in H_2O at 25 °C has now been measured as 4.71×10^{-4} s^{-1}, and for this reaction, the ratio *k*(**11**)/*k*(**10**) is only 3, as compared to the corresponding ratio for reaction with *n*-$BuNH_2$ estimated above of 1.8×10^5. This difference also reflects a much larger steric effect for the amination reaction.

Rate constants measured for reaction of $PhMe_2SiCH$=C=O (**6**) with $CF_3CH_2NH_2$ containing $CF_3CH_2NH_3^+CF_3CO_2^-$ (Table 6, Supporting Information) were strictly linear in [$CF_3CH_2NH_3^+$], with $k_{BH^+} = 3.91 \pm 0.05$ M^{-1} s^{-1}, indicating general acid catalysis of the reaction was occurring (eq 22). The initial protonation of **6** at C_β is

$$\underset{\mathbf{6}}{PhMe_2SiCH=C=O} \xrightarrow[-B]{BH^+} PhMe_2SiCH_2C^+=O \xrightarrow[-H^+]{CF_3CH_2NH_2} \underset{\mathbf{7b}}{PhMe_2SiCH_2CONHCH_2CF_3} \quad (22)$$

consistent with the enhanced electrophilic reactivity of silylketenes noted above.[6f] However the presence of *n*-$BuNH_3^+CF_3CO_2^-$ had no effect on the reactivity of **6** with *n*-$BuNH_2$, indicating this amine conjugate acid is insufficiently acidic to catalyze the reaction in competition with the uncatalyzed reaction.

General acid catalysis of the hydration of Me_3SiCH=C=O[6f] and of *t*-Bu_2C=C=O (**10**)[6g] has been observed previously. For the silylketene the process shown in eq 22 would be accelerated by electron donation from the C−Si bond to the developing positively charged center.

In summary whether ketene aminations occur with first-, second-, or third-order dependences on [amine] is contingent upon the ketene structure, in that unstable and reactive ketenes show only a first-order dependence on [amine], as the formation of the initial amine/ketene complex is rate limiting. With more stable and less reactive ketenes this first step is reversible, and reaction with a second or third amine becomes rate limiting, leading to dependences on [amine]^2 and [amine]^3. These findings are in harmony with previous theoretical studies.[6e] The observed absence[5a] of a systematic depen-

(9) (a) Sinsheimer, J. E.; Keuhnelian, A. M. *Anal. Chem.* **1974**, *46*, 89−93. (b) Peshekhodov, P. B.; Petrov, A. N.; Al'per, G. A. *Russ. J. Gen. Chem.* **1993**, *63*, 854−856.

dence of amination rates in H_2O on amine basicity arises from the rate-leveling effect of amine desolvation on the rates,[7a] as noted previously.[6e] Extremely high reactivity ratios $k(n\text{-BuNH}_2)/k(H_2O)$ for $PhMe_2SiCH{=}C{=}O$ of 10^{13} and for $k(t\text{-BuCH}{=}C{=}O)/k(t\text{-Bu}_2C{=}C{=}O)$ with $n\text{-BuNH}_2$ of 10^{12} are observed, as well as general acid-catalyzed amination of $PhMe_2SiCH{=}C{=}O$ with $CF_3CH_2NH_3^+$.

Experimental Section

Amination kinetics were measured either by conventional UV spectroscopy using a Perkin-Elmer Lambda 12 instrument or by stopped flow using a HiTech Scientific instrument. The program SigmaPlot was used to fit the kinetics, using a statistical error weighted fitting, as reported in Table 1. Other kinetic expressions and constant error weighting gave less satisfactory fits of the data, as detailed in the Supporting Information (Table 7, plots 1−21). The sample of the acid precursor to *t*-BuC(*i*-Pr)=C=O (**11**) (λ 225 nm, $\epsilon = 350$; 379 nm, $\epsilon = 5$) was prepared by Dr. Lynn Baigrie.[8d] The hydration of **11** was measured by injecting 20−50 μL of a 5.2×10^{-3} M solution of **11** in CH_3CN into 2 mL of H_2O and observing the decrease in absorption at 215 nm.

***N*-*n*-Butyl-2-(phenyldimethylsilyl)acetamide (7a).** A solution of $n\text{-BuNH}_2$ (20 μL, 2.07 M in $CDCl_3$, 0.041 mmol) was added to $PhMe_2SiCH{=}C{=}O$ (**6**, 0.0354 g, 0.201 mmol) in 0.8 mL of $CDCl_3$ in an NMR tube at −20 °C. The ^{1}H NMR spectrum revealed the presence of both reactants and the product so an additional 0.16 mmol $n\text{-BuNH}_2$ was added, and no more **6** was detected. The solvent was evaporated, and the product was purified by chromatography on silica gel (2% Et_3N in CH_2Cl_2) to give **7a** (0.0507 g, 0.204 mmol, 100%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.40 (s, 6, Me_3Si), 0.85 (t, $J = 7.4$ Hz, CH_3), 1.2−1.3 (m, 4, CH_2CH_2), 1.95 (s, 2, CH_2CO), 3.11 (m, 2, CH_2N), 5.08 (s, 1, NH), 7.3−7.5 (m, 5, Ph); ^{13}C NMR δ −3.07, 13.6, 19.9, 28.6, 31.7, 39.2, 127.9, 129.4, 133.5, 137.5, 171.3; IR ($CDCl_3$) 3452 (NH), 1648 (C=O), 1514 (NH) cm^{-1}; EIMS *m*/*z* 248 ($M^+ - H$, 3), 234 ($M^+ - CH_3$, 91), 192 ($M^+ - C_4H_9$, 50), 172 ($M^+ - C_6H_5$, 82), 135 ($PhSiMe_2^+$, 100); HRMS *m*/*z* calcd for $C_{14}H_{22}NOSi$ 248.1471, found 248.1461; calcd for $C_{13}H_{20}NOSi$ 234.1314, found 234.1308.

***N*-2′,2′,2′-Trifluoroethyl-2-(phenyldimethylsilyl)acetamide (7b).** Compound **7b** was prepared similarly to **7a** as the only observable product as a white solid without purification: mp 74−75 °C; ^{1}H NMR ($CDCl_3$) δ 0.42 (s, 6, Me_2Si), 2.05 (s, 2, CH_2Si), 3.78 (dq, $J = 9.2$ Hz, $J = 6.5$ Hz); ^{19}F NMR ($CDCl_3$) −73.05 (t, $J = 9$ Hz); ^{13}C NMR ($CDCl_3$) δ −3.3, 28.7, 40.4 (q, $J = 34.4$ Hz), 120.4 (q, $J = 278.3$ Hz), 128.1, 129.7, 133.4, 136.8, 171.7; ^{19}F NMR ($CDCl_3$) δ −73.05 (t, $J = 9$ Hz); IR ($CDCl_3$) 3457, 1674, 1513 cm^{-1}; EIMS *m*/*z* 274 ($M^+ - H$, 15), 260 ($M^+ - CH_3$, 90), 198 ($M^+ - C_6H_5$, 100), 139 ($M^+ - C_6H_5SiMe_2$, H, 66), 135 ($PhSiMe_2^+$, 98); HRMS *m*/*z* calcd for $C_{11}H_{13}F_3NOSi$ 260.0718, obsd 260.0732; calcd for $C_{12}H_{15}F_3NOSi$, 274.0875, found 274.0879.

***N*-*n*-Butyl-2,2-bis-*tert*-butylacetamide.** A solution of 0.0211 g (0.0137 mmol) $t\text{-Bu}_2C{=}C{=}O$ (**10**) was left for 8 days at room temperature in $n\text{-BuNH}_2$, and the solvent was evaporated to give the amide as the only observable product without purification: mp 78−80 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3, $J = 7.2$ Hz, CH_3), 1.10 (s, 18, $t\text{-Bu}_2$), 1.32 (sextet, 2, $J = 8.1$ Hz, CH_2), 1.46 (quintet, 2, $J = 8$ Hz, CH_2), 1.62 (s, 1, CH), 3.19 (q, 2, $J = 8$ Hz, NCH_2), 5.38 (s, 1, NH); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.2, 31.1, 31.6, 35.0, 38.7, 66.3, 174.3; IR ($CDCl_3$) 3456, 1663, 1506 cm^{-1}; EIMS *m*/*z* 228 (MH^+, 0.2), 171 (29), 156 ($M^+ - NC_4H_8$, 100); HRMS *m*/*z* calcd for $C_{14}H_{30}NO$ 228.2325, found 228.2327; calcd for $C_{10}H_{21}NO$ 171.1623, found 171.1620.

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Supporting Information Available: Kinetic and spectral data (52 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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