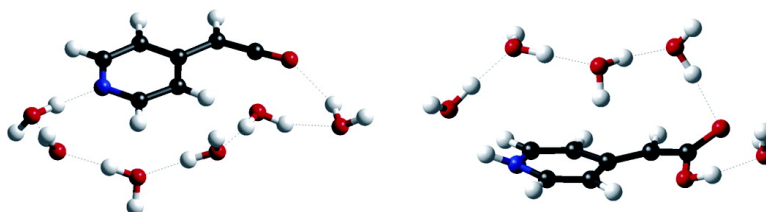**Article**

Hydration of Pyridylketenes: Formation of Acid Enol and Dihydropyridine (Eneaminone) Transients

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# Hydration of Pyridylketenes: Formation of Acid Enol and Dihydropyridine (Eneaminone) Transients

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Abstract: 2-, 3-, and 4-Pyridylketenes **4** formed in water by photochemical Wolff rearrangements using flash photolysis undergo rapid hydration forming transient intermediates observed by UV spectroscopy. 3-Pyridylketene (3-**4**) formed the acid enol intermediate 3-**10** which was converted to the acid 3-**11**, and phenylketene gave similar behavior. 4-Pyridylketene (4-**4**) reacted with a similar initial rate constant of 5.0 $\times$ 10^4 s^{-1} for decay of an absorption at 275 nm, with concomitant formation of a strong absorption at 370 nm with the same rate constant. The intermediate absorbing at 370 nm decayed with a lifetime 2.4 $\times$ 10^3 fold longer than that of the ketene, and is identified as 4-(carboxymethylene)-1,4-dihydropyridine (4-**13**), resulting from conjugate 1,6-addition of H_2O to 4-**4**. 2-Pyridylketene (2-**4**) underwent hydration with a similar rate constant of 1.1 $\times$ 10^4 s^{-1} forming a transient with a UV absorption with maxima at 310 and 380 nm that decayed with biexponetial kinetics, with rate constants slower than the rate of formation by factors of 5.2 and 110, respectively. These results are interpreted as indicating the presence of two species, namely *Z*- and *E*-2-(carboxymethylene)-1,2-dihydropyridines (2-**13**), resulting from conjugate 1,4-addition of H_2O to 2-**4**. The identifications of the 1,2- and 1,4-(carboxymethylene)dihydropyridines 2- and 4-**13** were confirmed by comparison of their UV spectra with those of the corresponding *N*-methyl derivatives. The amination of 2-pyridylketene in CH_3CN was reinvestigated, and spectroscopic evidence, computational studies, and preparation of the *N*-methyl analogue demonstrated formation of the 1,2-dihydropyridine *Z*-2-**8f** as the long-lived intermediate.

The mechanisms of ketene hydration[1] have been of great interest since the classic experimental studies by Schulte−Frohlinde and co-workers of the reactions of arylketenes[1a] and of ketene itself[1b] in water, and theoretical studies of Nguyen and Hegarty.[2a] The rate constants for reaction of arylketenes 1 with H_2O were correlated with Hammett sigma parameters of the substituents with a slope of 1.2,[1b] indicative of rate-limiting nucleophilic attack of water on the carbonyl carbon in the ketene plane,[2a−g] with stabilization of partial negative charge in the transition state by the aryl group (eq 1).[2g] For CH_2=C=O (2) itself there are suggestions that initial proton attack on C_2 may become competitive,[2b,d] but not for arylketenes.
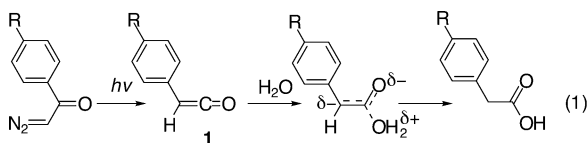
The hydration of carbonyl compounds is known to involve multiple water molecules in which water clusters effect net hydroxide addition to the carbonyl carbon and proton addition to the carbonyl oxygen through cyclic arrays.[2h−k] Computational studies of the hydration of CH_2=C=O (2)[2a−e,g] are generally in accord with this description, and for two water molecules a cyclic transition state **2a** leading to the enol **3** of acetic acid is preferred (eq 2), with a much lower barrier than for addition of a single water molecule, as confirmed by the most recent computation for a single water molecule.[2f] Structures with greater numbers of water molecules have also been considered,[2a,c] and the enol **3** would also be solvated by further water molecules. For hydration of some ketenes intermediate acid enols have been detected by UV spectroscopy,[1f,g] but had not previously been observed for phenylketene (**1**, R = H) itself. The acid enol Ar_2C=C(OH)$_2$ from ditipylketene (Ar_2C=C=O, Ar = 2,4,6-*i*-$Pr_3C_6H_2$) has been directly observed as a long-lived species in solution by NMR.[3a,b]
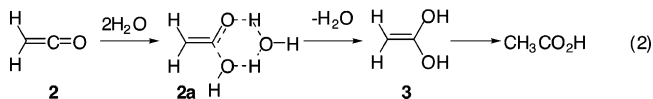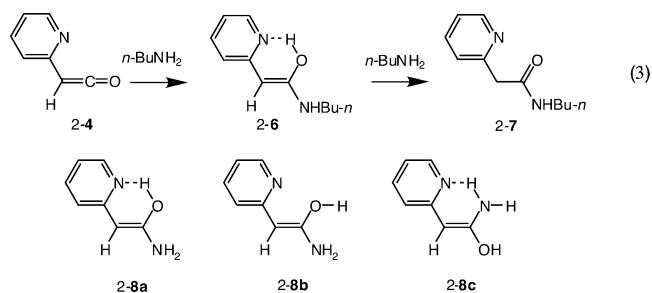

Pyridylketenes **4**[4] are of interest because of the possibility of direct involvement of the ring nitrogen in the reaction at the ketenyl group. In particular, the 2-pyridyl group can stabilize enols by the formation of intramolecular hydrogen bonds.[5] We have reported the generation of 2-, 3-, and 4-**4** as transient intermediates by laser flash photolysis of the corresponding diazo ketones **5** in CH_3CN solution, with confirmation of the structures by the observation of the characteristic ketenyl absorptions at 2127, 2125, and 2128 cm^{-1}, respectively, using time-resolved infrared spectroscopy (TRIR).[6a] The same method

was used to observe the formation and decay of amide enol intermediates in the amination of substituted phenylketenes.[6b] Other studies of pyridylketenes include the matrix isolation and dimerization of 2-pyridylketene,[4d] the observation of pyridylketenes bonding to Pt surfaces,[4e] and the generation of pyridylketenes by carbonylation of carbenes.[4a]

syn-2-**4**   *syn*-3-**4**   4-**4**   2-4-**5**
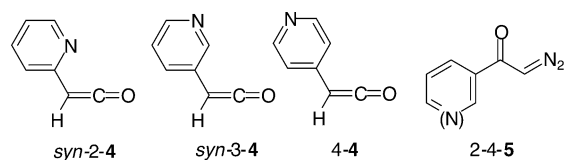
The reactivities of the three isomeric ketenes **4** with *n*-BuNH$_2$ in CH$_3$CN were measured, and in all cases initial transient intermediates described as enols of amides were observed by UV.[6a] The intermediate from 2-pyridylketene was longer lived than the amide enols from 3- and 4-pyridylketenes by factors of 1.8×10^7 and 4.8×10^7, respectively.[6a] This enormously greater lifetime was attributed to the formation of an amide enol *syn*-2-**6** with a strong intramolecular hydrogen bond of the enolic hydrogen to the pyridyl nitrogen (eq 3). This process was further examined by DFT calculation of the pathway for reaction of pyridylketene with NH$_3$.[6a] The computations indicated the hydrogen bonded amide enol 2-**8a** was stabilized by 15.4 kcal/mol compared to the comparable structure 2-**8b** with the hydrogen directed away.[6a] The isomer 2-**8c** with the NH$_2$ group hydrogen bonded to the pyridyl nitrogen was also less stable than 2-**8a**, by 6.5 kcal/mol.

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(3)

2-**8a**   2-**8b**   2-**8c**

2-Pyridylketene was a conceivable candidate for the occurrence of assistance to amination by hydrogen bonding of the amine hydrogen to the pyridyl nitrogen with nucleophilic attack on the ketenyl carbonyl through a pseudopericyclic transition state[7] resembling 2-**8d** forming a dihydropyridine *Z*-2-**8e** (eq 4). Such a process has been implicated in the hydration of imidoylketenes such as **9a**, which involves a near planar transition structure **9b** leading to the product **9c** (eq 5).[7c] However, in amination 2-pyridylketene was the least reactive of the isomers, so there was no kinetic evidence for acceleration of the reaction of 2-**4** with amines by a pseudopericyclic process.

2-**8d**   *Z*-2-**8e**   (4)

9a   **9b**   **9c**   (5)
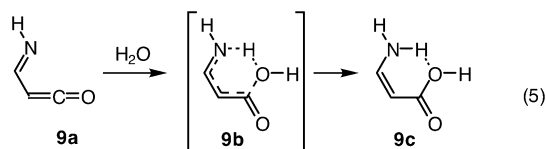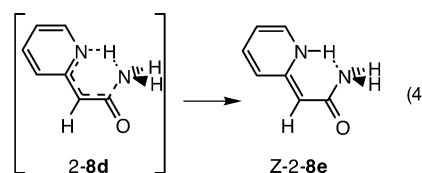
Results

To further elucidate the reactivity of the pyridylketenes **4** we have now examined their hydration reactions. 2-, 3-, and 4-Pyridylketenes **4**[6a] were generated by laser flash photolysis of the diazo ketones **5**[8] in water, and the reactions were monitored by UV spectroscopy. The reaction of phenylketene (**1**, R = H) was examined for comparison. Upon photolysis of the diazo ketone 3-**5** there was an initial increase in the UV absorption monitored at 320 nm, near the maximum at 330 nm, followed by a decay (Figure 1). These absorption changes gave a good fit to a biexponential function, with derived first-order rate constants of 2.5×10^4 s^{-1} and 2.0×10^4 s^{-1}, for the increase and decrease in absorption, respectively (Table 1).

The two processes observed in the reaction of 3-pyridylketene are assigned to the formation and decay of acid enol intermediate 3-**10** formed by hydration of the initial ketene 3-**4** (eq 6). This assignment is in agreement with previous theoretical studies of ketene hydration, which predict that acid enol intermediates are formed,[2] and experimental studies, in which these species have been observed as transients by UV[1f,g] or even long-lived

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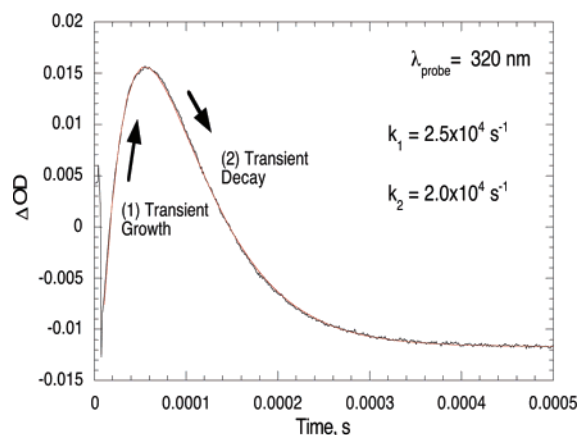(8) Ribereau, P.; Queguiner, G. *Can. J. Chem.* **1983**, *61*, 334−342.

Figure 1. Kinetic trace of UV absorption changes of transient from 3-pyridylketene (3-**4**) obtained by laser flash photolysis in 100% H$_2$O. Experimental data are fit with a biexponential function representing growth and decay of the transient absorption.

Table 1. Rate Constants for Reactions of Ketenes with H$_2$O[a]

| | k(obs) (s^{-1}) | | |
| | k_1 | k_2 | |
ketene	transient growth	transient decay	k_1/k_2
PhCH=C=O (**1a**)	3.3×10^4	4.3×10^3	7.7
	$(5.9 \times 10^3)^b$	$(2.4 \times 10^3)^b$	2.5[b]
2-PyCH=C=O (2-**4**)	1.1×10^4	2.1×10^3 (28%)^c	5.2
		9.8×10^1 (72%)^c	1.1×10^2
3-PyCH=C=O (3-**4**)	2.5×10^4	2.0×10^4	1.2
4-PyCH=C=O (4-**4**)	5.0×10^{4d}	2.1×10^1	2.4×10^3

[a] Measured at ambient temperature (22 °C). [b] 75% H$_2$O/25% CH$_3$CN. [c] Percentage of total absorbance change. [d] Increase at 370 nm and decrease at 275 nm.

intermediates by NMR.[3b,c] As noted above similar amide enol intermediates have been directly observed by TRIR from amination reactions of arylketenes.[6b] Rate constant ratios k(ketene to amide enol)/k(amide enol to amide) of 4.0 and 6.2, respectively, were observed for 3- and 4-pyridylketenes with n-BuNH$_2$ in CH$_3$CN (eq 3).[6a]
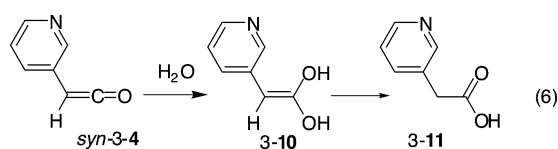
Hydration of phenylketene gave very similar behavior, with an initial increase in absorption at 280 nm followed by a decay (Figure 2), and derived rate constants 3.3×10^4 s^{-1} and 4.3×10^3 s^{-1}, respectively (Table 1). In solvent, 75% H$_2$O/25% CH$_3$-CN, both processes were slowed, and the growth and decay were more readily resolved, with rate constants of 5.9×10^3 and 2.4×10^3 s^{-1}, respectively (Figure 2). This is in contrast to previous studies of ketene hydration with an earlier apparatus, in which only the decay of the absorption was reported.[1c−g] This behavior indicates that both the conversion of the ketene **1a** to the acid enol **1b** and the decay of the acid enol are observed (eq 7).

Flash photolysis of the diazo ketone 4-**5** to generate 4-pyridylketene 4-**4** gave the immediate appearance of an absorption at 275 nm which decayed with a first-order rate constant of 5.0×10^4 s^{-1} (Figure 3a). There was concomitant growth with the same first-order rate constant of an absorption with a
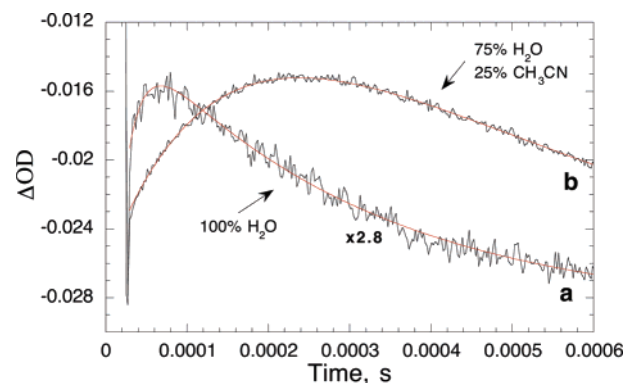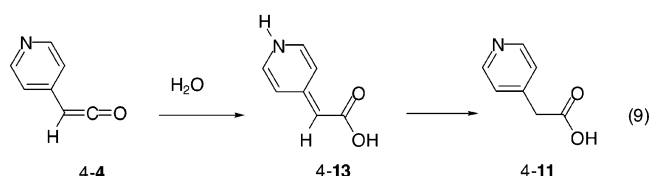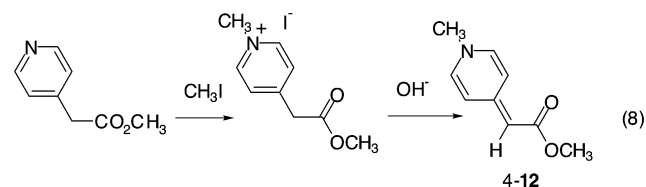

Figure 2. Kinetic trace of UV absorption changes at 280 nm of transient from phenylketene: (a) in 100% H$_2$O and (b) in 75% H$_2$O/25% CH$_3$CN. Experimental data are fit with a biexponential function representing growth and decay of the transient absorption.

maximum at longer wavelength, 370 nm (Figure 3b), followed by a much slower decay (Figure 3c), with a first-order rate constant of 2.1×10^1 s^{-1} (Table 1).
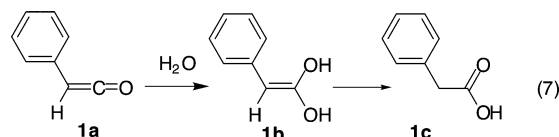
Flash photolysis of the diazo ketone 2-**5** formed 2-pyridylketene 2-**4** which underwent conversion to a new transient which showed two strong maxima at 310 and 380 nm, respectively (Figure 4a). The conversion of 2-**4** to the new transient was monitored by observing the increase of absorption at 320 nm with a first-order rate constant of 1.1×10^4 s^{-1} (Figure 4b). Decay of this transient monitored at 320 nm at a longer time scale was fit by a biexponential function (Figure 4c) which gave two first-order rate constants of 2.1×10^3 s^{-1} and 9.8×10^1 s^{-1}, attributable to 28 and 72% of the initial absorption, respectively (Table 1).

The key to the identification of the long-lived species formed from 4-pyridylketene was the reported preparation of 1-(carbomethoxymethylene)-4-N-methyl-1,4-dihydropyridine (4-**12**, eq 8).[9a,b] The reported UV spectrum of this species[9a] is essentially the same as that of the long-lived transient, and this was confirmed by preparation of authentic 4-**12**. The long-lived transient is therefore assigned the structure 4-**13** resulting from conjugate 1,6-addition to 4-pyridylketene (4-**4**) with N-protonation and OH addition to the ketenyl carbon (eq 9).

The UV spectrum of the analogous E-1-(carboethoxymethylidene)-2-N-methyl-1,4-dihydropyridine (E-2-**12**) has also been
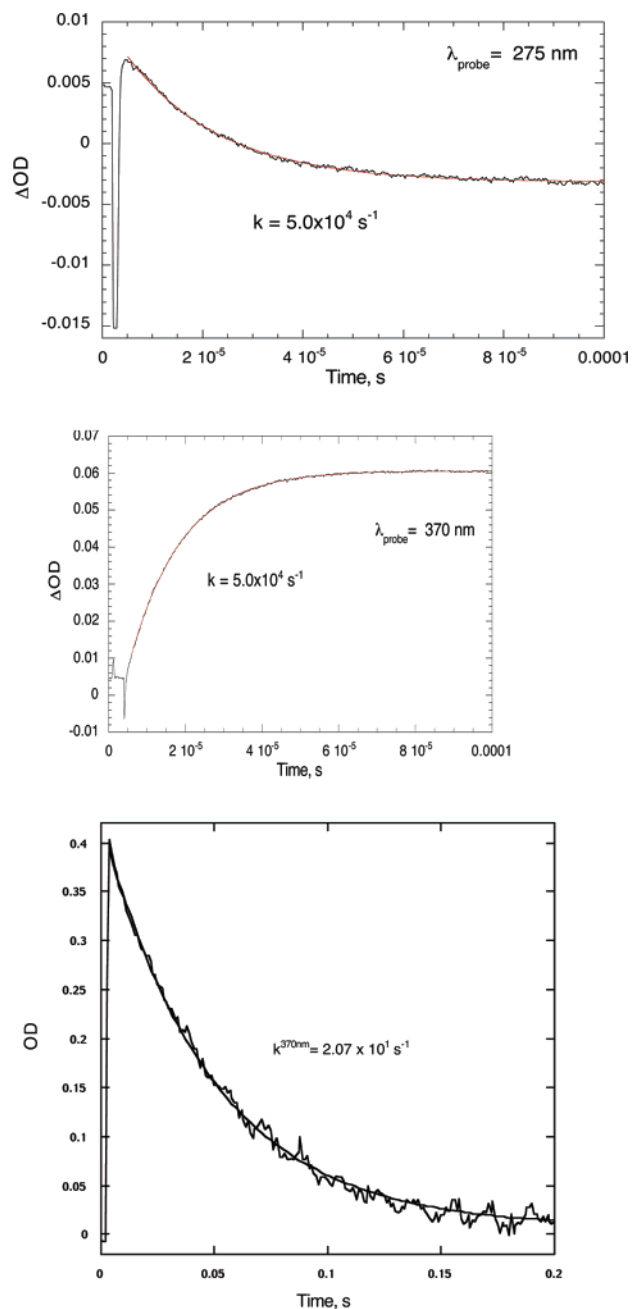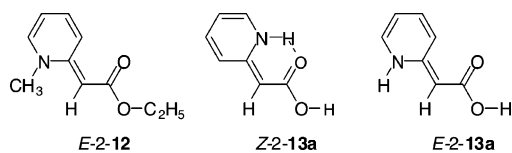
Figure 3. (a) Kinetic trace of UV absorption changes at 275 nm for transient decay from 4-pyridylketene in 100% H₂O. (b) Kinetic trace of UV absorption changes at 370 nm for transient growth from 4-pyridylketene in 100% H₂O. (c) Kinetic trace of UV absorption changes at 370 nm for transient decay from 4-pyridylketene in 100% H₂O.

reported,[9a] and this was essentially the same as that observed (Figure 4) for the product from hydration of 2-**4**. This transient is assigned as a mixture of *Z*- and *E*-2-**13a** based on the observed UV spectrum and biphasic kinetics.

The finding that the hydration of 2-pyridylketene (2-**2**) led to the formation of the 2-carboxymethylene-1,2-dihydropyridines 2-**13** brought into question the identity of the long-lived species
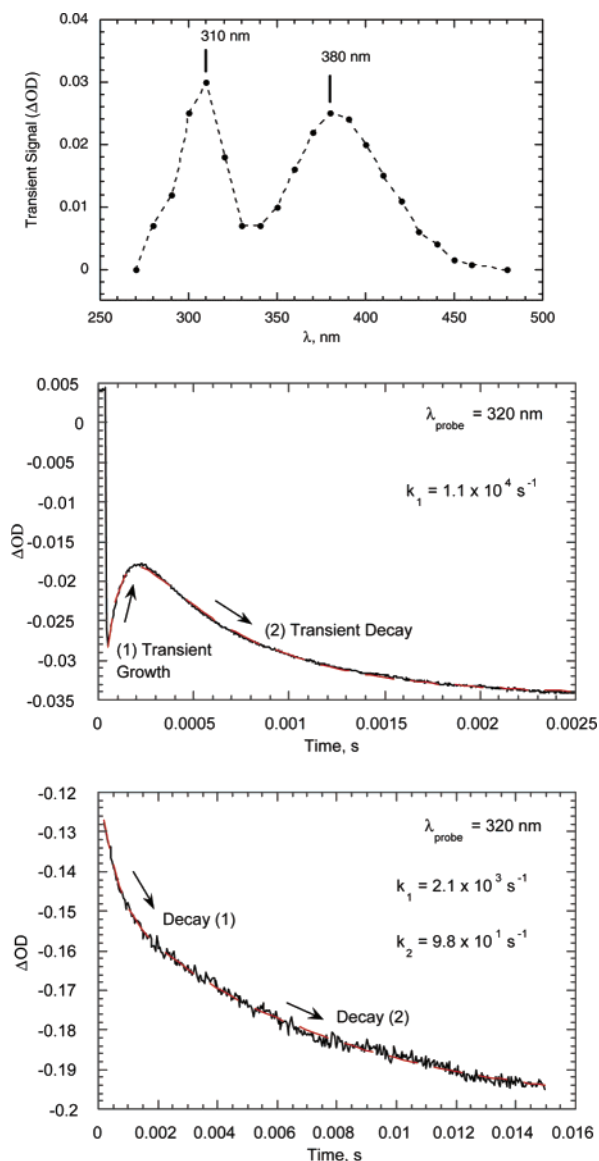
Figure 4. (a) UV spectrum of transient formed from 2-pyridylketene in 100% H₂O. (b) Kinetic trace for UV absorption changes at 320 nm of transient from 2-pyridylketene (2-**4**) in 100% H₂O. (c) Biexponential kinetic fit of experimental trace of UV spectrum at 320 nm for transient decay from 2-pyridylketene in 100% H₂O

from *n*-butylamine to 2-**4**, which had been assigned as amide enol 2-**6** (eq 3).[6a] Therefore, this reaction was reexamined, and transient UV absorption maxima at 310 and 380 nm in CH₃CN were observed (Figure 5a) indicating formation of the tautomer *Z*-2-**6a** as the intermediate converted to 2-**7** with catalysis by *n*-BuNH₂ (eq 10).[6a] The identification of *Z*-2-**6a** was confirmed
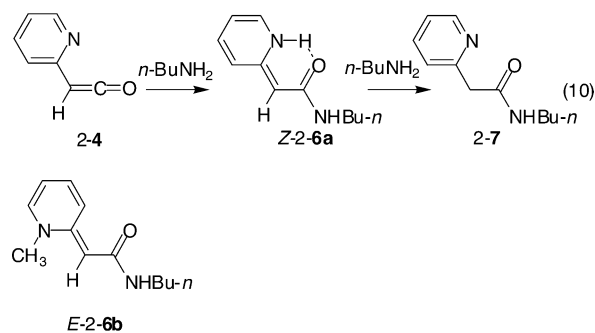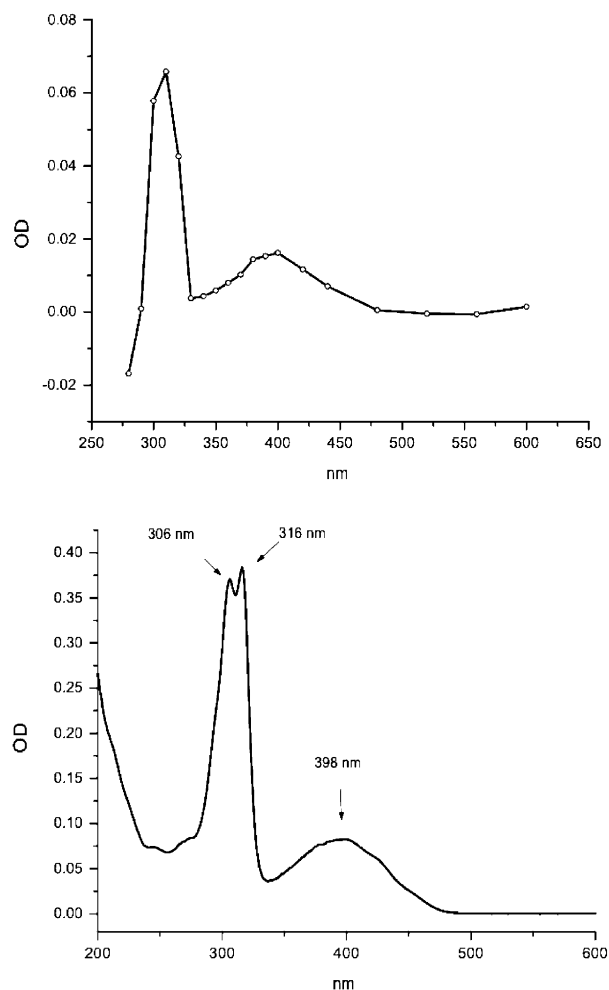
Figure 5. (a) Transient UV spectrum of amide enol *Z*-2-**6a** from 2-pyridylketene and *n*-BuNH$_2$ in CH$_3$CNb UV spectrum of 1-*N*-methyl-2-*n*-butylcarboxamidomethylene-1,2-dihydropyridine *E*-2-**6b** in CH$_3$CN.

by preparation of the *N*-methyl derivative *E*-2-**6b** as a stable solid by a route analogous to that of eq 8. The UV spectrum of the transient identified as *Z*-2-**6a** was almost identical to that of *E*-2-**6b** (Figure 5b), which had absorption maxima in CH$_3$-CN at 306 (log ϵ 3.88), 316 (log ϵ 3.89), and 398 (log ϵ 3.22) nm. The near identity of the UV spectra of similar *E*- and *Z*-acylmethylene-1,2-dihydropyridines has been noted before.[5e]

Previously the energy of the hydrogen bonded amide enol 2-**8a** was calculated at the B3LYP/6-31G*//B3LYP/6-31G* level,[6a] and now further calculation of the structure and energy of 2-methylene-1,2-dihydropyridine *Z*-2-**8f** at this level (Table 2, Supporting Information) reveals this to be 3.05 kcal/mol more stable than the previously calculated amide enol, with O···H and N···H hydrogen bond lengths of 1.812 and 1.643 Å in *Z*-2-**8f** and 2-**8a**, respectively. The strength of the hydrogen bond in *Z*-2-**8f** in the gas phase may be approximated from the energy difference between *Z*- and *E*-2-**8f** of 9.6 kcal/mol (Table 2, Supporting Information), but the energy difference between *E* and *Z* structures also enters into this comparison.
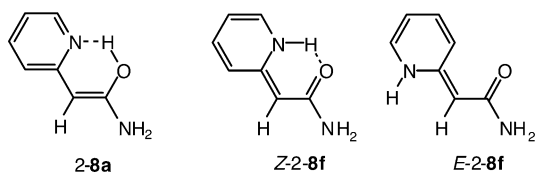

Discussion

Formation by hydration of 4-pyridylketene 4-**4** forming 4-carboxymethylene-1,4-dihydropyridine 4-**13** may be depicted as involving participation of a cluster of water molecules to facilitate proton addition to nitrogen and OH addition to the ketenyl carbon. Representations of an initial ketene complex 4-**4**·6H$_2$O with a chain of 6 water molecules between the nitrogen and the ketenyl group and a product 4-carboxymethylene-1,4-dihydropyridine 4-**13**·5H$_2$O with 5 coordinated water molecules are shown (Scheme 1). The complexed ketene 4-**4**·6H$_2$O has the water bridge largely in the plane of the pyridylketene, while the water bridge in 4-carboxymethylene-1,4-dihydropyridine 4-**13**·5H$_2$O is above the pyridyl plane. The conversion of 4-**4** to 4-**13** is expected to involve a stepwise process facilitated by water molecules forming transient zwitterions, with significant reorganization of the solvent shell. Many such structures with the same or different numbers of water molecules are expected to contribute to the species present in solution, and no single structure but rather many would be involved in the transformation.

Scheme 1. Depiction of a 4-Pyridylketene Complex 4-**4**·6H$_2$O with a Bridge of 6 H$_2$O Molecules and Dihydropyridine 4-**13**·5H$_2$O from Hydration of Ketene 4-**4** with a Bridge of 5 H$_2$O Molecules

4-**4**·6H$_2$O   4-**13**·5H$_2$O
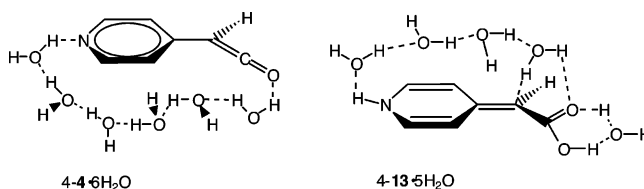
Precedent for such a stepwise relay process is found in the photochemically induced hydrogen transfer between oxygen and quinolyl nitrogen utilizing a bridge of 3 NH$_3$ molecules recently demonstrated in an experimental and computational study (eq 11).[10a] Other reactions involving chains of water molecules to effect proton transfer have also been reported.[10b−d]

(11)
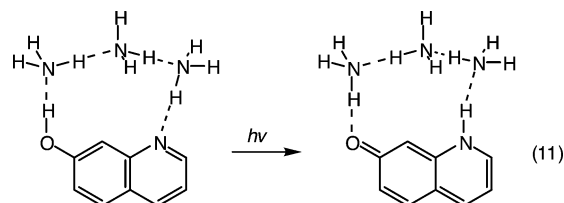
The results for hydration of 3-pyridylketene (3-**4**) and of phenylketene are similar in that the growth and the decay of an absorption following ketene generation are observed in each case, with rate ratios *k*(growth)/*k*(decay) of 1.2 and 7.7, respectively. This resembles the results for the amination reaction in acetonitrile solvent,[6a] in which the ketenes were directly observed by IR, and rate constant ratios *k*(ketene to amide enol)/*k*(amide enol to amide) of 4.0 and 22 were found for 3-pyridylketene and phenylketene, respectively.[6a] In previous studies of phenylketene hydration only the decay of an absorp-

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tion was noted,[1c−e] and the acid enol has now been detected for the first time in hydration by UV spectroscopy in this and a related study.[11a] However, because UV spectroscopy does not give distinctive structural signatures for the ketene and the enol there is some ambiguity about the specific identification of the growth and decay as being due to the ketene and the enol for 3-pyridylketene and phenylketene.[11] The rate constants for growth and decay are quite similar, and the identification of these processes is reported elsewhere.[11a] In any event the hydration of 3-**4** is found to proceed through formation of the acid enol 3-**10**, which is readily converted to the acid 3-**11** (eq 6), and phenylketene behaves analogously.

The initially formed 4-pyridylketene undergoes hydration to the long-lived 4-carboxymethylene-1,4-dihydropyridine 4-**13** (eq 9), and the identification of these two transients is unambiguous, based in the latter case upon comparison of the UV spectrum with the corresponding stable *N*-methyl derivative. The rate constant for initial hydration of 4-**4** is the largest of those for the three isomers, just as it is for amination, with rate constant ratios for 4-**4**/3-**4**/2-**4** of 4.5/2.3/1.0 for hydration and 17/4.0/1.0 for amination. The computed stability of the isomers at the B3LYP/6-311+G(d,p) level is 2-**4** > 4-**4** > 3-**4**,[6a] so the most stable 2-isomer is the least reactive in both reactions. The rate constant ratio k(ketene-to-intermediate)/ k(intermediate-to-product) for amination of 4-pyridylketene (4-**4**) is 6.2, but for hydration of 4-**4** this ratio is 2.4×10^3 (Table 1). The difference between the two lies in the fact that hydration of 4-pyridylketene results in formation of a long-lived intermediate shown to be the 4-carboxymethylene-1,4-dihydropyridine 4-**13** (Scheme 1), whereas no such intermediate is detected in amination.

In the hydration of 4-pyridylketene, 1,6-addition is facilitated by a network of water molecules through stepwise proton transfers to form the dihydropyridine 4-**13** (Scheme 1). This is not feasible for amination, in which the concentration of *n*-butylamine in CH_3CN used was between 10^{-4} to 10^{-3} M.[6a]

For hydration of 2-**4** formation of the 2-carboxymethylene-1,2-dihydropyridine intermediate *Z*-2-**13a** was confirmed by observation of new UV maxima at 310 and 380 nm (Figure 4a), and the kinetic data suggests there are two transient species that decay with rate constants 5.2 and 110 times less than the rate constant for ketene hydration, and these account for 28% and 72% of the dihydropyridine absorption, respectively (Table 1). The dihydropyridine intermediates can be assigned as the *E*- and *Z*-2-**13a** structures, respectively, as *Z*-2-**13a** is stabilized by an intramolecular hydrogen bond and may be expected to be longer lived than the *E*-stereoisomer.

2-Pyridylketene amination with *n*-BuNH₂ in CH₃CN gave an intermediate previously assigned as the intramolecularly H-bonded amide enol 2-**6** that was converted to the amide with a rate constant 1.8×10^7 less than that for conversion of the ketene to 2-**6** (eq 3).[6a] The stability of this species was ascribed to the formation of the strong intramolecular H-bond, and this intermediate can be formed without a chain of amine molecules (eq 3). However, the dihydropyridine *Z*-2-**6a** is now shown to be the intermediate observed in the amination of 2-**4** (Figure 5a),and this is confirmed by the computational results revealing the 2-methylene-1,2-dihydropyridine intermediate *Z*-2-**8f** is more

stable than the hydrogen bonded amide enol *syn*-2-**8a** by 3.4 kcal/mol (Table 2, Supporting Information).

The rate constant ratios for formation by hydration of the dihydropyridines *Z*- and *E*-2-**13** from 2-pyridylketene relative to their rates of decay of 110 and 5.2 (Table 1) are much less than that of 1.8×10^7 for the corresponding amination (eq 3).[6a] However, in hydration conversion to the pyridylacetic acid can be assisted by hydrogen bonding to the solvent water molecules, whereas in amination the solvent is acetonitrile, which has a much weaker hydrogen bonding ability, and the amine concentration is quite low. The assistance provided by additional hydrogen bonding molecules is shown by the second-order kinetic dependence on the concentration of *n*-butylamine observed in the conversion of the intermediate *Z*-2-**6a** from 2-pyridylketene to the final product 2-**7** (eq 10).[6a]

In both hydration and amination, 2-pyridylketene is the least reactive of the isomers, so there is no kinetic evidence for a pseudopericyclic pathway (eqs 4 and 5). In amination, the hydrogen bonded dihydropyridine *Z*-2-**6a** (eq 10) is formed and would result from attack opposite to the pyridyl nitrogen, whereas a pseudopericyclic pathway would form the *N*-*n*-butyl derivative of the less stable *Z*-2-**8e** (eq 4). In hydration formation of both *Z*- and *E*-2-carboxymethylene-1,2-dihydropyridines 2-**13** also argues against a pseuodopericyclic pathway, which would lead only to the *Z*-isomer.

For 2-pyridyketene, the transition structure 2-**8d** for pseudopericyclic NH₃ addition (eq 4) lacks developing amide conjugation, which is also absent in the product dihydropyridine carboxamide *Z*-2-**8e**, with the amide group twisted out of conjugation (eq 4).[6a] This was previously noted by Birney et al.[7a] for the addition of NH₃ to formylketene O=CH-CH=C=O. However amination by attack of 2 *n*-BuNH₂ molecules on *syn*-2-**4** from the side opposite the pyridyl group leads to *Z*-2-**6c** with a conjugated coplanar amide group and an intramolecular hydrogen bond (eq 12), and the pseudopericyclic mechanism does not intervene.

(12)
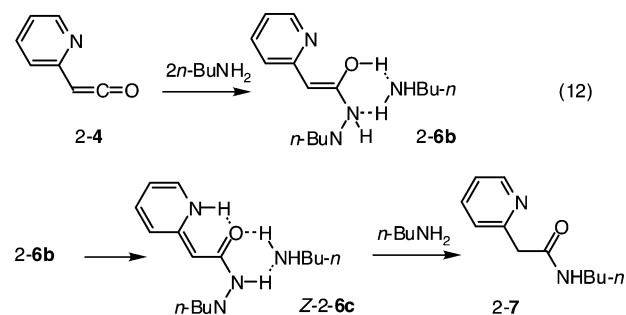
Conclusion

In summary, the hydration of 3-pyridylketene involves formation of a transient acid enol that is converted to the product acid in a subsequent rapid step. Hydration of phenylketene occurs similarly, and the corresponding acid enol has been detected for the first time. However, hydration of 4-pyridyl-ketene does not lead to an acid enol, but instead to a much longer lived 4-carboxymethylene-1,4-dihydropyridine 4-**13**, which is converted to 4-pyridylacetic acid in a process slower than its rate of formation by a factor of 10^3. 2-Pyridylketene undergoes hydration with formation of two isomeric 2-car-boxymethylene-1,2-dihydropyridines, one of which possesses an

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intramolecular hydrogen bond to the carboxy carbonyl group, and these undergo conversion to 2-pyridylacetic acid at intermediate rates compared to the 3- and 4-pyridylketenes. The structure of the product of amination of 2-pyridylketene has been reinterpreted on the basis of experimental and computational results as having the corresponding 1,2-dihyropyridine structure *Z*-2-**6a** instead of the previously proposed[6a] amide enol structure 2-**6**. No kinetic evidence for a pseudopericyclic pathway in either hydration or amination is found.

Supporting Information Available: Experimental and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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