Pure Appl. Chem., Vol. 76, No. 11, pp. 1953–1966, 2004.

Pyridylketenes: Structure reactivity effects in nucleophilic and radical addition*

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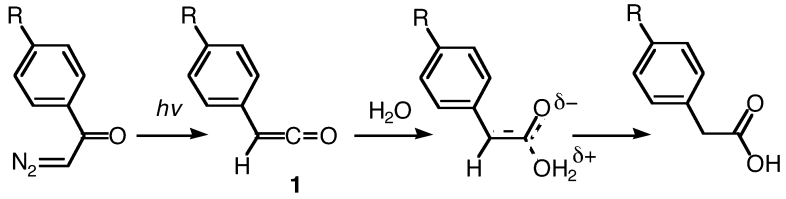
Abstract: 2-, 3-, and 4-Pyridylketenes have been generated in CH_3CN by photochemical Wolff rearrangements and identified by their ketenyl absorption in the infrared at 2127, 2125, and 2128 cm^{-1}, respectively. Reaction of these pyridylketenes with *n*-$BuNH_2$ results in the formation of intermediate amide enols from the 3- and 4-pyridylketenes, which are then converted to the corresponding pyridylacetamides. However, 2-pyridylketene forms a long-lived 1,2-dihydropyridine intermediate stabilized by an intramolecular hydrogen bond, and this is converted to the 2-pyridylacetamide with a rate constant 10^7 less than those for the conversion of the amide enols from the 3- and 4-pyridylketenes to amides. Hydration of the pyridylketenes results in the formation of an acid enol intermediate in the case of the 3-isomer, while the 2- and 4-isomers form longer-lived dihydropyridines. The pyridylketenes react with the stable free radical tetramethylpiperidinyloxyl (TEMPO, TO·) forming 1,2-diaddition products $ArCH(OT)CO_2T$.

INTRODUCTION

The elucidation of the structure and reactivity of ketenes is a classic problem in organic chemistry [1–4], and ketene hydration [1,2], amination [3], and free radical reactions [4] have been studied both computationally and experimentally. Interest in the mechanism of ketene hydration [1] received major impetus from the experimental studies by Schulte-Frohlinde and coworkers 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 [1a], indicative of rate-limiting nucleophilic attack of water on the carbonyl carbon in the ketene plane [2], with stabilization of partial negative charge in the transition state by the aryl group (eq. 1) [2f].



(1)

Computational studies of the hydration of CH_2=C=O (**2**) [2a–e] favor structures in which multiple water molecules are involved, and for two water molecules a cyclic transition state **2a** is preferred,

*Plenary lecture presented at the 5th Florida Heterocyclic Conference, Gainesville, FL, USA, 7–10 March 2004. Other presentations are published in this issue, pp. 1933–1983.

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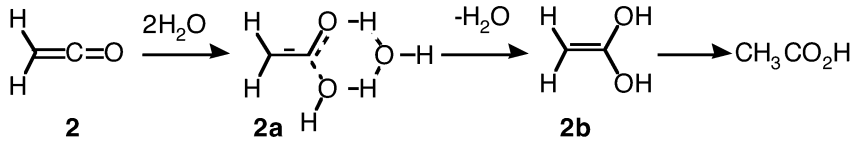
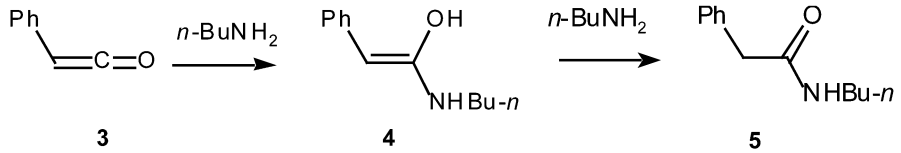
with a much lower barrier than for addition of a single water molecule. This leads to the enol **2b** of acetic acid (eq. 2), and for some ketenes acid enol intermediates have been detected by UV spectroscopy [1h,i] but had not previously been observed for phenylketene (**3**) itself. The acid enol $Ar_2C{=}C(OH)_2$ from ditipylketene ($Ar_2C{=}C{=}O$, Ar = 2,4,6-*i*-$Pr_3C_6H_2$) has been obtained in solution and characterized spectroscopically [2g,h].



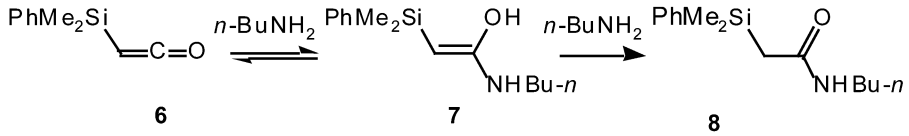
(2)

Kinetic measurements of amination of reactive ketenes such as phenylketene (**3**) in CH_3CN with monitoring of the disappearance of the ketenyl absorption by time-resolved infrared spectroscopy (TRIR) show only a first-order dependence on the amine concentration, indicating that the attack of the first amine molecule is rate-limiting [3b]. This process leads to an amide enol **4** observable by IR, and this is converted to the product amide **5** in a process, also first order in amine concentration (eq. 3) [3b].



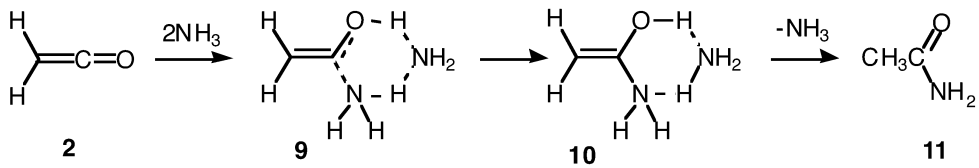
(3)

Experimental studies with the less reactive ketene **6** show a second- and even a third-order dependence on amine concentration for disappearance of the ketene, results attributed to reversible addition of amine to the ketene forming the amide enol, with participation of additional amine molecules to convert the initial amide enol to products (eq. 4) [3f].



(4)

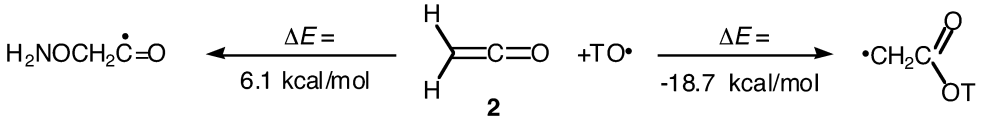
Computations [3d,e] reveal that reaction of ketene (**2**) with two NH_3 molecules gives a transition structure **9**, which forms an NH_3 complexed amide enol **10**, which tautomerizes to acetamide **11** (eq. 5). These computations are compatible with the experimental results as addition of the first amine molecule to reactive ketenes is rate-limiting, and participation of additional amine molecules occurs after the rate-limiting step.



(5)

Free radical reactions of ketenes have been less extensively studied, and computational studies at the B3LYP/6-31G*//B3LYP/6-31G* level for addition of radicals such as H·, CH_3·, SiH_3·, HO·, H_2N·, F·, and Cl· to $CH_2{=}C{=}O$ showed the reactions were strongly exothermic with low barriers for addition to either C_1 and C_2 [4a]. Computations for the less reactive aminoxy radical H_2NO· showed a 24.8 kcal/mol preference for addition to the carbonyl carbon over C_2 (eq. 6) [4h]. Experimentally, it proved possible to add the stable free radical tetramethylpiperidinyloxyl (TEMPO, TO·) to a variety of ketenes such as phenylketene (**3**) at measurable rates [4c,d,h]. The reactions were found to involve initial addition of TEMPO to the carbonyl carbon forming an enolic radical **12**, followed by addition of a

second TEMPO giving **13** (eq. 7), based on the strong rate accelerations shown by ketene-stabilizing substituents such as phenyl, and by the observation of allylic rearrangements for alkenyl and alkynylketenes [4c,d]. The reactivities of the ketenes with TEMPO gave a linear correlation with the rates of hydration of the ketenes by the expression: $\log k_2(\text{TEMPO}) = 1.20\log k(H_2O) - 4.45$ [4h].



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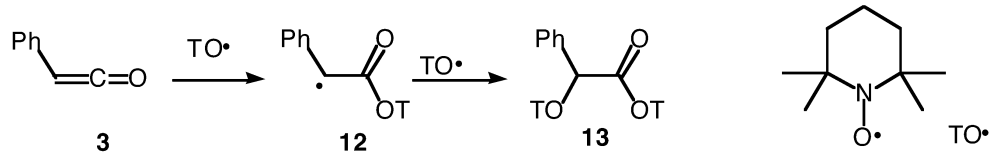
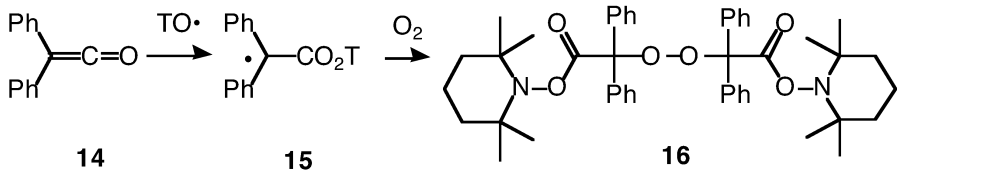


(7)

The reaction of TEMPO with diphenylketene (**14**) gave the peroxide **16**, and this was interpreted to form by attack of TO· at the carbonyl carbon C_1 forming the acyl radical **15**, which may be in equilibrium with a dimer, but the radical gradually reacts with O_2 giving **16** (eq. 8) [4b]. Upon thermolysis, the peroxide undergoes multiple-bond scission-forming benzophenone, CO_2, and tetramethylpiperidinyl radicals, which abstract hydrogen, forming tetramethylpiperidine (eq. 9) [4b].



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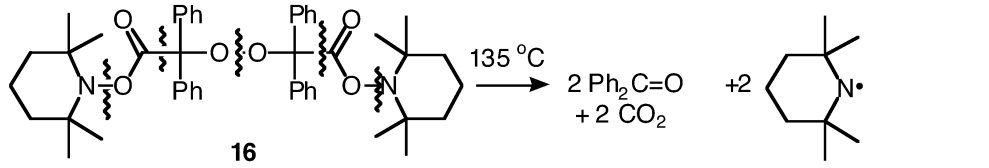
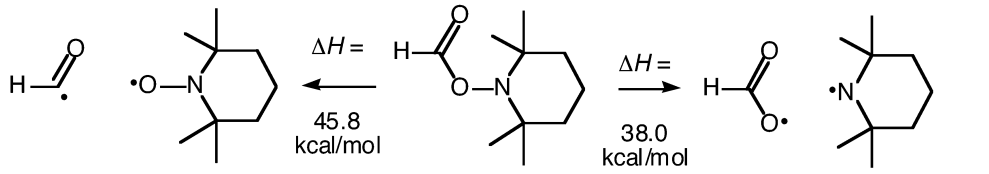


(9)

The chemistry of TEMPO esters are of great interest because of the use of these compounds in living free radical polymerization, and computations indicate these compounds would preferentially react with N–O bond fission (eq. 10) [4h]. The TEMPO esters **17** and **18** of pivalic and phenylacetic acid are known to be quite stable, but the TEMPO ester **19** of triphenylacetic acid, however, proved sufficiently reactive for study, and gave characteristic free radical products indicative of N–O bond scission, in agreement with the computations (eq. 11) [4g]. The reactivity was much greater than those of **17** and **18**, indicating C–C bond breaking was occurring in the rate-limiting step [4g].



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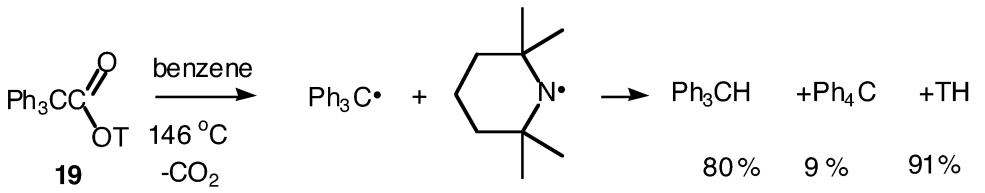

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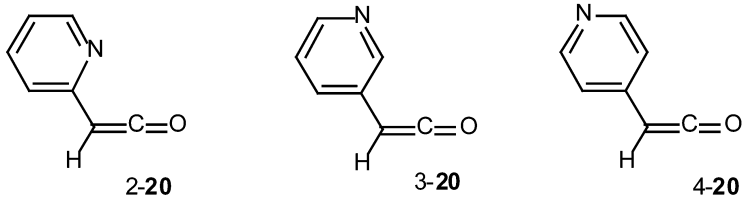
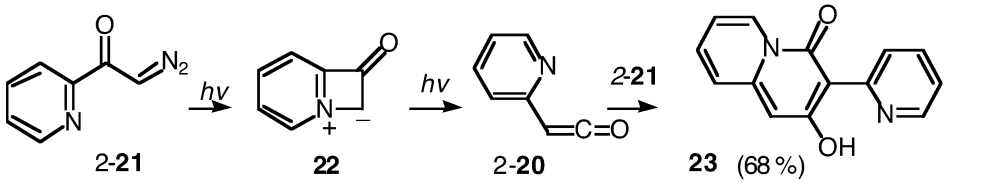
PYRIDYLKETENES

Pyridylketenes **20** [5a–d] provide an interesting comparison to phenylketene. The pyridyl ring is strongly electron-withdrawing compared to phenyl, and also has the ability of forming hydrogen bonds, which may modify the reactivity compared to the corresponding phenyl-substituted compounds.



2-**20** 3-**20** 4-**20**

2-Pyridylketene (2-**20**) has been generated by pyrolysis of ethyl 2-pyridylacetate [5a,b] with trapping in an argon matrix, and by the photochemical Wolff rearrangement of diazo ketone 2-**21** in a matrix, along with the zwitterionic species **22**, which forms **20** on photolysis (eq. 12) [5d]. The species were identified by their IR spectra: **20** had bands at 2123 and 2132 cm^{-1} for *E* and *Z* conformations, respectively [5d], and upon warming formed the dimer **23**. Pyridylketenes have also been generated and observed as monolayers on platinum surfaces (eq. 13) [5e]. Photolysis of the triazole **24** also gave 2-**20** (eq. 14) [5f].



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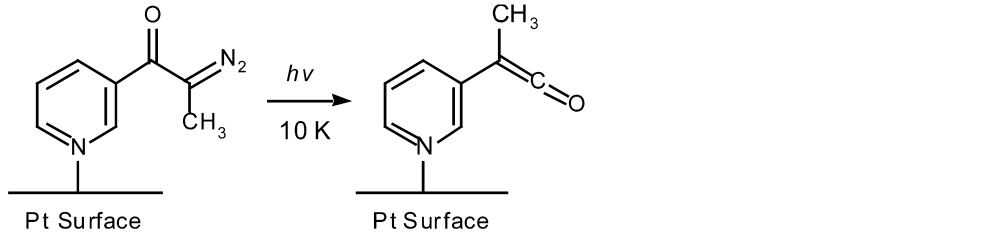

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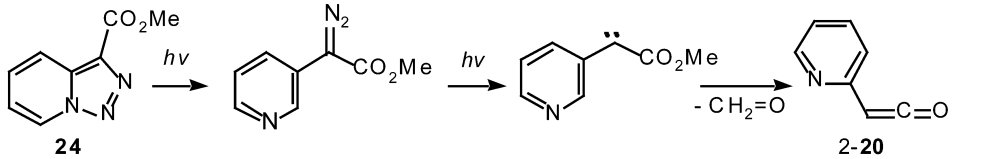

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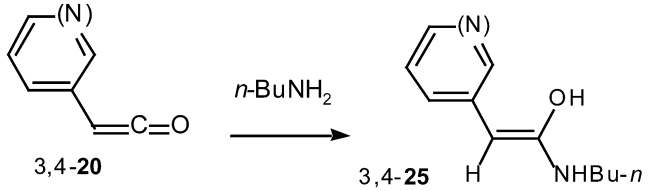
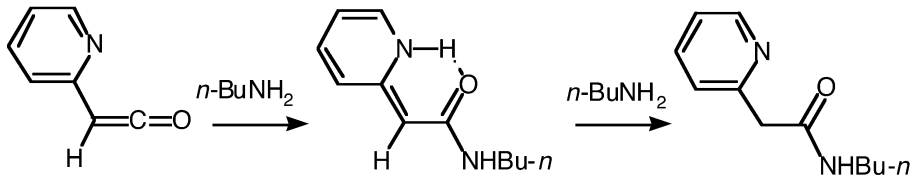
RESULTS AND DISCUSSION

The pyridylketenes 2-, 3-, and 4-**20** were generated as transient intermediates by laser flash photolysis of the corresponding diazo ketones 2-4-**21** 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 TRIR [3a]. The reactivities of 2-4-**20** with *n*-$BuNH_2$ were measured by monitoring the disappearance of the ketenyl absorption using TRIR. The ketenes each gave rise to a second transient intermediate observed by UV, and the rate constants for conversion of these transients to the product amides were measured by UV [3a]. The intermediates formed from 3- and 4-**20** were identified as the corresponding amide enols **25** by their characteristic UV spectra (eq. 15), but 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 [3a]. This longer-lived intermediate was first identified as an amide enol [3a], but this assignment was revised to the 2-caboxamidomethylene-1,2-dihydropyridine *Z*-2-**26** with a strong intramolecular hydrogen bond of the enolic hydrogen to the pyridyl nitrogen (eq. 16) [6a]. The UV spectrum of the transient **26** showed the features of the isolable *N*-methyl analog **28**, which absorbs at distinctly longer wavelength than do those of the amide enols.

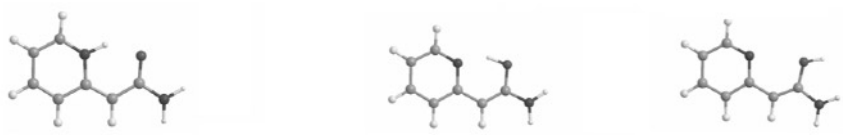


3,4-**20** 3,4-**25** (15)



2-**20** *Z*-2-**26** 2-**27** (16)

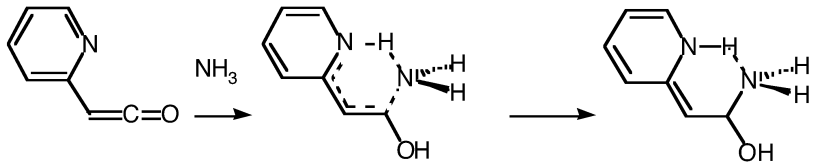
This process was further examined by DFT calculation of the pathway for reaction of pyridylketene with NH_3 [3a,6a]. The computations indicated the hydrogen-bonded dihydropyridine *syn*-2-**29** was more stable by 3.4 kcal/mol compared to the hydrogen-bonded amide enol *syn*-2-**30a**, which was 15.4 kcal/mol more stable than *syn*-2-**30b** with the hydrogen directed away [6a].



syn-2-**29a** *syn*-2-**30a** *syn*-2-**30b**

The N-H···O hydrogen bonding in *syn*-2-**29a** is of added interest for the resemblance to that observed in similar systems involving N-H···O hydrogen bonding proposed to be stabilized by resonance-assisted hydrogen bonds (RAHBs) [7a–c]. These include intramolecular hydrogen bonding in the enol of acetylacetone, which has recently been reinvestigated [7d].

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 [8] resembling 2-**31a** forming a dihydropyridine *Z*-2-**31b** (eq. 17). Such a process has been implicated in the hydration of imidoylketenes such as **32a**, which involves a near planar transition structure **32b** leading to the product **32c** (eq. 18) [8c]. However,



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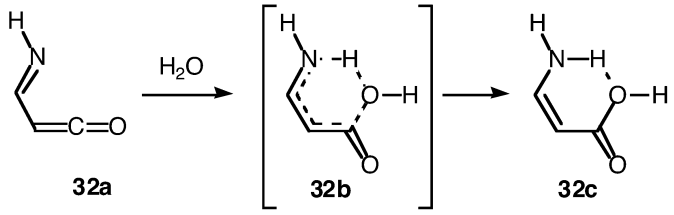


(18)

in amination, 2-pyridylketene was the least reactive of the isomers, so there was no kinetic evidence for acceleration of the reaction of 2-**20** with amines by a pseudopericyclic process.

For study of their hydration reactions, 2-, 3-, and 4-pyridylketenes **20** were generated by flash photolysis of the diazo ketones **21** in water, and the reactions were monitored by UV spectroscopy [6a]. The reaction of phenylketene (**3**) was examined for comparison. Upon photolysis of the diazo ketone 3-**21** there was an initial increase in the UV absorption monitored at the maximum near 320 nm, followed by a decay (Fig. 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. The two processes observed in the reaction of 3-pyridylketene are assigned to the formation and decay of acid enol intermediate 3-**33** formed by hydration of the initial ketene 3-**20** (eq. 19).

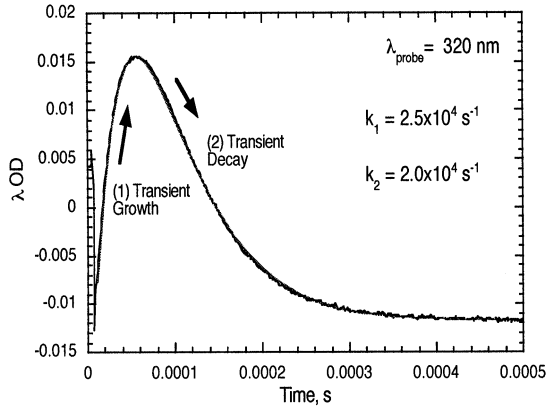
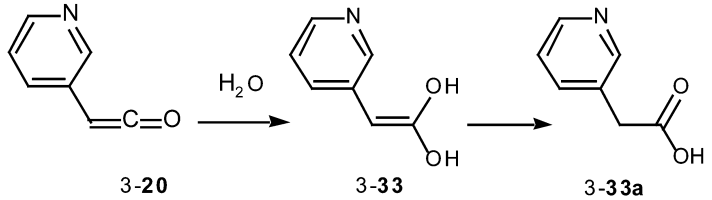


Fig. 1 UV absorption changes in hydration of 3-pyridylketene (3-**20**).



(19)

Hydration of phenylketene gave very similar behavior, with an initial increase in absorption at 280 nm followed by a decay (Fig. 2), and derived rate constants 3.3×10^4 and 4.3×10^3 s^{-1}, respectively. In solvent 75 % H_2O/25 % CH_3CN, 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 (Fig. 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], and indicates that both the conversion of the ketene **3** to the acid enol **34** and the decay of the acid enol to acid **35** are observed (eq. 20).

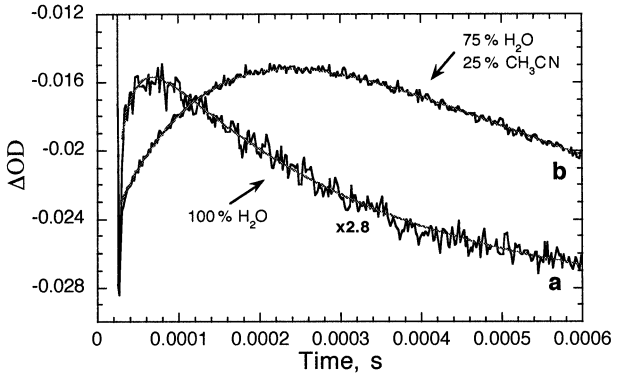
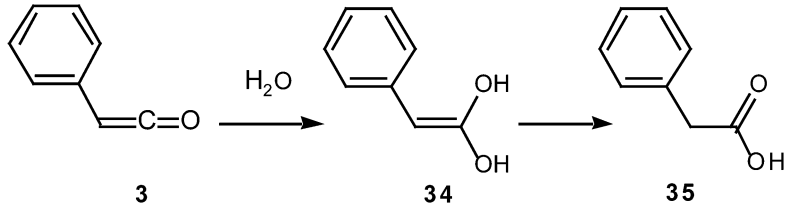


Fig. 2 UV absorption changes in hydration of phenylketene: (a) in H_2O (b) in 75 % H_2O/25 % CH_3CN.



(20)

From an analysis of the kinetic behavior of the two intermediates from the hydration of phenylketene, it has been concluded that the observed rise in absorption corresponds to the second step of the reaction, conversion of the acid enol to phenylacetic acid, while the decrease in absorption arises from conversion of phenylketene to the acid enol [9a]. This counterintuitive conclusion is a well-recognized possibility [9b].

Flash photolysis of the diazo ketone 4-**21** to generate 4-pyridylketene 4-**20** 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}. There was concomitant growth with the same rate constant of absorption with a maximum at longer wavelength, 370 nm, followed by a much slower decay (Fig. 3), with a first-order rate constant of 2.1×10^1 s^{-1}. The transient was identified as the 4-(carboxymethylene)-1,4-dihydropyridine 4-**36** resulting from conjugate 1,6-addition to 4-pyridylketene (4-**20**) with *N*-protonation and OH addition to the ketenyl carbon, and the identification was confirmed by the essential similarity of the transient UV spectrum with that of the stable ester **37a** [10a,b].

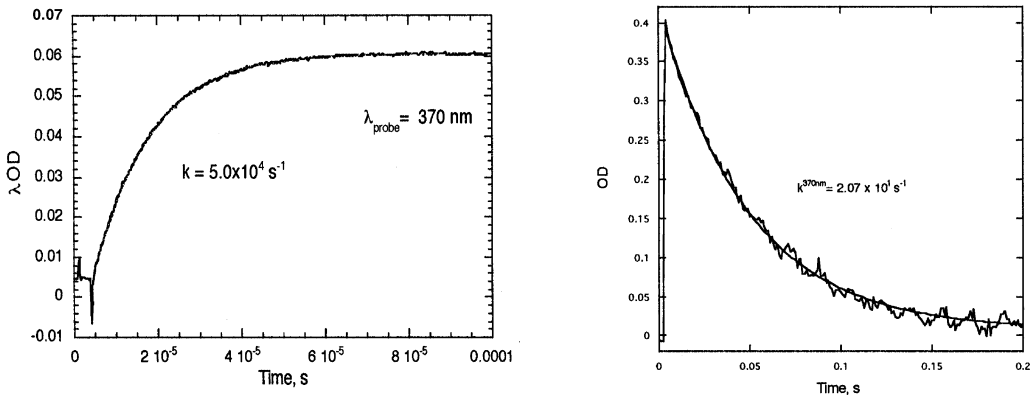
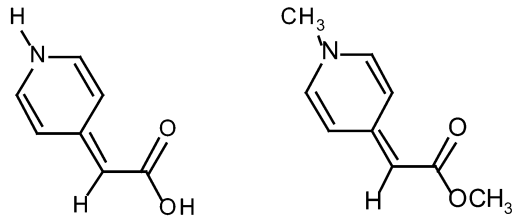


Fig. 3 Kinetic traces for growth of transient 4-**36** (left) and decay (right) in hydration of 4-pyridylketene measured at 370 nm.



4-**36** **37a**

Flash photolysis of the diazo ketone 2-**21** formed 2-pyridylketene 2-**20**, which underwent conversion to a new transient that showed strong maxima at 310 and 380 nm (Fig. 4). The conversion of 2-**20** 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} (Fig. 5). Decay of this transient monitored at 320 nm at a longer time scale was fit by a biexponential function (Fig. 5), which gave two first-order rate constants of 2.1×10^3 and 9.8×10^1 s^{-1}, attributable to 28 and 72 % of the initial absorption, respectively. The transients were identified as a mixture of the *E*-and *Z*-2-carboxymethylene-1,2-dihydropyridines *E*- and *Z*-2-**36** based on the observed kinetics and computational results, and the identification was confirmed by the near identity of the transient UV spectrum with that of the stable ester **37b** [10a,b].

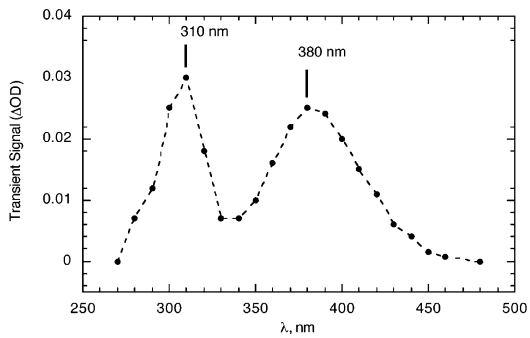


Fig. 4 UV spectrum of transient 2-**36** from hydration of 2-pyridylketene.

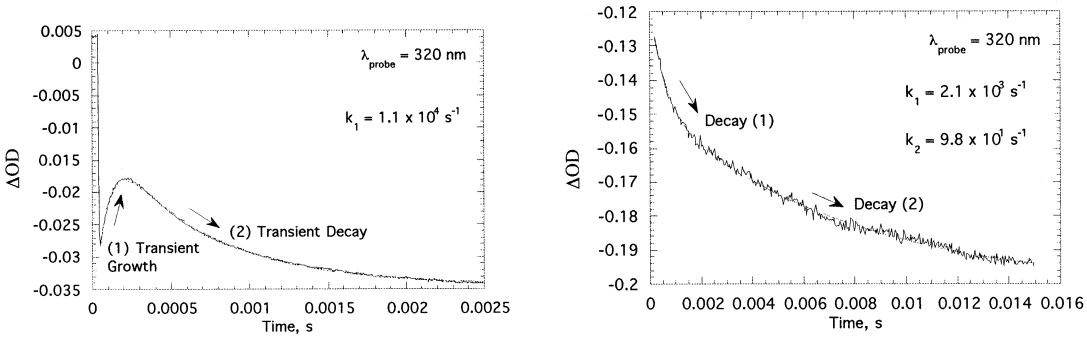
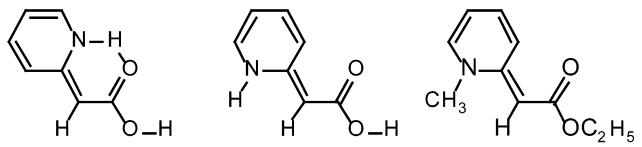


Fig. 5 Kinetic trace for hydration of 2-pyridylketene (left) and biexponential kinetic trace for transient decay from 2-pyridylketene (right).



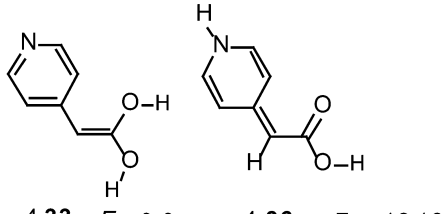
Z-2-**36** *E*-2-**36** **37b**

COMPUTATIONAL STUDIES

Structures and energies of the 2-, 3-, and 4-pyridylketenes and their hydration products were calculated at the B3LYP/6-311+G**//B3LYP/6-311+G** level. The energies were corrected using calculated zero point vibrational energies. Relative energies (kcal/mol) for the different conformations were *syn*-2-**20** 0.0, *anti*-2-**20** 1.32, *syn*-3-**20** 4.23, *anti*-3-**20** 3.93, and 4-**20** 2.91, and barriers for rotation about the aryl-ketenyl bond relative to the minimum energy conformation for each isomer were 7.21, 3.66, and 4.85 kcal/mol, respectively [6b].

The non-hydrogen-bonded acid enol *syn*-2-**33**·H_2O is calculated to be 5.43 kcal/mol more stable than the reactants (Fig. 6). The isomeric hydrogen-bonded acid enol *syn*-2-**33**·H_2O is a further 17.87 kcal/mol more stable, and this provides a measure of the strength of the intramolecular hydrogen bond. The dihydropyridine tautomer *Z*-2-**36**·H_2O is more stable by an additional 6.28 kcal/mol, with a hydrogen bond length NH···O of 1.812 Å, while the acid *syn*-2-**34**·H_2O is another 1.42 kcal/mol more stable [3a].

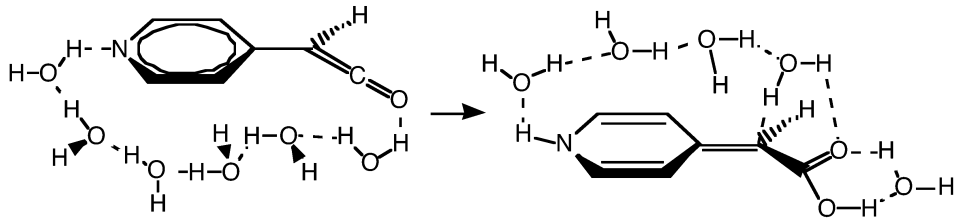
For hydration of 4-pyridylketene, the 1,6-addition product 4-(carboxymethylene)-1,4-dihydropyridine 4-**36** was calculated to be 12.18 kcal/mol more stable than the acid enol 4-**33** at the B3LYP/6-311+G**//B3LYP/6-311+G** level (Scheme 1) [6a].



4-**33** E_{rel} 0.0 4-**36** E_{rel} -12.18

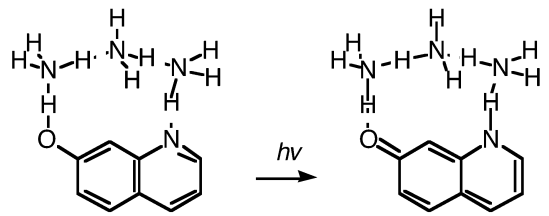
Scheme 1 Relative energies (kcal/mol) of hydrates of 4-pyridylketene.

Conversion of an initial ketene complex 4-**20**·6H_2O with participation of a bridge of water molecules to enable one-step proton addition to nitrogen and OH addition to the ketenyl carbon forming 4-(carboxymethylene)-1,4-dihydropyridine 4-**36** was simulated by a calculation with a chain of 6 water molecules between the nitrogen and the ketenyl group (Scheme 2). The complexed ketene 4-**20**·6H_2O has the water bridge largely in the plane of the pyridylketene, and was calculated to be 37.3 kcal/mol more stable than the separated reactants at the B3LYP/6-311+G**//B3LYP/6-311+G** level. This stabilization arises from the 7 hydrogen bonds present in the complex. The water bridge in the product 4-(carboxymethylene)-1,4-dihydropyridine 4-**36**·5H_2O is above the pyridyl plane, and is computed to be more stable than an alternative enediol 4-**33**·5H_2O by 7.4 kcal/mol at the B3LYP/6-31G*//B3LYP/6-31G* level [6b].



Scheme 2 Calculated structures of 4-pyridylketene complex 4-**20**·6H_2O and the product dihydropyridine 4-**36**·5H_2O from hydration with a bridge of 6 H_2O molecules.

Other 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 in solution. An analogous relay mechanism for hydrogen transfer between oxygen and quinolyl nitrogen utilizing a bridge of 3 NH_3 molecules has recently been demonstrated by an experimental and computational study (Scheme 3) [11a]. Other reactions involving chains of water molecules to effect proton transfer have also been reported [11b,c].



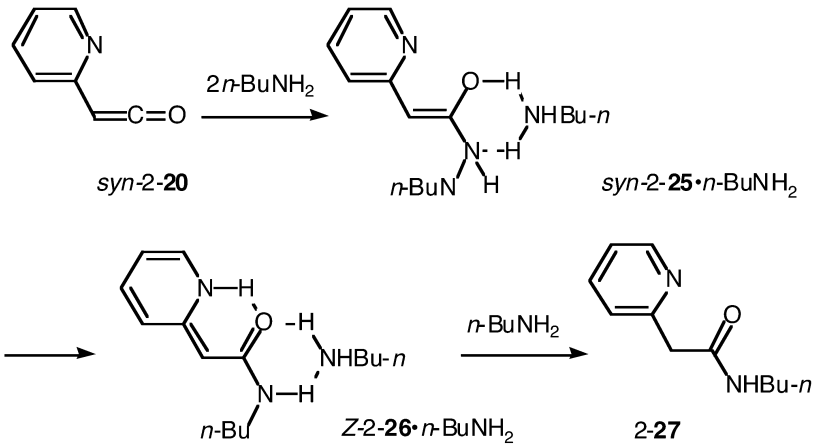
Scheme 3 Relay mechanism for hydrogen transfer from oxygen to nitrogen by a bridge of 3 ammonia molecules [11a].

MECHANISM OF HYDRATION AND AMINATION

The rate constant ratio k(ketene to intermediate)/k(intermediate to product) for amination of 4-pyridylketene (4-**20**) is 6.2, but for hydration of 4-**20** this ratio is 2.4×10^3. 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-**36** occurs by 1,6-addition of H_2O to 4-pyridylketene and this can be readily achieved in solvent H_2O, but is not feasible for amination, in which the concentration of n-butylamine used was between 10^{-4} to 10^{-3} M [3a].

2-Pyridylketene amination with *n*-$BuNH_2$ gave an intermediate dihydropyridine *Z*-2-**26** that was converted to the amide with a rate constant 1.8×10^7 less than that for conversion of the ketene to *Z*-2-**26** (eq. 17) [3a], while the rate constant ratios for formation by hydration of the dihydropyridines *Z*- and *E*-2-**36** from 2-pyridylketene relative to their rates of decay of 110 and 5.2 are much less [6a]. The computed strengths of the intramolecular hydrogen bonds are comparable in the two cases, 17.8 kcal for hydration, and 15.4 kcal/mol for amination [6b]. 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 kinetic dependence on the concentration of *n*-butylamine observed in the conversion of the intermediate from 2-pyridylketene to the amide product 2-**27** (Scheme 4) [3a].

In both hydration and amination, 2-pyridylketene is the least reactive of the isomers, so there is no kinetic evidence for a pseudopericyclic pathway (eq. 17) [8]. For 2-pyridyketene the transition structure 2-**31a** for pseudopericyclic NH_3 addition (eq. 17) lacks developing amide conjugation, which is also absent in the product dihydropyridine carboxamide 2-**31b**, with the amide group twisted out of conjugation (eq. 18) [3a]. This was previously noted by Birney et al. [8a], for the addition of NH_3 to formylketene O=CHCH=C=O. Amination by attack of 2 *n*-$BuNH_2$ molecules on *syn*-2-**20** from the side opposite the pyridyl group could lead from an amide enol 2-**25**·*n*-$BuNH_2$ to dihydropyridine *Z*-2-**26** ·*n*-$BuNH_2$ with a conjugated coplanar amide group and an intramolecular hydrogen bond (Scheme 4) without intervention of the pseudopericyclic mechanism.



Scheme 4 Pathway for addition of *n*-$BuNH_2$ to 2-pyridylketene.

The strong hydrogen bonds in 6-membered rings stabilizing 1,2-dihydropyridines *Z*-2-**26** (Scheme 4) formed in amination and *Z*-2-**36**·H_2O (Fig. 6) formed in hydration possess what have been termed resonance-assisted hydrogen bonds (RAHBs) by Gilli et al. [7a], and these have attracted wide attention [7]. Such hydrogen bonds are contained in cyclic potentially conjugated systems such as β-enaminones and acid or amide enols, and are proposed to gain extra stabilization from the contribution of other resonance structures (Scheme 5) [7]. For *Z*-2-**36**, this would correspond to a contribution from a resonance structure with an electron distribution resembling that of the acid enol *syn*-2-**33**. Such effects are not seen in nonresonant forms (Scheme 5). Our results neither require nor exclude the operation of this effect.

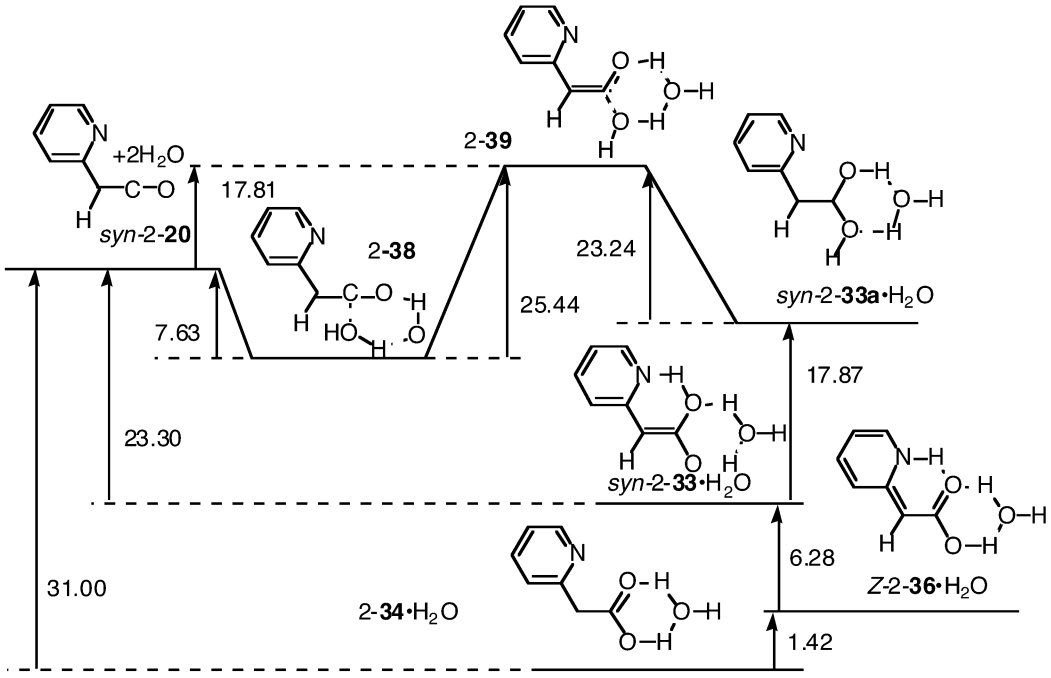
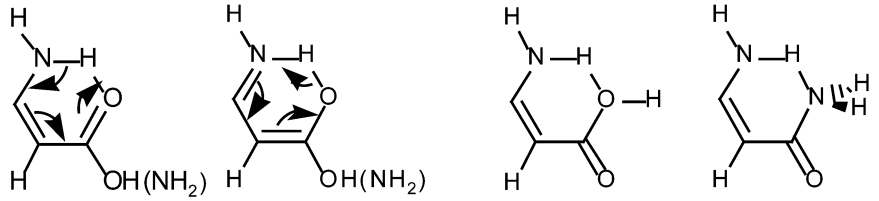


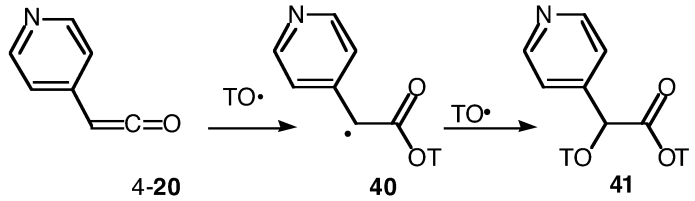
Fig. 6 B3LYP/6-311+G**//B3LYP/6-311+G** calculated energy changes (kcal/mol) for hydration of 2-pyridylketene (*syn*-2-**20**).



Scheme 5 Resonance-assisted hydrogen bonds in β-enaminones and enols, and nonresonant forms.

REACTION WITH TEMPO

Reaction of 4-pyridylketene 4-**20** with the nitroxyl radical TEMPO proceeded by 1,2-diaddition through the intermediate **40** forming the diadduct **41** (eq. 21) [6b], as had been found previously for phenylketene (eq. 7) [4b]. Measurement of the rate of reaction of the isomer 2-**20** with TEMPO and comparison with the measured rate of hydration gave a good fit as shown in Fig. 7 with the previously reported correlation $\log k_2(\text{TEMPO}) = 1.20\log k(H_2O) - 4.45$ [4h] between reactivity in hydration and reaction with TEMPO.



(21)

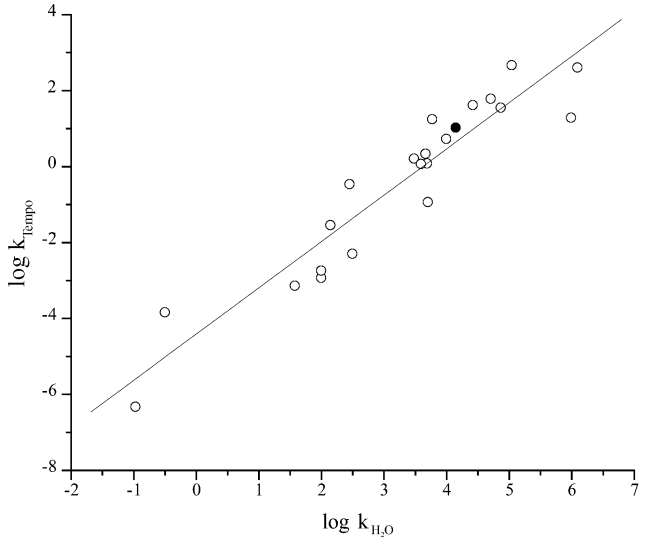


Fig. 7 Correlation of ketene reactivity with TEMPO compared to reactivity with H_2O (2-**20**, filled circle).

ACKNOWLEDGMENT

Financial support by the Natural Sciences and Engineering Research Council of Canada, the Petroleum Research Fund administered by the American Chemical Society, and a Killam Fellowship from the Canada Council for the Arts to T.T.T. is gratefully acknowledged.

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