Keto−Enol/Enolate Equilibria in the *N*-Acetylamino-*p*-methylacetophenone System. Effect of a β-Nitrogen Substituent

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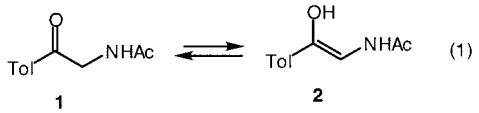
Abstract: The *cis*-enol of *N*-acetylamino-*p*-methylacetophenone was generated flash photolytically and its rates of ketonization in aqueous $HClO_4$ and NaOH solutions as well as in HCO_2H, CH_3CO_2H, $H_2PO_4^-$, $(CH_2OH)_3CNH_3^+$, and NH_4^+ buffers were measured. Rates of enolization of *N*-acetylamino-*p*-methylacetophenone to the *cis*-enol were also measured by hydrogen exchange of its methylene protons, and combination of the enolization and ketonization data gave the keto−enol equilibrium constant $pK_E = 5.33$, the acidity constant of the enol ionizing as an oxygen acid $pQ_a^E = 9.12$, and the acidity constant of the ketone ionizing as a carbon acid $pQ_a^K = 14.45$. Comparison of these results with corresponding values for *p*-methylacetophenone itself shows that the *N*-acetylamino substituent raises all three of these equilibrium constants: K_E by 3 orders of magnitude, Q_a^E by 1 order of magnitude, and Q_a^K by 4 orders of magnitude. This substituent also retards the rate of H^+ catalyzed enol ketonization by 4 orders of magnitude. The origins of these substituent effects are discussed.

There has recently been a remarkable revival of interest in the chemistry of enol isomers of simple aldehydes and ketones, fueled largely by the development of methods for generating these unstable substances in solution in greater than equilibrium amount under conditions where they can be observed directly and rate and equilibrium constants of their reactions can be measured accurately. As a result, much new information is now available on the chemistry of the enol isomers of simple aldehydes and ketones where enol is the only functional group present in the molecule.[1] Considerably less is known about the effect of heteroatom substituents on this chemistry, and we have consequently undertaken a program of research designed to supply some of the missing information. In this paper we report the results of our study of the *N*-acetylamino-*p*-methylacetophenone keto−enol (**1**−**2**) system, eq 1 (Tol = *p*-$CH_3C_6H_4$).



1 **2** (1)

In addition to its bearing on enol chemistry, this system is of biological interest in that its carbonyl-β-acylamino structure is not unlike the amide linkage in peptides and proteins, whose racemization very probably involves enol formation.

Keto−enol equilibria of carbonyl compounds with a single substituent in the β-position are complicated by the fact that the enol can usually exist in cis and trans isomeric forms. In such situations there are really two keto−enol equilibria, one producing the cis enol and another producing the trans enol. This complication can be handled,[2] but the method is laborious, and it is easier to study a system where formation of one enol is prevented by some structural constraint. Such a structural constraint operates in the reaction that we used to produce the present enol.

We generated the present enol by flash photolytic Norrish type II photoelimination of suitably constructed *p*-methylacetophenone derivatives, **3**. Irradiation of ketones such as this gives an excited state in which the carbonyl oxygen atom becomes a good hydrogen atom acceptor. Hydrogen transfer from a carbon−hydrogen bond in the γ-position then takes place producing a 1,4-diradical, **4**, which can either cyclize to a cyclobutanol derivative, **5**, or fragment to an enol, **6**, plus an olefin, **7**, eq 2. These transformations have recently been found to be quite regioselective.[3] For example, irradiation of the derivative related to isoleucine, **3** with $R_1 = R_3 =$ Me and $R_2 = R_4 =$ H, gives only fragmentation, whereas irradiation of that related to norleucine, **3** with $R_1 =$ Et and $R_2 = R_3 = R_4 =$ H, gives equal amounts of fragmentation and cyclization; the cyclized product, moreover, is produced as a single diastereomeric form. We performed flash photolysis on both the isoleucine and norleucine derivatives and in each case observed

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[||] University at Buffalo.

(1) See, for example: *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990.

(2) Chiang, Y.; Kresge, A. J.; Walsh, P. A.; Yin, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 869−871.

(3) Griesbeck, A. G.; Heckroth, H.; Lex, J. *Chem. Commun.* **1999**, 1109−1110. Griesbeck, A. G.; Heckroth, H. *Res. Chem. Intermed.* **1999**, *25*, 599−608.

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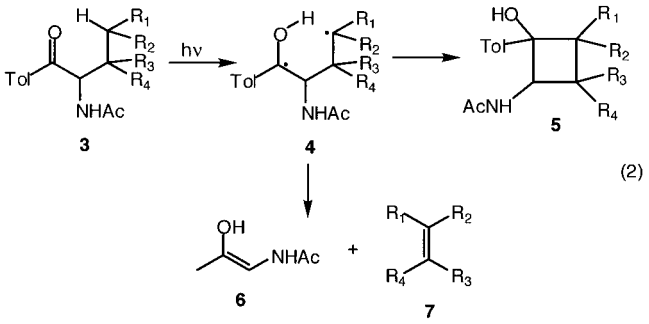
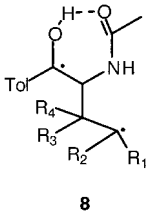


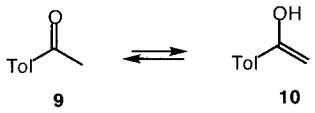
a transient species with the strong styrene-type of UV absorbance expected of enol **6**. The amount of transient formed from the isoleucine derivative, moreover, was considerably greater than that from the norleucine derivative, in keeping with the regiochemical results.

The regioselectivity of this photoreaction can be understood in terms of the size of the R-group substituents of the substrate and the additional requirement that the diradical intermediate be stabilized by formation of an intramolecular hydrogen bond between its hydroxyl group and the acetyl carbonyl group, **8**.

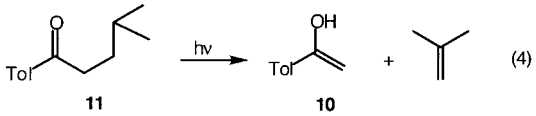


This hydrogen bond constrains the hydroxyl and *N*-acetylamino groups to lie on the same side of the bond that becomes the enol double bond in the fragmentation process, and only the cis enol is consequently formed.

To have an unsubstituted system with which to compare the chemistry of the *N*-acetylamino-*p*-methylacetophenone keto−enol pair, we also examined the *p*-methylacetophenone keto (**9**)−enol (**10**) system itself, eq 3. We generated this enol also



by flash photolytic Norrish type II photoelimination, using *p*-methylisocaprophenone, **11**, as the substrate, eq 4.



Experimental Section

Materials. The isoleucine and norleucine derivatives (**3**, $R_1 = R_3 = Me$, $R_2 = R_4 = H$ and **3**, $R_1 = Et$, $R_2 = R_3 = R_4 = H$, respectively) were samples that had been prepared before.[3] *p*-Methylisocaprophenone (**11**) was made by Friedel−Crafts acylation of toluene with isocaproyl chloride.[4] All other materials were best available commercial grades.

Ketonization Rate Measurements. Rates of ketonization of the enols of *N*-acetylamino-*p*-methylacetophenone and *p*-methylacetophenone were measured for the most part using conventional (microsecond) flash photolysis systems that have already been described.[5] Some rates, however, were too slow to be measured in this way, and in this case the enols were generated by a single flash in the flash photolysis apparatus, and the reacting solutions were then quickly transferred to the cell compartment of a Cary 2200 spectrometer. Reactions were monitored by following the decay of enol absorbance at $\lambda = 275-300$ nm. Substrate concentrations were ca. 5×10^{-4} M, and the temperature of the reacting solutions was controlled at 25.0 ± 0.05 °C. The data obtained conformed to the first-order rate law, and observed first-order rate constants were obtained by least-squares fitting of an exponential function.

Enolization Rate Measurements. Rates of enolization of *N*-acetylamino-*p*-methylacetophenone were measured by hydrogen exchange in D_2O solution using ^1H NMR to monitor conversion of the methylene group CH_2 singlet at δ 4.740 ppm into a CHD triplet at δ 4.714 ppm. A Varian Unity Inova 500 spectrometer was used; the resolution of this instrument was sufficient to give baseline separation of the CH_2 and CHD signals.

Reactions were initiated by making an 80-fold dilution of a solution of substrate in CD_3CN into 5−7 mL of DCO_3^-/CO_3^{2-} buffer at pD 10−11, to give a final substrate concentration of 0.0035−0.005 M. At timed intervals, 1.0 mL aliquots were removed and exchange was quenched by adjusting these aliquots to pD 2−3 with DCl (35%/D_2O). The resulting solutions were then immediately extracted with ca. 1 mL of $CDCl_3$, the aqueous layers were removed by Pasteur pipet, and 0.75 mL portions of the $CDCl_3$ solutions were injected into NMR tubes. These were stored in a desiccator at 4 °C until NMR analyses were performed; all analyses were completed within 2−3 days of storage. Chemical shifts were referenced to $CHCl_3$ at δ 7.27 ppm, and spectra (65−128 transients, 70 s relaxation delay) were obtained using a sweep width of 6000 Hz, a 90° pulse angle, and an acquisition time of 6 s.

Integrated areas of the CH_2 signals were referenced to the area of the multiplet at δ 7.882 ppm due to two aromatic protons of *N*-acetylamino-*p*-methylacetophenone. Disappearance of the CH_2 signal conformed to the first-order rate law well, and observed first-order rate constants were obtained by least-squares fitting of an exponential function.

Results

Ketonization Rates. Rates of ketonization of the enols of *N*-acetylamino-*p*-methylacetophenone and *p*-methylacetophenone were measured in dilute aqueous perchloric acid and sodium hydroxide solutions, and also in aqueous HCO_2H, CH_3CO_2H, $H_2PO_4^-$, $(CH_2OH)_3CNH_3^+$, and NH_4^+ buffers. The data so obtained are summarized in Tables S1−S6.[6]

The measurements in buffers were made in series of solutions of constant buffer ratio and constant ionic strength (0.10 M), and therefore constant $[H^+]$, but varying buffer concentration. Observed first-order rate constants increased with increasing buffer concentration and conformed to the buffer dilution expression shown in eq 5; the data were therefore analyzed by

$$k_{obs} = k_o + k_{cat}[buffer] \qquad (5)$$

linear least-squares fitting of this expression.[7] The zero-buffer-concentration intercepts, k_o, so obtained were then combined with the rate constants measured in $HClO_4$ and NaOH solutions to construct the rate profiles shown in Figure 1. Values of $[H^+]$ needed for this purpose were obtained by calculation using thermodynamic acidity constants of the buffer acids from the literature and activity coefficients recommended by Bates.[8]

(4) Rae, I. D.; Woolcock, M. L. *Aust. J. Chem.* **1987**, *40*, 1023−1029.
(5) Chiang, Y.; Kresge, A J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392−6395. Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A J.; Schepp, N. P.; Wirz, J. *J. Am Chem. Soc.* **1987**, *109*, 4000−4009.

(6) Supporting Information; see paragraph at the end of this paper regarding availability.
(7) Buffer catalysis became progressively weaker with decreasing buffer acid strength, until observed rate constants measured in the most basic NH_4^+ buffer used for the ketonization of *N*-acetylamino-*p*-methylacetophenone enol ($[H^+] = 1.4 \times 10^{10}$ M) no longer changed significantly with buffer concentration. A simple average of observed rate constants measured in this series of solutions was therefore used for rate profile construction.

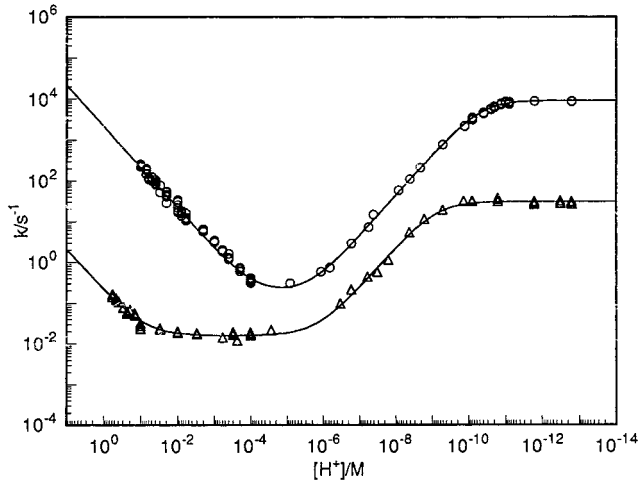


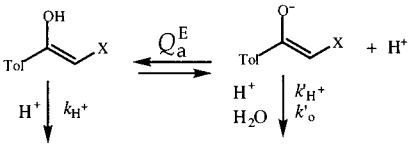
Figure 1. Rate profiles for the ketonization of the enols of *N*-acetylamino-*p*-methylacetophenone (△) and *p*-methylacetophenone (○) in aqueous solution at 25 °C.

These rate profiles are characteristic of enol ketonization reactions. They may be understood in terms of the accepted mechanism for this process, which consists of rate-determining protonation of the enol on its β-carbon atom by all available acids.[9] Since these profiles refer to reactions through solvent-related species only, the available acids will be the hydronium ion, written here as H^+, and the solvent water itself.

The acid-catalyzed portions at the high-acidity ends of these profiles then represent β-carbon protonation of the un-ionized enols by H^+. These portions are followed by "uncatalyzed" regions, which could be due either to carbon protonation of un-ionized enol by H_2O, or to ionization of the enol to the very much more reactive enolate anion[10] followed by carbon protonation of that by H^+; this latter route produces H^+ in a rapid equilibrium step and then uses it up in the rate-determining step, which gives an overall process independent of H^+ concentration. The first of these two alternative routes would give rate constants for carbon protonation of un-ionized enol by H_2O that are not very much less than those for the same protonation by H^+ ($k_{H^+} = 2.1 \times 10^{-1}$ M s^{-1} and $k_{H_2O} = 1.6 \times 10^{-2}$ s^{-1} for *N*-acetylamino-*p*-methylacetophenone enol, and $k_{H^+} = 2.2 \times 10^3$ M^{-1} s^{-1} and $k_{H_2O} = 1.8 \times 10^{-1}$ s^{-1} for *p*-methylacetophenone enol), which seems unlikely for acids of such widely different strength, and the second of these two routes is consequently to be preferred.

At sufficiently low acidities, H^+ concentrations are too small to sustain protonation of the enolate ions on carbon by H^+, and reaction through protonation by water takes over. A proton is now still produced in a rapid equilibrium step, but it is no longer used up in the rate-determining step; the result is a process whose rate is inversely proportional to [H^+], giving an apparent hydroxide ion catalysis. At even lower acidities, the enol−enolate ion equilibrium shifts over to the side of enolate, and the advantage of converting a less reactive (enol) to a more reactive (enolate) species is lost; this produces the final "uncatalyzed" low-acidity portions of the rate profiles.

The reaction scheme representing these mechanisms is shown in eq 6, and the rate law that applies is given in eq 7. Least-squares fitting of this expression produced the following



(6)

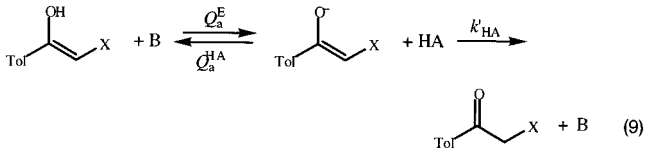
$$k_{obs} = k_{H^+}[H^+] + (k'_{H^+}[H^+] + k'_o)Q_a^E/(Q_a^E + [H^+]) \quad (7)$$

results: for *N*-acetylamino-*p*-methylacetophenone enol, $k_{H^+} = (2.07 \pm 0.08) \times 10^{-1}$ M^{-1} s^{-1}, $k'_{H^+} = (2.09 \pm 0.18) \times 10^7$ M^{-1} s^{-1}, $k'_o = (3.03 \pm 0.11) \times 10^1$ s^{-1}, $Q_a^E = (7.59 \pm 0.57) \times 10^{-10}$ M, and $pQ_a^E = 9.12 \pm 0.03$,[11] and for *p*-methylacetophenone enol, $k_{H^+} = (2.15 \pm 0.05) \times 10^3$ M^{-1} s^{-1}, $k'_{H^+} = (3.74 \pm 0.57) \times 10^9$ M^{-1} s^{-1}, $k'_o = (9.10 \pm 0.38) \times 10^3$ s^{-1}, $Q_a^E = (4.70 \pm 0.37) \times 10^{-11}$, and $pQ_a^E = 10.32 \pm 0.03$.[11]

The buffer catalytic coefficients, k_{cat}, obtained by analyzing the buffer data according to eq 5 were separated into their general acid, k_{HA}, and general base, k_B, components with the aid of eq 8, in which f_A is the fraction of the buffer present in the acidic form. Only general base catalysis was found,

$$k_{cat} = k_B + (k_{HA} - k_B)f_A \quad (8)$$

indicating that all of the reactions were proceeding through base-assisted ionization of the enol followed by rate-determining carbon protonation of the enolate ion by the conjugate acid of the general base, eq 9. The rate law for this process, shown in eq 10, can be rearranged to give an expression for the general



(9)

$$k_B = (Q_a^E/Q_a^{HA})k'_{HA} \quad (10)$$

acid catalytic coefficient of the enolate ion reaction, k'_{HA} in terms of the known quantities, Q_a^E, Q_a^{HA}, and k_B; the results so obtained are listed in Table 1.

Table 1. General Acid Catalytic Coefficients for the Ketonization of *N*-Acetylamino-*p*-methylacetophenone and *p*-Methylacetophenone Enolate Ions[a]

	k_{HA}/M^{-1} s^{-1}	
catalyst	TolC(OH)=CHNHAc	TolC(OH)=CH$_2$
H_3O^+	2.09×10^7	3.74×10^9
HCO_2H	7.14×10^5	
CH_3CO_2H	1.98×10^5	2.31×10^7
$H_2PO_4^-$	2.94×10^4	1.29×10^7
$(CH_2OH)_3CNH_3^+$	5.66×10^3	3.13×10^6
NH_4^+		3.94×10^5
H_2O	5.46×10^{-1}	1.65×10^2

[a] Aqueous solution; 25 °C; ionic strength = 0.10 M.

General acid catalytic coefficients for rate-determining proton-transfer reactions such as enolate ketonizations are expected to parallel the acid strength of the catalysts. The Bronsted relations of Figure 2 show that this is so for both of the present systems, despite the fact that these correlations are based upon a rather mixed bag of catalysts of different charge types and also include the solvent-related species H^+ and H_2O. The Bronsted exponents obtained by least-squares analysis of all of the data moreover,

(8) Bates, R. G. *Determination of pH Theory and Practice*; Wiley: New York, 1973; p 49.

(9) Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990; Chapter 7.

(10) Pruszynski, P.; Chiang, Y.; Kresge, A J.; Schepp, N. P.; Walsh, P. A. *J. Phys. Chem.* **1986**, *90*, 3760−3766. Chiang, Y.; Kresge, A. J.; Santabella, J. A.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 5506−5510.

(11) This is a concentration quotient applicable at the ionic strength of its determination, 0.10 M.

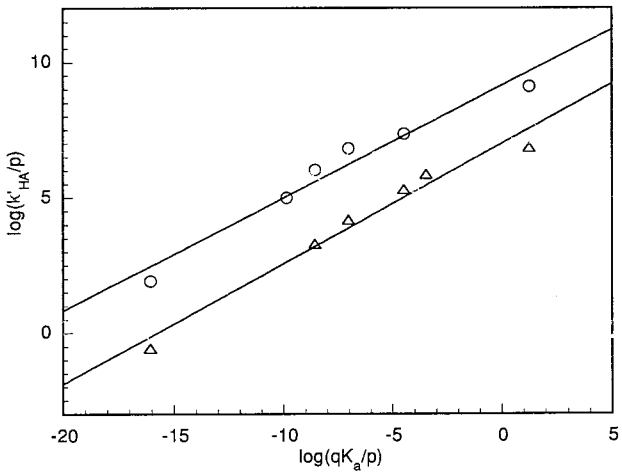


Figure 2. Bronsted plots for the ketonization of the enols of *N*-acetylamino-*p*-methylacetophenone (△) and *p*-methylacetophenone (○) in aqueous solution at 25 °C.

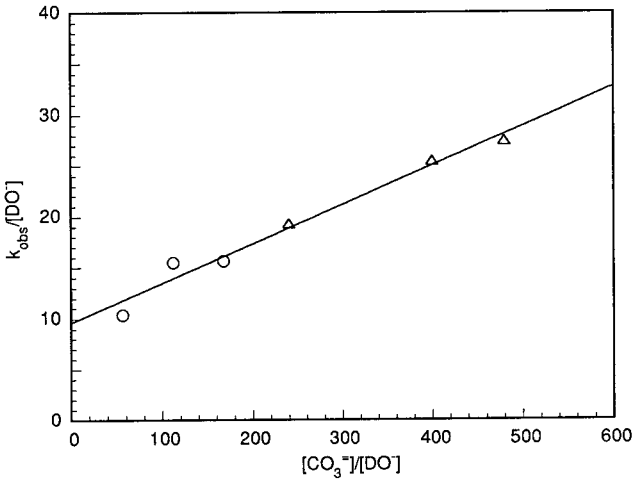


Figure 3. Data for the hydrogen exchange (enolization) of *N*-acetylamino-*p*-methylacetophenone in aqueous (D_2O) DCO_3^-/CO_3^{2-} buffer solutions at 25 °C plotted according to eq 12: (△) $[DCO_3^-]/[CO_3^{2-}] = 9$ and (○) $[DCO_3^-]/[CO_3^{2-}] = 1$.

$\alpha = 0.44 \pm 0.04$ for the enolate ion of *N*-acetylamino-*p*-methylacetophenone and $\alpha = 0.42 \pm 0.04$ for the enolate ion of *p*-methylacetophenone, are small, in keeping with the rapid nature of these reactions.

Enolization Rates. Rates of enolization of *N*-acetylamino-*p*-methylacetophenone, monitored by following loss of its CH_2 group ^{1}NMR signal in D_2O solution, were measured in DCO_3^-/CO_3^{2-} buffers, using a series of solutions of constant buffer ratio and constant ionic strength, and therefore constant $[D^+]$, but varying buffer concentration. Two different buffer ratios, $[DCO_3^-]/[CO_3^{2-}] = 9$ and $[DCO_3^-]/[CO_3^{2-}] = 1$, were used. The data so obtained are summarized in Table S7.[6]

Enolization of ketones is a rate-determining hydron transfer process and is therefore subject to general base catalysis. The rate law that applies in the presently used basic buffers consequently contains a term representing reaction through the carbonate anion in addition to that for hydroxide ion, eq 11. Division of this expression by $[DO^-]$ then gives a relationship,

$$k_{obs} = k_{DO^-}[DO^-] + k_B[CO_3^{2-}] \qquad (11)$$

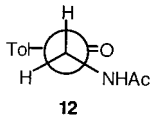
eq 12, that requires $k_{obs}/[DO^-]$ to be a linear function of the

$$k_{obs}/[DO^-] = k_{DO^-} + k_B[CO_3^{2-}]/[DO^-] \qquad (12)$$

concentration ratio $[CO_3^{2-}]/[DO^-]$, with k_{DO^-} as the zero intercept. Figure 3 shows that the present data conform to this relationship well, and least-squares analysis gives the result $k_{DO^-} = (9.59 \pm 0.90)\ M^{-1}\ s^{-1}$. Values of $[DO^-]$ needed for this purpose were obtained by calculation using literature values of thermodynamic acidity constants for DCO_3^- [12] and D_2O[13] plus activity coefficients recommended by Bates.[8]

This hydroxide ion catalytic coefficient for the enolization of *N*-acetylamino-*p*-methylacetophenone can be combined with ketonization rate measurements to estimate the keto−enol equilibrium constant for this system (vide infra), but it must first be converted from D_2O to a value for the H_2O medium in which the ketonization rate measurements were made. Solvent isotope effects on hydroxide ion catalyzed reactions have no primary component, but there is an inverse secondary component,[14] which, for the enolization of carbonyl compounds, generally amounts to about 40%. For example, $k_{DO^-}/k_{HO^-} = 1.37$ for the enolization of acetaldeheyde,[15] and $k_{DO^-}/k_{HO^-} = 1.46$ for the enolization of acetone and 1.39 for the enolization of mandelate ion.[16] Use of the rounded average value 1.4 then gives $k_{HO} = (6.85 \pm 0.81) \times M^{-1}\ s^{-1}$ for the enolization of *N*-acetylamino-*p*-methylacetophenone in H_2O solution.

Equilibrium Constants. An enol-forming reaction such as that used here to measure rates of enolization of *N*-acetylamino-*p*-methylacetophenone can in principle produce both cis and trans enols. It is likely, however, that in the present case there was a considerable bias favoring cis-enol formation. This follows from consideration of the substrate conformations shown in the Newman projection formulas **12** and **13**, which lead to the cis and trans enols, respectively. Structure **13** will be disfavored because it places the large tolyl and *N*-acetylamino groups together, whereas structure **12** juxtaposes each of these large groups with the smaller hydrogen and carbonyl-oxygen substituents. Structure **12** will also be favored by an electrostatic



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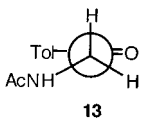

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interaction between the partial positive charge on the *N*-acetylamino nitrogen atom and the negative charge being generated on the erstwhile carbonyl oxygen atom in the transition state of this base-catalyzed enolate ion forming enolization reaction. It seems quite likely, therefore, that this enolization reaction produced mostly cis-enol, and that combination of the rate constant for this process with rates of ketonization measured flash photolytically, which also refer to the cis-enol, will provide an equilibrium constant for the keto−cis-enol reaction shown in eq 1.

This keto−enol equilibrium may be formulated as shown in eq 13, and evaluation of the expression for its equilibrium constant, $K_E = (k_{HO}/k'_o)(Q_w/Q_a^E)$, gives $K_E = (4.72 \pm 0.68) \times$

(12) Paabo, M.; Bates, R. G. *J. Phys. Chem.* **1969**, *73*, 3014−3017.
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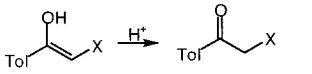
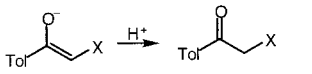
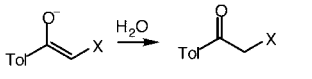
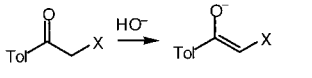
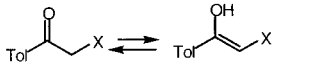
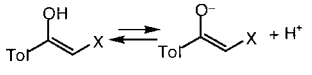
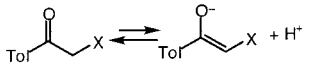
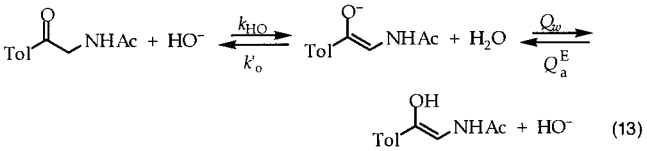
(15) Keeffe, J. R.; Kresge, A J. *Can. J. Chem.* **1988**, *66*, 2440−2442.
(16) Pocker, Y. *Chem. Ind. (London)* **1958**, 1117−1118.

Table 2. Summary of Rate and Equilibrium Constants[a]

Process		X = NHAc	X = H
	$k_{H^+}/M^{-1}s^{-1}$:	2.07×10^{-1}	2.15×10^{3}
	$k'_{H^+}/M^{-1}s^{-1}$:	2.09×10^{7}	3.74×10^{9}
	k'_o/s^{-1}:	3.03×10^{1}	9.10×10^{3}
	$k_{HO^-}/M^{-1}s^{-1}$:	6.85	-
	pK_E:	5.33	8.34
	pQ_a^E:	9.12	10.32
	pQ_a^K:	14.45	18.67

[a] Aqueous solution; 25 °C; ionic strength = 0.10 M.

10^{-6} and $pK_E = 5.33 \pm 0.06$. The first part of the relationship of eq 13 includes the ionization of *N*-acetylamino-*p*-methyl-



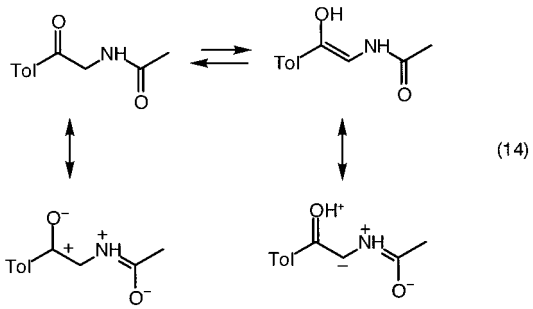
(13)

acetophenone as a carbon acid, and the equilibrium constant for this ionization may be evaluated as $Q_a^K = (k_{HO}/k'_o)Q_w = (3.59 \pm 0.36) \times 10^{-15}$ M and $pQ_a^K = 14.45 \pm 0.04$.[11]

The keto−enol equilibrium constant for the other system examined here, that of *p*-methylacetophenone, has been determined before.[17] Its value, $pK_E = 8.34$, when combined with $pQ_a^E = 10.33$ obtained here from the rate profile for ketonization of the enol of this ketone, gives $pQ_a^K = 18.67$ as the acidity constant of *p*-methylacetophenone ionizing as a carbon acid. The *p*-methyl group of this system is unlikely to exert much influence on these equilibrium constants, and it is significant therefore that the present results are quite similar to corresponding values for acetophenone itself, $pK_E = 7.96$, $pQ_a^E = 10.40$, and $pQ_a^K = 18.36$.[18]

Discussion

Equilibria. The present results, summarized in Table 2, show that introduction of an *N*-acetylamino group into the β-position of *p*-methylacetophenone raises the keto−enol equilibrium constant, K_E, by 3 orders of magnitude, giving a substituent effect of $\delta_R\Delta G° = 4.1$ kcal mol^{-1}. This sizable effect can be attributed to destabilization of the keto isomer plus stabilization of the enol isomer. The keto isomer is destabilized by the unfavorable interaction of the partial positive charge on its carbonyl carbon atom with the partial positive charge on the amide nitrogen atom of its *N*-acetylamino group, as shown by the ionic resonance forms given in eq 14. The enol, on the other



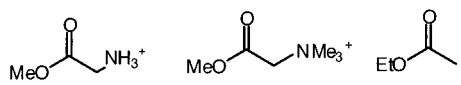
(14)

hand, is stabilized by the favorable interaction of this positively charged amide nitrogen with the partial negative charge on the enol β-carbon; this is also illustrated by eq 14. Both of these effects operate to decrease the energy difference between keto and enol forms, and they thus serve to increase K_E.

The *N*-acetylamino group also raises the acidity constant of the enol, Q_a^E, but by a much smaller amount—only 1 order of magnitude—than its influence on K_E; the substituent effect here amounts to just $\delta_R\Delta G° = 1.6$ kcal mol^{-1}. This effect is so much smaller than that on K_E because the enol rather than the keto isomer is the initial state for this acid ionization process, and destabilization of the keto form, which contributed to the substituent effect on K_E, is no longer a factor. Only stabilization of the partial negative charge on the system's β-carbon operates here, and since this charge is greater in the enolate ion than in the enol, the stabilization of enolate is greater than that of enol and the result is an increase in Q_a^E.

The substituent effect of *N*-acetylamino on the acidity constant of the keto isomer ionizing as a carbon acid, Q_a^K, is greatest of all: it amounts to 4 orders of magnitude, which makes for $\delta_R\Delta G° = 5.8$ kcal mol^{-1}. This, of course, is because the keto form is the initial state of this process, and both keto-form destabilization and enolate ion stabilization contribute to this substituent effect.

Carbon-acid acidity constants for the ionization of the β-carbon−hydrogen bonds of methyl ammonioacetate, **14**, and methyl trimethylammonioacetate, **15**, have recently been determined,[19] and comparison of the results with the acidity constant of ethyl acetate, **16**,[20] gives substituent effects of $\delta_R\Delta G°$



14 **15** **16**

= 6.3 kcal mol^{-1} for NH_3^+ and $\delta_R\Delta G° = 10.4$ kcal mol^{-1} for NMe_3^+. These effects are in the same direction and of roughly similar magnitude as that found here for the NHAc group, and they may be attributed to the same causes. They are, however, somewhat greater than the presently determined effects, which is consistent with the fact that these substituents bear full positive

(17) Hochstrasser, R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 7875−7876.

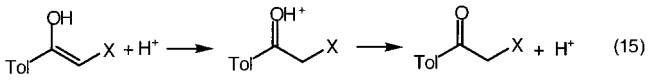
(18) Jefferson, E. A.; Keeffe, J. R.; Kresge, A. J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2041−2046. Keeffe, J. R.; Kresge, A. J.; Toullec, J. *Can J. Chem.* **1986**, *64*, 1224−1227. Chiang, Y.; Kresge, A. J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392−6395.

(19) Rios, A.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 9373−9385.

(20) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 3129−3141.

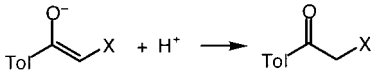
charges whereas the amide nitrogen atom of the *N*-acetylamino group possesses only a partial positive charge.

Kinetics. The considerable vertical displacement from one another of the rate profiles given in Figure 1 shows that the *N*-acetylamino group also has a strong influence on rates of ketonization. Ketonization of un-ionized enol catalyzed by H^+, for example, is slowed by 4 orders of magnitude, giving the substituent effect $\delta_R\Delta G^{\ddagger} = 5.5$ kcal mol^{-1}. This retardation must be due in part to stabilization of the enol initial state by the *N*-acetaylamino group, but another contributing factor is provided by the two-step nature of the acid-catalyzed ketonization of un-ionized enols, which involves a positively charged carbonyl-oxygen-protonated intermediate, eq 15.[9] The unfavor-



(15)

able interaction between this positive charge and the partially positively charged *N*-acetylamino nitrogen then raises the energy of the protonation transition state, and that lowers the rate of reaction. This explanation is supported by the fact that the substituent effect on the overall conversion of enol to keto forms, $\delta_R\Delta G^{\circ} = 4.1$ kcal mol^{-1}, is less than that on the rate, $\delta_R\Delta G^{\ddagger} = 5.5$ kcal mol^{-1}, inasmuch as the positive charge has been removed from the substrate in the final state of the overall process and the additional transition state interaction is no longer a factor. Further reinforcement of this explanation comes from ketonization of the enolate ion effected by H^+, eq 16, where



(16)

the substituent effect on the rate, $\delta_R\Delta G^{\ddagger} = 3.1$ kcal mol^{-1}, is less than that on the overall reaction, $\delta_R\Delta G^{\circ} = 5.8$ kcal mol^{-1}. This process is a one-step reaction with no intermediate[9] and, since the starting material is negatively charged, there is no generation of positive charge on the substrate.

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Supporting Information Available: Tables S1−S7 of rate data (14 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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