# The p$K_a$ of Acetophenone in Aqueous Solution

Michael Novak[1] and Gordon Marc Loudon*

*The Spencer Olin Laboratory of Chemistry, Department of Chemistry, Cornell University, Ithaca, New York 14853*

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A method is reported for the determination of the p$K_a$ of acetophenone based on the aqueous reference state. The basis of the method is the measurement of the rates of aminolysis of α-acetoxystyrenes. The correlation of the rates of the uncatalyzed aminolysis with p$K_a$ of the leaving group, established for aryl acetates, defines the p$K_a$ of the respective acetophenone enols. Detailed arguments concerning the microscopic steps in the aminolysis reaction are presented to show that steric effects on the aminolysis reaction should be minimal for the *uncatalyzed* aminolysis, and that aryl acetates and α-acetoxystyrenes should thus fall on the same correlation of rate vs. leaving group p$K_a$. The rates of aminolysis of phenyl acetate in the same solvent system are reported, and were determined to ensure the comparison of the aminolysis of the two classes of compounds under identical conditions. The enolization constant of acetophenone was determined using a potentiometric procedure, and was found to be $(1.92 \pm 0.03) \times 10^{-5}$ in 40 vol % *tert*-butyl alcohol–water. This value, together with the p$K_a$ of acetophenone enol estimated by the kinetic procedure to be 11.0 ± 1.0, defines the carbon p$K_a$ of acetophenone to be 15.8 ± 1.0. This number is compared with values obtained from previous determinations and with the absolute p$K_a$ determined in dimethyl sulfoxide.

The proton acidity and basicity of organic substances is one of the most important foundations for reasoning by analogy in organic chemistry. There exists a continuing interest in the acidity of weak acids, and in the relationship of ionization constants of acids whose p$K_a$ values are too weak to measure to the dilute aqueous reference state, where p$K_a$ measurements for relatively stronger acids are common. Absolute acidity scales have been developed in solvents such as dimethyl sulfoxide ($Me_2SO$) because, in this solvent in particular, ionization constants can be determined over a wide range of acidity.[2,3] A similar determination of a wide range of p$K_a$ values is not possible in aqueous solution, of course, because of the protic nature of the solvent. However, the facts that water is the solvent for biochemical process, and that water as a solvent is of interest for mechanistic investigations of a number of organic reactions, require the use of p$K_a$ values truly based on the aqueous (or largely aqueous) reference state. Since the p$K_a$ values of weak acids cannot be measured directly in water, it is of interest to have methods for estimating them indirectly. The $H_-$ acidity function has been used in an attempt to relate the p$K_a$ values of weak acids determined in water/$Me_2SO$ mixtures to p$K_a$ values determined in pure water.[4] The basis of this method is the use of a series of indicator overlaps which establish p$K_a$ values in mixtures of continuously variable solvent composition. Since relative acidities determined by this procedure can be substantially different from relative acidities in water, this procedure does not really provide access to the dilute aqueous reference state for weak acids. Furthermore, the approximations underlying the $H_-$ acidity function itself have in some cases been shown to fail badly.[5] In this paper, we report a novel method for estimating carbon p$K_a$ values of substituted acetophenones which should be applicable to other ketones as well. In this method, the p$K_a$ of acetophenone enols is estimated kinetically, and the enolization constant of acetophenone, redetermined by a method more reliable than that used previously, is used to complete a thermodynamic cycle to the p$K_a$ of acetophenone. The number obtained is considerably lower than previous values determined in other solvent systems.

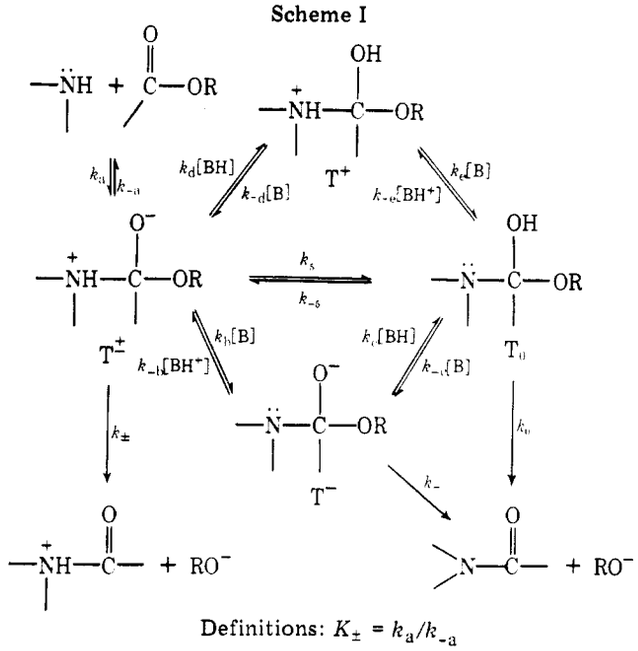
## Results and Discussion

**The p$K_a$ of Acetophenone Enol.** We recently found that the aminolysis of substituted α-acetoxystyrenes (**1a–f**) according to eq 1 follows the same general rate law observed for the similar reaction of other acetate esters, and is given by

$$k_{obsd} - k_0 = k_1[Am] + k_2[Am]^2 + k_3[Am][OH^-] + k_4[Am][Am \cdot H^+] \quad (1)$$

in which $k_{obsd}$ = observed first-order rate constant for appearance of acetophenone and $k_0$ = rate constant for hydrolysis. Our investigations of the mechanism of this reaction have been previously reported,[6,7] and may be summarized by the statement that the mechanism of aminolysis of α-acetoxystyrenes is identical with the mechanism of aminolysis of aryl acetates. This mechanism is summarized in Scheme I.[8] The

Scheme I



Definitions: $K_\pm = k_a/k_{-a}$

interpretation of the $k_1$ and the $k_3$ terms of eq 1, on which we shall focus in this paper, in terms of the mechanism of Scheme I are presented in eq 2 and 3.

$$k_1 = (k_a/k_{-a})k_\pm = K_\pm k_\pm \quad (2)$$

$$k_3 = (k_a/k_{-a})k_b = K_\pm k_b \quad (3)$$

In previous work,[6] detailed linear free energy relationships were developed for the effect of both leaving group and amine on the $k_1$ term of eq 1, and it was found that the sensitivity of the reaction rate of the p$K$ of the nucleophile, $\beta_{nuc}$, and the sensitivity of the reaction rate to the substituent effect on the leaving group enol, $\beta_{lg}$, are essentially identical with the values of these quantities found for aryl acetates.

It has been found that plots of log $k_1$ vs. p$K_a$ of the leaving group define excellent straight lines when leaving groups of related structure are considered. Thus, we were able to esti-

**Table I. Values of Some Observed and Elementary Rate Constants for Aminolysis of Phenyl Acetate and *m*-Chloro-α-acetoxystyrene**

| Registry no. | Amine | $pK_a$[b] | $k_1$,[a] $M^{-1}$ $min^{-1}$ | $k_3$,[a] $M^{-2}$ $min^{-1}$ | $K_\pm$, $M^{-1}$ | $k_\pm$, $min^{-1}$ |
|---|---|---|---|---|---|---|
| | | | Phenyl Acetate | | | |
| 110-89-4 | Piperidine[c] | 11.22 | 4.3 | 400 | $2.9 \times 10^{-10}$ | $15.0 \times 10^9$ |
| 107-10-8 | Propylamine[d] | 10.84 | 4.9 | 3480 | $2.5 \times 10^{-9}$ | $2.0 \times 10^9$ |
| 124-40-3 | Dimethylamine[c] | 10.64 | 4.5 | 2430 | $1.7 \times 10^{-9}$ | $2.6 \times 10^9$ |
| 109-76-2 | 1,3-Diaminopropane[d] | 10.62 | 19.9 | 11 300 | $8.1 \times 10^{-9}$ | $2.5 \times 10^9$ |
| 74-89-5 | Methylamine[e] | 10.62 | 17.0 | 7000 | $5.0 \times 10^{-9}$ | $3.4 \times 10^9$ |
| 109-73-9 | $n$-$C_4H_9NH_2$[c] | 10.59 | 4.5 | 1900 | $1.4 \times 10^{-9}$ | $3.2 \times 10^9$ |
| | $n$-$C_4H_9NH_2$[f] | 10.57 | 4.1 | 1500 | $1.1 \times 10^{-9}$ | $3.7 \times 10^9$ |
| 107-15-3 | $H_2NCH_2CH_2NH_2$[d] | 10.18 | 1.7 | 1000 | $7.1 \times 10^{-10}$ | $2.4 \times 10^9$ |
| 141-43-5 | $HOCH_2CH_2NH_2$[f] | 9.57 | 0.326 | 146 | $1.05 \times 10^{-10}$ | $3.1 \times 10^9$ |
| | | | *m*-Chloro-α-acetoxystyrene (1e) | | | |
| 123-75-1 | Pyrrolidine[f] | 11.32 | 19.6 | 4300 | $3.1 \times 10^{-9}$ | $6.3 \times 10^9$ |
| | $n$-$C_4H_9NH_2$[f] | 10.57 | 2.76 | 600 | $4.3 \times 10^{-10}$ | $6.4 \times 10^9$ |
| | $HOCH_2CH_2NH_2$[f] | 9.57 | 0.204 | 37 | $2.6 \times 10^{-11}$ | $7.8 \times 10^9$ |

[a] Equation 1. [b] The $pK_a$ reported under conditions of the experiment. [c] Source: ref 30. Conditions: water, $\mu$ = 1.0 M (KCl), 25 °C. [d] Source: ref 33. Conditions: water, $\mu$ = 1.0 M (KCl), 25 °C. [e] Source: ref 32. Conditions: water, $\mu$ = 1.0 M (KCl), 25 °C. [f] This work. Conditions: 5% ethanol water, $\mu$ = 0.5 M (KCl), 30 °C.

mate the relative $pK_a$s of acetophenone enols (using the reasonable assumption that $\rho$ for ionization of these compounds in water is about unity) from their ability to act as leaving groups in the reaction characterized by the $k_1$ term of eq 1. The slope of this line, $\beta_{lg}$, was essentially the same as the slope found for the aminolysis of aryl acetates. However, the question of the *absolute* $pK_a$ values for acetophenone enols remains. In order to estimate the absolute $pK_a$ values of acetophenone enols, one can assume that the log $k_1$ vs. leaving group $pK_a$ correlation for α-acetoxystyrenes is not only parallel to the correlation for aryl acetates, but also coincident with that correlation. The grounds for this assumption, however, have not been carefully examined. One could reasonably object that, although the lines might be parallel, they would not be expected to be coincident because of the differential steric effects in the aminolysis of the two classes of compounds. For example, the $k_2$ term of eq 1 shows parallel but separate lines for phenol and alcohols in the aminolysis of phenyl acetates and alkyl acetates.[8,9] Similarly, it has been found that the aminolysis of a gluconolactone derivative is much faster than would be predicted on the basis of the $pK_a$ of the leaving group because of the constraint of the lactone into the presumably more reactive cis ester conformation, and because of this increase in rotational freedom of the compound which attends ring opening.[10] On the other hand, the $n$-butylaminolysis of α-naphthyl acetate, which could roughly be considered to be an isostere of α-acetoxystyrene (and which is, if anything, more bulky in its leaving group than α-acetoxystyrene), has a rate which is only 2.5 times slower than one would predict from the $pK_a$ of α-naphthol and the $\beta_{lg}$ of unity for the aminolysis reaction.[11] This last result suggests that the $k_1$ term in eq 1 is only minimally sensitive to steric effects, and that the determination of $pK_a$ values by the correlation of $k_1$ terms in the aminolysis rates of various esters is justifiable.

The experimental data for the aminolysis of phenyl acetates and the relationships of eq 2 and 3 allow us to determine the values for $k_\pm$ and $K_\pm$ for α-acetoxystyrenes and aryl acetates (Scheme I). In order to ensure the greatest degree of accuracy, the data for the aminolysis of phenyl acetate were redetermined for several amines in our solvent system [5% ethanol, $\mu$ = 0.5 M (KCl), 30 °C]. The raw data from these determinations are reported in Table III (supplementary material). The $k_b$ in eq 3 is identified with a diffusion-controlled proton transfer from the amine in the tetrahedral intermediate $T_\pm$ to hydroxide ion. This number should be essentially independent of the nature of the leaving group. It is this independence, rather than the exact value of this number, on which subsequent calculations depend, but the number can nevertheless be estimated to be close to that observed for the known average rate of proton transfer from several ammonium ions to $OH^-$, determined by Eigen and his co-workers[12] to be $(1.4 \pm 0.4) \times 10^{12}$ $M^{-1}$ $min^{-1}$ at 25 °C. Assuming the constancy of this value for all acylated phenols and enols studies, one may then calculate $K_\pm$ from the $k_3$ term in the rate law of eq 1 and the relationship in eq 3. Knowing $K_\pm$ from this calculation, one may then revert to eq 2 and, using the observed $k_1$ values for phenyl acetate and α-acetoxystyrenes, one may calculate the $k_\pm$ value for these compounds. The values for $k_1$, $k_3$, $k_\pm$, and $K_\pm$ for phenyl acetate and *m*-chloro-α-acetoxystyrene are presented in Table I. A number of points should be noted about the values in this table. Inspection shows that the dependence of $K_\pm$ on the $pK_a$ of the attacking amine gives a $\beta$ value of about unity, as suggested by Satterthwait and Jencks.[8] On the other hand, $k_\pm$ is essentially independent of the identity of the amine, as suggested by Ritchie,[13] and is thus approximately constant for a particular leaving group. It has been found that, for hydrazinolysis of acetate esters, log $K_\pm$ correlates with the $pK_a$ of the leaving group with a $\beta_{lg}$ of −0.6.[8] Likewise, log $k_\pm$ also correlates with the $pK_a$ of the leaving group with a $\beta_{lg}$ of −0.4.[8] Since we now know the values of $K_\pm$ and $k_\pm$ for *m*-chloro-α-acetoxystyrene, it is of interest to use these $\beta_{lg}$ values and assumed correlations of log $K_\pm$ and log $k_\pm$ with leaving group $pK_a$ to calculate an apparent $pK_a$ of *m*-chloroacetophenone enol. The average $k_\pm$ for phenyl acetate (ignoring the apparently anomalous value for piperidine) is $(2.9 \pm 0.6) \times 10^9$ $min^{-1}$, whereas the average value for this quantity for *m*-chloro-α-acetoxystyrene is $(6.8 \pm 0.8) \times 10^9$ $min^{-1}$. With a $\beta_{lg}$ of −0.4 for this quantity, one can calculate an apparent $pK_a$ for *m*-chloroacetophenone enol which is 0.9 units lower than that of phenol. Since the $pK_a$ of phenol in a solvent system closely related to that used in the kinetic studies[31] is 10.24, the apparent $pK_a$ for *m*-chloro-α-acetoxystyrene is set in this way at 9.3. A comparison of $K_\pm$ for the reactions of both phenyl acetate and α-acetoxystyrene gives a $K_\pm$ for phenyl acetate which is (3.5 ± 0.5) times larger than the corresponding value of *m*-chloro-α-acetoxystyrene. The correlation of log $K_\pm$ with $pK_a$ of the leaving group defines the apparent $pK_a$ of *m*-chloroacetophenone enol to be 11.2.

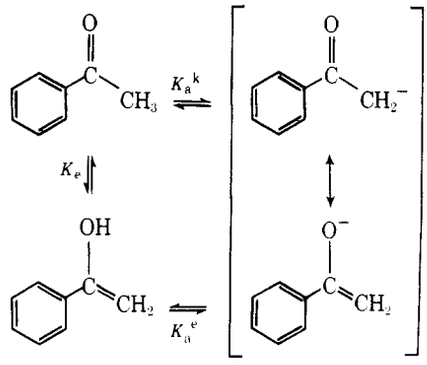
One can see that the apparent $pK_a$ values for *m*-chloroacetophenone enol calculated from these two correlations are

rather disparate. However, the disagreement between these two estimates is exactly what one would expect if steric effects in each of the microscopic steps of the aminolysis of phenyl acetates and α-acetoxystyrenes are different. Since correlations of log $K_{\pm}$ vs. leaving group p$K_a$ have been observed,[8] two compounds with leaving groups of similar p$K_a$ should have similar $K_{\pm}$ values for a given amine unless the tetrahedral intermediate, $T_{\pm}$, is more sterically crowded for one type of compound than the other. If this is so, then $K_{\pm}$ for the more encumbered intermediate will be smaller than expected for the p$K_a$ of the leaving group. In fact, this effect apparently occurs in the hydrazinolysis of various acetates. The $K_{\pm}$ values for the hydrazinolysis of primary alkyl and aryl acetates define two separate but parallel log $K_{\pm}$ vs. p$K_a$ linear free energy relationships.[8] The line for phenyl acetates lies about an order of magnitude below the line of aliphatic acetates, presumably because of increased steric crowding in the tetrahedral intermediates derived from the aryl acetates. The lack of an observed reaction between tertiary amines and α-acetoxystyrenes[6,7] is evidence that these esters form more sterically crowded tetrahedral intermediates than do aryl acetates. The disparity between the two p$K_a$ estimates above based on $K_{\pm}$ and $k_{\pm}$ is further evidence of the steric effect. If the tetrahedral intermediate formed from a given amine in **1e** is more sterically crowded than the corresponding intermediate in aryl acetate aminolysis, estimates of the p$K_a$ of the leaving group in **1e** based on the comparison of $K_{\pm}$ values of phenyl acetate *will be too high*, because $K_{\pm}$ will be lowered by steric hindrance in the intermediate formed from **1e**. Thus, the leaving group from **1e** will appear to be more basic than it is in reality. One would expect that the value of $k_{\bullet}$ will also be affected by steric hindrance in $T_{\pm}$. The decomposition of a sterically crowded intermediate will be accelerated by the relief of steric compression; that is, $k_{\pm}$ will be larger for **1e** than expected for the corresponding value derived for aryl acetates. Thus, values of the leaving group p$K_a$ in **1e** based on the correlation of log $k_{\pm}$ vs. the leaving group p$K_a$ in aryl acetates *will be too low*. Since $k_1$ of eq 1 is a composite of $K_{\pm}$ and $k_{\pm}$ (eq 2) in which the former is sterically depressed and the latter is sterically accelerated, the value of $k_1$ will tend to reflect a cancellation of these opposing steric effects and therefore estimates of p$K_a$ based on log $k_1$ will be relatively free from steric effects. The close correspondence of the log $k_1$ for the *n*-butylaminolysis of α-naphthyl acetate[11] to that calculated on the basis of the p$K_a$ of α-naphthol (see above) shows that these conclusions are reasonable. On the other hand, the abnormally high value of $k_1$ for the aminolysis of 3,4,6-*O*-trimethyl-2-deoxy-δ-gluconolactone[10] relative to the value predicted from the p$K_a$ of the leaving group is expected from an abnormally large value of $K_{\pm}$ attributable to the cis ester effect, and from an abnormally large value of $k_{\pm}$, attributable to the increase of rotational freedom which accompanies ring opening. In the latter case, both factors contributing to $k$ are changed in the same direction. It has been shown by Gerstein and Jencks[14] that equilibrium constants for ester aminolysis show an excellent correlation between the logarithm of the equilibrium constant for the aminolysis reaction vs. p$K_a$ of the ester leaving group for all types of leaving groups; that is, separate lines are not required to correlate the behavior of alkyl groups and aryl groups. Of course, equilibrium constants for aminolysis are expected to be more devoid of steric effects than the rate constants under consideration. Equilibrium constants for the aminolysis of α-acetoxystyrenes are inaccessible, however, and we must rely on kinetics for the estimate of the p$K_a$ of the leaving group. The kinetic constant in eq 1 which is expected to resemble most closely the equilibrium constant in its relative insensitivity to steric effects is $k_1$, because in the mechanism to which this constant is assigned (Scheme I, eq 2) bond formation to the amine is essentially complete, and bond breaking to the leaving group is substantial.

It is clear that the two estimates of the p$K_a$ for *m*-chloroacetophenone enol based respectively on $K_{\pm}$ and $k_{\pm}$ apparently bracket the real p$K_a$ of this substance. Thus, the p$K_a$ of *m*-chloroacetophenone enol may be estimated to be 10.5 ± 1.0 with a good deal of confidence; the error limits reflect the maximum uncertainty in this quantity. Since the steric effects inherent in $K_{\pm}$ and $k_{\pm}$ which lead to this uncertainty tend to cancel, the uncertainty is probably smaller. From the correlation of log $k_1$ for aminolysis of α-acetoxystyrenes against p$K_a$ of the leaving group ($\beta_{lg}$ = 1.0). the assumed value of $\rho$ of 1.0 for ionization of various substituted acetophenone enols justified previously,[6] and the relative values of $k_1$ for *n*-butylaminolysis of substituted α-acetoxystyrene,[6] the p$K_a$ of acetophenone enol itself may be estimated to be 11.0 ± 1.0.

**The Enolization Constant of Acetophenone.** The p$K_a$ of acetophenone is related to the p$K_a$ of acetophenone enol by the thermodynamic cycle shown in Scheme II. It is clear

Scheme II




from this thermodynamic cycle that the carbon p$K_a$ of acetophenone may be calculated from our enol p$K_a$ as derived above provided that an accurate value for the fraction enol in acetophenone is known.

A value for the enolization constant, $K_e$, of acetophenone was determined by Gero[15] to be $K_e = 3.5 \times 10^{-4}$. This value was determined by titration of the enol present in acetophenone by iodine monochloride. The fraction enol in a number of other ketones was also determined by this method, and subsequent, more accurate determinations[16] have shown that the numbers determined by Gero are consistently too high. Sources of error in this type of determination include the rather rapid formation of enol compared with the rate of enol titration, titration of impurities in the solvent, and titration of impurities in the ketone, which was claimed to be 95% pure (minimum). Therefore, we believed that it was important to determine accurately the value for the enolization constant of acetophenone by a more reliable method. The method of choice is an electrochemical technique which was described in detail by Bell and Smith.[16] The essence of this technique is the ability to determine accurately and almost instantly the concentration of small quantities of $Br_2$. Such determinations can be made repeatedly on the same ketone solution after allowing more enol to form. The values obtained for a number of ketones in such repetitive determinations were found to be self-consistent.[16] Impurities in the solvent may thus be titrated initially before the enol determination takes place. Applying the method of Bell and Smith[16] to the enolization of acetophenone, we obtained the value $K_e = (1.92 \pm 0.03) \times 10^{-5}$ in 40% *tert*-butyl alcohol–water.

Since the concentration of bromine is extremely low in these experiments relative to the concentration of acetophenone, the small amount of α-bromoacetophenone produced should have negligible effect on the values of $K_e$ determined by this method. Furthermore, repetitive determinations of $K_e$ on the

**Table II. Some Values of the $pK_a$ of Acetophenone**

| Value | Solvent | Ref | Method |
|---|---|---|---|
| 19.2 | Water | 17 | Rates of iodination |
| 19 | Ether | 19 | Colorimetric, spectroscopic; based on aqueous $pK_a$ of methanol (= 16)[21] |
| 19.1 | Polyethers | 21 | Equilibration with acids whose $pK_a$ is based on 15.9 for 4-nitrodiphenylamine (established by $H_-$ techniques)[24] |
| 20 | Ether | 22 | Acetophenone taken as arbitrary standard |
| 21.5 | $Me_2SO$/$H_2O$[a] | 24 | Rates of detritiation compared with standard compound of known $pK_a$ |
| 24.7 | $Me_2SO$ | 3, 18 | Determined directly using indicators (as 22.5) and corrected because of known (constant) difference of values provided by indicator and electrochemical techniques |
| 15.8 | 5 vol % ethanol–water | This work | |

[a] 0.011 M $Me_4N^+ OH^-$. [b] $\mu$ = 0.5 M (KCl).

same solution gave the same result; were $\alpha$-bromoacetophenone contributing to the observed value of $K_e$, a systematic drift in the results would be observed as more of this material is formed. The nonaqueous cosolvent was necessary for solubilization of the acetophenone, but was not expected to have a major effect on the value of $K_e$. An attempt was made to determine $K_e$ in an ethanol–water mixture, but the potentials were found to drift, apparently because of a slow oxidation of the ethanol by $Br_2$. Such a drift was not observed in the 40% *tert*-butyl alcohol–water system. As a check of the method in this solvent system, the enol content of cyclopentanone was determined in this solvent system. The value of $(3.32 \pm 0.07) \times 10^{-5}$ determined in this solvent system is in good agreement with the value $(1.3 \pm 0.1) \times 10^{-5}$ determined by Bell and Smith[16] for the enolization in water.

Although the values of enolization constants are expected to be solvent dependent, the comparison of the value determined by us for cyclopentanone in 40% *tert*-butyl alcohol with that determined in water[16] shows that the *tert*-butyl alcohol cosolvent has a relatively minor effect.

**The $pK_a$ of Acetophenone.** The value of $K_e$ for acetophenone combined with the estimate of the $pK_a$ of acetophenone enol calculated in the previous discussion yields a value for the carbon $pK_a$ of acetophenone itself of 15.8 ± 1.0. It is interesting to compare this value with other values for the $pK_a$ of acetophenone, some of which are tabulated in Table II. The only value in this table determined in aqueous solution is the determination of Bell,[17] which employed rates of deprotonation of various ketones as a method for $pK_a$ estimation. In this study the validity of the Brønsted correlation between the rates of exchange and the difference in basicity of the ketone and the catalyzing base was assumed. Furthermore, the $pK_a$ scale was anchored on a value of 10.7 for ethyl acetoacetate, and the extrapolation to the $pK_a$ of acetophenone was rather lengthy.

The assumptions used in the present study are fundamentally different. It could be argued that we have not taken adequate account of the steric effect on the aminolysis reaction on which the $pK_a$ correlation is based. However, it should be pointed out that the assumption of a greater steric retardation than that which we have analyzed above only serves to reduce the value of the $pK_a$ of acetophenone which emerges from the correlation.

It is interesting to compare the value which we calculate for the $pK_a$ of acetophenone and the corresponding values for cyclohexanone and cyclopentanone. Bell and Smith[16] considered the bromination of these two ketones as a function of pH (a technique which could not be used with acetophenone because of the more rapid self-condensation). Knowing the fraction enol, these authors were able to calculate the carbon $pK_a$ of these ketones and found a $pK_a$ value of 16.7 for both compounds. This number is rather close to the value which we have calculated for the $pK_a$ of acetophenone; the somewhat lower value for the latter compound, if it is real and not due to accumulated errors, is consistent with the greater electron-withdrawing character of the aromatic ring.

The other values for the $pk_a$ of acetophenone cited in Table II were determined in either nonaqueous or partially aqueous solvents using various methods, and all depend on arbitrary standards of reference, with the exception of the value in $Me_2SO$, which was determined as part of a study of absolute acidities in that solvent.[3,18] These acidities are ultimately referred to standard results of a potentiometric method for the determination of the acidities of weak acids in $Me_2SO$.[2a,b] As pointed out by Bordwell and co-workers, the apparent agreement of the remaining values in this table is fortuitous, and occurs largely because of the use of different standards of reference in the different studies.

It was noted by Rappoport[25] that rates of addition of amines to electrophilic olefins $CH_2{=}CHX$ in methanol correlate with the $pK_a$ of the carbon acid $CH_3X$; the point X = $-COC_6H_5$ was assigned a $pK_a$ value of 19 and fit the correlation well. Such a correlation, however, requires only correct *relative* $pK_a$ values, rather than absolute $pK_a$ values. Furthermore, most of the $pK_a$ values used in this correlation were obtained from kinetic measurements of the rate of ionization (e.g., rates of bromination or deuterium exchange).[17,26-28]

Although the concept of the inherent strength of an acid or base in solution has no meaning,[29] measurements of acidity of weak acids in various solvents when compared with gas phase acidity measurements can provide important information on solvation phenomena. Thus, there is no "correct" number for *the* $pK_a$ of acetophenone. The physical organic chemist interested in aqueous solution mechanisms or the biochemist interested in the $pK_a$ of a proton adjacent to a carbonyl group in a molecule of intermediary metabolism will find the $pK_a$ values implied by this study and others[16] to be appropriate. The synthetic organic chemist interested in the relative base strengths of anions in polar aprotic solvents such as $Me_2SO$, tetrahydrofuran, or other such solvents which are commonly used in organic synthesis would be more interested in the absolute scale of acidities in $Me_2SO$. The connection between the two kinds of $pK_a$ values of a weak acid is provided by the relative standard free energies of transfer of the components of the acid–base equilibrium between water and $Me_2SO$. The comparison between absolute acidities in the two types of solvents—polar aprotic vs. water—has been nicely summarized by Bordwell and co-workers.[3] Compounds whose conjugate bases have negative charge largely localized on a heteroatom (carboxylates, enolates) will have a higher absolute acidity in water than they do in $Me_2SO$, whereas compounds whose conjugate bases are highly delocalized anions will be relatively more acidic in $Me_2SO$. These conclusions follow from the relative importance of hydrogen bonding in anion stabilization in the former cases compared with the relative importance of other types of forces in the latter. In fact, the aqueous acidity of acetophenone estimated here compared with that in $Me_2SO$ is in exactly the order predicted by these conclusions, so that no conflict in these data exists.

Values of $pK_a$ determined by the $H_-$ scale incorporate effects of mixed solvents, and cannot be considered to be $pK_a$s which are based on the dilute aqueous reference state except in the limit of the rather strong bases whose $pK_a$ values are determined in essentially aqueous solution, as Bordwell et al. have pointed out.[3]

It may be that the method used here to determine the $pK_a$ of substituted acetophenones may be applicable to $pK_a$ determinations of other carbonyl compounds as well.

## Experimental Section

**Kinetics.** Phenyl acetate was obtained commercially and purified by preparative gas–liquid partition chromatography on a 0.25 in. × 8 ft SE-30 column at 130 °C. The method of performing the kinetics and the treatment of data has been described previously.[6] Concentrations of phenyl acetate used and the wavelength at which the reaction was monitored are from Jencks and Carriuolo.[30]

**$K_e$ Determination of Acetophenone and Cyclopentanone.** The procedure used for this determination is very similar to that described by Bell and Smith.[16] The solvent system chosen was 40 vol % *tert*-butyl alcohol–water so that the acetophenone would have adequate solubility. All measurements were performed at 25.0 ± 0.1 °C. The measuring buffer was 0.05 M in total acetic acid + acetate concentration (1:1 HOAc–KOAc) and 0.075 M in KBr. All water used in the measurement was distilled twice from $KMnO_4$, and *tert*-butyl alcohol was distilled under argon. The uncorrected pH of the measuring buffer was 5.36 ± 0.02. Solutions of the ketones were 0.5 M in ketone, and were otherwise identical with the measuring buffer.

Measurements were performed with a basket-type Pt electrode and a Radiometer G202C glass electrode. A Radiometer PHM 26 pH meter with expanded scale millivolt capability was used to monitor potentials. The concentration of $Br_2$ could be determined from the observed potential by the use of

$$E = E_0 + 29.58 \log [Br_2] \quad (4)$$

in which $E$ is the observed potential, and $E_0$ is a standard potential which depends on the electrode system, pH, ionic strength, etc. $E_0$ could be determined by measuring the potential of known concentrations of $Br_2$ in the measuring buffer; the value of $E_0$ was found to be 784.2 ± 0.1 mV.

Ketone solutions were pretreated with $Br_2$ ($\approx 10^{-3}$ M) to remove any impurities and were then incubated for about 1 h after the $Br_2$ had disappeared from the solution. Aliquots (5 mL) of the pretreated ketone solution were removed and injected into 50 mL of the rapidly stirred measuring buffer containing enough $Br_2$ ($\approx 2 \times 10^{-6}$ M) so that a 5–10 mV initial decrease in potential occurred. The potential stabilized at the new reading within 15 s of the injection and remained constant for 30–60 s before slowly decreasing further. The value of $K_e$ was determined from the potentials before and after injection (eq 4), the known concentration of ketone, and the known volumes of solutions by methods previously described.[16]

Control experiments in which the ketone was injected into a measuring buffer containing a high concentration of $Br_2$ ($3–7 \times 10^{-4}$ M) or in which a solution containing no ketone was injected into the measuring buffer at a $Br_2$ concentration of ca. $3 \times 10^{-6}$ M gave the potential drop expected for a simple dilution effect.

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**Supplementary Material Available.** Table III (rates of aminolysis of phenyl acetate in 5 vol % ethanol–water) (2 pages). Ordering information is given on any current masthead page.

## References and Notes

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