

# Equilibrium and Kinetic Acidities of Benzylic Ketones. Application of the Marcus Equation to the Deprotonation of Carbon Acids

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**Abstract:** Equilibrium constants and the rates of ketone-enolate ion equilibration have been measured for the deprotonation of eight 3-(X-phenylacetyl)pyridines **1** ( $pK_a$  13.2 for X = H), ten 4-(X-phenylacetyl)pyridines **2** ( $pK_a$  12.2 for X = H), nine 1-methyl-3-(X-phenylacetyl)pyridinium cations **3** ( $pK_a$  10.32 for X = H), and ten 1-methyl-4-(X-phenylacetyl)pyridinium cations **4** ( $pK_a$  9.02 for X = H) in aqueous solution at 25 °C and ionic strength 0.1. The  $pK_a$  values for each of these series of ketones are closely correlated with the  $pK_a$  values for the corresponding ring-substituted phenols. Pseudo-first-order rate constants for deprotonation of both series of neutral ketones (**1**, **2**) are strictly proportional to hydroxide ion concentration in the range pH 11–13, and second-order rate constants ( $k_{OH}$ ) for hydroxide ion catalyzed deprotonation have been evaluated. The pseudo-first-order rate constants ( $k_d$ ) for deprotonation of both series of *N*-methyl cations (**3**, **4**) are subject to hydroxide ion catalysis (second-order rate constant  $k_{OH}$ ) but display kinetic saturation effects consistent with kinetically controlled hydroxide ion addition to the carbonyl group of the ketone. In basic solution this addition competes with the thermodynamically more favorable enolate ion formation. These four series of ketones (**1**–**4**) display quite different linear Brønsted plots ( $\log k_{OH}$  vs  $pK_a$ ), with relative reactivities at constant  $pK_a$  being in the order  $4 < 3 < 2 < 1$ . The 4-NO<sub>2</sub> and 4-CN substituents in all four series of ketones, and also **4** with X = OCH<sub>3</sub>, show negative deviations from these Brønsted relationships. These deviations, and also the relative reactivities for **1**–**4**, can be traced to imbalances in both  $\pi$ -electron delocalization and solvent reorganization in the transition states relative to the enolate ion products. Brønsted  $\alpha$  values cover the range 0.66–0.76 and vary in the order  $1 < 2 < 3 < 4$ . Intrinsic barriers ( $\Delta G_o^*$ ) calculated from the Marcus equation vary systematically with free energies of reaction ( $\Delta G^\circ$ ) within each of these four series of ketones. With the exception of substituents that display special resonance effects (X = 4-NO<sub>2</sub>, 4-CN, 4-OCH<sub>3</sub>),  $\Delta G_o^*$  is linear in  $\Delta G^\circ$  within each series of ketones, and this observation suggests a two-parameter modification of the simple Marcus relationship, in which  $\Delta G_o^*$  is replaced by  $(A + B\Delta G^\circ)$ . In this expression, *A* is the "true" intrinsic barrier at  $\Delta G^\circ = 0$ , while *B* is a measure of the imbalance between transition state and product of those factors ( $\pi$  delocalization, solvation, etc.) that are particularly important to enolate ion stabilization relative to the ketone conjugate acid.

The  $\alpha$  deprotonation of a carbonyl compound to produce an enolate ion is the first step of a wide range of reactions in organic chemistry.<sup>1</sup> Most simple ketones are too weakly acidic to allow the direct measurement of their  $pK_a$  values for enolate ion formation in aqueous solution. Various indirect methods of evaluating the  $pK_a$  values of such weak acids have been developed,<sup>2–8</sup> and these efforts have recently allowed the accurate evaluation of the  $pK_a$  values in aqueous solution for acetone ( $pK_a$  19.16),<sup>6</sup> acetophenone ( $pK_a$  18.31),<sup>7</sup> isobutyrophenone ( $pK_a$  18.26),<sup>8</sup> and several related aldehydes.<sup>9,10</sup> Ketones bearing additional functional groups that can further delocalize the enolate ion charge are sufficiently acidic that acid–base equilibration can be investigated in the normal pH range in aqueous solutions. The  $pK_a$  values for a variety of such acidic ketones and related carbonyl derivatives have recently been tabulated.<sup>11</sup> These include species such as acetylacetone ( $pK_a$  8.84) and triacetylmethane ( $pK_a$  5.86).

The rates of deprotonation of most carbon acids in aqueous solution are usually readily measured. Such reactions have been the subjects of many rate–equilibrium investigations in recent years, and extensive  $\log k$  vs  $pK_{BH}$  correlations and Brønsted  $\beta$  values are now available for general-base- (B-) catalyzed de-

protonation.<sup>12–19</sup> However, as noted by Bell and Grainger,<sup>19</sup> there are relatively few examples of  $\log k$  vs  $pK_a$  correlations in which substituent effects upon both rate and equilibrium constant have been evaluated in a series of structurally related carbon acids. These latter correlations give Brønsted  $\alpha$  values, and it is amusing that for aqueous solutions there are nearly as many "anomalous"  $\alpha$  values  $> 1$  known<sup>16,20</sup> as there are measured  $\alpha$  values in the expected range of 0–1.0.<sup>19,21</sup>

Recently, the benzylic ketones **1a**, **2a**, **3a**, and **4a** (X = H) were synthesized in our laboratory and were observed to be appreciably more acidic in aqueous solution than benzyl phenyl ketone (**5**), for which  $pK_a$  16.1 has been reported<sup>3</sup> on the basis of a study in diglyme as solvent, but referenced to water as standard state. In fact, **4a** ( $pK_a$  9.02) is of similar acidity to acetylacetone ( $pK_a$  8.87), which has a methylene group that is activated by  $\beta$ -dicarbonyl groups, and also nitroethane ( $pK_a$  8.5), which has been much studied<sup>22–26</sup> in general-base-catalyzed deprotonations of carbon acids.

The relatively high acidities of these benzylic ketones (**1**–**4**) are of particular interest, since there seem to be few other examples of simple monoketones that are sufficiently acidic to allow direct

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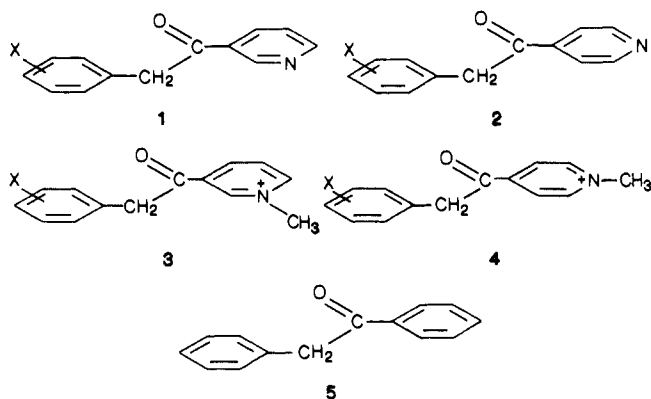
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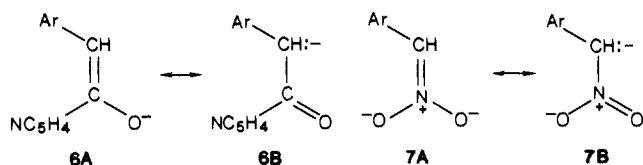
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$pK_a$  measurements in aqueous solutions.<sup>27</sup> Furthermore, since the rates of deprotonation of other carbon acids of similar acidity are readily measurable, it seemed likely that the rates of ketone-enolate ion equilibration of these benzylic ketones would also be readily accessible in aqueous solutions. This prospect is particularly intriguing when one compares the electronic structures of the enolate ions (**6**) derived from these benzylic ketones and

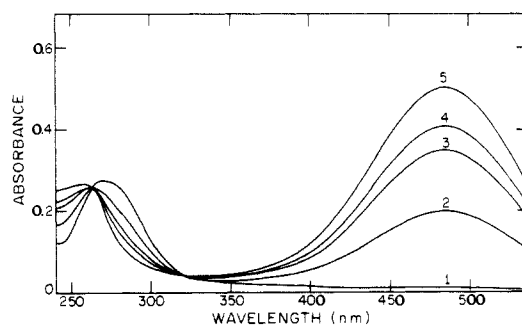


those of the conjugate bases (**7**) of the phenylnitromethanes that display the "nitroalkane anomaly" in rate-equilibrium correlations.<sup>20,30</sup> Since ring-substituted ketones of the types **1-4** are readily synthesized, it seemed of interest to investigate whether the acid-base equilibration of these species would also display any of the features of the nitroalkane anomaly. In fact, in his original work on Brønsted  $\alpha$  values larger than unity, Bordwell suggested<sup>30</sup> that ketones might also display such a phenomenon. To the best of our knowledge, the current work represents the first experimental test of this suggestion for relatively simple ketones, although Bell and Grainger<sup>19</sup> have reported  $\alpha$  values in the range 0.44–0.76 for the deprotonation of series of  $\beta$ -keto esters and  $\beta$ -diketones.

The four series of ring-substituted benzylic ketones (**1a, 1c-1k; 2a-2j; 3a, 3c-3j; and 4a-4j**, where the substituted species **a-k** are defined in Tables I and II) have now been synthesized, and rate and equilibrium constants for their equilibration with their enolate ion conjugate bases have been measured. Independent linear rate-equilibrium relationships are found for the hydroxide ion catalyzed deprotonation of these four classes of benzylic ketones. These data are discussed in terms of the Marcus theory for proton transfer from carbon acids.<sup>31-33</sup> It is shown that intrinsic barriers calculated from the simplest form of the Marcus equation vary systematically with free energies of reaction within each of these four series of ketones.

## Experimental Section

**Synthesis of (Phenylacetyl)pyridines **1** and **2**.** The ketones **1a-1j** and **2a-2j** were prepared by modifications of one or both of the general methods described by Burger and Walters<sup>34</sup> (method A below) or Zim-



**Figure 1.** pH-dependent electronic absorption spectrum of **4l** (0.02 mM) in aqueous solution. Curves: 1, pH 6.0; 2, pH 7.0; 3, pH 7.54; 4, pH 7.80; 5, pH 8.60.

mer and Bercz<sup>35</sup> (method B). These two methods, incorporating our own modifications, are described below for the synthesis of **2a**. The method of choice for any particular ketone was mainly dependent upon the ready availability of ring-substituted phenylacetonitriles or substituted benzaldehydes as starting materials. In general, we have found that the modification described below of the method of Zimmer and Bercz,<sup>35</sup> in which all intermediates are isolated and purified, usually gives substantially better yields of pure ketone. All starting materials were commercial products with the exception of 3,5-dinitrobenzaldehyde, which was prepared by the manganese dioxide oxidation of the corresponding alcohol<sup>36</sup> in ethyl acetate as solvent.

**Method A.** A mixture of methyl isonicotinate (11.8 g) and phenylacetonitrile (13.3 g) was added dropwise into an ethanolic solution of sodium ethoxide prepared by dissolution of sodium (1.7 g) in ethanol (25 mL). The yellow mixture was heated under reflux for 2 h, and the resulting product mixture was poured into water. Unreacted starting materials were removed by ether extraction, and the aqueous alkaline solution was neutralized to give a yellow precipitate of  $\alpha$ -isonicotinoylphenylacetonitrile. This material was collected, dried, and used directly for the following step, since attempted recrystallization, as described by Burger and Walters,<sup>34</sup> gave only a brown oil.

$\alpha$ -Isonicotinoylphenylacetonitrile (7 g) was dissolved in 48% hydrobromic acid (100 mL), and the mixture was heated under reflux for 12 h. The product solution was poured into 2-propanol (20 mL) and diluted with 4–5 parts of ether, and the precipitate of 4-(phenylacetyl)pyridinium bromide was collected. 4-(Phenylacetyl)pyridine (**2a**) was obtained by treating this salt with aqueous sodium bicarbonate solution, and the product was recrystallized several times from aqueous ethanol.

**Method B.** Equimolar amounts of freshly distilled 4-pyridinecarboxaldehyde and aniline (0.1 mol) were mixed at room temperature. After 15 min, the mixture was dissolved in 2-propanol (50 mL) cooled in an ice bath. The Schiff base product crystallized out and was recrystallized from 2-propanol in >95% yield.

This Schiff base was dissolved in ethanol (20 mL), and an ethanolic solution containing an equimolar amount of diphenyl phosphite was added dropwise. The resulting mixture was diluted with 4 parts of ether, and the  $\alpha$ -aminoalkyl phosphonate precipitated as tiny crystals. Recrystallization from ethanol-ether gave >90% yield.

A solution of the phosphonate ester (0.01 M) in dry tetrahydrofuran (75 mL) was cooled to  $-40^\circ\text{C}$ . An equimolar amount of 10% methanolic potassium hydroxide was added with constant agitation. A tetrahydrofuran solution of benzaldehyde (0.01 M) was added, and the solvent was removed on the rotary evaporator. The residue was washed with copious amounts of water to remove potassium diphenyl phosphate. The solid residue was dried, taken into a small amount of solvent (ether, acetone), and treated with a small amount of activated carbon. Removal of the solvent gave the enamine, 1-(phenylamino)-1-(4-pyridyl)-2-phenylethylene, in 50% yield.

The above enamine was hydrolyzed by dissolution in a small amount of concentrated hydrochloric acid. After the addition of a twofold volume of ethanol, the 4-(phenylacetyl)pyridinium chloride was precipitated with ether. This salt was converted to **2a** by treatment with aqueous sodium bicarbonate solution and recrystallized from ethanol-water.

The melting points and  $^1\text{H}$  NMR spectra of all **1** and **2** prepared by these routes are listed in Table I. Elemental analyses (C, H, N) of all compounds in this table were consistent with the molecular formulas.

**Synthesis of the Bromide Salts of **3** and **4**.** The appropriate 3- or 4-(X-phenylacetyl)pyridine (1 g) and a slight excess of bromomethane were stirred in acetone (25 mL) for 24 h at room temperature in a

(27) Measurements of  $pK_a$  values for the 2-, 3-, and 4-phenacylpyridines (isomeric with **1a** and **2a**), and their *N*-methyl cations (isomeric with **3a** and **4a**) have been reported.<sup>28</sup> Similar data for 2- and 4-phenacylquinolines and their *N*-methyl cations are also available.<sup>29</sup>

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Table I. Characterization of (Phenylacetyl)pyridines 1 and 2

ketone	X	mp, °C	<sup>1</sup> H NMR, <sup>a</sup> δ
1a	H	61–62 <sup>b</sup>	4.50 (2 H, s), 7.30–7.70 (6 H, m), 8.33–8.56 (1 H, m), 8.92 (1 H, m), 9.40 (1 H, m) <sup>c</sup>
1c	4-CH <sub>3</sub>	94–95	2.33 (3 H, s), 4.22 (2 H, s), 7.15 (4 H, s), 7.20–7.40 (1 H, m), 8.16–8.33 (1 H, m), 8.67–8.83 (1 H, m), 9.22 (1 H, d)
1d	4-Cl	95–96	4.33 (2 H, s), 7.25 (4 H, s), 7.20–7.30 (1 H, m), 8.33 (1 H, m), 8.72 (1 H, m), 9.25 (1 H, d)
1e	4-CF <sub>3</sub>	101–102	4.43 (2 H, s), 7.55 (5 H, m), 8.33 (1 H, m), 8.92 (1 H, m), 9.33 (1 H, d)
1f	3-NO <sub>2</sub>	114–115	4.50 (2 H, s), 7.20–7.40 (3 H, m), 8.17–8.41 (3 H, m), 8.92 (1 H, m), 9.33 (1 H, d)
1g	4-CN	110–112	4.47 (2 H, s), 7.30–7.80 (5 H, m), 8.33 (1 H, m), 8.90 (1 H, m), 9.30 (1 H, d)
1h	3-NO <sub>2</sub> , 4-Cl	120–121	4.40 (2 H, s), 7.20–7.60 (3 H, m), 7.80 (1 H, m), 8.23 (1 H, m), 8.83 (1 H, m), 9.22 (1 H, m)
1i	4-NO <sub>2</sub>	145 dec	4.50 (2 H, s), 7.20–7.40 (3 H, m), 8.17–8.50 (3 H, m), 8.87 (1 H, m), 9.27 (1 H, d)
1j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	136–137	5.03 (2 H, s), 8.33–9.00 (3 H, m), 9.20–9.87 (3 H, m)
1k	3-Cl	65–66	4.28 (2 H, s), 7.00–7.50 (5 H, m), 8.25 (1 H, m), 8.83 (1 H, m), 9.25 (1 H, s)
2a	H	89–90	4.70 (2 H, s), 7.50 (5 H, s), 8.63–9.25 (4 H, dd)
2b	4-OCH <sub>3</sub>	125–127	4.08 (3 H, s), 4.60 (2 H, s), 7.00–7.42 (4 H, dd), 8.60–9.25 (4 H, dd)
2c	4-CH <sub>3</sub>	118–120	2.20 (3 H, s), 4.60 (2 H, s), 7.50 (4 H, s), 8.60–9.25 (4 H, dd)
2d	4-Cl	84–85	4.63 (2 H, s), 7.40–7.87 (4 H, dd), 8.63–9.25 (4 H, dd)
2e	4-CF <sub>3</sub>	89–90	4.80 (2 H, s), 7.40–7.87 (4 H, dd), 8.67–9.33 (4 H, dd)
2f	3-NO <sub>2</sub>	120–121	4.90 (2 H, s), 7.67–7.75 (2 H, m), 8.33–8.47 (2 H, m), 8.73–9.33 (4 H, dd)
2g	4-CN	128–130	4.80 (2 H, s), 7.46–7.93 (4 H, dd), 8.67–9.33 (4 H, dd)
2h	3-NO <sub>2</sub> , 4-Cl	102–103	4.50 (2 H, s), 7.55 (2 H, s), 7.80 (1 H, s), 8.65–9.30 (4 H, dd) <sup>c</sup>
2i	4-NO <sub>2</sub>	126–127	4.80 (2 H, s), 7.53–8.46 (4 H, dd), 8.70–9.30 (4 H, dd)
2j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	154–156	5.00 (2 H, s), 8.75–9.47 (7 H, m) <sup>c</sup>

<sup>a</sup>All spectra for 1 are in CDCl<sub>3</sub>; spectra for 2 are in trifluoroacetic acid, unless otherwise indicated. All chemical shifts are relative to tetramethylsilane. <sup>b</sup>Lit.<sup>34</sup> mp 58–59 °C. <sup>c</sup>In CDCl<sub>3</sub>.

Table II. Characterization of the Bromide Salts of 3 and 4

bromide salt	X	mp, <sup>a</sup> °C	<sup>1</sup> H NMR, <sup>b</sup> δ
3a	H	135–137	4.57 (3 H, s), 4.63 (2 H, s), 7.33 (5 H, s), 8.17 (1 H, m), 8.83–9.25 (2 H, m), 9.53 (1 H, s)
3c	4-CH <sub>3</sub>	188–190	2.45 (3 H, s), 4.63 (2 H, s), 4.70 (3 H, s), 7.20 (4 H, s), 8.33 (1 H, m), 9.17 (2 H, m), 9.63 (1 H, s)
3d	4-Cl	193–195	4.67 (5 H, s), 7.30 (4 H, s), 8.07–8.46 (1 H, m), 8.97–9.33 (2 H, m), 9.60 (1 H, s)
3e	4-CF <sub>3</sub>	141–143	4.67 (3 H, s), 4.75 (2 H, s), 7.58 (4 H, dd), 8.16–8.50 (1 H, m), 8.92–9.33 (2 H, m), 9.58 (1 H, s)
3f	3-NO <sub>2</sub>	207–208	4.73 (3 H, s), 4.90 (2 H, s), 7.60–7.80 (2 H, m), 8.33 (3 H, m), 9.00–9.41 (2 H, m), 9.65 (1 H, s)
3g	4-CN	212 dec	4.73 (3 H, s), 4.87 (2 H, s), 7.75 (4 H, dd), 8.20–8.50 (1 H, m), 8.93–9.40 (2 H, m), 9.64 (1 H, s)
3h	3-NO <sub>2</sub> , 4-Cl	190 dec	4.67 (3 H, s), 4.73 (2 H, s), 7.58 (2 H, s), 7.92 (1 H, s), 8.13–8.45 (1 H, m), 8.88–9.30 (2 H, m), 9.53 (1 H, s)
3i	4-NO <sub>2</sub>	226 dec	4.72 (3 H, s), 4.87 (2 H, s), 7.58 (2 H, d), 8.23–8.53 (3 H, m), 9.00–9.43 (2 H, m), 9.63 (1 H, s)
3j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	222 dec	4.83 (3 H, s), 5.13 (2 H, s), 8.33–8.63 (1 H, m), 8.80 (2 H, s), 9.08–9.50 (3 H, m), 9.73 (1 H, s)
4a	H	145–146	4.65 (5 H, s), 7.40 (5 H, s), 8.60–9.20 (4 H, dd)
4b	4-OCH <sub>3</sub>	174–176	4.08 (3 H, s), 4.70 (3 H, s), 4.75 (2 H, s), 7.00–7.43 (4 H, dd), 8.60–9.22 (4 H, dd)
4c	4-CH <sub>3</sub>	84–87	2.20 (3 H, s), 4.67 (3 H, s), 4.70 (2 H, s), 7.50 (4 H, s), 8.60–9.25 (4 H, dd)
4d	4-Cl	86–88	4.65 (5 H, s), 7.40–7.85 (4 H, dd), 8.60–9.22 (4 H, dd)
4e	4-CF <sub>3</sub>	143–144	4.70 (3 H, s), 4.78 (2 H, s), 7.37–7.83 (4 H, dd), 8.76–9.33 (4 H, dd)
4f	3-NO <sub>2</sub>	185–187	4.75 (3 H, s), 4.90 (2 H, s), 7.82 (2 H, m), 8.45 (2 H, m), 8.76–9.30 (4 H, dd)
4g	4-CN	202–204	4.72 (3 H, s), 4.85 (2 H, s), 7.50–7.92 (4 H, dd), 8.67–9.33 (4 H, dd)
4h	3-NO <sub>2</sub> , 4-Cl	190 dec	4.73 (3 H, s), 4.83 (2 H, s), 7.67 (2 H, s), 8.03 (1 H, s), 8.67–9.33 (4 H, dd)
4i	4-NO <sub>2</sub>	190 dec	4.71 (3 H, s), 4.85 (2 H, s), 7.57–8.50 (4 H, dd), 8.70–9.27 (4 H, dd)
4j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	224 dec	4.75 (3 H, s), 5.10 (2 H, s), 8.67–9.33 (7 H, m)

<sup>a</sup>Most of these salts darken 10–20 °C below these stated melting points. <sup>b</sup>In trifluoroacetic acid, relative to tetramethylsilane as reference.

pressure bottle. The precipitated bromide salts were filtered off and recrystallized several times from 2-propanol. The <sup>1</sup>H NMR spectra and melting points of these salts are listed in Table II.

**pK<sub>a</sub> Values.** All pK<sub>a</sub> values of 3 and 4 were determined spectrophotometrically at 25 °C with a Cary 210 spectrophotometer via the general procedure described by Albert and Serjeant<sup>37</sup> in buffer solutions<sup>38</sup> that were adjusted to ionic strength 0.1 by the addition of potassium chloride. All solution pH values were measured on a Radiometer PHM82 pH meter.

For the neutral ketones 1 and 2, a slow decomposition, which was not further investigated, complicated attempts to determine pK<sub>a</sub> values from solutions that had been prepared by manual basification of the neutral solution of the ketone. This problem was overcome by evaluating pK<sub>a</sub> values from the pH dependence of the absorbances of equilibrated solutions in the stopped-flow kinetic studies described below.

Phenol pK<sub>a</sub> values were determined<sup>39</sup> potentiometrically at 25 °C in solutions of ionic strength 0.1.

**Kinetic Studies.** The equilibration of these ketones with their enolate ions was followed by mixing an aqueous solution of the ketone (0.05 mM for 1 and 2; 0.02 mM for 3 and 4) with aqueous potassium hydroxide solutions in the Durrum–Gibson stopped-flow spectrophotometer. All

solutions were adjusted to ionic strength 0.1 with appropriate concentrations of potassium chloride. All kinetic data were obtained at 25 °C by the observation of the time dependence of the concentration of the enolate ion at a wavelength in the vicinity of the maxima reported in Tables III and IV. Absorbance vs time curves were digitized into 118 data points covering at least 95% of the reaction and transferred to a Tektronix 4051 computer for data analysis. All reactions were kinetically first order in the pyridinium cation concentration. At each pH, data were collected for six to eight duplicate runs, with the pseudo-first-order rate constants from these runs usually agreeing within ±1%.

## Results

Each of the ketones 1–4 displays a pH-dependent electronic absorption spectrum in aqueous base. Figure 1 shows a typical case. Long-wavelength absorption maxima develop in basic solutions. Such solutions are yellow to red, depending upon the substituent X in 1–4. These spectral changes are readily reversible upon neutralization provided the exposure to the basic medium is not prolonged. The pH dependence of the long wavelength absorption is consistent with a simple acid–base equilibration.

The substituent dependences of the pK<sub>a</sub> values and the long-wavelength absorption maxima of basic aqueous solutions of 1–4 are summarized in Tables III and IV. While detailed consideration of these phenomena is presented later in the Discussion, we note here that the pK<sub>a</sub> values show a pronounced substituent

(37) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*, 3rd ed.; Chapman and Hall: London, 1984; Chapter 4.

(38) Perrin, D. D. *Aust. J. Chem.* **1963**, *16*, 572.

(39) Reference 37, Chapters 2 and 3.

**Table III.** Equilibrium and Rate Constants for Enolate Ion Equilibration with **1** and **2**<sup>a</sup>

ketone	X	pK <sub>a</sub>	k <sub>OH</sub> , M <sup>-1</sup> s <sup>-1</sup>	k <sub>H<sub>2</sub>O</sub> , s <sup>-1</sup>	λ <sub>max</sub> , nm
1a	H	(13.2) <sup>b</sup>	(38) <sup>c</sup>		
1d	4-Cl	12.74	74.4	4.1	340
1e	4-CF <sub>3</sub>	12.32	133	2.8	340
1f	3-NO <sub>2</sub>	11.96	231	2.1	340
1g	4-CN	11.59	304	1.18	374
1h	3-NO <sub>2</sub> , 4-Cl	11.61	434	1.8	346
1i	4-NO <sub>2</sub>	10.94	497	0.43	480
1j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	10.70	1640	0.82	331
1k	3-Cl	12.60	97.5	3.9	340
2a	H	12.26	60.3	1.16	356
2b	4-OCH <sub>3</sub>	12.42	44.7	1.17	365
2c	4-CH <sub>3</sub>	12.44	44.6	1.22	362
2d	4-Cl	11.84	120	0.83	362
2e	4-CF <sub>3</sub>	11.31	240	0.61	362
2f	3-NO <sub>2</sub>	11.04	389	0.47	356
2g	4-CN	10.60	562	0.23	384
2h	3-NO <sub>2</sub> , 4-Cl	10.67	774	0.36	360
2i	4-NO <sub>2</sub>	9.93	832	0.071	472
2j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	9.82	2700	0.178	352

<sup>a</sup> In aqueous solution, ionic strength 0.1, at 25 °C; standard deviations in pK<sub>a</sub> values are less than ±0.03, while k<sub>OH</sub> and k<sub>H<sub>2</sub>O</sub> are within ±3%. <sup>b</sup> Calculated from eq 7. <sup>c</sup> Calculated from eq 11.

**Table IV.** pK<sub>a</sub> Values and Electronic Absorption Maxima for Enolate Ion Formation from **3** and **4**<sup>a</sup>

ketone	X	λ <sub>max</sub> , nm	pK <sub>a</sub>	pK <sub>a</sub> (X-phenol) <sup>a</sup>
3a	H	360	10.32	9.86
3c	4-CH <sub>3</sub>	360	10.45	10.10
3d	4-Cl	360	9.93	9.30
3e	4-CF <sub>3</sub>	360	9.52	8.68
3f	3-NO <sub>2</sub>	381	9.26	8.23
3g	4-CN	375	9.00	7.85
3h	3-NO <sub>2</sub> , 4-Cl	360	8.93	7.82
3i	4-NO <sub>2</sub>	465	8.42	6.98
3j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	346	8.15	6.68
4a	H	446	9.02	9.86
4b	4-OCH <sub>3</sub>	460	9.01	10.07
4c	4-CH <sub>3</sub>	450	9.21	10.10
4d	4-Cl	445	8.63	9.30
4e	4-CF <sub>3</sub>	440	8.33	8.68
4f	3-NO <sub>2</sub>	435	8.08	8.23
4g	4-CN	445	7.80	7.85
4h	3-NO <sub>2</sub> , 4-Cl	438	7.79	7.82
4i	4-NO <sub>2</sub>	483	7.36	6.98
4j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	437	7.11	6.68

<sup>a</sup> In aqueous solution, ionic strength 0.1, 25 °C; standard deviations in pK<sub>a</sub> values are less than ±0.02.

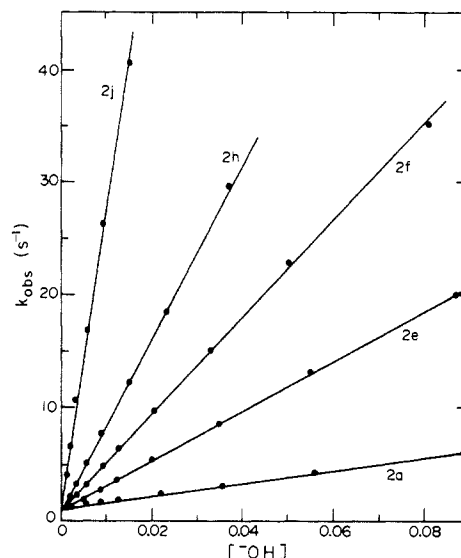
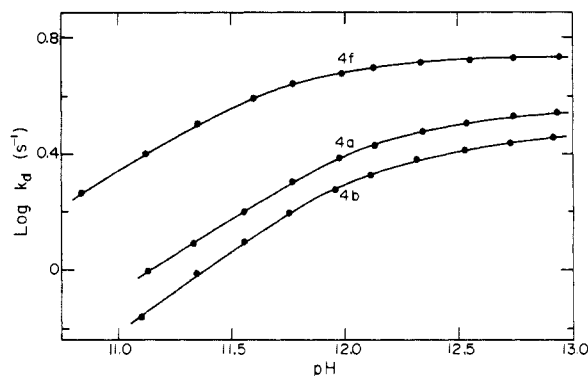
dependence and that λ<sub>max</sub> is also substituent dependent. Both of these observations are consistent with the interpretation of this acid-base equilibration as being the deprotonation of the benzylic methylene group to form the enolate anion **6**.

The time dependences of the development of these long-wavelength absorption maxima are measurable upon basification of neutral aqueous solutions of **1**–**4** in the stopped-flow spectrophotometer. In all experiments, the rates of acid-base equilibration, observed at the absorption maximum, are strictly first order in ketone concentration for greater than 95% reaction. Pseudo-first-order rate constants (k<sub>obsd</sub>) were evaluated in aqueous KOH + KCl solutions (ionic strength 0.1) over the range pH 10.8–13.

The pH dependences of the pseudo-first-order rate constants (k<sub>obsd</sub>) for acid-base equilibration of **1** and **2** are illustrated in Figure 2. These pH-rate profiles are accurately described by eq 1. Values of the parameters k<sub>OH</sub> and k<sub>H<sub>2</sub>O</sub> are included in Table III.

$$k_{\text{obsd}} = k_{\text{OH}}[\text{OH}^-] + k_{\text{H}_2\text{O}} \quad (1)$$

The pH-rate profiles for acid-base equilibration of **3** and **4** with their conjugate bases display a kinetic saturation effect at high

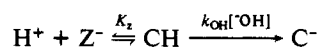
**Figure 2.** pH dependence of the pseudo-first-order rate constant (k<sub>obsd</sub>) for the equilibration of selected **2** with the corresponding enolate anions. Analogous linear plots are obtained for the corresponding experimental data for **1**.**Figure 3.** pH dependence of log k<sub>d</sub> for the deprotonation of selected **4**. Curves are calculated according to Scheme I by use of the parameters in Table V. Similar kinetic saturation effects are observed for the corresponding pH-rate profiles for all **3**.

pH. In all cases, k<sub>d</sub>, the pseudo-first-order rate constant for deprotonation of these carbon acids can be calculated from eq 2. For most of the ketones examined in the series **3** and **4**, the

$$k_d = k_{\text{obsd}} / (1 + [\text{H}^+] / K_a) \quad (2)$$

pK<sub>a</sub> value lies well below the pH range of the kinetic study, and thus k<sub>obsd</sub> is equivalent to k<sub>d</sub>. Typical pH profiles for k<sub>d</sub> are shown in Figure 3.

In general, k<sub>d</sub> shows a first-order dependence upon hydroxide ion concentration in the vicinity of pH 11, but this rate constant becomes almost independent of pH in the most basic solutions that were examined. [The cases of **4i** (X = 4-NO<sub>2</sub>) and **4j** (X = 3,5-(NO<sub>2</sub>)<sub>2</sub>) are exceptions to this general observation and are discussed separately below.] The simplest interpretation of such a pH dependence for k<sub>d</sub> is in terms of Scheme I. In this scheme, hydroxide ion catalyzed deprotonation of the carbon acid (CH) to give the enolate ion (C<sup>-</sup>) is assumed to occur more slowly than another acid-base equilibration in which the carbon acid is converted into an alternative conjugate base (Z<sup>-</sup>).

**Scheme I**

Algebraic analysis of Scheme I leads to eq 3, where K<sub>w</sub> is the ionic product of water. This equation predicts a linear dependence of 1/k<sub>d</sub> upon 1/[OH<sup>-</sup>], which is consistent with the current experimental observations. Values of the parameters k<sub>OH</sub> and K<sub>z</sub>

**Table V.** Kinetic Parameters for the Deprotonation of **3** and **4** by Hydroxide Ion<sup>a</sup>

ketone	X	$k_{\text{OH}}$ , $\text{M}^{-1} \text{s}^{-1}$	$\text{p}K_z$
3a	H	634	12.32
3c	4-CH <sub>3</sub>	473	12.40
3d	4-Cl	1190	12.15
3e	4-CF <sub>3</sub>	2210	12.04
3f	3-NO <sub>2</sub>	4020	11.88
3g	4-CN	4860	11.92
3h	3-NO <sub>2</sub> , 4-Cl	6680	11.70
3i	4-NO <sub>2</sub>	7690	11.78
3j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	22300	11.41
4a	H	801	11.81
4b	4-OCH <sub>3</sub>	576	11.85
4c	4-CH <sub>3</sub>	594	11.87
4d	4-Cl	1480	11.63
4e	4-CF <sub>3</sub>	2670	11.51
4f	3-NO <sub>2</sub>	4060	11.34
4g	4-CN	5230	11.38
4h	3-NO <sub>2</sub> , 4-Cl	6930	11.18
4i	4-NO <sub>2</sub>	7140	11.33
4j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	22500	10.88

<sup>a</sup> In aqueous solution, ionic strength 0.1, 25 °C;  $k_{\text{OH}}$  and  $K_z$  are defined in Schemes I and II; standard deviations in  $k_{\text{OH}}$  are less than  $\pm 3\%$ , and less than  $\pm 0.05$  for  $\text{p}K_z$ .

were evaluated for each of **3a**, **3c**–**3j** and **4a**–**4h**. These parameters are collected in Table V.

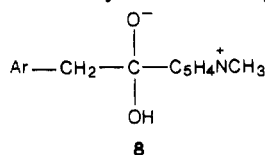
$$k_d = k_{\text{OH}}[\text{OH}^-]/(1 + K_z[\text{OH}^-]/K_w) \quad (3)$$

The requirement for Scheme I to describe the kinetics of ketone–enolate equilibration in basic solutions suggests that although the enolate ion ( $\text{C}^-$ ) is the thermodynamically preferred conjugate base in these reactions, there is a different kinetically controlled conjugate base species ( $\text{Z}^-$ ). The  $\text{p}K_z$  values listed in Table V show a clear substituent dependence and are closely correlated with the Hammett  $\sigma$  constants for benzoic acid ionization as shown by eq 4 and 5 for **3** and **4**, respectively. The only

$$\text{p}K_z^3 = -0.63 (\pm 0.02)\sigma + 12.31 (\pm 0.02) \quad r = 0.9945 \quad (4)$$

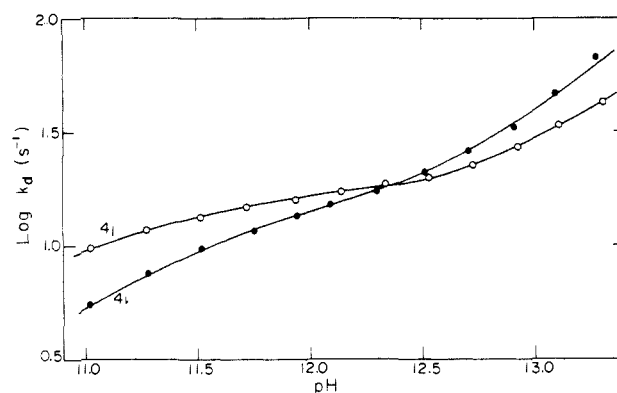
$$\text{p}K_z^4 = -0.60 (\pm 0.03)\sigma + 11.77 (\pm 0.02) \quad r = 0.9916 \quad (5)$$

obvious simple interpretation for  $\text{Z}^-$  is that it represents the *gem*-diol anion **8** formed by addition of hydroxide ion to the



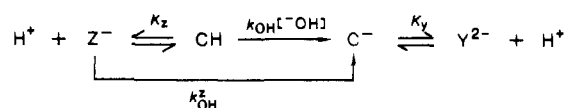
carbonyl group of **3** or **4**. This suggestion is supported by (1) the observed correlations in eq 4 and 5 with  $\sigma$  rather than  $\sigma^-$ , which indicate that electron-withdrawing resonance effects for X = 4-NO<sub>2</sub> or 4-CN are unimportant, (2) the similarity in the  $\rho$  values for  $\text{p}K_z^3$  and  $\text{p}K_z^4$  in these equations, and (3) the magnitudes of these  $\rho$  values, which are similar to  $\rho = 0.56$  for the deprotonation of ring-substituted phenylacetic acids ( $\text{XC}_6\text{H}_4\text{CH}_2\text{CO}_2\text{H}$ ).<sup>40</sup>

The 4-nitrobenzyl and 3,5-dinitrobenzyl ketones, **4i** and **4j**, display a different pH profile (Figure 4) for  $k_d$  than that observed for all other ketones **3** and **4**. In the most basic solutions, these two derivatives display a further increase in  $k_d$  above the pH-independent plateau region that characterizes the pH profiles for all other cations. A careful examination of the pH dependence of the absorbance near 450 nm after formation of the enolate ions of **4i** and **4j** in solutions of pH > 12 revealed that these absorbances unexpectedly decreased with increasing pH in the most basic solutions. These decreases in absorbance as a function of pH were found to be consistent with a second acid–base equilibrium having a  $\text{p}K_a$  12.8 for **4i** and 13.2 for **4j**. Further careful examination of other derivatives in quite basic solutions then revealed a similar second acid–base equilibration of  $\text{p}K_a$  13.8 for **4f** (X = 4-CN), although no such further acid–base equilibrium was apparent for



**Figure 4.** pH dependence of  $\log k_d$  for the deprotonation of **4i** and **4j**. Curves are calculated according to Scheme II by use of the parameters from Table V and  $k_{\text{OH}}^2$  in the text.

#### Scheme II



any other **4** or for any member of **3a**–**3j**.

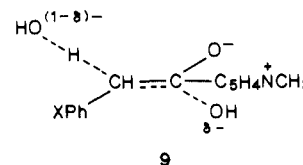
The unusual pH dependence of  $k_d$  (Figure 4) and the second acid–base equilibration ( $\text{p}K_y$ ), which are observed for **4i** and **4j**, are consistent with Scheme II.

Scheme II generates eq 6 for the pH dependence of  $k_d$ . The parameters  $k_{\text{OH}}$  and  $K_z$  for **4i** and **4j** were evaluated in the range

$$k_d = k_{\text{OH}}[\text{OH}^-]/(1 + K_z[\text{OH}^-]/K_w) + k_{\text{OH}}^2[\text{OH}^-] \quad (6)$$

pH 11–12 as described above (Scheme I), and values of  $k_{\text{OH}}^2 = 200 (\pm 40) \text{M}^{-1} \text{s}^{-1}$  for **4i** and  $k_{\text{OH}}^2 = 130 (\pm 20) \text{M}^{-1} \text{s}^{-1}$  for **4j** were determined from the data in the high-pH region. These  $k_{\text{OH}}^2$  values are relatively uncertain because of the limited data available and the requirement for pH > 13 (i.e., ionic strength > 0.1) to convincingly demonstrate these increases in  $k_d$ .

The close fits to the experimental data described by the curves in Figure 4 indicate that Scheme II is a reasonable description of this phenomenon. The  $k_{\text{OH}}^2$  term in Scheme II suggests that the enolate ion ( $\text{C}^-$ ) may also be formed by a base-catalyzed reaction of the species  $\text{Z}^-$ , which is believed to be the *gem*-diol anion **8**. The only simple mechanistic interpretation of this  $k_{\text{OH}}^2$  process appears to be an hydroxide ion catalyzed elimination of a molecule of water from **8** to give the enolate ion conjugate base of **4**. A transition state such as **9** for an E2 mechanism is consistent



with the current observation that this pathway is only observed for **4i** and **4j**, which are the most acidic of all the benzylic ketones examined and consequently have the most stable enolate ion conjugate bases. In so far as the transition-state **9** is “enolate-like”, this transition state will also be more stable for **4i** and **4j** than for any other species in this study.

The nature of the species  $\text{Y}^{2-}$  proposed in Scheme II is quite unclear. This species is only observable with very strongly electron-withdrawing substituents [4-NO<sub>2</sub>, 3,5-(NO<sub>2</sub>)<sub>2</sub>, 4-CN] in **4**. It is not observed in the corresponding series of 3-pyridyl isomers (**3**). This formation of  $\text{Y}^{2-}$  seems to involve further direct resonance interaction with the 4-nitro substituent, since  $\text{p}K_y$  is lower for this substituent than for the 3,5-dinitro-substituted derivative. Although several possibilities for  $\text{Y}^{2-}$  come to mind on the basis of these requirements, we can see no point in speculating upon this matter at present in the absence of any direct structural evidence.

**Table VI.** Experimental Hammett  $\rho$  and Brønsted  $\alpha$  Parameters for Deprotonation of Carbon Acids

acid	$pK_a(X = H)$	$\rho(K_a)$	$\rho(k_{OH})$	$\alpha$
1	13.20	1.70	1.12	0.66
2	12.26	1.70	1.16	0.68
3	10.32	1.44	1.05	0.73
4	9.02	1.29	0.98	0.76
$XC_6H_4CH_2NO_2^a$	6.88	0.82	1.26	1.54

<sup>a</sup>Data from ref 20.**Discussion**

The  $pK_a$  values for 1–4 in Tables III and IV are closely correlated with the  $pK_a$  values ( $pK_a^{XOH}$ ) for the correspondingly substituted phenols as shown by eq 7–10.

$$pK_a^1 = 0.79 (\pm 0.01)pK_a^{XOH} + 5.5 (\pm 0.1) \quad r = 0.9991 \quad (7)$$

$$pK_a^2 = 0.79 (\pm 0.01)pK_a^{XOH} + 4.5 (\pm 0.1) \quad r = 0.9989 \quad (8)$$

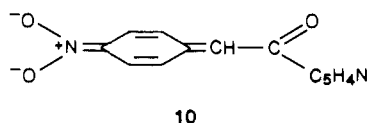
$$pK_a^3 = 0.67 (\pm 0.01)pK_a^{XOH} + 3.75 (\pm 0.07) \quad r = 0.9994 \quad (9)$$

$$pK_a^4 = 0.60 (\pm 0.01)pK_a^{XOH} + 3.2 (\pm 0.1) \quad r = 0.9987 \quad (10)$$

Equation 7 extrapolates to  $pK_a$  13.20 for 1a. This value is not accurately measurable under the current experimental conditions of strictly aqueous solutions of ionic strength 0.1, and the same is true for substituted 1 having an electron-releasing X substituent. The ketone 4b deviates significantly from eq 10 and has been ignored in the derivation of this equation (see below).

Since substituent effects upon  $pK_a^{XOH}$  (phenol ionization) are described by Hammett  $\sigma^-$  substituent constants, eq 7–10 require that the  $pK_a$  values for 1–4 are also correlated with  $\sigma^-$ . Taking  $\rho = 2.15$  for phenol ionization<sup>41</sup> allows the evaluation of the  $\rho(K_a)$  values in Table VI.

Most significantly, these correlations with  $\sigma^-$  require that the electron-withdrawing resonance effects of para X substituents that stabilize the negative charge in phenoxide ions are also important in stabilizing the conjugate bases obtained upon deprotonation of 1–4. This fact alone is sufficient to establish the enolate ions 6 as the conjugate bases formed in these acid–base equilibrations, since resonance contributors such as 10 are clearly important to



the stabilization of these enolate ions. The smaller  $\rho$  values for the ionization of 1–4 than for phenol ionization are also consistent with the expected predominance of 6a as the major resonance contributor and the consequent localization of negative charge further away from the X substituent in these species than in substituted phenoxide ions.

The dependences of  $\log k_{OH}$  upon  $pK_a$  are displayed in Figures 5 and 6. In each series of ketones, the 4-nitro (i) and 4-cyano (g) substituents show large negative deviations from the correlation lines (eq 11–14) defined by the remaining substituents. The ketone 4b (X = 4-OCH<sub>3</sub>) also shows a significant deviation and has been excluded in the calculation of eq 14. These deviations are considered further below.

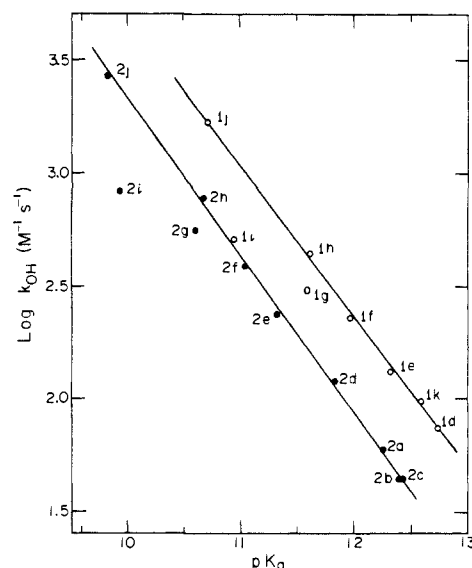
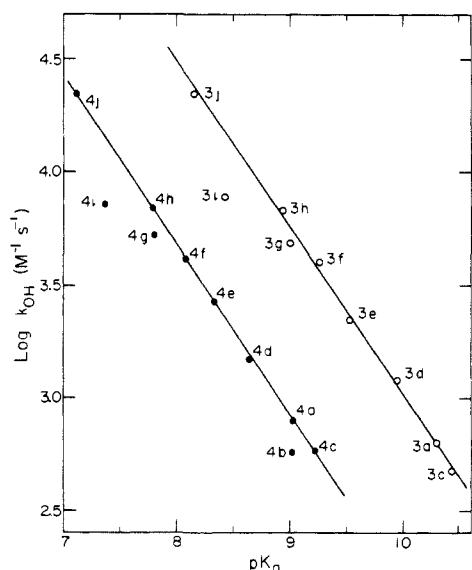
$$\log k_{OH}^1 = -0.66 (\pm 0.01)pK_a^1 + 10.3 (\pm 0.2) \quad r = 0.9991 \quad (11)$$

$$\log k_{OH}^2 = -0.68 (\pm 0.01)pK_a^2 + 10.1 (\pm 0.1) \quad r = 0.9993 \quad (12)$$

$$\log k_{OH}^3 = -0.73 (\pm 0.02)pK_a^3 + 10.4 (\pm 0.1) \quad r = 0.9988 \quad (13)$$

$$\log k_{OH}^4 = -0.76 (\pm 0.01)pK_a^4 + 9.74 (\pm 0.06) \quad r = 0.9997 \quad (14)$$

(41) Calculated under the current experimental conditions from  $pK_a$  vs  $\sigma^-$  by use of data in Table II for substituted phenols with the exception of the 4-NO<sub>2</sub> and 4-CN species.

**Figure 5.** Brønsted plots for the hydroxide ion catalyzed deprotonation of 1 and 2.**Figure 6.** Brønsted plots for the hydroxide ion catalyzed deprotonation of 3 and 4.

These correlations indicate that the Brønsted  $\alpha$  values are similar for the hydroxide ion catalyzed deprotonation of 3 and 4 and slightly larger than for the analogous reactions of 1 and 2. These  $\alpha$  values and their equivalent  $\rho(k_{OH})$  values are included in Table VI and are compared with analogous data<sup>20</sup> for the deprotonation of phenylnitromethanes. The equilibrium  $\rho$  value for each of these four classes of ketones is considerably larger than the  $\rho(K_a)$  for phenylnitromethane ionization. This is an indication that negative charge delocalization into the  $\alpha$ -nitro group in the conjugate bases of phenylnitromethanes is far more efficient than charge delocalization into the carbonyl and pyridyl units in the enolate ions derived from these benzylic ketones. On the other hand, the relative kinetic  $\rho$  values suggest that transition-state stabilization by the  $\alpha$ -nitro group of the phenylnitromethanes is somewhat less efficient than is transition-state stabilization by the carbonyl and pyridyl groups.

The data of Table VI suggest trends in both  $\rho(K_a)$  and  $\alpha$ , but not in  $\rho(k_{OH})$ , within the five series of carbon acids listed. These series of carbon acids are listed in order of increasing equilibrium acidity, which is also the order of decreasing kinetic acidity toward hydroxide ion catalyzed deprotonation (Table VII). The decreasing  $\rho(K_a)$  with decreasing  $pK_a$  reflects the reduced influence of substituent effects upon conjugate base stabilization as the primary  $\pi$ -electronic stabilization of this species becomes more

**Table VII.** Reactivities of Carbon Acids toward Deprotonation by Hydroxide Ion<sup>a</sup>

acid	pK <sub>a</sub>	k <sub>OH</sub> , M <sup>-1</sup> s <sup>-1</sup>	rel k <sub>OH</sub>	ref
CH <sub>3</sub> COCH <sub>2</sub> COCH <sub>3</sub> <sup>b</sup>	8.87	4 × 10 <sup>4</sup>	4 × 10 <sup>5</sup>	52
<b>1</b>	(9.0) <sup>d</sup>	2 × 10 <sup>4</sup>	2 × 10 <sup>5</sup>	c
<b>2</b>	(9.0) <sup>d</sup>	1 × 10 <sup>4</sup>	1 × 10 <sup>5</sup>	c
<b>3</b>	(9.0) <sup>d</sup>	6 × 10 <sup>3</sup>	6 × 10 <sup>4</sup>	c
<b>4a</b> (X = H)	9.02	801	8 × 10 <sup>3</sup>	c
CH <sub>3</sub> CH <sub>2</sub> NO <sub>2</sub>	8.5	8.91	90	50
XC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NO <sub>2</sub>	(9.0) <sup>d</sup>	0.1	1	20

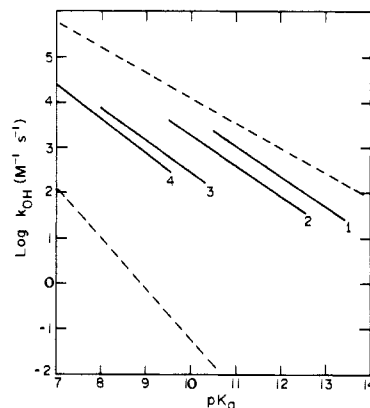
<sup>a</sup> In aqueous solution at 25 °C. <sup>b</sup> At 27 °C. <sup>c</sup> Current work. <sup>d</sup> k<sub>OH</sub> is calculated for pK<sub>a</sub> 9.0 from a linear free energy relationship.

efficient. However, the greater the resonance stabilization of the conjugate base species, the greater is the likelihood that there will be a lag in the development of this  $\pi$ -electron delocalization, along with its consequential geometric and solvational reorganization requirements, in the transition-state species. This imbalance<sup>42-44</sup> between substituent effects upon the stabilization of the product and transition-state species is reflected in the Brønsted  $\alpha$  values, which systematically increase with conjugate base stability in these five series of carbon acids. These  $\alpha$  values also systematically increase with decreasing reactivity (k<sub>OH</sub>) toward hydroxide ion catalyzed deprotonation. This result is consistent with what would be predicted on the basis of the usual reactivity-selectivity relationship.<sup>45</sup>

The 4-nitro and 4-cyano substituents show significant negative deviations from the rate equilibrium plots for each of **1-4** in Figures 5 and 6. Similar deviations for  $\sigma^-$  substituents were also observed by Bordwell and co-workers<sup>20,21</sup> for the rates of deprotonation of phenylnitromethanes. This is a clear indication that these substituents are far less effective in transition-state stabilization than expected from their resonance stabilization of the enolate ion products.

These deviations can be considered as examples of the principle of nonperfect synchronization enunciated by Bernasconi.<sup>44,46</sup> According to this principle, the product-stabilizing factor, i.e., electron-withdrawing resonance stabilization of the enolate ion by the 4-nitro or 4-cyano substituent, is expected to lower the intrinsic rate constant if it develops late along the reaction coordinate. In view of the extensive  $\pi$ -electron delocalization deduced for these enolate ions, it is not surprising that delocalization is not as advanced in the transition state as in the enolate ion products. Furthermore, since extensive charge delocalization is also involved, it might be expected that solvation of the final product would also not be accurately reflected in the transition-state species.

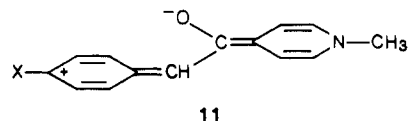
We suggest that a major reason for the deviation of the 4-nitro substituent from the correlation lines in Figures 5 and 6 lies in the fact that extensive solvent reorganization is required for the nitro group in the enolate ion product relative to the benzyl ketone reactant. Walters<sup>47</sup> has shown that solvation of the nitro group of 4-nitrobenzyl carbanions is important in his demonstration of the solvent dependence of the electronic absorption spectrum of the conjugate base of 4-nitrophenylacetonitrile, and Taft and co-workers<sup>48,49</sup> have shown that specific solvation of the nitro group is required to explain the aqueous acidity of 4-nitrophenol. Any lag in the reorganization of solvent molecules in the vicinity of the nitro group in the transition state will also contribute to a lag in electron delocalization into this nitro group in the transition



**Figure 7.** Brønsted plots for the hydroxide ion catalyzed deprotonation of **1-4**. The upper broken line represents eq 15 derived from data for acetone, acetophenone, acetylacetone, and ethyl acetoacetate as described in the text. The lower broken line represents the linear free energy relationship of Bordwell and Boyle<sup>20</sup> for the hydroxide ion catalyzed deprotonation of ring-substituted phenylnitromethanes.

state. The late development of such solvation in the product is then a further example of the principle of nonperfect synchronization.<sup>43,44</sup>

The ketones of the series **3** and **4** clearly define two quite different rate-equilibrium correlation lines (eq 13, 14; Figure 6), with the 4-pyridyl ketones (**4**) reacting with hydroxide ion more slowly than their 3-pyridyl isomers (**3**) of similar pK<sub>a</sub>. We suggest that this lower rate for the 4-pyridyl ketones can be traced to the importance of resonance contributors such as **11**, which can delocalize the cationic nitrogen charge in the conjugate bases of **4**, but not in the enolate ions derived from the 3-pyridyl ketones (**3**).



We believe that evidence for the involvement of **11** is also available from the difference in the  $\lambda_{\max}$  values of the enolate ions derived from **4** ( $\lambda_{\max}$  435–483 nm) and **3** ( $\lambda_{\max}$  360–381 nm) in Table II. In addition, this structure is also consistent with the deviations noted above for **4b** (X = 4-OCH<sub>3</sub>) in both the rate and equilibrium linear free energy relationships, since it would be particularly stabilized by the presence of a methoxy substituent upon the cationic ring carbon atom.

Analogous arguments can be made with respect to the importance of resonance contributor **11** and also solvent reorganization in the vicinity of the electron-deficient ring nitrogen atom between the ketone and enolate ion. Thus, the late development of the  $\pi$  delocalization associated with **11** and any consequential solvent reorganization will be product-stabilizing factors that will lead to a decrease in rate for the deprotonation of **4** relative to **3**. In this way, the slower rate of deprotonation of **4** than that of **1-3** can probably also be traced to the principle of nonperfect synchronization, since  $\pi$  delocalization into the pyridinium ring of the enolate ion derived from **1-3** does not lead to a formal positive charge neutralization such as that shown for **11**. Solvent reorganization in the vicinity of the pyridinium cation upon deprotonation of **1-3** should then be relatively unimportant in comparison to that implied by **11** for the deprotonation of **4**.

None of these ketones displays the "anomalously" high  $\alpha > 1$  that is found<sup>20</sup> for phenylnitromethane deprotonation, and thus Bordwell's conjecture<sup>30</sup> that ketones may also display this phenomenon is not supported. As noted by Bell and Grainger,<sup>19</sup> there are very few experimental Brønsted  $\alpha$  values available for the deprotonation of carbon acids in aqueous solutions. These workers report values covering the range 0.44–0.98 for the deprotonation of several  $\beta$ -dicarbonyl and 1,1-dicyano carbon acids catalyzed by carboxylate ions, pyridine, and water. Our own data for hydroxide ion catalyzed deprotonation of benzylic ketones lie in the middle of this range.

(42) Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335.

(43) Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219.

(44) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301.

(45) For a detailed discussion of many aspects of the reactivity-selectivity relationship, see: *Isr. J. Chem.* **1985**, *26*(4).

(46) This principle was originally referred to as the principle of imperfect synchronization.<sup>43</sup>

(47) Walters, E. A. *J. Phys. Chem.* **1977**, *81*, 1995.

(48) Fujio, M.; McIver, R. T., Jr.; Taft, R. W. *J. Am. Chem. Soc.* **1981**, *103*, 4017.

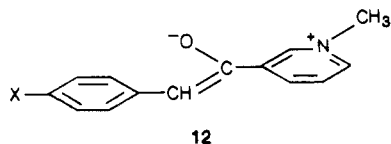
(49) Mashima, M.; McIver, R. T., Jr.; Taft, R. W.; Bordwell, F. G.; Olmstead, W. N. *J. Am. Chem. Soc.* **1984**, *106*, 2717.

(50) Bruce, P. Y. *J. Am. Chem. Soc.* **1984**, *106*, 5959.

The four series of ketones 1–4 clearly lie on quite different rate–equilibrium correlation lines (Figure 7). This figure also includes correlation lines based upon an extrapolation of the literature data<sup>20</sup> for ring-substituted phenylnitromethanes (lower broken line) and a line based upon literature data for acetone,<sup>6</sup> acetophenone,<sup>7</sup> ethyl acetoacetate,<sup>51</sup> and acetylacetone<sup>52</sup> (upper broken line). Although one may worry whether it is appropriate to consider the former two and latter two of these four ketones as belonging to a common series of carbon acids, we simply note that these four ketones do appear to describe a common correlation line (eq 15), and we use this line as a convenient reference for the discussion of the benzylic ketones of our study.<sup>53</sup>

$$\log k_{\text{OH}} = -0.55 (\pm 0.02) pK_a + 9.6 (\pm 0.3) \quad r = 0.9984 \quad (15)$$

All four series of benzylic ketones (1–4) lie within the extremes defined by these simpler ketones and phenylnitromethanes, with the relative reactivities at a common  $pK_a$  values being 3-pyridyl (1) > 4-pyridyl (2) > *N*-methyl-3-pyridyl (3) > *N*-methyl-4-pyridyl (4). The observation that the data for the neutral 3-pyridyl ketones (1) lie closest to the line defined for the simpler ketones is consistent with there being the least possibility of stabilization of either transition state or product in this series by either electrostatic or resonance interactions. The lower reactivity observed for 1–4 relative to the simpler ketones (upper broken line) in Figure 7 might be attributable to steric effects from the aromatic rings present in 1–4. However, the differences in reactivity observed between the four series of ketones, which should be susceptible to constant steric influences, must be traced to other factors. We discussed above the importance of the resonance contributor 11 to the stabilization of the enolate ion from 4. The 4-pyridyl ketones (2) have the possibility of resonance stabilization by a structure analogous to 11. However, since such a resonance contributor would bear a negatively charged ring nitrogen atom, it should be less important than 11 is to the stabilization of the enolate ions from 4. These product-stabilizing factors, although less well developed, should also be effective in stabilization of the transition states. The relative importance of these stabilization phenomena between transition state and enolate ion product must ultimately be the cause of the differing rate–equilibrium relationships for these four series of ketones. The different correlation lines for 1 and 3 indicate the possibility that electrostatic interactions such as that suggested between the cationic nitrogen and anionic oxygen atom of 12 may be important in the stabilization of the enolate ions and transition-state species derived from 3.



We have attempted a detailed analysis of our rate–equilibrium data for the four series of ketones in terms of the Marcus theory,<sup>31–33</sup> in view of the interest<sup>54–58</sup> in the interpretation of proton transfer from carbon acids in this context. All of the current Brønsted plots are apparently linear within the limited  $pK_a$  ranges ( $\sim 2.5$  log units) covered within any one series of substituted ketones. This observation allows only the use of the simplest form of the Marcus equation (eq 16). The more sophisticated forms

$$\Delta G^\ddagger = (1 + \Delta G^\circ / 4\Delta G_o^\ddagger)^2 \Delta G_o^\ddagger \quad (16)$$

of this relationship allow for work terms associated with reactant

Table VIII. Intrinsic Barriers ( $\Delta G_o^\ddagger$ ) for Deprotonation of Ketones by Hydroxide Ion<sup>a</sup>

ketone	subst	$\Delta G^\circ$	$\Delta G^\ddagger$	$\Delta G_o^\ddagger$	$\Delta G^\ddagger(\text{calcd})^b$
1a	H	-1.04	15.30	15.80	15.32
1d	4-Cl	-1.67	14.90	15.72	14.89
1e	4-CF <sub>3</sub>	-2.24	14.56	15.63	14.52
1f	3-NO <sub>2</sub>	-2.73	14.23	15.57	14.19
1g	4-CN	-3.24	14.07	15.65	
1h	3-NO <sub>2</sub> , 4-Cl	-3.21	13.85	15.41	13.88
1i	4-NO <sub>2</sub>	-4.13	13.77	15.77	
1j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	-4.45	13.07	15.21	13.08
1k	3-Cl	-1.86	14.74	15.66	14.77
2a	H	-2.41	15.02	16.20	14.99
2b	4-OCH <sub>3</sub>	-2.11	15.20	16.24	
2c	4-CH <sub>3</sub>	-2.08	15.20	16.22	15.22
2d	4-Cl	-2.89	14.62	16.03	14.66
2e	4-CF <sub>3</sub>	-3.62	14.21	15.97	14.15
2f	3-NO <sub>2</sub>	-3.99	13.92	15.85	13.90
2g	4-CN	-4.59	13.70	15.91	
2h	3-NO <sub>2</sub> , 4-Cl	-4.49	13.51	15.67	13.56
2i	4-NO <sub>2</sub>	-5.50	13.47	16.10	
2j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	-5.65	12.77	15.47	12.77
3a	H	-4.97	13.63	16.02	13.65
3c	4-CH <sub>3</sub>	-4.82	13.80	16.12	13.76
3d	4-Cl	-5.48	13.26	15.88	13.27
3e	4-CF <sub>3</sub>	-6.05	12.89	15.77	12.85
3f	3-NO <sub>2</sub>	-6.42	12.54	15.58	12.58
3g	4-CN	-6.77	12.42	15.63	
3h	3-NO <sub>2</sub> , 4-Cl	-6.87	12.24	15.48	12.27
3i	4-NO <sub>2</sub>	-7.56	12.15	15.70	
3j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	-7.93	11.52	15.23	11.51
4a	H	-6.79	13.50	16.70	13.48
4b	4-OCH <sub>3</sub>	-6.76	13.69	16.90	
4c	4-CH <sub>3</sub>	-6.49	13.67	16.76	13.67
4d	4-Cl	-7.28	13.13	16.57	13.10
4e	4-CF <sub>3</sub>	-7.69	12.78	16.40	12.79
4f	3-NO <sub>2</sub>	-8.03	12.53	16.30	12.53
4g	4-CN	-8.41	12.38	16.31	
4h	3-NO <sub>2</sub> , 4-Cl	-8.42	12.27	16.20	12.24
4i	4-NO <sub>2</sub>	-9.01	12.19	16.39	
4j	3,5-(NO <sub>2</sub> ) <sub>2</sub>	-9.35	11.52	15.80	11.54

<sup>a</sup> All data in kilocalories per mole;  $\Delta G_o^\ddagger$  calculated from eq 16 as described in text; standard deviations of  $\pm 3\%$  in  $k_{\text{OH}}$  correspond to  $\pm 0.02$  kcal/mol for  $\Delta G^\ddagger$  and  $\pm 0.05$  kcal/mol for  $\Delta G_o^\ddagger$ . <sup>b</sup> Calculated from eq 17 by using  $\Delta G^\circ$  given and the appropriate parameters from Table IX; no value is given for a substituent that displays deviations attributable to special resonance effects.

association and product dissociation processes.<sup>31</sup> However, such applications require nonlinear Brønsted relationships extending over quite large  $pK_a$  ranges before any reasonably accurate evaluation of these work terms is possible.

The free energies of activation ( $\Delta G^\ddagger$ ) for deprotonation of all ketones 1–4 were calculated from  $k_{\text{OH}}$  by the Eyring equation, while the free energies of reaction ( $\Delta G^\circ$ ) were calculated from  $\log K = pK_a - pK_w$ . The intrinsic barrier ( $\Delta G_o^\ddagger$ ) for each reaction was then calculated by solution of the appropriate quadratic equation in  $\Delta G_o^\ddagger$  that is derived from eq 16. In general, one of the roots of this quadratic equation gave  $\Delta G_o^\ddagger < 1$  kcal/mol, which is not physically reasonable when one considers that these barriers must include work terms of the order of 8–16 kcal/mol.<sup>56</sup> The other root was taken as the intrinsic barrier, and values of  $\Delta G_o^\ddagger$  obtained in this way are listed in Table VIII for all ketones 1–4.

From an inspection of the data in Table VIII, it is clear that within each series of ketones  $\Delta G_o^\ddagger$  varies systematically with  $\Delta G^\circ$ . This variation is displayed in Figure 8 for each class of ketones. There appears to be a linear dependence of  $\Delta G_o^\ddagger$  upon  $\Delta G^\circ$  within each class of ketones. Deviations from this linear relationship are obvious for the 4-methoxy-, 4-cyano-, and 4-nitro-substituted derivatives, which are shown above to also deviate from simple Brønsted rate–equilibrium correlations. Such a linear dependence of intrinsic barrier upon  $\Delta G^\circ$  suggests the modification of the Marcus eq 16 into the form expressed by eq 17.

$$\Delta G^\ddagger = [1 + \Delta G^\circ / 4(A + B\Delta G^\circ)]^2 (A + B\Delta G^\circ) \quad (17)$$

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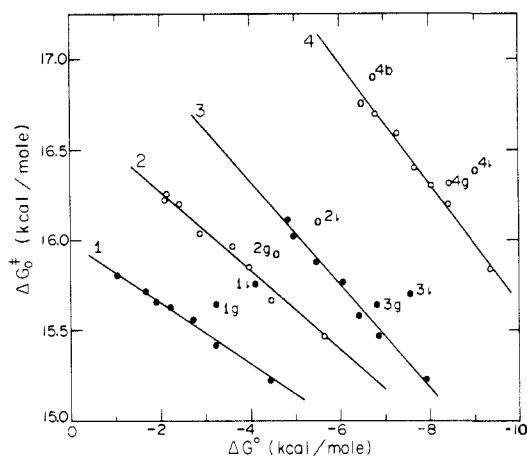
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**Figure 8.** Dependence of intrinsic barriers (calculated from eq 16) upon  $\Delta G^\circ$  for the hydroxide ion catalyzed deprotonation of 1-4. Data from Table VIII.

**Table IX.** Parameters for Eq 17 and Brønsted  $\alpha$  Values for Deprotonation of Ketones by Hydroxide Ion

ketones	$A$ , kcal/mol	$B$	$\alpha$ ( $\Delta G^\circ = 0$ ) <sup>a</sup>	$\alpha$ range <sup>b</sup>
1	16.0 <sup>c</sup>	0.18 <sup>c</sup>	0.68	0.64-0.67
2	16.7	0.22	0.72	0.67-0.70
3	17.4	0.28	0.78	0.71-0.74
4	18.9	0.32	0.82	0.73-0.77

<sup>a</sup> Calculated from eq 18. <sup>b</sup> Calculated from eq 18 for the range in  $\Delta G^\circ$  given in Table VIII for members of this series of ketones. <sup>c</sup> Standard errors are  $\pm 0.1$  kcal/mol for  $A$  and  $\pm 0.01$  for  $B$ , for each series of ketones.

This two-parameter relationship was tested by the evaluation of the parameters  $A$  and  $B$  by fitting the experimentally observed dependence of  $\Delta G^\ddagger$  upon  $\Delta G^\circ$  within each of the four series of ketones to eq 17 by use of the Marquardt algorithm<sup>59</sup> for parameter evaluation. Values for  $A$  and  $B$  obtained by this procedure are collected in Table IX. Values calculated for  $\Delta G^\ddagger$  via eq 17 by using these parameters and the experimental  $\Delta G^\circ$  are then compared with the experimental  $\Delta G^\ddagger$  in Table VIII. The close correspondence between these calculated and experimental free energies of activation indicates that the empirical modification to the Marcus equation which has been incorporated into eq 17 does satisfactorily reproduce the experimental results.

The above modification of the Marcus eq 16 to eq 17 is based purely upon empirical observations for the four series of ketones 1-4. However, the deprotonation of these ketones by hydroxide ions fits a class of reactions for which Marcus expressly considered<sup>33</sup> the possibility that the intrinsic barrier ( $\Delta G_0^\ddagger$ ) defined by eq 16 might vary within a series of related reactions; i.e.,  $d(\Delta G_0^\ddagger)/d(\Delta G^\circ) \neq 0$ . Equation 17 represents the case in which  $d(\Delta G_0^\ddagger)/d(\Delta G^\circ) = B$ , which is constant for a series of X substituents that do not have a special resonance interaction with the reaction center (i.e., excluding the 4-OCH<sub>3</sub>, 4-CN, and 4-NO<sub>2</sub> species).

The Brønsted  $\alpha$  value [ $d(\Delta G^\ddagger)/d(\Delta G^\circ)$ ] derived from eq 17 is given by eq 18. For  $\Delta G^\circ = 0$ , eq 18 defines  $\alpha = 0.5 + B$ . Such

$$\alpha = 0.5[1 + \Delta G^\circ / 4(A + B\Delta G^\circ)] + B[1 - [\Delta G^\circ / 4(A + B\Delta G^\circ)]^2] \quad (18)$$

$\alpha$  values are slightly larger (Table IX) than experimentally observed (Table VI). Equation 18 can also be used to calculate  $\alpha$  for any given  $\Delta G^\circ$  by use of the experimentally evaluated  $A$  and  $B$  parameters. The range of  $\alpha$  values predicted by the experimentally observed ranges of  $\Delta G^\circ$  for each series of ketones is also included in Table IX. While  $\alpha$  is thus predicted to vary somewhat

within each series of ketones, the variation is so small as to be experimentally undetectable over the readily accessible  $\Delta pK_a$  range within each series. The experimentally measured  $\alpha$  values (Table VI) are essentially the averages of these narrow ranges of  $\alpha$ .

Apart from Marcus' original consideration<sup>33</sup> of data for the deprotonation of a limited series of three nitroalkanes, we are only aware of one other serious attempt to make use of a "variable intrinsic barrier" for proton-transfer reactions. Rose and Stuehr<sup>60</sup> made use of a similar analysis to that which we present above, in their study of the rates of hydroxide ion catalyzed deprotonation of internally hydrogen-bonded phenols. It should be noted, however, that the concept of a structure-sensitive intrinsic barrier has recently been found necessary for the interpretation of the rate constants for identity reactions in both hydride-transfer<sup>61</sup> and methyl-transfer<sup>62</sup> processes.

In principle, an analysis via eq 17 is also applicable to the various anomalous  $\alpha$  values reported<sup>20,21,30,63</sup> by Bordwell and co-workers for the deprotonation of phenylnitromethanes and phenylnitroethanes. We have analyzed the data<sup>20</sup> for the reaction of hydroxide ion catalyzed deprotonation of ring-substituted (3-CH<sub>3</sub>, H, 3-Cl, 3-NO<sub>2</sub>) phenylnitromethanes in aqueous solution by the method described above for eq 17 and find  $A = 30.1$  kcal/mol and  $B = 1.14$  for this reaction. This result requires  $\alpha = 1.64$  (at  $\Delta G^\circ = 0$ ) and  $\alpha = 1.56$  for phenylnitromethane itself ( $\Delta G^\circ = -9.71$  kcal/mol), which is consistent with the experimental  $\alpha = 1.54$ . Equation 17 can also be applied to an analysis of the data for the simple ketones described by eq 15. This analysis gives  $A = 14.8$  kcal/mol and  $B = 0.05$  for these ketones, and  $\alpha = 0.55$  at  $\Delta G^\circ = 0$ . Cohen and Marcus<sup>32</sup> report  $\Delta G_0^\ddagger = 13.0$  kcal/mol when eq 16 is used to analyze the combined data for the deprotonation of a similar series of ketones by hydroxide ion or sulphydryl ion.

Although the four series of ketones 1-4 do not display  $\alpha > 1$  as found for many nitroalkane deprotonations by hydroxide ion, it is clear that, at least in terms of the Marcus theory, rate-equilibrium relationships for the deprotonation of these ketones do qualitatively resemble those found for nitro-activated carbon acids. The requirement for  $B \neq 0$  in eq 17 might be considered to be the source of anomalous  $\alpha$  values,<sup>64</sup> and in this light, these benzylic ketones do resemble their nitro-activated carbon acid analogues.<sup>30</sup> The question arises as to whether  $\Delta G_0^\ddagger$  of eq 16 or the  $A$  parameter defined in eq 17 should be considered as the real intrinsic barrier for these reactions. When  $\Delta G_0^\ddagger$  varies with simple substituents as it does in the current study, it is difficult to accept this parameter as having any fundamental significance for theoretical interpretations of rate-equilibrium data. The  $A$  parameter of eq 17 may be considered the intrinsic barrier at  $\Delta G^\circ = 0$  within any one series of ketones and, in combination with a  $B$  parameter, does predict an appropriate rate-equilibrium relationship, provided that substituents with special resonance effects are absent. However, since  $A$  varies by 2.9 kcal/mol between the four series of ketones 1-4, it is clearly of limited applicability. The order of  $A$  barriers does follow the order expected on the basis of the six independent correlation lines for the six series of carbon acids in Figure 7. The relative slopes of these correlation lines are also adequately described as functions of  $A$  and  $B$ , although in general eq 18 predicts nonlinear rate-equilibrium correlations over extended ranges of  $\Delta G^\circ$ .

We suggest that the testing of the empirically derived eq 17, as more experimental data become available for related series of reactions, will be an important step in the evaluation of the general usefulness of the Marcus theory to the understanding of proton-transfer reactions from carbon acids. The investigation of the variation of  $A$  and  $B$  as a function of a broad range of structural

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variations in both acid and base species should be considered an evolutionary step in the development of rate-equilibrium relationships for proton transfer from carbon acids. While eq 17 does not have the sophistication of relationships that incorporate work criteria, it is applicable to analyses over the limited  $\Delta pK_a$  ranges which are often the only ranges that are accessible in such studies. The  $A$  parameter must include the work terms for association of the acid and base species (and also the product species), in addition to the true intrinsic barrier at  $\Delta G^\circ = 0$  within this acid-base complex. Solvation differences, which are expected to be substantial between these carbon acids and their conjugate base species, will also influence  $A$  via substantially different work terms for the assembly of the reactant and product acid-base pairs. The  $B$  parameter should be the main reflection of imbalances between those factors (resonance, solvation, etc.) that are important to the stabilization of the transition state and conjugate base product species.  $B$  values should be largest in those systems in which these imbalances are greatest; i.e.,  $B$  values should be the largest in those systems in which Bernasconi's principle of nonperfect synchronization is most important.<sup>43,44</sup>

In principle, the data that we present in the current work for the deprotonation of ketones may be analyzed by the technique that Grunwald<sup>65</sup> has recently presented for the description of transition-state structure in terms of disparate reaction events. Grunwald included an analysis of Bordwell's data<sup>20</sup> for deprotonation of phenylnitromethanes as one of his examples of the power of this method. However, in view of the caveat that has been posed<sup>66</sup> regarding Grunwald's analysis of this reaction, we have refrained from presenting a similar analysis that is subject to the same uncertainties.

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## 2-Aza-2,4-cyclopentadienone. Existence and Reactivity

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**Abstract:** The elusive species 2-aza-2,4-cyclopentadienone has been generated from an insoluble polymeric precursor. The liberated intermediate can act either as a diene or as a dienophile in Diels-Alder reactions.

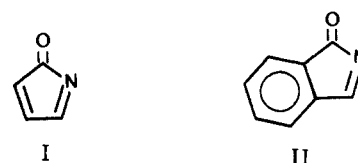
The existence of several diaza derivatives of 2,4-cyclopentadienone as reactive intermediates has been proposed by some authors. Thus, transient formation of 4,5-diphenyl-2,3-diaza-2,4-cyclopentadienone in elimination reactions has been postulated as a result of trapping experiments with 1,3-butadiene or 1,3-cyclopentadiene, giving the appropriate Diels-Alder adducts.<sup>1</sup> Also, generation of 5-phenyl-2,3-diaza-1,3-cyclopentadienone or 4-phenyl-5-benzyl-2,3-diaza-2,4-cyclopentadienone was proposed in some oxidation processes.<sup>2,3</sup> Nevertheless, monoaza derivatives of 2,4-cyclopentadienone, I (Chart I), have received no attention until now, although related indolone II has been shown to add readily to dienes at the imine bond, to afford Diels-Alder adducts.<sup>4</sup>

In our attempt to determine how the presence of a nitrogen atom in the cyclopentadienone ring might affect its stability and its reactivity in Diels-Alder processes, we developed an approach to 2-aza-2,4-cyclopentadienone (I). A suitable precursor for I was found in the polymeric 5-sulfonate of 3-pyrroline-2-one (IV) which can generate I via an elimination process.

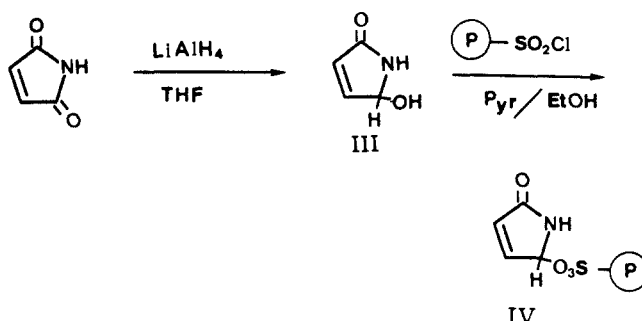
### Results and Discussion

**Synthesis of Precursor IV.** The synthesis of polymeric compound IV was carried out as shown in Scheme I. Maleimide was reduced to III according to the procedure of Kohn and Liao for hydantoins.<sup>5</sup> Reaction of III with chlorosulfonated macroreticular resin<sup>6</sup> gave IV (IR: 3410, 1700, 1570, 1410, 1150  $\text{cm}^{-1}$ ). Re-

Chart I



Scheme I



actions of IV with several eliminating agents, such as DMSO or  $\text{LiNH}_2/\text{HMPT}$ , always led to sulfonic resin and complex mixtures in solution. This behavior corresponds to that observed for nonnitrogenated 2,4-cyclopentadienones, which can only be isolated as dimers or as their decarbonylation products.<sup>6,7</sup>

**2-Aza-2,4-cyclopentadienone as a Diene.** The existence and reactivity of I were established by using the three-phase test.<sup>8</sup> A dienophilic reagent, the polymeric monoester of acetylenedi-

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