Transition State Imbalance in the Deprotonation of Substituted 2-Tetralones by Hydroxide Ion

John B. Nevy, David C. Hawkinson, Grzegorz Blotny, Xudong Yao, and Ralph M. Pollack*

Contribution from the Laboratory for Chemical Dynamics, Department of Chemistry and Biochemistry, 1000 Hilltop Circle, University of Maryland Baltimore County, Baltimore, Maryland 21250, and Center for Advanced Research in Biotechnology, 9600 Gudelsky Drive, Rockville, Maryland 20850

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Abstract: Rate and equilibrium constants for the deprotonation of a series of phenyl-substituted 2-tetralones in aqueous sodium hydroxide have been determined. A Brønsted plot of log *k* for deprotonation *vs* pK_a of the appropriate 2-tetralone is linear with a slope ($-\alpha$) of -0.60 ± 0.01, except for the point corresponding to 6-nitro-2-tetralone (**1b**). The negative deviation of **1b** from the correlation indicates that the transition state for deprotonation of 2-tetralone is imbalanced, with delocalization of charge into the phenyl ring lagging behind proton transfer. A semiquantitative assessment of the charge distribution in both the fully formed anion and the transition state for deprotonation was calculated from these results and ^{13}C NMR spectra of the 2-tetralone anion in methanol/water mixtures. Although approximately twice as much negative charge is localized on the oxygen than on the enolate carbon in the anion, slightly more charge is on the enolate carbon in the transition state.

Introduction

In contrast to the rapid rates of proton loss from oxygen and nitrogen acids, abstraction of a proton from the α carbon of carbonyl compounds is a relatively slow process.[1] Thus, monocarbonyl compounds with pK_a's of 10−13 react with hydroxide ion approximately 10^7 to 10^9-fold slower than the diffusion-controlled rate of deprotonation of oxygen and nitrogen acids of the same pK_a. The sluggishness of enolate formation may be attributed, at least in part, to a lag in the development of resonance stabilization in the transition state compared to the extent of proton transfer.[2] Delocalization of the charge into the carbonyl oxygen in the transition state is hindered by incomplete formation of the p orbital on the enolate carbon atom, leaving a larger fraction of charge at this carbon than in the product enolate ion.[3] Imbalanced transition states for deprotonation of ketones have been found for the deprotonation of several phenacylpyridines and phenacylpyridinium ions[4] and picrylacetophenones.[5] In addition, calculations[6,7] suggest that deprotonation of acetaldehyde in the gas phase occurs through an imbalanced transition state. This imbalance results in only minimal stabilization of the transition state by charge delocalization, leading to a low intrinsic rate constant for deprotonation.

The nature of the transition state for deprotonation of simple carbonyl compounds is of particular interest relative to the corresponding enzymatic reactions. A number of enzymes are able to abstract a proton from these carbon atoms with exceptional efficiency.[8] Thus, the rate constant (k_{cat}) for deprotonation of 5-androstene-3,17-dione (pK_a 12.7) by an active site aspartate (pK_a 4.7) of 3-oxo-Δ^5-steroid isomerase is $>10^7$-fold larger than the rate constant for reaction with 1 M acetate ion (pK_a 4.75).[9,10] Although there has been much speculation about the source of this extraordinary catalytic ability, no generally accepted explanation has emerged.[11]

Rate and equilibrium constants for the ionization of a large number of aldehydes and ketones have been accumulated, but little information is available about the dynamics of deprotonation of cyclic carbonyl compounds.[1] We,[12] and others,[13] have examined the enolization of the cyclic benzyl ketones 2-tetralone (**1a**, pK_a 12.9), 2-indanone (**2a**, pK_a 12.2), and 2-benzosuberone (**3**, pK_a 14.9) and found that these ketones are substantially more acidic than benzyl methyl ketone (**4a**, pK_a 16).[14] The enhanced acidity may be attributed to unfavorable steric interactions in the enolate of benzyl methyl ketone that hinder coplanarity.[12a,b] Delocalization of charge into the phenyl ring is greater for the cyclic anions, particularly those of 2-indanone and 2-tetralone,

* Address correspondence to this author at the University of Maryland Baltimore County.

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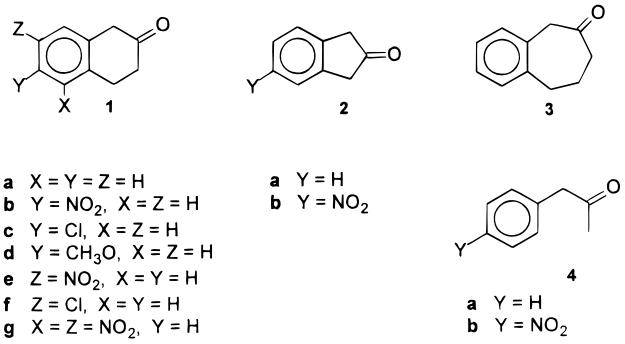
Scheme 1



than for the enolate of benzyl methyl ketone.[15] In the present work, we describe the effects of ring substituents on the kinetic and equilibrium acidities of 2-tetralone, and we discuss the nature of charge distribution in both the anion and the transition state for abstraction of the α proton by hydroxide ion.

Experimental Section

Unless otherwise mentioned, all chemicals were reagent grade or better and were purchased commercially. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ referenced to TMS as an internal standard using a General Electric QE-300 spectrometer. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on precoated (0.20 mm) silica gel (Merck 60 F-254) plates. Spectral titrations were performed on Gilford Response or Response II UV/vis spectrophotometers. Kinetic measurements were made using a Hi-Tech QP/SF-53 stopped-flow spectrophotometer. 4-Nitrobenzyl methyl ketone (**4b**) was purchased from Lancaster Synthesis Inc., mp 63−64 °C, TLC ($CHCl_3$), R_f 0.23, and 6-methoxy-2-tetralone (**1d**) was a gift from Dr. Mark Gold. The synthesis of 5,7-dinitro-2-tetralone (**1g**) will be described in a separate publication.

6-Nitro-2-tetralone (1b) and 7-Nitro-2-tetralone (1e). Compounds **1b** and **1e** were prepared by nitration of 2-tetralone (99%, Aldrich) as follows: 2-Tetralone (730 mg, 5.0 mmol) was slowly added to cold (−30 °C) concentrated nitric acid (8 mL, 90%) with vigorous stirring. After the addition was completed, the reaction mixture was stirred for 8 min, poured onto a mixture of sodium hydroxide (6.5 g) in water and ice (ca. 50 mL), and then extracted twice with ethyl acetate. The combined extracts were washed with water until neutral and dried over magnesium sulfate. After filtration and evaporation of the solvent under reduced pressure, the products were purified by column chromatography (silica, Merck 60) using hexane/ethyl acetate (4:1) as the solvent. The first compound eluted was 6-nitro-2-tetralone (**1b**), which was recrystallized from ethyl acetate (260 mg, 27%), mp 70−72 °C. TLC (hexane/ethyl acetate, 2:1), $R_f = 0.37$. ^{1}H NMR ($CDCl_3$): δ 2.60 (t, $J = 6.6$ Hz, 2H, H_4), 3.19 (t, $J = 6.6$ Hz, 2H, H_3), 3.69 (s, 2H, H_1), 7.30 (d, $J = 8.4$ Hz, 1H, H_8), 8.10 (dd, $J = 2.1$, 8.4 Hz, 1H, H_7), 8.13 (br s, 1H, H_5). IR (KBr): ν 3070, 2960, 2910, 1710, 1610, 1590, 1510, 1340 cm^{-1}. Anal. Calcd for $C_{10}H_9O_3N$: C, 62.82; H, 4.74; N, 7.32. Found: C, 62.58; H, 4.84; N, 7.33. UV (1 N NaOH) λ_{max} 514 nm.

7-Nitro-2-tetralone (1e) eluted as a second major product and was recrystallized from ethyl acetate/hexane (370 mg, 40%), mp 97−98 °C (lit.[16a,b] 94−96 °C; 96−97 °C). TLC (hexane/ethyl acetate, 2:1), $R_f = 0.32$. ^{1}H NMR ($CDCl_3$) δ 2.60 (t, $J = 6.6$ Hz, 2H, H_4), 3.18 (t, $J = 6.6$ Hz, 2H, H_3), 3.69 (s, 2H, H_1), 7.41 (d, $J = 8.1$ Hz, 1H, H_5), 8.03 (br s, 1H, H_8), 8.10 (dd, $J = 2.1$, 8.1 Hz, 1H, H_6). IR (KBr): ν 3080, 2950, 2900, 1710, 1610, 1590, 1515, 1340 cm^{-1}. Anal. Calcd for $C_{10}H_9O_3N$: C, 62.82; H, 4.74; N, 7.32. Found: C, 62.50; H, 4.82; N, 7.40. UV (1 N NaOH) λ_{max} 298.5 nm.

5-Nitro-2-indanone (2b) was prepared as above from 2-indanone (700 mg, 5.0 mmol), except that after addition of 2-indanone to the nitric acid, the reaction mixture was removed from the cooling bath and stirred for an additional 20 min before being poured onto ice. Chloroform was used as the eluent in column chromatography. Recrystallization from ethyl acetate/hexane gave 480 mg of product (54%), mp 141−143 °C (lit.[16c] 141−141.5 °C). TLC (chloroform/methanol, 100:1), $R_f = 0.60$. ^{1}H NMR ($CDCl_3$): δ 3.66 (s, 4H, H_1 and H_3), 7.48 (d, $J = 8.1$ Hz, 1H, H_8), 8.18 (d, $J = 8.1$ Hz, 2H, H_4 and H_8). IR (KBr): ν 3080, 2920, 2850, 1715, 1605, 1525, 1340 cm^{-1}. Anal. Calcd for $C_9H_7O_3N$: C, 61.01; H, 3.95; N, 7.90. Found: C, 61.53; H, 4.11; N, 7.86. UV (1 N NaOH): λ_{max} 513 nm.

6-Chloro-2-tetralone (1c) was prepared by the reaction of 4-chlorophenylacetyl chloride (8.93 g, 47.2 mmol) with excess ethylene and anhydrous $AlCl_3$ (13 g) in anhydrous dichloromethane (120 mL).[17,18] Column chromatography (silica, Merck 60, CH_2Cl_2), followed by recrystallization gave pure **1c** (7.11 g, 84%), mp 67.0−67.5 °C (lit.: 68−70 °C).[17] TLC (CH_2Cl_2), $R_f = 0.24$. ^{1}H NMR ($CDCl_3$): δ 2.54 (t, $J = 6.6$ Hz, 2H, H_4), 3.04 (t, $J = 6.6$Hz, 2H, H_3), 3.54 (s, 2H, H_1), 7.05 (d, $J = 8.1$Hz, 1H, H_8), 7.19 (dd, $J = 2.1$ Hz, 8.8 Hz, 1H, H_7), 7.23 (s, 1H, H_5). IR (CH_3Cl): ν 3010, 2950, 2900, 2850, 1710, 1595, 1480, 1410, and 1330 cm^{-1}.

7-Chloro-2-tetralone (1f). 3-Chlorophenylacetyl chloride (5.54 g, 32.5 mmol) was reacted with ethylene and anhydrous $AlCl_3$ (8 g) in anhydrous dichloromethane (120 mL) as for **1c**.[17] The product was purified by column chromatography (silica, Merck 60, 9:1 hexane/ethyl acetate) and recrystallized from ethyl acetate/hexane (3.58 g, 61%), mp 38−39 °C. TLC (hexane/ethyl acetate, 9:1), $R_f = 0.16$. ^{1}H NMR ($CDCl_3$): δ 2.54 (t, $J = 6.6$ Hz, 2H, H_4), 3.03 (t, $J = 6.6$ Hz, 2H, H_3), 3.55 (s, 2H, H_1), 7.12−7.18 (mult, 3H, H_5, H_6, H_8). IR (CH_3Cl): ν 3040, 3020, 2950, 2910, 2870, 2850, 1715, 1595, 1470, 1390, and 850 cm^{-1}. Anal. Calcd for $C_{10}H_9ClO$: C, 66.49; H, 5.02; Cl, 19.62. Found: C, 66.21; H, 5.16; Cl, 19.49.

NMR Determinations. ^{13}C proton decoupled NMR experiments were run on a General Electric QE-300 spectrometer at 25.0 ± 0.5 °C. Concentrations of 2-tetralone varied from 0.02 M to 0.85 M. For determinations in CD_3OD/D_2O, the 49.0 ppm peak of methanol was used as an internal standard. For solvents containing d_6-DMSO, the DMSO peak at 39.5 ppm was used as an internal standard.

Kinetic Measurements. All kinetic measurements were performed at 25.0 ± 0.1 °C and $\mu = 1.0$ M (NaCl, 1.6% MeOH). Solutions of ketones (ca. 85 μM, 1.6% MeOH) were prepared before each experiment. Base solutions ($\mu = 1.0$ M, NaCl) were prepared from 1.0 N standardized NaOH (J. T. Baker) and titrated with potassium hydrogen phthalate. Rates of enolate formation were determined by rapidly mixing solutions of the ketones with various concentrations of base in a 1:5 ratio (5:1 for 4-nitrobenzyl methyl ketone) in a HiTech QP/SF 53 stopped-flow spectrophotometer. The change in absorbance, corresponding to formation of the enolate ion, was monitored for at least 10 half-lives. Pseudo-first-order rate constants (k_{obs}) for the approach to equilibrium were obtained by monitoring the change in absorbance due to formation of the enolate at the absorbance maximum and fitting the data to the integrated form of the first-order rate equation by nonlinear least-squares regression. All compounds showed excellent fits to pseudo-first-order kinetics, except **2b**, which showed a noticeable drift of the infinity absorbance. A base line correction to account for this second reaction was included in the equation.

Spectral Determination of pK_a's. Stock solutions of ketones (50 μL ca. 1.25 mM in methanol) were added to either aqueous sodium hydroxide (3.00 mL, $\mu = 1.0$ M, NaCl, $[OH^-] = 0.1-1.0$ M) or buffer solutions (pH = 6.1−10.7, [buffer] = 0.2 or 0.3 M, $\mu = 1.0$ M with NaCl) and the absorbance determined at the λ_{max} of the enolate. Buffers used were *N*-(carbamoylmethyl)iminodiacetic acid (ADA, pK_a 6.6), 2-morpholinoethanesulfonic acid (MES, pK_a 6.1), 2-[*N*-[tris(hydroxymethyl)methyl]amino]ethanesulfonic acid (TES, pK_a 7.4), 3-[*N*-[tris(hydroxymethyl)methyl]amino]propanesulfonic acid (TAPS, pK_a 8.4), 2-(*N*-cyclohexylamino)ethanesulfonic acid (CHES, pK_a 9.3), and 3-(cyclohexylamino)-1-propanesulfonic acid (CAPS, pK_a 10.4). pH values for all buffer solutions were measured with a Radiometer PHM85 Precision pH meter and corrected for the concentration of sodium ion.

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Table 1. pK_a Values and Rate Constants for Enolization and Ketonization (25.0 °C, μ = 1.0 M)

compound	spectral pK_a[a]	kinetic pK_a[b]	k_1 (M^{-1} s^{-1})[b,c]	k_{-1} (s^{-1})[b,c]
1a	12.83 ± 0.01[d]	12.75 ± 0.02[e]	376 ± 14[e]	39.5 ± 0.7[e]
1b	10.09 ± 0.02	9.7 ± 0.4	6650 ± 450	0.6 ± 0.3
1c	12.51 ± 0.03	12.49 ± 0.01	515 ± 17	30.2 ± 0.3
1d	13.27 ± 0.01	13.07 ± 0.02	197 ± 3	43.9 ± 0.9
1e	11.76 ± 0.02	11.75 ± 0.02	1730 ± 34	18.4 ± 0.3
1f	12.30 ± 0.07	12.27 ± 0.01	775 ± 6	26.9 ± 0.1
1g	10.34 ± 0.03	10.3 ± 0.1	11000 ± 1000	4.4 ± 0.5
2a	12.15 ± 0.02[d]	12.16 ± 0.01[e]	216 ± 3[e]	5.92 ± 0.07[e]
2b	9.10 ± 0.04	n.d.	3150 ± 300	0.07 ± 0.01[f]
4	13.40 ± 0.03	13.25 ± 0.09	69 ± 8	23 ± 2

[a] 1.6% MeOH, μ = 1.0 M (NaCl). [b] 1.6% MeOH, μ = 1.0 M (NaCl), 25.0 ± 0.1 °C. [c] Values for k_1 and k_{-1} were determined from a plot of k_{obs} vs [OH^-] using the equation $k_{obs} = k_1[OH^-] + k_{-1}$. [d] Reference 12b, 1% MeOH, μ = 1.0 M (NaCl). [e] Reference 12b, 1% MeOH, μ = 0.1 M (NaCl), recalculated from k_1 and k_{-1} using $K_w = 1.88 \times 10^{-14}$ M^2. [f] The value for k_{-1} could not be determined experimentally. This value was calculated from the pK_a determined by spectral titration and the value of k_1.

Results

Acidities of Substituted 2-Tetralones. pK_a values for substituted tetralones **1a**−**g** were determined by spectral titration in aqueous sodium hydroxide for species with pK_a > 11.5 or in sodium hydroxide and buffer solutions for species with pK_a < 11.5. K_a values were obtained by fitting the data to either eq 1 or 2 using nonlinear least squares regression, where $A_0 = A$ at [OH^-] = 0, $A_{inf.} = A$ at [OH^-] = infinity (Table 1), a_H is 10^{-pH}, and K_w is the ionization constant of water.[19] pK_a's for 5-nitro-2-indanone (8.82 ± 0.04)[20] and 4-nitrobenzyl methyl ketone (13.4 ± 0.2) were determined similarly. For compounds that are incompletely ionized at high hydroxide ion concentrations, the absorbance at infinite hydroxide ion concentration in eq 1 was treated as an adjustable parameter.

$$A = A_0 + \{(A_{inf.} - A_0)K_a[OH^-]/K_W\}/\{1 + K_a[OH^-]/K_W\} \quad (1)$$

$$A = A_0 + \{(A_{inf.} - A_0)K_a/a_H\}/(1 + K_a/a_H) \quad (2)$$

NMR Studies. Carbon (δ_C) and hydrogen (δ_H) chemical shifts were determined for 2-tetralone in d_6-DMSO/D_2O (4:3 v/v) and CD_3OD/D_2O (2:1 v/v), and peaks were assigned based upon previous results in d_6-DMSO.[15] Although some ambiguities in the assignments remain in the aromatic region, these are unimportant for our purposes, since the calculations only require the sum of these peak positions. Because the C-1 and C-3 protons exchange with solvent deuterium, these peaks are split and are quite low in intensity. Spectra of 2-tetralone were also determined in the presence of various concentrations of NaOD in the same solvents and in CD_3OD/D_2O (2:1 and 3:1 v/v). In d_6-DMSO/D_2O (4:3) with ≥1 N NaOD, there is no detectable neutral species left and the peaks are assigned to the anion by analogy to assignments in d_6-DMSO.[15] An increase in the NaOD concentration results in no change in the spectrum. In CD_3OD/D_2O/NaOD, the major peaks in the spectra are those corresponding to the anion of 2-tetralone, although weak peaks due to the neutral species are also present. Within the CD_3OD/D_2O solvent series, the chemical shifts of both 2-tetralone and its anion are independent of solvent composition and base concentration. Assignments of these chemical shifts for the neutral and anionic forms of 2-tetralone are given in Table S1 (Supporting Information).

(19) $K_w = 1.88 \times 10^{-14}$ M^2 at μ = 1.0 (Harned, H. S.; Owens, B. B. *The Physical Chemistry of Electrolyte Solutions*, 3rd ed.; Reinhold: New York, 1958; p 752).

(20) Literature pK_a 8.94 (Tobias, P. S.; Kézdy, F. J. *J. Am. Chem. Soc.* **1969**, *91*, 5171).

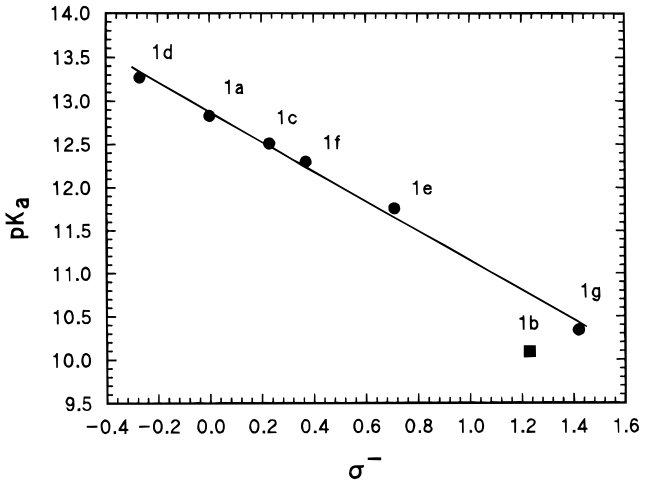
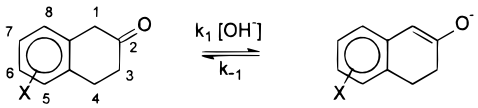


Figure 1. Plot of the pK_a of substituted 2-tetralones *vs* σ^-.

Scheme 2



Kinetics of Deprotonation by Hydroxide Ion. The rates of formation of the enolate anions were determined by rapidly mixing the ketones with various concentrations of hydroxide ion in a stopped-flow spectrophotometer (Scheme 2). Since for a first-order approach to equilibrium, k_{obs} is equal to the sum of the rate constants for the forward and reverse reactions (eq 3), k_1 and k_{-1} are given by the slope and *y*-intercept, respectively, of a plot of k_{obs} vs [OH^-] (Table 1). These rate constants were used to calculate independent values of the K_a's according to eq 4. In the case of **2b**, the value for k_{-1} could not be directly determined due to the large fraction of enolate at equilibrium, but rather was calculated using the spectral K_a and eq 4.

$$k_{obs} = k_1[OH^-] + k_{-1} \quad (3)$$

$$K_a = K_w k_1/k_{-1} \quad (4)$$

Discussion

Acidities of Substituted 2-Tetralones. 2-Tetralone and its ring-substituted derivatives are sufficiently acidic that their ionizations can be observed directly in the pH range.[21] As expected, electron-withdrawing substituents in the aromatic ring substantially increase the acidity. A plot of pK_a vs σ^- is linear, with a slope ($-\rho$) of −1.72 ± 0.07,[22] except for the point corresponding to 6-nitro-2-tetralone (**1b**), which is ca. 10-fold more acidic than predicted from the correlation based on the other substituents (Figure 1). pK_as of other substituted benzyl ketones give similar ρ values when plotted against σ^-, although the *p*-nitro-substituted compounds do not deviate from the correlation lines.[4a]

(21) pK_as determined in sodium hydroxide solutions are *concentration* pK_as based upon the concentrations of all species. Those pK_as determined in buffer solutions are *mixed* pK_as based upon concentrations of solute and activity of hydronium ion. We have used both types of pK_as in the same correlations, since the kinetic pK_a of **1g** (10.3 ± 0.1), which is a concentration pK_a, is identical within experimental error to the spectral pK_a (10.34 ± 0.04), which is a mixed pK_a.

(22) The value used for σ^- for **1g** is twice the σ^- (σ) value for a single *m*-nitro substituent. If this compound is not included in the plot, the calculated ρ is 1.47 ± 0.04.

Table 2. Calculated Charge Distribution in the Anion of 2-Tetralone in Various Deuterated Solvent Mixtures

solvent	q_{Ph}[a]	q_{C-1}[b]	q_{C-2}[c]	q_O[d]
DMSO[e]	−0.14	−0.36	+ 0.12	−0.62
DMSO/D_2O (4:3)	−0.11	−0.33	+ 0.10	−0.66
MeOD/D_2O (3:1)	−0.08	−0.33	+ 0.09	−0.68
MeOD/D_2O (2:1)	−0.08	−0.33	+ 0.09	−0.68
MeOD/D_2O (1:1)	−0.08	−0.33	+ 0.09	−0.68

[a] Total excess charge in the phenyl ring compared to the neutral species. [b] Total excess charge on the enolate carbon compared to the neutral species. [c] Total excess charge on the carbonyl carbon compared to the neutral species. [d] Total excess charge on the enolate oxygen compared to the neutral species. [e] From data in ref 15.

A plausible explanation for the "enhanced" effect of a 6-nitro group on the acidity of **1** relative to the effect of a *p*-nitro group on the acidity of phenol (the σ^- defining reaction) is the lack of a stabilizing effect of the nitro group on the free acid of **1**. Thus, phenol itself, as well as the anion, is stabilized by resonance with a *p*-nitro substituent, attenuating the acid strengthening effect of this group. With **1**, on the other hand, there is no free electron pair on the α carbon, so that there appears to be a larger effect of resonance stabilization of the anion. Consistent with this explanation, the effect of a *p*-nitro group on the acidity of 2-indanone (3.4 pK_a units) and 2-tetralone (3.0 pK_a units) is greater than the effect on benzyl methyl ketone (2.3 pK_a units), which shows diminished resonance interaction with the phenyl ring in the anion relative to 2-indanone and 2-tetralone.

Distribution of Charge in the 2-Tetralone Anion. The charge distribution in delocalized π systems can be calculated using the empirical formula of Spiesecke and Schneider.[23] If there is no change in hybridization at a carbon upon ionization, the excess negative charge at that carbon atom in the anion (q) is given by the difference in chemical shifts of the neutral carbon (δ_n) and the anionic carbon (δ_-) in ppm divided by 160 ppm/electron (eq 5).[24,25] Thus, the total charge introduced on the phenyl ring upon ionization can be calculated as the sum of ($\delta_n - \delta_-$)/160 for each of the ring carbons (Table 2).[26] Since there is a change in hybridization at C-1 upon ionization, the chemical shift of the neutral carbon cannot be used in eq 5. An appropriate value of δ_n, however, can be obtained from a model system.[24,27] We[15] have previously used a modification of the method of Bradamante and Pagani[27] to calculate appropriate values for δ_n and to determine the charge distribution in the 2-tetralone anion in DMSO. Similar calculations give the charge density for the anion at C-1, the phenyl ring, and (by difference) the carbonyl group in d_6-DMSO:D_2O (4:3 v/v) and mixtures of CD_3OD and D_2O.[28] The distribution of charge in the carbonyl group between the carbon and the oxygen may be estimated from the observed chemical shift of this carbon in the anion and the predicted chemical shift for C-3 of the model compound 3-methoxy-1,2-dihydronaphthalene. A summary of the charges as a function of solvent is given in Table 2.

$$(\delta_n - \delta_-)/160 = q \qquad (5)$$

Although most of the charge density in all of the solvent systems examined is on the enolate oxygen, more charge is delocalized into the oxygen in partially aqueous solutions (−0.66 in DMSO/water and −0.68 in methanol/water) than in pure DMSO (−0.62). This effect is presumably due to the greater ability of the hydrogen bonding solvents (methanol and water) to solvate charge on the oxygen, a conclusion that is supported by the insensitivity of the charge distribution to the dielectric constant of the methanol/water mixtures. Similarly, the amount of charge delocalized into the phenyl ring is diminished in the partially aqueous solvents (−0.08 to −0.11) relative to pure DMSO (−0.14).[15]

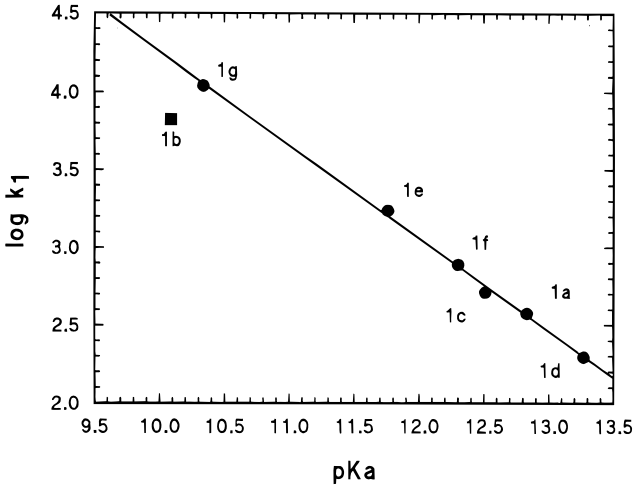


Figure 2. Plot of the rate constant for ionization of substituted 2-tetralones *vs* pK_a.

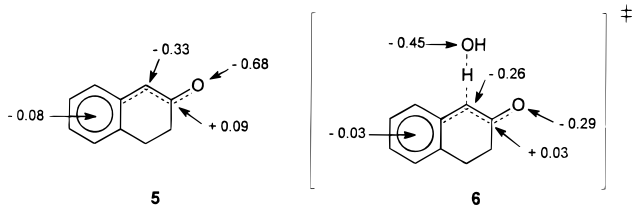
Nature of the Transition State for Proton Removal from 2-Tetralones by Hydroxide Ion. A Brønsted plot (log k vs pK_a) for proton abstraction by hydroxide ion is linear, except for the point corresponding to **1b**, with a slope ($-\alpha$) of −0.60 ± 0.01 (Figure 2). In contrast to the other substituents, the 6-nitro group of **1b** can directly delocalize charge through resonance. Thus, the negative deviation of **1b** from the correlation indicates that the resonance contribution of the phenyl ring to transition state stability is decreased relative to the inductive effect.

In order to determine the fraction of the resonance effect of the nitro substituent of **1b** that is expressed in the transition state, it is necessary to estimate a rate constant for a hypothetical 6-nitro-2-tetralone in which only the inductive effect operates. We use a σ value of 0.81 for *p*-nitro[29] to calculate a pK_a of 11.5 for this hypothetical acid from the correlation of Figure 1. From Figure 2, a rate constant for ionization of this acid can be obtained (log $k_{ind} = 3.36$), as well as the rate constant for **1b** if the entire resonance effect were operating (log $k_{pred} = 4.20$). A comparison of these rate constants with the observed rate constant for **1b** (log $k_{obs} = 3.82$) shows that about 55% of the expected resonance effect of the 6-nitro substituent is manifest in the transition state for ionization of **1b**.

We assume that the total amount of charge transferred into the incipient anion is equal to the fraction of p orbital formed (f_p), which is itself equal to the fraction of charge delocalized (55%).[30] Thus, the total amount of charge is equal to $-0.55 = q_{C-1} + q_{CO} + q_{ph}$, where q_{C-1} is the charge on the α carbon, q_{CO} is the charge on the carbonyl group and q_{ph} is the charge delocalized into the phenyl ring. The ratio q_{Ph}/q_{C-1} is equal to $0.55(q_{Ph}/q_{C-1})_o$, where $(q_{Ph}/q_{C-1})_o$ is equal to the ratio of charges in the fully formed anion. With the assumption that the extent

(23) Spiesecke, H.; Schneider, W. G. *Tetrahedron Lett.* **1961**, 468.
(24) (a) Bradamante, S.; Pagani, G.; *J. Chem. Soc., Perkin Trans. 2* **1986**, 1035. (b) House, H. O.; Prabu, A. V.; Phillips, W. V. *J. Org. Chem.* **1976**, *41*, 1209.
(25) Lambert, J. B.; Wharry, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5857.
(26) More precisely, it is the difference in charge at these carbons between the anion and the neutral species that is calculated.
(27) Bradamante, S.; Pagani, G. *J. Org. Chem.* **1984**, *49*, 2863.
(28) Small differences in chemical shifts of the aliphatic carbons are ignored in these calculations.
(29) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum, New York, 1978; p 201.
(30) Although the dependence of charge delocalization on the π-bond order is unknown, this approximation is not unreasonable.

Scheme 3



5 **6**

of delocalization of charge into the carbonyl group is proportional to the delocalization of charge into the phenyl ring,[31] the ratio q_{CO}/q_{C-1} is equal to $0.55(q_{CO}/q_{C-1})_o$. The charges on these three groups can then be calculated as $q_{C-1} = -0.26$, $q_{CO} = -0.26$, and $q_{Ph} = -0.03$. If the distribution of charge on the carbonyl carbon is the same as in the fully formed anion, the charge on the carbonyl carbon is $+0.03$ and the charge on the oxygen is -0.29. A summary of the charge distribution for the anion (**5**) and the transition state for deprotonation by hydroxide ion (**6**) is shown in Scheme 3.

It is of interest to speculate on the relevance of these observations to enzyme-catalyzed enolization reactions. A variety of enzymes catalyze enolizations of carbonyl compounds, including ketones, esters, and thioesters.[8,11b] In virtually all of these reactions, it has been postulated that the enzymatic rate acceleration is due in large part to stabilization of the transition state, either by hydrogen bonding[8,11b,32] or electrostatic effects.[11e] If, however, the transition state for the enzymatic enolizations resembles the one for hydroxide ion catalyzed enolization of 2-tetralone, then electrophilic assistance at the incipient enolate oxygen would be diminished relative to that expected for a balanced transition state. Thus, for a reaction in which total charge transfer is about 55%, the charge on the oxygen in the transition state is only -0.29, compared to a value of -0.37 that would be present had charge transfer been fully synchronous with bond cleavage. If, on the other hand, the transition state for deprotonation were later along the reaction coordinate, there would not only be a larger charge on the incipient anion at the transition state, but a larger fraction of this charge would be delocalized into the enolate oxygen and, consequently, hydrogen bonding at this oxygen would be more efficient.[33] Although late transition states for enzymatic enolizations have recently been postulated on the basis of a different rationale,[11b] there is little experimental evidence on this point.[34]

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Supporting Information Available: Table S1 giving the ^{1}H and ^{13}C chemical shifts for 2-tetralone and its anion and the charge distribution of the anion in DMSO/water and methanol/water mixtures (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(31) The rationale behind this assumption is that the ability to delocalize charge is dependent on the p-character of the orbital that is forming from the C−H bond that is being cleaved.

(32) Shan, S.-O., Herschlag, D. *Proc., Nat. Acad. Sci., U.S.A.* **1996**, *93*, 14474.

(33) It is also possible that much of the imbalance is caused by difficulties in solvent reorganization, which could be alleviated by an enzyme active site that has potential hydrogen bonding groups already in the optimum position for hydrogen bonding to the transition state (Ydav, A.; Jackson, R. M.; Holbrook, J. J.; Warshel, A. *J. Am. Chem. Soc.* **1991**, *113*, 4800).

(34) In work with 3-oxo-Δ^5-steroid isomerase, Holman and Benisek (Holman, C. M.; Benisek, W. F. *Biochemistry* **1994**, *33*, 2672) suggest, on the basis of modification of the active site base, that proton transfer is relatively far advanced at the transition state ($0.66 < \beta < 0.75$). However, their Brønsted plot is based on only two points, and is thus not definitive.