The Acidity of Benzyl Ketones in Aqueous Solution. Evaluation of the Intrinsic Acidifying Effect of a Phenyl Group

Angela M. Ross,[†] Dale L. Whalen,*[†] Sherif Eldin,[†] and Ralph M. Pollack*[‡,†]

Laboratory for Chemical Dynamics, Department of Chemistry, University of Maryland Baltimore County, Baltimore, Maryland 21228 Center for Advanced Research in Biotechnology 9600 Gudelsky Drive, Rockville, Maryland 20850

Received November 18, 1987

The determination of aqueous pK_a values for aldehydes and ketones has become a subject of much recent interest.[1] Since simple aldehydes and ketones generally have pK_a values of about 15–19,[1c–f] their acidities must be determined indirectly. We now wish to report the *direct* observation of the enolate ions of two substituted cyclic benzyl ketones (2-indanone and 2-tetralone) in aqueous solution. These two compounds are over 10^6-fold more acidic than simple aliphatic ketones and about 10^3-fold more acidic than an acyclic model benzyl methyl ketone.

When 2-indanone (1) is dissolved in moderately concentrated (ca. 0.01–1.0 M) hydroxide ion solutions, an intense (ϵ = 16 400 M^{-1} cm^{-1}) peak appears in the ultraviolet spectrum at 288 nm.[2] The high extinction coefficient and relatively long wavelength are consistent with the formation of the anion 1^- (eq 1). Titration

1. n = 1
2. n = 2

1^-. n = 1
2^-. n = 2
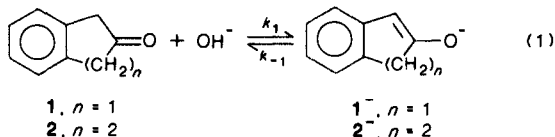
of this absorbance as a function of hydroxide ion concentration (10^{-7}–0.67 M, μ = 1.0, 25.0 °C, 4% MeOH) gives a value for the equilibrium constant of 39.0 ± 2.1 M^{-1}, which corresponds to a pK_a of 12.21 ± 0.03.[3] Similarly, 2-tetralone (2) exhibits a peak in basic solution at 300 nm (ϵ = 17 300 M^{-1} cm^{-1}), which can be assigned to its anion (2^-). Spectral titration of 2-tetralone gives a pK_a of 12.92 ± 0.02.

The rate of approach to equilibrium was measured by rapidly mixing 2-indanone with aqueous sodium hydroxide solutions (0.0025–0.03 M, μ = 0.1, 25.0 °C, 1% MeOH). A linear rela-

tionship between the observed rate constant and the hydroxide ion concentration (eq 2) allowed the determination of the rate

$$k^{obsd} = k_1[OH^-] + k_{-1} \qquad (2)$$

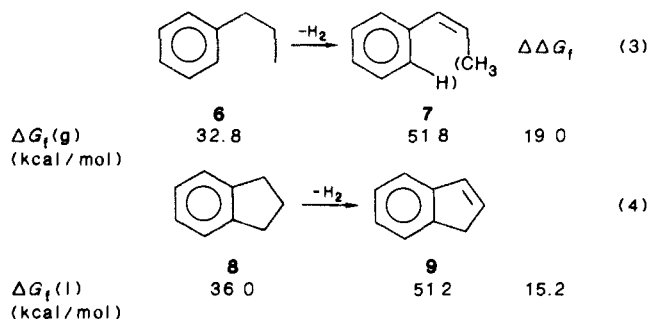constants for formation of the enolate ion (k_1 = 219 ± 3 M^{-1} s^{-1}) and reprotonation of the enolate ion by water (k_{-1} = 5.88 ± 0.05 s^{-1}). Division of k_1 by k_{-1} yields a value of K = 37.2 ± 0.7 M^{-1}, corresponding to a pK_a of 12.23 ± 0.01, in excellent agreement with the value obtained from spectral titration.

Both 1 and 2 are surprisingly acidic for simple ketones. Acetone (pK_a 19.16)[1d] is 10^7-fold less acidic that 2-indanone and more than 10^6-fold less acidic than 2-tetralone. However, benzyl methyl ketone (3, pK_a 15.9),[1b,4] an acyclic model for 2-indanone and 2-tetralone, is only about 10^3-fold more acidic than acetone.

In order to interpret the acidity difference between the cyclic benzyl ketones and benzyl methyl ketone, it is instructive to examine the steric interactions in both the starting ketones and the enolate ions. In the case of benzyl methyl ketone, there are several conformations with little steric interaction between the phenyl group and the rest of the molecule. Delocalization of the negative charge in the enolate requires that the anion be in either conformation 4 or 5, both of which have significant steric interactions between an ortho hydrogen of the phenyl ring and either the methyl group or the alkoxide oxygen.

4   5
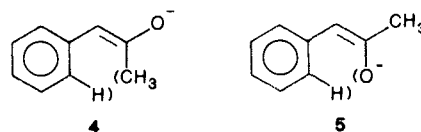
We expect conformation 4 to be preferred due to inhibition of solvation of the negatively charged oxygen in 5 by the ortho hydrogen. An estimate of the magnitude of the steric interaction of the methyl group and the ortho hydrogen in 4 can be obtained by comparing the difference in Gibbs energies of formation of 1-phenylpropane (6) and *cis*-1-phenylpropene (7) with the difference between indane (8) and indene (9) (eq 3 and 4).[5] The

	6	7	$\Delta\Delta G_f$ (3)
ΔG_f (g) (kcal/mol)	32.8	51 8	19 0

	8	9	(4)
ΔG_f (l) (kcal/mol)	36 0	51 2	15.2

energy cost of putting a double bond into 1-phenylpropane is ca. 3.8 kcal/mol higher than putting a double bond into indane.[7] Thus, benzyl methyl ketone should be ca. 2.8 pK_a units less acidic than 2-indanone, just on the basis of steric factors alone. These unfavorable steric interactions in the enolate of benzyl methyl

[†] University of Maryland.
[‡] Center for Advanced Research in Biotechnology.

(1) (a) Novak, M.; Loudon, G. M. *J. Org. Chem.* **1977**, *42*, 2494. (b) Guthrie, J. P. *Can. J. Chem.* **1979**, *57*, 1177. (c) Chiang, Y.; Kresge, A. J.; Walsh, P. A. *J. Am. Chem. Soc.* **1982**, *104*, 6122. (d) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460. (e) Chiang, Y.; Kresge, A. J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392. (f) Pruszynski, P.; Chiang, Y.; Kresge, A. J.; Schepp, N. P.; Walsh, P. A. *J. Phys. Chem.* **1986**, *90*, 3760. (g) Chiang, Y.; Kresge, A. J.; Walsh, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 6314. (h) Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, J.; Schepp, N. P. Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000. (i) Pollack, R. M.; Mack, J. P. G.; Eldin, S. *J. Am. Chem. Soc.* **1987**, *109*, 5048.

(2) In neutral solution the spectrum of 2-indanone shows peaks at 268 and 275 nm ($\epsilon \sim 1000$ M^{-1} cm^{-1}).

(3) This pK_a is a concentration equilibrium constant, based upon a value of 1.59 × 10^{14} M^2 for the ion product of water in solutions of ionic strength 0.1.[1d] Additional studies with 2-indanone in ionic strength = 0.1 show that the same value of K is obtained as in solutions of ionic strength = 1.0. Our pK_a value for 2-indanone agrees well with an independent measurement (12.20 ± 0.08) by Keeffe et al. (Keeffe, J. R.; Kresge, A. J.; Yin, Y., following paper in this issue).

(4) Benzyl methyl ketone gives no observable spectral change between pure water and 1.0 N sodium hydroxide solutions, consistent with Guthrie's[1b] previous estimate of pK_a 15.9.

(5) Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. *The Chemical Thermodynamics of Organic Compounds*; Wiley: New York, 1969. Although the Gibbs energies of formation for 6 and 7 are for the gas phase, while those for 8 and 9 are for the pure liquid, no significant error should result. The findings of Chickos et al.[6] suggest that the heat of vaporization should be nearly identical for indane and indene, since they have the same number of carbon atoms. Experimental values are 11.8 kcal/mol for indane and 12.6 kcal/mol for indene.[8]

(6) Chickos, J. S.; Hyman, A. S.; Ladon, L. H.; Liebman, J. F. *J. Org. Chem.* **1981**, *46*, 4294.

(7) This value is probably a lower limit since planarity in 4 or 5 is more important than in 7, due to a greater requirement for conjugation of the phenyl group with the negative charge in 4 and 5.

(8) Pedley, J. B.; Naylor, R. D.; Kirby, S. P. *Thermochemical Data of Organic Compounds*, 2nd ed.; Chapman and Hall: London, 1986.

ketone satisfactorily account for the major fraction of the difference of approximately 3.7 pK_a units between 2-indanone and benzyl methyl ketone and about 3.0 pK_a units between 2-tetralone and benzyl methyl ketone.

In conclusion, it appears that the intrinsic electronic effect of a phenyl group on the acidity of a ketone is approximately 10^6–10^7-fold. However, a reduced effect will normally be seen because of steric interactions in the enolate ion due to the necessity for the phenyl ring to remain in the same plane as the enolate system.

The Acidity of 2-Indanone. The Effect of a Conjugated Phenyl Group on Enolate Stability

J. R. Keeffe,*[‡] A. J. Kresge,*[†] and Y. Yin[†]

*Department of Chemistry, University of Toronto
Toronto, Ontario M5S 1A1, Canada*

Simple monofunctional ketones without heteroatom or pro-aromatic activators are generally only weak carbon acids.[1] We wish to report that 2-indanone, **1**, is a notable exception: it has pK_a = 12.2 in aqueous solution, which makes it 7 pK units more acidic than the simple non-benzolated analogue acetone, **2**.
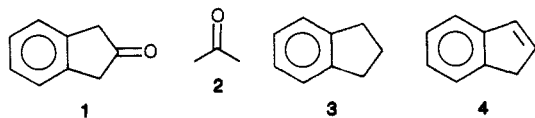
The ultraviolet spectrum of 2-indanone in acidic or neutral water is much like that of indane, **3**: the only prominent feature is an absorbance of moderate intensity at λ = 260–275 nm that is characteristic of the benzene ring. Addition of sodium hydroxide, however, produces a much stronger band with λ_{max} = 287 nm, which disappears upon reacidification of the solution. Indene, **4**, in aqueous solution has λ_{max} at 248 nm[2] and a shift of 40 nm upon substitution of O^- for H is consistent with known effects.[3] This suggests that the absorbance at λ = 287 nm is due to the enolate ion **5** formed by reaction of 2-indanone with hydroxide, eq 1.
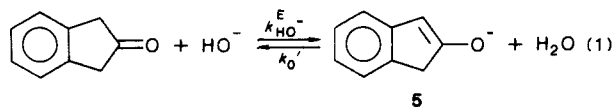
This hypothesis is confirmed by the fact that the intensity of this new absorbance depends upon hydroxide ion concentration in a way which describes a sigmoid titration curve, Figure 1.[4] At some of the acidities employed in gathering these data, enolate is partly protonated to give enol, and the scheme of eq 1 must be

[†]University of Toronto.
[‡]Permanent address: Department of Chemistry and Biochemistry, San Francisco State University, 1600 Holloway Avenue, San Francisco, CA 94132.
(1) Kresge, A. J. *CHEMTECH* **1986**, *16*, 250–254.
(2) Keeffe, J. R.; Fleischman, M. F., unpublished results. Fleischman, M. F. M.Sc. Thesis, San Francisco State University, 1969.
(3) Haspra, P.; Sutter, A.; Wirz, J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 617–619.
(4) 2-Indanone is not stable in basic solution, and quantitative measurements must be made promptly.
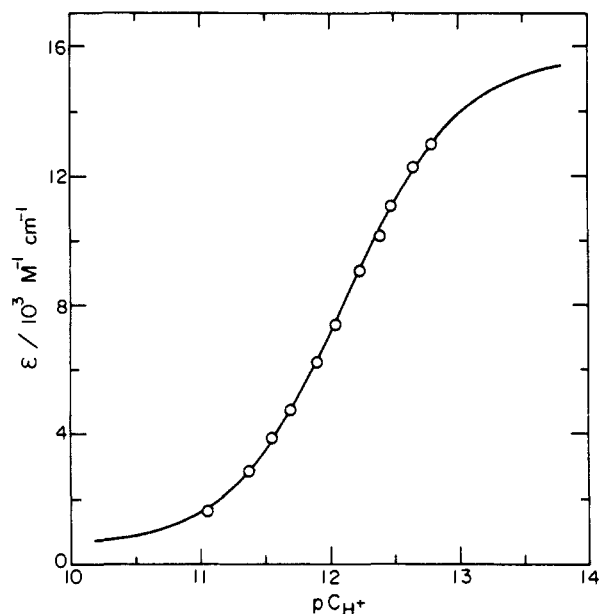

Figure 1. Titration curve for the reaction of 2-indanone with hydroxide ion in aqueous solution at 25 °C.

elaborated to include this species. Under these conditions, eq 2 applies; here ϵ_K, ϵ_E, and ϵ_{E^-} are the molar extinction coefficients

$$\epsilon_M = \frac{(\epsilon_E K_E + \epsilon_K) + \epsilon_{E^-}(K_a^K/K_w)[HO^-]}{1 + (K_a^K/K_w)[HO^-]} \quad (2)$$

of the keto, enol, and enolate forms of 2-indanone, ϵ_M is the molar extinction coefficient of the mixture being examined, K_E is the keto–enol equilibrium constant, K_a^K is the acid dissociation constant of 2-indanone ionizing as a carbon acid, and K_w is the autoprotolysis constant of water. Least-squares fitting of the data to this expression gave K_a^K = $(7.41 \pm 0.12) \times 10^{-13}$ M, pK_a = 12.13 $\pm$ 0.01,[5] ϵ_{E^-} = 15 700 $\pm$ 62 M^{-1} cm^{-1}, and $(\epsilon_E K_E + \epsilon_K)$ = 537 $\pm$ 41 M^{-1} cm^{-1}. The line shown in Figure 1 is drawn by using these parameters.

The rate of formation of enolate ion from 2-indanone in sodium hydroxide solutions, though rapid, may be measured by stopped-flow techniques. Rate constants determined under these conditions refer to the rate of approach to equilibrium and are the sum of specific rates for the forward ($k_{HO^-}^E$) and reverse (k_o') reactions, according to eq 3. This rate law was obeyed well:

$$k_{obsd} = k_{HO^-}^E[HO^-] + k_o' \quad (3)$$

observed rate constants were accurately first-order, as required, and showed a linear dependence upon hydroxide ion concentration. Least-squares analysis gave $k_{HO^-}^E$ = $(2.25 \pm 0.02) \times 10^2$ M^{-1} s^{-1} and k_o' = 6.95 $\pm$ 0.09 s^{-1}. These results may be combined to provide another estimate of the acid dissociation constant K_a^K = $(k_{HO^-}^E/k_o')K_w$ = $(5.15 \pm 0.08) \times 10^{-13}$ M, pK_a^K = 12.29 $\pm$ 0.01. This value is consistent with that obtained from the sigmoid titration curve;[7] the average of the two gives K_a^K = $(6.3 \pm 1.1) \times 10^{-13}$, pK_a^K = 12.20 $\pm$ 0.08, which is identical with pK_a^K = 12.18 obtained in a different laboratory.[8]

Comparison of this result with pK_a^K = 19.16 $\pm$ 0.02 for acetone[9] gives $\delta\Delta G$ = 9.5 $\pm$ 0.1 kcal mol^{-1} as the acid-strengthening effect

(5) Measurements were made at a constant ionic strength of 0.10 M, and this constant is therefore a *concentration quotient* appropriate to that ionic strength; K_w was assigned the value 1.59 × 10⁻¹⁴ M² by using activity coefficients for H⁺ and HO⁻ recommended by Bates.[6]
(6) Bates, R. G. *Determination of pH. Theory and Practice*; Wiley: New York, 1973; p 49.
(7) The difference between the two numbers is greater than the sum of the statistical precision indexes (standard deviations of mean values). This indicates the incursion of systematic errors, but the difference is still acceptably small.
(8) Ross, A. M.; Whalen, D. L.; Eldin, S.; Pollack, R. M. *J. Am. Chem. Soc.*, preceding paper in this issue.
(9) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460–462.