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.

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

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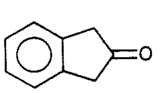
Simple monofunctional ketones without heteroatom or proaromatic activators are generally only weak carbon acids.[1] We wish to report that 2-indanone, **1**, is a notable exception: it has pK_a = 12.2 in aqueous solution, which makes it 7 pK units more acidic than the simple non-benzolated analogue acetone, **2**.



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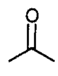

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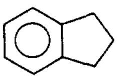

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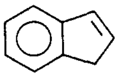

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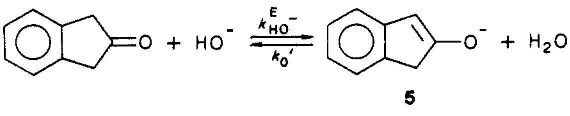
The ultraviolet spectrum of 2-indanone in acidic or neutral water is much like that of indane, **3**: the only prominent feature is an absorbance of moderate intensity at λ = 260–275 nm that is characteristic of the benzene ring. Addition of sodium hydroxide, however, produces a much stronger band with 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.



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

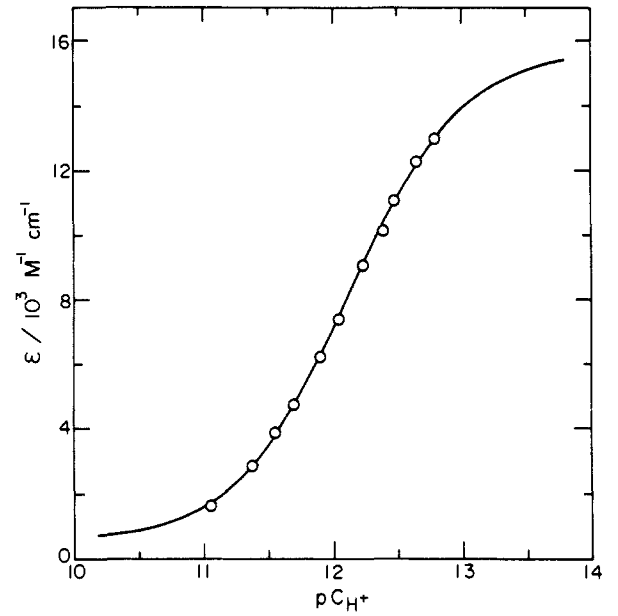


Figure 1. Titration curve for the reaction of 2-indanone with hydroxide ion in aqueous solution at 25 °C.

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

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 ± 0.01,[5] $\epsilon_{E^-} = 15\,700 \pm 62$ 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 ($k^E_{HO^-}$) and reverse (k_o') reactions, according to eq 3. This rate law was obeyed well:

$$k_{obsd} = k^E_{HO^-}[HO^-] + k_o' \qquad (3)$$

observed rate constants were accurately first-order, as required, and showed a linear dependence upon hydroxide ion concentration. Least-squares analysis gave $k^E_{HO^-} = (2.25 \pm 0.02) \times 10^2$ 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 $K_a^K = (k^E_{HO^-}/k_o')K_w = (5.15 \pm 0.08) \times 10^{-13}$ M, pK_a^K = 12.29 ± 0.01. This value is consistent with that obtained from the sigmoid titration curve;[7] the average of the two gives $K_a^K = (6.3 \pm 1.1) \times 10^{-13}$, p$K_a^K$ = 12.20 ± 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 ± 0.02 for acetone[9] gives $\delta\Delta G$ = 9.5 ± 0.1 kcal mol^{-1} as the acid-strengthening effect

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(2) Keeffe, J. R.; Fleischman, M. F., unpublished results. Fleischman, M. F. M.Sc. Thesis, San Francisco State University, 1969.

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(4) 2-Indanone is not stable in basic solution, and quantitative measurements must be made promptly.

(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} M^2 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.

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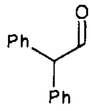
of the phenyl group on the ionization of 2-indanone. This effect must be due in large part to interactions in the enolate ion, inasmuch as the phenyl group is fairly well insulated from the carbonyl function in the ketone. Phenyl substituents are known to stabilize carbon-carbon double bonds, but the value assigned to this interaction, $D = 4.9$ kcal mol^{-1},[10] is much less than the substituent effect of 9.5 kcal mol^{-1} determined here. This suggests that there is an additional stabilizing effect in the present system produced by interaction of the phenyl and O$^-$ groups through the enolate double bond. A similar interaction, weakened by noncoplanarity, might be expected to operate in the acid ionization of diphenylacetaldehyde, **6**, and comparison of the pK_a of that substance (10.42)[11] with that of acetaldehyde, **7** (16.73),[12] gives $\delta\Delta G = 4.3$ kcal mol^{-1} as the effect per phenyl group. It is interesting in this connection that comparison of 9-formylfluorene, **8** (pK_a = 6.2),[13] where coplanarity is forced upon the system, with acetaldehyde gives $\delta\Delta G = 14.4$ kcal mol^{-1}: this is still short of twice the effect of the single ring in 2-indanone despite the fact that ionization of 9-formylfluorene generates a new aromatic ring.



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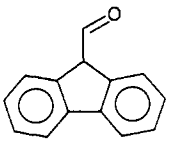

8

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council of Canada and by the donors of the Petroleum Research Fund, administered by the American Chemical Society. We are grateful to Professors Ralph M. Pollack and Dale L. Whalen for communicating the results of their work to us prior to publication and for helpful discussions.

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Molecular Recognition in Aqueous Media: Donor-Acceptor and Ion-Dipole Interactions Produce Tight Binding for Highly Soluble Guests

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Received October 19, 1987

Molecular recognition studies in aqueous media[2a] using synthetic receptors of the cyclophane type[2-6] have revealed two major binding forces.[7] The first is a hydrophobic effect, in which relatively water-insoluble guests associate with a hydrophobic cavity of the host.[2,3] Guests that can fit into the host binding site show trends in association constants (K_a) which correlate well with the water insolubility of the guest. Quite large values for K_a can be obtained with highly insoluble guests.[2] The second factor, generally seen in combination with the first, is an electrostatic effect in which, for example, cationic, water-solubilizing groups on the host come into close contact with anionic substructures in the guest. Studies in several host systems have shown that such direct electrostatic interactions can be quite favorable.[2-4]

Table I. Binding Parameters for P and C with Guests **1**-**9**

		host			
		P		C	
guest	solubility[a] (M)	$-\Delta G^{\circ}$ [b]	K (M^{-1})	$-\Delta G^{\circ}$ [b]	K (M^{-1})
1	0.078	5.4	10 000	5.9	22 000
2	0.023	5.5	11 000	5.8	20 000
3	0.014	6.2	38 000	6.0	30 000
4	0.037	6.3	47 000	6.3	46 000
5	0.030	6.4	55 000	6.7	100 000
6	0.016	4.2	1 400	4.3	1 600
7	0.0032	4.5	2 100	4.8	3 800
8	0.52	7.6	400 000	6.3	47 000
9	0.45	7.2	200 000	6.0	27 000

[a] Solubility of the guest determined in the operating buffer pD ≈ 9. [b] In kcal/mol at 295 K; values listed are accurate to ±200 cal/mol.

We demonstrate herein that donor/acceptor (D/A) π-stacking interactions[8,9] and ion-dipole attractions can also contribute significantly to aqueous binding.[9] Hosts P and C,[10] (Figure 1) were chosen as a pair with very similar binding site dimensions and comparable degrees of preorganization.[11] The rigid macrocyclic framework prevents the charged groups from achieving close contacts with encapsulated guest molecules. Certainly, any *differences* between P and C could not be ascribed to electrostatic effects. In fact, any such differences can confidently be ascribed to the different natures of the "linker" (⊗) group. If the hydrophobic effect is dominant, C should be the stronger binder, since cyclohexyl is generally considered to be more hydrophobic than phenyl.[2,4,12] On the other hand, P should be the better host

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