59.3 mg (0.344 mmol) of 85% *m*-chloroperbenzoic acid at 0 °C. After 10 min, the reaction mixture was warmed to room temperature, stirred for 3 h, and washed in turn with saturated $NaHSO_3$ solution, saturated $NaHCO_3$ solution, and brine. Following drying and solvent evaporation, the residue was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 67 mg (81%) of **24** as colorless prisms: mp 87-88 °C (from ether-hexanes); IR ($CHCl_3$, cm^{-1}) 2942, 1665, 1460, 1443, 1149, 1128, 1102, 1038; ^1H NMR (300 MHz, $CDCl_3$) δ 4.65 (dd, J = 6.7, 16.5 Hz, 2 H), 4.05-3.95 (m, 1 H), 3.36 (s, 3 H), 2.75-2.65 (m, 2 H), 2.65-2.60 (m, 2 H), 2.30-2.15 (m, 3 H), 2.10-1.85 (m, 3 H), 1.80-1.60 (m, 4 H), 1.60-1.45 (m, 4 H), 1.2-1.14 (m, 1 H), 1.06 (s, 6 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.85, 94.54, 72.99, 70.96, 61.44, 55.36, 51.64, 47.62, 45.43, 43.94, 42.16, 22.53, 26.28, 26.20, 25.63, 24.87, 23.98, 23.22, 19.98, 16.24; MS m/z (M^+) calcd 336.2300, obsd 336.2316; $[\alpha]^{20}_D$ -88.7° (c 0.56, $CHCl_3$).

X-ray Data Collection Structure Determination and Refinement for 24.[29-31] A transparent single crystal of **24** was mounted on a pin and transferred to the goniometer. The space group was determined to be acentric $P2_12_12_1$ from the systematic absences. A summary of data collection parameters is given in Table II (see supplementary material).

Least-squares refinement with isotropic thermal parameters led to R = 0.166. The geometrically constrained hydrogen atoms were placed in calculated positions 0.95 Å from the bonded carbon atom and allowed to ride on that atom with B fixed at 5.5 Å^2. The methyl hydrogen atoms were included as a rigid group with rotational freedom at the bonded carbon atom (C-H = 0.95 Å, B = 5.5 Å^2). High thermal motion was noted for the terminal methoxy group. However, disorder of this group could not be resolved. Refinement of non-hydrogen atoms with anisotropic temperature factors led to the final values of R = 0.081 and R_w = 0.082. The final values of the positional parameters are given in the supplementary material.

Epoxidation of 22c. A 280-mg (0.247-mmol) sample of **22c** was reacted with *m*-chloroperbenzoic acid (326 mg of 85%, 1.60 mmol) in phosphate-buffered dichloromethane (10 mL) as described previously. Chromatographic purification of the residue (silica gel, elution with 20% ethyl acetate in petroleum ether) afforded 166 mg (56%) of a 1:1.5 mixture of **24** and **25** as a colorless oil.

For **25**: IR ($CHCl_3$, cm^{-1}) 2937, 2893, 1686, 1467, 1447, 1389, 1374, 1347, 1330, 1152, 1131, 1103, 1047, 957; ^1H NMR (300 MHz, $CDCl_3$) δ 4.68 (s, 2 H), 3.80 (dt, J = 12.0, 4.1 Hz, 1 H), 3.37 (s, 3 H), 2.86 (dd, J = 1.5, 10.6 Hz, 1 H), 2.79 (d, J = 14.4 Hz, 1 H), 2.70-2.55 (m, 2 H), 2.55-2.49 (m, 2 H), 2.35-2.10 (m, 3 H), 2.10-1.85 (m, 3 H), 1.85-1.25 (m, 6 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.82, 95.31, 75.21, 70.89, 70.05, 62.25, 55.50, 54.76, 45.93, 44.89, 41.46, 32.14, 27.74, 27.39, 24.00, 23.09, 22.99, 21.47, 19.51, 19.30.

Kinetic Studies Involving 1 and 22b. Freshly chromatographed samples of **1** and **22b** (ca. 20 mg) were dissolved in C_6D_6 (1.2 mL) and placed in NMR tubes. A Bruker AM 300 NMR instrument equipped with automated acquisition programming was used for all of the kinetic studies. Percent composition of the two components in each case was determined at regular time intervals by relative integration of their vinyl proton absorptions. A minimum of 10-15 spectra were recorded for each kinetic run.

A nonlinear last-squares fit of the percent new atropisomer (B) versus time provided optimized values for the equilibrium distributions. Next, a linear least-squares fit of ln (% B_∞ - % B_t) versus time gave the overall rate constant k as the negative slope. These data, when taken in combination with K_{eq} provided the rate constants and activation energies for the forward and reverse reactions. Lastly, the kinetic data recorded at several temperatures made possible the construction of an Arrhenius plot from which the pertinent activation parameters could be extracted.

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Supplementary Material Available: Tables of X-ray crystal data, bond distances and angles, final fractional coordinates, and thermal parameters, as well as additional ORTEP diagrams for **11b**, **15**, and **24** (18 pages). Ordering information is given on any current masthead page.

Structural Effects on the Rates of Formation and the Stability of Enols of Cyclic Benzyl Ketones

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Abstract: The acid dissociation constants (K_a^K), the keto-enol equilibrium constants (K_E), and the rate constants for enolization of the cyclic benzyl ketones 2-indanone (**1a**), 2-tetralone (3,4-dihydro-2(1*H*)-naphthalenone, **1b**) and 2-benzosuberone (3,4-benzo-3-cyclohepten-1-one, **1c**) were measured in aqueous solution at 25 °C. The rate constants for ketonization of the enols and the acid dissociation constants (K_a^E) for the corresponding enols were also determined. The presence of a conjugating phenyl group provides sufficient stabilization of the negative charge to enable these ketones to ionize in the pH range. pK_a^K values were determined from the rate constants for ionization of the ketones and for ketonization of the enolate ions. These values were confirmed by spectral titration. The acidity of the ketones decreases with increasing size; pK_a^K values are 12.2 (**1a**), 12.9 (**1b**), and 14.9 (**1c**). Similarly, the acid dissociation constants of the enols decrease with increasing ring size; pK_a^E's are 8.3 (**2a**), 9.2 (**2b**), and 10.0 (**2c**). Equilibrium constants for enolization also vary with ring size; pK_E values are 3.8 (**1a**), 3.6 (**1b**), and 4.9 (**1c**).

A knowledge of the factors that control the rates and equilibria of proton transfers is fundamental for an understanding of reactivity in organic chemistry.[1] Particularly important is the effect of structure on the acidity of carbon acids. These acids cover an enormous range from the strongly acidic 1,2,3,4,5-pentacyanocyclopentadiene (pK_a -11)[2] to simple alkanes with pK_a's of ca. 55-70.[1] Although investigations leading to extensive tabulations of acidities of carbon acids in nonaqueous media have been carried out by several groups, notably those of Bordwell[3] and Streitwieser,[4]

(1) For an excellent recent monograph, see: Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic Press: New York, 1985.

(2) Webster, O. W. *J. Am. Chem. Soc.* **1966**, *88*, 3046.

(3) For recent reviews, see: (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 463.

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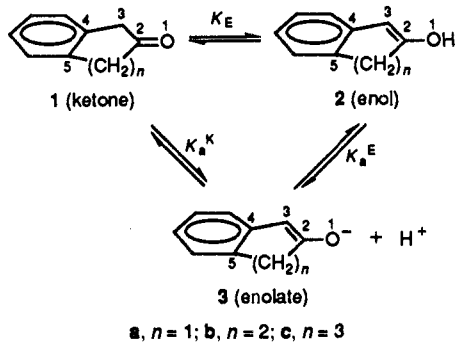
Scheme I



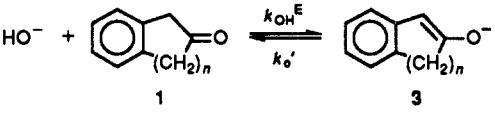
a, $n = 1$; **b**, $n = 2$; **c**, $n = 3$

much less data exist on aqueous pK_a values.

In the past decade, the development of techniques to obtain enols in greater than equilibrium concentrations has enabled the determination of aqueous pK_a values, as well as keto–enol equilibrium constants and enol acidities, for a variety of simple aldehydes and ketones.[5-7] We have been interested in the acid-strengthening effects of phenyl and vinyl substituents on protons adjacent to carbonyl groups.[8] The effect of a phenyl group in conjugation with the negative charge of the enolate ion in benzyl methyl ketone ($pK_a \sim 16$)[5j,9] relative to acetone (pK_a 19.2)[5b] is to increase the acidity by $\sim 10^3$-fold. Recently, however, we[8b] and Keeffe et al.[5i,j] found that the cyclic benzyl ketone 2-indanone is substantially more acidic (pK_a 12.2) than benzyl methyl ketone in aqueous solution. Similarly, 2-tetralone is more acidic than expected (pK_a 12.9).[8b] We report here the details of that study, including the rate constants for interconversion of the cyclic benzyl ketones 2-indanone (**1a**), 2-tetralone (**1b**), and 2-benzosuberone (**1c**) with their enols in aqueous solution, along with the acid dissociation constants of the ketones (pK_a^K) and the enols (pK_a^E) and the keto–enol equilibrium constants (pK_E) (Scheme I).

Results

pK_a^K Determinations. The cyclic benzyl ketones **1a–c** are sufficiently acidic to allow both kinetic and spectrophotometric determination of their pK_a^K's in the pH range in aqueous solution. The ultraviolet spectra of the un-ionized ketones at pH 7 show only weak absorbances with maxima at 268.5 nm (ϵ 950 M^{-1} cm^{-1}) and 275.5 nm (ϵ 910 M^{-1} cm^{-1}) for **1a**, 263 nm (ϵ 565 M^{-1} cm^{-1}) for **1b**, and 260.5 nm (ϵ 535 M^{-1} cm^{-1}) for **1c**. In 1.0 M sodium hydroxide solution, however, much more intense peaks due to the anions are observed at 288 nm (ϵ 16 400 M^{-1} cm^{-1}) for **1a**, 300 nm (ϵ 17 300 M^{-1} cm^{-1}) for **1b**, and 300 nm for **1c**. Since **1c** is not completely ionized in 1.0 M sodium hydroxide, it is impossible to directly determine the extinction coefficient of the anion. The large differences between the spectral characteristics of the ketones and their enolate ions permitted the measurements of the rates of formation of the enolate ions upon rapid mixing of solutions of the ketones and base (eq 1).



Benzyl ketones **1a–c** were mixed with sodium hydroxide solutions in a stopped-flow spectrophotometer at 25.0 °C to give final base concentrations of 1×10^{-3}–0.3 M (**1a**), 5×10^{-3}–0.1 M (**1b**), and 0.65–0.93 M (**1c**). The observed pseudo-first-order rate constants (k_{obsd}^E) for the approach to equilibrium were obtained by monitoring the rate of formation of the product anion at its λ_{max}. For a first-order approach to equilibrium, k_{obsd}^E is equal to the sum of the rate constants for the forward and reverse reactions. Under conditions where catalysis of the enolization by water is negligible and the enolate is not appreciably protonated to give the enol, the forward rate constant is $k_{OH}^E[OH^-]$, the reverse rate constant is k_0', and k_{obsd}^E is given by eq 2. Plots of

$$k_{obsd}^E = k_{OH}^E[OH^-] + k_0' \qquad (2)$$

k_{obsd}^E vs $[OH^-]$ are linear and give values of k_{OH}^E and k_0' (Table I). The acid ionization constants of the ketones (K_a^K) were calculated from the equilibrium constant for eq 1 ($k_{OH}^E/k_0' = [3]/[OH^-][1]$) and the autoprotolysis constant of water ($K_w = 1.62 \times 10^{-14}$ and 1.69×10^{-14} M^2 at $\mu = 0.1$ and 1.0, respectively).[10]

Spectral titration was also used to determine the acid dissociation constants of the ketones (Table I). The intensities of the absorbances in base are a function of the base concentration and the K_a^K values according to eq 3, where A is the absorbance at a given concentration of OH^-, A_∞ is the absorbance at infinite $[OH^-]$, and A_0 is the absorbance at $[OH^-] = 0$.

$$A = \frac{(A_\infty - A_0)(K_a^K/K_w)[OH^-]}{1 + (K_a^K/K_w)[OH^-]} + A_0 \qquad (3)$$

Values of the hydroxide concentrations and the corresponding absorbances were fitted to eq 3 by use of a nonlinear least-squares regression computer program to obtain the pK_a^K's for **1a** and **1b**. Since **1c** is only ionized to $\sim 10\%$ even in 1 M sodium hydroxide, the extinction coefficient of the anion could not be determined directly. Thus, a value similar to that for the anions of **1a** and **1b** (17 000 M^{-1} cm^{-1}) was used and the pK_a^K was estimated by least-squares fitting of the data.

Table I. Rate and Equilibrium Constants for the Ionization of 2-Indanone (**1a**), 2-Tetralone (**1b**), and 2-Benzosuberone (**1c**)

ketone	k_{OH}^E (M^{-1} s^{-1})	k_0' (M^{-1} s^{-1})	pK_a^K(kin)[a]	pK_a^K(titr)[b]
1a	216 ± 3[c]	5.92 ± 0.07[c]	12.33 ± 0.01[c]	12.21 ± 0.03[d]
	218 ± 8[e]	5.22 ± 0.10[e]	12.17 ± 0.02[4]e	12.15 ± 0.03[f]
				12.21 ± 0.03[g]
1b	376 ± 14[c]	39.5 ± 0.65[c]	12.81 ± 0.02[c]	12.99 ± 0.09[c]
				12.83 ± 0.01[f]
1c	3.7 ± 1.1[h]	49 ± 14[f]		14.90 ± 0.02[f]

[a] Measured kinetically. [b] Measured titrimetrically. [c] 1% methanol, μ = 0.1. [d] 5% methanol, μ = 0.1. [e] 0.5% methanol, μ = 0.1. [f] 1% methanol, μ = 1.0. [g] 2% methanol, μ = 1.0. [h] Calculated from k_0' and the titrimetric pK_a^K.

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(10) Harned, H. S.; Owens, B. B. *The Physical Chemistry of Electrolyte Solutions*, 3rd ed.; Reinhold: New York, 1958; p 752.

Table II. Rate and Equilibrium Constants for the Interconversion of **1**, **2**, and **3**[a]

reaction	catalyst	constant	2-indanone	2-tetralone	2-benzosuberone
1 → **3**	OH^-	k_{OH}^E, M^{-1} s^{-1}	216 ± 3	376 ± 14	3.67 ± 1.14
1 → **3**	H_2O	k_0^E, s^{-1}	(3.97 ± 0.14) × 10^{-5}	(6.47 ± 0.93) × 10^{-5}	(8.2 ± 1.3) × 10^{-6}
1 → **2**	H^+	k_H^E, M^{-1} s^{-1}	(3.51 ± 0.27) × 10^{-4}	(4.65 ± 0.37) × 10^{-3}	(1.15 ± 0.04) × 10^{-4}
3 → **1**	H_2O	k_0', s^{-1}	5.92 ± 0.07	39.5 ± 0.7	49 ± 14
3 → **1**	H^+	k_H', M^{-1} s^{-1}	(6.2 ± 1.0) × 10^7	(4.9 ± 1.2) × 10^8	(6.5 ± 1.1) × 10^9
2 → **1**	H^+	k_H^K, M^{-1} s^{-1}	2.88 ± 0.16	20.1 ± 0.6	8.54 ± 0.19
2 → **1**	H_2O	k_0^K, s^{-1}	0.198 ± 0.008	$<10^{-1}$	$\leq 10^{-1}$
2 → **1**	OAc^-	k_{OAc}^K, M^{-1} s^{-1}	42 ± 9	33 ± 4	
1 ⇌ **3** + H^+		K_a^K, M	(6.44 ± 0.28) × 10^{-13}	(1.33 ± 0.27) × 10^{-13}	(1.26 ± 0.04) × 10^{-15}
		pK_a^K	12.19 ± 0.03	12.88 ± 0.08	14.90 ± 0.02
2 ⇌ **3** + H^+		K_a^E, M	(5.3 ± 0.9) × 10^{-9}	(5.8 ± 1.3 × 10^{-10}	(9.3 ± 0.5) × 10^{-11}
		pK_a^E	8.28 ± 0.07	9.24 ± 0.09	10.03 ± 0.02
1 ⇌ **2**		K_E	(1.61 ± 0.39) × 10^{-4}	(2.31 ± 0.20) × 10^{-4}	(1.35 ± 0.06) × 10^{-5}
		pK_E	3.79 ± 0.12	3.64 ± 0.04	4.87 ± 0.02

[a] Rate and equilibrium constants are averages of measurements in 1%–5% aqueous methanol, with ionic strength of 0.1–1.0 (constant for each determination). Only slight variation was observed either with varying ionic strength or with varying methanol concentration. Equilibrium constants are concentration quotients.

Rates of Ketonization of the Enols. The benzyl ketones were mixed with sodium hydroxide solutions to give observable (in the UV) quantities of enolate ion. These solutions were then rapidly mixed in a stopped-flow spectrophotometer with buffer (acetate) or acid (H_3O^+) to generate the enol by rapid protonation on the enolate oxygen. The loss of absorbance of the enol was then monitored spectrophotometrically as tautomerization to the ketone proceeded. The observed ketonization rate constants (k_{obsd}^K) give a good fit to eq 4.

$$k_{obsd} = k_H^k[H^+] + k_0^k + k_{OAc}^k[OAc^-] \quad (4)$$

The acid term (k_H^k) and the water term (k_0^k) were determined in the absence of buffer by plotting the observed pseudo-first-order rate constants for ketonization against the hydrogen ion concentration (HCl), which ranged from 3.0 × 10^{-3} to 0.88 M for **1a**, 3.6 × 10^{-2} to 0.9 M for **1b**, and 0.042 to 0.820 M for **1c**. In the presence of acetate buffers, the observed rate constant is proportional to the concentration of the basic form of the buffer and is independent of the concentration of the acidic form. These rate constants are presented in Table II.

Acid-Catalyzed Enolizations. The rates of acid-catalyzed enolization of the ketones were measured by bromine scavenging of the enols as they formed. Zero-order bromination rate constants for 2-indanone were determined by monitoring the disappearance of Br_3^- at 266 nm in solutions of 1.0 × 10^{-3} M 2-indanone, 6.2 × 10^{-5} M Br_2, and 0.01–0.9 M HBr at 25.0 °C. The rates of decrease of absorbance with time were linear, and the decrease was monitored for the first 5% of the reaction to minimize contributions from bromination of 1-bromo-2-indanone. The observed rate constants for enolization are given by eq 5. The apparent acid-catalyzed rate constant (k_H^E) and water-catalyzed rate constant (k_0^E) determined by this method are (5.15 ± 0.15) × 10^{-4} M^{-1} s^{-1} and (4.57 ± 0.12) × 10^{-5} s^{-1}, respectively.

$$k_{obsd}^E = k_H^E[H^+] + k_0^E \quad (5)$$

In order to determine whether there is any significant contribution to the rate of loss of bromine from bromination of the initially formed 1-bromo-2-indanone, the rate constant for bromination of this species was determined in a similar manner. The first-order rate constant for the enolization of 1-bromo-2-indanone is 5.8 × 10^{-4} s^{-1} in solutions of HBr varying in acidity from 0.01 to 0.09 M. This value is about 10-fold larger than the observed rate constant for 2-indanone at 0.01 M HBr and greater than 5-fold larger than that at 0.09 M HBr. Thus, polybromination of 2-indanone is sufficiently facile to introduce uncertainty in the values of the enolization rate constants determined by bromine scavenging.

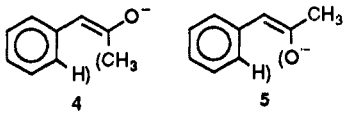
More reliable values for the rate constants of enolization of 2-indanone were determined by HPLC. The decrease in ketone concentration with time was monitored at 25.0 °C in HBr/Br_2 solutions at acid concentrations of 0.01 to ca. 0.09 M. The observed rate constants for **1a** measured by HPLC are somewhat lower (10–35%) than those obtained spectrophotometrically and are given in Table II. Similarly, enolization rate constants were determined by HPLC for **1b** (0.01–0.09 M HBr) and **1c** (0.14–0.86 M HBr) to eliminate any contribution of polybromination.

Discussion

Although the rate and equilibrium constants for **1b** and **1c** have not been determined previously, Keeffe et al.[5i,j] and Kwok[11] have independently determined most of these constants for **1a**. The only significant difference between our values and those previously reported is the rate constant for ketonization of the enol of 2-indanone catalyzed by water, given as 0.055 s^{-1} by Kwok,[11] 0.207 s^{-1} by Keeffe et al.,[5i,j] and 0.198 s^{-1} by us.

Acidity of Benzyl Ketones 1a–c. A comparison of the pK_a^K's of the cyclic benzyl ketones **1a–c** with the pK_a^K of acetone (pK_a^K 19.2)[5b] reveals that the effect of a phenyl group on acidity may be substantial (10^4–10^7-fold). In the case of acetone, the negative charge of the enolate is delocalized only onto a carbonyl group, whereas in **1a–c**, the negative charge is delocalized both onto a carbonyl oxygen and into a phenyl ring. Surprisingly, benzyl methyl ketone (pK_a^K ~16),[5j,9] which also has both a carbonyl group and a phenyl ring α to the acidic protons, is only 10^3-fold more acidic than acetone.

We[8b] have previously discussed the difference in acidity between 2-indanone (pK_a 12.2) and benzyl methyl ketone (pK_a 15.9) in terms of unfavorable steric interactions in the enolate of benzyl methyl ketone. It was assumed that conformation **4** of the enolate ion would be more stable than **5** in aqueous solution due to more favorable solvation of the negatively charged oxygen in **4**. The estimated[8b] steric interaction of the ortho hydrogen of the phenyl group and the methyl group in **4** can account for about 3.8 kcal/mol (=2.8 pK units) of the difference in acidity of **1a** and benzyl methyl ketone.



4 **5**

Molecular mechanics calculations by the PCMODEL PI program[12] also suggest that conformation **4** of the enolate is ca. 1 kcal/mol more stable than conformation **5**. Conformation **4** is predicted to be nonplanar with a phenyl ring double-bond torsional angle of 27°. Although a planar structure for the anion **4** of benzyl methyl ketone will allow maximum electron delocalization into the phenyl ring, this structure will also have the greatest steric interaction between the ortho hydrogen and the methyl group. Presumably, **4** adopts a conformation that balances these two

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(12) Molecular mechanics calculations were performed using PCMODEL PI Version 2, which uses MMX, an enhanced version of the MM2 and MMP programs (Serena Software, Box 3076, Bloomington, IN 47402-3076).

Table III. Results of Molecular Mechanics Calculations on the Enolate Ions of Some Benzyl Ketones[a]

	benzyl methyl ketone	2-benzo-suberone	2-tetra-lone	2-indanone
dihedral angle (O1-C2-C3-C4) (deg)	161	170	178	180
dihedral angle (C2-C3-C4-C5) (deg)	-27	-13	14	0
total twist (deg)	46	23	16	0

[a] Calculations performed on PCMODEL PI from Serena Software.

effects to allow as much electron delocalization as possible without having excessive steric strain.

2-Tetralone (pK_a 12.9) is also substantially more acidic than benzyl methyl ketone. With a statistical correction for the number of α-hydrogens, 2-tetralone is only 0.4 pK_a unit less acidic than 2-indanone. 2-Benzosuberone is consideraby less acidic than either 2-indanone or 2-tetralone, although still ca. 1 pK_a unit more acidic than benzyl methyl ketone. Molecular models suggest that there is significant strain in the enolate ion of 2-benzosuberone, possibly accounting for its lower acidity compared to 2-indanone and 2-tetralone. Molecular mechanics calculations of the strain energy of these benzyl ketones and their enolate ions qualitatively are consistent with this interpretation. The differences in the strain energies of the ketones and enolate ions of 2-indanone and 2-tetralone are calculated to be ca. 3–4 kcal/mol less than in the case of 2-benzosuberone. The increase in conformational strain when a benzyl ketone is deprotonated to give an enolate ion with optimal geometry for electron delocalization therefore appears to play a major role in determining the pK_a^K of the ketone.

The geometries calculated by PCMODEL PI for the enolate ions of **1a**–c and of benzyl methyl ketone are of considerable interest. Values for the dihedral angles O_1–C_2–C_3–C_4 and C_2–C_3–C_4–C_5 are summarized in Table III and reveal whether the enolate ion has a planar geometry or deviates from planarity. For maximum delocalization of the negative charge into the aromatic ring, the O_1–C_2–C_3–C_4 and C_2–C_3–C_4–C_5 dihedrals should be 180° and 0°, respectively. As these dihedrals deviate from the optimal values, π-overlap decreases and, consequently, stabilization of the anion by the phenyl group should decrease. The sum of the deviations of these two dihedrals from their optimal values is given as "total twist" in Table III and provides an estimate of the deviation of the calculated anion structure from planarity. From these values, it can be seen that the enolate ion of 2-indanone is predicted to be completely planar (no twist). This geometry allows maximum delocalization of negative charge into the aromatic ring, thus resulting in maximum stabilization of the enolate by the phenyl group. As the amount of twist calculated for the enolate ion increases, the pK_a of the corresponding ketone is observed to also increase. These calculations are thus consistent with the notion that the ability of the enolate ion of a benzyl ketone to achieve planarity is important in determining the extent to which the phenyl group increases the acidity of the ketone.

Enolization of the Ketones. The rates of enolization of the three ketones in acid, water, and base are in the order 2-tetralone > 2-indanone > 2-benzosuberone. It is significant that, although the rates of enolization of 2-tetralone are the greatest, the equilibrium enol content and the acidity of 2-indanone are higher than 2-tetralone. This dichotomy suggests that there are specific transition-state effects in enolization that are not manifest in either the reactant or the product.

Stereoelectronic considerations[13] may be used to rationalize the relative rates of enolization of **1a**–c. In order for the rate of proton abstraction to be maximized for enolization of a ketone, it is necessary that there be maximal overlap of the incipient p-orbital with the π-orbital of the C=O bond. This overlap is facilitated when the proton departs at a 90° angle to the plane of the C=O bond. Similarly, conjugation of the negative charge with the phenyl ring in the enolization of benzyl ketones is enhanced when the loss of the proton takes place perpendicular to the plane of the phenyl ring. In addition, the principle of least nuclear motion[14] predicts that this conformation is the most favorable for enolization.

Table IV. Selected Torsional Angles of **1a**–c[a]

	2-indanone	2-tetra-lone	2-benzo-suberone
dihedral angle (O1-C2-C3-H) (deg)	-63, 61	91, -27	140, 24
dihedral angle (C5-C4-C3-H) (deg)	118, -117	117, -124	58, 175

[a] Calculations performed on PCMODEL PI from Serena Software.

Molecular mechanics calculations (Table IV) indicate that one of the α-protons in the lowest energy conformation of 2-tetralone is favorably aligned with the carbonyl (91°) and only somewhat out of alignment with the phenyl ring (117°). Although the alignments of the two potential enolizing protons of 2-indanone with the phenyl ring are similar to that for 2-tetralone (118° or −117°), neither of these is well aligned with the carbonyl (−63°, 61°). In the case of 2-benzosuberone, orientation of the α-protons with both the carbonyl and the phenyl ring is less favorable, leading to slower enolization. Although the main factor that controls the equilibrium acidity of the ketones appears to be the ability of the negative charge to be delocalized in the enolate, the relative rates of enolate formation depend on the orientation of the hydrogen atom being abstracted.

The relative rates of ketonization of the enolate ions can also be correlated with the extent of charge delocalization in the anions. Delocalization of negative charge generally slows the rate of proton transfer to carbon.[15] Since charge delocalization is highest for the anion of 2-indanone and lowest for 2-benzosuberone anion, the rates of carbon protonation of the benzyl ketones in water (k_o') and in acid (k_H') are **3 > 2 > 1**.

Enol Content of the Ketones. The enol content of the cyclic benzyl ketones can be determined from the ratio of the ketonization rates to the enolization rates. In the case of 2-indanone, the K_E can be calculated from the ratios of these rate constants for catalysis by water (K_E 1.22×10^{-4}, pK_E 3.92) and by acid (K_E 2.00×10^{-4}, pK_E 3.70). Averaging these results gives K_E $(1.61 \pm 0.39) \times 10^{-4}$ and pK_E 3.79 ± 0.12. In the case of both 2-tetralone (pK_E 3.64) and 2-benzosuberone (pK_E 4.87), the water-catalyzed rate constants are too small to be determined reliably; thus, the pK_E's were only calculated from the ratios of the acid-catalyzed rate constants. All three ketones are substantially more enolized at equilibrium than the corresponding cyclic ketones without a conjugating phenyl: cyclopentanone (pK_E 7.94),[5f] cyclohexanone (pK_E 6.39),[5f] and cycloheptanone (pK_E 8.00).[5f] The effect of the added phenyl ring in **1a**–c is to increase the enol content 10^3–10^4-fold in all three systems.

Acidity of the Enols. The pK_a^E's can be calculated from a knowledge of the pK_a^K's and the pK_E's, since these are thermodynamically related (Scheme I). The pK_a^E values for the enols of 2-indanone, 2-tetralone, and 2-benzosuberone are 8.28, 9.24, and 10.03, respectively. Molecular mechanics calculations provide structures for the enols **2a**–c with phenyl–vinyl torsional angles (C2–C3–C4–C5) of 0°, 15°, and 20°, respectively. Thus, the acidity of the enols is greatest when this calculated torsional angle is close to 0° (2-indanone enol), providing a planar π-system. Such geometry allows maximum delocalization of negative charge into the phenyl ring upon ionization of the enol, with minimum conformational change. The substantially greater acidity of the enol of 2-indanone than those of 2-tetralone or 2-benzosuberone argues that the acidifying effect of the phenyl ring is primarily resonance, rather than inductive.

Effect of Phenyl Groups vs Double Bonds. The effect of the phenyl group of 2-tetralone (**1b**) can be compared with the corresponding effect of a double bond in 3-cyclohexenone (**7**) and

(13) For a recent review, see: Pollack, R. M. *Tetrahedron* **1989**, *45*, 4913.

(14) Tee, O. S.; Altmann, J. A.; Yates, K. *J. Am. Chem. Soc.* **1974**, *96*, 3141.

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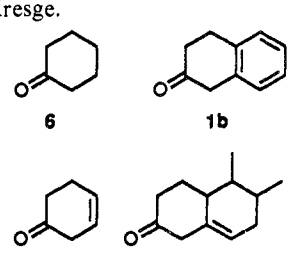
5-androstene-3,17-dione (**8**) on the enol content and the acidity relative to cyclohexanone (**6**). It is immediately clear that there is a relationship between the enol content and the acidities of the ketones. In fact, Keeffe and Kresge[16] have observed that there is a linear relationship between the pK_E and pK_a^K values for a variety of aldehydes and ketones with a slope of 1.4. Thus, the same factors are operative in the stabilization of enols and enolate ions, with a somewhat greater sensitivity of enolate ions to these effects. The following four ketones all fall on the regression line of Keeffe and Kresge.



6 **1b** **7** **8**

	6	**1b**	**7**	**8**
pK_E	6.4[5f]	3.6	5.3[8d]	2.7[17]
pK_a^k	18.1[5f]	12.9	15.2[8d]	12.7[8a,c]

The similar effects of a phenyl group and a double bond on the acidity and enol content of these ketones are not surprising. As shown by Liebman[18] and by George et al.,[19] on the basis of heats of formation of phenyl–X and vinyl–X, a phenyl group and a double bond are similar in their substituent effects on stabilities of neutral molecules. Hine's double-bond stabilization constants[20] suggest that the effect of a double bond should be comparable to or somewhat greater than the effect of a phenyl group on the equilibrium constant for the formation of the enols.

The effect of the phenyl group of **1b** on the acidity parallels the effect of the exocyclic double bond of **8** much more closely than it does the effect of the endocyclic double bond of **7**. Although there is some twisting about the two double bonds in the dienol of **7**, diminishing conjugation,[8d] the molecular mechanics calculations indicate that there is a similar twisting in the enol of **1b**, suggesting that the lower acidity of **7** is not due to this twisting. The effect of the phenyl group on the enol content is intermediate between that of the endocyclic double bond of **7** and the exocyclic double bond of **8**. Clearly, the exocyclic double bond, at least in this comparison, has a greater conjugative ability than the endocyclic double bond.

Experimental Section

Materials. All chemicals were reagent grade and were purchased commercially unless otherwise mentioned. All solutions were prepared with double-distilled water.

2-Indanone (1a). The compound was purchased from Aldrich (98%) and was recrystallized from 95% ethanol: mp 57 °C (lit.[21] 57–58 °C); ^{1}H NMR ($CDCl_3$) δ 7.19 (s, 4 H), 3.50 (s, 4 H). The compound showed only one spot on TLC (silica, 1:1 hexane/ethyl acetate) and one peak on HPLC (C_{18}, 40% methanol).

1-Bromo-2-indanone. The compound was prepared by bromination of 2-indanone[22] and was recrystallized from 95% ethanol (44%): mp 89–91 °C (lit.[22] mp 91 °C); ^{1}H NMR ($CHCl_3$) δ 7.3 (m, 4 H), 5.40 (s, 1 H), 3.65 (d, 2 H).

2-Tetralone (1b). The compound (99%, Aldrich) was distilled: $bp_{1.75}$ 100–115 °C; ^{1}H NMR ($CHCl_3$) δ 7.25 (m, 4 H), 3.60 (s, 2 H), 3.05 (t, 2 H), 2.55 (t, 2 H). Only one peak was observable upon analysis by HPLC (C_{18}, 25% acetonitrile).

2,3-Benzo-2-cyclohepten-1-ol. 1-Benzosuberone (Aldrich; 5.3 g, 33 mmol) was reduced in ethanol by the slow addition of $NaBH_4$ (2.5 g, 66 mmol), followed by stirring at room temperature for 45 min. The reaction mixture was worked up by the addition of 150 mL of distilled water and extraction with ethyl acetate. After the solution was dried with anhydrous magnesium sulfate, the solvent was evaporated to give the product in 96% yield (5.13 g, 32 mmol). This compound was used directly in the next step.

1,2-Benzo-1,3-cycloheptadiene.[23] 2,3-Benzo-2-cyclohepten-1-ol (5.13 g, 32 mmol) was dehydrated in benzene solution (150 mL) by the addition of *p*-toluenesulfonic acid (45 mg), followed by azeotropic removal of water. After 24-h reflux, the reaction was worked up by the addition of 100 mL of 5% aqueous sodium bicarbonate solution, followed by extraction with ether. Drying with magnesium sulfate and removal of the solvent gave 4.1 g (28 mmol, 90%) of 1,2-benzo-1,3-cycloheptadiene: ^{1}H NMR ($CHCl_3$) δ 7.15 (m, 4 H), 6.40 (d, 1 H), 5.9 (m, 1 H), 2.85 (t, 2 H), 2.40 (m, 2 H), 1.99 (m, 2 H).

3,4-Benzo-1,2-epoxy-1,3-cycloheptadiene.[24] *m*-Chloroperbenzoic acid (1.3 g, 7.6 mmol) was added to 1,2-benzo-1,3-cycloheptadiene (1 g, 6.9 mmol) in 20 mL of methylene chloride, and the mixture was stirred at 0 °C for 3 h. The reaction mixture was worked up by diluting it with 20 mL of cold methylene chloride followed by 40 mL of distilled water and extraction with ethyl acetate. The organic phase was washed with sodium carbonate solution and dried with anhydrous magnesium sulfate. The solvent was evaporated and the epoxide distilled at reduced pressure to give 0.8 g (5 mmol, 71% yield) of product, showing one spot on TLC (silica): ^{1}H NMR ($CHCl_3$) δ 7.2 (m, 4 H), 4.01 (d, 1 H), 3.4 (m, 1 H), 2.80 (m, 2 H), 2.3–1.6 (br m, 4 H).

3,4-Benzo-3-cyclohepten-1-ol. 3,4-Benzo-1,2-epoxy-1,3-cycloheptadiene (300 mg, 1.9 mmol) was reduced by dropwise addition in 1 mL of ether to $LiAlH_4$ (42 mg, 1.1 mmol) in anhydrous ether (4 mL) at 0 °C. The reaction mixture was quenched with saturated sodium chloride after 2.5 h of stirring in an ice bath. After filtration and being washed with 1 N HCl and saturated NaCl, the solution was extracted with ethyl acetate and dried (magnesium sulfate), and the solvent was evaporated. Removal of the solvent gave 275 mg (1.7 mmol, 89%) of a solid that was recrystallized from hexane: mp 71 °C (lit.[25] mp 71 °C).

2-Benzosuberone (1c).[24] 1-Benzocyclohepten-4-ol (250 mg, 1.5 mmol) was oxidized in acetone (3 mL) with Jones reagent (CrO_3/H_2SO_4, 2 mmol) with stirring at room temperature for 2 h. The mixture was worked up by the addition of 20 mL of distilled water, extraction with ether, drying (magnesium sulfate), and evaporation of the ether to give 208 mg (1.3 mmol, 87%) of the crude product. Column chromatography (silica, hexane/ethyl acetate (5:1)) followed by distillation under reduced pressure gave a colorless oil that showed only one peak when analyzed by HPLC (C_{18}, 50% methanol): ^{1}H NMR ($CHCl_3$) δ 7.17 (s, 4 H), 3.73 (s, 2 H), 2.88 (t, 2H), 2.57 (t, 2 H), 2.05 (m, 2 H).

Kinetic Measurements. All kinetic measurements were performed at 25.0 ± 0.1 °C and constant ionic strength. Solutions were degassed with argon to minimize oxidation when the enolate ions were formed. Stock solutions of the ketones were stored in the dark at 0 °C and the solutions discarded if decomposition had occurred, as manifested either by the appearance of color by a change in the ultraviolet spectrum. Routine kinetic measurements were performed on a Gilford Response spectrophotometer interfaced to an IBM-compatible personal computer for data analysis. Analysis of faster runs was facilitated by the use of a HiTech SFA-11 rapid-mixing device interfaced to the spectrophotometer, enabling reactions to be monitored with half-lives on the order of 50 ms. Alternatively, a HiTech QP/SF 53 stopped-flow spectrophotometer was used for the determination of rates with half-lives of ≥10 ms and for sequential mixing stopped-flow studies. These sequential mixing experiments were performed by rapidly mixing a solution of ketone in one syringe of the stopped-flow spectrophotometer with a sodium hydroxide solution in a second syringe. After a delay sufficient to produce the enolate ion, this solution was rapidly mixed with a third solution containing either acid or buffer to produce a solution of enol at the desired pH, and the decay of absorbance was monitored. pH measurements were made with a Radiometer PHM85 pH meter. Acid-catalyzed enolizations were monitored with use of a Waters HPLC with a μBondapak (3.9 × 300 mm) C_{18} column. The kinetic data were fit to the integrated form of the first-order rate equation by least-squares fitting.

Kinetic Measurements of pK_a^K's. Rates of reaction were monitored at 288 nm (**1a**) or 300 nm (**1b,c**) by rapidly mixing solutions of the ketone (2×10^{-4} M for **1a,b**; 3×10^{-5} M for **1c**) in water (2% methanol) with

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sodium hydroxide solutions in a 1:1 ratio. The data showed good fits to pseudo-first-order kinetics.

Spectral Measurements of pK_a^K's. A 10-20-μL portion of a stock solution of the ketone in methanol (ca. 1×10^{-2} M) was added to 2.0 mL of a sodium hydroxide solution (0.001-0.66 M for **1a**; 0.01-0.075 M for **1b**; 0.15-1.0 M for **1c**) at constant ionic strength. The absorbances (288 nm for **1a**; 300 nm for **1b,c**) were extrapolated to zero time, and the pK_a^K's were calculated from eq 3.

Ketonization of the Enols. The enol of 2-indanone was prepared under argon by mixing a 0.50 M solution of 2-indanone in methanol with a solution of sodium hydroxide (0.1 M, 2% methanol) in a 1:100 ratio. This solution was filtered through a micro-filtering disk and then mixed in a 1:50 ratio with acid (HCl) or buffer (acetate) with use of a HiTech SF-11 rapid-mixing apparatus and a Gilford Response spectrophotometer. The enols of 2-tetralone and 2-benzosuberone were prepared in a HiTech QP/SF stopped-flow apparatus. A methanol/water solution of ketone (2.2×10^{-3} M for **1b**; 1.2×10^{-3} M for **1c**) was mixed in a 1:1 ratio with sodium hydroxide (0.1 M for **1b**; 2.07 M for **1c**) by use of two syringes of the stopped-flow apparatus. After a delay of a few seconds to allow for formation of the enolate ion, this solution was rapidly mixed with a solution of acid or buffer. The decay in absorbance was monitored at 265 nm.

Acid-Catalyzed Enolization. The acid-catalyzed enolization of 2-indanone was monitored by adding 5.0 μL of an aqueous bromine solution (6.5×10^{-3} M) with a glass capillary to a solution of ca. 10^{-3} M 2-indanone in HBr (0.01-0.09 M) and NaBr (μ = 0.1 or 1.0). Extinction coefficients for the Br_2/HBr solutions were measured for each concentration of HBr. The decrease in absorbance was monitored at both 266 and 310 nm for approximately the first 5% disappearance of 2-indanone. The exact concentration of 2-indanone was determined spectrally before the addition of the bromine solution.

Enolization rate constants for **1a,b,c** were determined by HPLC monitoring the loss of ketone in aqueous HBr/Br_2 solutions with 0.1-3% acetonitrile as cosolvent. A saturated solution of bromine in water (600 μL to 2.0 mL) was added to 50 mL of an aqueous solution of HBr (0.01-0.10 N, μ = 0.1 for **1a**; 0.01-0.07 N, μ = 0.1 for **1b**; 0.14-0.86 N, μ = 1.0 for **1c**), followed by the addition of 50 μL of a 0.4-0.7 M solution of the ketone in acetonitrile. Aliquots of 2 mL of the reaction solution were taken at various time intervals (to 90% completion) and quenched with 3 mL of an aqueous solution of sodium thiosulfate (3.6-8.6 mM) and sodium acetate (0.1 or 1.0 M). 90-150-μL portion of the quenched mixture was injected into the HPLC, and the disappearance of ketone was monitored at 268 (**1a**) or 264 nm (**1b,c**) by use of a C_{18} column and 40% methanol (**1a**), 25% acetonitrile (**1b**), or 50% methanol (**1c**) as the eluting solvent.

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Molecular Recognition and Stereoselectivity: Geometrical Requirements for the Multiple Hydrogen-Bonding Interaction of Diols with a Multidentate Polyhydroxy Macrocycle[1]

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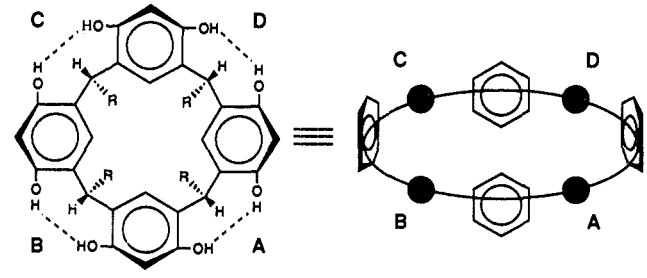
Abstract: Resorsinol-dodecanal cyclotetramer **1** in $CDCl_3$ forms hydrogen-bonded, 1/1 complexes with cyclohexanediols as well as with 2,4-pentane- and 2,5-hexanediol as their open-chain analogues and cyclohexanol and *cis*- and *trans*-4-*tert*-butylcyclohexanol. The affinities to **1** of cyclic diols (K = (1.1-10) $\times 10^2$ M^{-1} at 25 °C) are significantly larger than those of open-chain diols (36-43 M^{-1}) and monools (8-11 M^{-1}). Those of regio- and stereoisomers of cyclohexanediol depend on the configuration (axial-equatorial > diequatorial) and relative positions (1,4 ≫ 1,2 > 1,3) of the two OH groups involved and decrease in the order cis-1,4 ($K = 1.04 \times 10^3$) > cis-1,2 (2.64×10^2) > trans-1,3 (1.81×10^2) > trans-1,4 (1.29×10^2) > cis-1,3 (1.24×10^2) > trans-1,2 (1.06×10^2 M^{-1}); the stereoselectivities are thus cis-1,4/trans-1,4 = 8.0, cis-1,2/trans-1,2 = 2.5, and trans-1,3/cis-1,3 = 1.5. The selectivities in the diol binding are discussed in terms of multiple hydrogen bonding of diol and **1**. The relatively large binding constant (K) for *cis*-1,4-diol with one axial and one equatorial OH group is attributed to an effective and simultaneous two-point hydrogen bonding of the two OH groups with two adjacent binding sites of **1** as a multidentate host.

The recent several years have seen a rather explosive development in molecular recognition based on hydrogen bonding.[3-7] Much work has been concerned with the preorganized or oriented multipoint hydrogen-bonding fixation of *two-dimensional* and flat heteroaromatic guests such as nucleobases and related nitrogen heterocycles.[6] Many other biorelevant molecules including sugars, steroids, alkaloids, and so on also have rigid and cyclic structures, but they are *three-dimensional*, giving rise to not only two-dimensional regiochemical but also three-dimensional stereochemical problems.

Resorcinol-dodecanal cyclotetramer **1** is what may be called a tetradentate host having four independent binding sites (A-D) composed of a pair of hydrogen-bonded OH groups on adjacent benzene rings. It is capable of selective *extraction* of sugars from water into CCl_4.[7] A better understanding of the phenomenologically interesting selectivities observed, however, is hindered



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