J. Org. Chem. **1990**, *55*, 1019–1023

and 37.34 kcal mol^{-1} at MP2/6-31G*. The barrier for the reaction of H_3NO and PH_3 is 28.31 kcal mol^{-1} at HF/6-31G*//HF/6-31G* and increases by only 2.01 kcal mol^{-1} with the inclusion of diffuse functions.

We conclude that nucleophilic displacement at the oxygen in an *N*-oxide will proceed via an S_N2 pathway, whether the nucleophile is nitrogen or phosphorus based. Nitrogen nucleophiles will attack in a linear approach, while phosphorus nucleophiles are predicted to attack at a slightly askew angle, though not at a small enough angle to allow for intramolecular S_N2 substitution via a 5- or 6-membered ring TS. This difference can be explained in terms of the difference in the nature of the LUMOs of the nucleophiles. Finally, nucleophilic substitution at the oxygen of an *N*-oxide proceeds by a mechanism different than in reaction 1, where the proposed mechanism[5] for displacement at the oxygen of an hydroxylamine involves an addition step. Further investigations of displacement reactions at oxygen are underway and will be reported in due course.

Acknowledgment. I thank Dr. Peter Beak for suggesting the problem and providing helpful comments and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support.

Supplementary Material Available: Z-Matrices, as used in GAUSSIAN-86, and energies for all structures reported (8 pages). Ordering information is given on any current masthead page.

Kinetics of the Acetate Ion Catalyzed Ketonization of 1,3-Cyclohexadienol: Equilibrium Constants for the Enolization of 2- and 3-Cyclohexenone

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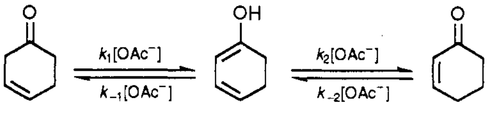
The conjugated enol 1,3-cyclohexadienol (**2**) has been generated in aqueous solution by the acid phosphatase catalyzed hydrolysis of 1,3-cyclohexadienyl phosphate. In acetate buffers (pH 4.2–5.1), **2** ketonizes almost exclusively to the unconjugated ketone 3-cyclohexenone (**1**), rather than the conjugated ketone 2-cyclohexenone (**3**). The rate constants for acetate-catalyzed ketonization of **2** ($k^{OAc} = 16.3 \pm 1.5\ M^{-1}\ s^{-1}$) and for acetate ion catalyzed deuterium exchange of the C-2 hydrogen of **1** ($k_{ex}^{OAc} = (9.3 \pm 1.5) \times 10^{-5}\ M^{-1}\ s^{-1}$) were utilized, along with extrapolated literature data on the general base catalyzed isomerization of **1** → **3**, to calculate all of the microscopic rate constants for the isomerization of **1** → **3**. These rate constants provide values for the keto–enol equilibrium constants for 3-cyclohexenone ($pK_E = 5.3$) and 2-cyclohexenone ($pK_E = 7.7$).

Introduction

The properties of enols of aldehydes and ketones in both the gas phase[1] and solution phase[2] have intrigued chemists for a long time. Although enols of monofunctional aldehydes and ketones are generally unstable (both thermodynamically and kinetically) in aqueous solution and they rapidly revert back to the carbonyl compounds, Kresge,[2a] Capon,[2b] and their co-workers have developed methods to generate solutions of these enols in greater than equilibrium concentration and to investigate their rates of ketonization. This work has been instrumental in elucidating the properties of simple enols and has provided rate constants for ketonization, keto–enol equilibrium constants, and pK_a's for both enols and ketones. In a complementary study, Rappoport's group[2c] has examined the keto–enol equilibria of a variety of sterically hindered, polyaryl-substituted, stable enols.

In our laboratory,[3] we have been interested in the properties of conjugated dienols and dienolate ions as intermediates in the isomerization of β,γ-unsaturated ketones to their α,β-unsaturated isomers (eq 1), both in the absence and the presence of the enzyme steroid isomerase.[4] Although dienols have often been generated and observed,[5] it is only recently that their rates of ketonization have been determined in aqueous solution.[3,4b,6] We report here the generation of 1,3-cyclohexadienol and its rate of ketonization in acetate buffer to a mixture consisting of predominantly 3-cyclohexenone (**1**) with minor amounts of 2-cyclohexenone (**3**). These results, in combination with the rates of exchange of the 2-hydrogens of **1** and literature data on the isomerization of **1** → **3**, allow the determination of all the microscopic rate constants for the isomerization of **1** → **3** and the keto–enol equilibrium constants for both **1** ⇌ **2** and **3** ⇌ **2**. In addition, we are able to estimate the



1 **2** **3** (1)

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(5) (a) Schmidt, E. A.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1972**, *94*, 7832. (b) Noyori, R.; Inoue, H.; Katô, M. *J. Am. Chem. Soc.* **1970**, *92*, 6699. (c) Noyori, R.; Inoue, H.; Katô, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3673. (d) Turecek, F.; Havlas, Z. *J. Org. Chem.* **1986**, *51*, 4066.

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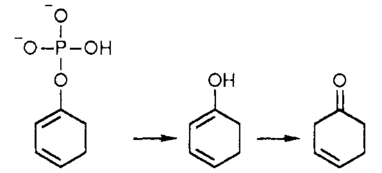
Table I. Rate Constants for Ketonization of 1,3-Cyclohexadienol

pH	k^{OAc}, M^{-1} s^{-1}	k^{H_2O}, s^{-1}
4.21	12.4 ± 3.0	0.164 ± 0.016
4.65	19.2 ± 1.5	0.130 ± 0.006
5.11	16.7 ± 1.7	0.146 ± 0.007

carbon pK_as of **1** (C-2) and **3** (C-4) in aqueous solution.

Results

1,3-Cyclohexadienol (**2**) was generated in situ by treating the bis(cyclohexylammonium) salt of 1,3-cyclohexadienyl phosphate (**2P**) with sweet potato acid phosphatase.[7] Addition of moderate quantities of sweet potato acid phosphatase (0.5–1 mg/mL in the final solution) to **2P** in acetate buffers (pH ca. 4–5) resulted in a first-order decrease in absorbance at 265 nm, with a definite induction period. The final product showed no appreciable absorbance above 220 nm, consistent with protonation of the dienol at C-2 to give 3-cyclohexenone, rather than at C-4 to give 2-cyclohexenone. This type of decay is characteristic of a series reaction **2P** → **2** → **1** (eq 2) that can be analyzed in terms of a double exponential for two pseudo-first-order reactions. Alternatively, the data can be analyzed by ignoring the initial portion of the reaction and fitting the absorbances at long times to a first-order kinetic equation. Although we were able fit the data for **2** → **2P** → **1** in deuterium oxide to a double exponential,[3a] analysis of the results in water by this method gives nonrandom deviations from the calculated line, probably due to non-first-order behavior in the first reaction. Thus, high concentrations of phosphatase (ca. 1 mg/mL) were used to make the phosphate cleavage rapid with respect to the subsequent ketonization of the dienol, and the last half of the curve was fit to a single exponential equation.



2P **2** **1** (2)

In sequential reactions of this type, the observed first-order rate constant may, in principle, be either the rate constant for **2P** → **2** or **2** → **1**.[8] To verify that the measured rate constant is that for the ketonization of **2**, the rate constant was determined at several concentrations of acid phosphatase and of acetate buffer. At low concentration of acetate (1–10 mM), the observed rate constant is proportional to buffer concentration and invariant with changes in phosphatase concentration. At higher buffer concentrations, however, where the ketonization should be rapid, an increase in phosphatase concentration does cause an increase in the observed rate constant.

First-order rate constants for ketonization at acetate concentrations of 1–10 mM and pH values of 4.21, 4.65, and 5.11 (μ = 0.1, $NaClO_4$) are proportional to the concentration of acetate ion and independent of the concentration of acetic acid. Plots of k^{obsd} vs [acetate] give the second-order rate constants for acetate ion catalyzed ketonization at each pH (Table I). A composite plot of all observed rate constants vs the concentration of acetate anion (Figure 1) gives the rate constant for catalysis by acetate ion (k^{OAc} = 16.6 ± 1.5 M^{-1} s^{-1}). This value may be compared to the acetate-catalyzed rate constant for ketonization of **2** in deuterium oxide[3a] to give an isotope effect ($k_{H_2O}{}^{OAc}/k_{D_2O}{}^{OAc}$) of 4.6 ± 0.5. The rate constants for the solvent-catalyzed ketonization are obtained from the intercepts of these plots and are invariant with pH in this pH range (k^{H_2O} = 0.15 ± 0.02 s^{-1}), giving a solvent isotope effect (k^{H_2O}/k^{D_2O}) for the uncatalyzed reaction of 10.3 ± 1.5.

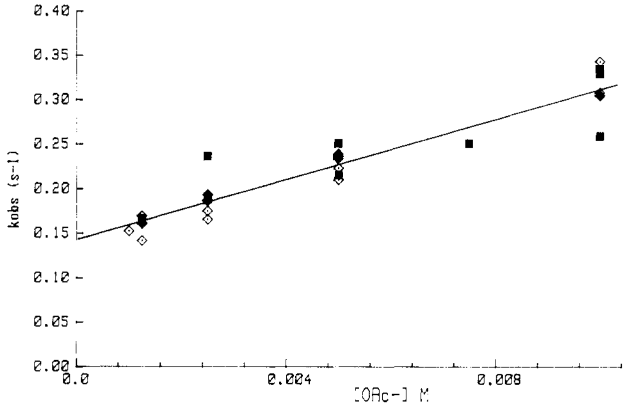


Figure 1. Observed pseudo-first-order rate constants for the ketonization of 1,3-cyclohexadienol. (■) pH 4.21; (◇) pH 4.65; (◆) pH 5.11.

The rate of exchange of the C-2 hydrogens of 3-cyclohexenone (**1**) in deuterium oxide solutions of acetate buffer (pD 5.15) was monitored by ^1H NMR spectroscopy. The ^1H NMR spectrum of 3-cyclohexenone shows signals at δ 2.5 (m, 4 H), 2.9 (m, 2 H), 5.75 (m, 1 H), and 5.9 (m, 1 H) ppm, with splitting patterns that are not cleanly resolved even at 500 MHz. Exchange was observed for the hydrogens at 2.9 ppm but not for those at 2.5 ppm. The exchangeable peaks were assigned to the C-2 hydrogens on the basis of the following reasoning. Calculations based upon the deshielding effect of the vinyl and carbonyl groups give predicted values of δ 3.05 ppm for the C-2 hydrogens, 2.35 ppm for the C-6 hydrogens, and 2.26 ppm for the C-5 hydrogens,[9] allowing the 2.9 ppm signal to be assigned to the C-2 hydrogens. Confirmation of this assignment was obtained in a 500-MHz COSY spectrum, which showed a substantial cross peak for the 2.9 ppm hydrogens and one of the vinyl hydrogens (5.9 ppm), eliminating the possibility of the 2.9 ppm signal being due to the C-6 hydrogens, as they are too far away from the vinyl hydrogens to couple significantly. The C-5 hydrogens are adjacent only to a double bond and therefore are not expected to exchange, consistent with the assignment.

The exchange of hydrogen for deuterium was followed by monitoring the decrease in the NMR signal of the C-2 hydrogens through 3 or more half-lives. This decrease follows a first-order decay, with a rate constant that is linear with acetate ion concentration ($k_{ex}{}^{OAc}$ = (9.3 ± 1.5) × 10^{-5} M^{-1} s^{-1}).

We attempted to determine rate constants for the overall isomerization **1** → **3** in acetate buffer by observing the appearance of the conjugated product in the ultraviolet spectrum. Since this reaction is very slow it was necessary to employ an initial rate technique. However, even over

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[7] Acid phosphatase catalyzed hydrolysis of phosphoenol pyruvate has been used previously to generate enol pyruvate. (a) Kuo, D. J.; Rose, I. A. *J. Am. Chem. Soc.* **1978**, *100*, 6288; **1982**, *104*, 3235. (b) Kuo, D. J.; O'Connell, E. L.; Rose, I. A. *J. Am. Chem. Soc.* **1979**, *101*, 5025. (c) Miller, B. A.; Leussing, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 7146. (d) Cheong, M.; Leussing, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 2541.

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[9] Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; Wiley: New York, 1981; p 225.

Table II. Rate and Equilibrium Constants for the Acetate-Catalyzed Isomerization of 2-Cyclohexenone to 3-Cyclohexenone[a]

K	275[b]
k_1	$(9.3 \pm 1.5) \times 10^{-5}$ M^{-1} s^{-1}
k_{-1}	16.6 ± 1.5 M^{-1} s^{-1}
k_2	0.38 ± 0.09 M^{-1} s^{-1}
k_{-2}	$(7.7 \pm 3.0) \times 10^{-9}$ M^{-1} s^{-1}
K_E^1	$(5.6 \pm 1.6) \times 10^{-6}$ ($pK_E^1 = 5.3$)
K_E^3	$(2.0 \pm 0.6) \times 10^{-8}$ ($pK_E^3 = 7.7$)

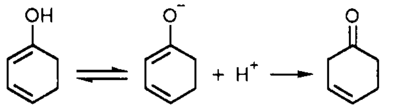
[a] Rate constants are defined in eq 1 and calculated as described in the text, except for k_{-2}, which is calculated from K_E^3 and k_2. Equilibrium constants are $K = k_1k_2/k_{-1}k_{-2}$, $K_E^1 = k_1/k_{-1}$, $K_E^3 = k_{-2}/k_2$. [b] From ref 10.

very short time intervals, the increase in absorbance at 240 nm is not linear, but shows downward curvature, precluding efforts to evaluate the rate constant for isomerization by this method.

Discussion

The general base catalyzed isomerization of 3-cyclohexenone to 2-cyclohexenone has been investigated previously by Whalen et al.,[10] who found catalysis by a variety of general bases, with neutral bases (tertiary amines) being much more effective catalysts than negatively charged bases of the same pK_a. Determination of the rate of exchange of the hydrogens at C-2 catalyzed by phosphate, coupled with measurements of the overall phosphate-catalyzed isomerization rate, enabled them to assign the rate-limiting step to protonation at C-4. The large discrimination between the rates of protonation at C-2 and at C-4 in the cyclohexadienolate ion was attributed to a dihedral angle between the double bonds significantly different from zero (ca. 18°), decreasing charge delocalization to C-4 in the anion. We have determined the rate of ketonization of the dienol and the rate of exchange of the C-2 hydrogens of 1 in acetate buffer. These data, coupled with the results of Whalen et al.,[10] allow the evaluation of the microscopic rate constants for each step in the reaction pathway and, consequently, the equilibrium constants for the enolization of both 1 and 3 (Table II).

Rates of Protonation of 2 at C-2 and C-4. The most reasonable mechanism to account for the observed general base catalysis of the ketonization of 2 is preequilibrium ionization to the dienolate ion, followed by protonation by the conjugate acid of the general base (eq 3), in analogy



(3)

with the generally accepted mechanism of ketonization of simple enols.[11] The partitioning ratio of the dienol in acetate buffer can be calculated from the ratio of the rate of exchange of the C-2 hydrogens of 2 to the overall rate of isomerization of 2. Although we were unable to determine the rate of isomerization catalyzed by acetate ion, an estimate of this rate constant can be obtained from the results of Whalen et al.[10] Extrapolation of the Brønsted plot of rate constants for general base catalyzed isomerization for negatively charged bases gives a value for the acetate-catalyzed isomerization ($k_{iso}^{OAc} = (2.1 \pm 0.3) \times 10^{-6}$ M^{-1} s^{-1}). The kinetic product ratio [1]/[3] can be obtained by dividing the rate constant for exchange by the rate constant for isomerization, giving a value of 44 ± 10. This ratio can also be estimated by using the results of Whalen et al.[10] that the exchange of hydrogen is approximately 575 times faster than the isomerization in DPO_4^{2-}/D_2O. This number has to be corrected for the isotope effect caused by exchange of the C-2 hydrogens before the isomerization occurs; dividing 575 by the observed isotope effect of 7.7 ($k_{HPO_4^{2-}}/k_{DPO_4^{2-}}$)[10] gives the initial product ratio of 75 for phosphate catalysis. This value agrees reasonably well with the ratio for acetate ion catalysis calculated using the first method, given the precision of the data and the assumption that acetate behaves similarly to phosphate. The high ratio of k_{-1}/k_2 is also consistent with the lack of any observable production of 2-cyclohexenone in the ultraviolet spectrum of the product for the ketonization of 2. Since protonation of the dienolate ion gives almost exclusively 1, the observed second-order rate constant for ketonization corresponds to the rate constant for protonation at C-2. The rate constant for protonation at C-4 will be approximately 44-fold slower (k_{-1}/k_2) or about 0.38 ± 0.09 M^{-1} s^{-1}.

The observed rate constant for the water-catalyzed ketonization ($k^{H_2O} = 0.15$ s^{-1}) corresponds to a half-life of <5 s. If the partitioning ratio is similar for the water-catalyzed and acetate-catalyzed reactions, then the rate constant for reaction of the dienol with water at C-4 is about 0.15/50 = 3×10^{-3} s^{-1}. Rate constants for water-catalyzed ketonization of other dienols have been reported by Weedon[6b] and Capon[6d] (Table III). Although the series is limited, several observations may be made. The rate constant for ketonization of 1,3-cyclohexadienol at the α-carbon is quite a bit larger than the corresponding rate constant for either (*E*)- or (*Z*)-1,3-butadien-1-ols (about 50-fold), although the difference in the rate constants for protonation at the γ-carbon is substantially less (<5-fold). The more rapid reaction of 1,3-cyclohexadienol at the α-carbon may be due to greater localization of negative charge at this carbon in the dienolate ion of 2 than the dienolate ions of the 1,3-butadien-1-ol. Twisting about the C–C bond between the double bonds of the dienolate ion of 2 leads to poorer overlap of the π orbitals and consequently inefficient delocalization of charge to the γ-carbon.[10] The effect of the alkyl groups of the ring at C-1 of 2 on the rate of ketonization is likely to be small, as the rate constants for water-catalyzed ketonization of the enols of acetaldehyde and acetone differ by less than a factor of 2.[11,12]

The rate constants for water-catalyzed ketonization of dienols at the γ-carbon fall into two categories. Compounds 6, 7, and 8 ketonize about 10^4-fold faster than the other dienols. Duhaime and Weedon[6] have suggested that the rapid ketonization rate for these dienols is due to a 1,5-sigmatropic hydrogen shift. Since 2 is locked in a conformation that does not allow the 1,5 shift, the relatively slow rate of protonation of 2 at the γ-carbon is understandable. Similarly, 4 cannot undergo intramolecular rearrangement and thus does not ketonize rapidly. However, as noted by Capon,[6d] 5 could ketonize by the sigmatropic pathway, but appears not to do so. The probable explanation for the slow ketonization of 5 is similar to that postulated by Duhaime and Weedon to explain the slower ketonization of 9 compared to 6.[6] The s-cis conformation of 5 that is necessary for cyclic ketonization may be sufficiently high in energy so that it is only present in small amounts relative to the unreactive s-trans conformation.

Equilibrium Constants for the Enolization of 1 and 3. The equilibrium constant for the enolization of 1 (K_E^1

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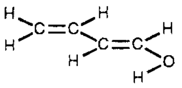
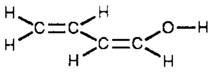
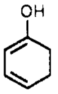
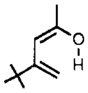
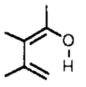
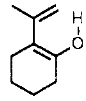
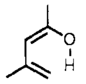
[10] Whalen, D. L.; Weimaster, J. F.; Ross, A. M.; Radhe, R. *J. Am. Chem. Soc.* **1976**, *98*, 7319.

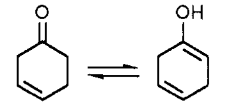
[11] Chiang, Y.; Kresge, A. J.; Santaballa, J. A.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 5506.

[12] Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000.

Table III. Rate Constants for Water-Catalyzed Ketonization of Conjugated Enols

compound		k_α/k_γ	k_α, s^{-1}	k_γ, s^{-1}	ref
	(4)	2.6	2.18×10^{-3}	8.5×10^{-4}	6d
	(5)	4.8	3.30×10^{-3}	6.9×10^{-4}	6d
	(2)	50	0.15	3×10^{-3}	this work
	(6)			36	6b
	(7)			56	6b
	(8)			14	6b
	(9)			<5	6b

= $(5.6 \pm 1.6) \times 10^{-6}$) can be calculated from the ratio of the rate constants k_1 and k_{-1}; the equilibrium constant for the enolization of **3** ($K_E{}^3 = (2.0 \pm 0.6) \times 10^{-8}$) is simply the ratio of $K_E{}^1$ to the overall equilibrium constant for the conversion of **1** → **3** (K = 275).[10] These equilibrium constants for enolization (p$K_E{}^1$ = 5.3 and p$K_E{}^3$ = 7.7) can be compared to the equilibrium constant for the enolization of cyclohexanone (pK_E = 6.39).[13] The greater amount of enol at equilibrium for **1** than for cyclohexanone can be attributed to the resonance stabilization of the dienol of **1**. If the enolization of 3-cyclohexenone to produce the *non*conjugated dienol (eq 4) is used as a model for the



(4)

enolization of cyclohexanone, then the difference in energy between the unconjugated and conjugated dienols of 3-cyclohexenone will approximate the difference in enol content to be expected between cyclohexanone and 3-cyclohexenone.

Hine[14] has calculated a "double bond stabilization parameter" (D) that can be used to calculate this value. This parameter gives a value for the free energy change for the transformation of vinyl-X plus propylene to allyl-X plus ethylene for a substituent X, relative to hydrogen, which is given a value of zero. The D values for a vinyl group and alkyl group are 5.9 and 2.8 kcal/mol, respectively.[14d] Thus, migration of the double bond of the unconjugated dienol to form the conjugated dienol should result in a gain of 5.9 − 2.8 = 3.1 kcal/mol. This result suggests that the equilibrium constant for enolization of 3-cyclohexenone to the conjugated dienol should be approximately 2.2 log units (equivalent to 3.1 kcal/mol) greater than that for cyclohexanone. The observed difference of 1.3 log units is substantially less than predicted, consistent with impaired resonance interaction between the two double bonds in 1,3-cyclohexadienol.

Similarly, Hine's double bond stabilization parameters for vinyl and for acetyl (5.9 and 3.8 kcal/mol, respectively)[14d] imply that carbonyl double bond resonance is generally less favorable than double bond–double bond resonance. Thus, cyclohexanone is predicted to have *less* enol at equilibrium than 2-cyclohexenone (**3**). Instead, cyclohexanone exists to greater extent in its enol form than does **3**. This initially surprising result, too, can be rationalized by a decrease of resonance in the dienol **2**, caused by poorer overlap of the π-orbitals than the π-orbitals of **3**, destabilizing the dienol relative to the ketone.

Carbon Acidities of 2- and 3-Cyclohexenones. Carbon acidities of simple aldehydes and ketones in aqueous solution generally are difficult to measure directly, as these compounds usually have pK_a's substantially greater than 14.[8,12,15,20] However, it is often possible to combine keto–enol equilibrium measurements with values for the pK_a's of the corresponding enols to obtain aqueous pK_a's of the carbonyl compounds.[21] Although the pK_a of **2**, the dienol common to 2- and 3-cyclohexenone, has not been measured, an approximate value may be estimated from the pK_a's of several other dienols. A comparison of

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(15) Examples of ketones that are acidic enough so that their pK_a's can be measured directly in aqueous solution are 5-androstene-3,17-dione (pK_a 12.7),[3b,d] 2-indanone (pK_a 12.2),[16,17] 2-tetralone (pK_a 12.9),[16] 2-benzosuberone (pK_a 14.9),[18] and diphenylacetaldehyde (pK_a 10.4).[19]

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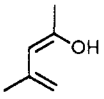
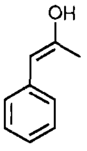
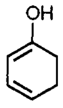
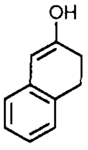
the pK_a's of **9** and **10** suggests that a phenyl group is somewhat more effective at stabilizing the negative charge in a dienolate ion than a vinyl group (ΔpK 0.67). If the same relationship holds for **11** and **2**, then the pK_a of **2** should be approximately 9.19 + 0.67 = 9.86. This estimate, coupled with the pK_E values for the ketones, allows the carbon pK_a's to be estimated for the C-2 proton of 3-cyclohexenone (p$K_a \simeq$ 15.2) and the C-4 proton of 2-cyclohexenone (p$K_a \simeq$ 17.6). These values may be compared with pK_a's for the saturated ketones acetone (pK_a 19.2)[20b] and isobutyrophenone (pK_a 18.2).[20c] The only other β,γ-unsaturated ketone whose pK_a has been determined is 5-androstene-3,17-dione, which is substantially more acidic (pK_a 12.7)[3b,d] than 3-cyclohexenone. It is not clear whether the twisting about the double bonds of **2** is sufficient to account for this difference.









	9	10	2	11
pK_a	10.42[6b]	9.75[17b]		9.19[18b]

Experimental Section

Materials. Bis(cyclohexylammonium) 1,3-Cyclohexadienyl Phosphate (2P). Trimethylsilyl bromide (0.52 mL, 4 mmol) was added dropwise to 408 mg (2 mmol) of dimethyl 1,3-cyclohexadienyl phosphate[22] in 5 mL of anhydrous methylene chloride under argon at 0 °C. The mixture was stirred at room temperature for 2 h, under a slow flow of argon to avoid evaporating the methylene chloride. After that time all volatile substances were removed by increasing the argon flow over the solution for 1 h. Then 2 mL of a 1 M solution of cyclohexylamine in THF and 2 mL of absolute ethyl alcohol were added cautiously with stirring. The white precipitate was filtered off, washed with THF, and recrystallized from methyl alcohol to give 460 mg (61%) of white crystals: mp 163-5 °C; ^{1}H NMR (D_2O, DSS) δ 1-2 (m, 11 H), 2.31 (m, 4 H, CH_2), 5.60 (m, 2 H, CH), 5.81 (m, 1 H, CH) ppm; IR (KBr) 3060-2200 (broad), 1650, 1550, 1180, 1100, 1090 cm^{-1}.

Anal. Calcd for $C_{18}H_{35}N_2PO_4$: C, 57.73; H, 9.42; N, 7.48; P, 8.27. Found: C, 57.81; H, 9.41; N, 7.59; P, 8.21.

4,5-Epoxycyclohexene was prepared by epoxidation of 1,4-cyclohexadiene according to the literature procedure[23] for epoxidation of 1,3-cyclohexadiene. This procedure gives a symmetrical epoxide which, when reduced, will give one major product regardless of which carbon-oxygen bond breaks (52%); bp$_{14\text{mm}}$ 43-45 °C.

3-Cyclohexenol was prepared by reduction of 4,5-epoxycyclohexene with lithium aluminum hydride[23] (yield 80%, bp$_{14\text{mm}}$ = 68 °C, literature value bp$_{12\text{mm}}$ 63-4 °C.[27]

3-Cyclohexenone (1) was prepared by oxidation of 3-cyclohexenol with pyridinium chlorochromate.[25,26] Pyridinium chlorochromate (99 g, 0.45 mol) was suspended in 400 mL of anhydrous dichloromethane containing 2% pyridine at 5 °C. 3-Cyclohexenol (29.6 g, 0.3 mol) was added with stirring, and the progress of the reaction was monitored by TLC. After 2 h, 400 mL of ether was added, and the supernatant liquid was decanted from a black residue, which was washed with ether. The combined organic extracts were passed through a pad of Florisil. The solvents were removed by distillation, and the ketone was distilled under reduced pressure to give 20.77 g (72%, bp$_{13\text{mm}}$ 35-37 °C). IR and ^{1}H NMR spectra were in agreement with the literature data.[27]

Other Materials. 2-Cyclohexenone (3) was obtained from Aldrich and vacuum distilled. Sweet potato acid phosphatase was a Sigma product and was used as received. Acetate buffers were prepared from reagent grade sodium acetate and acetic acid or acetic acid-d_4. Doubly distilled water was used for all kinetic runs. Deuterium oxide was >99.9 atom % *d*.

Isotope Exchange Kinetics. The isotope exchange of 1 was followed with an IBM NR/80 Fourier transform NMR equipped with a variable-temperature probe. The sample was maintained at 25 ± 2 °C. Buffers of 1:1 DOAc-OAc were made by titrating a DOAc-d_4/D_2O solution with 40% NaOD (pD = pH meter reading + 0.4[28] = 5.15). 3-Cyclohexenone (ca. 30-50 μL) was added to approximately 2 mL of the buffer plus 20 μL of MeOH and a trace of DSS. Repetitive scans were taken, and the peak areas were normalized to the methanol methyl resonance. The disappearance of the absorption at 2.5 ppm was followed; a plot of the logarithm of the peak area/*Me*OD peak area ratio vs time gave a straight line. The pseudo-first-order rate constant was determined by fitting the data using a linear least-squares program.

Ketonization of 1,3-Cyclohexadienol (2). Two milliliters of buffer containing sweet potato acid phosphatase were placed in the thermostated compartment (25 ± 0.2 °C) of a Gilford Response spectrophotometer and allowed to reach thermal equilibrium (5-10 min). Twenty to forty microliters of a stock solution of bis(cyclohexylammonium) 1,3-cyclohexadienyl phosphate (2.5-4.0 mg/mL) was added with stirring to initiate the reaction, and the absorbance was monitored at 265 nm. The enzyme blank with no substrate showed a very slow linear increase. The absorbance change due to the enzyme alone was subtracted from the change in absorbance during the isomerization runs. Large concentrations (ca. 1 mg/mL, 40 units/mL) of phosphatase were used to make the phosphate cleavage reaction rapid with respect to ketonization, and the second half of the absorbance vs time curve was fit to a single exponential equation using an iterative nonlinear least-squares fit program that allows variation in the infinity point. The pH of the buffer solutions did not change after addition of the enzyme or after the reaction was complete. The ionic strength was maintained at 0.1 with $NaClO_4$.

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