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Mechanism of the Acid- and General-Base-Catalyzed Conjugation of 3-Cyclopentenone and 3-Cyclohexenone; Electrostatic Effects in the Conjugation of β,γ-Unsaturated Ketones

Dale L. Whalen,* John F. Weimaster, Angela M. Ross, and Richard Radhe

Contribution from the Laboratory for Chemical Dynamics, Department of Chemistry, University of Maryland Baltimore County, Baltimore, Maryland 21228.

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Abstract: The rates of isomerization of 3-cyclohexenone and 3-cyclopentenone by a variety of general bases were determined. It was found that the α-hydrogens of 3-cyclopentenone were exchanged for deuterium by a given general base in D_2O at a rate slower than that for exchange of the α-hydrogens in 3-cyclohexenone. However, the rates of conjugation of 3-cyclopentenone were considerably faster than the rates of conjugation of 3-cyclohexenone. It was determined that for isomerization of 3-cyclohexenone, protonation of the intermediate dienolate ion was solely rate determining, whereas for isomerization of 3-cyclopentenone, formation of the dienolate ion was partially rate determining. The rate-limiting step for the acid-catalyzed conjugation of 3-cyclopentenone was shown to be formation of the intermediate dienol. This result differs from that obtained in the acid-catalyzed conjugation of 3-cyclohexenone, where published data show that protonation of the intermediate dienol is the rate-limiting step. The observed results in the acid- and base-catalyzed conjugation of 3-cyclopentenone and 3-cyclohexenone are interpreted in terms of different geometries of the intermediate dienols and dienolate anions. The rates of isomerization of 3-cyclohexenone and 3-cyclopentenone were found to depend markedly on the charge type of the general base. Neutral tertiary amines were much more effective catalysts than negatively charged bases. This difference in catalytic effectiveness was attributed to electrostatic interactions at the transition state.

The conjugation of β,γ-unsaturated ketones to their conjugated isomers has received considerable attention. The isomerization of $\Delta^{5(6)}$-3-ketosteroids[1] and the deconjugation of prostaglandins in the A series[2] are catalyzed by enzymes. Because of the importance of these reactions, the mechanisms for conjugation of the parent β,γ-unsaturated ketones, 3-cyclohexenone and 3-cyclopentenone, take on added significance. Although the acid-catalyzed isomerizations of 3-cyclohexenones have been thoroughly studied,[3] and mechanisms for the acid- and base-catalyzed conjugation of $\Delta^{5(6)}$-3-ketosteroids have been reported,[4] no systematic studies of the conjugation of cyclopentenones have appeared.

Protonation of the γ-position of an intermediate dienolate ion is generally assumed to be the rate-limiting step in the base-catalyzed conjugation of β,γ-unsaturated ketones (i.e., $k_2 \ll k_{-1}$, Scheme I).[5] In this paper, however, it is shown that enolization (k_1) is partially rate determining in the general-base-catalyzed isomerization of 3-cyclopentenone (IV). The rates of conjugation of I and IV by a given general base were also found to depend markedly on the charge of the catalytic species, in addition to its strength as a base.

Results and Discussion

The rate constants for isomerization of I and IV at pH >6 in solutions of constant buffer ratio but varied buffer concentrations fit the rate expression given by the equation

$$k_{\text{obsd}} = k_{\text{OH}^-}[\text{OH}^-] + k_{\text{B}}[\text{B}] \qquad (1)$$

where B represents the base form of the buffer. The values for the rate constants are listed in Table I.

The isomerization of I with $HPO_4^{2-}(H_2O)$ and $DPO_4^{2-}(D_2O)$ solutions exhibited a normal isotope effect ($k_{HPO_4^{2-}}/k_{DPO_4^{2-}}$) of 7.7, which indicated a pre-equilibrium formation of a dienolate ion followed by rate-determining protonation of the dienolate ion by the buffer acid ($k_2 < k_{-1}$, Scheme I).[6] This mechanism is consistent with the observation that the exchange of α-hydrogens in I, catalyzed by DPO_4^{2-} in D_2O, occurred at a rate 575 times greater than the isomerization of I to III.[7]

In contrast to the isomerization of I, the isomerization of IV in DPO_4^{2-}-D_2O solutions did not exhibit pseudo-first-order kinetics throughout the reaction. An initial value of the isotope effect ($k_{HPO_4^{2-}}/k_{DPO_4^{2-}}$) for the isomerization of IV through 4% reaction in $HPO_4^{2-}(H_2O)$ and $DPO_4^{2-}(D_2O)$ solutions was measured to be 0.9. As the reaction in DPO_4^{2-}-D_2O solution proceeded, however, the instantaneous value for $k_{DPO_4^{2-}}$ decreased until it became significantly less than $k_{HPO_4^{2-}}$ for

Scheme I

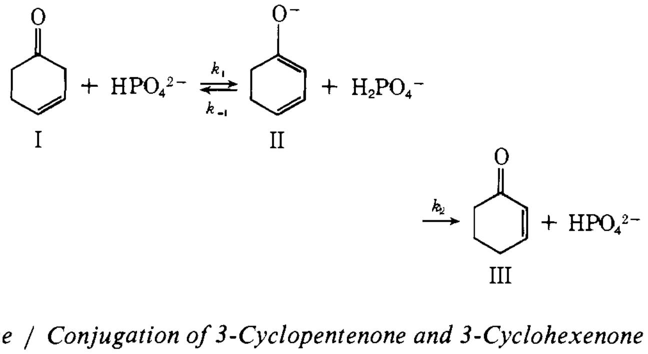
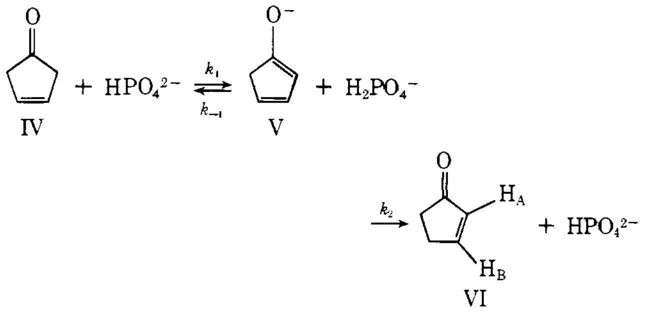


Table I. Rate Constants[a] for the Buffer-Catalyzed Conjugation of 3-Cyclohexenone (I) and 3-Cyclopentenone (IV)

B	pK_a (BH$^+$)	$10^3 k_B$, M^{-1} s^{-1} I	 IV
$(CH_3)_2AsO_2^-$	6.4[d]		0.94 ± 0.03
HPO_4^{2-}	7.2[d]	0.031 ± 0.001[b]	0.69 ± 0.02
N-Methylmorpholine	7.4[e]	1.3 ± 0.1	31 ± 1
N-Ethylmorpholine	7.7[e]	1.2 ± 0.2	21.8 ± 0.2
Trimethylamine	9.8[e]	84 ± 4	1195 ± 18
3-Quinuclidinol	10.1[f]	62 ± 1	850 ± 7
CO_3^{2-}	10.2[d]	2.1 ± 0.7[c]	15 ± 3
Triethylamine	10.6[e]	33 ± 4	565 ± 35
PO_4^{3-}	12.3[g]	7.2 ± 0.9[b,c]	116 ± 2
HO$^-$	15.8	197 ± 19	4050 ± 160

[a] Rates were monitored at 225–230 nm in the thermostated cell compartment (25.0 ± 0.1 °C) of either a Cary 16K or Gilford 2400 spectrophotometer. Rate constants were obtained from the slopes of least-squares plots of k_{obsd} vs. [B] or, in cases where intercepts of such plots were negligible, by dividing k_{obsd} by [B] for a series of buffer dilutions. Generally four solutions of a given buffer, at constant pH but varied buffer concentrations, were utilized for each data point. All solutions were at constant ionic strength of 1.0 (KCl) except where noted. A value of k_B for cacodylate in the isomerization of I is not listed because apparent complexation with the catalyst led to the buildup of an intermediate with λ_{max} 310 nm. [b] Ionic strength was 2.0 (KCl). The rate constant for isomerization of IV by PO_4^{3-} at $\mu = 2.0$ (KCl) agreed to within 10% of the value obtained at $\mu = 1.0$ (KCl). [c] Estimated by initial rates. A second reaction, presumably the conjugate addition of hydroxide to the initially formed 2-cyclohexenone, occurred at high pH. [d] P. M. Laughton and R. E. Robertson in "Solvent-Solute Interactions", J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N.Y., 1969, pp 407–412. [e] H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957). [f] W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968). [g] N. Bjerrum and A. Unmack, *Chem. Soc., Spec. Publ.*, **No. 17**, 1 (1964).

Scheme II



H_2O solutions. These data suggest that the rate of exchange of the α-hydrogens of IV in D_2O solution is comparable to the rate of isomerization to VI and that as exchange occurs, the specific rate for isomerization decreases. The study of exchange and isomerization of IV in DPO_4^{2-}–D_2O solution by NMR showed that very little exchange of the α-hydrogens of IV had occurred during the time required for 4% reaction to VI. If one assumes that k_{-1} and k_2 (Scheme II) possess identical primary kinetic isotope effects of ca. 5–7, which would be reasonable for transition states involving deuterium transfer from $D_2PO_4^-$ to V,[8] the equation

$$k_{obsd} = k_1k_2[HPO_4^{2-}]/(k_{-1} + k_2) \qquad (2)$$

reveals that the initial isotope effect ($k_{HPO_4^{2-}}/k_{DPO_4^{2-}}$) of 0.9 becomes the value for the isotope effect on removal of an α-proton from IV by DPO_4^{2-}(k_1).[9] As the isomerization of IV to VI proceeds, α-hydrogens in IV are exchanged for deuteriums. As a result, the specific rate decreases due to a primary kinetic isotope effect on removal of an α-deuterium by DPO_4^{2-}.

Table II. Isomerization Rates of 3-Cyclopentenone in HCl–H_2O Solutions[a]

[HCl], M	$k_{obsd} \times 10^6$, s^{-1}	(k_{obsd}/[HCl]) × 10^5, M^{-1} s^{-1}
0.10	9.73	9.73
0.20	18.6	9.35
0.30	28.2	9.43
	Av	9.5 ± 0.2

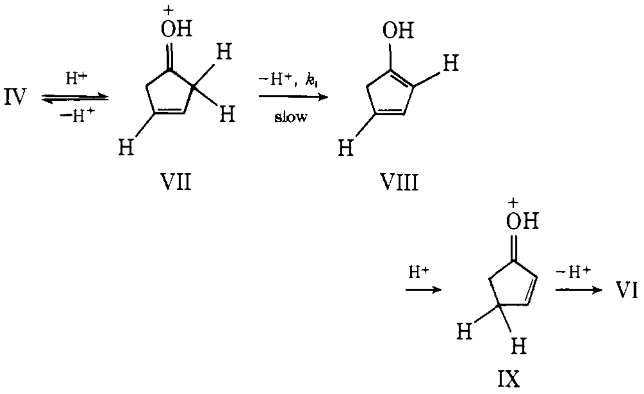
[a] 25.0 °C; $\mu = 1.0$ (KCl).

Table III. Isomerization Rates of 3-Cyclopentenone in DCl–D_2O Solutions[a]

[DCl], M	$k_{obsd} \times 10^5$, s^{-1}	(k_{obsd}/[DCl]) × 10^4, M^{-1} s^{-1}
0.246	2.64	1.07
0.369	3.86	1.05
0.492	5.05	1.03
	Av	1.05 ± 0.02

[a] 25.0 °C; $\mu = 1.0$ (KCl).

Scheme III

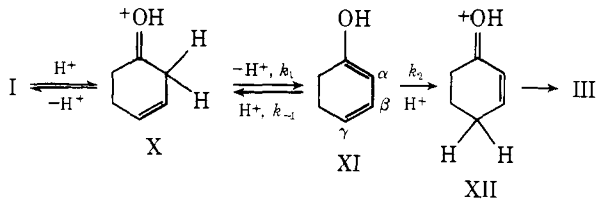


The conjugated isomer VI, obtained from the isomerization of IV by DPO_4^{2-} in D_2O, possessed an NMR spectrum in which the absorption areas due to H_A and H_B were in the ratio of 2.4:1.0. If secondary deuterium isotope effects are neglected and primary isotope effects for deuterium transfer from C_α to DPO_4^{2-} and $D_2PO_4^-$ to C_γ are taken to be ca. 6, then the ratio k_{-1}/k_2 can be estimated to be ca. 3.2.[10] Therefore, although the isomerization of I by HPO_4^{2-} (and other bases) is considerably slower than the isomerization of IV by the same bases (Table I), the actual rate of enolization (k_1) is larger than the rate of enolization for IV.[11] The lower rate of isomerization of I compared to IV is therefore due to a much larger k_{-1}/k_2 ratio for I.

We have also examined the acid-catalyzed isomerization of IV in H_2O and D_2O solutions and the results are summarized in Tables II–III. The small inverse solvent isotope effect ($k_{H_3O^+}/k_{D_3O^+}$) of 0.91 ± 0.03 is not consistent with a rate-limiting proton transfer from solvent to an intermediate dienol (VIII → IX, Scheme III), which would be expected to give rise to a normal solvent isotope effect ($k_{H_3O^+}/k_{D_3O^+}$) of ca. 3–7, but rather suggests that the rate-limiting step is formation of the dienol (k_1). The NMR spectrum of the product VI obtained from the acid-catalyzed isomerization of IV in DCl–D_2O solution confirmed that formation of the dienol VIII was indeed the rate-limiting step. The ratio of the absorption areas for H_B (δ 8.25) compared to H_A (δ 6.40) in VI was 1.0. Exchange of the α-hydrogens in IV, which would have occurred if protonation of the enol were the rate-limiting step, would have yielded product VI in which the H_A/H_B absorption ratio would have been <1.0.

The mechanism for the acid-catalyzed conjugation of IV

Scheme IV



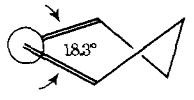
also contrasts with that for the acid-catalyzed conjugation of I, in which protonation (k_2) of the intermediate dienol XI (Scheme IV) was demonstrated to be the rate-limiting step.[3] Therefore, the relative C_γ/C_α protonation rate ratios for the dienolate ion V and dienol VIII were significantly larger than the corresponding C_γ/C_α protonation rate ratios, respectively, of the analogous intermediates II and XI in the conjugation of I.

The acid-catalyzed conjugation of β,γ-unsaturated ketones in which the β-carbon is tertiary generally occurs with rate-limiting formation of the dienol (i.e., protonation of the dienol at the γ-position is faster than at the α-position).[3,4b] It has also been proposed that if the β-carbon is secondary, then the acid-catalyzed conjugation of β,γ-unsaturated ketones should occur with rate-limiting protonation of the dienol (i.e., protonation at the α-carbon is faster than that at the γ-carbon).[3] 3-Cyclopentenone, therefore, is an example of a β,γ-unsaturated ketone with a secondary β-carbon that does not undergo acid-catalyzed rearrangement via the expected rate-limiting step.

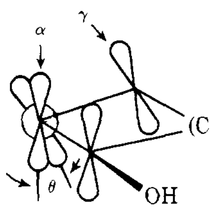
It has been suggested that protonation of a dienolate anion should occur preferentially at the α-position due to a greater negative charge density, and that since there is little bond formation at the transition state, product stability would be unimportant.[4b,12] It was also suggested that protonation of a neutral dienol must result in a greater degree of bond formation at the transition state, with some development of ketonic character, and consequently the more stable product would be favored.[4b]

Such proposal does not adequately explain the fact that dienol XI protonates at the α-position to yield the less stable β,γ-unsaturated ketone I at a rate faster than protonation at the γ-position to yield III. The actual C_γ/C_α protonation rate ratio for protonation of a dienol must be a result of the relative abilities of the transition states to stabilize developing positive charge. In view of the fact that I and IV exist almost completely in the ketonic forms, then dienols VIII and XI must be thermodynamically less stable than the keto forms. Therefore, by Hammond's postulate,[13] the structures of the transition states for protonation of dienols VIII and XI should more closely resemble the dienol reactants rather than the ketonic products. Consideration of the geometries of the dienols, in addition to substituent effects introduced by alkyl substitution, should therefore allow one to explain the observed C_γ/C_α protonation rate ratios that have been observed in ketone isomerization reactions.

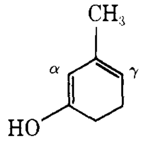
The molecular structures of 1,3-cyclohexadiene and 1,3-cyclopentadiene should serve as reasonable models for dienols VIII and XI. Whereas the carbon atoms in cyclopentadiene all lie in the same plane,[14] the carbon skeleton of 1,3-cyclohexadiene is not planar. The dihedral angle formed by the two double bonds (XIII) has been determined to be 18.3°.[15] The relative rate of protonation of a dienol at C_γ compared to C_α will depend on the dihedral angle θ in XIV at the transition state. It is this angle that determines the extent to which positive charge can be delocalized onto the oxygen atom. For θ equal to 0°, all p orbitals of the basis set are collinear, and therefore positive charge generated by addition of a proton to C_γ will be most effectively transmitted to the oxygen. However, as θ increases, overlap between the orbitals of C_α and C_β decreases, and therefore the positive charge generated by addition of a proton to C_γ cannot be stabilized by the nonbonding electrons of oxygen so effectively. For θ equal to 90°, protonation at C_γ would be comparable to protonation of an isolated double bond, whereas protonation at C_α would be comparable to protonation of a vinyl ether, a more favorable process. One can therefore predict that the C_γ/C_α protonation rate ratio should be maximum at $\theta = 0°$ and then decrease as θ increases.



XIII



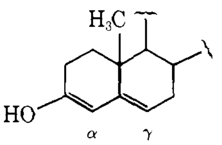
XIV



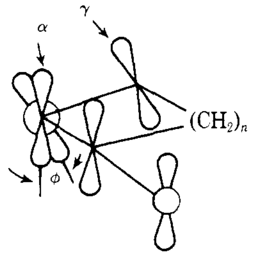
XV

The observations in the acid-catalyzed conjugation of I and IV are in agreement with this model. For cyclopentadienol VIII, where θ (XIV) is near zero and the positive charge generated from protonation at C_γ can be most effectively stabilized by the hydroxyl group, protonation at C_γ is more favorable than at C_α. For cyclohexadienol XI, where θ (XIV) is most likely about 18°, the positive charge generated by protonation at C_γ cannot be as effectively stabilized by the hydroxyl group, and consequently, protonation at C_α is more favorable than protonation at C_γ.

The effect of alkyl substitution at C_β in the conjugation of β,γ-unsaturated ketones is predictable and has been discussed previously.[3] For instance, a methyl group at C_β will stabilize positive charge generated by protonation at C_γ, but will not stabilize positive charge so effectively when protonation occurs at C_α. As a result, protonation at C_γ in dienol XV, derived from 3-methyl-3-cyclohexenone, is more favorable than at C_α. The dienol XVI, an intermediate in the acid-catalyzed conjugation of Δ^5-3-ketosteroids, also possesses alkyl substitution at C_β and protonates at C_γ faster than at C_α.[4b]



XVI



XVII

If only the relative charge densities at C_α and C_γ of the intermediate dienolate ion dictate the relative protonation rates at those carbons, then the large difference in the k_{-1}/k_2 ratios for the general-base-catalyzed conjugation of I and IV (Schemes I and II) would imply significantly different charge distributions in dienolate ions II and V. Such charge density variations would result if the atoms of the π-system of one dienolate ion were distorted from planarity more than the atoms of the other dienolate ion. If the structures II and V were similar to those of the parent dienes, then these charge density variations would indeed arise. The negative charge densities on C_α and C_γ of a dienolate ion XVII would be a function of the dihedral angle φ. For φ equal to 0°, the negative charge ratio q_γ/q_α will be at its greatest value, although the charge

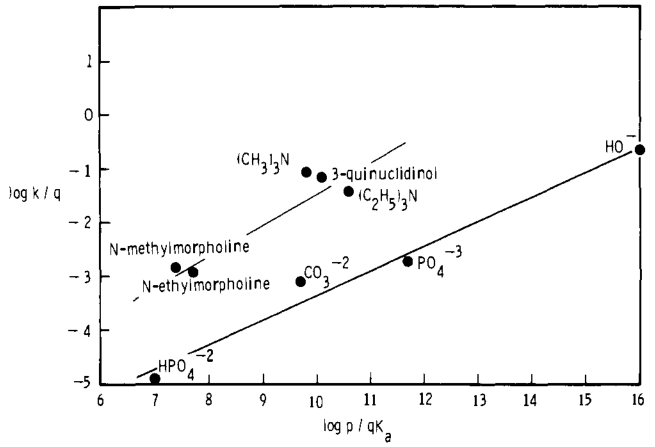


Figure 1. Plot of log k_B/q vs. log p/qK_a for the general-base-catalyzed isomerization of 3-cyclohexenone (I).[16]

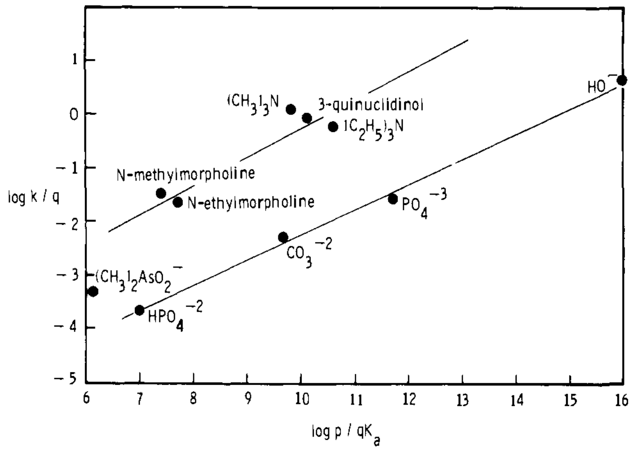
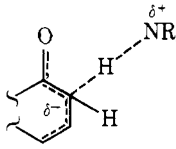


Figure 2. Plot of log k_B/q vs. log p/qK_a for the general-base-catalyzed isomerization of 3-cyclopentenone (IV).[16]

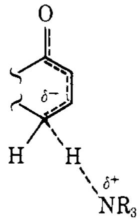
density at C_α is still larger than at C_γ.[12] As ϕ increases, however, the charge density at C_γ decreases, while at C_α it increases. As a consequence, the C_γ/C_α protonation rate ratio should decrease as ϕ increases. The k_{-1}/k_2 value for the general-base-catalyzed isomerization of IV ($\theta \simeq 0°$) means that protonation at C_α in II is favored over protonation at C_γ, but only by a factor of ca. 3. However, protonation at C_α in V is favored over protonation at C_γ by a factor of ca. 575. We attribute this large increase in the rate of protonation of C_α relative to C_γ in the dienolate II compared to the same ratio in dienolate V to be the result of an increase of ϕ from 0° in V to perhaps 10-15° in II (see XVII).

The relative stabilities of unconjugated and conjugated ketone isomers must also exert some influence on the C_γ/C_α protonation rate ratio for II and V, however, since the transition state (however early) must reflect at least some relative product stability. The equilibrium constants for the interconversion of 2-cyclopentenone and 2-cyclohexenone to their β,γ-unsaturated isomers, respectively, were therefore measured in water solutions. Whereas ca. 0.36% of the equilibrium mixture of cyclohexenones was in the form of the unconjugated isomer, less than 0.01% of the equilibrium mixture of cyclopentenones was in the form of the unconjugated isomer. The larger value of the equilibrium constant for the cyclopentenone interconversion (IV $\rightleftharpoons$ VI) compared to the cyclohexenone interconversion (I $\rightleftharpoons$ III) probably reflects a greater planarity of the enone system in IV and also contributes to greater C_γ/C_α protonation rate ratios in dienol VIII and dienolate V.

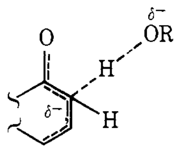
Electrostatic Effects in the Conjugation of β,γ-Unsaturated Ketones. Brønsted plots of the catalytic constants for isomerization of I and IV by general bases as a function of their base strengths are presented in Figures 1-2.[16] These plots reveal that the catalytic effectiveness of a general base in the isomerization of I and IV is very dependent upon its charge type. The Brønsted lines generated by the five tertiary amines in the isomerization of I (β = 0.6) and IV (β = 0.5) lie approximately two log units above the lines generated by the negatively charged bases HPO_4^{2-}, CO_3^{2-}, PO_4^{3-}, and OH^- (β = 0.5 for both I and IV).[17] Smaller deviations from within the Brønsted lines generated by tertiary amines in the conjugation of I and IV also suggest the presence of steric effects. The fact that bifunctional bases with negative charge are substantially less effective than the monofunctional amine catalysts is somewhat surprising because cyclic "push-pull" transition states for proton transfer from C_α to C_γ is possible for the bifunctional bases. The catalytic effectiveness of tertiary amines, compared with negatively charged bases of the same pK_b, is nicely explained by electrostatic effects.[18] If the rate-limiting transition state is either removal of the α-hydrogen by the tertiary amine



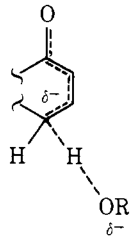
XVIII



XIX



XX



XXI

(i.e., XVIII) or donation of a proton to the γ-carbon by the corresponding buffer acid (i.e., XIX), there is a favorable electrostatic interaction between the negative charge on the substrate and the positive charge on the catalyst. In the corresponding transition states, where the catalyst is a negatively charged base (i.e., XX and XXI), there is negative charge on both substrate and catalyst. Electrostatic interactions would therefore be relatively unfavorable in XX and XXI and would explain the fact that negatively charged bases are not as effective as neutral amines in catalyzing the isomerization of β,γ-unsaturated ketones.

Experimental Section

NMR spectra were recorded by an Hitachi Perkin-Elmer Model R-20A spectrometer and chemical shifts in D_2O are reported relative to internal sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS). Infrared spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer. A Corning Model 112 pH meter was utilized for pH measurements, and the pD for a D_2O solution was estimated to be pH + 0.4.

3-Cyclopentenone (IV). Cyclopentadiene oxide (Willow Brooks Laboratory, 0.37 g) was added to distilled water maintained at pH 7.5 by a pH stat and the resulting solution was stirred at room temperature for 40 min. The product mixture, analyzed by gas chromatography (10% diisodecyl phthalate column, 60°) and uv spectroscopy, consisted of 35% of 3-cyclopentenone, 35% of *cis*-2,4-pentadienal ($\lambda_{max}^{H_2O}$ 269 nm, ϵ 19 500), and 30% of cyclopentenediols.[19]

The reaction solution was extracted with methylene chloride (2 × 40 ml). The methylene chloride extracts were combined, dried with anhydrous calcium sulfate, and concentrated by distillation of the solvent through a 10-cm column packed with glass helices. The residual solution contained equal amounts of 3-cyclopentenone, ir (CCl_4) 1750 cm^{-1}, and *cis*-2,4-pentadienal, ir (CCl_4) 1678 cm^{-1}, which were separated by preparative gas chromatography (10% diisodecyl phthalate column).

3-Cyclohexenone (I). 3-Cyclohexenol[20] (2.7 g) in 25 ml of acetone (distilled from $KMnO_4$) was oxidized with 7.0 ml of chromium trioxide-sulfuric acid solution according to the Jones procedure.[21] The reaction mixture was diluted with 150 ml of water and extracted twice with 150-ml portions of ether. The ethereal extracts were combined, washed with water (2 × 50 ml), dried over anhydrous calcium sulfate, and concentrated by distillation of the solvent through a 10-cm fractionating column packed with glass helices. The residue was distilled under reduced pressure (20 nm) at a bath temperature of 60 °C to yield 0.81 g (31%) of 3-cyclohexenone, ir (CCl_4) 1710 cm^{-1}.[22]

Reagents. Triethylamine was distilled immediately prior to use. Trimethylamine hydrochloride was recrystallized from methanol. The remainder of the buffering reagents were available commercially and used without further purification. Buffered solutions were prepared by adding standard HCl or KOH solutions to base or acid forms of the buffer, respectively. The ionic strength of the solutions was maintained at 1.0 with added KCl, except where noted.

Kinetic Methods. Stock solutions of I and IV (ca. 0.05 M) in dioxane were prepared from samples of I and IV that had been collected from gas chromatography (10% diisodecyl phthalate column). Approximately 5 μl of stock solution was added to 3.0 ml of buffered solution in the cell compartment, maintained at 25.0 ± 0.1 °C, of either a Cary 16K or Gilford 2400 spectrophotometer. The solution was thoroughly stirred and isomerization of the unconjugated ketone to the conjugated isomer was monitored at 225–230 nm.

The second-order rate constant for a given general base was obtained from the slope of a least-squares plot of k_{obsd} vs. [general base], or, in cases where the intercept of such plot was negligible, by dividing k_{obsd} by [general base], for a series of buffer dilutions. Generally four solutions of a buffer, at constant pH but varied buffer concentrations, were utilized to obtain each second-order rate constant.

The pseudo-first-order rate constants (k_{obsd}) were obtained by nonlinear regression analysis of the data for each kinetic run by a Wang 700 calculator–computer.

The rates of exchange of the α-hydrogens in I and IV were determined in D_2O solutions with added buffer, maintained at an ionic strength of 1.0 with KCl. Approximately 25 μl of the ketone was added to 0.5 ml of the kinetic solution in an NMR tube. The tube was shaken vigorously until the ketone dissolved and then was inserted in the probe (ca. 35 °C) of a Perkin-Elmer Model R-20A NMR spectrometer. Spectra were then recorded at regular time intervals.

Isomerization of IV in DCl–D_2O Solution. To 0.5 ml of a solution of 0.13 M DCl in D_2O (μ = 1.0, KCl) was added 25 μl of IV. The solution was maintained at 35 °C for 23 h and the NMR spectrum of the product was recorded. The spectrum showed that isomerization of IV to VI was ca. 90% completed. The ratio of the absorption areas for H_B (δ 8.25) compared to H_A (δ 6.40) was 1.0. The ratio of the absorption areas for the α-hydrogens (δ 3.03) of unreacted IV compared to the olefinic hydrogens (δ 6.25) was still 2.0, which, together with the ratio of 1.0 for the absorption areas of H_B and H_A, indicated that negligible exchange of the α-hydrogens of IV occurred prior to isomerization.

Equilibration of I and III. When the equilibrium of I and III was approached from GLC-collected I, approximately 75% of the material was converted to undetected product (perhaps aldol?) after ca. 20 half-lives of reaction at pH 11.7. A GLC peak with the same retention time as starting material constituted 3% of the detectable material, with the remaining 97% being the conjugated isomer III. In view of the uncertainty of the purity of our starting material I and also the fact that most of the mass balance could not be accounted for on GLC, we felt that the equilibrium value of 3% of I was unreliable and studied the approach to equilibrium from the conjugated isomer III.

A commercial sample of III (Aldrich), contaminated with 1% of I, was subjected to gas chromatographic purification on a 10% silicone DC-550 column (⅜ in.) with silylated solid support. The purified sample of III was analyzed on a 10% DC-550 analytical column (⅛ in., hydrogen flame detector), and contained 0.02–0.03% of a material with the same retention time as I. Collection of III from other columns without silylated solid support resulted in material that was still contaminated with I (1–3%), even though the peaks were well separated.

Table IV. Percent of I in a Mixture of I and III, as a Function of Time, in the Approach to Equilibrium from III; Water Solution, pH 11.76 (KOH), 25.0 °C[a]

III, %[b]	Time, s	III, %[b]	Time, s
0.024	0	0.146	480
0.035	60	0.175	660
0.056	120	0.215	900
0.075	180	0.250	1200
0.088	240	0.36 ± 0.02[c]	∞
0.121	360		

[a] $k_{obsd} = (9.5 \pm 0.7) \times 10^{-4}\ s^{-1}$. [b] Analyzed by gas chromatography (hydrogen flame detector) on a ⅛ in. 10% silicone DC-550 column with silylated solid support. [c] Extrapolated with the aid of a nonlinear least-squares program for calculating first-order rate constants.

The approach to equilibrium from III in water solution at pH 11.76 was monitored by GLC. A sample of purified III (10.0 μl) was injected into 0.5 ml of dilute potassium hydroxide solution (pH 11.76) under a nitrogen atmosphere. The solution was maintained at 25.0 °C and quenched at a given time with ca. 50 μl of 0.1 M HCl solution. The quenched solution was then extracted with 0.5 ml of diethyl ether and the ethereal solution was analyzed on GLC. Injection of the quenched aqueous solution (pH 6–8) directly on GLC gave erroneous results, as equilbration under the analytical conditions always gave rise to ca. 1% of I. Therefore, extraction of the quenched solution by ether was necessary and the products were then stable under analytical conditions. Table IV lists the percent of I that is formed as a function of time. From these data, the rate for the approach to equilibrium ($k_{obsd} = (k_f + k_r)[^{-}OH]$) was determined. Because $k_f \ll k_r$ then $k_{obsd} \simeq$

$$\mathrm{III} \underset{k_r}{\overset{k_f}{\rightleftarrows}} \mathrm{I}$$

$k_r[^{-}OH]$. The value of k_{obsd} was found to be $(9.5 \pm 0.7) \times 10^{-4}\ s^{-1}$, which yielded a value of 0.17 $M^{-1}\ s^{-1}$ for k_r when divided by hydroxide ion concentration. Considering the experimental uncertainties, this value agrees well with the value of 0.20 $M^{-1}\ s^{-1}$ listed (Table I) for k_{OH^-} in the approach to equilibrium from I. Extrapolation of the amount of I listed in Table IV to infinite time yielded a value of 0.36% for the equilibrium concentration of I.

Equilibration of IV and VI. 3-Cyclopentenone (Aldrich, 35 mg, purified by GLC) was injected into 2.0 ml of dilute KOH solution, which was then maintained at pH 11.7 under nitrogen with a pH stat for 10–30 min (18–53 half-lives for approach to equilibrium). The pH of the solution was then adjusted to pH 6–8 and analyzed directly with gas chromatography on a ⅛ in. 10% silicone DC-550 column. No unconjugated isomer IV was detected under conditions in which 0.01% of IV in VI could be detected in a reference solution.

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(7) The rate of exchange of the α-hydrogens in I was determined by ^1H NMR spectroscopy at ca. 35 °C (half-life of 22 min in 0.05 M DPO_4^{2-}–D_2O) and isomerization of I at 35 °C in DPO_4^{2-}–D_2O solutions was followed by uv spectroscopy.
(8) Rate-limiting transfer of D^+ to C_γ in D_2O solution would be expected to give rise to a normal solvent isotope effect of ca. 5–8, as was found for isomerization of I.
(9) For identical normal isotope effects on k_2 and k_{-1}, the ratio $[k_2/(k_{-1} + k_2)](H_2O)/[k_2/(k_{-1} + k_2)](D_2O)$ will have a value of unity.

(10) The total product was analyzed after isomerization of IV to VI was complete.
(11) The rates of exchange of I and IV in 0.05 M DPO_4^{2-}–D_2O solutions at ca. 35 °C were 5.3×10^{-4} and 1.6×10^{-4} s^{-1}, respectively.
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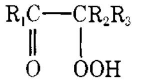
Photolysis of α-Hydroperoxy Ketones

Yasuhiko Sawaki and Yoshiro Ogata*

Contribution No. 224 from the Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya 464, Japan. *Received November 18, 1975*

Abstract: Photolysis of α-hydroperoxy ketones (**1**) has been studied, and a radical chain mechanism involving an acyl radical is proposed. Thus, the photolysis of α-hydroperoxy-α,α-diphenylacetophenone (**1a**) in benzene affords benzophenone and benzoic acid together with a small amount of biphenyl and phenol. The addition of O_2 or CCl_4 affords peracid or benzoyl chloride, respectively; and the photolysis in the presence of toluene gives products from benzyl radical. Similar products were obtained from other α-ketohydroperoxides. Quantum yields are mostly in the range of 2–3, which together with the product study suggests a radical chain decomposition involving the acyl radical as a chain carrier. Sensitization experiments indicate that the primary photoreaction of **1** is the O–O homolysis rather than the type-I or the type-II reaction as a ketone.

α-Hydroperoxy ketones (**1**) are intermediates in the autoxidative cleavage of ketones[1] and in the reaction of olefins with ozone.[2] Recently, we have shown that the alkaline decomposition of **1** proceeds mainly via a C=O addition mechanism[3] and that the thermal or redox decomposition produces acyl radicals.[4] Our interests extended to the photolysis of **1** from a viewpoint of photochemistry of ketones and photochemical air pollution. The Norrish type-I and -II reactions have been well established for the photolysis of ketones,[5] and a recent communication[6] describes the type-II reaction for the photolysis of **1**. As will be described, however, our data favor an O–O homolysis mechanism involving acyl radicals.



$R_1C(=O)—CR_2R_3(OOH)$

1

a, $R_1 = R_2 = R_3 = Ph$
b, $R_1 = p\text{-MeOPh}, R_2 = R_3 = Ph$
c, $R_1 = R_2 = Ph, R_3 = Me$
d, $R_1 = R_2 = Ph, R_3 = PhCH_2$
e, $R_1 = Mes, R_2 = R_3 = Me$
f, $R_1 = i\text{-Pr}, R_2 = R_3 = Me$
g, $R_1 = R_2 = R_3 = Me$
($Ph = C_6H_5$ or C_6H_4; Mes = mesityl)

Results and Discussion

Photolysis Products. The photolysis of α-hydroperoxy ketones (**1**) in benzene occurred easily by Pyrex-filtered irradiation. As shown in Table I, the products in benzene are ketones (55–100%) and carboxylic acids (50–80%) together with a small amount of biphenyl (1–3%) and phenol (3–5%). On addition of toluene to the reaction mixture there were obtained additional products which seem to be derived from benzyl radical, e.g., bibenzyl, benzyl alcohol, and 1,1,2-triphenylethanol.

The photolysis under O_2 affords peracids in 22–84% selectivities. These yields are lower limits, since the peracid is probably consumed by its induced decomposition.[7] The peracid formation under O_2 suggests the intervention of acyl radical; this could be ascertained by the formation of benzoyl chloride (34–94%) in the presence of CCl_4 for the case of peroxides with $R_1 = Ph$. Peracid was also formed from a photolysis of a parent ketone $PhCOCHPh_2$ under O_2 (Table I).

Product ratios at low conversions (<50%) were not significantly altered from those of high conversions (>95%). For example, the photolysis of **1a** in benzene resulted always in similar product ratios, i.e., PhCHO (2–4%), Ph_2 + PhOH (total 2–4%), $PhCO_2H$ (70–80%), and $Ph_2C=O$ (>95%). The selectivities of peracid in the presence of O_2 and acyl chloride in 50% CCl_4 were higher at lower conversions; e.g., 84% perbenzoic acid and 94% benzoyl chloride were obtained at 48 and 17% conversions, respectively.

Photolysis of peroxide **1e** (R_1 = Mes) and **1f** (R_1 = *i*-Pr) for 30 min under O_2 (78 and 33% conversions) yielded peracids in 30 and 38% selectivities, respectively. But photolysis of the parent ketones, $MesCOCHMe_2$ and $i\text{-PrCOCHMe}_2$, under the same conditions was very slow (<5% conversion), affording no peracid.

Noticeably, the yields of α-hydroxy ketones were always low (<1%) in contrast to the case of other hydroperoxides, where the alcohol formation is a main reaction.[8]

Quantum Yields and Sensitizations. The photolysis of **1a** (0.005–0.02 M) in benzene afforded comparable quantum yields of ca. 2.5; but the yields varied with the photolysis conditions, i.e., solvents or the presence of O_2 (Table II). Lower yields were obtained for the photolysis of **1a** in CCl_4 ($\Phi = 0.9$) and in *n*-hexane ($\Phi = 1.3$), and the lowest value seems to be in agreement with the reported values of $\Phi = 0.5$–1.4 for 0.025–0.5 M of **1c** in CCl_4.[6] However the photolysis of **1a** and **1d** under various conditions mostly resulted in the quantum