The Mechanism of the Acid-Catalyzed Double Bond Migration in 3-Cyclohexen-1-one and 3-Methyl-3-cyclohexen-1-one[1]

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The solvent isotope effect (k_{D_2O}/k_{H_2O}) of 1.3 observed in the acid-catalyzed isomerization of 3-methyl-3-cyclohexen-1-one to 3-methyl-2-cyclohexen-1-one in aqueous sulfuric acid demonstrates that this reaction occurs through a rate-determining enolization. However, the isomerization of 3-cyclohexen-1-one to 2-cyclohexen-1-one has a solvent isotope effect of 0.2, and the rate of hydrogen exchange (enolization) at C-2 is much faster than the rate of isomerization. Thus, it is concluded that this latter reaction occurs through a rate-determining protonation of the enol. The nature of the rate-limiting step in acid-catalyzed double bond migrations in unsaturated ketones is determined by the alkyl substitution at the carbon β to the carbonyl.

Recent results have indicated that the acid-catalyzed isomerization of β,γ to α,β unsaturated ketones proceeds *via* a rate-determining formation of the enol. In a study of the conversion of $\Delta^{5(6)}$- to Δ^4-3-keto steroids, Malhotra and Ringold[3] have concluded that a mechanism of protonation at C-6 followed by deprotonation at C-4 is ruled out by the rate reduction caused by deuterium substitution at C-4 (k_H/k_D = 4.1) and the inverse solvent isotope effect (k_{D_2O}/k_{H_2O} = 1.64). Rather, the data were consistent with an equilibrium protonation on oxygen, followed by a rate-determining formation of the enol 3-hydroxy-3,5-diene.

Closely related work by Talalay,[4] Nes,[5] and their coworkers showed that the reaction rate is proportional to the hydronium ion concentration in the pH region and that the $\Delta^{5(6)}$-3-keto steroids isomerize more than ten times faster than the $\Delta^{5(10)}$ isomers. Others have determined an entropy of activation for the isomerization of a $\Delta^{5(6)}$-3-keto steroid of -19.6 cal/deg mol.[6]

In a study initiated before these results were published, we also have examined the mechanism of this reaction in simple systems. Here we report results for the isomerization of 3-cyclohexen-1-one and 3-methyl-3-cyclohexen-1-one. Our results for 4-methyl-4-penten-2-one and 2-cyclohexen-1-yl methyl ketone are reported in the following paper.[7]

Experimental Section

1-Methoxycyclohexa-1,4-diene and 1-methoxy-5-methylcyclohexa-1,4-diene were prepared by the Birch[8] reductions of methoxybenzene and 3-methylmethoxybenzene using redistilled liquid ammonia. Addition of sodium was stopped when the blue color persisted.

3-Cyclohexen-1-one.—Two drops of 70% perchloric acid were added to a mixture of 4 g of 1-methoxycyclohexa-1,4-diene, 10 ml of carbon tetrachloride, and 25 ml of water. The two-phase system was shaken vigorously. The reaction was monitored by the nmr spectrum of aliquots from the carbon tetrachloride layer (the disappearance of the ether methyl absorbance was particularly apparent). When the reaction was nearly complete, the carbon tetrachloride layer was separated, dried with anhydrous magnesium sulfate, and filtered. After partial removal of the solvent on a rotary evaporator, the product was purified by gas chromatography (Carbowax 20M on Chromosorb W): ir (CCl_4) 1725 cm^{-1} (C=O); nmr (CCl_4) δ 2.4 (m, 4), 2.75 (m, 2), and 5.8 ppm (m, 2).

3-Methyl-3-cyclohexen-1-one.—1-Methoxy-5-methylcyclohexa-1,4-diene was hydrolyzed with a saturated solution of sodium bisulfite in water,[8] and the resulting bisulfite addition compound was converted to the desired ketone with aqueous potassium carbonate. Hydrolysis proceeded quite slowly. Purification was by preparative gas chromatography (Carbowax 20M on Chromosorb W): ir (CCl_4) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 1.7 (m, 3), 2.3 (m, 4), 2.7 (m, 2) and 5.5 ppm (m, 1).

Kinetic Procedures.—Stock solutions of about 10^{-3} mol/l. were prepared by dilution with water of a weighed sample (0.01–0.1 g) of substrate in a volumetric flask (10–100 ml). Aqueous sulfuric acid (3.0 ml) was pipetted into a 1-cm quartz spectrophotometric cell, which was then placed in the water-jacketed cell compartment of a Gilford 2000 spectrophotometer; the circulating water was supplied from a bath thermostated at 25.00 ± 0.02°. Some of the stock solution (0.05–0.1 ml) was added to the cell with a Hamilton syringe. After the solution was stirred with a glass rod, the cell was stoppered and measurements were commenced. The formation of the conjugated isomer was monitored by its absorbance at 235–237 nm.

For the experiments in heavy water solutions, 99.8% deuterium oxide was used for the stock solutions and for dilution of concentrated deuteriosulfuric acid.[9]

After completion of a kinetic run, the acidity of the solution was determined as weight per cent sulfuric acid by titration with standardized sodium hydroxide solutions of weighed aliquots of the kinetic solution to a potentiometric end point with a Metrohm Herisau 336 A potentiograph.

The Hammett acidities, H_0, were determined from the data of Bascombe and Bell[10] and of Jorgenson and Hartter.[11] The corresponding data for the deuterated media, D_0, were from Sierra, Ojeda, and Wyatt.[12]

The reactions showed pseudo-first-order behavior through at least three half-lives. Least-squares rate constants were determined by the use of the computer program LSKIN1.[13] The error limits (standard deviation) were about ±1% of the observed rate constants.

In the exchange experiment for 3-cyclohexen-1-one a mixture of 5 ml of 31.25% D_2SO_4 in D_2O and 1 ml of dioxane was diluted to 10 ml with D_2O. To 1 ml of this solution in an nmr tube was added 40 μl of 3-cyclohexen-1-one. A series of spectra was then taken (Varian A-60).

(1) Supported in part by grants from the National Science Foundation, GP-1572 and GP-6133X.

(2) National Institutes of Health Predoctoral Fellow, 1966–1968 (GM-30, 162).

(3) S. K. Malhotra and H. J. Ringold., *J. Amer. Chem. Soc.*, **87**, 3228 (1965).

(4) F. S. Kawakara, S. F. Wang, and P. Talalay, *J. Biol. Chem.*, **237**, 1500 (1962).

(5) W. R. Nes, E. Loeser, R. Kirdani, and J. Marsh, *Tetrahedron*, **19**, 299 (1963).

(6) J. B. Jones and D. C. Wigfield, *J. Amer. Chem. Soc.*, **89**, 5294 (1967).

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(8) A. J. Birch, *J. Chem. Soc.*, **593**, (1946).

(9) D. S. Noyce and M. D. Schiavelli, *J. Amer. Chem. Soc.*, **90**, 1023 (1968).

(10) K. N. Bascombe and R. P. Bell, *J. Chem. Soc.*, 1096 (1959).

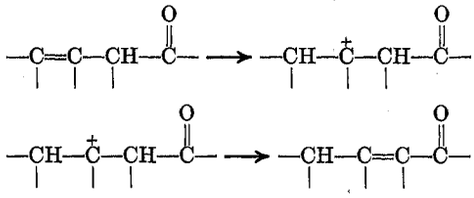
(11) M. J. Jorgenson and D. R. Hartter, *J. Amer. Chem. Soc.*, **85**, 878 (1963).

(12) J. Sierra, M. Ojeda, and P. A. H. Wyatt, *J. Chem. Soc. B*, 1570 (1970).

(13) D. F. DeTar and C. E. DeTar in D. F. DeTar, Ed., "Computer Programs for Chemistry," W. A. Benjamin, New York, N. Y., 1968, Chapter 6.

Results and Discussion

There are two plausible mechanisms for the acid-catalyzed isomerization of β,γ to α,β unsaturated ketones. One consists of protonation on the γ carbon, followed by deprotonation from the α carbon (eq 1 and 2). The other involves a dienol intermediate



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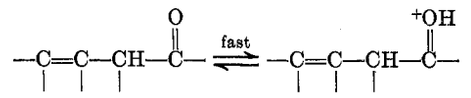
(eq 3–6). Equations 3 and 6, involving proton transfers to and from oxygen, are expected to be fast with respect to the other processes.[14]



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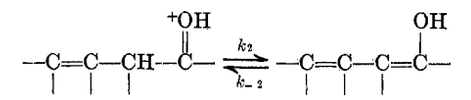

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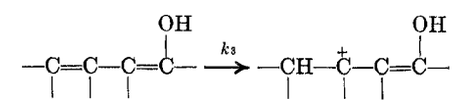

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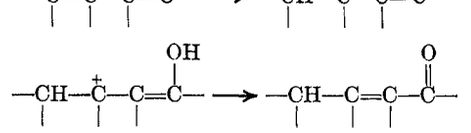

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Of the various ways of distinguishing between these mechanisms, the solvent isotope effect appears to be the most direct and conclusive.[15] Because the enolization mechanism (eq 3–6) involves a prior equilibrium protonation,[14] the solvent isotope effect (k_{D_2O}/k_{H_2O}) is expected to be greater than one. Table I summarizes the solvent isotope effects which have been observed for rate-determining acid-catalyzed enolizations.

TABLE I

SOLVENT ISOTOPE EFFECT FOR RATE-DETERMINING ENOLIZATIONS (HALOGENATIONS)

Compd	k_{D_2O}/k_{H_2O}	Ref
Acetaldehyde	1.67	*a*
Acetone	1.67	*a*
Acetone	2.1	*b*
Ethyl methyl ketone	1.67	*c*
Acetophenone	2.5	*c*

[a] P. T. McTigue and J. M. Sime, *Aust. J. Chem.*, **20**, 905 (1967). [b] O. Reitz, *Z. Phys. Chem. Abt. A*, **179**, 119 (1937). [c] B. T. Baliga and E. Whalley, *Can. J. Chem.*, **42**, 1835 (1964).

The expected solvent isotope effect for the direct protonation route (eq 1 and 2) depends upon the fact that the protonation step is rate determining, as established in an important series of experiments with steroids.[16] Thus, in the acid-catalyzed isomerization of 3-methylenecholestane to 3-methylcholest-2-ene, it was observed that the parent compound and its 2α- and 2β-deuterio and 2,2,4,4-tetradeuterio derivatives all isomerized at rates which were the same within experimental error. Proton transfers such as the second step of this route should exhibit a primary isotope effect. Since no effect is observed, it must be concluded that the second step occurs *after* the rate-determining step; *i.e.*, the reaction is a rate-determining protonation.

(14) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(15) C. A. Bunton and V. J. Shiner, Jr., *J. Amer. Chem. Soc.*, **83**, 42, 3207, 3214 (1961).
(16) R. C. Cookson, D. P. G. Hamon, and R. E. Parker, *J. Chem. Soc.*, 5014 (1962).

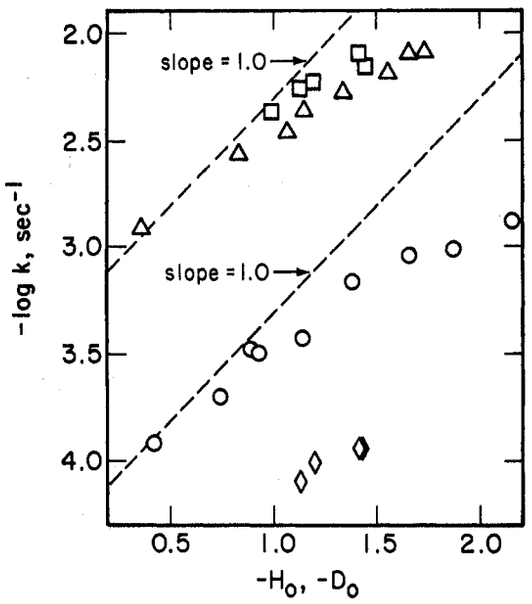


Figure 1.—Rate constants for the isomerization of 3-cyclohex-1-one and 3-methyl-3-cyclohexen-1-one in H_2SO_4 and D_2SO_4: ○, 3-cyclohexen-1-one in H_2O–H_2SO_4; ◇, 3-cyclohexen-1-one in D_2O–D_2SO_4; △, 3-methyl-3-cyclohexen-1-one in H_2O–H_2SO_4; □, 3-methyl-3-cyclohexen-1-one in D_2O–D_2SO_4.

Unfortunately, the solvent isotope effect has not been measured for olefin bond migrations occurring *via* direct protonation. However, the effects are available for other rate-determining olefin protonations. As can be seen from Table II, rate-determining protonations show solvent isotope effects significantly less than one.

TABLE II

SOLVENT ISOTOPE EFFECTS FOR RATE-DETERMINING OLEFIN PROTONATIONS

Substrate	Reaction	k_{D_2O}/k_{H_2O}
Isobutylene	Hydration	0.69[a]
Styrenes	Hydration	0.25–0.53[b]
cis-Stilbenes	Cis–trans isomerization	0.17–0.42[c]
cis-Cinnamic acids	Cis–trans isomerization	0.19–0.27[d]

[a] V. Gold and M. A. Kessick, *Pure Appl. Chem.*, **8**, 421 (1964). [b] W. M. Schubert, B. Lamm, and J. R. Keeffe, *J. Amer. Chem. Soc.*, **86**, 4727 (1964). [c] D. S. Noyce, D. R. Hartter, and F. B. Miles, *J. Org. Chem.*, **33**, 4260 (1968). [d] D. S. Noyce, H. S. Avarbock, and W. L. Reed, *J. Amer. Chem. Soc.*, **84**, 1647 (1962).

With these criteria in mind, we have measured the kinetics of the formation of 2-cyclohexen-1-one from 3-cyclohexen-1-one and of 3-methyl-2-cyclohexen-1-one from 3-methyl-3-cyclohexen-1-one in aqueous sulfuric acid and deuteriosulfuric acid at 25°. The results of the pseudo-first-order rate measurements are listed in Tables III–VI and are displayed in Figure 1. The range of acidities covered in H_2SO_4–H_2O is wide enough to show that the logarithm of the rate constant increases less rapidly than the Hammett acidity function,

TABLE III

ISOMERIZATION OF 3-CYCLOHEXEN-1-ONE TO 2-CYCLOHEXEN-1-ONE IN AQUEOUS SULFURIC ACID[a]

% H_2SO_4	$-H_0$	10^4k, sec^{-1}
10.6	0.41	1.18
14.9	0.72	1.97
17.4[b]	0.89	3.23
18.0[b]	0.93	3.15
20.9	1.14	3.73
24.4	1.38	5.38
28.3	1.66	9.05
31.2	1.87	9.79
35.0	2.17	13.3

[a] Temperature = 25.00°. [b] Stock solutions of 3-cyclohexen-1-one in water deteriorate (turn yellow) with time. These runs were done some time after the others.

TABLE IV

ISOMERIZATION OF 3-METHYL-3-CYCLOHEXEN-1-ONE TO 3-METHYL-2-CYCLOHEXEN-1-ONE IN AQUEOUS SULFURIC ACID[a]

% H_2SO_4	$-H_0$	10^3k, sec^{-1}
9.81	0.35	1.20
14.15	0.67	2.24
16.4	0.82	2.71
19.8	1.06	3.46
21.1	1.14	4.23
23.7	1.33	5.26
26.7	1.54	6.46
28.2	1.65	7.88
29.2	1.72	8.06

[a] Temperature = 25.00°.

TABLE V

SOLVENT ISOTOPE EFFECT FOR 3-CYCLOHEXEN-1-ONE

% D_2SO_4	$-D_0$	10^4k, sec^{-1}	k_{D_2O}/k_{H_2O}[a]
19.4	1.12	0.803	0.22
20.4	1.19	0.949	0.24
23.3	1.39	1.13	0.20
23.6	1.41	1.15	0.18
			Av 0.22 ± 0.03

[a] Rates in H_2O–H_2SO_4 interpolated from the data of Table III.

TABLE VI

SOLVENT ISOTOPE EFFECT FOR 3-METHYL-3-CYCLOHEXEN-1-ONE

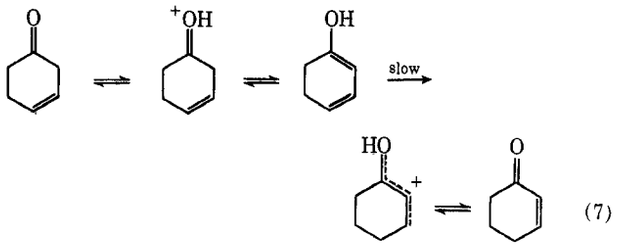
% D_2SO_4	$-D_0$	10^3k, sec^{-1}	k_{D_2O}/k_{H_2O}[a]
17.3	0.96	4.20	1.26
19.3	1.11	5.45	1.35
20.1	1.17	5.93	1.35
23.2	1.38	7.99	1.38
23.5	1.40	7.10	1.18
			Av 1.30 ± 0.08

[a] Rates in H_2O–H_2SO_4 interpolated from the data of Table IV.

as has been observed for rate-determining enolizations.[17]

The solvent isotope effect (k_{D_2O}/k_{H_2O}) of 1.3 for the isomerization of 3-methyl-3-cyclohexen-1-one is consistent with a rate-determining enolization and is in agreement with that observed by Malhotra and Ringold[3] (1.6) for this reaction. On the other hand, the solvent isotope effect of 0.2 for 3-cyclohexen-1-one is inconsistent with this mechanism. One is tempted to attribute this result to the direct protonation route, but this interpretation is clearly at odds with the comparatively rapid rate observed. In order to estimate the rate for the direct protonation route, we have interpolated the data of Beishline[18,19] for the protonation (hydration) of propylene in aqueous perchloric acid to the temperature and acidity of our experiments. Using the additional data of Taft[19,20] for the effect of substituents on the protonation (hydration) of 3-substituted isobutenes to estimate the effect of the presence of the carbonyl group, we estimate that the observed rate of isomerization of 3-cyclohexen-1-one is more than 1000 times faster than that predicted for a direct protonation of the olefin. This large difference more than compensates for any weakness in the analogies.

We conclude then that the isomerization of cyclohex-3-en-1-one also follows the lower-energy enolization route, but that the protonation of the enol has become the rate-limiting step (7). When enol formation is nearly at equilibrium (*i.e.*, relatively fast), it is little affected by the medium, and the observed solvent isotope effect is due for the most part to the slower rate of deuteration of the enol in D_2SO_4–D_2O. In general, proton transfers are slower in deuterated media; solvent isotope effects of 0.3–0.4 for the protonation of a series of enol ethers[21] and of 0.3 for acetone's enol[22] have been measured.



(7)

We have confirmed that exchange is indeed much faster than isomerization in an nmr experiment. The nmr spectrum of cyclohex-3-en-1-one in D_2O had multiplets at about 1.5 and 1.8 ppm upfield from the HDO absorbance. Presumably the former is due to the hydrogens on C-2. In the D_2SO_4–D_2O–dioxane mixture these absorbances occurred at 2.6 and 3.0 ppm upfield from HDO. The first spectrum was completed about 3 min after the substrate was added to the acid solution. At this point the absorbance due to the hydrogens at C-2 was nearly half gone. Within another 10 min no absorbance was discernible at its position. On the other hand, an absorbance appears upfield from the other absorbances at 3.4 ppm upfield from HDO, due to the C-5 hydrogens of 2-cyclohexen-1-one, which are no longer allylic after isomerization. However, about 1.5 hr were required for this peak to reach half of its final height. Thus the rate of exchange (enolization) is about 50 times the rate of isomerization; *i.e.*, the protonation of the enol at the γ position is the rate-determining step.

In the complete mechanism of the acid-catalyzed double-bond migration in unsaturated ketones shown

(17) L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.*, **61**, 2791 (1939). G. Archer and R. P. Bell, *J. Chem. Soc.*, 3228 (1959). C. G. Swain and A. S. Rosenberg, *J. Amer. Chem. Soc.*, **83**, 2154 (1961).

(18) R. R. Beishline, Ph.D. Thesis, Pennsylvania State University, University Park, Pa., 1962.

(19) P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, London, 1966, p 26.

(20) R. W. Taft, Jr., Office of Naval Research Project NR055-295 Final Report, University Park, Pa., Sept 1960. The authors are grateful to Professor Taft for copies of this report.

(21) A. J. Kresge, D. S. Sagatys, and H. L. Chen, *J. Amer. Chem. Soc.*, **90**, 4174 (1968).

(22) J. E. Dubois and J. Toullec, *Chem. Commun.*, 478 (1969).

in eq 3-6, either step 4 or step 5 will be rate-limiting depending on the relative values of the rate constants k_{-2} and k_3. Both the literature and this work confirm the role of alkyl substitution at the β carbon in determining this ratio. In those cases where this carbon is tertiary ($\Delta^{5(6)}$-3-keto steroids,[3] 3-ethoxycholesta-3,5-diene,[3] and 3-methyl-3-cyclohexen-1-one), protonation of the enol or ether occurs preferentially at the γ carbon. In those cases where the β carbon is secondary (2-hydroxyhexa-2,4-diene[23] and 3-cyclohexen-1-one), protonation at the α carbon dominates.

In the systematic study by Rogers and Sattar,[24] the acid-catalyzed hydrolysis of several conjugated enol ethers showed protonation at the α and/or γ carbon as indicated by the formation of the corresponding β,γ or α,β unsaturated ketone, respectively. Their data clearly indicate that substitution at the β carbon enhances γ over α protonation. On the other hand, substitution at the α or the γ carbon inhibits protonation at that carbon. These results are consistent with the well-known effects[25] of substitution on olefin protonation.

We conclude that in general one may expect the acid-catalyzed isomerization of β,γ unsaturated ketones to α,β unsaturated ketones to occur *via* enol intermediates. The enolization step will be rate-determining if the α carbon is primary, but the protonation of the enol will be rate-limiting if the β carbon is secondary. These two situations will be distinguishable in general by the solvent isotope effect, although intermediate cases[7] may occur.

Registry No.—3-Cyclohexen-1-one, 4096-34-8; 3-methyl-3-cyclohexen-1-one, 31883-98-4; 2-cyclohexen-1-one, 930-68-7; 3-methyl-2-cyclohexen-1-one, 1193-18-6.

(23) H. Morrison and S. R. Kurowsky, *Chem. Commun.*, 1098 (1967).
(24) N. A. J. Rogers and A. Sattar, *Tetrahedron Lett.*, 1471 (1965).
(25) Reference 19, p 43.

The Mechanism of the Acid-Catalyzed Double-Bond Migration in 4-Methyl-4-penten-2-one and 2-Cyclohexen-1-yl Methyl Ketone[1]

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The solvent–isotope effect (k_{D_2O}/k_{H_2O}) of about 1.4 observed in the acid-catalyzed isomerization of 4-methyl-4-penten-2-one to 4-methyl-3-penten-2-one in aqueous sulfuric acid demonstrates that this reaction occurs through a rate-determining enolization. The isomerization of 2-cyclohexen-1-yl methyl ketone to 1-cyclohexen-1-yl methyl ketone has a solvent–isotope effect of 1.0, and the rate of hydrogen exchange (enolization) at the α carbon is faster than the rate of isomerization; thus this reaction occurs through a rate-limiting protonation of the enol. These results are in agreement with previous results showing the role of substitution at the carbon β to the carbonyl in determining the nature of the rate-limiting step.

The acid-catalyzed isomerization of β,γ- to α,β-unsaturated ketones occurs *via* an enol intermediate. Malhotra and Ringold[3] have shown by the solvent isotope effect (k_{D_2O}/k_{H_2O}) of 1.6 that the isomerization of $\Delta^{5(6)}$- to Δ^4-3-keto steroids occurs *via* a rate-determining formation of the enol. Similarly,[4] we have concluded from the solvent isotope effect (k_{D_2O}/k_{H_2O}) of 1.3 that the isomerization of 3-methyl-3-cyclohexen-1-one to 3-methyl-2-cyclohexen-1-one also occurs by a rate-determining enolization. On the other hand, the isomerization of 3-cyclohexen-1-one to 2-cyclohexen-1-one shows a reversed solvent isotope effect (k_{D_2O}/k_{H_2O}) of 0.2, indicating a rate-limiting protonation of the enol. We concluded that, in general, β,γ unsaturated ketones with a tertiary β carbon will isomerize *via* a rate-determining enolization, while those with a secondary β carbon will isomerize *via* a rate-limiting protonation of the enol.

We describe here the results obtained for the acid-catalyzed isomerizations of 4-methyl-4-penten-2-one and 2-cyclohexen-1-yl methyl ketone. In both cases the rate of appearance of the conjugated isomer shows complex kinetic behavior, as monitored by uv measurements. A complete kinetic analysis has been carried through, and the results are consistent with the above generalization.

Experimental Section

1-(Acetoxyethylidenyl)-2-cyclohexene.—Following the method of House and Trost,[5] 5 ml of 70% perchloric acid was added to a mixture of 500 ml of carbon tetrachloride, 150 g of acetic anhydride, and 25 g of 1-cyclohexen-1-yl methyl ketone under nitrogen. After stirring for 2 hr, the solution was neutralized with a saturated solution of sodium bicarbonate. Two ether extracts of the neutral mixture were combined, washed with a saturated solution of sodium chloride, and dried with magnesium sulfate. The solvent was removed by rotary evaporation after the drying agent was removed by filtration. The 31.2 g of crude material resulting showed 84% conversion to the enol ester by gas chromatography (Carbowax 20M on Chromosorb W). Because distillation [bp 71–72° (1.2 mm)] resulted in large amounts of pot residue, analytical samples were obtained by gas chromatography: ir (CCl_4) 1750, 1670, and 1220 cm^{-1}; nmr (CCl_4) δ 1.5–2.4 (m, 6), 1.8 (s, 3), 2.0 (s, 3), 5.6 (m, 1), and 6.1 ppm (m, 1).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.09; H, 8.26.

1-Cyclohexen-1-yl Methyl Ketone.—Prepared by the rearrangement of 1-ethynylcyclohexanol according to the procedure of Newman,[6] a small sample was purified by gas chromatography (Carbowax 20M on Chromosorb W), $\lambda_{max}^{H_2O}$ 239 nm (ϵ 12,000).

2-Cyclohexen-1-yl methyl ketone was prepared by the addition of the conjugated enol acetate, 1-(acetoxyethylidenyl)-2-cyclohexene, to methyllithium according to the method of House and

(1) Supported in part by grants from the National Science Foundation, GP-1572 and GP-6133X.
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