[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Enolization as Directed by Acid and Basic Catalysts. I. The Acid-Catalyzed Enolization of Menthone

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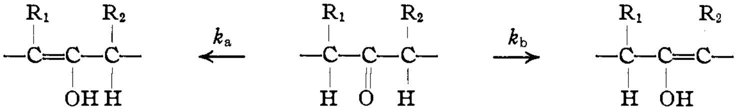
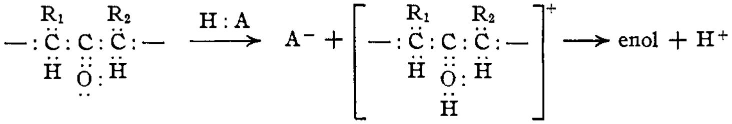
There are two reactions of ketones which have long been considered to involve enolization as a rate-controlling step. These are halogenation in the α-position to the carbonyl group,[1] and racemization (where the center of asymmetry is the α-carbon atom).[2] In a ketone having hydrogen atoms available for enolization on both sides of the carbonyl group, two enols are possible



$$-\overset{R_1}{C}=\underset{OH}{C}-\underset{H}{\overset{R_2}{C}}- \xleftarrow{k_a} -\underset{H}{\overset{R_1}{C}}-\underset{\overset{\|}{O}}{C}-\underset{H}{\overset{R_2}{C}}- \xrightarrow{k_b} -\underset{H}{\overset{R_1}{C}}-\underset{OH}{C}=\overset{R_2}{C}-$$

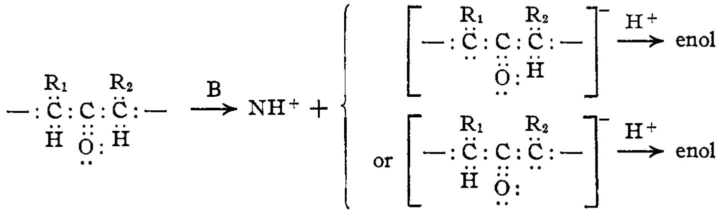
If the carbon atom bearing R_1 is asymmetric, the rate of racemization measures k_a, while the rate of halogenation of the same ketone measures $(k_a + k_b)$. A kinetic method is thus available for determining the relative amounts of enolic hydrogen furnished by the carbon atoms bearing the radicals R_1 and R_2.

This proportion is of interest in view of modern theories of the mechanism of enolization. The results of Watson and his co-workers[3] on the acid and basic catalysis of bromination of substituted acetones are best interpreted by postulating separate paths for the catalysis by acids and by bases, in accordance with the ideas of Lapworth,[4] Lowry,[5] and others. An acid, HA, functions catalytically by delivering a proton to the position on oxygen which it will occupy in the enol



$$-:\underset{H}{\overset{R_1}{\ddot{C}}}:C:\underset{H}{\overset{R_2}{\ddot{C}}}:- \xrightarrow{H:A} A^- + \left[-:\underset{H}{\overset{R_1}{\ddot{C}}}:\underset{\underset{H}{\ddot{O}:}}{C}:\underset{H}{\overset{R_2}{\ddot{C}}}:-\right]^+ \longrightarrow \text{enol} + H^+$$

A base, B, functions catalytically by removing a mobile proton from one of the α-carbon atoms



$$-:\underset{H}{\overset{R_1}{\ddot{C}}}:\underset{\ddot{O}:}{C}:\underset{H}{\overset{R_2}{\ddot{C}}}:- \xrightarrow{B} NH^+ + \begin{cases} \left[-:\overset{R_1}{\ddot{C}}:\underset{\ddot{O}:}{C}:\underset{H}{\overset{R_2}{\ddot{C}}}:-\right]^- \xrightarrow{H^+} \text{enol} \\ \text{or } \left[-:\underset{H}{\overset{R_1}{\ddot{C}}}:\underset{\ddot{O}:}{C}:\overset{R_2}{\ddot{C}}:-\right]^- \xrightarrow{H^+} \text{enol} \end{cases}$$

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(1) For a review of the literature, see Watson, *Chem. Rev.*, **7**, 173 (1930).

(2) Beckmann, *Ann.*, **250**, 360 (1889); up-to-date discussion by Wagner-Jauregg in "Stereochemie," ed. Freudenberg, Franz Deuticke, Vienna, 1933, p. 858.

(3) Hughes, Watson and Yates, *J. Chem. Soc.*, 3318 (1931); Watson and Yates, *ibid.*, 1209 (1932).

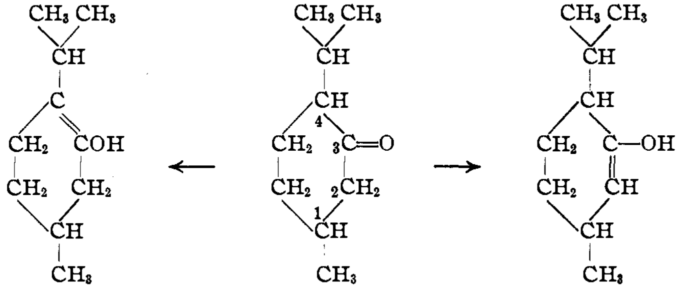
(4) Lapworth and Hann, *ibid.*, **81**, 1513 (1902).

(5) Lowry, *Chem. Rev.*, **4**, 231 (1927).

the point of attack depending upon which substituent, R_1 or R_2, more greatly enhances the removal of the nearby hydrogen as a proton.

The relative amounts of the two enols formed with a given catalyst may be expected to be some function of the polarity of R_1 and R_2, as is the case with the relative susceptibility to acid and basic catalysis of series of esters,[6] and of substituted acetones.[7] We have chosen the readily available *l*-menthone as a first example to which to apply the method. Under typical conditions of acid catalysis, we have found that 79 ± 5% of the enol produced is the form I (Δ^3-menthenol-3)

I



II

Our results using nitric acid as a catalyst in glacial acetic acid at 30.9° are

Average rate of inversion, 0.00872		
Average rate of iodination:	using 2 cc. stock iodine solution	0.01109
	using 1 cc. stock iodine solution	0.01101
	Average	0.01105

0.00872/0.01105 = 78.7% = fraction of enolic hydrogen furnished from C-atom 4.

Method.—The catalytic "inversion" of *l*-menthone has been much studied.[8] The reaction is slow in aqueous media, but proceeds at a measurable rate with strong acids or sodium alkoxides in alcohols. Since it was necessary for us to measure inversion and halogenation in the same medium, we have chosen glacial acetic acid for a solvent, which is inert to halogens in the presence of acids and bases alike.

For the halogenation experiments we used iodine, following the reaction by a colorimetric method. Iodine reacts reversibly with menthenol, according to the equation $C_{10}H_{18}O + I_2 \rightleftharpoons C_{10}H_{17}OI + HI$, and in acid media the equilibrium is largely to the left. Therefore hydrochloric and sulfuric acids, though good enolization catalysts, do not bring about iodination of menthone. Nitric acid in glacial acetic acid, however, oxidizes hydrogen iodide to iodine, thus making the reaction effectively irreversible. By using small enough amounts of iodine relative to the nitric acid present the concentration of the latter can be kept constant during reaction.

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(6) Ingold, *J. Chem. Soc.*, 1033 (1930).

(7) Hughes, Watson and Yates, *ibid.*, 3318 (1931); Watson and Yates, *ibid.*, 1207 (1932).

(8) Beckmann, *Ann.*, **250**, 355 (1889); Tubandt, *ibid.*, **339**, 41 (1904); *ibid.*, **377**, 284 (1910).

The measurement of enolization by the consumption of halogen depends on the latter's reacting instantly with the enol, so that the formation of enol is the rate-controlling step. As is seen by Fig. 1, this is not strictly so in the present case, the reaction of iodine with the enol having a finite rate which slows down the iodine consumption toward the end of a run. A few experiments showed that this is also the case with bromine. This fact makes even the initial rate of reaction to a slight degree a function of the iodine concentration, since it is easily seen that if any enol has time to revert to the keto form before reacting with iodine, the measured rate of enolization will be too low. We have corrected for this effect by applying an equation to the data which yields two constants: the true rate of enolization, and a second constant dependent upon the rate of iodination of the enol. The values for enolization rate obtained from four runs at two different iodine concentrations are in agreement, and we have accepted this value. The information obtained on the rate of iodine addition to the enol is less satisfactory. This reaction may be catalyzed in unknown ways, and even by light.[9] However, its rate is such that it can vary largely without very great effect upon the determined rate of enolization.

Experimental

Preparation of Materials.—*l*-Menthone was prepared by the dichromate oxidation of *l*-menthol:[10] yield, 76%; b. p. 204–207°; $[\alpha]^{30^\circ}_{5461}$ -33.85°.

Nitric acid was purified by distillation from an equal volume of concentrated sulfuric acid in an all-glass apparatus, then drawing dried air through the distillate under 25 mm. pressure until it was colorless. The nitric acid on standing slowly acquired a straw color, which did not affect its catalytic power.

A stock solution of iodine in glacial acetic acid was made up roughly half-saturated, and standardized. It was 0.210 *N*.

Measurement of Inversion.—To make sure that none of the catalysis involved was due to the solvent, a solution of *l*-menthone in glacial acetic acid was kept at room temperature for sixty-five hours. There was no change in optical rotation. 1 cc. of menthone and 1 cc. of nitric acid in 25 cc. of glacial acetic acid solution were used for inversion measurements. The work was carried out in a dark room whose temperature varied less than 0.1° from 30.9° during the experiments. A 1-dm. tube was used for the measurements. The total change of rotation during the reaction was about 2°. In a typical run nine readings were taken, five of them near the beginning and four near the middle of the inversion. The equilibrium value was determined in a solution to which sulfuric acid had been added,

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(9) It may also be that the reaction of hydrogen iodide with nitric acid, and not the addition of iodine to the enol, controls the rate.

(10) "Organic Syntheses," Collective, Vol. I, p. 333.

since this catalyst brought about the inversion very rapidly. Data for an inversion run are

Time interval, minutes	$\text{Log}_{10}(\alpha_1 - \alpha_\infty)/(\alpha_2 - \alpha_\infty)$	$k_1 + k_2$
95	0.3547	0.00860
94	.3501	.00859
93	.3588	.00890
93	.3547	.00879
	Average	.00872
	Mean deviation	1.5%

α_1, α_2 = optical rotations at t_1, t_2, respectively.
α_∞ = optical rotation at equilibrium.
$k_1 + k_2$ = sum of rate constants for both opposing reactions.

Iodination of Menthone.—This was followed colorimetrically, the colorimeter tube being provided with a water-jacket to maintain the temperature at 30.9°. Two pairs of runs were made, both using 1 cc. of nitric acid and 1 cc. of menthone in a total volume of 25 cc. of solution. In one pair 2 cc. of the iodine stock solution was used, in the other pair 1 cc. These concentrations of iodine gave the greatest accuracy of color matching, together with a convenient rate of reaction. Readings could be made within half a minute after mixing the solutions, and the reaction took about ten and five minutes, respectively, in the two series. The original color value was obtained by graphical extrapolation. Sample data are represented in Fig. 1. The constants were determined from the equation

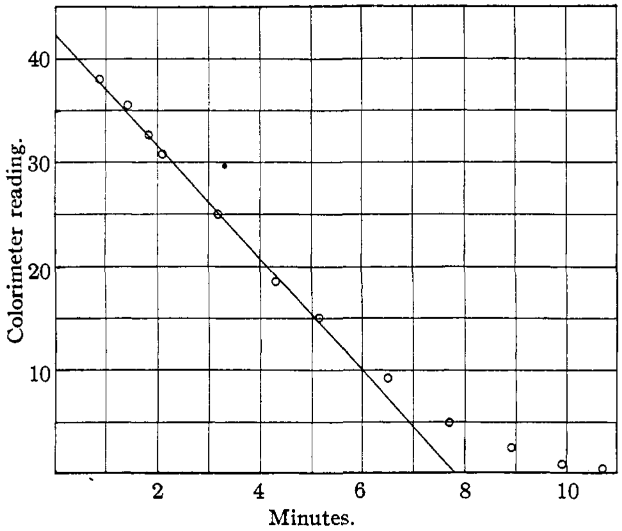

Fig. 1.

$$k_1 = \frac{1}{t}\ln\frac{x_0 + c}{x + c} + \frac{k_4}{ct}\ln\frac{x_0(x + c)}{x(x_0 + c)} \qquad (1)$$

by plotting $\frac{1}{t}\ln\frac{x_0 + c}{x + c}$ against $\frac{1}{ct}\ln\frac{x_0(x + c)}{x(x_0 + c)}$, k_1 is the $\left(\frac{1}{t}\ln\frac{x_0 + c}{x + C}\right)$ intercept of the straight line through these points. Figure 2 shows this plot for the data of Fig. 1.

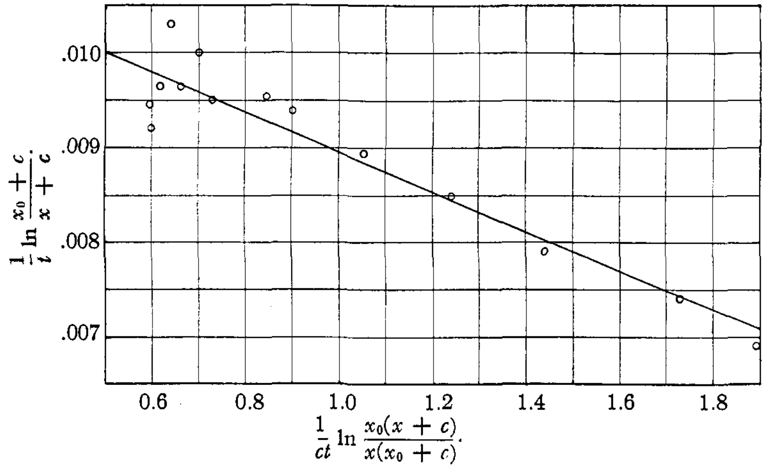

Fig. 2.

Theoretical

Relation between Rate of Enolization and Rate of Inversion.—For a true racemization *d*-ketone $\underset{k_2}{\overset{k_1}{\rightleftarrows}}$ *l*-ketone, $k_1 = k_2$ and for each two enol molecules formed, one will revert to the *d*-ketone and one to the *l*-ketone. Therefore the rate of enolization is equal to $k_1 + k_2$, which is the constant measured in racemization.

The inversion of menthone is not a true racemization, since it is the establishment of an equilibrium between diamers, *l*-menthone and *d*-isomenthone. However, the equilibrium constant between these two forms lies very close to unity,[11] and we have made the assumption that, as in racemization, the rates of enolization of *l*-menthone and *d*-isomenthone are equal. This is supported by some iodination measurements made on "inverted" menthone, in which the rate was the same as that with *l*-menthone, within the experimental error.

Derivation of Equation (1).—Given

$$\text{Menthone} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \text{menthenol}$$

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[11] Read [*Chem. Rev.*, **7**, 1 (1930)] calculates the equilibrium proportions as 52% *l*-menthone and 48% *d*-isomenthone.

$$\text{Menthenol} + I_2 \xrightarrow{k_3} \text{iodomenthone} + HI$$

$$HI \xrightarrow[\text{instant}]{HNO_3} {}^1/_2\, I_2$$

Let $x = 2[I_2]$

$e = [\text{Menthenol}]$

$x + C - e = [\text{Menthone}]$

C and $[HNO_3]$ are constant then

$$de/dt = k_1(x + c - e) - k_2e - k_3ex$$

Neglecting de/dt in comparison with dx/dt

$$de/dt = 0 = k_1(x + c) - k_1e - k_2e - k_3ex$$

$e = k_1(x + c)/(k_1 + k_2 + k_3x)$

Then $-dx/dt = k_3ex = k_1k_3x(x + c)/(k_1 + k_2 + k_3x)$

Defining $k_4 = (k_1 + k_2)/k_3$, and integrating, we have equation (1)

Discussion

That carbon atom (4) in menthone provides 79% of the enolic hydrogen is in accordance with expectations from the electronic theory. The isopropyl group, like all akyl groups, is an electron-repelling group.[12] The enolization intermediate represented above for acid-catalyzed reaction tends to stabilize itself by drawing an electron pair to the central carbon and saturating the OH group. This electron pair is most readily supplied from that carbon atom which holds electron-repelling substituents.

Summary

1. A quantitative method is described for determining the relative amounts of enolic hydrogen provided from competing positions in an optically active ketone.

2. A probable relationship of this ratio to the chemical character of substituent groups is discussed.

3. The method has been applied to the acid-catalyzed enolization of menthone, and it has been found that 79% of the enolic hydrogen is provided by the carbon atom holding the isopropyl group.

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[12] R. Robinson, "Versuch einer Elektronentheorie organisch-chemischer Reaktionen" [Ahrens Sammlung, N. F. No. 14], Stuttgart, 1932, p. 37.