# Use of Hydrogen Isotope Effects to Determine the Timing of Proton Transfer Relative to Nucleophilic Attack in the Enolization of Ketones and Reactions of Epoxides Catalyzed by Acetic Acid[1-3]

By C. Gardner Swain, Anthony J. Di Milo and John P. Cordner

Catalysis by acetic acid of enolization of $\alpha$-phenylisocaprophenone in aqueous dioxane at 100° or of reaction of epichlorohydrin with iodide ion in water solution at 25° is not due to proton transfer during the rate-determining step, i.e., concerted with nucleophilic attack, but instead to proton transfer in a prior fast equilibrium step in each case, with the conjugate acid oxonium ion as a true intermediate. The magnitude of the proton/deuterium isotope effect determined by running these reactions in both light and heavy water is approximately unity, which is low considering that acetic acid is a considerably stronger acid than acetic acid-$d$ but explicable if all proton transfers between oxygen atoms are equilibrium-controlled. The conspicuous absence of any third-order term in the mutarotation of tetramethylglucose in aqueous acetone catalyzed by pyridinium ion and by pyridine is consistent with a prior equilibrium for protonation by pyridinium ion. Evidence suggests that special cyclic polyfunctional mechanisms are responsible for the third-order acetic acid–acetate ion term in the enolization of acetone in water at 25° and for the acetic acid term in the mutarotation of glucose in water at 18°.

Hydrogen isotope effects provide a powerful tool for determining whether proton transfers occur during, prior to, or subsequent to the rate-determining step.[4,5] This paper will illustrate their use in mechanistic studies of enolization of ketones and reactions of epoxides both catalyzed by acetic acid in aqueous solutions.

**Enolization of $\alpha$-Phenylisocaprophenone Catalyzed by Acetic Acid.**—In the previous paper[2] it was established that when acetic acid acts as a catalyst for the enolization of $\alpha$-phenylisocaprophenone in aqueous dioxane at 100°, the base which removes the proton from carbon is not water but acetate ion. Therefore the mechanism

$$\text{AcOH} + \text{O=CCH} + \text{H}_2\text{O} \longrightarrow$$
$$\text{AcO}^- + \text{HOC=C} + \text{H}_3\text{O}^+$$
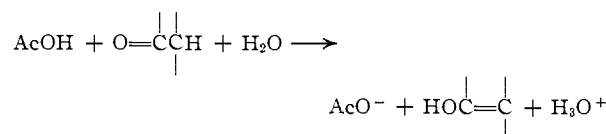
is eliminated, but two possibilities still remain. The enolization may have a "Lowry type" concerted (one-step) mechanism[6-8]

$$\text{H}_3\text{O}^+ + \text{O=CCH} + \text{AcO}^- \longrightarrow$$
$$\text{H}_2\text{O} + \text{HOC=C} + \text{HOAc} \quad (1)$$
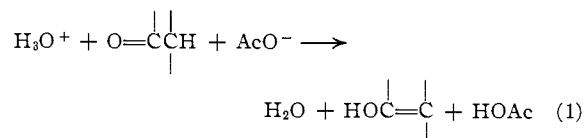
of a "Pedersen" type stepwise mechanism[9]

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(2) For Part I on use of hydrogen isotope effects to identify the attacking nucleophile in the enolization of ketones catalyzed by acetic acid, cf. C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, This Journal, 80, 5885 (1958).

(3) For complete experimental data on the mutarotation of tetramethylglucose in aqueous acetone, cf. Anthony J. Di Milo, Ph.D. Thesis in Organic Chemistry, M.I.T., September, 1953, pp. 1–193.
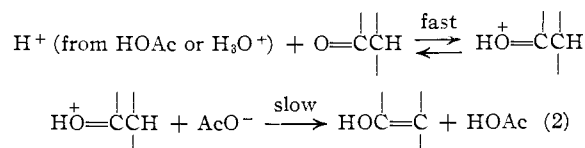
(4) K. B. Wiberg, Chem. Revs., 55, 713 (1955).

(5) C. G. Swain and A. D. Ketley, This Journal, 77, 3410 (1955).

(6) T. M. Lowry and I. J. Faulkner, J. Chem. Soc., 2883 (1925).

(7) C. G. Swain, This Journal, 72, 4578 (1950).

(8) C. G. Swain and J. F. Brown, ibid., 74, 2534, 2538, 2691 (1952).

(9) K. J. Pedersen, J. Phys. Chem., 38, 590 (1934).

$$\text{H}^+ \text{(from HOAc or H}_3\text{O}^+\text{)} + \text{O=CCH} \overset{\text{fast}}{\underset{}{\rightleftharpoons}} \text{HO=CCH}^+$$

$$\text{HO=CCH}^+ + \text{AcO}^- \overset{\text{slow}}{\longrightarrow} \text{HOC=C} + \text{HOAc} \quad (2)$$

If the two-step mechanism (2) is correct, the isotope effect can be estimated from the relationships

$$\begin{aligned}
\text{rate} &= k_0(\text{R}_2\text{CO}) + k_{\text{H}^+}(\text{H}^+)(\text{R}_2\text{CO}) + \\
&\qquad k_{\text{HA}}(\text{RCOOH})(\text{R}_2\text{CO}) \\
&= k_0(\text{R}_2\text{CO}) + k(\text{R}_2\text{COH}^+) + \\
&\qquad k'(\text{RCOO}^-)(\text{R}_2\text{COH}^+) \quad (3)
\end{aligned}$$

$$K_{\text{HA}} = (\text{H}^+)(\text{RCOO}^-)/(\text{RCOOH})$$
$$K_{\text{HS}} = (\text{H}^+)(\text{R}_2\text{CO})/(\text{R}_2\text{COH}^+)$$
$$k_{\text{H}^+} = k/K_{\text{HS}}$$
$$k_{\text{HA}} = k'K_{\text{HA}}/K_{\text{HS}} \quad (4)$$
$$k_{\text{H}^+}/k_{\text{D}^+} = K_{\text{DS}}/K_{\text{HS}} \quad (5)$$
$$\frac{k_{\text{HA}}}{k_{\text{DA}}} = \frac{K_{\text{DS}}}{K_{\text{HS}}}\frac{K_{\text{HA}}}{K_{\text{DA}}} = \frac{k_{\text{H}^+}}{k_{\text{D}^+}}\frac{K_{\text{HA}}}{K_{\text{DA}}} \quad (6)$$

The rate constants $k$ and $k'$ cancel in the isotope effects (equations 5 and 6) because it is assumed that they are not affected by the variation from light to heavy solvent. The ratio of isotope effects $k_{\text{H}^+}/k_{\text{D}^+}$ for many hydrogen ion-catalyzed reactions of ketones, esters and sugars in water at 25°, where a prior equilibrium is almost certainly involved, is 0.49–0.35.[4] The ratio of acidities of the carboxylic acids in light and heavy solvent $k_{\text{HA}}/K_{\text{DA}}$ is 3.3 for acetic acid in water at 25°.[10] The expected isotope effect for catalysis by acetic acid in water solution at 25° should therefore be the product of these numbers, or 1.6–1.15, provided that protonation of the substrate occurs in a prior equilibrium step.

At 100° the isotope effect would be expected to be less. The ratio of ionization constants for light and heavy water[11] drops from 5.1 at 25°, where $K_{\text{H}_2\text{O}} = 1 \times 10^{-14}$, to 3.3 (extrapolated) at 100°, where $K_{\text{H}_2\text{O}} = 3.3 \times 10^{-13}$. The ratios $K_{\text{HA}}/K_{\text{DA}}$ and $K_{\text{HS}}/K_{\text{DS}}$ would be expected to fall also. Therefore a reasonable estimate for the isotope effect at 100° corresponding to mechanism 2 would be even closer to unity than at 25°.

(10) C. K. Rule and V. K. LaMer, This Journal, 60, 1974 (1938); F. Brescia, V. K. LaMer and F. C. Nachod, ibid., 62, 614 (1940).

(11) W. F. K. Wynne-Jones, Trans. Faraday Soc., 32, 1397 (1936).

If the one-step mechanism (1) were correct, there would be a proton transfer from $H_3O^+$ to ketone in the rate-determining step. Then because of the difference in zero-point vibrational energy between OH and OD bonds, the isotope effect in water at 25° should be *larger* by a factor of at least two than calculated for mechanism 2. We might first illustrate this factor in a system not complicated by differences in ionization of weak acids. In the uncatalyzed mutarotation of glucose in water at 25° the factor $k_{H_2O}/k_{D_2O}$ is 3.8 due to proton transfer from one oxygen to another in the rate-determining step. The decomposition of diazo compounds by hydrogen ion in ethanol provides another illustration. It is known from independent evidence on rate of deuterium exchange of the reactant that the decomposition of ethyl diazoacetate involves protonation in a prior equilibrium.[12-14] On the other hand, kinetics and competition experiments show that the proton transfer occurs in the rate-determining step with diphenyldiazomethane. The isotope effects $k_{H^+}/k_{D^+}$ are in accord with this, 0.55 for ethyl diazoacetate and 1.45 for diphenyldiazomethane.[12-14] Thus there is a factor here of nearly three. Therefore an isotope effect greater than two would be expected for a reaction catalyzed by acetic acid proceeding by mechanism 1.

The measured isotope effect ($k_{HOAc}/k_{DOAc}$ from studies of the acetic acid-catalyzed racemization of phenylisocaprophenone in light and heavy water with 59 mole % water–41 mole % dioxane (approximately 72% dioxane by volume) at 100° is 1.09, *i.e.*, very close to unity. Details are given in the Experimental section. This is clearly inconsistent with mechanism 1, but in accord with mechanism 2.

Strictly speaking, the isotope effect proves only that the bonds to the hydrogens which are isotopically substituted are normal (not stretched) in the transition state. However, the mechanism cannot be a one-step process in which the transition state comes before the OH bond of the hydrogen ion has stretched significantly because then water should have almost as high a catalytic coefficient as hydrogen ion instead of one too small to be detectable. The other possibility, *viz.*, completed transfer of the proton to the ketonic oxygen before the transition state, would be physically practically equivalent to mechanism 2 in which the proton transfer occurs in a rapid prior equilibrium step.

Our results on α-phenylisocaprophenone in aqueous dioxane at 100° are quite similar to those of Reitz[15,16] on acetone in water at 25°, and this indicates a close similarity of mechanism. Reitz found an isotope effect ($k_{HA}/k_{DA}$) of 1.5 for acetic acid catalysis, suggesting that the two-step mechanism also applies to the enolization of acetone catalyzed by acetic acid in water solution at 25°.

This conclusion is consistent with those of Pedersen,[9] Reitz,[15,16] and Bell.[17] It is contrary to conclusions based on the existence of a third-order

(12) J. D. Roberts, W. Watanabe and R. E. McMahon, THIS JOURNAL, **73**, 760 (1951).
(13) J. D. Roberts, C. M. Regan and I. Allen, *ibid.*, **74**, 3679 (1952).
(14) J. D. Roberts and C. M. Regan, *ibid.*, **74**, 3695 (1952).
(15) O. Reitz, *Z. physik. Chem.*, **A179**, 119 (1937).
(16) O. Reitz and J. Kopp, *ibid.*, **A184**, 429 (1939).
(17) R. P. Bell and P. Jones, *J. Chem. Soc.*, **88** (1953).

term involving both acetic acid and acetate ion,[18] and the assumption that the process responsible for the third-order term has a mechanism similar in type to that for the other terms in the rate expression.[19]

Bell and Lidwell determined the catalytic effect of four carboxylic acids and their anions on the iodination of acetone in water at 25°.[20] These (and their acid dissociation constants $K_{HA}$ in water at 25°) were trimethylacetic ($9.1 \times 10^{-6}$), acetic ($1.75 \times 10^{-5}$), glycolic ($1.54 \times 10^{-4}$) and monochloroacetic ($1.38 \times 10^{-3}$). The Brönsted catalysis law correlating the catalytic coefficients for the four carboxylic acids is

$$k_{HA} = 2.4 \times 10^{-3} K_{HA}^{0.55} \qquad (7)$$

The law correlating the catalytic coefficients for the four corresponding carboxylate anions is

$$k_B = 9.1 \times 10^{-10}(1/K_{HA})^{0.88} \qquad (8)$$

The fits are excellent. The equations would not be significantly different if determined just from the pair trimethylacetic and acetic alone, or just from the pair acetic and glycolic alone.

The fact that the sum of the two exponents is 1.43 rather than 1.00 may be significant. We assume that at least one other of these acids is reacting by the same mechanism as acetic acid, *viz.*, by prior protonation of the acetone followed by rate-determining attack by the carboxylate anion on the oxonium ion. If the relative reactivities of the two anions were the same toward the oxonium ion (which they attack in the $k_{HA}$ process) as toward the free acetone (which they attack in the $k_B$ process) then the sum of the exponents ($\alpha + \beta$) should be 1.00. This follows from equations 3 and 4 and the relationships

$$k_{HA} = C_1 K_{HA}{}^\alpha$$
$$k' = C_2(1/K_{HA})^\beta$$
$$k_B = C_3(1/K_{HA})^\beta$$

where $C_1$, $C_2$ and $C_3$ are parameters independent of the carboxylic acid. The fact that $\alpha$ is 0.55 rather than the calculated $1.00 - 0.88 = 0.12$ means that the acetone oxonium ion is much *less* discriminating among the different carboxylate anions than is acetone, with a $\beta$ which is 0.45 instead of 0.88. Thus the reactivities of the four carboxylate ions relative to acetate ion are only 1.34:1.00:0.38:0.14 toward acetone oxonium ion *vs.* 1.68:1.00:0.16:0.02 toward acetone itself. This is a change by a factor of $10^{0.43} = 2.7$ in relative reactivity for each power of ten change in basicity. Extrapolating over the much larger change from acetate ion to hydroxide ion predicts a decreased relative reactivity of hydroxide ion toward acetone oxonium ion of the order of $(10^9)^{0.43} \cong 10^4$, and an increase for water of the order of $(10^5)^{0.43} \cong 10^2$. Such extrapolations to bases of such different structural type and basicity are certainly not justifiable quantitatively, but they do show the danger in assuming that there will be no change at all in relative reactivity of the different bases on changing from acetone to acetone oxonium ion. Recognition of such changing rela-

(18) H. M. Dawson and E. Spivey, *ibid.*, 2180 (1930).
(19) C. G. Swain, THIS JOURNAL, **72**, 4581 (1950).
(20) R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc. (London)*, **A176**, 96 (1940).

tive reactivities has the effect of increasing the calculated proportion of the "uncatalyzed" term which is due to only water molecules rather than to hydrogen ion and hydroxide ion.[21]

**The Third-order Acetic Acid-Acetate Ion Term in the Enolization of Acetone.**—The third-order acetic acid–acetate ion term in the enolization of acetone in water at 25° observed by Dawson and Spivey[18] and confirmed by Bell and Jones[17] then becomes a special problem to interpret. Bell found

$$k_1 = 2.8 \times 10^{-8} + 1.6 \times 10^{-3}(\text{H}^+) + 15(\text{HO}^-) + 5.0 \times$$
$$10^{-6}(\text{HOAc}) + 1.5 \times 10^{-5}(\text{AcO}^-) +$$
$$2.0 \times 10^{-5}(\text{HOAc})(\text{AcO}^-)$$

The third-order term contributes 16% of the total rate with 0.2 $M$ acetic acid and 0.2 $M$ acetate ion. A stepwise mechanism involving reversible protonation by acetic acid followed by slow reaction with acetate ion predicts only a second-order term, first order in acetic acid but zero order in acetate ion. We earlier suggested that the third-order term represents a concerted reaction with acetic acid as the electrophile and acetate ion as nucleophile. However, this now seems strange because acetic acid apparently does not catalyze either the reaction with hydroxide ion (a stronger base than acetate ion) or water (a weaker base than acetate ion). Why should acetic acid be effective in catalyzing only the reaction in which acetate ion is the nucleophile? Perhaps there is a special cyclic transition state, peculiar to mixtures of carboxylic acid and carboxylate anion.
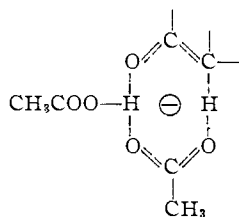


Note that this transition state has the same favorable geometry as acetic acid dimer.[22] The hydrogen on the left was bonded to the acetate on the left in the ground state; it will be on the enol in the product. The acetate at the bottom is the nucleophile which is removing the proton from the $\alpha$-carbon. An acetic acid molecule alone might not be able to engage in a cyclic process as effectively because the Brönsted $\beta$ is so large for enolization and because the basicity (and hence nucleophilic reactivity) of acetic acid is so very much less than that of an acetate ion. The advantage of this cyclic transition state, possible only with a carboxylate ion, is the additional stabilization which it provides for the proton close to the carbonyl oxygen.

**Mutarotation of Glucose Catalyzed by Acetic Acid.**—Our previous conclusion that catalysis of the mutarotation of glucose by acetic acid is due to acetic acid rather than to hydrogen ion and acetate ion[7] was based on assuming constant relative reactivities. Since the assumption of constant rela-

tive reactivities is now in doubt we must reexamine the interpretation. Here the Brönsted law slopes are only 0.27 for 8 carboxylic acids and 0.36 for 13 carboxylate anions (each set including trimethylacetic, acetic, glycolic and monochloroacetic).[23,24] If we were to assume that all carboxylic acid catalysis is really due to hydrogen ion and carboxylate anions, we would calculate that glucose oxonium ion is considerably *more* discriminating ($\beta = 0.73$) among the different carboxylate ions than glucose itself. We consider this conclusion untenable, and therefore again conclude that, in mutarotation, acetic acid molecules really are involved. Perhaps carboxylic acids are effective catalysts for mutarotation because they can react in water by almost the same mechanism earlier proposed for benzene,[8]
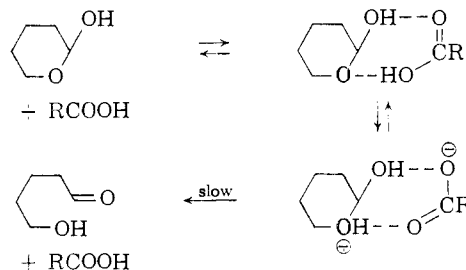


utilizing their bifunctional character and special spacing of functional groups, which permits *hydrogen-bonding at two point simultaneously*. This is consistent with the much lower $\alpha$ (0.27) than the $\alpha$ calculated from the behavior of carboxylate anions (0.64), because this reaction is a cyclic process in which the higher reactivity of a more basic anion in proton removal in the slow step is partially offset by reduced acid activation due to hydrogen-bonding of the glucose oxonium ion with that same base at the other center. The mechanism in which *both* protons are transferred prior to the rate-determining step can be excluded by the isotope effects observed in light and heavy water. These are 3.8 for the uncatalyzed term involving only water, 2.5 for acetic acid, 2.6 for acetate ion and 1.37 for hydrogen ion.[25] The isotope effect for acetic acid should have been about unity (as with $\alpha$-phenylisocaprophenone above and epichlorohydrin below) if all proton transfers were complete before the rate-determining step.

**Proof of Absence of Third-order Terms in Mutarotation Catalyzed by Pyridinium Ion and Pyridine.**—The special cyclic mechanisms that we have proposed for the third-order acetic acid–acetate ion term in the enolization of acetone and for the acetic acid term in the mutarotation of glucose would not be possible with catalysts like pyridinium ion and pyridine. Here the ring sizes are unfavorable because, excluding the hydrogens, they are four-membered. It seems proper to exclude the hydrogens because hydrogen bonds are linear and hydrogen-bonded oxygen or nitrogen atoms are almost as close together as if they were directly bonded without hydrogen between. There-

(21) The extrapolation to water is especially uncertain because, unlike the other acids, water merely provides dipolar solvation or hydrogen-bonding to the enolate anion, rather than transferring a proton to it to give an enol. This difference in the usual function of this particular acid makes it especially hard to predict its reactivity quantitatively relative to the other acids.

(22) G. Allen and E. F. Caldin, *Quart. Revs.*, **7**, 255 (1953).

(23) J. N. Brönsted and E. A. Guggenheim, THIS JOURNAL, **49**, 2554 (1927).

(24) L. P. Hammett, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1940, p. 226.

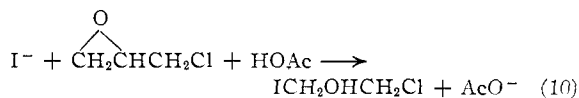(25) W. H. Hamill and V. K. LaMer, *J. Chem. Phys.*, **4**, 395 (1936).

fore, by analogy to enolization, pyridinium ion catalysis should involve proton transfer in a prior equilibrium step and we would predict that there would be no observable third-order term even if the water concentration were considerably reduced. The experimental expression for the mutarotation of tetramethylglucose in pyridinium ion–pyridine buffers in aqueous acetone containing only 5.50 $M$ water at 25° is

$$k_1 = [4.0 \times 10^{-6} + 4.52 \times 10^{-2} (H^+) + 1.26 \times 10^3 (HO^-) + 8.4 \times 10^{-4} (C_5H_5NHClO_4) + 1.3 \times 10^{-4} (C_5H_5N)]e^{0.450\mu}$$
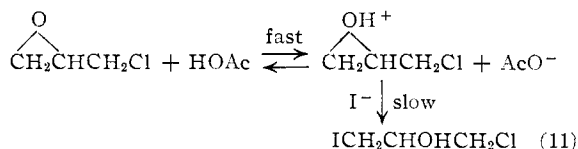
(9)

where $\mu$ is the ionic strength. No third-order pyridinium ion-pyridine term was detected in spite of a careful search.[3] This is in striking contrast to the mutarotation of tetramethylglucose by phenol and pyridine in benzene solution where no term less than third-order was found.[8] Apparently, with pyridinium ion and pyridine in aqueous acetone, only the Pedersen mechanism is at work; yet in benzene the Lowry mechanism predominates.

In several other reactions, third-order terms are conspicuously missing. Hill and Thumm found none in the mutarotation of glucose in aqueous solutions of varying methanol content at 35–45°.[26] Bell and Clunie found none in the hydration of acetaldehyde catalyzed by acetic acid and acetate ion in water solution at 0°.[27] Evidently the Pedersen mechanism also operates in these reactions. The failure of acetic acid–acetate ion terms to appear in mutarotation of glucose or hydration of acetaldehyde in highly aqueous solutions as a result of the cyclic mechanism proposed for enolization of acetone is evidently a result of the much lower discrimination (Brönsted $\alpha$ and $\beta$) toward acids and bases shown by glucose and acetaldehyde, which favors participation of water, because of its higher concentration, as acid or base or both.

**Reaction of Iodide Ion with Epichlorohydrin Catalyzed by Acetic Acid.**—Two mechanistic possibilities exist for catalysis of the reaction of iodide ion with epichlorohydrin in water solution at 25°. It could be a concerted mechanism

$$I^- + CH_2CHCH_2Cl + HOAc \longrightarrow$$
$$ICH_2OHCH_2Cl + AcO^- \quad (10)$$

or a stepwise one

$$CH_2CHCH_2Cl + HOAc \underset{fast}{\rightleftarrows} CH_2CHCH_2Cl + AcO^-$$
$$I^- \downarrow slow$$
$$ICH_2CHOHCH_2Cl \quad (11)$$

The concerted mechanism suggested earlier[28] has been disproved by measuring the isotope effect in light vs. heavy water. The isotope effect $k_{HA}/k_{DA}$ is 1.0, which is remarkably low even for the Pedersen mechanism (equation 11), for which 1.6-1.15 was expected, and certainly inconsistent with the Lowry mechanism (10), for which an isotope effect of at least two was expected.

(26) D. G. Hill and B. A. Thumm, This Journal, **74**, 1380 (1952).

(27) R. P. Bell and J. C. Clunie. Proc. Roy. Soc. (London), **A212**, 33 (1952).

(28) C. G. Swain, This Journal, **74**, 4108 (1952).

## Experimental

**Reactants.**—D(+)-$\alpha$-Phenylisocaprophenone was prepared as described earlier,[2] except on a larger scale. From 197 g. of L(−)-leucine, 103 g. of ketone was obtained, m.p. 51.5–52.5°, $[\alpha]^{30}D$ 150° (absolute ethanol), $[\alpha]^{23}D$ 157° (dioxane).

Epichlorohydrin (Eastman Kodak Co. white label) was distilled through a 30-in. glass-helices column at a reflux ratio of 15:1, collecting a small center cut, b.p. 116.1°.

Tetramethylglucose was prepared by the method of West and Holden.[29] After purification, it was enriched with respect to the $\alpha$-form by repeated crystallization and dissolution in petroleum ether. The sugar was filtered only after the tenth crystallization. The crystallization was continued until the specific rotation in 90% acetone-10% water at 5461 Å. exceeded 100°.

Sodium chloride and iodide were reagent grades dried two days at 130°. Sodium acetate and perchlorate were anhydrous reagent grades dried two days at 200°. Pyridine was reagent grade dried over Drierite. Pyridinium perchlorate was precipitated from a well-stirred aqueous solution of pyridine at 0° by addition of reagent perchloric acid. After filtering and drying overnight at 110° it had m.p. 293.8–294.7° (dec.), neutral equivalent 179.1.

**Solvent.**—Distilled water was redistilled from potassium permanganate in an all-glass apparatus. Heavy water was used as supplied by Stuart Oxygen Co. (99.5% $D_2O$). Acetic acid and acetic acid-$d$ stock solutions were prepared by dissolving acetic anhydride (Merck analytical reagent 97%) in light or heavy water. Dioxane was prepared and stored as described earlier.[2] Acetone was Mallinckrodt analytical reagent used without further purification. Aqueous acetone solutions were made by weighing the water for 5.50 $M$ in a volumetric flask.

The preparation of ketone reaction mixtures was altered slightly from the procedure described earlier[2] in order to keep the dioxane–water ratio constant. In the previous work the molarity of dioxane was kept constant and therefore the water concentration decreased slightly (from 26% to 21.5% by volume) as the acetic acid concentration increased from 0 to 1.0 $M$. In the work reported in this paper, the solvent only (water plus dioxane) was constant at 59 mole % water-41 mole % dioxane in most of the experiments, but a few were done with 49 mole % water-51 mole % dioxane to find how dependent the results were on the exact composition of the solvent. It is hard to say whether it is better to keep the molarity of dioxane constant, as was done earlier,[2] or to keep the ratio of dioxane to water constant, as is done here. In any case this slight change in conditions would be expected to have practically no effect on the ratios of catalytic coefficients involved in isotope effects.

**Kinetic Procedure for $\alpha$-Phenylisocaprophenone.**—In general the procedure was the same as described in the previous paper.[2] All reaction solutions were initially 0.100 $M$ in ketone and 0.100 $M$ in sodium chloride. As an example of the preparation of the solutions, the 0.75 $M$ acetic acid solutions were made by combining 37 ml. of 0.135 $M$ ketone in dioxane, 6.00 ml. of 6.25 $M$ HOAc or DOAc in water (containing 3.98 ml. of $H_2O$ or $D_2O$), 2.00 ml. of 2.50 $M$ sodium chloride (containing 1.87 ml. of $H_2O$ or $D_2O$), 5.20 ml. of $H_2O$ or $D_2O$ and 0.56 ml. of dioxane. Because of the 1.5% contraction in volume in mixing, the final volume was 50 ml., and these 0.75 $M$ acetic acid solutions contained 8.5 $M$ dioxane and, in the one with $H_2O$, 12.3 $M$ water. The temperature was 99.6 ± 0.1° for all runs.

Table I presents the kinetic data. The figures reported are averages of duplicate runs with an average range of 3% and maximum range of 8%. Of each duplicate pair, one was carried out in a sealed Pyrex tube, the other in soft glass. Polarimetric readings to four figures were taken on a Rudolph model 80 high-precision polarimeter in a 2-dm. (2.3-ml.) cell. The initial measured rotations were about 7.4°. Catalytic coefficients for acetic acid in 59.4 mole % water calculated from the data of Table I are $k_{HOAc}$ = 0.1044 × $10^{-6} M^{-1}$ sec.$^{-1}$, $k_{DOAc}$ = 0.0958 × $10^{-6} M^{-1}$ sec.$^{-1}$, corresponding to an isotope effect $k_{H2O}/k_{D2O}$ of 1.09.

**Kinetic Procedure for Tetramethylglucose.**—All mutarotations were run in a 4-dm. water-jacketed polarimeter tube supplied from a 25.00 ± 0.5° thermostat bath. Readings were taken on a Rudolph model 80 high-precision polarimeter using a General Electric type S-4 sunlight lamp and

(29) E. S. West and R. F. Holden, Org. Syntheses, **20**, 97 (1940).

## TABLE I

RACEMIZATION OF D(+)-α-PHENYLISOCAPROPHENONE CATALYZED BY ACETIC ACID IN LIGHT AND HEAVY WATER–DIOXANE SOLUTIONS AT 99.6°

| (HOAc), M | Water[a] mole % | Observed rate constants | |
|---|---|---|---|
| | | $k_{H_2O}$[b] $\times 10^6$, sec.$^{-1}$ | $k_{D_2O}$[c] $\times 10^6$, sec.$^{-1}$ |
| 0.50 | 59.4 | 0.0710 | 0.0635 |
| .75 | 59.4 | .0971 | .0877 |
| 1.00 | 59.4 | .1230 | .1111 |
| 1.00 | 49.2 | .1110 | .0858 |

[a] Expressed as mole per cent. of solvent (water plus dioxane) only, excluding moles of acetic acid and sodium chloride. The 59.4 mole % water is approximately the solvent used by Stivers[2] and is approximately 72% dioxane. [b] First-order rate constant in H$_2$O. [c] First-order rate constant in D$_2$O.

a filter to isolate the 5461 Å. mercury line. Perchloric acid was used as the source of hydrogen ion. In this paper, $k_1$ for mutarotation is the sum of forward and reverse rate constants. Some of the observed $k_1$ values are compared with $k_1$ values calculated from equation 9 in Table II. Any effect of complexing is neglected.

The pH values were determined with a Beckman model G pH meter and glass electrode. The meter was calibrated against the buffers of Cray and Westrip for 90% acetone.[30] The meter readings on these buffers were uniformly 1.5 units lower than the known pH values in 90% acetone and independent of pH in the region tested. The buffers were composed of various acid–base combinations, including both neutral acid–anionic base and cationic acid–neutral base charge types. Consequently all meter readings of unknown solutions were corrected by adding 1.5 to obtain the pH. This method for measuring pH is an empirical one restricted to work in one solvent (here 90% acetone), but in no way depends on the (invalid) assumption that all $K_{HA}$ values shift equally on going from water to 90% acetone. The pH values thus obtained with equimolar pyridine–pyridinium perchlorate buffers were linear in square root of ionic strength.

$$pK_A = 4.08 + 2.11\sqrt{\mu}$$

The autoprotolysis constant of water is $3.3 \times 10^{-20}$ in 90% acetone.[31] This value was used to calculate hydroxide concentrations from the measured pH readings for use in evaluating the catalytic coefficient for hydroxide ion. The ionization constants of pyridinium ion and pyridine at zero ionic strength in this medium at 25° were calculated from these data to be $8.3 \times 10^{-5}$ and $4.0 \times 10^{-16}$.

The complexing between pyridinium ion and pyridine in the aqueous acetone was studied by use of a Jones–Kaplan equilibrator.[32] Because of the slowness of attainment of equilibrium it was possible to conclude only that the complex instability constant is *greater than* 0.25 M in this medium. For example, a solution initially 0.10 M pyridinium perchlorate and 0.10 M pyridine in this medium at 25° lost pyridine to one initially 0.05 M in pyridine. The first solution fell to 0.0809 M and the second rose to 0.0613 M in 17 days (not yet equilibrium). Thus the constant is greater than 0.0613 (0.0804)/0.0196 = 0.25. There was no transfer of water as shown by titration of acid after reaction of aliquots of the final solutions with acetyl chloride.[33] This constant (0.25) is sufficiently high to ensure that less than half of the pyridinium ion is complexed even at the highest concentrations that we used (0.02 M pyridinium ion plus 0.25 M pyridine).[3]

Assuming constant relative reactivities for all the acids and likewise for all the bases and assuming that all terms correspond to Lowry-type mechanisms gives an expression differing from the experimental one by the term $2.3 \times 10^{-2}$ [C$_5$H$_5$NHClO$_4$][C$_5$H$_5$N]$e^{0.450\mu}$. The rate constants calculated with inclusion of this term are in complete disagreement with the experimental results, even after correction for the maximum amount of complexing between pyridinium

(30) F. M. Cray and G. M. Westrip, *Trans. Faraday Soc.*, **21**, 326 (1925).

(31) J. N. Pring, *ibid.*, **19**, 705 (1924).

(32) G. Jones and B. B. Kaplan, THIS JOURNAL, **50**, 1600 (1928).

(33) D. M. Smith and W. M. D. Bryant, *ibid.*, **57**, 841 (1935).

## TABLE II

KINETIC DATA FOR MUTAROTATION OF TETRAMETHYLGLUCOSE IN ACETONE WITH 5.50 M. WATER AT 25°

| Acid | | Base | | | $k_1 \times 10^5$, sec.$^{-1}$ | |
|---|---|---|---|---|---|---|
| Species | M | Species | M | pH[a] | Obsd. | Calcd.[b] |
| H$^+$ | 0.00115 | | | 2.94 | 6.0 | 5.6 |
| | .00257 | | | 2.59 | 11.2 | 12.0 |
| | .00457 | | | 2.34 | 21.2 | 21.0 |
| | 0.00550 | | | 2.26 | 25.0 | 25.3 |
| H$_2$Phth[c] | .000169 | Na$_2$Phth[d] | 0.00108 | 11.9 | 5.0 | 4.4 |
| | .000063 | | .00118 | 12.2 | 7.4 | 7.7 |
| | | HO$^-$ | .000048[e] | 12.39 | 10.7 | 11.3 |
| | | | .000095[e] | 12.46 | 13.2 | 13.1 |
| | | | .000190[e] | 12.56 | 16.8 | 16.2 |
| | | C$_5$H$_5$N | .00010 | | 0.53 | 0.40 |
| | | | .00101 | | .42 | .41 |
| | | | .0101 | | .45 | .53 |
| | | | .101 | | 1.70 | 1.71 |
| | | | .132 | | 2.12 | 2.12 |
| | | | .163 | | 2.53 | 2.52 |
| C$_5$H$_5$NH$^+$ | 0.050 | | | 3.09 | 8.8 | 8.6 |
| | .100 | | | 3.10 | 12.8 | 13.0 |
| | .130 | | | 3.10 | 16.3 | 15.8 |
| | .160 | | | 3.10 | 19.0 | 18.7 |
| | .200 | | | 3.11 | 22.0 | 22.7 |
| | .0100 | | 0.0100 | 4.30 | 1.40 | 1.60 |
| | .0100 | | .0508 | 4.85 | 1.77 | 1.97 |
| | .0001 | | .100 | 6.93 | 1.62 | 1.71 |
| | .0100 | | .100 | 5.24 | 2.52 | 2.58 |
| | .0200 | | .101 | 5.06 | 3.10 | 3.46 |
| | .0200 | | .151 | 5.19 | 4.00 | 4.11 |
| | .0100 | | .153 | 5.35 | 3.25 | 3.27 |
| | .0100 | | .203 | 5.45 | 3.72 | 3.92 |
| | .0200 | | .252 | 5.48 | 4.98 | 5.42 |
| | .0100[f] | | .0100 | 4.83 | 1.40 | 1.50[f] |
| | .0200[g] | | .201 | 5.94 | 4.97 | 5.14[g] |
| | .0200[h] | | .201 | 6.22 | 5.30 | 5.63[h] |

[a] pH measured as described in text. [b] Calculated from equation 9. [c] Phthalic acid. [d] Disodium phthalate. [e] Also 0.00100 M disodium phthalate. [f] Also 0.09 M sodium perchlorate. [g] Also 0.18 M sodium perchlorate. [h] Also 0.38 M sodium perchlorate.

## TABLE III

REACTION OF 0.150 M IODIDE ION WITH 0.129 M EPICHLOROHYDRIN CATALYZED BY ACETIC ACID IN LIGHT AND HEAVY WATER AT 25°

| (HOAc), M | (NaOAc), M | (NaClO$_4$), M | Observed rate constants | |
|---|---|---|---|---|
| | | | $k_2{}^{H_2O} \times 10^3$, M$^{-1}$ sec.$^{-1}$ | $k_2{}^{D_2O} \times 10^3$, M$^{-1}$ sec.$^{-1}$ |
| 0.00 | 0.00 | 1.00 | 0.053 | 0.053 |
| 0.40 | 0.10 | 0.90 | 1.5 | 1.4 |
| 4.00 | 1.00 | 0.00 | 2.7 | 2.7 |

ion and pyridine. Thus the rate constants for the run with 0.02 M pyridinium perchlorate and 0.25 M pyridine are $4.98 \times 10^{-5}$sec.$^{-1}$ observed, $5.42 \times 10^{-5}$ or $4.45 \times 10^{-5}$ calculated, without the third-order term and neglecting complex or assuming the minimum instability constant of 0.25, respectively, but $17.2 \times 10^{-5}$ or $10.2 \times 10^{-5}$ with the third-order term and the same two assumptions about complexing. The latter two figures are well outside the experimental error. Best agreement of observed and calculated rates was obtained with no third-order term and a complexing instability constant of 1.0.

**Kinetic Procedure for Epichlorohydrin.**—The procedure was that described earlier,[28] except that iodide ion was titrated with 0.0402 M AgNO$_3$ instead of Hg(NO$_3$)$_2$. Epichlorohydrin (0.298 g.) was weighed into a 25-ml. volumetric flask and the required amounts of 10.00 M HOAc (or DOAc)–2.50 M NaOAc buffer, 4.50 M NaClO$_4$ and water to a volume of about 18 ml. were added. No difficulty was experienced in dissolving the epichlorohydrin rapidly by shaking. After 20 minutes in a 25.0° water-bath, 5 ml. of 0.75 M NaI at 25° was added, the volume made up with water to 25 ml., and the contents shaken thoroughly. Aliquot samples (2 ml.) were run into a flask containing 10

nil. of water and almost enough silver nitrate, then rapidly titrated to the coagulation end-point.

Table III gives second-order rate constants calculated from initial slopes (not over 60% reaction) since curvature appeared later in the runs with high concentration of acetate

ion due to competition by acetate ion for the epichlorohydrin. The increased rate with the highest concentration of buffer must be due to a medium effect on equilibrium or rate constants, rather than to general acid catalysis.
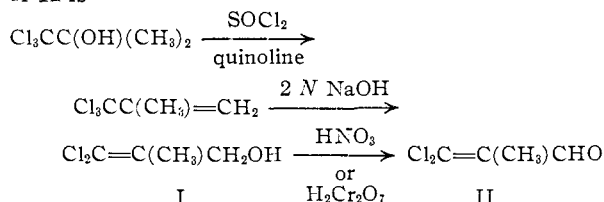
Cambridge 39, Massachusetts

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# The Preparation and Reactions of 3,3-Dichloro-2-methylpropenal

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The preparation of 3,3-dichloro-2-methylpropenal by oxidation of the corresponding alcohol is described. This aldehyde undergoes normal reactions with carbonyl reagents but gives interesting and unexpected reactions with piperidine and with chlorobenzene in the presence of sulfuric acid.

The chemistry of $\beta,\beta$-dichloro-$\alpha$-substituted acroleins has received very limited study. Previous work has been concerned primarily with the synthesis of $\beta,\beta$-dichloroacrolein[1] and $\alpha$-($p$-tolyl)-$\beta,\beta$-dichloroacrolein.[2] The methods for obtaining these two aldehydes, however, differ essentially from the methods used in the present work, which was initiated as a study of the reactivity of the chlorine substituents in such a conjugated system as 3,3-dichloro-2-methyl-2-propenal (II). This unsaturated aldehyde was prepared in good yields (54–60%) by the oxidation of the corresponding alcohol I with either nitric or chromic acids. The stability of the aldehyde to further oxidation by these reagents is remarkable. The route used for the preparation of II is

$$Cl_3CC(OH)(CH_3)_2 \xrightarrow[\text{quinoline}]{SOCl_2}$$

$$Cl_3CC(CH_3)=CH_2 \xrightarrow{2\ N\ NaOH}$$

$$Cl_2C=C(CH_3)CH_2OH \xrightarrow[\text{or}\ H_2Cr_2O_7]{HNO_3} Cl_2C=C(CH_3)CHO$$

$$\text{I} \qquad\qquad\qquad \text{II}$$

There were trace amounts of nitrogenous impurities in the distilled samples of II when nitric acid was used in the oxidation. When chromic acid was used, a small amount (8–10%) of the aldehyde II was converted to the acetal $Cl_2C=C(CH_3)CH(O-CH_2C(CH_3)=CCl_2)_2$ by reaction with the alcohol I.

The literature contains no examples of formation of aliphatic aldehydes from the use of nitric acid on alcohols. Helferich, et al.,[3] have reported the oxidation of o- and p-nitrobenzyl alcohol to the corresponding aldehydes by this reagent.

Compound II gave normal derivatives with hydroxylamine and with p-nitro- and 2,4-dinitrophenylhydrazine and formed acetals and thioacetals readily.

(1) (a) E. Levas and E. Levas, Compt. rend., 232, 521 (1951); (b) E. Levas and E. Levas, ibid., 230, 1669 (1950); (c) M. Levas, Ann. chim., 7, 697 (1952); (d) M. S. Kharasch, Otto Reinmuth and W. H. Urry, This Journal, 69, 1105 (1947); (e) A. N. Nesmeyanov, R. Kh. Freidlina and L. I. Zakharkin, Doklady Akad. Nauk S.S.S.R., 97, 91 (1954); (f) 99, 781 (1954).

(2) R. L. Tse and M. S. Newman, J. Org. Chem., 21, 638 (1956).

(3) B. Helferich, R. Streeck and E. Günther, J. prakt. Chem., 151, 251 (1938); C. A., 33, 1689 (1939).

Direct reaction of a large molar excess of piperidine with the aldehyde II gave in addition to the theoretical amount of piperidine hydrochloride 1-(2-methyl-3-(1-piperidyl)-propenoyl)-piperidine (III) in 49% yield.
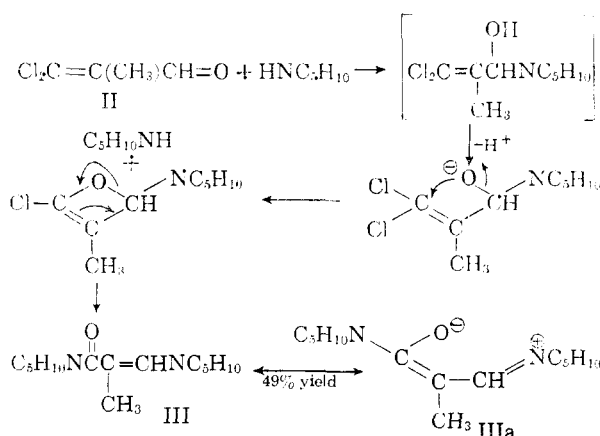


Its structural assignment is based on its composition, its molecular weight and its hydrolysis with dilute sodium hydroxide to two equivalents of piperidine and an amorphous waxy white solid, probably an aldol polymer of propionaldehyde, derived from the primary hydrolysis product HOOCCH-(CH₃)CHO by decarboxylation and polymerization. Presumably the dipolar structure IIIa makes a substantial contribution to the structure of III, since its water solubility is unusually high (about 9%) and its infrared carbonyl stretching frequency occurs at $6.22\ \mu$. The structure $RCOC=C-N-$ is known[4] to cause a shift in the carbonyl frequency of $20–80\ cm.^{-1}$, attributed to the contribution of an ionic resonance form analogous to IIIa. The shift of the carbonyl frequency for the amide structure of III in our case is a shift of $22–62\ cm.^{-1}$ and thus is in qualitative agreement with the results observed for $\beta$-amino-$\alpha,\beta$-unsaturated ketones.[4,5] In the case at hand, the contribution of IIIa should be somewhat less than that of the dipolar forms of $\beta$-amino-$\alpha,\beta$-

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London. 1956, Ch. 9, pp. 125–126.

(5) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank and D. J. Wallace, This Journal, 71, 3337 (1949).