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**Supplementary Material Available:** Tables of data for the X-ray

crystal and molecular structure, final positional parameters, bond distances and angles, and final thermal parameters for HO(S)-P(OCH<sub>2</sub>)<sub>2</sub>CCH<sub>3</sub>(CH<sub>2</sub>OH) (**8**) (5 pages); table of structure factors (1 page). Ordering information is given on any current masthead page.

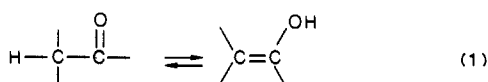
## Generation of Simple Enols in Aqueous Solution from Alkali Metal Enolates. Some Chemistry of Isobutyraldehyde Enol

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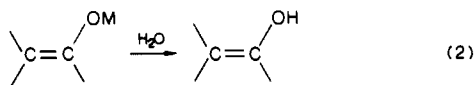
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**Abstract:** The enol isomer of isobutyraldehyde was generated in aqueous solution by reaction of its lithium and potassium enolates with water and of the trimethylsilyl enol ether with fluoride ion, and rates of ketonization of the enol were measured in HCl, DCl (in D<sub>2</sub>O), and NaOH solutions and in CNCH<sub>2</sub>CO<sub>2</sub>H, HCO<sub>2</sub>H, CH<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>ClPO<sub>3</sub>H<sup>-</sup>, and H<sub>2</sub>PO<sub>4</sub><sup>-</sup> buffers. Rates of enolization of isobutyraldehyde were also determined, by iodine scavenging, in HClO<sub>4</sub> and NaOH solutions. The reaction rates in HCl and NaOH give two independent estimates of the keto-enol equilibrium constant for isobutyraldehyde in aqueous solution at 25 °C, which are in good agreement with each other and whose average is  $K_E = (1.37 \pm 0.09) \times 10^{-4}$ ,  $pK_E = 3.86 \pm 0.03$ . The ketonization rates in NaOH solution also provide an estimate of the acidity constant of isobutyraldehyde enol ionizing as an oxygen acid,  $K_a^E = (2.37 \pm 0.14) \times 10^{-12}$  M,  $pK_a^E = 11.63 \pm 0.03$ , which, when combined with  $K_E$ , gives the acidity constant of the keto form of isobutyraldehyde ionizing as a carbon acid,  $K_a^K = (3.23 \pm 0.29) \times 10^{-16}$  M,  $pK_a^K = 15.49 \pm 0.04$ . The ketonization reaction in buffer solutions shows both general-acid and general-base catalysis, consistent with two parallel reaction paths involving rate-determining  $\beta$ -carbon protonation of both enol and enolate ion. Analysis of the data in terms of this scheme shows enolate to be 10<sup>8</sup> times more reactive than enol. Arguments are advanced to the effect that all of the present data are consistent with stepwise reaction mechanisms and do not require a concerted reaction path.

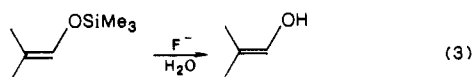
The equilibrium between simple monofunctional aldehydes and ketones and their enol isomers, eq 1, is generally quite mobile, and its position usually favors the carbonyl isomer quite strongly. This has made direct observation of simple enols difficult and has hampered the development of their chemistry.



Simple enols can, however, be produced in greater than equilibrium proportions by, for example, the rapid reaction of alkali metal enolates with water, eq 2. The isomerization of enols to their keto tautomers may, moreover, be slowed markedly by an appropriate selection of double-bond substituents.<sup>1</sup> We have



shown, for example, that the enol of isobutyraldehyde can be generated in aqueous solution from lithium isobutyraldehyde enolate and that its conversion to isobutyraldehyde in that medium is sufficiently slow to allow rate measurements by conventional or stopped-flow methods.<sup>2</sup> In this paper we describe that work, which was published before only in preliminary form, in full. We also show that this enol can be produced in aqueous solution from its potassium salt as well as by reaction of its trimethylsilyl ether with fluoride ion, eq 3. We also report measurements of the rate



of enolization of isobutyraldehyde, determined by iodine scavenging, which, when combined with our rates of ketonization, provide the keto-enol equilibrium constant for this system in aqueous solution. Our rate measurements in basic solution give a value of the acidity constant of isobutyraldehyde enol ionizing as an oxygen acid, and that, in combination with the keto-enol equilibrium constant, provides the acidity constant of isobutyraldehyde ionizing as a carbon acid.

### Experimental Section

**Materials.** Isobutenyl trimethylsilyl ether was prepared from isobutyraldehyde and trimethylsilyl chloride, and it was converted to lithium isobutyraldehyde enolate by treatment with methylolithium in tetrahydrofuran solution.<sup>3</sup> When this method of forming lithium enolates is used, triphenylmethane or 2,2'-bipyridine are sometimes employed as indicators to determine whether sufficient methylolithium has been supplied. We found, however, that triphenylmethane, even at the very low concentrations required for this purpose, was not soluble in the essentially aqueous solutions formed when small quantities of this lithium enolate stock solutions were added to water for kinetic determinations and that the suspensions thus formed, through barely discernible as such by the naked eye, interfered badly with kinetic measurements. Bipyridyl indicator, on the other hand, presented no difficulty; nevertheless, we used no indicator most of the time and simply supplied a 10% excess of methylolithium to ensure complete formation of the lithium enolate.

Potassium isobutyraldehyde enolate was made from isobutyraldehyde and potassium hydride.<sup>4</sup> Metal enolate stock solutions were stored under argon in Pierce Reacti vials fitted with Pierce Mininert valves; samples for kinetic measurement were withdrawn by hypodermic syringe. Isobutyraldehyde for kinetic determinations was fractionally distilled under argon; all other materials were the best available commercial grades. Solutions were prepared by using deionized water, purified further by distillation, or D<sub>2</sub>O (Merck Sharp & Dohme, 99.8 atom % deuterium) as received.

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**Kinetics of Ketonization.** Rates of ketonization of isobutyraldehyde enol were measured spectroscopically by monitoring the decrease of strong absorption due to enol at  $\lambda = 205\text{--}220$  nm. Determinations of HCl and buffer solutions were made by using a Cary 118C spectrometer with the cell compartment thermostated at  $25.0 \pm 0.05$  °C. Aqueous acids or buffer solutions contained in 3-mL cuvettes were first allowed to come to temperature equilibrium with the cell compartment; reactions were then initiated by injecting ca. 1- $\mu$ L portions of stock solution of enolate in tetrahydrofuran, or trimethylsilyl enol ether in dioxane, into the cuvettes. Final concentrations of enol in the reaction mixtures were of the order of  $10^{-4}$  M.

Rates of ketonization in sodium hydroxide solutions were too fast to be determined by this method, and measurements were therefore made by using a Durrum-Gibson stopped-flow spectrometer. Aqueous sodium hydroxide solutions were mixed in a 1:1 ratio with an essentially aqueous solution of enol in a buffer formed by adding 30  $\mu$ L of lithium enolate in tetrahydrofuran to 5 mL of 0.004 M aqueous acetic acid. The half-life of the enol in this buffer is ca. 15 min, which is sufficient time to load the solution into the stopped-flow machine and carry out several rate measurements before the absorbance decrease becomes too small to be useful.

Rate data obtained by both of these methods were found to conform to the first-order rate law well, and observed rate constants were evaluated by linear least-squares analysis of the relationship between  $\ln(A - A_\infty)$  and time.

**Kinetics of Enolization.** Rates of enolization of isobutyraldehyde were measured by using iodine to scavenge the enol as it formed. Determinations in HClO solution were done under zero-order conditions with a 500-fold excess of aldehyde over  $I_2$ . Reaction solutions also contained iodide ion, and measurements were made by monitoring the decrease in  $I_3^-$  absorption, either at the absorption maximum,  $\lambda_{\max} = 350$  nm, or at the  $I_2$ - $I_3^-$  isosbestic point,  $\lambda = 470$  nm. Solutions containing  $HClO_4$ ,  $I_2$ , NaI, and  $NaClO_4$  (to keep ionic strength constant at 0.10 M) were first allowed to come to temperature equilibrium with the cell compartment of the Cary 118C spectrometer; reactions were then initiated by adding a known volume of isobutyraldehyde with a calibrated microsyringe (Hamilton CR-700-20). Absorbance decreases,  $-dA/dt$ , were accurately linear over the entire course of the reaction, and first-order rate constants were calculated by using either eq 4 for the determinations made at the

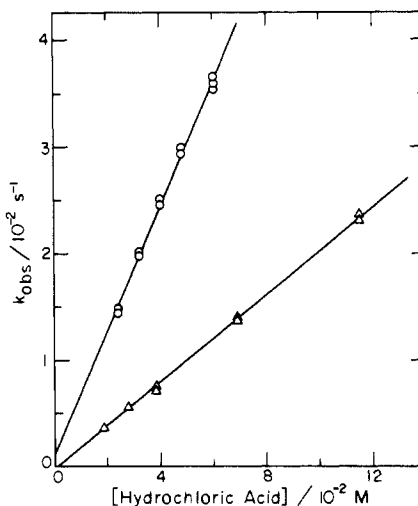
$$k = (-dA/dt)/\epsilon[Al] \quad (4)$$

$$k = \{(-dA/dt)/\epsilon[Al]\} \{1 + (K/[I^-])\} \quad (5)$$

isosbestic point or eq 5 for those using  $\lambda_{\max}$ . In these equations,  $\epsilon$  is the molar extinction coefficient of  $I_3^-$  or  $I_2^- + I_2$  ( $\epsilon = 675$   $M^{-1} \text{ cm}^{-1}$  at  $\lambda = 470$  nm and  $\epsilon = 26000$   $M^{-1} \text{ cm}^{-1}$  at  $\lambda = 350$  nm),<sup>5</sup>  $[Al]$  is the isobutyraldehyde concentration, and  $K$  is the equilibrium constant for the  $I_3^- = I_2 + I^-$  reaction ( $K = 1.5 \times 10^{-3}$  M).<sup>5</sup>

Rates of isobutyraldehyde enolization in sodium hydroxide solutions were measured under first-order conditions by using a slight excess of  $I_2$  ( $2\text{--}5 \times 10^{-5}$  M, stoichiometric concentration) over aldehyde ( $1.5\text{--}2.0 \times 10^{-5}$  M). The reaction was followed by monitoring either the decrease in absorption at  $\lambda = 260\text{--}265$  nm or the somewhat stronger increase at 230 nm; similar results were obtained by the two methods. Reaction mixtures were made by first allowing ca. 1.2-mL portions of aqueous sodium hydroxide contained in cuvettes to come to temperature equilibrium with the Cary 118C cell compartment, then adding ca. 6  $\mu$ L of aqueous  $I_2/I^-$  stock solution ( $[I_2]/[I^-] = 0.4\text{--}0.7$ , both stoichiometric concentrations), and finally adding ca. 2  $\mu$ L of aqueous isobutyraldehyde stock solution. Solutions of  $I_2/I^-$  in sodium hydroxide are not stable, but blank runs showed negligible decomposition over the times required for 3-4 half-lives of the enolization reactions. Because of this instability, end points were not measured and first-order rate constants were calculated by least-squares fitting to an exponential function.

**Concentrations.** Values of  $[H^+]$  and concentrations of other solution species needed for the kinetic analyses described below were obtained by calculation using literature values of ionization constants for  $CNCH_2CO_2H$ ,<sup>6</sup>  $HCO_2H$ ,<sup>7</sup>  $CH_3CO_2H$ ,<sup>8</sup>  $CH_2ClPO_3H^-$ ,<sup>9</sup> and  $H_2PO_4^-$ <sup>10</sup> plus ionic activity coefficients recommended by Bates,<sup>11</sup> determined experimentally (for  $CH_2ClPO_3H^-$  and  $CH_2ClPO_3^{2-}$ )<sup>9</sup> or calculated by the Debye-Huckel



**Figure 1.** Relationship between hydrochloric acid concentration and observed first-order rate constants for the ketonization of isobutyraldehyde enol in aqueous solution at 25 °C: (O) HCl in  $H_2O$  and ( $\Delta$ ) DCl in  $D_2O$ .

equation with an ion-size parameter of 4.5 Å (for  $CNCH_2CO_2^-$ ).

## Results

**Reaction Identification.** The essentially aqueous solutions formed when lithium or potassium enolates of isobutyraldehyde, dissolved in tetrahydrofuran, are added to large excesses of water show, at first, a strong absorbance of UV light at  $\lambda = 200$  nm. Such absorption is characteristic of carbon-carbon double bonds bearing hydroxy or alkoxy substituents, and this initial UV spectrum is in fact quite similar to that of methyl isobutenyl ether. This strong initial absorbance begins to decrease immediately upon formation of these solutions, at rates which depend upon the acidity or basicity of the medium; it is eventually replaced by a much weaker band with  $\lambda_{\max} = 282$  nm. The final spectrum is identical with that of isobutyraldehyde; that isobutyraldehyde is formed is also evident from the reaction product's NMR spectrum and GC retention time, as well as from its 2,4-dinitrophenylhydrazone derivative which did not depress the melting point of an authentic sample.

Isobutyraldehyde enol was also generated in aqueous solution by the reaction of its trimethylsilyl ether with fluoride ion (eq 3). Trialkylsilyl enol ethers are known to produce enolate salts upon treatment with fluoride in aprotic solvents, and this reaction is in fact a useful synthetic method.<sup>12</sup> Trimethylsilyl enol ethers also undergo acid-catalyzed hydrolysis in aqueous solution, through nucleophilic attack on silicon, to give enols, which then ketonize.<sup>13</sup> When this method of generating isobutyraldehyde enol was used here, the trimethylsilyl enol ether was added directly to aqueous buffer solutions containing fluoride ion, and the immediately ensuing decrease in carbon-carbon double-bond UV absorbance was monitored. This decrease could in principle have been due to the disappearance of either the silyl enol ether or the enol. The fact that rate constants based upon this change agreed well with those determined by using enol generated from alkali metal enolates shows that the reaction being monitored was in fact ketonization of the enol and that conversion of the silyl ether to enol is fast in the solutions employed and ketonization is rate-determining.

**Ketonization Rates.** Rates of ketonization of isobutyraldehyde enol were measured in hydrochloric acid solutions, both in  $H_2O$  and in  $D_2O$ ; the data are summarized in Table S1<sup>14</sup> and are displayed in Figure 1. The absorbance change used to follow the reaction was large, and kinetic results of good quality could

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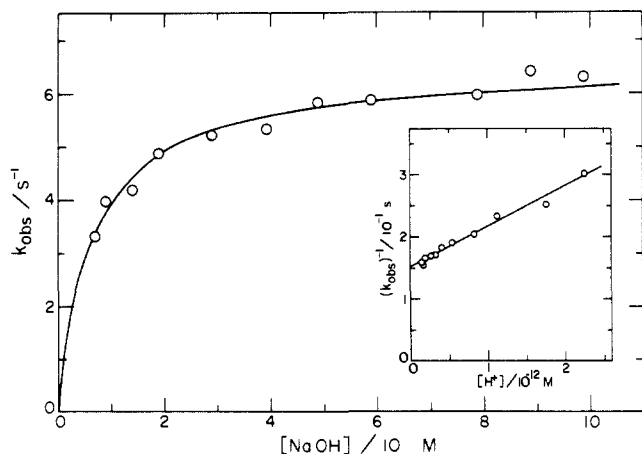
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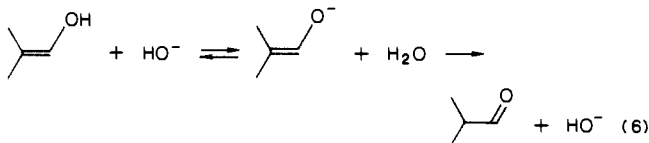
(14) Supplementary material. See paragraph at end of paper regarding availability.



**Figure 2.** Relationship between sodium hydroxide concentration and observed first-order rate constants for the ketonization of isobutyraldehyde enol in aqueous solution at 25 °C; each circle represents the average of seven to eight separate rate determinations. The insert shows these data plotted according to eq 8.

be obtained; it may be seen in Figure 1 that replicate determinations agree with each other well and that observed first-order rate constants are accurately proportional to acid concentration. Linear least-squares analysis gives the bimolecular rate constants  $k_{H^+} = (5.85 \pm 0.11) \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$  and  $k_{D^+} = (2.06 \pm 0.02) \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ , which provide the isotope effect  $k_{H^+}/k_{D^+} = 2.84 \pm 0.06$ .

Rates of ketonization of isobutyraldehyde enol were also measured in sodium hydroxide solutions. These data are summarized in Table S2<sup>14</sup> and are displayed in Figure 2. They show that the ketonization reaction is catalyzed by hydroxide ion at low  $[\text{HO}^-]$  but that this catalysis becomes saturated as  $[\text{HO}^-]$  is increased. This behavior can be interpreted in terms of a rapidly established acid-base equilibrium between enol and hydroxide ion followed by rate-determining ketonization of the enolate ion through proton transfer to carbon from water, eq 6;<sup>2,15</sup> saturation



of the catalysis then occurs when  $[\text{HO}^-]$  is sufficiently high to drive the preequilibrium completely to the right and convert the less reactive enol completely to the more reactive enolate. The rate law for this process is given in eq 7, in which  $K_a^E$  and  $K_w$  are

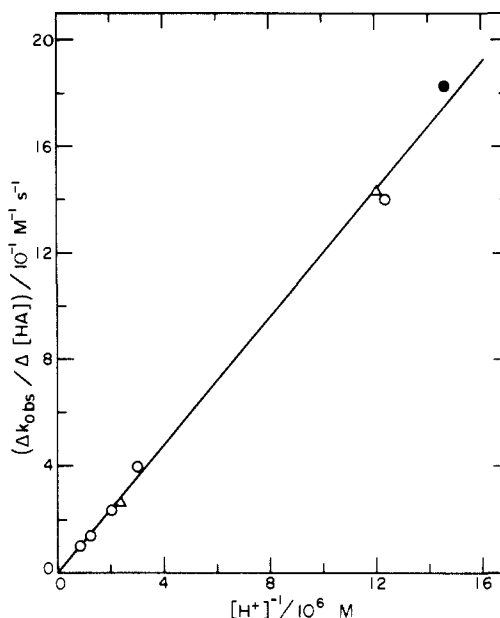
$$k_{\text{obsd}} = \frac{k_o'(K_a^E/K_w)[\text{HO}^-]}{(K_a^E/K_w)[\text{HO}^-] + 1} = \frac{k_o K_a^E}{K_a^E + [\text{H}^+]} \quad (7)$$

the acidity constant of the enol and the autoprotolysis constant of water (and whose ratio  $K_a^E/K_w$  is the equilibrium constant for the first step) and  $k_o'$  is the rate constant of the rate-determining step. This rate law requires that  $1/k_{\text{obsd}}$  be a linear function of  $[\text{H}^+]$ , eq 8, and the insert of Figure 2 shows that the experimental

$$1/k_{\text{obsd}} = (1/k_o') + [\text{H}^+]/k_o'K_a^E \quad (8)$$

data do conform to this prediction. Linear least-squares analysis of the relationship between  $1/k_{\text{obsd}}$  and  $[\text{H}^+]$  gives slope and intercept parameters (Table S2) which lead to the values  $k_o' = 6.55 \pm 0.15 \text{ s}^{-1}$  and  $K_a^E = (2.37 \pm 0.14) \times 10^{-12} \text{ M}$ ,<sup>16</sup>  $\text{p}K_a = 11.63 \pm 0.03$ .

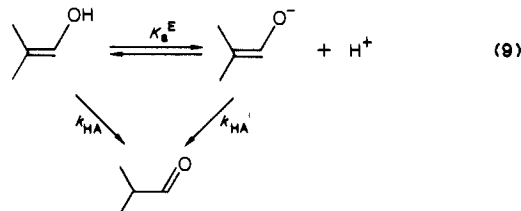
The  $\text{p}K_a$  of isobutyraldehyde enol in aqueous solution has not been measured before, but the presently determined value is nicely



**Figure 3.** Relationship between  $\Delta k_{\text{obsd}}/\Delta[\text{HA}]$  and  $[\text{H}^+]^{-1}$  for the ketonization of isobutyraldehyde enol in aqueous  $\text{H}_2\text{PO}_4^-/\text{HPO}_4^{2-}$  buffer solutions at 25 °C: (O) enol generated from lithium enolate, (●) enol generated from potassium enolate, and (Δ) enol generated from trimethylsilyl enol ether.

consistent with a recent estimate,  $\text{p}K_a^E = 11.7 \pm 1.0$ , based upon free-energy relationships.<sup>17</sup>

Rates of ketonization of isobutyraldehyde enol were also measured in aqueous buffer solutions of cyanoacetic, formic, and acetic acids and of chloromethylphosphonate and biphosphate ions. The data, which are summarized in Table S3,<sup>14</sup> show both general-acid and general-base catalysis. The results were analyzed according to the reaction scheme given in eq 9, in which keton-



ization occurs by two parallel reaction paths, one involving rate-determining carbon protonation of the enol and the other rate-determining carbon protonation of the enolate ion. (This scheme is based upon the currently accepted reaction mechanism for the enolization of simple aldehydes and ketones,<sup>1b,18</sup> which, according to the principle of microscopic reversibility, should occur by the same mechanism as the ketonization of simple enols.) This scheme requires general-acid catalysis for that part of the ketonization process occurring through rate-determining protonation of the enol and specific hydroxide ion general-acid catalysis for ketonization occurring through the enolate ion; the latter will of course appear operationally as general-base catalysis.

The rate law for this scheme, eq 10, predicts that observed general-acid catalytic coefficients, determined as slopes of plots

$$k_{\text{obsd}} = k_{\text{HA}}[\text{HA}] + k_{\text{HA}}'K_a^E[\text{HA}]/[\text{H}^+] \quad (10)$$

of  $k_{\text{obsd}}$  vs.  $[\text{HA}]$  at constant  $[\text{H}^+]$ ,  $\Delta k_{\text{obsd}}/\Delta[\text{HA}]$ , will be linear functions of  $[\text{H}^+]^{-1}$ , eq 11. This was found to be the case. Figure 3 shows our most extensively documented example of this behavior,

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(16) This equilibrium constant is a concentration quotient at ionic strength = 0.10 M.

$$\Delta k_{\text{obsd}}/\Delta[\text{HA}] = k_{\text{HA}} + k_{\text{HA}}'K_{\text{a}}^{\text{E}}/[\text{H}^+] \quad (11)$$

that for series of  $\text{H}_2\text{PO}_4^-/\text{HPO}_4^{2-}$  buffer solutions of constant buffer ratio but varying buffer concentration; in such solution series  $[\text{H}^+]$  and  $[\text{HO}^-]$  remain constant, and contributions to  $k_{\text{obsd}}$  from catalysis by these species, and by solvent, are fixed.

Figure 3 also demonstrates that rates of ketonization of isobutyraldehyde enol measured with enol generated in three different ways are independent of the source of the enol; it may be seen that data obtained by using lithium enolate (open circles), potassium enolate (filled circle), and isobutyraldehyde trimethylsilyl enol ether (triangles) are in good agreement with each other.

The slope of the line correlating the data of Figure 3 is equal to  $k_{\text{HA}}'K_{\text{a}}^{\text{E}}$ , and since  $K_{\text{a}}^{\text{E}}$  is known from the rate measurements in sodium hydroxide solutions,  $k_{\text{HA}}'$  may be evaluated. The intercept of the line in this particular case, however, is zero; least-squares analysis gives the value  $-(0.48 \pm 2.65) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ , and  $k_{\text{HA}}$  therefore cannot be determined. This is because at the low acidities of these biphosphate buffers ( $[\text{H}^+] = (0.7-12) \times 10^{-7} \text{ M}$ ), little if any reaction occurs by direct protonation of the enol, and essentially all of it takes place through the enolate ion. The same proved to be the case for buffer solutions of chlorophosphonate ion and also acetic acid; only in the more acidic media provided by formic acid and cyanoacetic acid buffers could reaction via direct carbon protonation of the enol be detected.

The cyanoacetic acid buffers, however, presented another problem, for "buffer failure"<sup>19</sup> occurred. Cyanoacetic acid is a fairly strong acid, and it therefore dissociated to a significant extent in the buffer solutions employed; this changed the buffer ratio from its stoichiometric value, and the extent of the change increased regularly with decreasing buffer concentration. Consequently,  $[\text{H}^+]$  dropped significantly along a series of buffer solutions of constant stoichiometric buffer ratio but decreasing buffer concentration. This variation in  $[\text{H}^+]$  changed the contribution to  $k_{\text{obsd}}$  from catalysis by  $\text{H}^+$ , it also changed the relative amounts of reaction occurring through enol and enolate, and that invalidated the procedure of obtaining observed general-acid catalytic coefficients as slopes of plots of  $k_{\text{obsd}}$  vs.  $[\text{HA}]$  and then analyzing these quantities according to eq 11.

This problem was handled by fitting the data to an expression in which  $[\text{H}^+]$  is an additional independent variable. The complete rate law for a reaction scheme such as that of eq 9 involving rate-determining protonation of both enol and enolate ion will contain terms for each of the three available acids,  $\text{H}_2\text{O}$ ,  $\text{H}^+$ , and  $\text{HA}$ , reacting with each of the two substrate species. This is shown in eq 12, where unprimed rate constants refer to reactions of the

$$k_{\text{obsd}} = (k_0 + k_{\text{H}^+}[\text{H}^+] + k_{\text{HA}}[\text{HA}])[\text{H}^+]/([\text{H}^+] + K_{\text{a}}^{\text{E}}) + (k_0' + k_{\text{H}^+}'[\text{H}^+] + k_{\text{HA}}'[\text{HA}])K_{\text{a}}^{\text{E}}/([\text{H}^+] + K_{\text{a}}^{\text{E}}) \quad (12)$$

enol and primed rate constants to reactions of the enolate ion; each group of three rate constants is multiplied by a fraction,  $[\text{H}^+]/([\text{H}^+] + K_{\text{a}}^{\text{E}})$  or  $K_{\text{a}}^{\text{E}}/([\text{H}^+] + K_{\text{a}}^{\text{E}})$ , which denotes the portion of substrate in the enol or the enolate form. This rate law, when applied to cyanoacetic acid buffers, can be simplified to eq 13,

$$k_{\text{obsd}} = k_0 + k_{\text{H}^+}[\text{H}^+] + k_{\text{HA}}[\text{HA}] + k_0'K_{\text{a}}^{\text{E}}/[\text{H}^+] + k_{\text{H}^+}'K_{\text{a}}^{\text{E}} + k_{\text{HA}}'K_{\text{a}}^{\text{E}}[\text{HA}]/[\text{H}^+] \quad (13)$$

for in these solutions  $[\text{H}^+] \gg K_{\text{a}}^{\text{E}}$  ( $=2.4 \times 10^{-12} \text{ M}$ ). The "hydroxide ion" term,  $k_0'K_{\text{a}}^{\text{E}}/[\text{H}^+]$ , moreover, will make a negligible contribution, for  $k_0'K_{\text{a}}^{\text{E}} = 1.6 \times 10^{-11} \text{ M}^{-1} \text{ s}^{-1}$ , and values of  $k_{\text{H}^+}'[\text{H}^+]$  may be calculated, since  $k_{\text{H}^+}$  is known from measurements made in hydrochloric acid solutions. This leads to eq 14, in which observed rate constants corrected for hydronium ion contributions are related to the two independent variables  $[\text{HA}]$  and  $[\text{H}^+]$ .

$$k_{\text{obsd}} - k_{\text{H}^+}[\text{H}^+] = k_0 + k_{\text{H}^+}'K_{\text{a}}^{\text{E}} + k_{\text{HA}}[\text{HA}] + k_{\text{HA}}'K_{\text{a}}^{\text{E}}[\text{HA}]/[\text{H}^+] \quad (14)$$

Table I. Summary of Rate Constants for the Ketonization of Isobutyraldehyde Enol in Aqueous Solution at 25 °C<sup>a</sup>

catalyst	$k$ , $\text{M}^{-1} \text{ s}^{-1}$	
	enol	enolate
$\text{H}^+$	$5.85 \times 10^{-1}$	$1.7 \times 10^8$
$\text{D}^+$	$2.06 \times 10^{-1}$	
$\text{CNCH}_2\text{CO}_2\text{H}$	$5.72 \times 10^{-2}$	
$\text{HCO}_2\text{H}$	$2.2 \times 10^{-3}$	$1.11 \times 10^6$
$\text{CH}_3\text{CO}_2\text{H}$		$1.91 \times 10^5$
$\text{CH}_2\text{ClPO}_3\text{H}^-$		$8.81 \times 10^4$
$\text{H}_2\text{PO}_4$		$5.08 \times 10^4$
$\text{H}_2\text{O}$		$1.18 \times 10^{-1}$

<sup>a</sup> Ionic strength = 0.10 M.

Least-squares fitting of the data to this equation gave  $k_{\text{obs}} - k_{\text{H}^+}[\text{H}^+] = (3.75 \pm 2.46) \times 10^{-4} + (5.72 \pm 0.41) \times 10^{-2}[\text{HA}] - (3.99 \pm 1.97) \times 10^{-5}[\text{HA}]/[\text{H}^+]$ . This result shows that there was insufficient reaction through the enolate ion in these fairly acidic buffers to determine  $k_{\text{HA}}'$ , which is the converse of the situation in the more basic biphosphate buffers discussed above, where  $k_{\text{HA}}$  could not be determined. It shows also that the interesting quantity  $k_0 + k_{\text{H}^+}'K_{\text{a}}^{\text{E}} = (3.75 \pm 2.46) \times 10^{-4} \text{ s}^{-1}$ , from which an estimate of  $k_{\text{H}^+}'$  might be obtained, was not well-defined by these experiments.

Fortunately, this latter quantity may be evaluated somewhat more precisely by measurements made in formic acid and acidic acid buffers where it makes a stronger contribution to observed rates. In these solutions, buffer failure did not occur, and the data were therefore analyzed in the usual way by determining observed general-acid catalytic coefficients as slopes of plots of  $k_{\text{obs}}$  against  $[\text{HA}]$ . The intercepts of such plots represent reaction through all solvent-derived species and contain all of the nonbuffer acid-containing terms of eq 13, as shown in eq 15. Since the rate intercept =  $k_0 + k_{\text{H}^+}'K_{\text{a}}^{\text{E}} + k_{\text{H}^+}[\text{H}^+] + k_0'K_{\text{a}}^{\text{E}}/[\text{H}^+]$  (15)

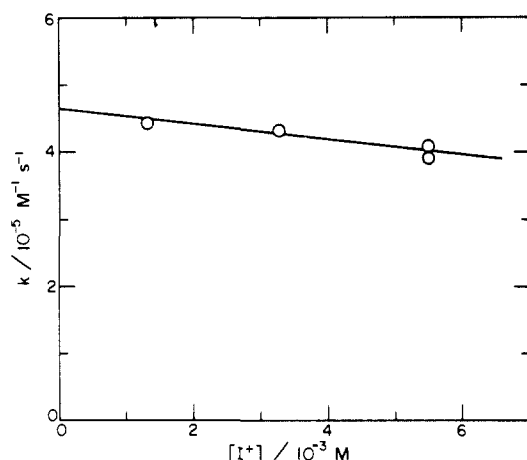
and equilibrium constant coefficients of the last two terms of eq 15 are known, these terms can be calculated, and the remainder,  $k_0 + k_{\text{H}^+}'K_{\text{a}}^{\text{E}}$ , may be determined from these intercepts. Data from five determinations in acetic acid buffers and two in formic acid buffers give  $k_0 + k_{\text{H}^+}'K_{\text{a}}^{\text{E}} = (3.93 \pm 0.49) \times 10^{-4} \text{ s}^{-1}$ , which is in good agreement with the less precise results obtained from cyanoacetic acid buffers. The weighted average of these two values is  $k_0 + k_{\text{H}^+}'K_{\text{a}}^{\text{E}} = (3.92 \pm 0.48) \times 10^{-4} \text{ s}^{-1}$ .

This quantity could in principle also be determined from intercepts measured in the more basic chloromethylphosphonate and biphosphate ion buffers. These solutions, however, gave values of this quantity which were consistently greater, by factors of 2-4, than results obtained from the more acidic carboxylic acid buffers. This difference might be an experimental artifact, for buffer catalysis in the more basic solutions was very strong and the intercepts were only small fractions of overall observed rates. Alternatively, the difference could signify incursion of a competing reaction which appears only in these solutions. Any such interference, however, would be minor and would have no significant impact on the results of this kinetic analysis.

The quantity  $k_0 + k_{\text{H}^+}'K_{\text{a}}^{\text{E}}$  determined above may be used to estimate  $k_{\text{H}^+}'$ , for  $K_{\text{a}}^{\text{E}}$  is known and  $k_0$  is likely to make an insignificantly small contribution. This may be shown by estimating  $k_0$  from the known value of  $k_{\text{H}^+}$  by using the Bronsted relation with an exponent  $\alpha = 0.5$ , a reasonable value for this system, to calculate the ratio  $k_0/k_{\text{H}^+}$ . This procedure gives  $k_0 \cong 6 \times 10^{-8} \text{ s}^{-1}$ , which is 4 orders of magnitude less than the experimental result  $k_0 + k_{\text{H}^+}'K_{\text{a}}^{\text{E}} = (3.92 \pm 0.48) \times 10^{-4} \text{ s}^{-1}$ . Elimination of  $k_0$  and the use of  $K_{\text{a}}^{\text{E}} = 2.37 \times 10^{-12} \text{ M}$  then lead to  $k_{\text{H}^+}' = 1.7 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ .

The various catalytic coefficients determined by this analysis are listed in Table I. They provide two comparisons of specific rates for  $\beta$ -carbon protonation of enol and enolate by the same acid; when the acid is hydrogen ion, the enolate reaction is  $3 \times 10^8$  times faster than the enol reaction, and when it is formic acid, the ratio is  $5 \times 10^8$ . These very large rate differences demonstrate the very powerful activating effect of a negatively charged oxygen

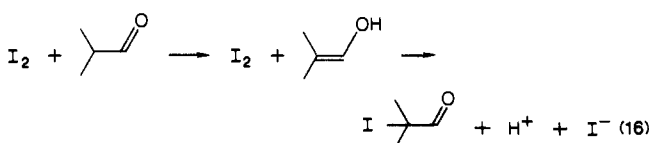
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**Figure 4.** Relationship between iodide ion concentration and observed second-order rate constants for the iodination of isobutyraldehyde in aqueous solution at 25 °C.

substituent upon electrophilic addition to carbon-carbon double bonds.

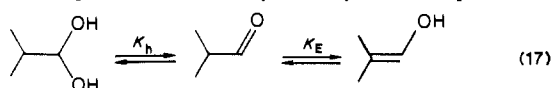
**Enolization Rates and Keto-Enol Equilibrium Constants.** Rates of enolization of isobutyraldehyde were measured in dilute perchloric acid solution by using iodine to scavenge the enol as it formed, eq 16. The halogenation of carbonyl compounds under



acidic conditions such as this is sometimes appreciably reversible,<sup>20</sup> and the effect of reversibility is to give an observed rate constant lower than the true value for the forward direction. Since the rate of the reverse reaction depends upon iodide ion concentration, we measured rates of acid-catalyzed iodination at several different values of [I<sup>-</sup>] in order to determine whether reversibility was occurring in the present case.

Rates of iodination were measured at three different values of [I<sup>-</sup>], and at each [I<sup>-</sup>], over a range of concentrations of perchloric acid (0.02–0.10 M). The data are summarized in Table S4.<sup>14</sup> Observed first-order rate constants proved to be directly proportional to acid concentration, and second-order hydrogen ion catalytic coefficients were evaluated by linear least-squares analysis of the relationship between  $k_{\text{obs}}$  and [H<sup>+</sup>]. As Figure 4 shows, these catalytic coefficients did decrease somewhat with increasing [I<sup>-</sup>], showing that this iodination is in fact slightly reversible. The data were therefore extrapolated to zero [I<sup>-</sup>] to give the enolization rate constant  $k_{\text{H}^+\text{E}} = (4.66 \pm 0.12) \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ . This result is in reasonably good agreement with a value,  $k_{\text{H}^+\text{E}} = (4.95 \pm 0.03) \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ , reported before.<sup>21</sup>

This rate constant may be combined with the hydrogen ion catalytic coefficient for the ketonization reaction determined above,  $k_{\text{H}^+\text{K}} = (5.85 \pm 0.11) \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ , to calculate the isobutyraldehyde keto-enol equilibrium constant,  $K_{\text{E}}$ , according to the relationship  $K_{\text{E}} = k_{\text{H}^+\text{E}}/k_{\text{H}^+\text{K}}$ . In doing this, however, it is necessary to take into account the fact that isobutyraldehyde is in rapid equilibrium with a significant amount of aldehyde hydrate and that the measured enolization rate constant therefore refers to an initial state which is an equilibrium mixture of aldehyde and hydrate, eq 17. Fortunately, the hydration equilibrium

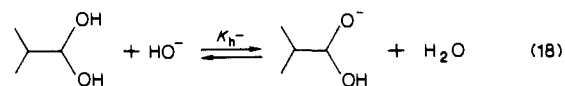


constant for isobutyraldehyde has been determined accurately,<sup>22</sup>

and the necessary correction can easily be made. The result,  $K_{\text{E}} = k_{\text{H}^+\text{E}}(1 + K_{\text{h}})/k_{\text{H}^+\text{K}} = (4.66 \pm 0.12) \times 10^{-5}(1 + 0.600)/(5.85 \pm 0.11) \times 10^{-1} = (1.27 \pm 0.04) \times 10^{-4}$ , is the keto-enol equilibrium constant for this system referred to an initial state consisting of free aldehyde only.

Rates of enolization of isobutyraldehyde monitored by iodine scavenging were also measured in sodium hydroxide solutions. Three sets of determinations, each over a range of hydroxide ion concentrations ([HO<sup>-</sup>] = 0.02–0.10 M), were made; the data are summarized in Table S5.<sup>14</sup>

Analysis of these data must also take into account the aldehyde hydration reaction plus an additional rapid equilibrium involving ionization of the hydrate, eq 18, which occurs to a significant extent

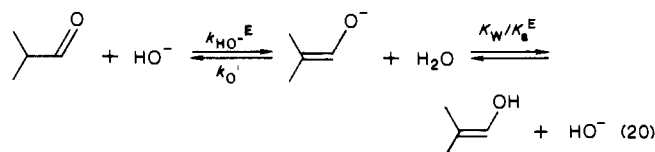


at the hydroxide ion concentrations used here. Once again, a good value of the equilibrium constant is available,  $K_{\text{h}^-} = 1.03$ ,<sup>22</sup> and the correction can readily be made. Since this correction depends upon [HO<sup>-</sup>], eq 19, and since [HO<sup>-</sup>] was varied in these sets of

$$k_{\text{corr}} = k_{\text{obs}}\{1 + K_{\text{h}}(1 + K_{\text{h}^-}[\text{HO}^-])\} \quad (19)$$

rate measurements, the correction was applied to individual values of observed first-order rate constants. The rate constants so corrected proved to be accurately proportional to [HO<sup>-</sup>], and second-order hydroxide ion catalytic coefficients were obtained by linear least-squares analysis. The three sets of determinations gave three values whose average is  $k_{\text{HO}^-\text{E}} = (1.42 \pm 0.11) \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ .

The immediate product of the hydroxide ion catalyzed enolization reaction is enolate ion, but this can be converted to enol by a rapidly established equilibrium whose equilibrium constant is equal to the autoprotolysis constant of water divided by the acidity constant of the enol, eq 20. Since the overall reaction



is the keto-enol interconversion, it follows then that the keto-enol equilibrium constant,  $K_{\text{E}}$ , is equal to the ratio of rate constants for the first step of eq 20 multiplied by the equilibrium constant for the second, as in eq 21. All of the quantities on the right-hand

$$K_{\text{E}} = \left( \frac{k_{\text{HO}^-\text{E}}}{k_{\text{o}'}} \right) \left( \frac{K_{\text{w}}}{K_{\text{a}}^{\text{E}}} \right) \quad (21)$$

side of eq 20 are now known, and  $K_{\text{E}}$  can therefore be evaluated. The result,  $K_{\text{E}} = (1.46 \pm 0.14) \times 10^{-4}$ , is in good agreement with the value obtained above from measurements made in acid solutions,  $K_{\text{E}} = (1.27 \pm 0.04) \times 10^{-4}$ . The average of these two determinations is  $K_{\text{E}} = (1.37 \pm 0.09) \times 10^{-4}$ ,  $\text{p}K_{\text{E}} = 3.86 \pm 0.03$ .<sup>16</sup> This quantity has not been measured directly before, but recent approximate estimates have put it at  $\text{p}K_{\text{E}} = 2.8 \pm 1.1$ ;<sup>17</sup> the agreement between this and our empirically founded result shows that the assumptions upon which these estimates were based are not unreasonable.

The two equilibrium constants which our investigation has determined,  $K_{\text{E}}$  and  $K_{\text{a}}^{\text{E}}$ , constitute two legs of a thermodynamic cycle whose third step is the ionization of isobutyraldehyde as a carbon acid, eq 22. The equilibrium constant for this third leg,  $K_{\text{a}}^{\text{K}}$ , may therefore be calculated from the known values of  $K_{\text{E}}$  and  $K_{\text{a}}^{\text{E}}$ . The result is  $K_{\text{a}}^{\text{K}} = (3.23 \pm 0.29) \times 10^{-16} \text{ M}$ ,  $\text{p}K_{\text{a}}^{\text{K}} = 15.49 \pm 0.04$ .

## Discussion

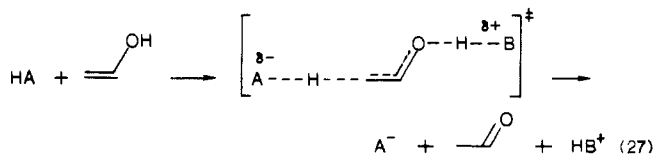
The results obtained here show that the ketonization of isobutyraldehyde enol is an acid-catalyzed reaction, that the form

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that a change in reaction medium from pure water to 60–70 mol % aqueous dimethyl sulfoxide produced a 50-fold depression in the rate of hydrolysis of ethyl vinyl ether, which is reminiscent of the behavior of A-1 reactions, whereas the same solvent change produced a much smaller, only 4-fold, depression in the rate of ketonization of acetaldehyde enol, reminiscent of the behavior of A-2 reactions.

Such a difference in solvent effect, however, might be expected even if ketonization and vinyl ether hydrolysis were both occurring by the same stepwise mechanism. The difference in behavior of A-1 and A-2 reactions<sup>30</sup> has been rationalized in terms of differential solvation of reactants and transition state,<sup>30b</sup> using arguments similar to those now employed to explain differences in various concentrated-acid acidity functions. In both A-1 and A-2 reactions, rapid protonation of the substrate by hydronium ion is followed by rate-determining reaction of the substrate conjugate acid, but in the A-1 process this rate-determining step is unimolecular, whereas in the A-2 process it is a bimolecular attack of water in which the water molecule is taking on positive charge. There is thus a greater difference in the number of positively charged O–H bonds, which are the principle sites for solvational stabilization, between the initial-state hydronium ion and the rate-determining transition state in the A-1 process than in the A-2 process; the A-1 process will consequently experience the greater solvent effect. A similar difference in the balance of

positively charged O–H bonds between initial and transition states exists for vinyl ether hydrolysis and enol ketonization proceeding by a stepwise mechanism, for the enol has an O–H bond not present in the vinyl ether. The solvent effect on vinyl ether hydrolysis should therefore be stronger than the solvent effect on enol ketonization, even if both reactions occur by the same stepwise mechanism.

A concerted reaction mechanism for the ketonization of enols of course implies a concerted mechanism for the reverse process, the enolization of carbonyl compounds. It has been known for some time that the rate law for the enolization of acetone contains a third-order term<sup>18a,c,d,31</sup> and that this third-acid term very probably represents a concerted reaction path; a similar term has recently been detected in the enolization of cyclohexanone.<sup>32</sup> It is believed, however, that, at least in the case of acetone, the concerted mechanism is of minor importance.<sup>1b,18a,c,e,33</sup>

**Acknowledgment.** We are grateful to the Natural Sciences and Engineering Research Council of Canada and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their financial support of this research.

**Registry No.** Me<sub>2</sub>C=CHOTMS, 6651-34-9; Me<sub>2</sub>C=CHOH·Li, 32970-42-6; Me<sub>2</sub>C=CHOH·K, 103818-01-5; Me<sub>2</sub>C=CHOH, 56640-70-1; Me<sub>2</sub>CHCHO, 78-84-2; Me<sub>2</sub>C=CHO<sup>-</sup>, 77212-99-8; F<sup>-</sup>, 16984-48-8; HCl, 7647-01-0; DCl, 7698-05-7; NaOH, 1310-73-2; CNCH<sub>2</sub>CO<sub>2</sub>H, 372-09-8; HCO<sub>2</sub>H, 64-18-6; AcOH, 64-19-7; CH<sub>2</sub>ClPO<sub>3</sub>H<sup>-</sup>, 54947-16-9; H<sub>2</sub>PO<sub>4</sub><sup>-</sup>, 14066-20-7; H<sub>2</sub>O, 7732-18-5; H<sup>+</sup>, 12408-02-5; D<sup>+</sup>, 14464-47-2; D, 16873-17-9; MeLi, 917-54-4; KH, 7693-26-7.

**Supplementary Material Available:** Tables S1–S5 of rate constants (11 pages). Ordering information is given on any current masthead page.

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## Transannular Bond Formation between the Amino and the Sulfonio Groups in 6,7-Dihydro-6-methyl-5H-dibenzo[*b,g*][1,5]thiazocinium Salts. The First Example of a Sulfurane with an Apical Alkyl Group

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**Abstract:** A series of *S*-substituted *N*-methyl-6,7-dihydro-5H-dibenzo[*b,g*][1,5]thiazocinium salts (**5a–e**) have been prepared from the *S*-chloro derivative (**5e**), which was obtained from the corresponding sulfoxide (**6**) and thionyl chloride. An excellent linear relationship is observed between the <sup>1</sup>H and the <sup>13</sup>C NMR chemical shifts of the *N*-methyl group and Hammett's  $\sigma_m$  substituent constants at the sulfur. The structures of **5a–e** have been shown to be ammoniosulfuranes with a distorted trigonal-bipyramidal geometry around the sulfur atom. The nitrogen atom lies well within the sum of the van der Waals radii of N and S, and the N–S distance (2.10–2.50 Å) shortens according to the increase of electron-withdrawing character of the substituent on the sulfur atom. Additional evidence for (methylammonio)sulfurane (**5a**) came from the low reactivity (1/1300) of transmethylation to pyridine compared with its related diphenylmethylsulfonium tetrafluoroborate (**11**). In connection with transmethylation of *S*-adenosylmethionine, intramolecular interactions between the amino and sulfonio groups are discussed for some methylsulfonium salts (**5a**, **13**, **14**, and **16**) in which the nitrogen base (amino or pyridyl group) is substituted at the side chain.

In the last decade, many kinds of sulfuranes (**1**) have been synthesized and most of the stable isolable ones share the feature

of a five-membered ring linking an apical electronegative group and an equatorial aromatic ring carbon on the sulfur.<sup>1</sup> Not-