Some Kinetic and Equilibrium Isotope Effects in the Isobutylphenone Enol and Enolate Ion System

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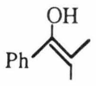
This paper is dedicated to Professor Jacob Bigeleisen on the occasion of his 70th birthday

The following kinetic isotope effects were determined for acid-catalyzed ketonization of isobutyrophenone enol and enolate ion through rate-determining hydron transfer from catalyst to substrate: enol, $k_H/k_D = 3.30 \pm 0.07$ (hydronium ion catalysis), $k_H/k_D = 4.0 \pm 2.8$ (acetic acid catalysis); enolate ion, $k_H/k_D = 1.00 \pm 0.21$ (hydronium ion catalysis), $k_H/k_D = 3.11 \pm 0.20$ (acetic acid catalysis), $k_H/k_D = 7.48 \pm 0.23$ (water catalysis). The magnitude of these isotope effects, when assessed in terms of the free energies of reaction for the processes in which they occur, are consistent with Melander-Westheimer-Bigeleisen theory. An equilibrium isotope effect of $K_H/K_D = 5.88 \pm 0.32$ was also determined for the ionization of isobutyrophenone enol as an oxygen acid.

There has been a renaissance of interest in the chemistry of simple enols lately, fueled by the invention of methods for generating these unstable species in solution in greater than equilibrium amounts under conditions where they can be observed directly. This has allowed accurate measurement of rate and equilibrium constants for their reactions, and that has led to much new enol chemistry [1]. In this paper we add some kinetic and equilibrium isotope effects to this store of information. In particular, we compare isotope effects on the same reaction of an enol and its enolate ion; this is of special interest because enolate ions are much more reactive than enols [2], and the comparison therefore involves substrates of closely similar structure but grossly different reactivity.

We have chosen the enol of isobutyrophenone, **1**, for this study because there is a background of information on this keto-enol system [2b] which allows comparison of isotope effects with other reaction parameters, notably free energies of reaction. We have also carried out some studies on the related methyl enol ether, **2**, for comparison.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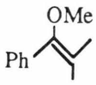
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Experimental Section

Materials. Isobutyrophenone enol was generated in aqueous solution by hydrolysis of its potassium or lithium enolate, as described [2b]. Isobutyrophenone enol ether, **2**, was prepared by acid-catalyzed elimination of methanol from isobutyrophenone dimethyl ketal, which in turn was made from isobutyrophenone and methanol using a standard method [3]. The elimination was conducted by heating the ketal with a catalytic amount of p-toluenesulfonic acid at 120° for 2 hours, under slightly reduced pressure, and removing methanol as it formed. The product enol ether was separated from the catalyst by distillation, and final purification of a sample for kinetic measurements was performed by gas chromatography; the material had a proton NMR spectrum consistent with its structure: ($CDCl_3$/TMS) $:= \delta$ 7.30 (5 H, s), 3.30 (3 H, s), 1.83 (3 H, s), 1.66 (3 H, s), and a high resolution mass spectrum consistent with its elemental composition: $M/\varepsilon = 162.1039$, expected for $C_{11}H_{14}O$, 162.1041.

All other materials were best available commercial grades. Solutions were prepared using deionized H_2O, purified further by distillation, or D_2O (MSD, 99.8 atm% D) as received.

Kinetics. Rates of ketonization of isobutyrophenone enol were measured spectroscopically by monitoring the increase of ketone absorbance at $\lambda = 245$ nm, as described [2b]. Rates of hydrolysis of isobutyrophenone enol methyl ether were also measured spectro-

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scopically by monitoring either the increase of ketone absorbance at $\lambda = 245$ nm or the decrease of enol ether absorbance at $\lambda = 217$ nm; similar rate constants were obtained by the two methods.

Results

Ketonization. Rates of ketonization of isobutyrophenone enol were measured in D_2O solutions of DCl and $DClO_4$. The data conformed to the first-order rate law precisely, and observed first-order rate constants were accurately proportional to acid concentration over the range employed (0.008 – 0.03 M for DCl and 0.008 – 0.04 M for $DClO_4$). These results are summarized in Table S 1.

Linear least squares analysis gives the hydronium ion catalytic coefficients $k_{D^+} = 0.652 \pm 0.009$ M^{-1} s^{-1} for the DCl solutions and $k_{D^+} = 0.643 \pm 0.013$ M^{-1} s^{-1} for the $DClO_4$ solutions. The measurements in DCl solutions were done at ionic strengths equal to the DCl concentration, while those in $DClO_4$ solutions were performed at a constant ionic strength, $\mu =$ 0.10 M, maintained by adding NaCl. The fact that the catalytic coefficients obtained by these two methods are closely similar shows that there is no salt effect on the ketonization reaction over the concentration range studied. The weighted average of the two values is $k_{D^+} = 0.648 \pm 0.007$, and combination of that with the protio rate constant determined before [2b] gives the isotope effect $k_{H^+}/k_{D^+} = 3.30 \pm 0.07$.

Rates of ketonization of isobutyrophenone enol were also measured in D_2O solutions of NaOD. Once again the data conformed to the first-order rate law accurately. Determinations were made over the concentration range [NaOD] = 0.005 – 0.1 M at constant ionic strength (0.10 M). The results are summarized in Table S 2.

Table S 1. Rate data for the ketonization of isobutyrophenone enol in D_2O solutions of hydrochloric and perchloric acids at 25 °C.

[Acid]/10^{-2} M	$k_{obs}/10^{-2}$ s^{-1}
DCl [a]	
0.78	0.498, 0.477
1.17	0.732, 0.769
1.56	1.04, 1.03
2.60	1.68, 1.71, 1.71
3.25	2.07, 2.12
$k_{obs}/s^{-1} = -(0.58 \pm 1.82) \times 10^{-4} + (6.52 \pm 0.09) \times 10^{-1}$ [DCl]	
$DClO_4$ [b]	
0.72	0.550, 0.548
1.40	0.957, 0.966, 0.944, 0.975
2.20	1.53, 1.58, 1.56
2.77	1.94, 1.88, 1.79
2.87	1.94
3.65	2.40, 2.41
$k_{obs}/s^{-1} = (8.75 \pm 2.99) \times 10^{-4} + (6.43 \pm 0.13) \times 10^{-1}$ [$DClO_4$]	

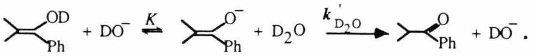
[a] Ionic strength = [DCl]. – [b] Ionic strength = 0.10 M (NaCl)

Table S 2. Rate data for the ketonization of isobutyrophenone enol in D_2O solutions of sodium hydroxide at 25.0 °C [a].

[NaOD]/ 10^{-2} M	k_{obs}/s^{-1}
0.50	3.54, 3.66, 3.73, 3.67, 3.80, 3.60, 3.70, 3.67, 3.66
0.66	4.29, 4.44, 4.11, 4.48, 4.24, 4.89, 4.10, 4.80, 4.09
0.80	5.43, 4.84, 5.57, 4.66, 4.48, 4.07, 4.48, 4.18, 4.83
0.82	4.27, 4.35, 4.32, 4.71, 4.84, 4.55, 4.85, 4.77, 4.83
0.92	5.53, 5.20, 5.55, 5.82, 4.80, 5.26, 5.75
1.10	5.58, 5.11, 5.00, 5.15, 5.09, 5.48, 5.24, 5.51
1.53	6.74, 6.87, 6.28, 5.85, 6.86, 6.03, 6.42, 6.77
2.91	6.98, 6.66, 6.68, 7.13, 6.91
3.93	7.59, 7.96, 7.44
6.01	8.17, 8.14, 8.27, 8.26
7.91	8.36, 9.27, 9.17, 8.92, 8.74, 9.23, 9.21
9.91	8.97, 8.61, 8.80, 8.97, 8.72, 8.97, 8.73, 8.76
$k_{obs}^{-1}/s = (1.08 \pm 0.03) \times 10^{-1} + (3.82 \pm 0.16) \times 10^{11}$ [D^+]	

[a] Ionic strength = 0.10 M (NaCl).

These observed first-order rate constants obtained in NaOD solutions were proportional to hydroxide ion concentration at low [NaOD], but, as the concentration increased, the hydroxide-ion catalysis of the ketonization reaction diminished and rate constants eventually reached a limiting value, Figure 1. Such behavior is characterized of the ketonization of simple enols in basic solutions [2]. It is due to the fact that the hydroxide-ion catalyzed reaction occurs through conversion of the enol to the much more reactive enolate ion followed by rate-determining acid-catalyzed ketonization of the enolate ion by hydron transfer from water,



(1)

Eventually, however, at sufficiently high hydroxide ion concentrations, the equilibrium preceeding the rate-determining step shifts completely to the side of enolate; further increases in hydroxide ion concentration then have no effect, and catalysis becomes saturated.

The rate law which applies to this reaction scheme is

$$k_{obs} = k'_{D_2O}\, K\,[DO^-]/(K\,[DO^-] + 1). \qquad (2)$$

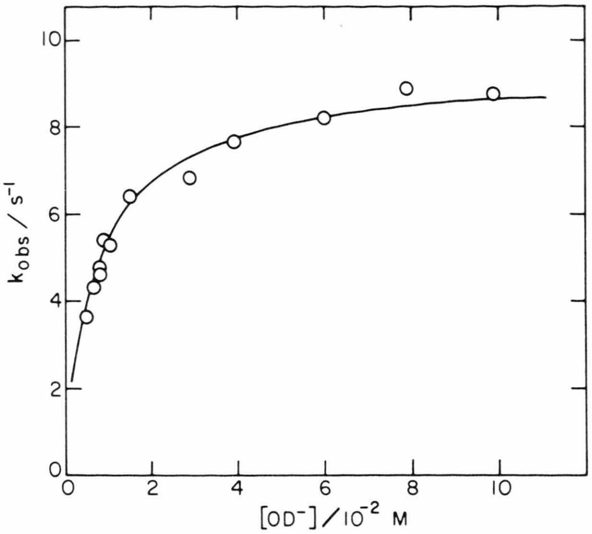


Fig. 1. Relationship between observed rate constants and hydroxide ion concentration for the ketonization of isobutyrophenone enol in D_2O solutions of NaOD. Each point represents the average of a number, usually 8–9, separate rate constant measurements at the same sodium hydroxide concentration.

Since the equilibrium constant for the reaction of enol with hydroxide ion is equal to the acidity constant of the enol, K_a^E, divided by the ionization constant of water, K_w: $K = K_a^E/K_w$, and since $[DO^-] = K_w/[D^+]$, this expression is equivalent to the equation

$$k_{obs} = k'_{D_2O}\, K_a^E/(K_a^E + [D^+]). \tag{3}$$

The dependence of k_{obs} on $[D^+]$ may be made linear by taking reciprocals of both sides of this expression, and the result,

$$(1/k_{obs}) = (1/k'_{D_2O}) + [D^+]/k'_{D_2O}\, K_a^E, \tag{4}$$

shows that both k'_{D_2O} and K_a^E can be evaluated from the intercept and slope of the linear relationship. Least squares analysis of the data gives $k'_{D_2O} = 9.26 \pm 0.26\ s^{-1}$ and $(K_a^E)_D = (2.83 \pm 0.14) \times 10^{-13}$, $(pK_a^E)_D = 12.55 \pm 0.01$ [4, 5], and combination of these results with the corresponding values determined in H_2O solution [2 b] provides the isotope effects $k'_{H_2O}/k'_{D_2O} = 7.48 \pm 0.23$ and $(K_a^E)_H/(K_a^E)_D = 5.88 \pm 0.32$, $\Delta pK_a = 0.77 \pm 0.02$.

Rates of ketonization of isobutyrophenone enol were also measured in D_2O solutions of acetic acid buffers. Again, the data fit the first-order rate law accurately. Determinations were made in series of buffers of varying buffer concentration but constant buffer ratio and constant ionic strength (0.10 M). Five such series were used, and buffer concentrations were varied by factors ranging from 3 to 6. These data are summarized in Table S 3.

Table S 3. Rate data for the ketonization of isobutyrophenone enol in D_2O solutions of acetic acid buffers at 25.0 °C [a].

$[DOAc]/10^{-2}$ M	$k_{obs}/10^{-4}\ s^{-1}$
$[DOAc]/[NaOAc] = 5.21$	
20.3	5.42, 5.19, 5.08
15.3	4.83, 4.34, 4.62
10.1	2.82, 3.25, 3.67, 3.35
6.68	2.77, 2.99, 3.19
5.15	1.85, 2.07, 2.46
$k_{obs}/s^{-1} = (1.37 \pm 0.19) \times 10^{-4} + (1.97 \pm 0.15) \times 10^{-3}\,[DOAc]$	
$[DOAc]/[NaOAc] = 4.14$	
12.2	3.73, 4.13, 3.89
6.12	2.32
4.06	1.61, 1.60, 1.66, 1.66
$k_{obs}/s^{-1} = (5.16 \pm 0.97) \times 10^{-5} + (2.79 \pm 0.11) \times 10^{-3}\,[DOAc]$	
$[DOAc]/[NaOAc] = 2.71$	
13.9	7.27, 7.15
5.57	3.28, 3.25, 3.39
4.52	3.05, 3.06, 2.86
3.18	2.19
2.98	2.20
2.44	2.06
1.22	1.24
$k_{obs}/s^{-1} = (8.11 \pm 0.57) \times 10^{-5} + (4.60 \pm 0.08) \times 10^{-3}\,[DOAc]$	
$[DOAc]/[NaOAc] = 0.928$	
5.58	6.67, 6.55, 6.13
3.84	4.60, 4.90, 4.53
2.23	3.43, 3.27
2.12	3.10
1.82	2.46, 2.90
1.41	2.60
$k_{obs}/s^{-1} = (1.09 \pm 0.15) \times 10^{-4} + (9.53 \pm 0.41) \times 10^{-3}\,[DOAc]$	
$[DOAc]/[NaOAc] = 0.248$	
1.91	7.31, 7.63
1.54	6.92, 6.93
1.06	4.93, 4.69, 4.66
1.01	4.65, 4.94, 4.86
0.52	3.09, 2.89
0.49	3.09, 2.82
$k_{obs}/s^{-1} = (1.24 \pm 0.24) \times 10^{-4} + (3.50 \pm 0.20) \times 10^{-2}\,[DOAc]$	
For all CH_3CO_2D buffers:	
$(\Delta k_{obs}/\Delta[DA])_{constant\,[D^+]}$	
$= (7.52 \pm 3.02) \times 10^{-4} + (7.04 \pm 0.13) \times 10^{-8}\,[D^+]$	

[a] Ionic strength = 0.10 M (NaCl).

The ketonization reaction showed both general acid and general base catalysis in these buffer solu-

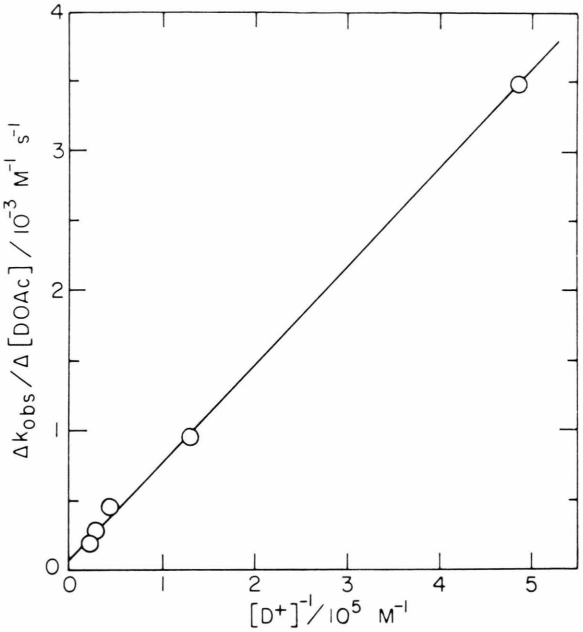


Fig. 2. Relationship between slopes of buffer dilution plots and $1/[D^+]$ for the ketonization of isobutyrophenone enol in D_2O solutions of acetic acid buffers.

Table S 4. Rate data for the hydrolysis of isobutyrophenone enol methyl ether in aqueous hydrochloric acid solutions at 25.0 °C.

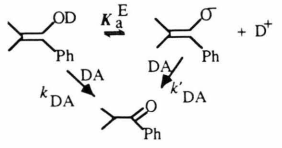
$[Acid]/10^{-2}$ M	$k_{obs}/10^{-3}$ s^{-1}
H_2O solutions [a]	
2.00	0.345, 0.363, 0.310
4.00	0.702, 0.773
6.00	1.11, 1.16, 1.08, 1.05, 1.10
8.00	1.33, 1.51, 1.49
10.0	1.68, 1.78, 1.88, 1.97, 1.91 [b], 1.89 [b], 1.95 [b] 2.00, 1.91, 1.78
$k_{obs}/s^{-1} = -(4.54 \pm 4.14) \times 10^{-5} + (1.91 \pm 0.06) \times 10^{-2}$ [HCl]	
D_2O solutions [c]	
1.56	0.122, 0.121
5.85	0.471, 0.462
7.80	0.641, 0.648
9.75	0.845, 0.832
$k_{obs}/s^{-1} = -(2.44 \pm 1.33) \times 10^{-5} + (8.69 \pm 0.19) \times 10^{-3}$ [DCl]	
$k_{H^+}/k_{D^+} = 2.20 \pm 0.08$	

[a] Ionic strength = 0.10 M (NaCl).

[b] Measured by monitoring disappearance of enol ether at $\lambda = 217$ nm; all others measured by monitoring appearance of isobutyrophenone at $\lambda = 245$ nm.

[c] Ionic strength = [DCl].

tions. This again is characteristic of the ketonization of simple enols in buffers of this pH [2]; it is caused by simultaneous reactions through both the enol and enolate ion forms of the substrate,



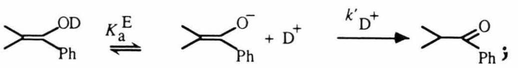
(5)

The rate law which applies to the buffer-catalyzed portion of the reaction in this situation is given by

$$(k_{obs})_{buffer} = k_{DA}[DA] + k'_{DA} K_a^E [DA]/[D^+]. \qquad (6)$$

It requires observed rate constants to be linearly proportional to buffer acid concentration, which proved to be the case, and it also requires the slopes of buffer dilution plots, $\Delta k_{obs}/\Delta[DA]$, to be linear functions of $1/[D^+]$, which also proved to be the case, Figure 2. Least squares analysis gives the catalytic coefficients for the reaction of enol with acetic acid, $k_{DA} = (7.5 \pm 3.0) \times 10^{-4}$ M^{-1} s^{-1}, and that for the reaction with the enolate ion, $k'_{DA} = (2.49 \pm 0.13) \times 10^5$ M^{-1} s^{-1} [8]. Combination of these results with the corresponding values obtained in H_2O solution [2b] provides the isotope effects $k_{HA}/k_{DA} = 4.0 \pm 2.8$ and $k'_{HA}/k'_{DA} = 3.11 \pm 0.20$. In both solvents the rate constant for the reaction of the enol was not well determined but that for the reaction of the enolate ion was; this is because in both cases virtually all of the reaction occurred via the enolate ion.

The zero-buffer-concentration intercepts of the buffer dilution plots showed no systematic variation with acidity, and they thus represent an "uncatalyzed" reaction. It has been shown [2e] that this "uncatalyzed" reaction takes place through ionization of the enol to enolated ion followed by rate-determining ketonization of enolate catalyzed by the hydronium ion,



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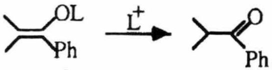
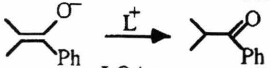
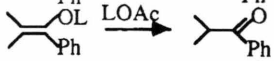
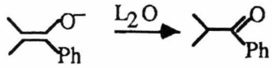
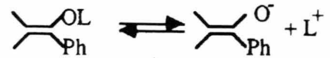
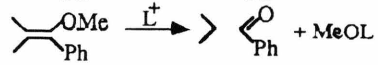
since a hydron is produced in the first step and another is consumed in the second, the overall reaction is independent of hydron concentration. The rate law for such a reaction scheme is simply the product of the equilibrium constant for the first step and the rate constant for the second, $k_{uncat} = K_a^E k'_{D^+}$, and, since K_a^E has been evaluated, k'_{D^+} may be calculated. The average value of k_{uncat} for the five buffer series used gives $k'_{D^+} = (3.04 \pm 0.62) \times 10^8$ M^{-1} s^{-1}, and that coupled with the result obtained in H_2O solution [2b] provides the isotope effect $k'_{H^+}/k'_{D^+} = 1.00 \pm 0.21$.

Table 1. Summary of isotope effects[a].

Process	Isotope effect	ΔG°/ kcal mol^{-1}
	$k_{H^+}/k_{D^+} = 3.30 \pm 0.07$	-3.4
	$k'_{H^+}/k'_{D^+} = 1.00 \pm 0.21$	-24.9
	$k_{HA}/k_{DA} = 4.0 \pm 2.8$	$+3.1$
	$k'_{HA}/k'_{DA} = 3.11 \pm 0.20$	-18.4
	$k'_{H_2O}/k'_{D_2O} = 7.48 \pm 0.23$	-5.8
	$(K_a^E)_H/(K_a^E)_D = 5.88 \pm 0.32$	–
	$k_{H^+}/k_{D^+} = 2.20 \pm 0.08$	–

[a] Aqueous solution, 25 °C, ionic strength = 0.10 M.

Enol Ether Hydrolysis. Rates of hydrolysis of isobutyrophenone enol methyl ether were measured in H_2O and D_2O solutions of hydrochloric acid. The data conformed to the first-order rate law. Determinations were made over the concentration range 0.02 – 0.10 M in both solvents. The results are summarized in Table S4.

Observed first-order rate constants measured in both solvents were accurately proportional to acid concentration. Linear least squares analysis gives the hydronium ion catalytic coefficients

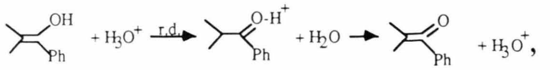
$$k_{H^+} = (1.91 \pm 0.06) \times 10^{-2}\ M^{-1}\ s^{-1} \quad \text{and}$$
$$k_{D^+} = (8.69 \pm 0.19) \times 10^{-3}\ M^{-1}\ s^{-1},$$

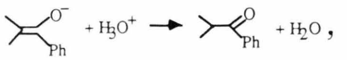
whose ratio provides the isotope effect $k_{H^+}/k_{D^+} = 2.20 \pm 0.08$.

Table 1 summarizes the isotope effects determined in the present study.

Discussion

The present measurements show a striking difference between the isotope effect on the ketonization of isobutyrophenone enol catalyzed by the hydronium ion, $k_{H^+}/k_{D^+} = 3.3$, and that on the corresponding reaction of the enolate ion, $k'_{H^+}/k'_{D^+} = 1.0$. Both reactions occur through rate-determining hydron transfer from the hydronium ion,

 (8)

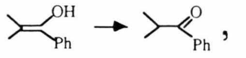
 (9)

and the two substrates have closely similar structures at this site. And yet the enol reaction shows an isotope effect that is large for a process of this kind [10], whereas the enolate reaction gives no isotope effect at all.

The two substrates, however, do differ strongly in reaction rate: $k_{H^+} = 2.1\ M^{-1}\ s^{-1}$ for the enol and $k'_{H^+} = 3.0 \times 10^8\ M^{-1}\ s^{-1}$ for the enolate ion. So large a difference can be expected to produce a significant change in transition state structure, and that should influence the magnitude of the isotope effect.

It is now well known that primary hydrogen isotope effects vary with transition state structure, passing through a maximum value for symmetrical transition states in which the atom in flight is half transferred, and falling off from this maximum for reactant-like or product-like transition states [12]. Since transition state structure in turn is believed to vary with the free energy of reaction, with reactant-like transition states occurring in exoergic reactions, symmetrical transition states in ergoneutral reactions, and product-like transition states in endoergic reactions [13], it is of interest to compare these isotope effects with free energy changes for the reactions in which they occur.

The reaction of the enolate ion, (9), is a simple one-step process whose reverse is ionization of isobutyrophenone as a carbon acid; this ionization constant is known, $pK_a^K = 18.26$ [2b], and that leads to $\Delta G^\circ = -24.9$ kcal mol^{-1} for (9). The reaction of the enol, on the other hand, is a two-step process, (8), but the isotope effect occurs in the first, rate-determining step, and that is the step whose free energy change is of interest here. This change may be calculated by breaking the reaction down into two processes, ketonization of the enol, (10), and oxygen protonation of the ketone so formed, (11). The keto-enol equilibrium constant for the isobutyrophenone system is known,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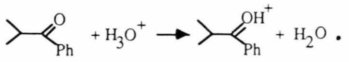
(11)

$pK_E = 6.48$ [2b], and an estimate of the acidity constant of oxygen-protonated isobutyrophenone, $pK_a = -4.0$, may be made from the known value for acetophenone, $pK_a = -4.16$ [14], and the expectation that isobutyrophenone would be slightly more basic. This leads to $\Delta G^\circ = -3.4$ kcal mol^{-1} for (8).

These free energy changes show the enolate reaction to be a strongly exoergic process, for which a small isotope effect might be expected, and the enol reaction to be an approximately ergoneutral process, for which a large isotope effect might be expected. These expectations are nicely consistent with the experimental results. Free energy changes may be calculated in the same way for the other reactions of the enol and enolate ion for which kinetic isotope effects have been determined; the results are listed in Table 1. It may be seen that in the case of the two reactions involving acetic acid, which also occur by rate determining hydron transfer from acid to substrate [2], the more exogeric reaction of the enolate ion has the smaller isotope effect, although here the argument is weakened somewhat by the large uncertainty in the isotope effect on the enol reaction. The nearly ergoneutral reaction of the enolate ion with water, on the other hand, does show a large isotope effect.

A quantitative relationship between isotope effect and free energy of reaction has been derived from Marcus rate theory [15]. This is shown in (12)

$$\ln(k_H/k_D) = (\ln\ k_H/k_D)_{\max}\,[1-(\Delta G^\circ/4\,\Delta G_0^{\neq})^2], \qquad (12)$$

where $(k_H/k_D)_{\max}$ is the maximum semiclassical (no tunneling) value of the isotope effect that occurs when $\Delta G^\circ = 0$, and $\Delta G_0^{\neq}$ is the intrinsic barrier for the reaction series. This equation can be applied only to a homogenous group of reactions with a common intrinsic barrier, and the presently determined isotope effects unfortunately pertain to reactions that are too diverse to allow a significant correlation of the group as a whole. The relationship can, however, be applied usefully to the single present reactions which has an isotope effect of unity. This equation predicts that isotope effects of unity occur when $|\Delta G^\circ| = |4\,\Delta G_0^{\neq}|$, and use of the data for the enolate plus hydronium ion reaction then leads to $\Delta G_0^{\neq} = 24.9/4 = 6.2$ kcal mol^{-1}. This is a reasonable value for a reaction such as this, and it is consistent with $\Delta G_0^{\neq} = 5.1 \pm 2.7$ kcal mol^{-1} estimated from the Bronsted relation for ketonization of isobutyrophenone enolate ion by a series of oxygen acids [2b].

This Marcus theory expression has been extended to systems for which the free energy of reaction is not known by replacing ΔG° with an equivalent expression involving the free energy of activation, $\Delta G^{\neq}$, and the result has been used to correlate isotope effects on the hydrolysis of a large group of enol ethers catalyzed by the hydronium ion through rate-determining hydron transfer from catalyst to substrate [16]. The correlating relationship is

$$\begin{aligned}\ln(k_{H^+}/k_{D^+}) &= \ln(k_{H^+}/k_{D^+})_{\max}\left[2\left(\frac{\Delta G^{\neq}-w_r}{\Delta G_0^{\neq}}\right)^{1/2}-\frac{\Delta G^{\neq}-w^r}{\Delta G_0^{\neq}}\right]\\ &\quad+(\ln l)\left(\frac{\Delta G^{\neq}-w^r}{\Delta G_0^{\neq}}\right)^{1/2}. \qquad (13)\end{aligned}$$

Its first term represents the primary isotope effect and its second term, the secondary isotope effect [10]; l is the D-H fractionation factor for the hydronium ion and w^r is a work term representing the free energy needed to bring the reactants together and form them into a reaction complex. Use of this expression with parameters obtained from the correlation of enol ether reactions leads to the prediction $k_{H^+}/k_{D^+} = 2.21$ for the reacdtion of isobutyrophenone enol ether with the hydronium ion, which is in very good agreement with the measured value $k_{H^+}/k_{D^+} = 2.20 \pm 0.08$.

This correlation of isotope effects on enol ether hydrolysis might also be expected to make reasonable predictions of isotope effects on the ketonization of enols, inasmuch as these two reactions occur by the same mechanism. There is an important difference, however, in that the enol hydroxyl group will become deuterated when the rate of enol ketonization is measured in D_2O solution in order to evaluate k_{D^+}. Since this hydroxyl group takes on positive charge during the rate-determining step of the reaction, an appreciable secondary isotope effect will be produced, and that will make the observed effect greater than it would otherwise be. The enol ether correlation should therefore underestimate isotope effects on enol ketonization. This expectation is borne out by the present results for the enol plus hydronium ion reaction: the correlation predicts $k_{H^+}/k_{D^+} = 3.00$ whereas $k_{H^+}/k_{D^+} = 3.30 \pm 0.07$ is observed.

This correlation breaks down, however, when applied to the ketonization of isobutyrophenone enolate ion catalyzed by the hydronium ion, because this reaction is so fast that its free energy of activation, $\Delta G^{\neq} = 5.9$ kcal mol^{-1}, is less than the work term for enol ether hydrolysis, $w^r = 8.4$ kcal mol^{-1}. This means that enolate ions belong to a different reaction series with a smaller work term, which is not surprising inasmuch as electrostatic attraction between the negatively charged enolate and positively charged hydronium ions should facilitate reaction complex formation.

Equilibrium isotope effects generally show less variation in magnitude than do kinetic isotope effects, and those on the ionization of oxygen acids, such as the enol studied here, tend to fall in the range $K_H/K_D = 2-4$ when measured in aqueous solution [17]. Some variation does exist, however, with the isotope effect increasing in magnitude with diminishing strength of the acid [11 b, 17, 18], and the large isotope effect found here for the ionization of isobutyrophenone enol, $K_H/K_D = 5.9 \pm 0.3$, for which $pK_a = 11.78$ [2 b], is consistent with this trend. This isotope effect is also consistent with $K_H/K_D = 5.1$ for the ionization of trifluoroethanol ($pK_a = 12.37$) [19, 20] and $K_H/K_D = 5.4$ for the ionization of chloroethanol ($pK_a = 14.31$) [20, 21].

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