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Keto−Enol/Enolate Equilibria in the Isochroman-4-one System. Effect of a *β*-Oxygen Substituent

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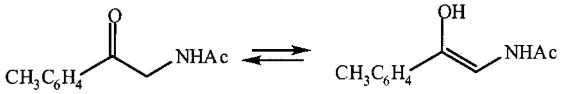
Abstract: The enol of 1-tetralone was generated flash photolytically, and rates of its ketonization were measured in aqueous $HClO_4$ and NaOH solutions as well as in CH_3CO_2H, $H_2PO_4^-$, $(CH_2OH)_3CNH_3^+$, and NH_4^+ buffers. The enol of isochroman-4-one was also generated, by hydrolysis of its potassium salt and trimethylsilyl ether, and rates of its ketonization were measured in aqueous $HClO_4$ and NaOH. Rates of enolization of the two ketones were measured as well. Combination of the enolization and ketonization data for isochroman-4-one gave the keto−enol equilibrium constant $pK_E = 5.26$, the acidity constant of the enol ionizing as an oxygen acid $pQ_a^E = 10.14$, and the acidity constant of the ketone ionizing as a carbon acid $pQ_a^K = 15.40$. Comparison of these results with those for 1-tetralone shows that the β-oxygen substituent in isochroman-4-one raises all three of these constants: K_E by 2 orders of magnitude, Q_a^E by not quite 1 order of magnitude, and Q_a^K by nearly 3 orders of magnitude. The β-oxygen substituent also retards the rate of hydronium-ion-catalyzed ketonization by more than 3 orders of magnitude. The origins of these substituent effects are discussed.

Although the enol isomers of simple aldehydes and ketones are generally quite unstable, both kinetically and thermodynamically, a variety of methods have recently been developed for generating these substances in solution in greater than equilibrium amounts under conditions where they can be observed directly and rate and equilibrium constants of their reactions can be measured accurately. Much new information is consequently now available on the chemistry of enols of simple aldehydes and ketones where enol or enolate ion is the only functional group present in the molecule.[1] Much less is known about the effect of hetereoatom substituents on this chemistry, and we have therefore undertaken a program of research designed to supply some of the missing information. We have recently reported on the effect of the β-nitrogen substituent in the *N*-acetylamino-*p*-methylacetophenone keto−enol system, eq 1,[2] and we now add to that the effect of the β-oxygen substituent in the isochroman-4-one system, eq 2. In addition to its bearing on enol chemistry, a β-oxygen substituent such as this is of biological interest in connection with the mechanism of aldose−ketose isomerases, a process known to involve enediol/enediolate intermediates; a well-known example is the conversion of dihydroxyacetone phosphate into glyceraldehyde phosphate, a necessary step in the metabolism of glucose.[3]



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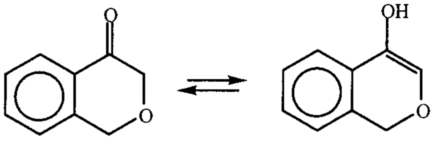

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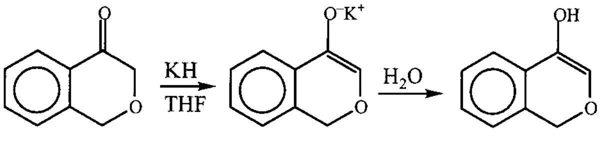
We generated the enol of isochromanone by hydrolysis of its potassium salt, itself prepared by treating isochroman-4-one with potassium hydride in an aprotic solvent, eq 3, and also by hydrolysis of the trimethylsilyl enol ether, eq 4.



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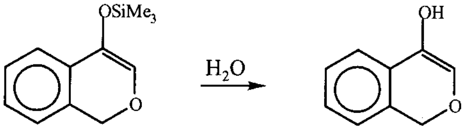

(4)

To have an unsubstituted system with which to compare the chemistry of the isochroman-4-one keto−enol pair, we also examined the 1-tetralone keto−enol system, eq 5. We generated this enol by flash photolytic Norrish type II photoelimination of 2-isobutyl-1-tetralone, eq 6.

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(1) See, for example: *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990.

(2) Chiang, Y.; Griesbeck, A. G.; Heckroth, H.; Hellrung, B.; Kresge, A. J.; Meng, Q.; O'Donoghue, A. C.; Richard, J. P.; Wirz, J. *J. Am. Chem. Soc.* **2001**, *123*, 8979−8984.

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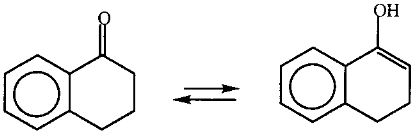
10.1021/ja0112801 CCC: $20.00



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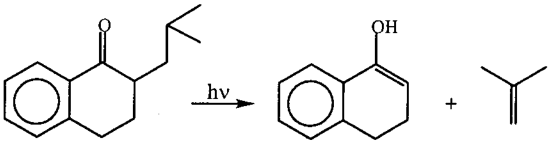

(6)

Experimental Section

Materials. Isochroman-4-one was prepared by Dieckman cyclization of ethyl *o*-carbethoxybenzyloxyacetate followed by saponification and decarboxylation of the β-keto ester so produced,[4] and also by Perkin ring closure of *o*-carboxybenzyloxyacetic acid.[4a,5]

Isochroman-4-one silyl enol ether was obtained by treating isochroman-4-one with the trimethylchlorosilane−sodium iodide−tertiary amine reagent.[6] To a stirred solution of 0.86 g of sodium iodide in 10 mL of anhydrous acetonitrile were added 0.58 g of triethylamine (dried before use) and 0.70 g isochroman-4-one. When these substances had dissolved, 0.63 g of trimethylchlorosilane was added, which caused a white precipitate to form immediately. The resulting mixture was stirred at room temperature for 3 h. It was then extracted with *n*-pentane, and the extracts were concentrated to give 0.82 g (79%) of the silyl ether as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 7.29−7.01 (m, 4H), 6.45 (s, 1H), 4.93 (s, 2H), 0.25 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 136.7, 133.1, 130.9, 129.1, 128.2, 127.4, 123.7, 119.5, 68.5, 0.27. HRMS: *m*/*e* = 220.0920 (calcd), 220.0919 (found).

2-Isobutyl-1-tetralone was synthesized by alkylating 2-ethoxycarbonyl-1-tetralone[7] using a published procedure[8] and then saponifying and decarboxylating the product obtained. A solution of sodium ethoxide was prepared by dissolving 0.24 g of sodium in 30 mL of absolute ethanol, and to this was added a solution of 2.00 g of 2-ethoxycarbonyl-1-tetralone in 10 mL of absolute ethanol. This mixture was heated under reflux for 0.5 h. It was then cooled to room temperature, 1.6 mL of isobutyl iodide was added, and the resulting mixture was heated under reflux for 20 h. The reaction mixture was then poured into water, and the resulting mixture was extracted with ether. The ether was removed from this extract, and the residue was purified by flash chromatography on silica gel using 5% ethyl acetate in hexane as the eluent.

The 2-isobutyl-2-ethoxycarbonyl-1-tetralone so obtained was then saponified and decarboxylated by heating under reflux for 3 h 1.00 g of this substance in 20 mL of 95% aqueous ethanol to which 2.0 g of potassium hydroxide had been added. The reaction mixture was then cooled, and water was added. The resulting mixture was extracted with chloroform, and the extract was washed with water and brine and then dried over magnesium sulfate. The solvent was removed from the dried extract, and the residue was purified by flash chromatography on silica gel using 2% ethyl acetate in hexane as the eluent. This produced 0.50 g (68%) of 2-isobutyl-1-tetralone, whose ^{1}H NMR spectrum agreed with a published report.[9]

All other materials were the best available commercial grades.

Ketonization Rate Measurements. (a) 1-Tetralone Enol. The enol of 1-tetralone was generated flash photolytically by Norrish type II photoelimination of 2-isobutyl-1-tetralone according to eq 6. Rate measurements were made using a conventional microsecond flash system that has already been described,[10] whose reaction cell was thermostated at 25.0 ± 0.05 °C. Decay of the enol was monitored at $\lambda = 290$ nm in acidic and buffer solutions, and decay of the enolate ion was monitored at $\lambda = 300$ nm in basic solutions. Observed first-order rate constants were obtained by least-squares fitting of an exponential function.

(b) Isochromanone Enol, Potassium Salt Method. Rate measurements in perchloric acid solution were made by conventional spectroscopy using a Cary 2200 spectrometer whose cell compartment was thermostated at 25.0 ± 0.05 °C. Stock solutions of the potassium enolate were prepared by treating 0.02 M solutions of isochroman-4-one in anhydrous tetrahydrofuran with a slight excess of potassium hydride. This operation was carried out under an argon atmosphere in a plastic glovebag, and the stock solutions were stored under argon in Pierce Reacti vials fitted with Pierce Mininert valves; samples for kinetic measurement were withdrawn by hypodermic syringe. Reactions were initiated by adding 7 μL aliquots of these stock solutions to 3.0 mL portions of aqueous acid solutions contained in spectrometer cuvettes that had been allowed to come to temperature equilibrium with the spectrometer cell compartment. Reactions were monitored by following the increase in isochromanone absorbance at $\lambda = 255$ nm or the decrease in enol absorbance at $\lambda = 290$ nm.

Rates of ketonization in sodium hydroxide solution were too fast to be measured by conventional spectroscopy in this way, and determinations were therefore made using a High-Tech Scientific SF-S1 stopped-flow spectrometer. Aqueous sodium hydroxide solutions were mixed in a 1:1 ratio with an essentially aqueous solution of enol in a very dilute buffer formed by adding 30 μL of potassium enolate stock solution to 6.0 mL of 0.005 M aqueous acetic acid. The lifetime of the enol in this buffer solution was sufficiently long to carry out several stopped-flow rate measurements before the absorbance change became too small to be useful.

Observed first-order rate constants for both acid and base solutions were obtained by least-squares fitting of an exponential function.

(c) Isochromanone Enol, Silyl Ether Method. Rate measurements in perchloric acid solution were made by conventional spectroscopy using the Cary 2200 spectrometer. Reactions were initiated by adding 4 μL aliquots of ca. 0.04 M acetonitrile stock solutions of isochroman-4-one trimethylsilyl enol ether to 2.8 mL portions of acid solution that had been allowed to come to temperature equilibrium with the thermostated (25.0 ± 0.05 °C) spectrometer cell compartment. The silyl ether was not very soluble in these aqueous acid solutions, and the mixtures had to be shaken for ca. 30 s in order to effect complete solution. This gave sufficient time for hydrolysis of the silyl ether to enol to go to completion, and observed first-order rate constants for enol decay could be obtained by least-squares fitting of a single exponential function. In some cases, however, this first-order decay was followed by a subsequent slow downward absorbance drift, and the least-squares fitting was consequently done using an exponential plus linear function.

Rate measurements in sodium hydroxide solutions were again done by stopped-flow spectroscopy, mixing aqueous silyl ether and sodium hydroxide solutions in a 1:1 ratio. Measurements were limited to sodium hydroxide concentrations equal to or greater than 0.01 M, where hydrolysis of the silyl ether, which is catalyzed by hydroxide ion, is considerably faster than ketonization of the enol, whose rate in this region is independent of hydroxide ion concentration. Observed first-order rate constants were obtained by least-squares fitting of a single-exponential function.

Enolization Rate Measurements. (a) Basic Solution. Rates of enolization of 1-tetralone and isochroman-4-one were measured in sodium hydroxide solutions using iodine to scavenge the enols as they formed. The reactions were carried out under first-order conditions using an excess of iodine ($(1{-}3) \times 10^{-5}$ M) over ketone (0.5×10^{-5} M) in the presence of iodide ion ($(3{-}15) \times 10^{-5}$ M). The reactions were monitored by following the absorbance change at $\lambda = 230$ nm using the Cary 2200 spectrometer with cell compartment thermostated at 25.0

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± 0.05 °C. Observed first-order rate constants were obtained by least-squares fitting of a single-exponential function.

(b) Acid Solution. Rates of enolization of isochroman-4-one were also measured in acid solutions, but, because the reaction in these media was very much slower than that in base, an initial rate method that consumed only about 0.2% of the ketone substrate (initial concentration $= 1.37 \times 10^{-3}$ M) was used. The reaction was followed by bromine scavenging of the enol as it formed, and because the acid used was hydrogen bromide in the concentration range 0.9−2.7 M, most of the bromine was complexed as the Br_3^- ion. Measurements were made by monitoring the decrease in Br_3^- absorbance at $\lambda = 320$ nm using the Cary 2200 spectrometer with cell compartment thermostated at 25.0 ± 0.05 °C.

In a typical procedure, 3.00 mL of aqueous HBr was allowed to come to temperature equilibrium with the spectrometer cell compartment, and a small amount (less than 2 μL) of bromine water of concentration sufficient to give an absorbance reading of 0.1−0.3 at $\lambda = 320$ nm was added. The enolization reaction was then initiated by adding 20.0 μL of a 0.200 M acetonitrile solution of isochromanone. This produced an initial small fast drop in absorbance, probably due to bromination of the enol initially in equilibrium with the keto form of isochromanone, followed by a slower linear decay; the latter was monitored for about 60 min.

These zero-order rates of absorbance decay, $\Delta A/\Delta t$, were converted into first-order enolization rate constants, k^E, with the aid of eq 7, in

$$k^E = \{(\Delta A/\Delta t)/[\text{ketone}]\}/\epsilon_{\text{eff}} \tag{7}$$

which ϵ_{eff} is an effective extinction coefficient that relates the total stoichiometric bromine concentration to the absorbance of Br_3^-. This effective extinction coefficient depends on the true extinction coefficient of Br_3^- at $\lambda = 320$ nm, ϵ_{320}, the equilibrium constant for the $Br_2 + Br^- \rightleftarrows Br_3^-$ association reaction, K_{ass}, and the bromide ion concentration, $[Br^-]$, as shown in eq 8. This relationship works well in dilute

$$\epsilon_{\text{eff}} = \epsilon_{320}K_{\text{ass}}[Br^-]/(1 + K_{\text{ass}}[Br^-]) \tag{8}$$

bromide ion solutions, but, at the high HBr concentrations used in the present study ($[Br^-] = 0.9-2.7$ M), it breaks down because of medium effects on ϵ_{320} and/or K_{ass}. We therefore determined ϵ_{eff} for these solutions empirically by measuring the absorbance at $\lambda = 320$ nm of solutions containing the same constant stoichiometric concentration of bromine both in dilute solution with $[Br^-] = 0.100$ M, $A_{0.1}$, and also in more concentrated solutions with variable $[Br^-]$ ($=x$), A_x. These data are summarized in Table S1.[11] The ratio $A_x/A_{0.1}$ proved to be a linear function of x over the concentration range employed for the present rate measurements: $A_x/A_{0.1} = 1.519 + 0.1125x$. This relationship, together with the dilute solution values $\epsilon_{320} = 5155$ M^{-1} cm^{-1} [12] and $K_{\text{ass}} = 17.0$,[12,13] was then used to calculate ϵ_{eff} at the bromide ion concentrations needed to evaluate the rate data.

Acidity Constant Determinations. The acidity constant of isochroman-4-one ionizing as a carbon acid was determined by monitoring the reversible UV spectral change that this substance undergoes upon ionization. Measurements were made at $\lambda = 320$ nm in potassium hydroxide solutions at a constant stoichiometric concentration (1.26×10^{-4} M) of isochromanone. The Cary spectrometer operating at 25.0 ± 0.05 °C was used.

Results

Isochroman-4-one Acidity Constant. The extent of ionization of isochroman-4-one as a carbon acid was determined by measuring the absorbance of the enolate ion product in a series of potassium hydroxide solutions over the concentration range $[KOH] = 0.1-10$ M. The data so obtained, summarized in Table S2,[11] were transformed into values of I (=[enolate]/[ketone]), and the fit of log I to different basicity functions was examined. Three functions were tried: an H_- scale based on neutral indole indicators,[14] an $H_=$ scale based on indoles bearing carboxylate groups,[14] and an $H_=$ scale based on aromatic amines bearing carboxylate and sulfonate groups.[15] The H_- scale based on indoles proved to be the most appropriate; it gave a plot of log I vs H_- whose slope was unity (1.02 ± 0.05), whereas the other basicity functions produced slopes significantly different from unity (0.83 ± 0.04 and 0.86 ± 0.04). The data were therefore analyzed using the titration curve expression shown in eq 9, in

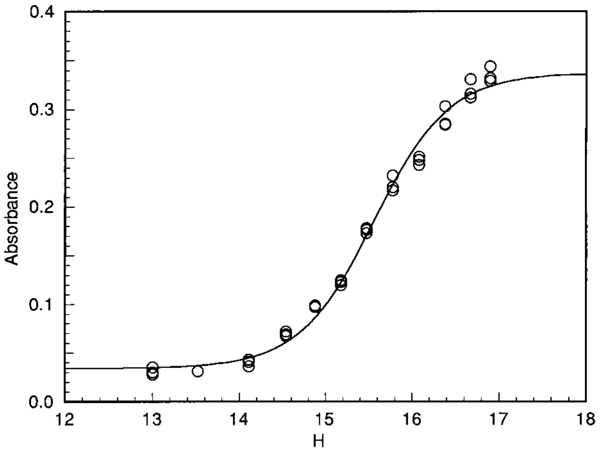

Figure 1. Titration curve for the ionization of isochroman-4-one as a carbon acid in aqueous solution at 25 °C.

$$A = (A_{\text{BH}}10^{(-H_-)} + A_{\text{B}}K_{\text{a}})/(10^{(-H_-)} + K_{\text{a}}) \tag{9}$$

which the H_- scale serves as a measure of the basic strength of the solutions employed. Figure 1 shows that the data conformed to this relationship well; least-squares analysis produced the result $K_a = (2.73 \pm 0.19) \times 10^{-16}$ M, $pK_a = 15.564 \pm 0.030$.

Basicity functions such as the H_- scale used here are anchored to an infinitely dilute standard state, and the acidity constant determined here is therefore a thermodynamic value applicable at zero ionic strength. This acidity constant was also determined from kinetic measurements described below that were carried out at an ionic strength of 0.10 M. Comparison of the two values therefore requires application of activity coefficients, and use of $f = 0.83$ for the hydrogen ion[16] plus $f = 0.79$ for the enolate ion[17] leads to $Q_a = (4.17 \pm 0.29) \times 10^{-16}$ M, $pQ_a = 15.380 \pm 0.030$.[19]

Ketonization of 1-Tetralone Enol. HPLC analysis of spent ketonization reaction mixtures using tetralone enol generated by flash photolysis of 2-isobutyl-1-tetralone (cf. eq 6) showed the presence of only 1-tetralone and unphotolyzed isobutyltetralone. The flash photolysis and ketonization reactions are therefore clean processes, giving only the intended products. Rates of the ketonization reaction were measured in dilute aqueous (H_2O) perchloric acid and sodium hydroxide solutions and also in aqueous (H_2O) CH_3CO_2H, $H_2PO_4^-$, $(CH_2OH)_3CNH_3^+$,

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[11] Supporting Information; see paragraph at the end of this paper regarding availability.

[12] Keeffe, J. R., unpublished work.

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[16] Bates, R. G. *Determination of pH Thoery and Practice*; Wiley: New York, 1973; p 49.

[17] This activity coefficient was calculated using a modified form of the Davies equation that works well for bulky organic anions such as substituted phenols.[18]

[18] King, E. J. *Acid−Base Equilibria*; MacMillan: New York, 1965; p 101.

[19] This is a concentration quotient, applicable at ionic strength = 0.10 M.

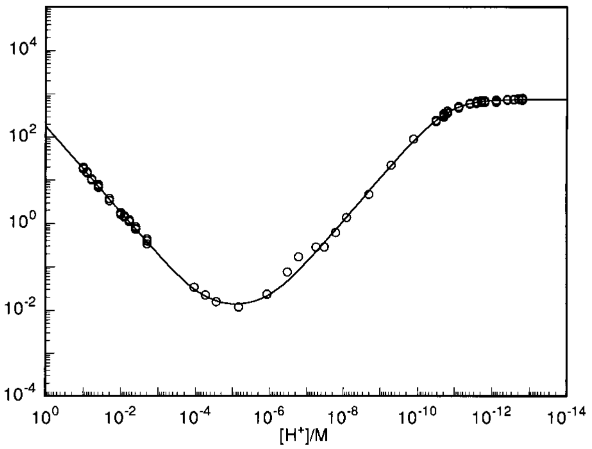


Figure 2. Rate profile for the ketonization of the enol of 1-tetralone in aqueous solution at 25 °C.

and NH_4^+ buffers. The data so obtained are summarized in Tables S3−S5.[11]

The measurements in buffers were made in series of solutions of constant buffer ratio and constant ionic strength (0.10 M), and therefore constant $[H^+]$, but varying buffer concentration. Observed first-order rate constants were found to increase linearly with increasing buffer concentration, in keeping with the buffer dilution rate expression of eq 10, and the data were therefore analyzed by linear least-squares fitting of this equation.

$$k_{\rm obs} = k_{\rm o} + k_{\rm cat}[\text{buffer}] \tag{10}$$

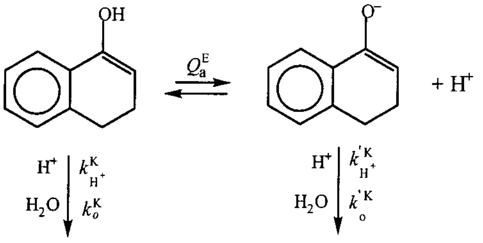
The zero-buffer-concentration intercepts, $k_{\rm o}$, obtained in this way were then combined with the rate constants measured in perchloric acid and sodium hydroxide solutions to construct the rate profile shown in Figure 2. Values of $[H^+]$ needed for this purpose were obtained by calculation, using thermodynamic acidity constants of the buffer acids from the literature and activity coefficients recommended by Bates.[16]

This rate profile is characteristic of enol ketonization reactions. It may be understood in terms of the generally accepted mechanism for this reaction, which consists of rate-determining protonation of the enol or the enolate ion on their β-carbon atoms by all available acids.[20] Since this profile refers to reaction through solvent-related species only, the available acids will be the hydronium ion, written here as H^+, and the solvent water itself.

The acid-catalyzed portion of this rate profile at its high acidity end then represents β-carbon protonation of the un-ionized enol by H^+. This is followed by an “uncatalyzed” region, which could be due either to carbon protonation of un-ionized enol by H_2O or to equilibrium ionization of the enol to the very much more reactive enolate ion[21] followed by carbon protonation of that by H^+; the latter route produces H^+ in a rapid equilibrium step and then uses it up in the rate-determining step, to give an overall process whose rate is independent of H^+ concentration. The second of these two alternative reaction routes may sometimes be ruled out because the data require a rate constant for carbon protonation of the enolate ion that is greater than the encounter-controlled limit, but that is not so in the present case (vide infra).

This “uncatalyzed” portion of the rate profile is followed by a region of apparent hydroxide ion catalysis, which may be attributed to equilibrium ionization of the enol to enolate ion followed by carbon protonation of that by a water molecule. This mechanism produces H^+ in the rapid equilibrium step but does not use it in the rate-determining step, which gives an overall process whose rate is inversely proportional to $[H^+]$ or directly proportional to $[HO^-]$. At sufficiently low acidities, the position of the enol ionization equilibrium switches from enol to enolate ion; the latter then becomes the initial state of the ketonization reaction, and, with water still as the carbon-protonating agent, this leads to the final “uncatalyzed” plateau of the rate profile.

The reaction scheme representing these mechanisms is shown in eq 11, and the rate law that applies is given in eq 12, in which $k_{\rm uc}$ is equal either to $k_{\rm o}^{\rm K}$ or to $k_{\rm H^+}^{\prime\rm K}Q_{\rm a}^{\rm E}$. Least-squares



(11)

$$k_{\rm obs} = k_{\rm H^+}^{\rm K}[H^+] + k_{\rm uc} + k_{\rm o}^{\prime\rm K}Q_{\rm a}^{\rm E}(Q_{\rm a}^{\rm E} + [H^+]) \tag{12}$$

fitting of this expression gave $k_{\rm H^+}^{\rm K} = (1.80 \pm 0.03) \times 10^2$ M^{-1} s^{-1}, $k_{\rm o}^{\rm K} = (1.10 \pm 0.08) \times 10^{-2}$ s^{-1}, $k_{\rm H^+}^{\prime\rm K} = (7.25 \pm 0.60) \times 10^8$ M^{-1} s^{-1}, $k_{\rm o}^{\prime\rm K} = (7.43 \pm 0.13) \times 10^2$ s^{-1}, and $Q_{\rm a}^{\rm E} = (1.52 \pm 0.06) \times 10^{-11}$ M, $pQ_{\rm a}^{\rm E} = 10.82 \pm 0.02$.[19]

Some rates of ketonization of 1-tetralone enol were also measured in dilute D_2O solutions of perchloric acid and sodium hydroxide. The results, summarized in Tables S3 and S4,[11] when combined with their H_2O counterparts, give the following isotope effects: $k_{\rm H^+}^{\rm K}/k_{\rm D^+}^{\rm K} = 4.56 \pm 0.12$ and $(k_{\rm o}^{\prime\rm K})_{\rm H_2O}/(k_{\rm o}^{\prime\rm K})_{\rm D_2O} = 7.80 \pm 0.35$. These isotope effects provide good support for the interpretation of the rate profile given above. The isotope effect on $k_{\rm H^+}^{\rm K}$, for example, is large, as expected for rate-determining hydrogen transfer from the hydronium ion to a substrate of moderate reactivity. Such isotope effects contain an inverse ($k_{\rm H}/k_{\rm D} < 1$) secondary component that offsets the normal ($k_{\rm H}/k_{\rm D} > 1$) primary component,[22] and the result obtained here is, in fact, a near maximum value;[23] similar isotope effects on this rate constant have been found for other enol ketonization reactions.[20] The isotope effect on $k_{\rm o}^{\prime\rm K}$ also contains a secondary component, but this time in the normal direction,[22] and that serves to augment the primary component, making this isotope effect much larger than that on $k_{\rm H^+}^{\rm K}$. The striking difference in magnitude between these two isotope effects is, in fact, a hallmark of enol ketonization reactions. Similarly large isotope effects on $k_{\rm o}^{\prime\rm K}$ have been measured for the carbon protonation by H_2O of the enolate ions of isobutyrophenone ($k_{\rm H}/k_{\rm D} = 7.5$),[24] mandelic acid ($k_{\rm H}/k_{\rm D} = 6.9$),[25] methyl mandelate ($k_{\rm H}/k_{\rm D} = 7.7$),[26] and 4-hydroxyisochroman-3-one ($k_{\rm H}/k_{\rm D} = 7.8$).[27]

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(23) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228−7233.

(24) Chiang, Y.; Kresge, A J.; Walsh, P. A. *Z. Naturforsch. A* **1988**, *44*, 406−412.

(25) Chiang, Y.; Kresge, A. J.; Popik, V V.; Schepp, N. P. *J. Am. Chem. Soc.* **1997**, *119*, 10203−10212.

Table 1. Summary of Catalytic Coefficients for Ketonization of the Enol of 1-Tetralone in Aqueous Solution at 25 °C[a]

catalyst	k^{K}/M^{-1} s^{-1} [b]	k'^{K}/M^{-1} s^{-1} [c]
H_3O^+	1.80×10^2	7.25×10^8
CH_3CO_2H	9.82×10^{-1}	5.64×10^7
$H_2PO_4^-$		1.07×10^6
$(CH_2OH)_3CNH_3^+$		1.62×10^5
NH_4^+		2.10×10^4
H_2O		$(7.43/55.5) \times 10^2$

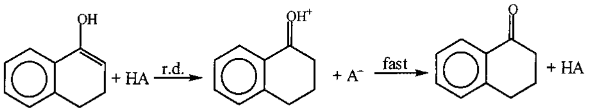
[a] Ionic strength = 0.10 M. [b] Rate constant for carbon protonation of the un-ionized enol. [c] Rate constant for carbon protonation of the enolate ion.

The buffer catalytic coefficients, k_{cat}, obtained by analyzing the buffer data according to eq 10, were separated into their general acid, k_{HA}, and general base, k_{B}, components with the aid of eq 13, in which f_{A} is the fraction of buffer present in the acid form. Both general acid and general base catalysis were

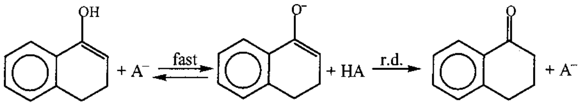
$$k_{\mathrm{cat}} = k_{\mathrm{B}} + (k_{\mathrm{HA}} - k_{\mathrm{B}})f_{\mathrm{A}} \qquad (13)$$

found for the acetic acid buffers, but the other buffers gave only general base catalysis.

This pattern of buffer catalysis provides further support for the interpretation of the rate profile of Figure 2 advanced above. The acidity of the acetic acid buffers used corresponds to the end of the acid-catalyzed region and the beginning of the central "uncatalyzed" plateau of the rate profile, where rate-determining carbon protonation of both enol and enolate ion by H^+ is taking place. The buffer analogues of these H^+ reactions are rate-determining carbon protonation of the enol by the buffer acid, eq 14, leading to general acid catalysis, and buffer-base-assisted ionization of the enol to enolate ion plus a molecule of buffer acid followed by rate-determining carbon protonation of the enolate by buffer acid, eq 15, leading to general base catalysis.



(14)



(15)

The acidity of the remaining buffers, on the other hand, corresponds to the rate profile region of apparent hydroxide ion catalysis, where only the analogue of eq 15 is taking place, and only general base catalysis is observed in these solutions.

The general base catalytic coefficients for the reaction of eq 15 may be formulated as the equilibrium constant for the initial step, which is equal to the ratio of the acidity constants of the enol, $Q_{\mathrm{a}}^{\mathrm{E}}$, and the buffer acid, $Q_{\mathrm{a}}^{\mathrm{HA}}$, times the rate constant, $k'^{\mathrm{K}}_{\mathrm{HA}}$, for the rate-determining step: $k_{\mathrm{B}} = (Q_{\mathrm{a}}^{\mathrm{E}}/Q_{\mathrm{a}}^{\mathrm{HA}})k'^{\mathrm{K}}_{\mathrm{HA}}$. Since both $Q_{\mathrm{a}}^{\mathrm{E}}$ and $Q_{\mathrm{a}}^{\mathrm{HA}}$ are known, $k'^{\mathrm{K}}_{\mathrm{HA}}$ may be evaluated. The results obtained in this way are listed in Table 1.

General acid catalytic coefficients for rate-determining proton-transfer reactions such as these enolate ion ketonizations are expected to conform to the Brønsted relation. Figure 3 shows that this is, indeed, the case for the rate constants of Table 1, taken together with the H^+ and H_2O catalytic coefficients of the enolate ion reaction determined from the rate profile, despite the fact that these catalysts make up a rather mixed group of different charge types. Linear least-squares analysis of the data gives the Brønsted coefficient $\alpha = 0.47 \pm 0.06$. This somewhat small value is consistent with the moderately rapid nature of these ketonization reactions and their consequent rather early, reactant-like transition states.

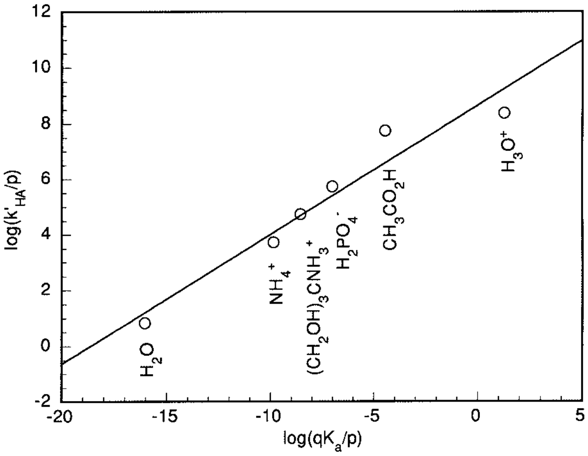


Figure 3. Brønsted plot for the ketonization of 1-tetralone enolate ion in aqueous solution at 25 °C.

Ketonization of Isochroman-4-one Enol. HPLC analysis of spent ketonization reaction mixtures using isochromanone enol generated by hydrolysis of the potassium enolate (eq 3) or the trimethylsilyl ether (eq 4) showed that isochroman-4-one was the principal product formed when these reactions were carried out in dilute aqueous perchloric acid or sodium hydroxide solutions. A minor amount of a second unidentified substance, however, was formed as well. In HCO_2H, $H_2PO_4^-$, and NH_4^+ buffers, on the other hand, apparently comparable amounts of isochromanone and this second substance were produced, and only rate data collected in $HClO_4$ and NaOH solutions were consequently used to characterize the enol ketonization reaction. The results obtained are summarized in Tables S6 and S7.[11]

The measurements in aqueous (H_2O) $HClO_4$ solution were carried out over the concentration range $[HClO_4] = 0.01-0.1$ M. Observed first-order rate constants increased linearly with increasing acid concentration, and linear least-squares analysis gave $k^{\mathrm{K}}_{\mathrm{H+}} = (9.55 \pm 0.49) \times 10^{-2}$ M^{-1} s^{-1} for enol generated by the potassium salt method, in good agreement with $k^{\mathrm{K}}_{\mathrm{H+}} = (8.80 \pm 0.29) \times 10^{-2}$ M^{-1} s^{-1} for enol generated from the silyl ether. The weighted average of these results gives $k^{\mathrm{K}}_{\mathrm{H+}} = (9.00 \pm 0.25) \times 10^{-2}$ M^{-1} s^{-1} as the best value of this rate constant. Some rate measurements were also made in D_2O solutions of perchloric acid, again over the concentration range $[DClO_4] = 0.01-0.1$ M, and combination of those results with their H_2O counterparts gives the isotope effect $k^{\mathrm{K}}_{\mathrm{H+}}/k^{\mathrm{K}}_{\mathrm{D+}} = 3.92 \pm 0.20$.

The rate measurements in aqueous (H_2O) sodium hydroxide solutions gave observed first-order rate constants that remained invariant over the concentration range used ($[NaOH] = 0.008-0.1$ M), as expected for the ketonization via carbon protonation of the enolate ion by H_2O under conditions where enolate is the principal enol species, and as represented by the final plateau of the rate profile for ketonization of tetralone enol shown in Figure 2. Best values of rate constants were therefore determined as simple averages of all observed values. Once again, the result obtained using enol generated by the potassium salt method, $k'^{\mathrm{K}}_{\mathrm{o}} = 10.4 \pm 0.1$ s^{-1}, was consistent with that obtained using enol generated from the silyl ether, $k'^{\mathrm{K}}_{\mathrm{o}} = 11.2 \pm 0.1$ s^{-1}. The average of these values is $k'^{\mathrm{K}}_{\mathrm{o}} = 10.8 \pm 0.5$ s^{-1}.

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(26) Chiang, Y.; Kresge, A. J.; Schepp, N. P.; Xie, R.-Q. *J. Org. Chem.* **2000**, *65*, 1175−1180.

(27) Chiang, Y.; Eustace, S. E.; Jefferson, E. J.; Kresge, A. J.; Popik V. V.; Xie, R.-Q. *J. Phys. Org. Chem.* **2000**, *13*, 461−467.

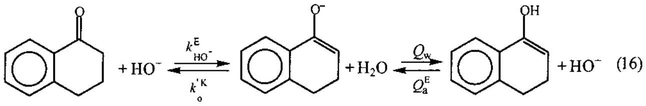
Ketonization rate measurements were also made in D_2O solutions of sodium hydroxide, over the concentration range [NaOD] = 0.01−0.07 M. Once again, observed first-order rate constants did not change with changing sodium hydroxide concentration, and combination of the average value of this rate constant with its H_2O counterpart gave the isotope effect $(k_o^{\prime K})_{H_2O}/(k_o^{\prime K})_{D_2O} = 8.17 \pm 0.42$.

These isotope effects determined in acid and base solution are strikingly similar to those obtained for the corresponding reactions of tetralone enol in acid and base, which, as pointed out above, are fully consistent with expectation for enol ketonization in these solutions and provide strong support for the formulation of the reactions observed as ketonization. The isotope effect similarity therefore adds strong support to the assignment of the isochromanone enol reactions as ketonizations as well, despite the fact that they give a minor amount of a second unknown product.

Enolization of Tetralone. Rates of enolization of 1-tetralone were measured by iodine scavenging in aqueous (H_2O) sodium hydroxide solutions over the concentration range [NaOH] = 0.02−0.1 M. The data so obtained are summarized in Table S8.[11]

Observed first-order enolization rate constants increased linearly with increasing base concentration, and least-squares analysis gave concordant results for measurements made at two different initial iodine concentrations: $k_{HO^-}^{E} = (3.46 \pm 0.05) \times 10^{-2}$ M^{-1} s^{-1} ($[I_2]_o = 1.33 \times 10^{-5}$ M) and $k_{HO^-}^{E} = (3.69 \pm 010) \times 10^{-2}$ M^{-1} s^{-1} ($[I_2]_o = 2.67 \times 10^{-5}$ M). The weighted average of these values is $k_{HO^-}^{E} = (3.51 \pm 0.04) \times 10^{-2}$ M^{-1} s^{-1}.

This result can be combined with the rate constant for ketonization of tetralone enol in basic solutions to provide the keto−enol equilibrium constant of the tetralone system. Formulation of the keto−enol equilibrium as shown in eq 16 leads



(16)

to the expression $K_E = (k_{HO^-}^{E}/k_o^{\prime K})(Q_w/Q_a^{E})$, in which Q_w is the acid ionization constant of water, and insertion of the appropriate values of the rate and equilibrium constants into this expression gives $K_E = (4.93 \pm 0.21) \times 10^{-8}$, p$K_E = 7.31 \pm 0.02$.

The first part of the relationship of eq 16 includes the ionization of 1-tetralone as a carbon acid, and the equilibrium constant for this reaction, Q_a^{E}, may consequently be evaluated as $Q_a^{E} = (k_{HO^-}^{E}/k_o^{\prime K})Q_w = (7.49 \pm 0.16) \times 10^{-19}$ M, p$Q_a^{E} = 18.13 \pm 0.01$.[19]

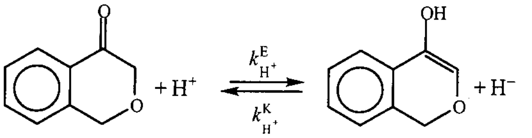
Enolization of Isochromanone. Rates of enolization of isochroman-4-one also were measured by iodine scavenging in aqueous (H_2O) sodium hydroxide solutions over the concentration range [NaOH] = 0.02−0.1 M. The data so obtained are summarized in Table S9.[11]

Observed first-order rate constants again increased linearly with increasing base concentration, and least-squares analysis once more gave concordant results for measurements made at two different initial iodine concentrations: $k_{HO^-}^{E} = (2.87 \pm 0.05) \times 10^{-1}$ M^{-1} s^{-1} ($[I_2]_o = 1.33 \times 10^{-5}$ M) and $k_{HO^-}^{E} = (2.47 \pm 0.07) \times 10^{-1}$ M^{-1} s^{-1} ($[I_2]_o = 2.67 \times 10^{-5}$ M). The weighted average of these values is $k_{HO^-}^{E} = (2.73 \pm 0.04) \times 10^{-1}$ M^{-1} s^{-1}.

Rates of enolization of isochroman-4-one were also measured by bromine scavenging in aqueous (H_2O) hydrobromic acid solutions. Because these reactions were slow, concentrated acid solutions over the range [HBr] = 0.9−2.7 M were used. The data so obtained are summarized in Table S10.[11]

Analysis of data obtained in concentrated acid solutions requires the use of an acidity function, and such analysis was done here by the Cox−Yates method[28] employing the X_o function,[29] which appears to be the best scale currently available for this purpose.[30] This produced the hydronium ion catalytic coefficient for enolization $k_{H^+}^{E} = (4.94 \pm 0.30) \times 10^{-7}$ M^{-1} s^{-1}.

This result can be used, in combination with the hydronium ion catalytic coefficient for ketonization of isochromanone enol, to provide the keto−enol equilibrium constant for the isochromanone system. Formulation of the equilibrium as shown in eq 17 leads to the expression $K_E = k_{H^+}^{E}/k_{H^+}^{K}$, and insertion of the values of the rate constants into this expression gives $K_E = (5.49 \pm 0.37) \times 10^{-6}$, p$K_E = 5.26 \pm 0.03$.



(17)

Another estimate of K_E using rate constants determined in basic solution according to the isochromanone analogue of eq 16 could not be made because the required value of Q_a^{E} was not available. A value of this equilibrium constant for tetralone enol was supplied by analysis of the rate profile for its ketonization reaction (Figure 2), but a rate profile for ketonization of isochromanone enol could not be constructed because formation of a second reaction product interfered with rate measurements in buffer solutions (vide supra).

The basic solution rate constants can nevertheless be employed to provide an estimate of the equilibrium constant for ionization of isochromanone as a carbon acid, Q_a^{E}, using the relationship provided by the first part of eq 16, $Q_a^{K} = (k_{HO^-}^{E}/k_o^{\prime K})Q_w$. This gives $Q_a^{K} = (4.00 \pm 0.20) \times 10^{-16}$ M, p$Q_a^{K} = 15.40 \pm 0.02$,[19] in very good agreement with $Q_a^{K} = (4.17 \pm 0.29) \times 10^{-16}$ M, p$Q_a^{K} = 15.38 \pm 0.03$, obtained directly by measuring the extent of ionization of isochroman-4-one in concentrated potassium hydroxide solutions (vide supra). The weighted average of these two values then gives $Q_a^{K} = (4.06 \pm 0.17) \times 10^{-16}$ M, p$Q_a^{K} = 15.39 \pm 0.02$,[19] as the best value of this constant.

Although a rate profile for the ketonization of isochromanone enol could not be constructed and a value of Q_a^{E} be determined from it, this equilibrium constant can nevertheless be evaluated using the thermodynamic cycle of eq 18. This cycle leads to the relationship $Q_a^{E} = Q_a^{K}/K_E$, and insertion of the known values of Q_a^{K} and K_E then gives $Q_a^{E} = (7.39 \pm 0.58) \times 10^{-11}$, p$Q_a^{K} = 10.13 \pm 0.03$.[19]

Discussion

Equilibria. The present results, summarized in Table 2, show that introduction of an oxygen atom into the β-position of 1-tetralone raises the keto−enol equilibrium constant, K_E, by 2 orders of magnitude, giving a β-oxygen substituent effect of $\delta_R \Delta G^\circ = 2.8$ kcal mol^{-1}. This effect can be attributed to destabilization of the keto isomer plus stabilization of the enol

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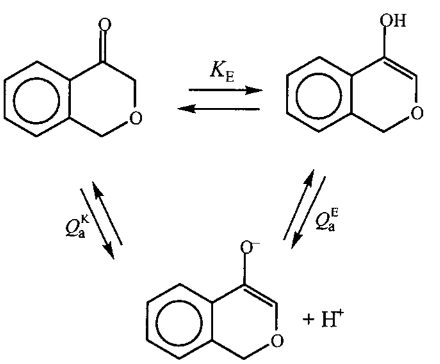
(28) Cox, R. A.; Yates, K. *Can. J. Chem.* **1979**, *57*, 2944−2951.

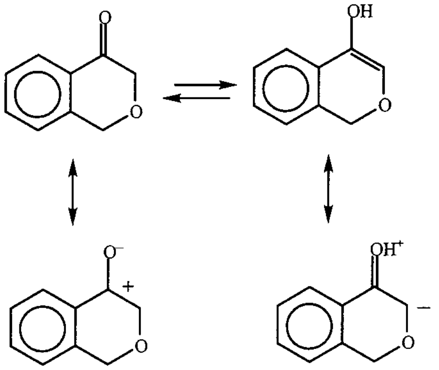
(29) Cox, R. A.; Yates, K. *Can. J. Chem.* **1981**, *59*, 2116−2124.

(30) Kresge, A. J.; Chen, H. J.; Capen, G. L.; Powell, M.F. *Can. J. Chem.* **1983**, *61*, 249−256.



(18)

form. The oxygen atoms of keto groups are electron-withdrawing, and that gives these groups dipolar character with partial positive charges on their keto carbon atoms, as illustrated by the ionic resonance form shown in eq 19; such a partial positive charge will interact unfavorably with an electronegative *β*-oxygen substituent, and that will destabilize the keto isomer. The hydroxyl groups of enols, on the other hand, are electron-supplying, and that puts a partial negative charge on the enol *β*-carbon atom, as again illustrated by the second ionic resonance form of eq 19; this partial negative charge will interact favorably with an electronegative *β*-oxygen substituent, and that will stabilize the enol isomer. The enol will also be stabilized by delocalization of its *β*-oxygen lone electron pair into the aromatic ring. All of these effects operate to decrease the energy difference between keto and enol isomers, and they thus serve to increase K_E.

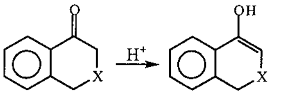
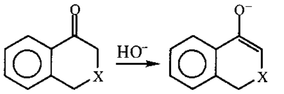
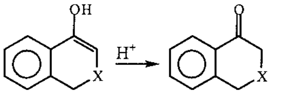
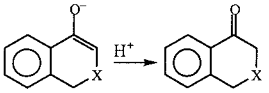
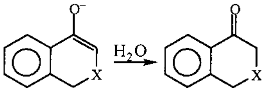
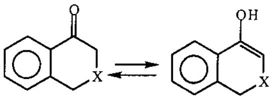
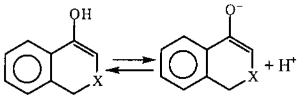
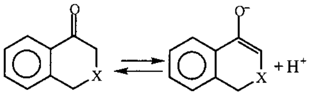


(19)

The *β*-oxygen substituent also increases the acidity constant of the enol, Q_a^E, but by a much smaller amount than its effect on K_E: the substituent effect here is less than 1 order of magnitude and amounts to only $\delta_R\Delta G° = 0.9$ kcal mol^{-1}. This is because the enol isomer rather than the keto form is the initial state for the acid ionization process, and destabilization of the keto form, which made a contribution to the substituent effect on K_E, no longer plays a role. Only stabilization of the partial negative charge on the *β*-carbon atom of the enol by the *β*-oxygen atom and delocalization of the *β*-oxygen lone pair into the aromatic ring, plus corresponding interactions in the enolate ion acid ionization product, operate here. It is likely that the delocalization effect will be much the same in the enol and the enolate ion, but the partial negative charge will, of course, be greater in the negatively charged enolate ion than in the neutral enol; the enolate ion is consequently stabilized more than is the enol, and the result is an increase in Q_a^K.

The *β*-oxygen substituent effect on Q_a^K, the acidity constant of the keto isomer ionizing as a carbon acid to give enolate ion, on the other hand, is greater than the substituent effect on K_E: it is nearly 3 orders of magnitude and amounts to $\delta_R\Delta G° = 3.7$ kcal mol^{-1}. This is because the keto form is the initial state of this process, and both destabilization of that form as well as stabilization of the enolate ion contribute to this substituent effect.

Table 2. Summary of Rate and Equilibrium Constants[a]

Process		X = CH$_2$	X=0
	$k^E_{H^+}$ /M^{-1} s^{-1}:	-	4.94×10^{-7}
	$k^E_{HO^-}$ / M^{-1} s^{-1}:	3.51×10^{-2}	2.73×10^{-1}
	$k^K_{H^+}$ / M^{-1} s^{-1}:	1.80×10^2	9.00×10^{-2}
	$k^K_{H^+}/k^K_{D^+}$:	4.56	3.92
	$k'^K_{H^+}$ / M^{-1} s^{-1}:	7.25×10^8	-
	k'^K_o /s^{-1}:	7.43×10^2	1.08×10^1
	$(k'^K_o)_{H_2O}/(k'^K_o)_{D_2O}$:	7.80	8.17
	pK_E:	7.31	5.26
	pQ_a^E:	10.82	10.13
	pQ_a^K:	18.13	15.39

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

These *β*-oxygen substituent effects are in the same direction as the substituent effects of a *β*-*N*-acetylamino group (NHAc) found before.[2] The present effects, however, are uniformly somewhat weaker and amount to only about two-thirds of the NHAc group effects. This difference is consistent with the facts that the Swain−Lupton field effect substituent constant, *F*, for the simple oxygen-containing group OMe, which could be taken as a surrogate for the OCH$_2$ moiety in isochroman-4-one, is also less than that for NHAc and that the ratio of these two *F* values is likewise about 2/3.[31] The Charton field effect scale,[32] however, as well as various scales cited by Hansch,[33] give field effect substituent constants for OMe and NHAc that are substantially the same.

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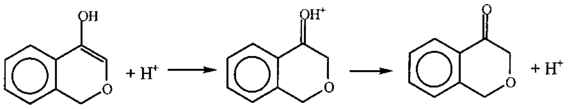
(31) Swain, C. G.; Unger, S. H.; Rosenquist, N. R.; Swain, M S. *J. Am. Chem. Soc.* **1983**, *105*, 492−502.

(32) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119−251.

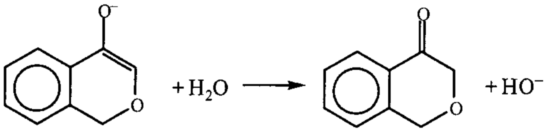
(33) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

Another comparison of the acidifying effects of oxygen and *N*-acetylamino substituents is provided by the simple series water (HOH), hydrogen peroxide (HOOH), and acetohydroxamic acid ($CH_3CONHOH$), whose pK_a values are 15.7, 11.6, and 9.4, respectively.[34] These acidity constants give oxygen an acidifying effect two-thirds of that of the *N*-acetylamino group, just like the influence of these groups on enol acidity. The effects in the simple series, however, are considerably stronger than those on the enols, which is consistent with the fact that in the enols the substituents must act through an intervening carbon−carbon double bond and their influence is consequently attenuated.

Kinetics. The data of Table 2 also show strong β-oxygen substituent effects on rates of ketonization. The rate of ketonization of un-ionized enol catalyzed by H^+, $k^K_{H^+}$, for example, is slowed by more than 3 orders of magnitude, giving the substituent effect $\delta_R\Delta G^{\ddagger} = 4.5$ kcal mol^{-1}. A substantial part of this rate retardation must be due to stabilization of the enol initial state by the β-oxygen atom, but another contributing factor is provided by the two-step nature of the acid-catalyzed ketonization of un-ionized enols, which involves a positively charged carbonyl-oxygen-protonated intermediate, eq 20.[20] The unfavorable interaction between this positive charge and the electronegative β-oxygen atom then raises the energy of the ketonization reaction's transition state, and that lowers the rate of reaction. This explanation is supported by the fact that the β-oxygen substituent effect on the rate of ketonization of ionized enol effected by proton transfer from H_2O, k'^K_o, at $\delta_R\Delta G^{\ddagger} = 2.5$ kcal mol^{-1}, is considerably weaker than that on $k^K_{H^+}$. The ionized enol reaction is a single-step process with no positive charge buildup on the substrate,[20] eq 21, and the additional transition state interaction that contributes to the β-oxygen effect on $k^K_{H^+}$ is consequently absent.

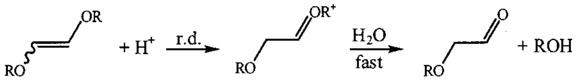


(20)



(21)

Rate retardations effected by β-oxygen atoms similar to that found here on $k^K_{H^+}$ have been reported for the hydronium-ion-catalyzed hydrolysis of several vinyl ethers.[35] Vinyl ether hydrolysis is a rate-determining proton-transfer reaction with a positively charged intermediate, eq 22,[36] analogous to that formed in the ketonization of enols, and interaction of the positive charge of this intermediate with the β-oxygen atom must be a factor contributing to the β-oxygen effect on vinyl ether hydrolysis as well. The vinyl ether hydrolysis effect is, in fact, slightly stronger than that on enol ketonization, which is consistent with the ability of a positively charged hydroxyl group, such as that formed in enol ketonization, to distribute part of its charge onto the solvent through hydrogen bonding. Such charge distribution cannot, of course, take place from a positively charged ether group, such as that formed in vinyl ether hydrolysis, and that makes the effective positive charge on the substrate in vinyl ether hydrolysis greater than that in enol ketonization, leading to a stronger β-oxygen effect in the former case than in the latter. This ability of positively charged hydroxyl to distribute charge onto the solvent enhances the electron-supplying ability of hydroxyl over that of methoxyl, a difference that is manifest in the magnitude of the resonance effect substituent constants of these groups, that of hydroxyl being stronger than that of methoxyl.[31−33]



(22)

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this work.

Supporting Information Available: Tables S1−S10 of rate and equilibrium data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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