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Comparison of Oxygen and Sulfur Effects on Keto−Enol Chemistry in Benzolactone Systems: Benzo[*b*]-2,3-dihydrofuran-2-one and -2-thione and Benzo[*b*]-2,3-dihydrothiophene-2-one and -2-thione

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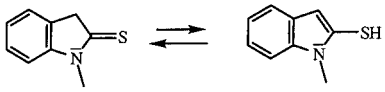
Abstract: Carbon-acid ionization constants, Q_a^K (concentration quotient at ionic strength = 0.10 M), were determined by spectrophotometric titration in aqueous solution for benzo[*b*]-2,3-dihydrofuran-2-one (**3**, $pQ_a^K = 11.87$), benzo[*b*]-2,3-dihydrothiophene-2-one (**2**, $pQ_a^K = 8.85$), and benzo[*b*]-2,3-dihydrofuran-2-thione (**1**, $pQ_a^K = 2.81$). Rates of approach to keto−enol equilibrium were also measured for the latter two substrates in perchloric acid, sodium hydroxide, and buffer solutions, and the rate profiles constructed from these data gave the ionization constants of the enols ionizing as oxygen or sulfur acids $pQ_a^E = 5.23$ for **2** and $pQ_a^E = 2.69$ for **1**. Combination of these acidity constants with the carbon-acid ionization constants according to the relationship $Q_a^K/Q_a^E = K_E$ then gave the keto−enol equilibrium constants $pK_E = 3.62$ for **2** and $pK_E = 0.12$ for **1**. The fourth, all-sulfur, member of this series, benzo[*b*]-2,3-dihydrothiophene-2-thione (**4**), proved to exist solely as the enol in aqueous solution, and only the enol ionization constant $pQ_a^E = 3.44$ could be determined for this substance; the limits $pK_E < 1.3$ and $pQ_a^K < 2.1$, however, could be set. The unusually high acidities and enol contents of these substances are discussed, as are also the relative values of the ketonization and enolization rate constants measured; in the latter cases, Marcus rate theory is used to determine intrinsic kinetic reactivities, free of thermodynamic effects.

Enol isomers of simple carboxylic acid esters and their enolate anions are essential intermediates in many important chemical and biological reactions. These enols and enolates, however, are also quite unstable, both kinetically and thermodynamically,[1] and relatively little hard quantitative information on the rate and equilibrium constants of their reactions is consequently available. Some of what is known has been determined through the study of systems in which the enol is stabilized by some special structural feature,[2] notably the presence of bulky substituents in the β-position.[2a] Such substituents block access to the enol double bond, through whose protonation reversion of the enol to its keto isomer must take place.[3] Some ester enols have also been observed using flash photolytic fast reaction techniques.[4] Carbon-acid ionization constants for enolate ion formation from some acetic acid esters and their derivatives have also been determined by combining very slow rates of enolization with estimates of rate constants for the reverse reactions.[5]

Enols of simple carboxylic acid amides can be expected to be as unstable as simple ester enols.[6] We have recently found, however, that amide enols can be stabilized, sufficiently to allow examination by stopped-flow techniques, through benzene-ring annelation plus replacement of carbonyl oxygen by sulfur, as in the *N*-methylindoline-2-thione system, eq 1.[7] Enol formation



(1)

here produces a new aromatic ring, and the enol also gains stabilization through the well-known greater enol content of thiocarbonyl compounds over their oxygen counterparts,[8] recently found to be 6 orders of magnitude in a simple ketone system.[9]

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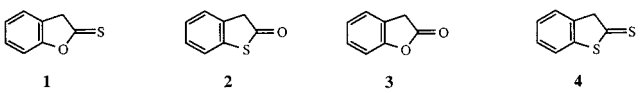
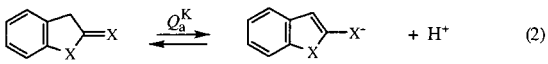
(8) See, for example: Duus, F. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol. 3, pp 385−388.
(9) Kresge, A. J.; Meng, Q. *J. Am. Chem. Soc.* **1998**, *120*, 11830−11831.

We have now extended this method to carboxylic acid esters by examining the benzo[*b*]-2,3-dihydrofuran-2-thione, **1**, keto−enol system. To compare the effects of sulfur and oxygen at the carbonyl and ether positions, we have also investigated benzo[*b*]-2,3-dihydrothiophene-2-one, **2**, as well as the all-oxygen and all-sulfur substrates, benzo[*b*]-2,3-dihydrofuran-2-one, **3**, and benzo[*b*]-2,3-dihydrothiophene-2-thione, **4**.



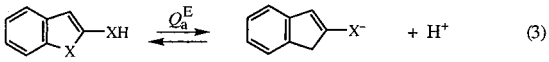
1 **2** **3** **4**

Our investigative method involves determining the acidity constants of the substrates ionizing as carbon acids, Q_a^K, eq 2, by spectrophotometric titration. Acidity constants of the enols



(2)

ionizing as oxygen acids, Q_a^E, eq 3, are then determined from the rate profiles for keto−enol equilibration, and these two acidity constants are combined to provide keto−enol equilibrium constants, K_E, according to the relationship $K_E = Q_a^K/Q_a^E$. We



(3)

were able in this way to obtain all three of these equilibrium constants for the mixed sulfur and oxygen substrates, benzo[*b*]-2,3-dihydrofuran-2-thione (**1**) and benzo[*b*]-2,3-dihydrothiophene-2-one (**2**). Rates of keto−enol equilibration for benzo[*b*]-2,3-dihydrofuran-2-one (**3**) in the acidic solutions needed to determine Q_a^E, however, proved to be too fast for our stopped-flow techniques, and only Q_a^K could be obtained for this substrate. Rates of equilibration for the fourth system, benzo[*b*]-2,3-dihydrothiophene-2-thione (**4**), could also not be measured because the enol, benzo[*b*]thiophene-2-thiol, was the stable isomer here, and only Q_a^E was determined for this substrate.

Experimental Section

Materials. Benzo[*b*]-2,3-dihydrothiophen-2-one (**2**) was prepared from benzo[*b*]-2,3-dihydrothiophene by a published procedure.[10] Benzo[*b*]-2,3-dihydrofuran-2-thione (**1**) was prepared from benzo[*b*]furan, also by a published procedure.[11] Its ^{1}H NMR spectrum in $CDCl_3$ solution was consistent with that reported in the literature[12] and showed it to be a 60:40 mixture of keto and enol isomers in that solvent. Benzo[*b*]-thiophene-2-thiol was prepared by a published procedure from benzo[*b*]thiophene.[13] Its ^{1}H NMR spectrum, which agreed with a literature report,[12] showed the presence of only the enol isomer in $CDCl_3$ solution.

All other materials were of the best available commercial grades.

Spectrophotometric Titrations. Acidity constants were determined by monitoring the reversible UV spectral changes that the substrates underwent upon ionization. Absorbance (A) measurements were made in perchloric acid, sodium hydroxide, and buffer solutions at wavelengths in the range $\lambda = 275-310$ nm, using a Cary Model 2200 spectrometer whose cell compartment was thermostated at 25.0 ± 0.05 °C. Constant stoichiometric substrate concentrations (2×10^{-5} M) were used, and the data were analyzed by nonlinear least-squares fitting of the titration curve expression shown as eq 4, where Q_a is the acid ionization constant of the substrate, and A_B and A_{HA} are the limiting absorbances of its basic and acidic forms, respectively.

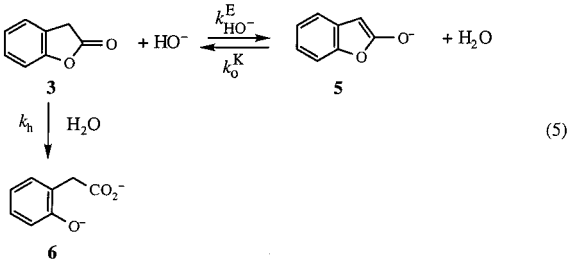
$$A = (A_B Q_a + A_{HA}[H^+])/(Q_a + [H^+]) \qquad (4)$$

Kinetics. Rates of approach to keto−enol/enolate equilibrium were measured using a Hi-Tech Scientific Model SF-S1 stopped-flow spectrometer operating at 25.0 ± 0.05 °C. For studies on solutions more basic than the carbon-acid dissociation constant of the substrate, Q_a^K, kinetic runs were initiated by mixing a solution of substrate in 0.0002 M $HClO_4$ contained in one syringe with a solution of sodium hydroxide or buffer contained in the other syringe, and, for studies on solutions more acidic than Q_a^K, runs were initiated by mixing a solution of initially deprotonated substrate in 0.0002 M NaOH in one syringe with a solution of perchloric acid or buffer in the other syringe. Reactions were monitored by following changes in either enol absorbance at $\lambda = 230-255$ nm or enolate ion absorbance at $\lambda = 290-305$. Substrate concentrations in the reaction mixtures were ca. 10^{-5} M. The rate data conformed to the first-order rate law well, and observed first-order rate constants were obtained by least-squares fitting of an exponential expression.

Rates of hydrolysis of benzo[*b*]-2,3-dihydrofuran-2-one in sodium hydroxide solutions were determined by monitoring the decrease in enolate ion absorbance at $\lambda = 275$ nm. Measurements were made using the Hi-Tech stopped-flow spectrometer again operating at 25.0 ± 0.05 °C. These rate data also conformed to the first-order rate law well, and observed first-order rate constants were obtained by least-squares fitting of an exponential function.

Results

Benzo[*b*]-2,3-dihydrofuran-2-one (3). The absorbance of this substrate at $\lambda = 275$ nm in aqueous sodium hydroxide solutions underwent a rapid increase followed by a slower decay. This behavior has been noted before and has been interpreted as reversible formation of the strongly absorbing enolate ion, **5**, in competition with slower, nonreversible hydrolysis of the lactone function of the keto form **3**, to give a less strongly absorbing carboxylate-phenolate ion product, **6**, as shown in eq 5.[14]



3 **5** **6** (5)

We found that rates of hydrolysis were always at least 2 orders of magnitude slower than keto−enol equilibration. On a time scale convenient for measuring rates of keto−enol equilibration, hydrolysis could therefore be well represented by a simple linear absorbance decay, and the data were therefore fitted using the exponential plus linear function shown as eq 6.

$$\text{absorbance} = A_\infty + A_o \exp(-k_{obs}t) + St \qquad (6)$$

Measurements were made in aqueous sodium hydroxide solu-

(10) Bordwell, F. G.; Fried, H. E. *J. Org. Chem*. **1991**, *56*, 4218−4223.
(11) Anisimov, A. V.; Babaitsev, V. S.; Kolosova, E. A. *Chem. Heterocycl. Compd.* **1982**, *18*, 1335−1337.
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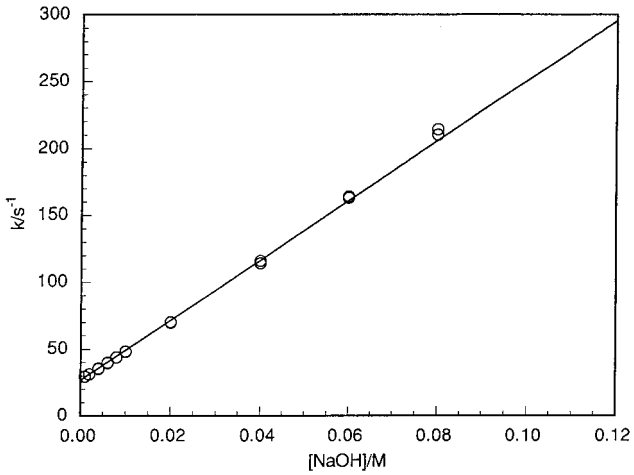


Figure 1. Relationship between sodium hydroxide concentration and rates of keto−enol equilibration of benzo[*b*]-2,3-dihydrofuran-2-one in aqueous solution at 25 °C.

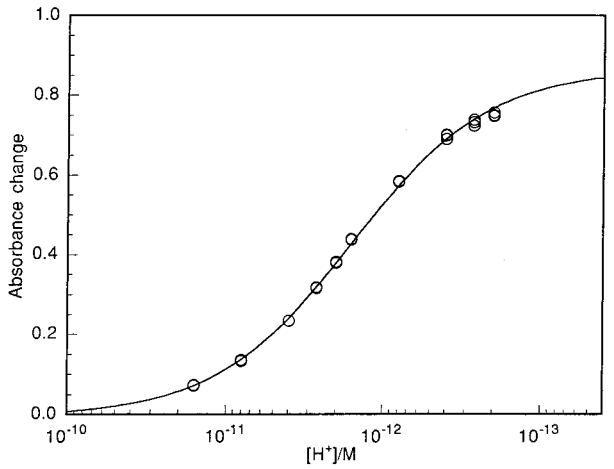


Figure 2. Spectrophotometric titration curve for the ionization of benzo-[*b*]-2,3-dihydrofuran-2-one in aqueous solution at 25 °C.

tions over the concentration range [NaOH] = 0.001−0.08 M at a constant ionic strength of 0.10 M. The data so obtained are summarized in Table S1.[15]

Figure 1 shows that observed first-order rate constants, k_{obs}, obtained in this way increase linearly with increasing sodium hydroxide concentration, as expected for hydroxide-ion promoted enolization. The data also give a finite zero-concentration intercept, which represents the reverse reaction: ketonization of the enolate ion by proton transfer from a water molecule. The ratio of the slope, $k^{E}_{HO^-}$, to the intercept, k^{K}_{o}, of this plot gives an estimate of the equilibrium constant for the enolization process, which is also equal to the acidity constant of the keto form ionizing as a carbon acid, Q^{K}_{a}, divided by the ionization constant of water: $k^{E}_{HO^-}/k^{K}_{o} = Q^{K}_{a}/Q_w$. Least-squares analysis gave $k^{E}_{HO^-} = (2.24 \pm 0.02) \times 10^3\ M^{-1}\ s^{-1}$ and $k^{K}_{o} = (2.65 \pm 0.02) \times 10^1\ s^{-1}$, and these results led to $Q^{K}_{a} = (1.34 \pm 0.10) \times 10^{-12}$ M, $pQ^{K}_{a} = 11.87 \pm 0.01$.[16,17]

Another estimate of Q^{K}_{a} may be obtained from the parameter A_o of eq 6, which represents the absorbance change produced by keto−enol equilibration corrected for the change caused by lactone hydrolysis. Values of A_o are also listed in Table S1.[15] Figure 2 shows that these data describe the sigmoid curve expected of a spectrophotometric titration. Least-squares analysis using eq 4 gave $Q^{K}_{a} = (1.56 \pm 0.103) \times 10^{-12}$ M, $pQ^{K}_{a} = 11.81 \pm 0.01$,[16] which is consistent with the value obtained from rates of keto−enol equilibration as described above.

Rates of lactone hydrolysis were also measured in sodium hydroxide solutions using a longer time scale than that employed for the keto−enol equilibration, and these data could consequently be fitted well using a single-exponential function. Measurements were made over the concentration range [NaOH] = 0.002−0.1 M, again at a constant ionic strength of 0.10 M. The data so obtained are summarized in Table S2.[15]

Figure 3 shows that observed first-order rate constants for this hydrolysis reaction increase with increasing sodium hydroxide concentration at low [NaOH] but that the effect becomes saturated at higher [NaOH], as expected when the reactive keto form of the substrate becomes depleted through enolate ion formation. The rate law that applies to this situation is shown in eq 7, in which k_h is the hydroxide-ion catalyzed hydrolysis rate constant. Least-squares analysis of the data using this

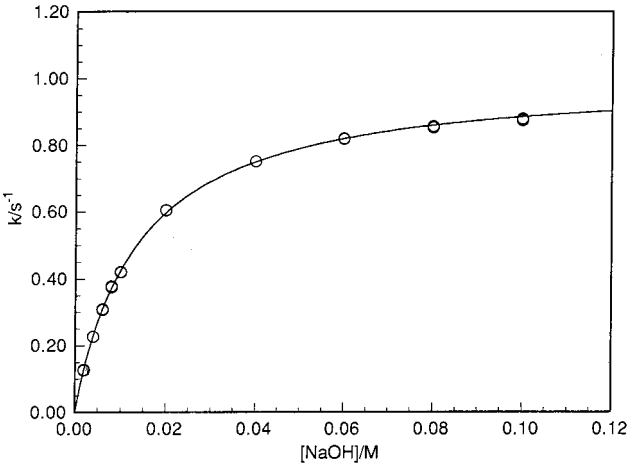


Figure 3. Relationship between sodium hydroxide concentration and rates of hydrolysis of benzo[*b*]-2,3-dihydrofuran-2-one in aqueous solution at 25 °C.

$$k_{obs} = k_h Q_w/(Q^{K}_{a} + [H^+]) \qquad (7)$$

function gave $k_h = (7.34 \pm 0.03) \times 10^1\ M^{-1}\ s^{-1}$ and $Q^{K}_{a} = (1.16 \pm 0.01) \times 10^{-12}$ M, $pQ^{K}_{a} = 11.94 \pm 0.01$.[16] This value of k_h agrees well with $k_h = 7.24 \times 10^1\ M^{-1}\ s^{-1}$ reported before,[14] and the value of Q^{K}_{a} is consistent with results obtained from rates of keto−enol equilibration and from spectrophotometric titration described above. The average of all three determinations of Q^{K}_{a} is $Q^{K}_{a} = (1.35 \pm 0.20) \times 10^{-12}$ M, $pQ^{K}_{a} = 11.87 \pm 0.06$.

The acidity constant of benzo[*b*]-2,3-dihydrofuran-2-one was determined before, as was done here, by measuring rates of hydrolysis of this substance in aqueous sodium hydroxide solutions at an ionic strength of 0.10 M. The result reported, $pK_a = 12.25$, is somewhat greater than the values determined here. It seems likely, however, that in the previous work hydroxide ion concentrations were converted to hydronium ion

(15) Supporting Information; see paragraph at the end of this paper regarding availability.
(16) This is a *concentration* equilibrium constant, applicable at the ionic strength of the present measurements, 0.10 M.
(17) The thermodynamic ionization constant of water, $pK_w = 14.00$, was converted into the concentration quotient $pQ_w = 13.80$ using activity coefficients for H^+ and HO^- recommended by Bates.[18]

concentrations using the thermodynamic ionization constant of water, $pK_w = 14.00$, rather than the concentration quotient used here, $pQ_w = 13.80$. Making allowance for this difference lowers the previously reported value to $pQ_a^K = 12.05$, which puts it more in line with our result.

Both the present results and the previously reported value show benzo[*b*]-2,3-dihydrofuran-2-one to be a moderately stronger acid in H_2O than in DMSO solution, for which $pK_a = 13.5$ has been determined.[10] This difference is consistent with the relatively small acid-weakening effect expected in going from water to DMSO solution for acids whose ionization produces delocalized anions.[19]

Benzo[*b*]-2,3-dihydrothiophene-2-one (2). This substrate also underwent reversible ionization to its enolate anion in basic solutions, as evidenced by the appearance of a strong new absorption band with $\lambda_{max} = 290$ nm, that could be removed by making the solution acidic. In this case, however, hydrolysis of the thiolactone keto form did not compete with keto−enolate equilibration, and a spectrophotometric titration curve could be constructed by straightforward measurement of the absorbance at $\lambda = 290$ nm at different hydronium ion concentrations. This was done in aqueous sodium hydroxide solutions and in aqueous bicarbonate ion, ammonium ion, tris-(hydroxymethyl)methylammonium ion, biphosphate ion, and acetic acid buffers. The ionic strength of these solutions was kept constant at 0.10 M, and the stoichiometric substrate concentration was fixed at 2×10^{-5} M. The data so obtained are summarized in Table S3.[15]

These data gave the expected sigmoid titration curve, and least-squares analysis with the aid of eq 4 produced the carbon-acid acidity constant $Q_a^K = (1.42 \pm 0.04) \times 10^{-9}$ M, $pQ_a^K = 8.85 \pm 0.01$.[16] This result makes benzo[*b*]-2,3-dehydrothiophene-2-one a somewhat stronger acid in H_2O than in DMSO solution, for which $pK_a = 10.7$ has been reported;[10] the difference is similar to that found for benzo[*b*]-2,3-dihydrofuran-2-one (vide supra) and is again consistent with expectation.[19]

Rates of keto−enol/enolate equilibration of this substrate were slow enough to be measured by stopped-flow techniques. Such measurements were made in aqueous perchloric acid and sodium hydroxide solutions and also in aqueous acetic acid, biphosphate ion, tris-(hydroxymethyl)methylammonium ion, and ammonium ion buffers. The ionic strength of these solutions was maintained constant at 0.10 M. The data so obtained are summarized in Tables S4−S6.[15]

The measurements in buffers were done in series of solutions of constant buffer ratio but varying total buffer concentration; because ionic strength was constant, hydrogen ion concentrations were constant as well. Pronounced buffer catalysis was found, with observed first-order rate constants increasing linearly with increasing buffer concentration. The data were therefore analyzed by least-squares fitting of the buffer dilution expression shown as eq 8. The zero-concentration intercepts obtained in this way, k_o, together with the rate constants measured in perchloric acid and sodium hydroxide solutions, are displayed

$$k_{obs} = k_o + k_{buff}[buffer] \qquad (8)$$

as circles in the rate profile shown in Figure 4. Hydronium ion concentrations needed for this purpose were obtained by

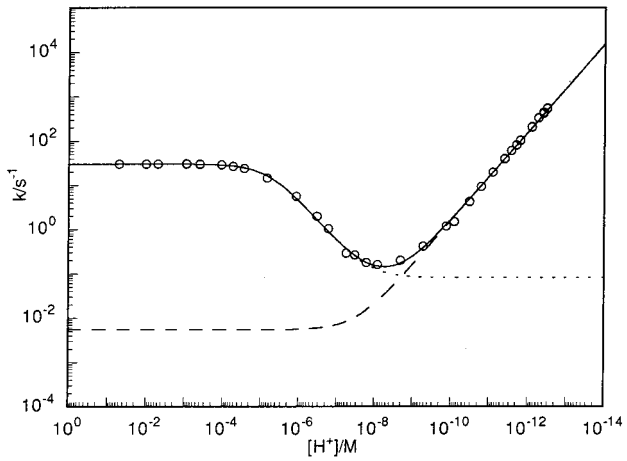
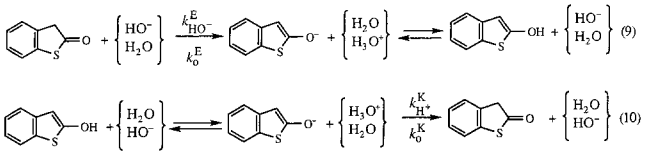


Figure 4. Rate profile for keto−enol/enolate equilibration in the benzo-[*b*]-2,3-dihydrothiophene-2-one system in aqueous solution at 25 °C; circles and solid line, observed rate of approach to equilibrium; dashed line, rate of enolization; dotted line, rate of ketonization.

calculation, using thermodynamic acidity constants of the buffer acids and activity coefficients recommended by Bates.[18]

This rate profile describes the rate of approach to keto−enol/enolate equilibrium catalyzed by solvent-related acidic and basic species. It can be analyzed as the sum of rate constants for enolization occurring through rate-determining proton removal from the keto isomer by either hydroxide ion or a water molecule to give an equilibrium mixture of enol and enolate, eq 9, plus rate constants for ketonization occurring through rate-determining carbon protonation of enolate ion, in equilibrium with enol, by either hydronium ion or a water molecule, eq 10. This



interpretation is consistent with the established reaction mechanisms for enolization and ketonization,[3] and it is supported in the present instance by isotope effects and the form of acid−base catalysis by buffer species (vide infra).

The rate law for this reaction scheme is shown in eq 11, whose rate constants are defined by eqs 9 and 10, and Q_a^E is the acidity constant of the enol ionizing as an oxygen acid.

$$k_{obs} = k_o^E + k_{HO^-}^E[HO^-] + (k_o^K + k_{H^+}^K[H^+])\{Q_a^E/(Q_a^E + [H^+])\} \qquad (11)$$

Analysis of the data using this rate law by a method that has been described in detail before[7] produced the following results: $k_o^E = (5.41 \pm 0.44) \times 10^{-3}$ s^{-1}, $k_{HO^-}^E = (9.55 \pm 0.18) \times 10^3$ M^{-1} s^{-1}, $k_o^K = (7.94 \pm 0.93) \times 10^{-2}$ s^{-1}, $k_{H^+}^K = (5.10 \pm 0.36) \times 10^6$ M^{-1} s^{-1}, and $Q_a^E = (5.94 \pm 0.47) \times 10^{-6}$ M, $pQ_a^E = 5.23 \pm 0.03$.[16] Combination of the latter constant with Q_a^K, determined by spectrophotometric titration (vide supra), according to the relationship $Q_a^K/Q_a^E = K_E$ then led to the keto−enol equilibrium constant $K_E = (2.39 \pm 0.20) \times 10^{-4}$, $pK_E = 3.62 \pm 0.04$.

These results provide complete rate laws for the enolization and ketonization reactions over the entire range of acidity

(18) Bates, R. G. *Determination of pH Theory and Practice*; Wiley: New York, 1973; p 49.
(19) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

Table 1. General Acid and General Base Catalytic Coefficients for Enolization and Ketonization in the Benzo[*b*]-2,3-dihydrothiophene-2-one and Benzo[*b*]-2,3-dihydrofuran-2-thione Systems in Aqueous Solution at 25 °C[a]

catalyst		benzo[*b*]-2,3-dihydrothiophene-2-one (**2**)		benzo[*b*]-2,3-dihydrofuran-2-thione (**1**)	
acid	pK_a	$k_{HA}^K/10^2$ M^{-1} s^{-1}	$k_B^E/10^2$ M^{-1} s^{-1}	$k_{HA}^K/10^2$ M^{-1} s^{-1}	$k_B^E/10^2$ M^{-1} s^{-1}
CH_3CO_2H	4.76	264.			1.09
$H_2PO_4^-$	7.20	29.1			9.44
$(CH_2OH)_3CNH_3^+$	8.07	3.23	0.660		18.7
NH_4^+	9.25	0.140	0.506		9.92

[a] Ionic strength = 0.10 M.

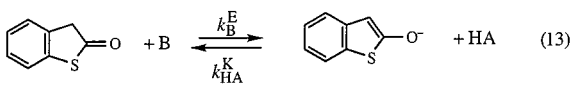
studied. Observed rates of keto−enol/enolate equilibration may consequently be separated into rates of enolization and rates of ketonization, as illustrated in Figure 4. Such dissection shows that ketonization dominates the equilibration process in acidic solutions down to about $[H^+] = 10^{-8}$ M and enolization dominates in basic solutions beginning at about $[H^+] = 10^{-9}$ M.

These dominances are consistent with the nature of buffer catalysis in the buffer solutions examined. The buffer catalytic coefficients, k_{buff}, of eq 8 may be separated into general acid, k_{HA}, and general base, k_B, contributions with the aid of eq 12, in which f_A is the fraction of buffer present in the acid form.

$$k_{buff} = k_B + (k_{HA} - k_B)f_A \qquad (12)$$

The data obtained obeyed this relationship well, and least-squares analysis gave the results listed in Table 1. This analysis shows that only general acid catalysis is significant in acetic acid and biphosphate ion buffers, which is consistent with the fact that these buffers gave solutions in the region $[H^+] = 1 \times 10^{-4}$ to 6×10^{-8} M where ketonization is the dominant reaction; ketonization, being a rate-determining proton transfer from acid catalyst to substrate, can be expected to show only general acid catalysis. Tris(hydroxymethyl)methylammonium ion and ammonium ion buffers, on the other hand, showed both general acid and general base catalysis, which is consistent with the fact that these buffers gave solutions in the region $[H^+] = 3 \times 10^{-8}$ to 1×10^{-10} M, where both enolization and ketonization make significant contributions to observed rates; enolization, being a reaction that involves rate-determining proton removal from the substrate by a basic catalyst, will show general base catalysis.

The numerical values of these last two sets of general acid and general base catalytic coefficients provide further support for the mechanistic interpretation of the rate profile given in eqs 9 and 10. The equilibrium constant for keto−enolate interconversion catalyzed by a general acid−base pair, shown in eq 13, has the value Q_a^K/Q_a^{HA}, in which Q_a^{HA} is the acidity constant of the catalyzing acid. This equilibrium constant is also



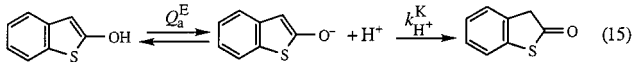
(13)

equal to the rate constant ratio, k_B^E/k_{HA}^K, and equating these two values leads to eq 14

$$Q_a^K = Q_a^{HA} k_B^E / k_{HA}^K \qquad (14)$$

which shows that an estimate of Q_a^K may be obtained from the rate constant pair and Q_a^{HA}. The data for tris(hydroxymethyl)-methylammonium ion give $pQ_a^K = 8.78 \pm 0.04$ and those for ammonium ion give $pQ_a^K = 8.73 \pm 0.05$, both of which are consistent with $pQ_a^K = 8.85 \pm 0.01$ obtained by spectrophotometric titration.

Further support for the interpretation given in eqs 9 and 10 comes from the solvent isotope effect determined in the plateau region of the acid portion of the rate profile. This is based upon rate measurements made in D_2O solutions of perchloric acid over the concentration range $[D^+] = 0.0004-0.05$ M. These data, summarized in Table S4, when combined with their H_2O counterparts, provide the rate ratio $k(H_2O)/k(D_2O) = 8.37 \pm 0.03$. Only ketonization makes a significant contribution to observed rates in this profile region, and, because acid concentrations are greater than the enol acidity constant, the reaction starts with un-ionized enol as the initial state. Ketonization thus proceeds with the enol first ionizing to the more reactive enolate ion, and this ion then undergoes carbon protonation in the rate-determining step, as shown in eq 15. Observed rate constants



(15)

for this reaction are therefore the product of the acidity constant Q_a^E, times the rate constant $k_{H^+}^K$, and the observed isotope effect is consequently the product of isotope effects on each of these quantities. Solvent isotope effects on the equilibrium ionization of oxygen acids, such as this enol, usually lie in the range $K_a(H_2O)/K_a(D_2O) = 3-4$,[20] which leaves an isotope effect on the rate process of $k_{H^+}^K/k_{D^+}^K = 2-3$. This is a reasonable value for a reaction involving rate-determining protonation by hydronium ion of an activated carbon−carbon double bond such as that in the present substrate,[21] and it is consistent as well with isotope effects on the ketonization of other enols catalyzed by the hydronium ion.[3]

Benzo[*b*]-2,3-dihydrofuran-2-thione (1). Rates of keto−enol/enolate equilibration of this substrate could also be measured by stopped-flow techniques, and determinations were consequently made in aqueous perchloric acid and sodium hydroxide solutions and in acetic acid, biphosphate ion, *tris*-(hydroxymethyl)methylammonium ion, and ammonium ion buffers. The ionic strength of these solutions was maintained constant at 0.10 M. The data so obtained are summarized in Tables S7−S9.[15]

The measurements in buffers were once again done in series of solutions of constant buffer ratio and therefore constant hydrogen ion concentrations, and the data were analyzed by least-squares fitting of eq 8. The zero-concentration intercepts obtained in this way, together with the rate constants determined

(20) Laughton, P. M.; Robertson, R. E. In *Solute−Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; Chapter 7.
(21) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228−7233.

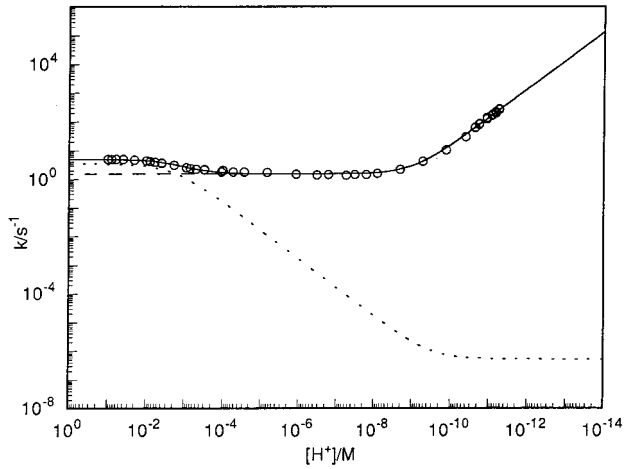
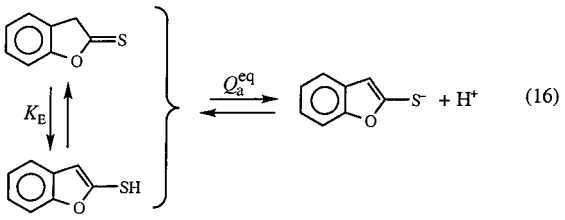


Figure 5. Rate profile for keto−enol/enolate equilibration in the benzo[*b*]-2,3-dihydrofuran-2-thione system in aqueous solution at 25 °C; circles and solid line, observed rate of approach to equilibrium; dashed line, rate of enolization; dotted line, rate of ketonization.

in perchloric acid and sodium hydroxide solutions, were then used to construct the rate profile shown in Figure 5. These data were once more interpreted in terms of the reaction schemes of eqs 9 and 10, and least-squares analysis using the rate law of eq 11 gave the following results: $k_o^E = (1.54 \pm 0.03)$ s^{-1}, $k_{HO^-}^E = (8.32 \pm 0.12) \times 10^4$ M^{-1} s^{-1}, $k_o^K = (5.10 \pm 1.51) \times 10^{-7}$ s^{-1}, $k_{H^+}^K = (1.66 \pm 0.15) \times 10^3$ M^{-1} s^{-1}, and $Q_a^E = (2.04 \pm 0.20) \times 10^{-3}$ M, $pQ_a^E = 2.69 \pm 0.04$.[16]

Benzo[*b*]-2,3-dihydrofuran-2-thione also underwent reversible ionization to its enolate anion, and a spectrophotometric acidity constant determination was made by measuring the enolate ion absorbance at $\lambda = 305$ nm. Measurements were performed at constant ionic strength (0.10 M) in perchloric acid solutions and in acetic acid, biphosphate ion, tris-(hydroxymethyl)-methylammonium ion, and ammonium ion buffers. The data, summarized in Table S10,[15] conformed to the titration curve expression of eq 4 well, and least-squares analysis gave the result $Q_a^{eq} = (8.81 \pm 0.26) \times 10^{-4}$ M, $pQ_a^{eq} = 3.05 \pm 0.01$.[16]

Use of this acidity constant to evaluate K_E according to the relationship $K_E = Q_a^K/Q_a^E$, under the assumption that $Q_a^{eq} = Q_a^K$, leads to a result that gives K_E a value close to unity: $K_E = 0.4$. This is consistent with the ^{1}H NMR spectrum of benzo[*b*]-2,3-dihydrofuran-2-thione in $CDCl_3$ solution, which shows the presence of comparable amounts of keto and enol forms (vide supra), and it indicates that the initial state of the ionization process monitored in the spectrophotometric titration was a mixture of keto (KH) and enol (EH) isomers, as shown in eq 16. The ionization constant determined was therefore an apparent



(16)

or "equilibrium" acidity constant as defined by eq 17. The assumption that $Q_a^{eq} = Q_a^K$ is consequently unwarranted. This is apparent, for example, from eq 18

$$Q_a^{eq} = \frac{[E^-][H^+]}{[KH] + [EH]} \tag{17}$$

$$Q_a^{eq} = Q_a^K/(K_E + 1) \tag{18}$$

which can be derived from eq 17 and shows that $Q_a^{eq} = Q_a^K$ only when K_E is very much less than unity.

A value of K_E may nevertheless be derived from Q_a^{eq} and Q_a^E, inasmuch as replacement of Q_a^K in eq 18 by its equivalent, $K_E Q_a^E$, and rearrangement of the resulting expression lead to eq 19.

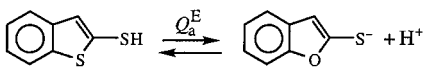
$$K_E = Q_a^{eq}/(Q_a^E - Q_a^{eq}) \tag{19}$$

Insertion of the known values of Q_a^{eq} and Q_a^E into this relationship then gives $K_E = (7.62 \pm 1.33) \times 10^{-1}$, $pK_E = 0.12 \pm 0.07$, and use of that in the expression $Q_a^K = K_E Q_a^E$ then leads to the further result $Q_a^K = (1.55 \pm 0.31) \times 10^{-3}$ M, $pQ_a^K = 2.81 \pm 0.09$.[16]

Our results provide complete rate laws for the enolization and ketonization reactions in the benzo[*b*]-2,3-dihydrofuran-2-thione system over the entire range of acidity investigated. Observed rates of keto−enol/enolate equilibration may consequently once again be separated into their enolization and ketonization components, as is illustrated in Figure 5. It may be seen that enolization dominates this equilibration process strongly and that ketonization makes the greater contribution to observed rates only at acidities above $[H^+] = 10^{-3}$ M; even here, however, the contribution made by ketonization is only 3 times that made by enolization. This stands in striking contrast to the behavior of benzo[*b*]-2,3-dihydrothiophene-2-one, shown in Figure 4, and is a consequence of the much greater acidity of benzo[*b*]-2,3-dihydrofuran-2-thione: $pQ_a^K = 2.81$ versus 8.85.

This dominance of enolization is reflected in the nature of the buffer catalysis observed in the buffer solutions investigated. Separation of the buffer catalytic coefficients, k_{buff}, obtained through the application of eq 8, into general acid and general base contributions with the acid of eq 12 shows only general base catalysis in all four buffers examined, as is expected for an enolization-dominated process involving rate-determining proton removal from the substrate by the catalyst. The results obtained are listed in Table 1.

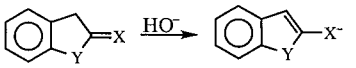
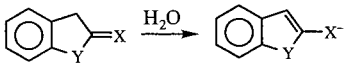
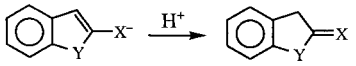
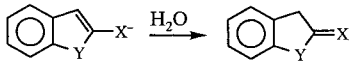
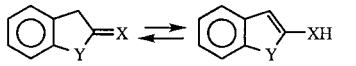
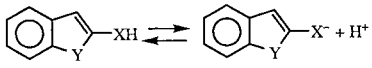
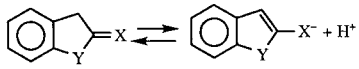
Benzo[*b*]-thiophene-2-thiol (4). Neither the IR nor the ^{1}H NMR spectra of this substrate shows any sign of the keto isomer, which indicates that this substance exists essentially completely in the enol form. The reversible UV spectral change that this substance undergoes, from $\lambda_{max} = 275$ nm in 0.1 M HCl to $\lambda_{max} = 305$ in 0.1 M NaOH, may therefore be attributed to ionization of the enol to its enolate ion, eq 20.



(20)

This spectral change was monitored by measuring the absorbance at $\lambda = 305$ nm in aqueous perchloric acid solutions and in acetic acid and biphosphate ion buffers, all at a constant ion strength of 0.10 M. The data so obtained, summarized in Table S11,[15] conformed to the titration curve expression of eq

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

Process		**3** (X=O, Y=O)	**2** (X=O, Y=S)	**1** (X=S, Y=O)	**4** (X=S, Y=S)
	$k^{E}_{HO^-}/M^{-1}\,s^{-1}$:	2.24×10^{3}	9.55×10^{3}	8.32×10^{4}	-
	k^{E}_{o}/s^{-1}:	-	5.41×10^{-3}	1.54×10^{0}	-
	$k^{K}_{H^+}/M^{-1}\,s^{-1}$:	-	5.10×10^{6}	1.66×10^{3}	-
	k^{K}_{o}/s^{-1}:	2.65×10^{1}	7.94×10^{-2}	5.10×10^{-7}	-
	K_E:	-	2.39×10^{-4}	7.62×10^{-1}	-
	pK_E:	-	3.62	0.12	< -1.3
	Q^{E}_{a}/M:	-	5.94×10^{-6}	2.04×10^{-3}	3.62×10^{-4}
	pQ^{E}_{a}:	-	5.23	2.69	3.44
	Q^{K}_{a}/M:	1.35×10^{-12}	1.42×10^{-9}	1.55×10^{-3}	-
	pQ^{K}_{a}:	11.87	8.85	2.81	< 2.1

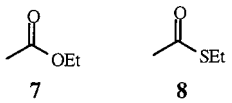
[a] 25 °C, aqueous solution, ionic strength = 0.10 M.

4 well. Least-squares analysis gave the result $Q^{E}_{a} = (3.62 \pm 0.19) \times 10^{-4}$ M, $pQ^{E}_{a} = 3.44 \pm 0.02$.[16]

Because the present system exists essentially completely as the enol isomer, a carbon-acid acidity constant for ionization starting with the keto form as the initial state, Q^{K}_{a}, could not be measured, and a keto−enol equilibrium constant, K_E, could not be determined. A lower limit for K_E can nevertheless be estimated on the assumption that 5% of the keto isomer would have produced a detectable signal in the ^{1}H NMR spectrum of the enol form. Because no such signal was seen, K_E must be greater than 20, which makes pK_E less than −1.3. The relationship $Q^{K}_{a} = K_E Q^{E}_{a}$ then leads to $Q^{K}_{a} > 7.2 \times 10^{-3}$ M, $pQ^{K}_{a} < 2.1$.

Discussion

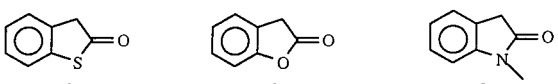
Equilibria. The present results, summarized in Table 2, show the substances investigated to be remarkably strong carbon acids. Benzo[*b*]-2,3-dihydrofuran-2-one (**3**), for example, is more acidic by 14 p*K* units than its simple acyclic analogue ethyl acetate, **7**, whose acidity constant for ionization as a carbon acid has been estimated as $pK_a = 25.6$.[5b] A similar, if slightly



7 **8**

less, difference of 12 p*K* units exists between the carbon-acid acidity constant of benzo[*b*]-2,3-dihydrothiophene-2-one (**2**) and its acyclic analogue, ethyl thioacetate, **8**, for which $pK_a = 21.0$ has been estimated.[5a] These striking differences may be attributed to formation of the new aromatic furan and thiophene rings generated upon ionization of the present substrates. This newly formed aromaticity will stabilize the ionization products and thus make these substances stronger acids than their acyclic counterparts, whose ionization does not benefit from such aromatic stabilization.

It is significant that benzo[*b*]-2,3-dihydrothiophene-2-one, **2**, with $pQ^{K}_{a} = 8.85$ is more acidic than benzo[*b*]-2,3-dihydrofuran-2-one, **3**, with $pQ^{K}_{a} = 11.87$, because the thiophene ring formed upon ionization of **2** is considered to be more aromatic, and therefore more strongly stabilizing, than the furan ring formed upon the ionization of **3**.[22] This comparison of acid



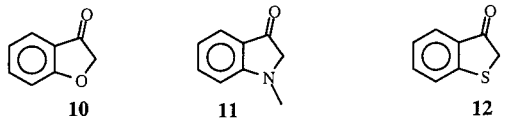
2 **3** **9**

pQ^{K}_{a}: 8.85 11.87 15.70

strength with aromatic character may be extended to *N*-methylindoline-2-one, **9**, for which a similar enhancement of acidity attributable to the formation of an aromatic pyrrole ring has been observed.[7] The acidity of **9**, however, at $pQ^{K}_{a} = 15.70$ makes this substance less acidic than either **2** or **3**, and yet the

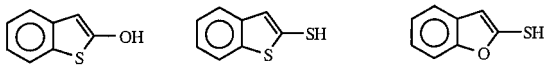
(22) Bird, C. W. *Tetrahedron* **1985**, *41*, 1409−1414.

Scheme 1



	10	11	12
pK_a:	13.22	11.28	9.93

Scheme 2



	13	14	15
pQ_a^E:	5.23	3.44	2.69

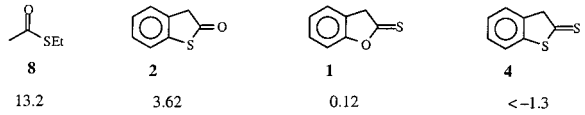
aromaticity of pyrrole is believed to lie between that of thiophene and furan.[22]

This deviation from a parallelism between acid strength and aromaticity suggests that another effect must be operating, and that effect can be identified as conjugation between the endocyclic heteroatom and the carbonyl group in the initial state of the acid ionization reaction. This conjugation will stabilize the initial state, thereby making the substrate a weaker acid, in opposition to the effect of aromaticity, which makes the substrate a stronger acid. Such conjugation will be strongest in the case of a nitrogen heteroatom and will fall off going to oxygen and sulfur, as evidenced, for example, by the resonance substituent constants $R^+ = -1.85$ for NMe_2, $R^+ = -1.07$ for OMe, and $R^+ = -0.83$ for SMe.[23] This effect will make **3** a weaker acid than **2**, reinforcing the acidity order imposed by aromaticity there. The effect will also weaken the acid strength of **9** relative to **2**, and apparently it does so strongly enough to invert the aromaticity-induced order here. This rationalization is substantiated by the acid strengths of benzo[*b*]-2,3-dihydrofuran-3-one, **10**, *N*-methylindoline-3-one, **11**, and benzo[*b*]-2,3-dihydrothiophene-3-one, **12**, shown in Scheme 1,[24] which fall in the order expected from the aromaticity of the furan, pyrrole, and thiophene rings; the carbonyl group in these substrates is separated from the endocyclic heteroatom by a methylene spacer, and initial state conjugation, opposing the effect of aromaticity, therefore cannot operate.

The present results also show interesting differences in acid strengths of the enol isomers. The data summarized in Scheme 2, for example, make **14** a substantially stronger acid than **13**, which is consistent with the commonly found greater acidity of S−H bonds than O−H bonds: simple thiols are stronger acids than their simple alcohol counterparts,[25] and the thioenols, triphenylethenethiol, and 2-(2′,4′,6′-trimethylphenyl)ethenethiol are stronger acids than their oxygen enol analogues.[26]

The present results also show the substances investigated here to have remarkably high enol contents. The keto−enol equilibrium constant for benzo[*b*]-2,3-dihydrothiophene-2-one, **2**, for example, at $pK_E = 3.62$, is nearly 10 orders of magnitude greater than the keto−enol equilibrium constant for its acyclic analogue, ethyl thioacetate, **8**, for which $pK_E = 13.2$ has been estimated.[27]

Scheme 3



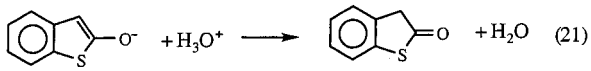
	8	2	1	4
pK_E:	13.2	3.62	0.12	<−1.3

The data summarized in Scheme 3 show the enol contents of benzo[*b*]-2,3-dihydrofuran-2-thione, **1**, and benzo[*b*]-2,3-dihydryothiophene-2-thione, **4**, to be even greater than that of **2**.

The stabilization provided by generation of new aromatic rings upon enol formation must be a major factor responsible for the large enol contents of **2**, **1**, and **4**. The presence of thiocarbonyl groups in **1** and **4**, however, must also play a role: thiocarbonyl compounds are well known to have greater enol contents than their oxygen−carbonyl counterparts,[8,9] a phenomenon that has been attributed to the weakness of the bonding in the C═S group relative to C═O, which is not quite compensated for by the difference in C−S and S−H bond strengths relative to those of C−O and O−H.[28]

Sulfur in the ether position of esters also raises enol contents relative to those of oxygen analogues, through its lower ability to conjugate with the carbonyl group and its consequent lower stabilization of the keto form. The fact that the enol content of **2** is less than that of **1**, however, shows that the enol-content enhancing effect of sulfur in the ether position is smaller than that of sulfur in the carbonyl position. Both of these effects are of course present in **4**, which is reflected in the very high enol content of this substance.

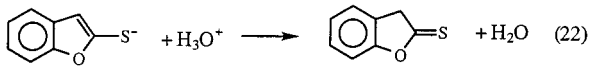
Reaction Rates. The rate constants determined here and summarized in Table 2 show that ketonization of the enolate ion derived from benzo[*b*]-2,3-dihydrothiophene-2-one, **16**, in which oxygen bears the negative charge, through rate-determining β-carbon protonation by the hydronium ion, eq 21, is some



(21)

16 **2**

3.1×10^3 times faster than the corresponding reaction of the enolate ion derived from benzo[*b*]-2,3-dihydrofuran-2-thione, **17**, in which sulfur bears the negative charge, eq 22. The



(22)

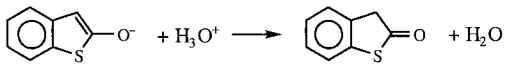
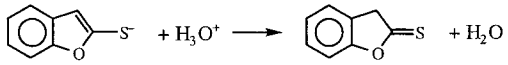
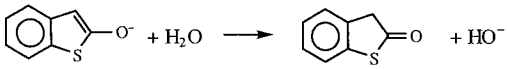
17 **1**

analogous reaction pair in which water rather than the hydronium ion is the proton donor gives the even greater rate ratio 1.6×10^5, again with the enolate ion that bears the negative charge on oxygen, **16**, being the more reactive substrate. The greater rate ratio for the more slowly reacting pair with water as the proton donor is of course consistent with the reactivity-selectivity principle.[29]

This reactivity order is reversed in the enolization reaction, with benzo[*b*]-2,3-dihydrofuran-2-thione, **1**, reacting to give the anion **17** more rapidly than benzo[*b*]-2,3-dihydrothiophene-2-

(23) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(24) Capon, B.; Kwok, F.-C. *J. Am. Chem. Soc.* **1989**, *111*, 5346−5356.
(25) Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic Press: New York, 1985; pp 45−46.
(26) Chiang, Y.; Kresge, A. J.; Schepp, N. P.; Popik, V. V.; Rappoport, Z.; Selzer, T. *Can. J. Chem.* **1998**, *76*, 657−661. Kresge, A. J.; Meng, Q. *J. Am. Chem. Soc.* **1998**, *120*, 11830−11831.
(27) Richard, J. P.; Williams, G.; O'Donoghue, A. C.; Amyes, T. *J. Am. Chem. Soc.* **2002**, *124*, 2957−2968.
(28) Sklenak, S.; Apeloig, Y.; Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2269−2279. The bond energy of C−S was mistakenly given in this paper as 41 instead of 61 kcal mol^{-1}.
(29) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper and Row: New York, 1987; p 148.

Table 3. Energetics of the Ketonization and Enolization Reactions in the Benzo[*b*]-2,3-dihydrothiophene-2-one and the Benzo[*b*]-2,3-dihydrofuran-2-thione Systems[a]

Entry	Reaction	$\Delta G^{\ddagger}$	ΔG^{o}	$\Delta G_o^{\ddagger}$
1		8.3	-12.2	13.7
2		13.1	-4.1	15.1
3		20.5	12.2	13.7
4		17.2	4.1	15.1
5		19.0	6.9	15.3
6		26.0	15.3	17.6
7		12.0	-6.9	15.3
8		10.7	-15.3	17.6

[a] 25 °C, aqueous solution, ionic strength = 0.10 M; energies are in kcal mol^{-1}.

one, **2**, to give anion **16** in both the hydroxide ion- and the water-promoted reactions. This reversal of reactivity order, however, may be an artifact stemming from the use in these comparisons of rate constants for systems in which the free energy of reaction, $\Delta G°$, is not zero. Such rate constants contain a thermodynamic component in addition to intrinsic kinetic factors; that is, exoergic reactions benefit from an "extra drive" that their exoergicity provides, and endoergic reactions suffer from an impediment provided by their endoergicity.[30] Intrinsic reactivity orders should therefore be assessed by comparing systems for which the free energy of reaction is zero and where the thermodynamic factors are thus eliminated.

This may be done by applying Marcus rate theory[31] in the form of eq 23.[32] In this expression, $\Delta G^{\ddagger}$ is the free energy of

$$\Delta G^{\ddagger} = (1 + \Delta G°/4\Delta G_o^{\ddagger})^2 \Delta G_o^{\ddagger} \qquad (23)$$

activation, $\Delta G°$ is the free energy of reaction, and $\Delta G_o^{\ddagger}$ is the intrinsic barrier that applies when $\Delta G° = 0$. Use of this expression to determine $\Delta G_o^{\ddagger}$ requires knowledge of $\Delta G°$, which is not always available. In the present case, however, because rate constants for the reaction under discussion in both forward and reverse directions have been determined, $\Delta G°$ is available from the ratio of forward, k_f, to reverse, k_r, rate constants: $\Delta G° = -RT \ln(k_f/k_r)$.[33]

The values of $\Delta G°$ obtained in this way are listed in Table 3, together with values of $\Delta G^{\ddagger}$ representing the various rate constants. It may be seen that in all cases the faster reaction of any given benzothiophene and benzofuran reaction pair has the more favorable value of $\Delta G°$; for example, entry 1 with $\Delta G^{\ddagger} = 8.3$ kcal mol^{-1} is faster than entry 2 with $\Delta G^{\ddagger} = 13.1$ kcal mol^{-1}, and entry 1 also has the stronger thermodynamic drive with $\Delta G° = -12.2$ kcal mol^{-1} versus $\Delta G° = -4.1$ kcal mol^{-1} for entry 2. This reactivity order is reversed in entries 3 and 4, which are the reverse enolization reactions of ketonization entries 1 and 2, and yet the faster reaction, entry 4, again benefits from a better thermodynamic situation with its much lower free energy impediment, $\Delta G° = 4.1$ kcal mol^{-1}, than $\Delta G° = 12.2$ kcal mol^{-1} for entry 3. The same holds true for the pairs 5 with 6, and 7 with 8.

This close correspondence of relative reactivity of benzothiophene and benzofuran systems with thermodynamic drive or impediment, coupled with the reversal of observed reactivity order in going from ketonization to enolization, implies that one or the other of these reactions is governed by thermodynamics and that the measured rate constants are consequently not reflecting true intrinsic reactivity. The intrinsic barriers listed in Table 3 indicate that it is the enolization reaction whose intrinsic reactivity is masked by thermodynamic effects: in each enolization reaction, the more slowly reacting member of a given pair, that is, the one with the greater value of $\Delta G^{\ddagger}$, has the lower value of $\Delta G_o^{\ddagger}$ and is consequently the intrinsically more reactive substrate. For the ketonization reactions, on the other hand, it is the more rapidly reacting member of a given pair

(30) Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354−360.
(31) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891−899.
(32) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475−503.

(33) Values of $\Delta G°$ may also be obtained from the substrate acidity constants Q_a^K determined here. Because of experimental uncertainties, however, these are slightly different from those derived from rate constants and consequently do not form a wholly self-consistent set with the free energies of activation.

that has the lower value of $\Delta G_o^{\ddagger}$, and observed relative reactivity and intrinsic reactivity here consequently go hand in hand.

This analysis shows that benzo[*b*]-2,3-dihydrothiophene-2-one, **2**, is an intrinsically more reactive substrate than benzo-[*b*]-2,3-dihydrofuran-2-thione (**1**) in both its enolization and its ketonization reactions. Because these enolizations are enolate-ion forming reactions that put negative charge on an exocyclic oxygen or sulfur atom, the greater reactivity of the benzothiophene, with an exocyclic oxygen, over the benzofuran, with an exocyclic sulfur, implies that it is easier to move negative charge to and from oxygen than to and from sulfur.

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Supporting Information Available: Tables S1−S11 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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