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Does Aromaticity in a Reaction Product Increase or Decrease the Intrinsic Barrier? Kinetics of the Reversible Deprotonation of Benzofuran-3(2*H*)-one and Benzothiophene-3(2*H*)-one

Claude F. Bernasconi* and Moisés Pérez-Lorenzo

Contribution from the Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064

Received October 4, 2006; E-mail: bernasconi@chemistry.ucsc.edu

Abstract: A kinetic study of the reversible deprotonation of benzofuran-3(2*H*)-one (**3H-O**) and benzothiophene-3(2*H*)-one (**3H-S**) by amines and hydroxide ion in water at 25 °C is reported. The respective conjugate bases, **3**$^-$**-O** and **3**$^-$**-S**, represent benzofuran and benzothiophene derivatives, respectively, and thus are aromatic. The main question addressed in this paper is whether this aromaticity has the effect of enhancing or lowering intrinsic barriers to proton transfer. These intrinsic barriers were either determined from Brønsted plots for the reactions with amines or calculated on the basis of the Marcus equation for the reaction with OH^-; they were found to be lower for the more highly aromatic benzothiophene derivative, indicating that aromaticity lowers the intrinsic barrier. It is shown that the reduction in the intrinsic barrier is not an artifact of other factors such as inductive, steric, resonance, polarizability, and π-donor effects, although these factors affect the intrinsic barriers in a major way. Our results imply that aromatic stabilization of the transition state is ahead of proton transfer; this contrasts with simple resonance effects, which typically lag behind proton transfer at the transition state, thereby increasing intrinsic barriers.

Introduction

This paper deals with an important and fundamental question regarding chemical reactivity: how does aromatic stabilization of a reactant or product affect the intrinsic barrier[1] of reactions? Surprisingly, this is a question that only recently started to get the attention it deserves.

Inasmuch as aromaticity is a special case of resonance or delocalization of electrons, one might expect that the effect of aromaticity on intrinsic barriers is qualitatively similar to that of resonance. There exists a large body of evidence that shows that resonance effects tend to increase intrinsic barriers of reactions. Most of the early examples referred to proton transfers involving carbon acids activated by strong π-acceptors.[4−12] These reactions are typically much slower than proton transfers involving normal acids. A major factor that accounts for the slow rates is that the transition states of these reactions are imbalanced, in the sense that charge delocalization lags behind proton transfer,[8−12] which results in an increase of the intrinsic barrier, $\Delta G_o^{\ddagger 1}$ (decrease in the intrinsic rate constant, k_o^1). Thus, the greater the resonance stabilization of the carbanion, the greater the imbalance, and hence the larger the intrinsic barrier.

This relationship between intrinsic barriers and transition-state imbalances holds not only for proton transfers but for any chemical reaction that leads to resonance-stabilized/delocalized products[13−15] and is the manifestation of a general principle called the principle of nonperfect synchronization (PSN).[8] The

(1) The intrinsic barrier (intrinsic rate constant) of a reaction with a forward rate constant k_1 and a reverse rate constant k_{-1} is defined as $\Delta G_o^{\ddagger} = \Delta G_1^{\ddagger} = \Delta G_{-1}^{\ddagger}$ when $\Delta G_o = 0$ (as $k_o = k_1 = k_{-1}$ when $K_1 = 1$).[2,3]

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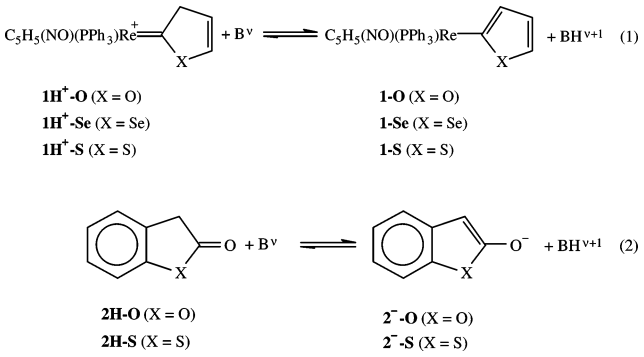
PNS states that any product-stabilizing feature whose development at the transition state lags behind bond changes invariably increases the intrinsic barrier, while a product-stabilizing features whose development is more advanced than bond changes lowers the intrinsic barrier.

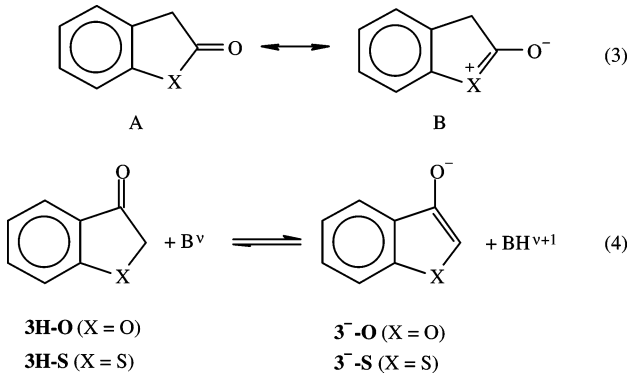
Recently, we have turned our attention to proton transfers from carbon acids that lead to *aromatic* conjugated bases.[16−18] The question we are asking is whether the effect of product aromaticity is qualitatively the same as that of product resonance; i.e., does the development of aromaticity at the transition state also lag behind proton transfer, leading to a higher intrinsic barrier? Results obtained from kinetic studies of the reaction systems shown in eqs 1[16] and 2[18] have led to some conflicting conclusions. In both systems, the respective conjugate bases are



derivatives of aromatic heterocycles, and their relative stabilities are expected to reflect the aromaticity order furan < selenophene < thiophene,[19−21] or benzofuran < benzothiophene,[19−21] respectively. This expectation is confirmed by the relative acidities of the respective carbon acids, i.e., **1H**$^+$**-O** (pK_a = 5.78)[16] < **1H**$^+$**-Se** (pK_a = 4.18)[16] < **1H**$^+$**-S** (pK_a = 2.51)[16] and **2H-O** (pK_a = 11.68)[18] < **2H-S** (pK_a = 8.82).[18]

For the **1H**$^+$**-X** system, the intrinsic barriers for proton transfer to amine bases and carboxylate ions were found to follow the order $\Delta G_o^{\ddagger}$(O) > $\Delta G_o^{\ddagger}$(Se) > $\Delta G_o^{\ddagger}$(S), or, in terms of intrinsic rate constants, the order was k_o(O) < k_o(Se) < k_o(S); i.e., the intrinsic barrier is reduced (the intrinsic rate constant is enhanced) as the aromaticity of **1-X** increases. This order is the opposite of that found for reactions that lead to products stabilized by simple resonance effects. Unless there are other factors present that completely overshadow the effect of aromaticity, according to the PNS these results therefore imply that aromatic stabilization of the transition state is ahead of proton transfer. On the other hand, for the **2H-X** system, the order of the intrinsic barriers for proton transfer to amine bases was found to be $\Delta G_o^{\ddagger}$(O) < $\Delta G_o^{\ddagger}$(S) (k_o(O) > k_o(S)); i.e., here the intrinsic barrier is enhanced (the intrinsic rate constant reduced) as the aromaticity of **2**$^-$**-X** increases, which is the same trend as for reactions that lead to resonance-stabilized products. However, a detailed analysis suggested that other factors, such as differences in the inductive, steric, and π-donor effects of the heteroatoms (O vs S), might mask the effect of the difference in aromaticity between **2**$^-$**-O** and **2**$^-$**-S**. This may have led to the observed trends in $\Delta G_o^{\ddagger}$ and k_o, even though aromatic stabilization at the transition state would still be ahead of proton transfer.

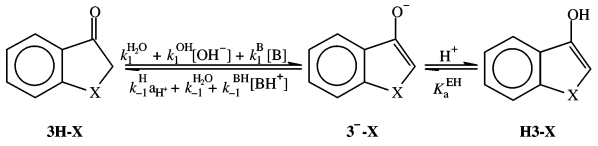
One factor, not related to aromaticity, that is likely to play an important role is the reactant-stabilizing π-donor effect of the heteroatom (eq 3), which is stronger for X = O than for X = S. The study of a system without such π-donor effects could therefore be revealing. The isomeric carbon acids **3H-X**



represent such a system. The present paper reports a kinetic study of the reactions of **3H-O** and **3H-S** with OH$^-$ and amine bases. The results remove the above ambiguities and support the notion that aromaticity develops ahead of proton transfer and that it is the combination of inductive, steric, and π-donor effects which is responsible for the fact that k_o(O) > k_o(S) in the **2H-X** system. We note that there is some overlap between our study and that of Capon and Kwok,[22] although the emphasis, approach, objectives, and even some of the results in the two papers are quite different, as described in the Discussion.

Results

General Features. All kinetic experiments were conducted in water at 25 °C and an ionic strength of 0.5 M (KCl). Reactions were performed in KOH solutions and amine buffers. The kinetic scheme can be described by eq 5, where **H3-X** is



the enol form of **3H-X**, which is in rapid acid−base equilibrium with the enolate ion, B is the buffer base, and BH$^+$ is the buffer acid. The acidities of the keto forms (pK_a^{KH}) as well as those of the enol forms (pK_a^{EH}) were determined kinetically; for **3H-O**, the pK_a^{KH} was also confirmed by a spectrophotometric method. All kinetic experiments were run under pseudo-first-order conditions with the substrate as the minor component. The observed pseudo-first-order rate constants for the equilibrium approach are given by eq 6. All rates were in the stopped-flow time range.

In highly basic solution (pH > pK_a^{KH}), the reactions were run in the "forward direction", i.e., by mixing the keto form with KOH or the appropriate buffer; in solutions at pH <

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$$k_{obsd} = k_1^{H_2O} + k_1^{OH}[OH^-] + k_1^B[B] + (k_{-1}^H a_{H^+} + k_{-1}^{H_2O} + k_{-1}^{BH}[BH^+])\frac{K_a^{EH}}{K_a^{EH} + a_{H^+}} \quad (6)$$

pK_a^{KH}, the runs were performed in the "reverse direction", i.e., the ketone was first incubated in a 0.025 M KOH solution in order to generate the enolate ion, followed by mixing the enolate ion solution with the appropriate buffer.

Benzofuran-3(2*H*)-one, 3H-O. A. Spectrophotometric pK_a^{KH} Determination. The pK_a^{KH} of **3H-O** was determined by classic spectrophotometric methodology applying eq 7, where

$$pK_a^{KH} = pH + \log\frac{A_{C^-} - A}{A - A_{CH}} \quad (7)$$

A is the absorbance at pH $\approx pK_a^{KH}$ measured in piperidine buffers, A_{CH} is the absorbance of **3H-O**, and A_{C^-} is the absorbance of **3-O**$^-$, respectively. A plot of pH versus $\log(A_{C^-} - A)/(A - A_{CH})$ is shown in Figure S1 (Supporting Information).[23] It yields $pK_a^{KH} = 11.71 \pm 0.05$.

B. Kinetics in KOH Solutions. Rates were measured at seven KOH concentrations ranging from 0.005 to 0.05 M. In this range, eq 6 simplifies to eq 8. The results are shown in Figure

$$k_{obsd} = k_1^{H_2O} + k_1^{OH}[OH^-] \quad (8)$$

1. They yield $k_1^{OH} = 83.7 \pm 0.4$ M^{-1} s^{-1} and $k_{-1}^{H_2O} = 1.09 \pm 0.01$ s^{-1}, from which $K_a^{KH} = (k_1^{OH}/k_{-1}^{H_2O})K_w$[24] $= (1.80 \pm 0.04) \times 10^{-12}$ M^{-1} or $pK_a^{KH} = 11.75 \pm 0.02$ was obtained.

C. Kinetics in Amine Buffers. Proton-transfer rates were measured with four primary aliphatic amines (*n*-butylamine, 2-methoxyethylamine, glycinamide, and aminoacetonitrile) and four secondary alicyclic amines (piperidine, piperazine, 1-(2-hydroxyethyl)piperazine (HEPA), and morpholine). For each amine, rates were determined at seven different pH values and at seven amine concentrations for any given pH. Representative plots of k_{obsd} versus free amine concentration for the reaction with piperidine are shown in Figure S2.[23] According to eq 6, the slopes of these plots are given by eq 9. For the reactions

$$\text{slope} = k_1^B + k_{-1}^{BH}\frac{a_{H^+}}{K_a^{BH}}\frac{K_a^{EH}}{K_a^{EH} + a_{H^+}} = k_1^B + k_1^B\frac{a_{H^+}}{K_a^{KH}}\frac{K_a^{EH}}{K_a^{EH} + a_{H^+}} \quad (9)$$

with piperidine and *n*-butylamine which were conducted in the pH ranges of 10.89−11.89 (piperidine) and 10.28−11.28 (*n*-butylamine), the relationship $K_a^{EH} \gg a_{H^+}$ holds, and hence eq 9 simplifies to eq 10. A plot of slope versus a_{H^+} for the piperidine

$$\text{slope} = k_1^B + k_{-1}^{BH}\frac{a_{H^+}}{K_a^{BH}} = k_1^B + k_1^B\frac{a_{H^+}}{K_a^{KH}} \quad (10)$$

reaction is shown in Figure S3.[23] It yields $k_1^B = 41.7 \pm 0.5$ M^{-1} s^{-1} and $pK_a^{KH} = 11.68 \pm 0.04$, in close agreement with the value of 11.75 obtained in KOH solution and by the spectrophotometric method. We shall adopt the average value, 11.72, as the pK_a^{KH} of **3H-O**. Using the relationship $k_1^B/k_{-1}^{BH} = K_a^{KH}/K_a^{BH}$ and $pK_a^{BH} = 11.39$, one calculates $k_{-1}^{BH} = 90.7 \pm 1.1$ M^{-1} s^{-1}.

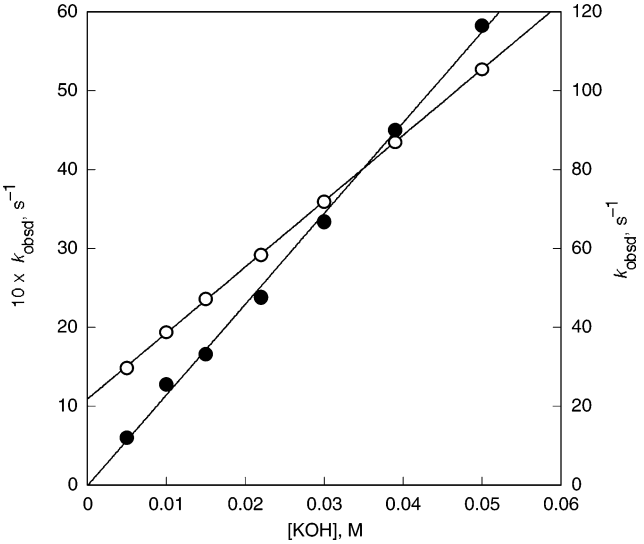


Figure 1. Reactions of **3H-O** (○, left axis) and **3H-S** (●, right axis) with KOH.

A similar plot of slope versus a_{H^+} for the *n*-butylamine reactions (not shown) yields $pK_a^{KH} = 11.45 \pm 0.05$. However, since the data were obtained at lower pH values than for the piperidine reaction, the intercept of this plot is quite small and potentially associated with a larger error than suggested by its standard deviation. Hence, this pK_a^{KH} value is deemed less reliable than the other values. For the same reason, the adopted k_1^B value (Table 2, below) is that obtained from the slope (k_1^B/K_a^{KH}) using $pK_a^{KH} = 11.72$ rather than from the intercept (k_1^B).

For the reactions with piperazine (conducted at pH 9.65−10.65) and 2-methoxyethylamine (conducted at pH 9.10−10.10), the slope in eq 10 (plots not shown) is completely dominated by the $(k_1^B/K_a^{KH})a_{H^+}$ term. For the reactions with glycinamide (pH 7.73−8.73), HEPA (pH 8.93−9.93), and morpholine (pH 8.47−9.47), k_1^B contributes even less to the slopes. Furthermore, the plots of slope versus a_{H^+} are characterized by downward curvature, as shown in Figure 2 for the glycinamide reaction. The curvature is due to the enolate ion/enol equilibrium, which becomes important in this pH range; i.e., the $K_a^{EH}/(K_a^{EH} + a_{H^+})$ term in eq 9 is no longer equal to 1, and eq 11 applies.[26]

$$\text{slope} = k_1^B\frac{a_{H^+}}{K_a^{KH}}\frac{K_a^{EH}}{K_a^{EH} + a_{H^+}} \quad (11)$$

$$\frac{1}{\text{slope}} = \frac{K_a^{KH}}{k_1^B K_a^{EH}} + \frac{K_a^{KH}}{k_1^B a_{H^+}} \quad (12)$$

From inversion plots according to eq 12 (Figure S4[23]) and using the known K_a^{KH} value, one can calculate k_1^B and K_a^{EH}. The following pK_a^{EH} values were obtained: 8.62 ± 0.05 from the

(23) See paragraph concerning Supporting Information at the end of this paper.
(24) $pK_w = 13.63$ at $\mu = 0.5$ M (KCl).[25]
(25) Brandariz, I.; Fiol, S.; Sastre Vicente, M. *Ber. Bunsenges. Chem.* **1995**, *99*, 749.
(26) Even for the reaction with 2-methoxyethylamine, there is an onset of slight curvature at the highest amine concentrations.

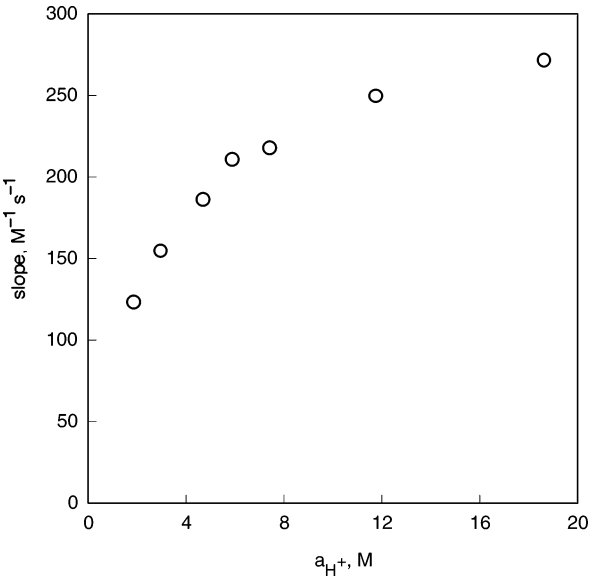


Figure 2. Reaction of **3H-O** with glycinamide. Plot of slopes versus a_{H^+} according to eq 11.

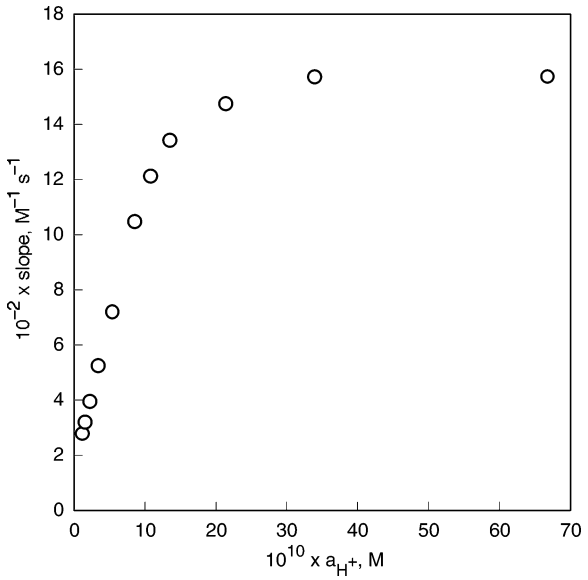


Figure 3. Reaction of **3H-S** with morpholine. Plot of slopes versus a_{H^+} according to eq 8.

HEPA reaction, 8.81 ± 0.04 from the morpholine reaction, and 8.56 from the glycinamide reaction. We shall adopt the average value, 8.66, as the actual pK_a^{EH}.

The aminoacetonitrile reaction was conducted in the pH range of 5.11−6.11. In this range, $K_a^{EH} \ll a_{H^+}$, and eq 9 simplifies to eq 13; i.e., the slopes should be pH independent, as observed (plot not shown).

$$\text{slope} = k_1^B \frac{K_a^{EH}}{K_a^{KH}} \qquad (13)$$

Benzothiophene-3(2*H*)-one, 3H-S. This compound was subjected to the same kinetic experiments as **3H-O**. However, because the pK_a^{KH} of **3H-S** is much lower than that of **3H-O** and the difference between pK_a^{EH} and pK_a^{KH} for **3H-S** is much smaller than for **3H-O**, significant differences were observed in the kinetic behavior of **3H-S**; a spectrophotometric pK_a^{KH} determination was also impractical.

A. Kinetics in KOH Solution. A plot of k_{obsd} vs [KOH] is shown in Figure 1. Because of the relatively high acidity of **3H-S**, $k_{-1}^{H_2O} \ll k_1^{OH}[OH^-]$ under all experimental conditions, as indicated by the absence of a measurable intercept. The slope yields $k_1^{OH} = (2.30 \pm 0.06) \times 10^3$ M^{-1} s^{-1}. In contrast to the situation with **3H-O**, these data do not allow a determination of the pK_a^{KH} from the $k_1^{OH}/k_{-1}^{H_2O}$ ratio.

B. Kinetics in Amine Buffers. With 2-methoxyethylamine (pH 9.10−10.10), glycinamide (pH 7.73−8.73), HEPA (pH 9.43−10.43), and morpholine (pH 8.47−9.47), rates were determined at seven different pH values and at six amine concentrations for any given pH. With the other amines, the reactions were run at one pH only: pH 10.78 for *n*-butylamine, pH 5.61 for aminoacetonitrile, pH 11.39 for piperidine, and pH 10.15 for piperazine.

A representative series of plots of k_{obsd} versus free amine concentration is shown in Figure S5[23] for the reaction with HEPA. The slopes of these plots depend linearly on a_{H^+}, as called for by eq 10; they yield $k_1^B = (6.20 \pm 0.15) \times 10^2$ M^{-1} s^{-1} and $pK_a^{KH} = 9.51 \pm 0.04$. The reaction of 2-methoxyethylamine behaves similarly; it also yields a linear plot (not shown) of slope versus a_{H^+}, from which $k_1^B = 8.04 \pm 0.03$ M^{-1} s^{-1} and $pK_a^{KH} = 9.39 \pm 0.02$ can be calculated. This pK_a^{KH} value is in good agreement with that obtained from the HEPA reaction. We shall adopt the average of the two values, 9.45, as the actual pK_a^{KH} of **3H-S**.

For the reactions with piperidine, piperazine, and *n*-butylamine, eq 10 was used to calculate k_1^B on the basis of $pK_a^{KH} = 9.45$; k_{-1}^{BH} was obtained as $k_{-1}^{BH} = k_1^B K_a^{BH}/K_a^{KH}$.

For the reactions of glycinamide (pH 7.73−8.73) and morpholine (pH 8.47−9.47), the enolate ion/enol equilibrium becomes significant, which leads to nonlinear plots of slope versus a_{H^+}, as shown in Figure 3 for the reaction with morpholine. Because the pK_a^{KH} of **3H-S** is much lower than that of **3H-O** and quite close to the pK_a^{EH}, the k_1^B term is not negligible, even at these relatively low pH values, and hence the full eq 9 applies here. A nonlinear least-squares analysis yields $k_1^B = (3.64 \pm 0.38) \times 10^2$ M^{-1} s^{-1} and $pK_a^{EH} = 8.76 \pm 0.10$ for the morpholine reaction. Analysis of the data for the glycinamide reaction using $pK_a^{KH} = 9.45$ yields $k_1^B = 26.6 \pm 2.2$ M^{-1} s^{-1}.

For the aminoacetonitrile reaction, the slope of a plot of k_{obsd} versus amine concentration is given by eq 13, from which $k_1^B = 1.95 \pm 0.03$ M^{-1} s^{-1} was calculated.

Discussion

Rate constants and pK_a values are summarized in Tables 1 and 2.

pK_a^{KH} and pK_a^{EH}. A. Comparisons with Previous Work. Capon and Kwok[22] published an extensive study on the tautomerism of the monohydroxy derivatives of a series of heterocycles, a series that includes the enol forms of **3H-O** and **3H-S**, i.e., **H3-O** and **H3-S**, respectively. The pK_a^{KH} and pK_a^{EH} determined by these authors are included in Table 1. For reasons that are not clear, the agreement between our results and theirs is not very good, especially with respect to the pK_a^{KH} of **3H-O**, which in our hands (11.72) is 1.50 p*K* units lower than theirs (13.22). The discrepancies are less severe for the pK_a^{EH} of

Table 1. Rate Constants, Intrinsic Barriers, and pK_a Values for the Reversible Deprotonation of **3H-O**, **3H-S**, **2H-O**, and **2H-S** by OH^- in Water at 25 °C, μ = 0.5 M (KCl)

	3H-O		3H-S			
parameter	this work	Capon et al.[a]	this work	Capon et al.[a]	2H-O[b]	2H-S[b]
pK_a^{KH}	11.72 ± 0.03[c]	13.22	9.45 ± 0.04	9.93	11.68	8.82
pK_a^{EH}	8.66 ± 0.12[d]	9.16	8.76 ± 0.14[e]	8.86	8.10	5.82
$pK_E = pK_a^{KH} - pK_a^{EH}$	3.06 ± 0.15	4.06	0.69 ± 0.14	1.07	3.58	3.00
k_1^{OH}, $M^{-1}\,s^{-1}$	83.7 ± 0.4		(2.30 ± 0.06) × 10^3		2.44 × 10^3	1.05 × 10^4
$k_{-1}^{H_2O}$, s^{-1}	1.09 ± 0.01		(1.52 ± 0.18) × 10^{-1}		20.2	0.113
$\Delta G_o^{\ddagger}$, kcal/mol	16.0 ± 0.1		15.5 ± 0.1		14.1	15.1

[a] Reference 22. [b] Reference 18; μ = 0.1 M (KCl). [c] Average pK_a^{KH} determined from kinetic measurements with KOH and piperidine and the spectrophotometric determination. [d] Average pK_a^{EH} determined from kinetic measurements with 1-(2-hydroxyethyl)piperazine, morpholine, and glycinamide. [e] pK_a^{EH} determined from kinetic experiments with morpholine.

Table 2. Rate Constants for the Reversible Deprotonation of **3H-O** and **3H-S** by Amines in Water at 25 °C, μ = 0.5 M (KCl)

B	pK_a^{BH}	k_1^B ($M^{-1}\,s^{-1}$)	k_{-1}^{BH} ($M^{-1}\,s^{-1}$)
3H-O (pK_a^{KH} = 11.72 ± 0.03)			
n-$BuNH_2$	10.78	6.59 ± 0.18	(5.37 ± 0.08) × 10^1
$MeOCH_2CH_2NH_2$	9.60	1.53 ± 0.07	(2.16 ± 0.09) × 10^2
$H_2NCOCH_2NH_2$	8.23	0.20 ± 0.01	(6.46 ± 0.18) × 10^2
$NCCH_2NH_2$	5.61	(3.90 ± 0.17) × 10^{-3}	(5.40 ± 0.23) × 10^3
piperidine	11.39	(4.17 ± 0.05) × 10^1	(9.07 ± 0.11) × 10^1
piperazine	10.15	(2.31 ± 0.10) × 10^1	(9.32 ± 0.42) × 10^2
HEPA[a]	9.43	(1.24 ± 0.02) × 10^1	(2.59 ± 0.03) × 10^3
morpholine	8.97	5.25 ± 0.21	(3.16 ± 0.13) × 10^3
3H-S (pK_a^{KH} = 9.45 ± 0.04)			
n-$BuNH_2$	10.78	(3.79 ± 0.09) × 10^2	(1.77 ± 0.04) × 10^1
$MeOCH_2CH_2NH_2$	9.60	(8.04 ± 0.03) × 10^1	(5.18 ± 0.14) × 10^1
$H_2NCOCH_2NH_2$	8.23	(2.66 ± 0.22) × 10^1	(4.42 ±0.02) × 10^2
$NCCH_2NH_2$	5.61	1.95 ± 0.03	(1.35 ± 0.02) × 10^4
piperidine	11.39	(2.39 ± 0.13) × 10^3	(2.75 ± 0.14) × 10^1
piperazine	10.15	(1.25 ± 0.08) × 10^3	(2.49 ± 0.16) × 10^2
HEPA[a]	9.43	(6.20 ± 0.15) × 10^2	(7.18 ± 0.58) × 10^2
morpholine	8.97	(3.64 ± 0.39) × 10^2	(1.10 ± 0.22) × 10^3

[a] 1-(2-Hydroxyethyl)piperazine.

H3-O (0.50 p*K* unit), the pK_a^{KH} of **3H-S** (0.48 p*K* unit), and the pK_a^{EH} of **H3-S** (0.10 p*K* unit).

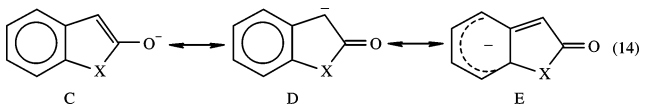
We submit that the pK_a^{KH} value reported by Capon and Kwok for **3H-O** (13.22) cannot be correct for the following reasons. (1) If their value were correct, this would require the slope/intercept ratio of the plot of k_{obsd} versus [KOH] (Figure 1) to be 2.57 instead of the observed 83.7. (2) It would also mean that, at the KOH concentrations used in our study (0.005−0.05 M), the deprotonation reaction would be unfavorable, so much so at the low end of the concentration range that virtually no absorbance change would have been observable. This contrasts with the fact that we observed strong absorbance changes even at the lowest [KOH]. (3) The fact that our spectrophotometric and two kinetic determinations yielded the same result constitutes strong evidence that our pK_a^{KH} value is the correct one.

B. Comparison with 2H-O and 2H-S. 3H-S (pK_a^{KH} = 9.45) is substantially more acidic than **3H-O** (pK_a^{KH} = 11.72), which, as with the higher acidity of **2H-S** (pK_a^{KH} = 8.82) relative to that of **2H-O** (pK_a^{KH} = 11.68), can be mainly attributed to the greater anion aromaticity of the respective thiophene derivatives. Regarding the enol forms, the pK_a^{EH} values of **H3-O** (8.66) and **H3-S** (8.76) are very similar to each other, but for **H2-O** (8.10) and **H2-S** (5.82) they are very different from each other. As a result, the enolization constants are very different for **H3-O** (pK_E = 3.06) versus **H3-S** (pK_E = 0.69), while for **H2-O** (pK_E = 3.58) versus **H2-S** (pK_E = 3.00) they are very similar.

These patterns may be understood as the result of an interplay between charge delocalization, π-donation, polarizability, and anomeric effects as follows.

(1) **2H-X** is stabilized by π-donation from the ring heteroatom (eq 3); this leads to a reduction in acidity. This effect is more important for **2H-O** than for **2H-S** because oxygen is a better π-donor.[27] There is no comparable effect in **3H-X**.

(2) The conjugate base of **2H-X** can delocalize its negative charge into the benzene ring (structure E in eq 14); this leads to an increase in acidity. Inasmuch as the resonance form E



carries a fractional charge close to the X atom, the acidity of **2H-S** will be enhanced more than that of **2H-O** because the sulfur can stabilize this fractional charge more effectively than oxygen due to its greater polarizability.[29] There is no analogous effect on the conjugate base of **3H-X**.

What is the result of the interplay of these factors? For **2H-O**, the acidity-reducing π-donor effect and the acidity-enhancing delocalization effect essentially offset each other, as can be seen from the almost identical pK_a^{KH} values of **3H-O** and **2H-O**. On the other hand, for **2H-S**, the weaker acidity-reducing π-donor effect and the stronger acidity-enhancing delocalization effect lead to a net increase in acidity, as is apparent from the lower pK_a^{KH} of **2H-S** (8.82) compared to that of **3H-S** (9.45).

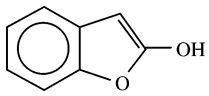
Regarding the various enols, the aromaticity of the enolate ions and that of the respective enols are probably quite similar and hence should not substantially affect the pK_a^{EH} values. The fact that the pK_a^{EH} values of **3H-O** (8.66) and **3H-S** (8.76) are nearly equal is consistent with this notion. By the same token, since the enolization constant (pK_a^E) is related to the pK_a^{KH} and pK_a^{EH} values through eq 15, the more favorable enolization of

$$pK_E = pK_a^{KH} - pK_a^{EH} \qquad (15)$$

(27) For example, the σ_R value for MeO (−0.43) is much more negative than that for MeS (−0.15).[28]
(28) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(29) (a) Streitwieser, A., Jr.; Williams, J. E. *J. Am. Chem. Soc.* **1975**, *97*, 191. (b) Lehn, J.-M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498. (c) Bernardi, F.; Cszizmadia, I. G.; Mangini, A.; Schlegel, H. B.; Whangbo, M.-H.; Wolfe, S. *J. Am. Chem. Soc.* **1975**, *97*, 2209. (d) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rhode, C.; Arad, D.; Houk K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467.

3H-S ($pK_E = 0.69$) than that of **3H-O** ($pK_E = 3.06$) can then be understood as being mainly the result of the greater aromaticity of **H3-S** compared to that of **H3-O**, just as the higher acidity of **3H-S** is mainly the result of the greater aromaticity of $\mathbf{3S}^-$ compared to that of $\mathbf{3\text{-}O}^-$.

There are two factors that render the pK_a^{EH} value of **H2-S** (5.82) so much lower than that of **H2-O** (8.10). The first is the greater stabilization of the resonance form E of the sulfur derivative (eq 14), which was invoked as a partial explanation of why **2H-S** is more acidic than **3H-S**. The second, more important factor is the stabilizing effect of having two geminal oxygen atoms in the enol form of **2H-O** (**H2-O**), which lowers



H2-O

the acidity of **H2-O** and thus enhances the pK_a^{EH} difference between **H2-S** and **H2-O**. This kind of anomeric stabilization is well documented for systems where the two oxygens are attached to sp^3 carbons[30] but has also been found in systems where the oxygens are attached to sp^2 carbons.[31,32] If the geminal oxygen stabilization of **H2-O** by the geminal oxygen effect is a significant factor, it would also help explain why the enolization of **2H-S** ($pK_E = 3.00$) is only slightly more favorable than that of **2H-O** ($pK_E = 3.58$): the geminal oxygen effect would partially offset the greater aromaticity of **H2-S** compared to that of **H2-O**.

Brønsted Plots and Intrinsic Rate Constants. Brønsted plots for the reactions of **3H-O** with amines are shown in Figure 4, and those for **3H-S** in Figure 5. The Brønsted α and β values are summarized in Table 3. Included in Table 3 are the log k_o values for the intrinsic rate constants,[1] determined from the points where the lines for k_1^B and k_{-1}^{BH} intersect, and the intrinsic barriers,[1] $\Delta G_o^{\ddagger}$, calculated from the respective k_o values by means of the Eyring equation.

The α and β values are in the normal range for proton transfers involving carbon acids.[5,34,35] The fact that the intrinsic rate constants are higher ($\Delta G_o^{\ddagger}$ lower) for the reactions with the secondary alicyclic amines than with the primary aliphatic amines is also typical; it reflects the greater solvation energies of the respective protonated primary amines, combined with the fact that the transition-state solvation of the incipient protonated amines lags behind proton transfer.[5,36]

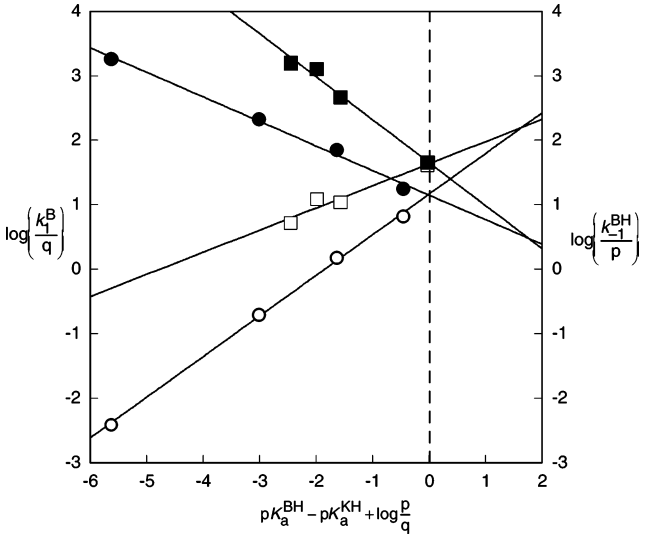


Figure 4. Statistically corrected Brønsted plots for the reactions of **3H-O** with amine buffers: open symbols, k_1^B; filled symbols, k_{-1}^{BH}. ○ and ●, primary aliphatic amines; □ and ■, secondary alicyclic amines. The dashed line goes through the points where the $\log(k_1^B/q)$ and $\log(k_{-1}^{BH}/p)$ lines intersect, which corresponds to log k_o.

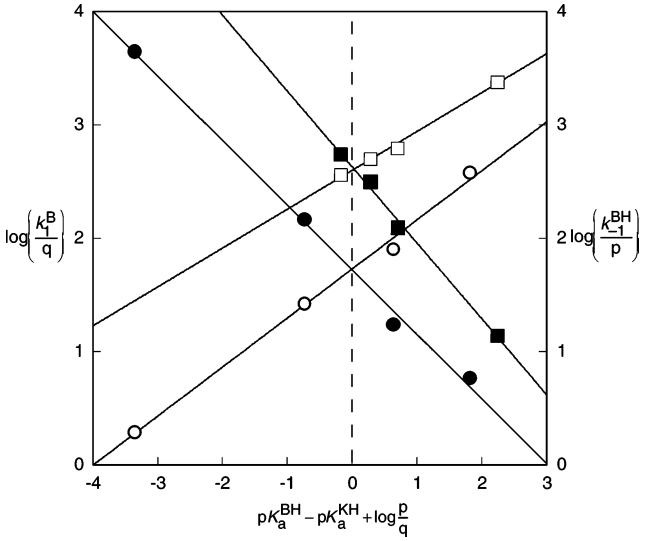


Figure 5. Statistically corrected Brønsted plots for the reactions of **3H-S** with amine buffers: open symbols, k_1^B; filled symbols, k_{-1}^{BH}. ○ and ●, primary aliphatic amines; □ and ■, secondary alicyclic amines. The dashed line goes through the points where the $\log(k_1^B/q)$ and $\log(k_{-1}^{BH}/p)$ lines intersect, which corresponds to log k_o.

The main focus of our results is on the comparison between the intrinsic rate constants (intrinsic barriers) for the reactions of **3H-O** versus **3H-S** as well as the corresponding comparisons for the reactions of **2H-O**, **2H-S**, $\mathbf{1H^+\text{-}O}$, and $\mathbf{1H^+\text{-}S}$; all these parameters are summarized in Table 4. The following points are of interest.

(1) The intrinsic rate constants for the deprotonation of **3H-S** by amines are higher (the intrinsic barrier is lower) than for the deprotonation of **3H-O** derivatives (Δ log $k_o = 0.56$ for the primary amines, Δ log $k_o = 1.02$ for the secondary amines). This contrasts with the reactions of **2H-O** and **2H-S**, where it is the furan derivative which has the higher log k_o (lower $\Delta G_o^{\ddagger}$) values (Δ log $k_o = -0.69$ for the primary amines, Δ log $k_o = -0.24$ for the secondary amines), but our results are comparable

(30) (a) Hine, J.; Klueppel, A. W. *J. Am. Chem. Soc.* **1974**, *96*, 2924. (b) Wiberg, K. B.; Squires, R. R. *J. Chem. Thermodyn.* **1979**, *11*, 773. (c) Harcourt, M. P.; More O'Ferrall, R. A. *Bull. Soc. Chim. Fr.* **1988**, 407.
(31) Sklenák, S.; Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* **1998**, *120*, 10359.
(32) Based on B3LYP/6-311G* calculations, the gas-phase isodermic reaction 2-hydroxyfuran + 2 cyclopentane → tetrahydrofuran + cyclopentadiene + hydroxycyclopentane is about 7 kcal/mol more endothermic than the corresponding reaction 2-hydroxythiophene + 2 cyclopentane → tetrahydrothiophene + hydroxycyclopentane + cyclopentadiene.[33] This implies a rather strong anomeric stabilization of 2-hydroxyfuran relative to that of 2-hydroxythiophene and suggests that **2H-O** may enjoy a stabilization comparable to that of **2H-S**.
(33) Karni, M. personal communication.
(34) Kresge, A. J. In *Proton Transfer Reactions*; Caldin, E. F., Gold, V., Eds.; Wiley: New York, 1975; p 179.
(35) (a) Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.* **1986**, *108*, 2969. (b) Bernasconi, C. F.; Terrier, F. *J. Am. Chem. Soc.* **1987**, *109*, 7115. (c) Bernasconi, C. F.; Kliner, D. A. V.; Mullin, A. S.; Ni, X. *J. Org. Chem.* **1988**, *53*, 3342.
(36) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; p 178.

Table 3. Brønsted α and β Values, log k_o for the Intrinsic Rate Constants, and Intrinsic Barriers ($\Delta G_o^{\ddagger}$) for the Reversible Deprotonation of **3H-O** and **3H-S** by Amines in Water at 25 °C

	$\beta =$ d log k_1^B/ d pK_a^{BH}	$\alpha =$ d log k_{-1}^{BH}/ d log K_a^{BH}	log k_o	$\Delta G_o^{\ddagger}$ (kcal/mol)
		3H-O		
primary amines	0.63 ± 0.02	0.37 ± 0.02	1.16 ± 0.06	15.8 ± 0.1
secondary amines	0.34 ± 0.06	0.66 ± 0.06	1.64 ± 0.11	15.1 ± 0.1
		3H-S		
primary amines	0.44 ± 0.02	0.56 ± 0.02	1.72 ± 0.05	15.0 ± 0.1
secondary amines	0.32 ± 0.04	0.64 ± 0.04	2.64 ± 0.05	13.8 ± 0.1

to those for the $\mathbf{1H^+}$**-X** system (Δ log k_o = 1.10 and 1.51, respectively).

A similar conclusion emerges from a comparison of the intrinsic barriers for deprotonation of **3H-O** and **3H-S** by OH^-, with approximate $\Delta G_o^{\ddagger}$ values calculated by applying the Marcus[2] relationship (eq 16), where $\Delta G^{\ddagger}$ refers to the actual

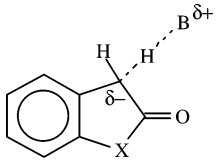
$$\Delta G^{\ddagger} = \Delta G_o^{\ddagger}\left(1 + \frac{\Delta G^{\circ}}{4\Delta G_o^{\ddagger}}\right)^2 \qquad (16)$$

barrier and ΔG° is the standard free energy of the reaction. $\Delta G_o^{\ddagger}$ for **3H-S** (15.5 kcal/mol) is seen to be 0.5 kcal/mol lower than for **2H-O** (16.0 kcal/mol) (Table 1).

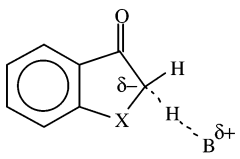
(2) The intrinsic reactivity of **3H-O** is substantially lower than that of **2H-O**: for the reactions with the primary amines, log(k_o(**3H-O**)/k_o(**2H-O**)) = −1.61, while for the reactions with the secondary amines the value is −1.59. On the other hand, the intrinsic rate constants for **3H-S** and **2H-S** are only marginally different, with log(k_o(**3H-S**)/k_o(**2H-S**)) = −0.36 for the primary amines and −0.33 for the secondary amines, respectively.

The key question we are asking in this paper is whether anion aromaticity increases or decreases the intrinsic rate constants (decreases or increases the intrinsic barriers). No definite answer emerged from the study of the reactions of **2H-O** and **2H-S**,[18] because several factors besides aromaticity may contribute to the differences in their intrinsic reactivities. These factors were discussed in detail before[18] and can be summarized as follows.

(a) The stronger electron-withdrawing inductive effect of the ring oxygen compared to that of the ring sulfur enhances k_o for **2H-O** relative to that of **2H-S**. The reason for this is that, at the transition state (**TS(2H-X)**), the delocalization of the



TS(2H-X)



TS(3H-X)

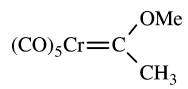
incipient anionic charge lags behind proton transfer (transition-state imbalance), and hence the bulk of this charge is on carbon rather than on the carbonyl oxygen, which makes it more susceptible to inductive stabilization. It is this disproportionately strong transition-state stabilization relative to that of the anion that enhances the intrinsic rate constant.[8]

(b) The stronger resonance stabilization of $\mathbf{2\text{-}S^-}$ due to the polarizability effect of the sulfur atom on the resonance form E (eq 13) is expected to lower k_o of **2H-S** relative to that of **2H-O**. This is because the transition state does not benefit significantly from this stabilization, since delocalization of the charge into the benzene ring has made very little progress. Note that in our previous discussion[18] this factor was neglected; our analysis of the pK_a^{KH} values presented above suggests that this factor is not negligible.

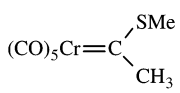
(c) The larger size of the sulfur atom creates more crowding at the transition state, which lowers k_o for the thiophene derivative more than for the furan derivative.

(d) The heteroatom may exert two opposing effects, leading to either a net increase or decrease in k_o. The first factor (type I π-donor effect) is the loss of the resonance stabilization of the keto form (eq 3) upon deprotonation. According to the PNS,[8] this loss is expected to lower k_o, because it runs ahead of proton transfer at the transition state.[37] The decrease in k_o should be stronger for the reactions of **2H-O** due to the greater π-donor strength of oxygen compared to that of sulfur.[27] This effect parallels the stronger pK_a^{KH} enhancing effect on **2H-O** relative to that on **2H-S**. The second factor (type II π-donor effect) is the preorganization of the carbonyl group toward its electronic configuration in the anion (C is the main resonance in eq 14). By virtue of the resonance structure B (eq 3), this preorganization facilitates and enhances the delocalization of charge into the carbonyl group at the transition state. The result is a reduction of the imbalance, which is the main reason for the rather low intrinsic rate constants in the deprotonation of carbon acids activated by π-acceptors.[38] **2H-O** should benefit more from this preorganization effect than **2H-S**.

Table 5 provides a schematic summary of the various effects discussed above on the intrinsic rate constants of **2H-O**(k_o(O)) and **2H-S**(k_o(S)) as well as on the k_o(S)/k_o(O) ratio. Ignoring the potential influence of anion aromaticity for a moment, there is only one factor, the type I π-donor effect, that increases the k_o(S)/k_o(O) ratio, but four factors, the inductive, resonance, steric, and type II π-donor effects, contribute to a lowering of this ratio. This preponderance of k_o(S)/k_o(O) ratio-reducing factors suggests that, even if the aromaticity effect were to increase the intrinsic rate constants (hypothesis B)[18] and hence raise the k_o(S)/k_o(O) ratios, this increase may not be sufficient to offset all the decreases, and thus k_o(S)/k_o(O) may still be <1, as observed. By the same token, if the effect of aromaticity is to decrease intrinsic rate constants (hypothesis A)[18] and thereby lower the k_o(S)/k_o(O) ratios further, these ratios should be significantly lower than the observed values (log(k_o(S)/k_o(O)) = −0.69 and −0.24, respectively, see Table 4); they also should be lower than the corresponding ratios for the deprotonation of **4H-O** and **4H-S**[12b] (log(k_o(S)/k_o(O)) = −0.95 for primary



4H-O



4H-S

amines, −1.09 for secondary amines), where no aromaticity and

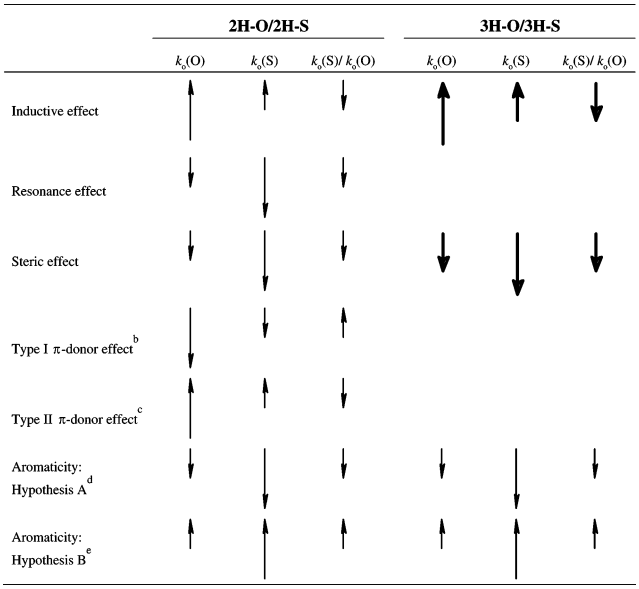
(37) The effect of resonance in a reactant being lost ahead of proton transfer at the transition state is equivalent to resonance development in the product lagging behind proton transfer.[8]
(38) For a more detailed discussion, see ref 39 and references cited therein.
(39) Bernasconi, C. F.; Ali, M. *J. Am. Chem. Soc.* **1999**, *121*, 3039.

Table 4. Intrinsic Rate Constants and Intrinsic Barriers of the Reversible Deprotonation of Carbon Acids Whose Conjugate Bases are Aromatic

	primary amines				secondary amines			
carbon acid	log k_o	$\Delta \log k_o = \log(k_o(S)/k_o(O))$	$\Delta G_o^{\ddagger}$ (kcal/mol)	$\Delta\Delta G_o^{\ddagger}$ (kcal/mol)	log k_o	$\Delta \log k_o = \log(k_o(S)/k_o(O))$	$\Delta G_o^{\ddagger}$ (kcal/mol)	$\Delta\Delta G_o^{\ddagger}$ (kcal/mol)
3H-O[a]	1.16 ± 0.06	0.56 ± 0.11	15.8 ± 0.1	-0.76 ± 0.15	1.64 ± 0.11	1.02 ± 0.16	15.1 ± 0.1	-1.39 ± 0.21
3H-S[a]	1.72 ± 0.05		15.0 ± 0.1		2.64 ± 0.05		13.8 ± 0.1	
2H-O[b]	2.77 ± 0.03	-0.69 ± 0.08	13.6 ± 0.1	0.94 ± 0.16	3.23 ± 0.08	-0.24 ± 0.16	13.0 ± 0.1	0.33 ± 0.21
2H-S[b]	2.08 ± 0.05		14.5 ± 0.1		2.99 ± 0.08		13.3 ± 0.1	
1H$^+$**-O**[c]	-0.83 ± 0.22	1.10 ± 0.56	18.5 ± 0.3	-1.50 ± 0.76	-0.46 ± 0.35	1.51 ± 0.89	17.9 ± 0.5	-2.05 ± 1.21
1H$^+$**-S**[c]	0.27 ± 0.34		17.0 ± 0.5		1.05 ± 0.54		15.9 ± 0.7	

[a] In water at 25 °C, this work. [b] In water at 25 °C, ref 18. [c] In 50% MeCN−50% water (v/v) at 25 °C, ref 16.

Table 5. Effect of Heteroatom on Intrinsic Rate Constants[a]



[a] Arrows pointing up imply an increase, and arrows pointing down imply a decrease. The length of the arrows indicates whether the effect is large or small. The heavier arrows for the **3H-O/3H-S** system indicate stronger effects than those for the **2H-O/2H-S** system. [b] Loss of resonance stabilization of the carbon acid. [c] Preorganization factor. [d] Aromaticity lags behind proton transfer. [e] Aromaticity is ahead of proton transfer.

no delocalization effects contribute to the lowering of the $k_o(S)/k_o(O)$ rates. On the basis of this type of reasoning, we tentatively favored hypothesis B in our previous paper.[18]

The results for **3H-O** and **3H-S** greatly strengthen hypothesis B, because differences between the **2H-X** and **3H-X** systems with regard to the factors outside of aromaticity that affect the respective intrinsic rate constants (Table 5) eliminate some ambiguities. First, there are no π-donor effects on **3H-O** and **3H-S** and no charge delocalization into the benzene rings of **3**$^-$**-O** and **3**$^-$**-S**. The inductive and steric effects are qualitatively the same as in the **2H-X** system, but they are stronger, as indicated by the heavier arrows in Table 5. The inductive effect is stronger because the incipient charge at the transition states, **TS(3H-X)**, is closer to the heteroatom than at the transition states of the **2H-X** system (**TS(2H-X)**). The steric effect is stronger because of the closer proximity of the acidic proton to the heteroatom.

In view of these differences between the **2H-X** and **3H-X** systems, how can we understand that k_o(O) for **2H-O** is so much greater than for **3H-O** (1.61 log units with the primary amines, 1.59 log units with the secondary amines), while k_o(S) for **2H-S** is only marginally larger than for **3H-S** (0.36 log unit for the primary amines, 0.33 log unit for the secondary amines)? Since the combined result of the inductive, steric, and resonance effects on k_o for **2H-X** is unlikely to be much different than the combined result of the inductive and steric effects on k_o for **3H-X**, the key factor must be π-donation by the heteroatom. Specifically, π-donation must be mainly responsible for the much larger k_o(O) value for **2H-O** compared to that for **3H-O**. This implies that the type II π-donor effect is more important than the type I effect, leading to a net increase in intrinsic rate constants.[40] The much smaller difference in the k_o(S) values between **2H-S** and **3H-S** is also consistent with this interpretation, since π-donor effects are smaller for the sulfur derivative.

The main conclusion from the above analysis is that the previous ambiguity regarding which type of π-donor effect is dominant has been removed; i.e., it is now clear that *all* factors outside of aromaticity, namely the inductive, steric, resonance, and net π-donor effects, reduce the $k_o(S)/k_o(O)$ ratios for the **2H-X** system. It therefore greatly strengthens our previous hypothesis that the aromaticity of **2**$^-$**-X** increases the intrinsic rate constants and would have resulted in $k_o(S)/k_o(O)$ ratios greater than unity were it not for the strong reduction of those values by the four factors mentioned above. Turning to the $k_o(S)/k_o(O)$ ratios for the **3H-X** system, the fact that these ratios are substantially larger than unity, despite the strongly depressing influence of the inductive and steric effects, would be an unambiguous indication that aromaticity enhances the k_o values if no other factor were to contribute to an increase in the $k_o(S)/k_o(O)$ ratios. However, there *is* such a factor: the high polarizability of sulfur. Since polarizability acts only at very short distances,[42] its main stabilizing effect is on the incipient anionic charge of **TS(3H-S)** but not on the delocalized charge of **3-S**$^-$. This leads to an increase in k_o(S)[44] for **3H-S** and hence to an increase in the $k_o(S)/k_o(O)$ ratio.

Could the large $k_o(S)/k_o(O)$ ratios be entirely due to this polarizability effect while aromaticity has no effect or even decreases this ratio? This is highly unlikely. A detailed analysis of the potential magnitude of the polarizability effect on the deprotonation of $PhSCH_2NO_2$ suggested that the enhancement

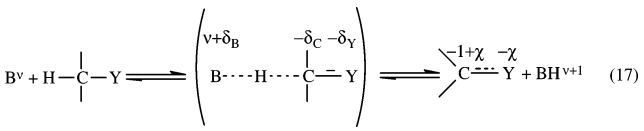
(40) Other examples where type II π-donor effects override type I π-donor effects have been reported.[41]
(41) (a) Bernasconi, C. F.; Renfrow, R. A.; Tia, P. R. *J. Am. Chem. Soc.* **1986**, *108*, 4541. (b) Bernasconi, C. F.; Zitomer, J. L.; Schuck, D. F. *J. Org. Chem.* **1992**, *57*, 1132.
(42) Polarizability effects fall off with the fourth power of distance; in contrast, inductive effects fall off with the square of distance.[43]
(43) (a) Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247. (b) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.
(44) Similar increases in the intrinsic rate constants have been observed in the deprotonation of $PhSCH_2NO_2$[45] and other carbon acids.[46]

of the intrinsic rate constant would be less than a factor of 10.[45] Furthermore, the deprotonation of nitroalkanes is characterized by much larger transition-state imbalances than the deprotonation of any other carbon acids,[8] which renders the polarizability effect on the intrinsic rate constants in the deprotonation of nitroalkanes particularly large.[47] This implies that the polarizability effect on k_o for the deprotonation of **3H-S** should be quite small and cannot account for the observed positive log(k_o(S)/k_o(O)) values.

Conclusions

Why Does Aromaticity Affect Intrinsic Barriers Differently than Resonance? The main conclusion from this work is that the aromaticity of the enolate ions $\mathbf{2}^-$**-X** and $\mathbf{3}^-$**-X** increases the intrinsic rate constants (decreases the intrinsic barriers) of the deprotonation of the respective carbon acids **2H-X** and **3H-X**. This conclusion is consistent with an earlier suggestion that the aromaticity of **1-X** lowers the intrinsic barriers to the deprotonation of $\mathbf{1H}^+$**-X** (eq 1). It also agrees with preliminary ab initio calculations on the gas-phase proton transfers from benzenium ion to benzene and from cyclopentadiene to its conjugate anion.[17,48] Since aromaticity is a product-stabilizing feature, the PNS[8] implies that the development of aromaticity along the reaction coordinate must be ahead of proton transfer; i.e., the stabilization of the transition state by the developing aromaticity is disproportionately strong relative to the degree of proton transfer, and this is what lowers the intrinsic barrier. This contrasts with simple resonance/delocalization effects, whose development at the transition state always lags behind proton transfer.

Why are the effects of simple resonance and of aromaticity on intrinsic barriers so different? In the case of resonance, there exists an insurmountable constraint that prevents charge delocalization at the transition state. The gist of this constraint was captured in a model initially proposed by Kresge[49] in the context of proton transfers from nitroalkanes, a model we have refined[8,50] and applied to the generalized reaction scheme of eq 17. The basic idea is that the delocalization of the negative



(17)

charge into the π-acceptor Y can occur only if there is development of the C−Y π-bond. Hence, the fraction of charge on Y depends on the fraction of π-bond formation, and the fraction of π-bond formation in turn depends on the fraction of charge transferred from the base to the carbon acid. This means that, at the transition state, the charge on Y can never be very high, since it represents only a fraction of a fraction.

Our results suggest that no such constraint applies to the development of aromaticity. One way to envision how aromaticity may develop early is to assume that the conversion of the sp^3 orbital of the breaking C−H bond into a p orbital has made disproportionate progress at the transition state. Or it may be that only relatively minor progress in the conversion of the sp^3 orbital to a p orbital is needed for aromatic stabilization to become disproportionately effective.

Experimental Section

Substrates. 3H-O was purchased from Acros and used without further purification. **3H-S** was synthesized by converting 3-bromobenzothiophene (Aldrich) into 3-methoxybenzothiophene (**5**) according to Fournier Dit Chabert et al.[51] and hydrolyzing the methoxy compound as follows. To a 100 mL round-bottom flask were added **5** (1.24 g, 7.55 mmol), CH_3CN (45 mL). and HCl 20% (5 mL), and the solution was refluxed for 24 h. CH_3CN was then evaporated, and the residue was washed several times with dichloromethane. The extracted organic layer was dried over $MgSO_4$, filtered, and evaporated. The resulting purple tar was then purified by flash chromatography using a linear gradient of 0−5% ethylacetate in hexane to yield an orange solid. The dried product was recrystallized from EtOH to give **3H-S** as a pink solid, mp 63−65 °C (lit.[52] mp 62−64 °C). The spectral data are as follows: ^{1}H NMR δ (500 MHz, $CDCl_3$) 3.81 (s, 2H, $-SCH_2-$), 7.23 (t, 1H), 7.45 (d, 1H), 7.57 (t, 1H), 7.79 (d, 1H).

Buffers and Other Reagents. Amines were obtained from Aldrich and Acros as analytical grade and purified as follows. Piperidine, morpholine, *n*-butylamine, methoxyethylamine, and HEPA were refluxed over CaH_2 for 1 h and distilled under nitrogen. Aminoacetonitrile hydrochloride and glycinamide hydrochloride were recrystallized twice from 1:1 2-propanol/ethanol; piperazine was used without further purification. KOH and HCl solutions were made from DILUT-IT analytical concentrates (J.T. Baker). Ultrapure water was obtained from a Millipore MILLI-Q Plus water system.

Kinetic Experiments. All kinetic experiments were conducted in water at 25 °C and μ = 0.5 M (KCl). Rates were measured in a stopped-flow apparatus. Kinetics were followed by monitoring the reaction at 330 (**3H-O**) or 370 nm (**3H-S**). In highly basic solution (pH > pK_a^{KH}), the reactions were run by mixing the keto form with KOH or amine buffer. In solutions at pH < pK_a^{KH}, runs were performed generating either $\mathbf{3}^-$**-O** or $\mathbf{3}^-$**-S** by means of a 0.025 M KOH solution and subsequently mixing the enolate ion with the appropriate buffer. Typical substrate concentrations were $(1-3) \times 10^{-4}$ M. KOH, amine, and acid concentrations were always in large excess over the substrate, ensuring pseudo-first-order conditions. All pH measurements were carried out with an Orion 611 pH meter equipped with a glass electrode and a Sure-Flow (Corning) reference electrode and calibrated with standard aqueous buffers.

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Supporting Information Available: Figures S1−S5, showing kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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