

Transition State Imbalance in Proton Transfer from Phenyl Ring-Substituted 2-Tetralones to Acetate Ion

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Abstract: Rate constants for the acetate ion-catalyzed ketonization of phenyl-substituted 2-tetralone enols have been determined by stopped-flow UV spectroscopy. From these rate constants and the keto–enol equilibrium constants, the rate constants (k_{-2}) for enolization were calculated. A Brønsted plot of these rate constants ($\log k_{-2}$) vs the acidity of the appropriate 2-tetralone ($\text{p}K_{\text{a}}^{\text{K}}$) is linear, with a slope ($-\alpha^{\text{E}}$) of -0.78 ± 0.03 , except for the point corresponding to 6-nitro-2-tetralone (**4b**). Rate constants for the ionization of 2-tetralone by substituted acetates were determined directly by NMR, giving a corresponding Brønsted β^{E} of 0.54 ± 0.03 . Both the negative deviation of the point for **4b** from the correlation line for α^{E} and the inequality between α^{E} and β^{E} indicate an imbalanced transition state for the proton abstraction of 2-tetralone by acetate ion. This reaction is impeded by a thermodynamic barrier of 11 kcal/mol, along with an intrinsic kinetic barrier of 14 kcal/mol. A comparison of the transition states for proton abstraction of 2-tetralone by hydroxide ion and by acetate ion shows similar transition state imbalance and intrinsic kinetic barriers for both reactions. The relevance of these results to the mechanism of enzymatic acceleration of enolization is discussed.

Introduction

Although proton transfer from carbon atoms adjacent to carbonyl groups (enolization) is an inherently slow reaction,^{1,2} this reaction is catalyzed by a variety of enzymes with extraordinary efficiency.³ We have been interested for some time in the isomerization of 5-androstene-3,17-dione (**1**) to 4-androstene-3,17-dione (**3**), catalyzed by 3-oxo- Δ^5 -steroid isomerase from *Pseudomonas testosteroni* (3-ketosteroid isomerase, KSI, EC 5.3.3.1),⁴ and the mechanism by which this enzyme enhances the rate over the nonenzymatic reaction. A variety of experiments are consistent with a mechanism of catalysis that involves the carboxyl group of Asp-38 acting as a proton shuttle, with the hydroxyl group of Tyr-14 and the carboxyl group of Asp-99 functioning as electrophilic catalysts (Scheme 1).^{4c}

Since KSI uses the carboxylate group of Asp-38 as the base in the initial deprotonation of **1**, we have used the reaction of **1** with acetate ion as a model to aid in the evaluation of the efficiency of KSI.⁵ A comparison of the free energy profiles for the acetate ion-catalyzed isomerization and the enzymatic isomerization revealed that KSI stabilizes both the intermediate

dienolate ion (**2**) and the flanking transition states by about 11 kcal/mol.⁶ However, although much is known about the mechanisms of both the enzymatic reaction and the acetate ion-catalyzed reaction,^{5,6} detailed structures of the transition states for both of these reactions have remained elusive.

Structure–reactivity correlations can be extremely valuable in the determination of transition state structures, specifically the charge distribution. Since this method is not applicable to **1**, we have chosen the 2-tetralone system (**4**) as a model in which the acidity of the α hydrogens (H-1) can be systematically varied by phenyl ring substitution (Scheme 2). 2-Tetralone (**4a**) provides a good model for the A and B rings of 5-androstene-3,17-dione (**1**), and importantly, H-1 of **4a** has a $\text{p}K_{\text{a}}$ (12.8)⁷ similar to that of H-4 of **1** (12.7).⁵

In our previous studies on the deprotonation of substituted 2-tetralones by hydroxide ion, the transition state was found to be imbalanced, with charge reorganization through resonance lagging behind proton transfer.⁷ In this work, we describe investigations into the nature of the transition state for the proton transfer to substituted acetates, a more realistic model for the KSI reaction. Thus, the $\text{p}K_{\text{a}}$ of the base can be varied, giving a value for the Brønsted β , as well as an α value from variation of the tetralone substituent. We compare the transition states for enolization of 2-tetralones by hydroxide ion and by acetate ion, and we discuss the possible relevance of these results to enzymatic mechanisms of deprotonation of ketones.

Experimental Section

Unless otherwise mentioned, all chemicals were reagent grade or better and were purchased commercially and used without further

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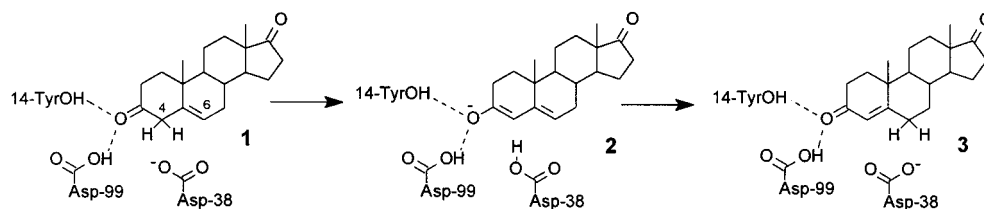
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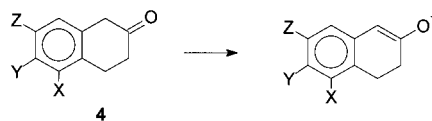
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Scheme 1



Scheme 2



- a X = Y = Z = H
 b Y = NO₂, X = Z = H
 c Y = Cl, X = Z = H
 d Y = CH₃O, X = Z = H
 e Z = NO₂, X = Y = H
 f Z = Cl, X = Y = H
 g X = Z = NO₂, Y = H
 h Z = CH₃, X = Y = H
 i Y = I, X = Z = H
 j Y = Cl, Z = NO₂, X = H

purification. Water was purified as previously described.⁸ All 2-tetralones, except 6-methoxy-2-tetralone, were available from previous work.^{7,9} 6-Methoxy-2-tetralone was prepared according to the literature (mp 34.0–35.5 °C, lit. mp 33.5–35 °C).¹⁰ Deuterated stock solutions of the carboxylic acids were prepared by partial neutralization of the acids with NaOD, followed by dilution in D₂O to concentrations that gave less than 5 atom % exchangeable protium. The pH was measured at room temperature with a Radiometer PHM85 pH meter and a Radiometer PHC2406 combination electrode standardized at pH 7.00 and either 4.00 or 10.00. Melting points are uncorrected. ¹H NMR spectra were recorded at 300 MHz with sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) or tetramethylsilane (TMS) as the reference.

The rates of ketonization of substituted 2-tetralone enols were obtained using the sequential mixing capabilities of the Hi-Tech QP/SF 53 stopped-flow spectrophotometer. Basic solutions of the enolates were formed by mixing an aqueous solution of the tetralone (ca. 0.5 mM), containing 6.6% (v/v) MeOH, with 0.1 or 0.01 N NaOH in a 1:1 ratio. After a delay of 0.5–2 s, these solutions were rapidly quenched with excess buffer (acetate containing 3.3% (v/v) MeOH) in a ratio of 1:5. The first-order decay of the absorbance of the enols was monitored for greater than 10 half-lives at 265 nm (306 nm for 6-chloro-7-nitro-2-tetralone and 340 nm for 6-nitro-2-tetralone enol). The temperature was maintained at 25.0 ± 0.1 °C, and the ionic strength was controlled by NaCl ($\mu = 0.16$). The final pH of the solution was determined by mixing equivalent solutions outside the stopped flow. Buffer compositions were calculated from the initial concentrations of buffer and sodium hydroxide in the enolate solution.

Rate constants for H to D exchange of 2-tetralone in the presence of acetate buffers and 3.3% (v/v) acetonitrile-*d*₃ (D₂O, $\mu = 1.0$ with KCl) were determined by NMR spectrometry at 300 or 500 MHz. All reactions were carried out at 25.0 ± 0.1 °C regulated by a gas flow at the probe, which was calibrated according to the method of Raiford et al.¹¹ Buffer was incubated for ca. 15 min at 25.0 ± 0.1 °C, and the exchange reaction was initiated by addition of substrate in acetonitrile-*d*₃.¹² The reaction mixture was vortexed and transferred to an argon-flushed NMR tube, and spectra were recorded so that at least 10 time points were collected during the first three half-lives. The spectrometer magnet was previously shimmed using a test sample, which enabled exchange rates to be accurately determined with half-lives as low as

100 s. For reactions with half-lives >60 min, the NMR sample tubes were incubated at 25.0 ± 0.1 °C and removed periodically to record spectra. The exchange reactions were generally followed for greater than four half-lives. Values for pD were obtained by adding 0.4 to the observed pH of these D₂O solutions.¹³ The apparent pK_a values of the buffers in D₂O were determined from the pD values of the solutions containing the acid and base forms in a 1:1 ratio.

Results

General Base Catalysis of Ketonization of Substituted 2-Tetralone Enols by Acetate Ion. The enolate ions of substituted 2-tetralones were generated as before⁹ by mixing sodium hydroxide solutions (0.01–0.1 M) with an aqueous solution of the appropriate tetralone. Since these ketones all ionize in the pH range,⁹ significant quantities of the enolate ions are formed. When these solutions are rapidly quenched in acetate buffers, rapid protonation occurs on the enolate oxygen producing the enol. The conversion of these enols to the corresponding ketones was monitored by observing the loss of absorbance due to the enol as a function of time. Analysis of the absorbance decrease gives pseudo-first-order rate constants, which are linearly related to the concentration of acetate ion in the buffer. These rate constants are independent of both the HOAc:OAc⁻ ratio (from 3:7 to 7:3) and the pH (Figure S1, Supporting Information), demonstrating that these reactions are catalyzed by acetate ion with no contribution from acetic acid. The calculated second-order rate constants for ketonization (k^K) are given in Table 1.

Ketonization (k^K) may be divided into two elementary steps: deprotonation of the enol (k_1) and protonation of the resulting enolate (k_2), according to Scheme 3. With the assumption that protonation on the carbonyl oxygen of the enolate to regenerate enol (k_{-1}) is much faster than protonation on the carbon (k_2), k^K is given by eq 1. Rate constants for protonation of 2-tetralone enolates at the carbon by acetic acid (k_2) and conversion of ketones to enolate ions by acetate ion (k_{-2}) were calculated from eqs 2 and 3 (Table 1).

$$k^K = k_1 k_2 / k_{-1} \quad (1)$$

$$k_2 = k^K K_a^{\text{HOAc}} / K_a^{\text{E}} \quad (2)$$

$$k_{-2} = k_2 K_a^{\text{K}} / K_a^{\text{HOAc}} = k^K K_a^{\text{K}} / K_a^{\text{E}} \quad (3)$$

General Base Catalysis of Enolization of 2-Tetralone by Substituted Acetates. Rate constants for the enolization of 2-tetralone were determined by NMR from the rates of deuterium exchange of the C-1 protons in solutions of substituted acetates in deuterium oxide. Pseudo-first-order rate constants (k^{obs}) for exchange were obtained from nonlinear curve fits of

(12) Stock solutions in acetonitrile-*d*₃ were prepared daily and stored at -20 °C, since these solutions of 2-tetralone begin to change from clear to yellow/brown soon after mixing. The effect of this decomposition on k^{obs} is assumed to be unimportant, since good first-order kinetics were obtained for all reactions and no new peaks were detectable by NMR during the course of the reaction (up to 15 h).

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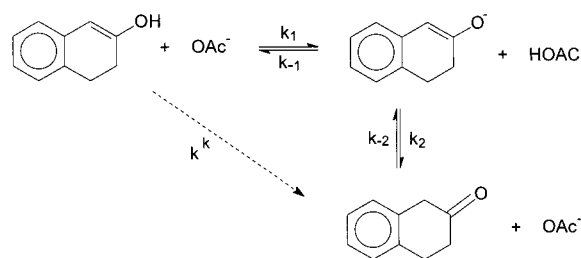
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Table 1. Rate Constants for Enolization of 2-Tetralones by Acetate Ion

substituent	σ^-^a	$\text{p}K_a^{\text{K}^b}$	$\text{p}K_a^{\text{E}^b}$	$\text{p}K_{\text{E}}^b$	$k^{\text{K}} (\text{M}^{-1} \text{s}^{-1})$	$k_2 \times 10^{-6} (\text{M}^{-1} \text{s}^{-1})^c$	$k_{-2} \times 10^3 (\text{M}^{-1} \text{s}^{-1})$
6-MeO	-0.27	13.27(± 0.05)	9.64(± 0.05)	3.63(± 0.10)	19.7(± 0.1)	2.01(± 0.31)	4.6(± 1.2)
7-Me	-0.17	12.94(± 0.01)	9.52(± 0.01)	3.42(± 0.02)	33.5(± 0.4)	2.60(± 0.16)	12.8(± 0.8)
H	0	12.83(± 0.01)	9.44(± 0.04)	3.39(± 0.05)	33.6(± 0.1)	2.17(± 0.27)	13.7(± 1.7)
6-Cl	0.19	12.51(± 0.03)	9.31(± 0.02)	3.20(± 0.05)	42.8(± 0.4)	2.05(± 0.16)	27.0(± 3.6)
6-I	0.27	12.36(± 0.02)	9.23(± 0.02)	3.13(± 0.04)	49.9(± 1.4)	1.99(± 0.20)	37.0(± 4.7)
7-Cl	0.37	12.30(± 0.07)	9.09(± 0.06)	3.21(± 0.13)	58.5(± 0.5)	1.69(± 0.26)	36(± 13)
7-NO ₂	0.71	11.76(± 0.02)	8.81(± 0.01)	2.95(± 0.03)	84.9(± 0.4)	1.29(± 0.06)	95(± 7)
6-Cl-7-NO ₂	0.90	11.34(± 0.03)	8.56(± 0.01)	2.78(± 0.04)	102(± 1)	0.87(± 0.05)	170(± 20)
5,7-(NO ₂) ₂	1.42	10.34(± 0.06)	8.14(± 0.03)	2.20(± 0.09)	186(± 2)	0.60(± 0.01)	1170(± 290)
6-NO ₂	1.23	10.09(± 0.02)	7.69(± 0.02)	2.40(± 0.04)	171(± 2)	0.20(± 0.02)	680(± 73)

^a The σ^- for 5,7-(NO₂)₂ is calculated as 2 times the σ_{m} of a nitro group; the σ^- for 6-Cl-7-NO₂ as the sum of the σ_{m} of a nitro group and the σ_{p} of a chloro group. The σ values are from the following: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. ^b Reference 9. Either concentration $\text{p}K_a$'s based upon the concentration of all species or mixed $\text{p}K_a$'s based upon concentrations of solute and activity of hydronium ion have been used in the same correlations. ^c The $\text{p}K_a$ of HOAc used for calculation is measured as 4.63 ± 0.01 at $\mu = 0.16$ M, 21.6 °C, and 3.3% MeOH.

Scheme 3

the integrated peak area for the exchangeable C-1 protons normalized to the peak area for the nonexchanging C-3 protons vs time. Semilogarithmic plots of peak area versus time for proton exchange were linear for greater than three half-lives. Where duplicate measurements of k^{obs} were performed, these values agree within $\pm 5\%$. Slopes of linear plots of k^{obs} vs the total concentration of buffer give the rate constants for the buffer-catalyzed reaction. Plots of these slopes vs the mole fraction of the base give rate constants for proton abstraction by each base (k_{B}) (Table S1, Supporting Information). Since these rate constants are determined from measurements of exchange of *both* α hydrogens with deuterium, they need to be statistically corrected (multiplied by a factor of 2) to be compared to the k_{-2} values in Table 1. For the deprotonation of 2-tetralone by acetate ion, for which the rate constants were determined by both methods, the corrected exchange rate constant ($k_{\text{ex}}^{\text{corr}}$) is $1.05 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$, in good agreement with the rate constant from stopped-flow UV spectral measurements (k_{-2}) of $1.37 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$.

Discussion

Nature of the Transition State for Proton Transfer from 2-Tetralones to Acetate Ion. It has been known for a long time that ionization of carbon acids generally occurs much more slowly than ionization of oxygen or nitrogen acids of the same $\text{p}K_a$.¹⁴ Since the acidity of carbon acids is typically due to the presence of a functional group that can stabilize the anion by resonance, a delay in the delocalization of this charge at the transition state results in a reaction that is slower than expected based upon the acidity.^{2a,c} Evidence for this type of imbalance was first obtained for the ionization of arylnitromethanes,¹⁵ and subsequent studies have shown that transition state imbalance

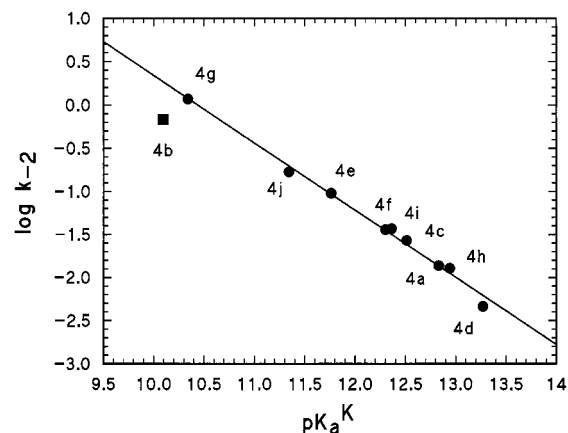


Figure 1. Plot of $\log k_{-2} (\text{M}^{-1} \text{s}^{-1})$ vs $\text{p}K_a^{\text{K}}$ for proton abstraction by acetate ion from substituted 2-tetralones (3.3% (v/v) methanol, $\mu = 0.16$, 25.0 ± 0.1 °C).

is a general phenomenon for reactions that involve delocalization of charge into a π -acceptor.^{2a,c,16}

We have previously analyzed the charge distribution of the transition state for abstraction of the α proton (H-1) of 2-tetralone by hydroxide ion.⁷ This transition state is imbalanced, with charge delocalization into the phenyl ring and into the carbonyl oxygen lagging behind C-H bond cleavage and charge transfer from the hydroxide ion. An estimate of the charge distribution in the transition state was based upon the slope of the Brønsted plot for this reaction ($\alpha = 0.60$), the negative deviation of the point for 6-nitro-2-tetralone (**4b**) from this plot, and the charge distribution of the fully formed anion.⁷ These results indicate a decreased resonance effect in the transition state relative to the inductive effect. We now have extended this work to the reaction with substituted acetate ions, which allows variation of the $\text{p}K_a$ of the base, giving a value for the Brønsted β , in addition to an α value.

A plot of $\log k_{-2}$ vs $\text{p}K_a^{\text{K}}$ for proton abstraction from substituted 2-tetralones by acetate ion is linear, with a slope ($-\alpha^{\text{E}}$) of -0.78 ± 0.03 (Figure 1), giving a somewhat greater dependence on substituent than the reaction with hydroxide ion ($\alpha = 0.60 \pm 0.01$).⁷ As with proton abstraction by hydroxide ion,⁷ the point corresponding to **4b** shows a negative deviation. Transition state imbalance due to a delay in charge delocalization

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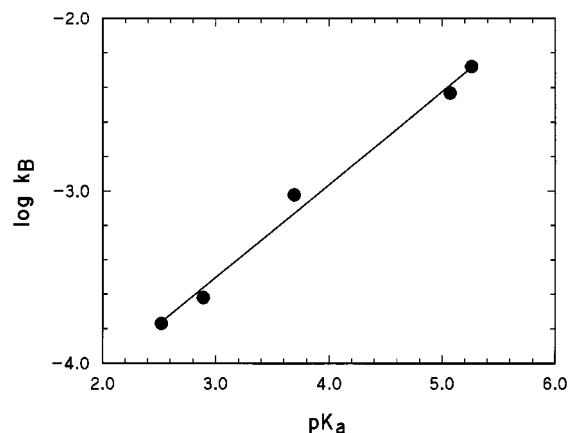


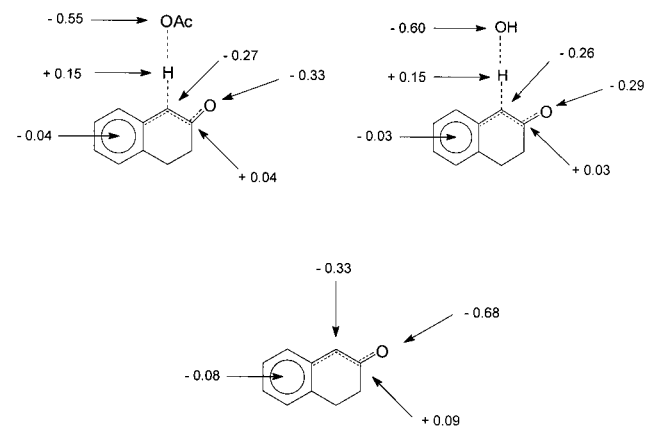
Figure 2. Plot of the logarithm of the rate constant for ionization of substituted 2-tetralones ($\log k_B$ in $M^{-1} s^{-1}$) vs pK_a of substituted acetic acid (3.3% (v/v) acetonitrile, $\mu = 1.0$, 25 ± 0.1 °C).

may be probed by a comparison of the observed rate constant for **4b** to that of a hypothetical 6-nitro substitution (pK_a^K 11.5)⁷ with no resonance effect.¹⁷ From the correlation of Figure 1, a rate constant for proton abstraction from this hypothetical acid may be obtained ($\log k_{ind} = -0.826$). The predicted rate constant for reaction of **4b** in which the resonance stabilization from the 6-nitro group in the transition state is as large as in the fully formed anion (or a balanced transition state) is obtained from Figure 1 ($\log k_{pred} = 0.269$). A comparison of these rate constants with the observed rate constant for **4b** ($\log k_{-2} = -0.167$) shows that about 60% of the expected resonance stabilization of the 6-nitro group operates at the transition state for the proton transfer to acetate. This result is similar to that obtained previously for the transition state for deprotonation by hydroxide, in which 55% of the full resonance stabilization of the 6-nitro group is manifest.⁷ Using this result and the assumption that the fraction of charge transferred to the tetralone is equal to the fraction of p-orbital formed, we estimated that 55% of a full negative charge is located on the tetralone system at the transition state for deprotonation by hydroxide.⁷ For the acetate reaction, the comparable figure would be 60%.

These calculations depend on the assumption that the fraction of charge transferred to the 2-tetralone is equal to the fraction of the p-orbital formed in the transition state.⁷ This assumption can be tested by using the effect of a change in the pK_a of the attacking base as an experimental probe for charge transfer (or C–H bond breakage). From the Brønsted plot of the logarithm of the rate constants for the deprotonation of 2-tetralones by substituted acetates (Figure 2), a β value of 0.54 ± 0.02 is obtained. Consideration of the effect of solvation of the acid gives a corrected value of $\beta_{corr} = 0.45$.¹⁸ Thus, the charge left on the acetate ion at the transition state may be calculated to be -0.55 . Since the charge on the tetralone at the transition state is about -0.60 , there must be a charge of ca. $+0.15$ on the hydrogen being transferred to balance charge. This conclusion is in qualitative agreement with computational results on the deprotonation of acetaldehyde by acetaldehyde enolate in the gas phase, which predict a charge on the proton being

(17) The amount of transition state imbalance is somewhat underestimated by these methods of detection, since the enolate of 2-tetralone is significantly stabilized by conjugation between the phenyl ring and the double bond that does not involve charge transfer.⁹ This conjugation is also limited by hybridization changes at the transition state, and it, too, could contribute to the transition state imbalance. However, the lack of charge transfer means that this contribution cannot be probed by the methods that we use.

Scheme 4



transferred of $+0.20$ at the transition state.¹⁹ The charge distributions²⁰ for the transition states for enolization of 2-tetralone by acetate and by hydroxide ion, as well as the fully formed anion of 2-tetralone,⁷ are summarized in Scheme 4.^{7,21,22}

Several authors have used inequality of the Brønsted α and β for a reaction as evidence for an imbalanced transition state.^{2c,23,24} In a balanced reaction, the extent of charge transfer as determined from each of these plots should be identical, after a correction for solvation.²⁵ On the other hand, an imbalanced transition state for enolization of 2-tetralone would have a greater fraction of negative charge on C-1 than a balanced transition state. Since α^E is detected by ring substitution, it will be greater for an imbalanced transition state than for a balanced one. Thus, α^E should be greater than β_{corr} in the enolization of 2-tetralone by acetate ion. The large difference in the magnitude of the α^E value observed here (0.78) compared to β^E (0.54) or β_{corr} (0.45) is consistent with an imbalanced transition state.²⁶

Position of the Transition States for Enolization of 2-Tetralone by Acetate Ion and by Hydroxide Ion. It is

(18) To estimate the charge transferred from a carboxyl group in the transition state from this β value, it is necessary to correct for solvation of the carboxyl acid by hydrogen bonding to water.^{2c,27} The effect of solvation (α_{sol}) of the carboxyl acid is about 0.2, which enlarges the β scale for the protonation of acetate ion from 1.0 to 1.2. Thus, the corrected value (β_{corr}) can be calculated from the observed β (β_{obs}) by $\beta_{corr} = \beta_{obs}/(1 + \alpha_{sol}) = \beta_{obs}/1.2$. For deprotonation of 2-tetralone by acetate, β_{corr} is then equal to $0.54/1.2 = 0.45$.

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(20) Charges specified are relative (differences between the neutral molecule and the anion or the transition state), not absolute. The charge distribution in the anion of 2-tetralone is calculated from the difference between the ¹³C chemical shifts for the anion and for 2-tetralone.

(21) The charge on the transition state for the ionization of 2-tetralone by hydroxide ion was recalculated by putting a partial positive charge ($+0.15$) on the proton being transferred as for the reaction with acetate, thus increasing the partial negative charge on the hydroxide group (-0.60 instead of -0.45).

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(25) For proton-transfer reactions, this probe for transition state imbalance assumes that there is no partial charge in the transition state on the proton being transferred. The presence of a partial charge would predict a difference between the Brønsted α and β , even for a balanced transition state. Thus, a small difference between α and β should be interpreted with caution.

(26) The use of the 6-nitro substituent as a probe only partially detects a delay in solvent reorganization, since the majority of the incipient negative charge on C-1 is delocalized into the carbonyl group. However, the inequality of α and β could be due to a lag in either solvent reorganization or rehybridization.

difficult to compare the position of the transition states for enolization along the reaction coordinates, because bond breakage (charge transfer) is not synchronous with electron delocalization, and thus there is no single reaction parameter that can describe the position of an imbalanced transition state. However, if we define "position" as the degree of proton transfer, β_{corr} may be used as an estimate of the position of the transition state in the acetate reaction. In the deprotonation of 2-tetralones by acetate ion, the corrected β_{corr} of 0.45 implies that the transition state is approximately halfway along the reaction coordinate. However, the lack of a β value for the hydroxide ion reaction makes it impossible to directly compare the positions of the two transition states.

The calculated structures of the transition states for enolization by acetate and by hydroxide ion are similar, but these calculations involve some approximations and are thus imprecise. The use of α values to estimate the extent of proton transfer is complicated by the existence of transition state imbalance. However, the similar magnitude of the imbalance for the two transition states should enable a qualitative comparison of the two α values. Thus, the more negative α (0.78) for proton abstraction by acetate than by hydroxide (0.60) suggests a later transition state for the acetate reaction. Similar phenomena have been observed in the other proton-transfer reactions.²⁷

Intrinsic Barriers for Proton Transfer of 2-Tetralone by Acetate Ion. The slow rate of abstraction of protons from carbon atoms adjacent to carbonyl groups has been attributed to relatively high barriers to reaction that exist even when the reaction is thermodynamically favorable.^{1,2} Marcus²⁸ has dissected the kinetic barrier (ΔG^\ddagger) for a reaction into an intrinsic barrier ($\Delta G_{\text{int}}^\ddagger$) and a thermodynamic barrier (ΔG°) (eq 4).

$$\Delta G^\ddagger = \Delta G_{\text{int}}^\ddagger (1 + \Delta G^\circ / 4 \Delta G_{\text{int}}^\ddagger)^2 = \Delta G_{\text{int}}^\ddagger + \Delta G^\circ / 2 + (\Delta G^\circ)^2 / 16 \Delta G_{\text{int}}^\ddagger \approx \Delta G_{\text{int}}^\ddagger + \Delta G^\circ / 2 \quad (4)$$

Because the intrinsic barrier for a proton-transfer reaction, in principle, describes the rate of the reaction at $\Delta pK_a = 0$ (difference between the acid and the base), it is simplest to determine it from the Brønsted correlation by extrapolation. Application of this method to the substituted acetate data (Figure 2) gives the intrinsic rate constant (k_o) for 2-tetralone ($260 \text{ M}^{-1} \text{ s}^{-1}$),²⁹ which can be converted to an intrinsic barrier (ΔG_o^\ddagger) of about 14 kcal/mol. Thus, the barrier for deprotonation of 2-tetralone by acetate (20 kcal/mol, $k_{-2} = 13.7 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$) is composed of this intrinsic barrier (14 kcal/mol) and about half of the thermodynamic barrier ($11/2 = 6 \text{ kcal/mol}$).³⁰ The total barrier for proton transfer to hydroxide is about 14 kcal/mol ($k = 376 \text{ M}^{-1} \text{ s}^{-1}$).⁷ The intrinsic barrier for this reaction (16 kcal/mol) can be estimated from eq 4 and the ΔpK of ca. 3 for water and 2-tetralone. The similar intrinsic barriers for deprotonation by hydroxide ion and acetate ion are consistent with a similar transition state imbalance for both reactions.²

(27) (a) Jencks, W. P.; Haber, M. T.; Herschlag, D.; Nazaretian, K. L. *J. Am. Chem. Soc.* **1986**, *108*, 479. (b) Murray, C. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1990**, *112*, 1880.

(28) (a) Marcus, R. A. *J. Chem. Phys.* **1956**, *24*, 966. (b) Marcus, R. A. *J. Chem. Phys.* **1957**, *26*, 867. (c) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155.

(29) The intrinsic rate constant (k_o) was corrected for a statistical factor of 2. The relative pK_a^{K} of 2-tetralone and acetate was assumed to be invariant in H_2O and D_2O .

(30) According to eq 4, the effect of the thermodynamic barrier on the energy of the transition state can be estimated as half of the thermodynamic barrier ($\Delta G^\circ/2$) by ignoring the small interaction between the thermodynamic barrier and the intrinsic barrier for this specific enolization of 2-tetralone [$(\Delta G^\circ)^2/16\Delta G_{\text{int}}^\ddagger = 0.5 \text{ kcal/mol}$].

Transition State Imbalance and Enzymatic Enolization.

It is of interest to estimate the contribution of transition state imbalance to the intrinsic barrier for the proton transfer of 2-tetralones to acetate ion, and therefore whether minimization of this transition state imbalance could be significant in an enzymatic acceleration of enolization. Bernasconi^{2c} has proposed a mathematical relationship between a change of the intrinsic rate constant for a reaction and the imbalance in the reaction. For a reaction that leads to a resonance-stabilized carbanion, the intrinsic rate constant is given by eq 5,³¹ where $\delta \log k_o^{\text{res}}$ is the difference between the intrinsic rate constant for the reaction in question and a hypothetical reaction of the same pK_a without resonance stabilization of the anion, λ_{res} is the fraction of the charge that is delocalized in the transition state relative to the product, β is the total amount of charge transferred in the transition state (equivalent to the Brønsted β), and $\delta \log K_a^{\text{res}}$ is the difference in pK_a between the acid and a hypothetical acid with no resonance stabilization.

$$\delta \log k_o^{\text{res}} = (\lambda_{\text{res}} - \beta) \delta \log K_a^{\text{res}} \quad (5)$$

For enolization of 2-tetralone by acetate ion, the corrected value of β is 0.45, and λ_{res} is 60% β_{corr} , or 0.27. The contribution of resonance stabilization from the phenyl and carbonyl groups to the increased acidity of 2-tetralone ($\delta \log K_a^{\text{res}}$) relative to methane ($pK_a \sim 50$)³² can be estimated from the relative contributions of resonance and inductive effects to the electron-withdrawing nature of these substituents. To do this, we use σ^- as a measure of the sum of the resonance and inductive effects and σ as a measure of the inductive effect. Thus, the fraction of resonance stabilization from both groups is calculated through $\sum_i(\sigma^-_i - \sigma_i)/\sum_i\sigma^-_i = 43\%$, and $\delta \log k_o^{\text{res}} = (0.27 - 0.45) \times (43\% \times 37) = -2.9$. This value corresponds to an increase in the intrinsic barrier of 4 kcal/mol over that for a hypothetical balanced transition state.

We⁶ have suggested that the rate enhancement for the isomerization of 5-androstene-3,17-dione by steroid isomerase (KSI) is due to contributions from lowering of both the thermodynamic barrier (by ca. 11 kcal/mol, of which ca. 5 kcal/mol shows up in the transition state) and the intrinsic barrier (by ca. 3 kcal/mol). Thus, although the predominant mode of catalysis by KSI involves a decrease in the thermodynamic barrier, there is a substantial contribution from a decreased intrinsic barrier, which could be accomplished by minimization of transition state imbalance. The source of the high intrinsic barriers in these reactions may be attributed to a combination of two causes.³³ One is the incomplete rehybridization of the incipient p-orbital at C-1 in the transition state,^{7,34} which limits delocalization of the negative charge transferred at the transition state. The other is a delay in solvent reorganization around the

(31) Bernasconi has further generalized this equation to quantitate the increase of the intrinsic barrier of a reaction caused by the transition state imbalance from any factor.^{2c}

(32) Pross, A. *Theoretical and Physical Principles of Organic Reactivity*; John Wiley & Sons: New York, 1995; p 200.

(33) The additional delay in conjugation with the phenyl ring with C-1 at the transition state could lead to a further increase in the intrinsic barrier. There is an increase (2–3 kcal/mol) of the intrinsic barrier for deprotonation of 2-tetralone by hydroxide ion over those for enolization of acetone (13 kcal/mol: Albery, W. J. *J. Chem. Soc., Faraday Trans. 1* **1982**, *78*, 1579) and for enolization of simple aldehydes and ketones (12.1 kcal/mol: Guthrie, J. P. *Can. J. Chem.* **1979**, *57*, 1177). It is likely that the higher intrinsic barrier for enolization of 2-tetralone is caused by the phenyl ring fused to the α carbon of the carbonyl group. Thus, enolization involves conjugation of a p-orbital at C-1 with the carbonyl group and the phenyl group, both of which are important in stabilizing the enolate of 2-tetralone.⁹

(34) Kresge, A. J. *Can. J. Chem.* **1974**, *52*, 1897.

oxygen at the transition state,^{2a,c,7,35} inhibiting charge dispersal onto this atom. Although it is unlikely that an enzyme can do much about the first of these difficulties, preorganization of the atoms at the enzyme active site that are involved in solvation of the negative charge at the incipient oxyanion could result in a substantial lowering of the intrinsic barrier. Thus, imbalance caused by a lag in solvent reorganization could be eliminated (or at least reduced).^{2c,7,36,37}

(35) Bernasconi, C. F.; Wenzel, P. J.; Keeffe, J. R.; Gronert, S. *J. Am. Chem. Soc.* **1997**, *119*, 4008.

(36) Ydav, A.; Jackson, R. M.; Holbrook, J. J.; Warshel, A. *J. Am. Chem. Soc.* **1991**, *113*, 4800.

(37) Peräkylä, M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2185.

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Supporting Information Available: Table of rate constants for proton exchange of 2-tetralone catalyzed by substituted acetate ions, and a plot for the observed rate constant for acetate-catalyzed ketonization of 2-tetralone enol vs the concentration of acetate ion in the buffer (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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