Enolization and Hydrolysis of 7-Nitroisochroman-3-one in Aqueous Solution: Generation of a Relatively Stable Lactone Enolate

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The enolization and hydrolysis of the lactone 7-nitroisochroman-3-one (7-nitro-1,4-dihydro-3*H*-2-benzopyran-3-one, **1**) has been studied in aqueous sodium hydroxide. In solutions of sufficient basicity ([NaOH] ≥ ca. 0.1 mM), **1** undergoes reversible deprotonation to form the corresponding enolate. Although ester hydrolysis accompanies enolization, observable quantities of the enolate persist for several seconds. Rate constants for deprotonation by hydroxide ion ($k_1 = 1.31(\pm 0.06) \times 10^4$ M^{-1} s^{-1}), protonation of the enolate by water ($k_{-1} = 212 \pm 24$ s^{-1}), and lactone hydrolysis ($k_{OH} = 19.0 \pm 0.3$ M^{-1} s^{-1}) have been determined by monitoring the rates of formation and disappearance of the enolate. The kinetic data can be used to calculate the acid dissociation constant for **1** (pK_a 11.98).

Formation of an enol(ate) is a compulsory step in a variety of reactions (e.g., condensation, isomerization, elimination), including many important enzymatic processes.[1] While base-promoted enolization of ketones in water has been extensively investigated,[2] studies of the aqueous acidity of carboxylate esters are relatively scarce. Direct examination of the enolization of carboxylate esters in aqueous solution is possible, but complicated by two factors: the inability to generate appreciable concentrations of the ester enolates (enol(ate)s of simple esters are highly unstable with respect to their keto tautomers)[3] and the susceptibility of esters to hydroxide ion-promoted hydrolysis. To date, studies of the enolization of carboxylate esters in aqueous solution have typically utilized enolates stabilized by "secondary" groups (i.e., β-ketoesters[4] and fluorene-9-carboxylate esters).[5] Only recently has Richard determined the aqueous pK_a of a simple carboxylate ester, ethyl acetate.[6]

To further study the effects of the alkoxycarbonyl group on enolate formation and stability, we have examined the reactivity of the lactone 7-nitroisochroman-3-one (7-nitro-1,4-dihydro-3*H*-2-benzopyran-3-one, **1**) in aqueous sodium hydroxide. Although ester hydrolysis accompanies enolization, observable quantities of the enolate persist for several seconds, allowing direct determination of the acid dissociation constant (pK_a 11.98) and the rate constant for deprotonation by hydroxide ion ($k_1 = 1.31 \times 10^4$ M^{-1} s^{-1}).

Results and Discussion

Synthesis of 7-Nitroisochroman-3-one (1). 7-Nitroisochroman-3-one (**1**) was prepared by nitration of isochroman-3-one using nitronium tetrafluoroborate (NO_2BF_4), a reagent useful in the nitration of compounds susceptible to oxidation and/or hydrolysis.[7] GC/MS and NMR spectra of the isolated product indicate formation of a single mononitrated isomer, which was identified using ^1H NMR and UV/vis spectroscopy. Analysis of the chemical shifts and coupling patterns of the aromatic protons in the NMR spectrum are consistent with nitration at position 6 or 7 of the isochroman-3-one ring system. Final assignment as the 7-substituted isomer was made on the basis of the UV/vis absorption spectrum of the enolate (λ_{max} 532 nm, Figure 1). That is, the enolate of the 7-substituted lactone is expected to absorb at relatively long wavelengths due to extended conjugation in the anion, while the enolate of the 6-substituted isomer should not absorb in the visible region of the spectrum. In comparison, the enolates of 6-nitro-2-tetralone (**2**) and 7-nitro-2-tetralone (**3**) absorb at λ_{max} 513.5 nm and λ_{max} 298 nm, respectively.[8]

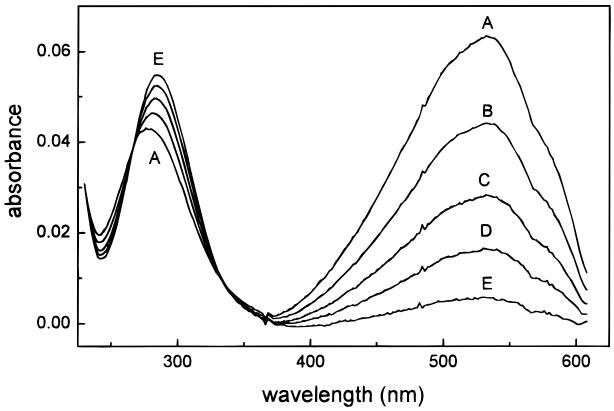

Figure 1. Absorption spectra of 7-nitroisochroman-3-one in 0.5 M sodium hydroxide. Times after mixing (Hi-Tech SFA-12 Rapid Kinetics Accessory): A, immediately after mixing; B, ca. 1.2 s; C, ca. 2.7 s; D, ca. 4.6 **s;** E, ca. 8.2 s.

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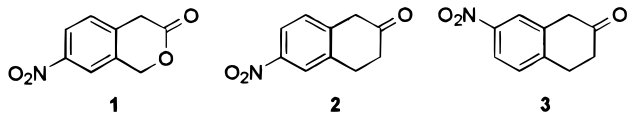


1 **2** **3**

Reactivity of 7-Nitroisochroma-3-one in Aqueous Sodium Hydroxide. Adding 7-nitroisochroma-3-one (**1**) to aqueous NaOH (ca. 0.5 M) yields a deep red-purple solution (λ_{max} 532 nm) which fades to colorless, with first-order decay, in about 10 s (Figure 1). Rapid acidification of the solution with HCl brings about immediately decolorization. The species absorbing at 532 nm, apparently formed by reversible deprotonation of **1**, is characterized as the enolate of **1** by comparison with the UV/vis absorption spectrum of 6-nitro-2-tetralone enolate (**2**$^-$, λ_{max} 513.5 nm).[8] Thus, although decomposition of **1**, or its enolate, proceeds at a fairly rapid rate, observable quantities of the enolate persist for several seconds.

Isolation of the decomposition product, expected to be 2-hydroxymethyl-4-nitrophenylacetate formed via ester hydrolysis, was attempted by acidification of the reaction mixture to pH 2 and extraction with ethyl ether. This procedure yielded only **1** as demonstrated by melting point, GC/MS, and ^{1}H NMR. Although 2-hydroxymethyl-4-nitrophenylacetic acid was not recovered, isolation of **1**, apparently formed by lactonization of the hydroxyacid in acidic solution, is consistent with decomposition via ester hydrolysis rather than some other process (e.g., oxidation of the enolate).[9] This interpretation is supported by studies of hydrolysis of phenylacetate esters in aqueous base. Like **1**, ethyl 4-cyanophenylacetate[10] and methyl 4-nitrophenylacetate[11] show rapid formation of brightly colored enolate solutions (λ_{max} 535 nm (EtOH) and λ_{max} 466 nm (H_2O), respectively) which undergo subsequent decolorization; in both cases the substituted phenylacetic acids are isolated.

Hydrolysis of 7-Nitroisochroman-3-one in Aqueous Sodium Hydroxide. Hydrolysis of **1** was studied by monitoring the disappearance of the enolate (λ_{max} 532 nm) at varying concentrations of sodium hydroxide ([NaOH] = 5−500mM; [**1**] = 26 μM; μ = 1.00 M (NaCl); 5.0% MeOH). First-order kinetics were observed in all cases and the observed pseudo-first-order rate coefficients (k_{hyd}) for hydrolysis of **1** are listed in Table 1. Studies of the rate dependence on substrate concentration (data not listed) show that 20-fold variation in [**1**] ([NaOH] = 100 mM) has no effect on k_{hyd}. The observed rates of hydrolysis show hyperbolic dependence on [HO$^-$]; at relatively low hydroxide concentrations k_{hyd} is proportional to [NaOH], while at higher hydroxide concentrations the reaction approaches a pH-independent rate (Figure 2). This observation indicates that the mechanism of hydrolysis involves rapid equilibrium proton transfer prior to the rate-determining step.[12]

Hydrolysis of **1** could proceed by nucleophilic attack of hydroxide on the neutral lactone[13] ($B_{AC}2$; bimolecular base-promoted acyl-oxygen cleavage), with the competing rapid equilibrium between the lactone and enolate giving rise to the hyperbolic pH−rate profile (Scheme 1, mechanism I). The steady-state rate law for mechanism I is given in eq 1, where K = [S$^-$]/[SH][OH$^-$] and k_{OH} is the bimolecular rate coefficient for hydroxide ion-promoted hydrolysis. However, esters possessing relatively acidic α-protons have been shown to hydrolyze via rate-limiting elimination of alkoxide from the enolate to give a ketene (E1cB; unimolecular elimination via the conjugate base) which subsequently undergoes rapid hydrolysis (Scheme 1, Mechanism II).[14] The steady-state rate law for mech-

Table 1. Pseudo-First-Order Rate Coefficients (k_{hyd}) for Hydrolysis of 7-Nitroisochroman-3-one (1) in Aqueous Sodium Hydroxide[a]

[OH$^-$] (mM)	k_{hyd} (s^{-1})[b]	[OH$^-$] (mM)	k_{hyd} (s^{-1})[b]
500	0.295 ± 0.002	10.0	0.113 ± 0.002
250	0.279 ± 0.003	5.0	0.070 ± 0.001
100	0.256 ± 0.003	485 (H_2O)[c]	0.273 ± 0.003
50.0	0.229 ± 0.004	485 (D_2O)[c]	0.195 ± 0.002
25.0	0.178 ± 0.002		

[a] [**1**] = 26 μM; μ = 1.00 M (NaCl); 5% MeOH. [b] Average of 8−10 determinations at each [OH$^-$]. [c] [**1**] = 26 μM, μ = 0.485 M, 5% MeOH(D). Average of 12 determinations at each [NaOH(D)].

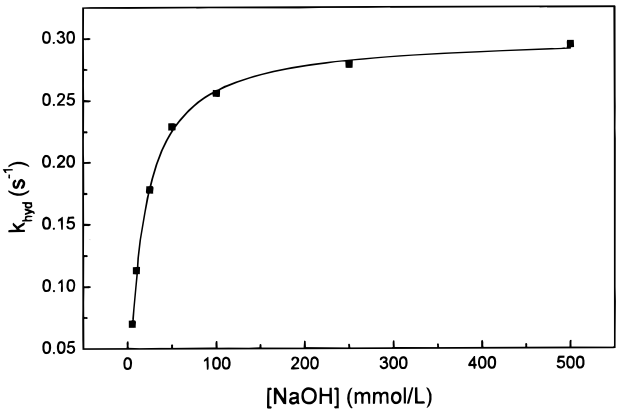
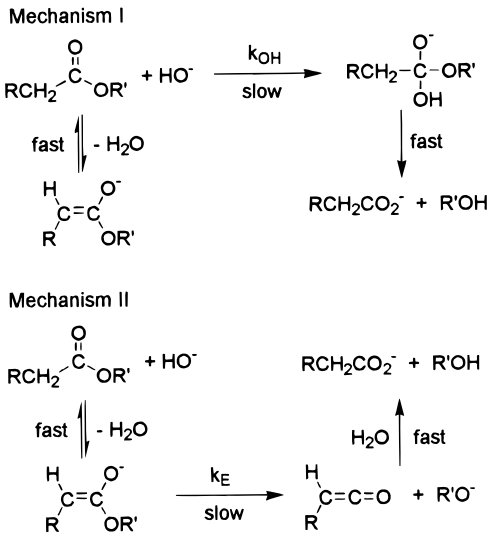


Figure 2. Plot of k_{hyd} against [NaOH] for hydrolysis of 7-nitroisochroman-3-one in aqueous sodium hydroxide ([**1**] = 26 μM; μ = 1.00 M (NaCl); 5.0% MeOH; 25 °C). The theoretical line is calculated from eq 1 with the following parameters: k_{OH} = 18.7 M^{-1} s^{-1} and K = 61.0 M^{-1}.

Scheme 1



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anism II is given by eq 2, where $K = [S^-]/[SH][OH^-]$ and k_E is the unimolecular rate coefficient for rate-determining elimination of alkoxide ion. Since both mechanisms involve rapid equilibrium proton transfer prior to the rate-determining step, they are indistinguishable by ordinary kinetic methods.

$$k_{hyd} = k_{OH}[OH^-]/(1 + K[OH^-]) \quad (1)$$

$$k_{hyd} = k_E K[OH^-]/(1 + K[OH^-]) \quad (2)$$

Kézdy and Tobias[15] have suggested that mechanisms I and II should show different kinetic solvent isotope effects in strongly basic media (pH > pK_a). Under these conditions the ester will be almost fully ionized and the high pH limits of eqs 1 and 2 describe the reaction kinetics. Accordingly, since the limiting rate law is dependent on the rapid-equilibrium proton transfer ($k_{hyd} = k_{OH}/K$), the rate of reaction via mechanism I should show a significant solvent isotope effect ($k_{D_2O}/k_{H_2O} < 1$); Kézdy and Tobias predict $k_{D_2O}/k_{H_2O} = 0.65$. On the other hand, it was suggested that hydrolysis by mechanism II would show a solvent independent rate ($k_{D_2O}/k_{H_2O} = 1$) since the limiting rate law ($k_{hyd} = k_E$) contains only a term for unimolecular elimination of alkoxide from the enolate.

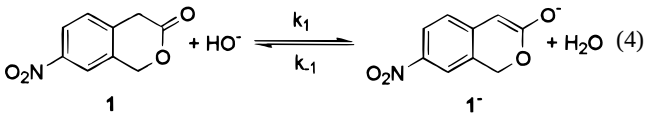
For hydrolysis of **1** in 0.485 M NaOH(D), where **1** is ca. 98% ionized, the observed rate constant for hydrolysis in water ($k_{hyd}(H_2O) = 0.273 \pm 0.003$ s^{-1}) is somewhat larger than that in deuterium oxide ($k_{hyd}(D_2O) = 0.195 \pm 0.002$ s^{-1}). By the above analysis, the kinetic solvent isotope effect of $k_{D_2O}/k_{H_2O} = 0.71 \pm 0.02$ would be consistent with hydrolysis of **1** via mechanism I. However, while there is a general trend in kinetic solvent isotope effects for ester hydrolyses by these mechanisms, the crossover point between the $B_{AC}2$ and E1cB mechanisms is not well-defined. Values of k_{D_2O}/k_{H_2O} for E1cB hydrolysis of aryl acetoacetates range from 0.87 (*p*-nitrophenyl acetoacetate) to 0.69 (phenyl acetoacetate).[16] Such deviations of k_{D_2O}/k_{H_2O} from unity in E1cB hydrolyses have generally been attributed to large changes in solvation between the ground and transition states in the rate-determining step, but might also reflect nucleophilic solvent assistance to the elimination [14b,16,17] Studies of the equilibrium solvent isotope effect on K_a for ketones suggest that k_{D_2O}/k_{H_2O} for $B_{AC}2$ hydrolysis could be significantly larger than the value of ca. 0.65 predicted by Kézdy and Tobias.[18] Therefore, the kinetic solvent isotope effect cannot be used to unambiguously designate the mechanism of hydrolysis of **1**.

The mechanism of alkaline hydrolysis for esters bearing relatively acidic α-protons ($B_{AC}2$ vs E1cB) has been shown to be dependent on the basicity of the oxide leaving group (pK_{LG}). Limiting rates of hydrolysis (pH > pK_a) for aryl esters of acetoacetic[16] and fluorene-9-carboxylic[5a] acid show much better correlation with Hammett σ^- constants than with σ constants and give large values of ρ^- (2.8 and 2.1, respectively), consistent with rate-limiting elimination of phenoxide. In comparison, rates of alkaline hydrolysis ($B_{AC}2$) of aryl acetates correlate well with σ constants to give $\rho = 0.8$.[19] Transition to the $B_{AC}2$ mechanism for acetoacetate[16] and fluorene-9-carboxylate[5a] esters with poorer leaving groups is indicated by an abrupt change in the slope of the Brønsted plot (log k_{OH} vs pK_{LG}). For the aryl esters (pK_{LG} < 10), which hydrolyze via E1cB, large negative slopes ($\beta_{LG} = -1.29$ and -1.01, respectively) are observed. In contrast, the decreased sensitivity of rate on pK_{LG} ($\beta_{LG} = -0.30$ and 0.11, respectively) for alkoxide leaving groups is consistent with rate-determining attack of hydroxide at the carbonyl carbon of the neutral ester ($\beta_{LG} = -0.26$ for alkaline hydrolysis of acetate esters).[20] The crossover between mechanisms occurs at pK_a ca. 11 for acetoacetates and pK_a ca. 10 for fluorene-9-carboxylates.

While it is difficult to reliably estimate pK_{LG} for the alkoxide moiety eliminated during hydrolysis of **1**, a calculated pK_a of ca. 14.8 for 3-nitrobenzyl alcohol[21] can be used as a first approximation. Since this value is much greater than the maximum pK_{LG} observed for E1cB hydrolysis of acetoacetate and fluorene-9-carboxylate esters (pK_{LG} < 11), we tentatively assign the mechanism of hydrolysis of **1** as $B_{AC}2$. Fitting the observed rates of hydrolysis of **1** (Table 1) to eq 1 gives $k_{OH} = 18.7 \pm 0.3$ M^{-1} s^{-1} and $K = 61.0 \pm 2.5$ M^{-1}. A replicate set of experiments (data not shown) gives $k_{OH} = 19.3 \pm 0.2$ M^{-1} s^{-1} and $K = 61.2 \pm 1.6$ M^{-1}. The value of K can be used to calculate the acid dissociation constant for **1** by eq 3 ($K_a = 1.15 (\pm 0.04) \times 10^{-12}$), where $K_w = 1.88 \times 10^{-14}$ M^2.[22] It should be noted that since both the $B_{AC}2$ and E1cB mechanisms predict the same pH dependence for k_{hyd}, the calculated value of K_a for **1** is independent of the choice of mechanism; fitting the data of Table 1 to eq 1 and eq 2 yields identical values of K_a.

$$K_a = KK_w \quad (3)$$

Rates of Proton Transfer for 7-Nitroisochroman-3-one in Aqueous Sodium Hydroxide. Rate constants for deprotonation of **1** by hydroxide ion (k_1) and ketonization of the corresponding enolate (k_{-1}) were determined by monitoring the formation of the enolate in aqueous NaOH at 532 nm in a stopped-flow spectrophotometer (eq 4). Hydroxide ion concentrations were chosen



1 **1⁻** (4)

to give 35−85% enolization of **1** ([NaOH] = 4.17−62.5 mM; [**1**] = 50 μM; μ = 1.00 M (NaCl); 5.0% MeOH). Under these conditions formation of the enolate ($t_{1/2}$ < 3

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(18) (a) The kinetic solvent isotope effect on k_{hyd} under strongly basic conditions (k_{D_2O}/k_{H_2O}) is proportional to the equilibrium solvent isotope effect on K_a ($^HK_a/^DK_a$): $k_{D_2O}/k_{H_2O} = {}^Dk_{OH}/{}^Hk_{OH}\}\{{}^DK_w/{}^HK_w\}\{{}^HK_a/{}^DK_a\}$. Kézdy and Tobias (ref 15) use a value of $^HK_a/^DK_a = 3.5$ to calculate $k_{D_2O}/k_{H_2O} = 0.65$. Values of $^HK_a/^DK_a$ for 3-methyl-2,4-pentadione (6.0, ref 8b) and isobutyrophenone (5.4, ref 18c) result in predicted values of k_{D_2O}/k_{H_2O} near unity. (b) Dahlberg, D. B.; Long, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 3825. (c) Keefe, J. R.; Kresge, A. J. *Can. J. Chem.* **1996**, *74*, 2481.
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(21) (a) Estimated using pK_a = 15.4 for benzyl alcohol (ref 21b) by two methods: (i) from an estimated pK_a of 14.4 for 3,5-dinitrobenzyl alcohol (ref 21c) assuming the effects of the two nitro groups are additive and (ii) using a Hammett ρ value of 1.01 for dissociation of 1-aryl-2,2,2-trifluoroethanols in water (ref 21d). (b) Murto, J. *Acta Chem. Scand.* **1964**, *18*, 1043. (c) Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205. (d) Stewart, R.; Van der Linden, R. *Can. J. Chem.* **1960**, *38*, 399.
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Table 2. Pseudo-First-Order Rate Coefficients (k_{ion}) for Ionization of 7-Nitroisochroman-3-one (1) in Aqueous Sodium Hydroxide[a]

[OH^-] (mM)	k_{ion} (s^{-1})[b]
62.5	1006 ± 9
41.7	793 ± 11
8.33	311 ± 3
4.17	262 ± 2

[a] [**1**] = 50 μM; μ = 1.00 M (NaCl); 5% methanol. [b] Average of 8 determinations at each [OH^-].

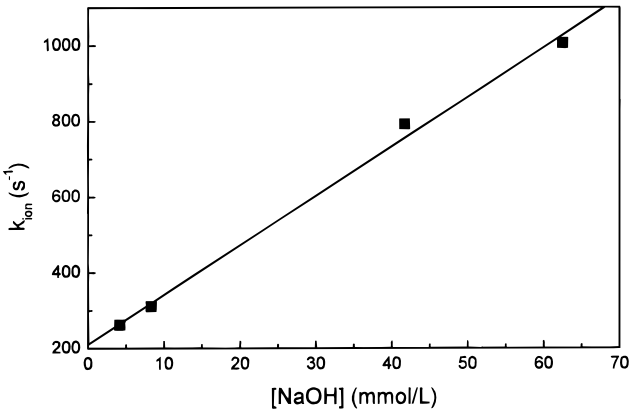


Figure 3. Plot of k_{ion} against [NaOH] for enolization of of 7-nitroisochroman-3-one in aqueous sodium hydroxide ([**1**] = 50 μM; μ = 1.00 M (NaCl); 5.0% MeOH; 25 °C). The theoretical line is calculated from eq 5 with the following parameters: k_1 = 13 100 M^{-1} s^{-1} and k_{-1} = 212 s^{-1}.

ms) is much faster than hydrolysis ($t_{1/2}$ > 2.7 s), and appearance of the enolate follows first-order kinetics. Pseudo-first-order rate coefficients (k_{ion}, Table 2) for formation of $\mathbf{1}^-$ were obtained by fitting the absorption data for the enolization of **1** (the first 0−6 ms to 0−25 ms of the reaction, depending on [NaOH]) to a first-order rate equation. These rate constants show a linear dependence on hydroxide ion concentration (Figure 3). Fitting the data of Table 2 to eq 5 yields the rate constants for deprotonation of **1** by hydroxide ion (k_1 = 1.31(±0.06) × 10^4 M^{-1} s^{-1}) and C-protonation of the enolate by water (k_{-1} = 212 ± 24 s^{-1}). The value of K_a (1.16(±0.18) × 10^{-12}) calculated from these rate constants (eq 6) is in excellent agreement with the value calculated from the kinetic studies of the hydrolysis reaction.[23]

$$k_{ion} = k_1[OH^-] + k_{-1} \quad (5)$$

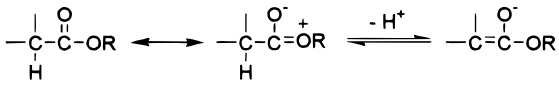
$$K_a = k_1K_w/k_{-1} \quad (6)$$

Acidity of 7-Nitroisochroman-3-one. Acid dissociation constants for four ketone−ester pairs are listed in Table 3; in all cases the esters are of considerably lower acidity than their ketone counterparts. The lower aqueous acidity of the esters can be accounted for, in part, by resonance interaction of alkoxy lone pair electrons with the carbonyl group, which imparts substantial stabilization to the carbon acid form of the ester (ground-state stabilization, eq 7).[24] However, the observation that the

Table 3. Acid Dissociation Constants for Esters and Ketones[a]

ester	pK_a	ketone	pK_a
7-nitroisochroman-3-one (**1**)	11.9[b]	6-nitro-2-tetralone (**2**)	9.9[c]
ethyl acetate	25.6[d]	acetone	19.3[d]
methyl fluorene-9-carboxylate	11.5[e]	9-acetylfluorene	9.4[e]
ethyl acetoacetate	10.6[f]	acetylacetone	8.9[d]

[a] pK_a for ionization of the carbon acid at 25 °C. [b] This work. [c] Data from ref 8. [d] Data from ref 6 and references therein. [e] Data from ref 5b and references therein. [f] Data from ref 4.



(7)

difference in acidity between ester and ketone is dramatically less (ca. 4 pK units) for those pairs where the enolates are stabilized by "secondary" substituents suggests ground-state stabilization of the ester cannot be the only factor affecting acidity. For example, the nitrophenyl ring in the cyclic benzylic system in **1** and **2** provides ca. 16000-fold greater stabilization of the enolate in the ester compared to the ketone (**1** is 13.6 pK units more acidic than ethyl acetate whereas 6-nitro-2-tetralone (**2**) is only 9.4 pK units more acidic than acetone). Since resonance stabilization by the nitrophenyl group should be most prominent where demand is the greatest,[25] this observation suggests that the alkoxycarbonyl group is a poorer enolate-stabilizing group than the carbonyl group. The inferior enolate-stabilizing effect of the alkoxycarbonyl group is most likely due to less efficient resonance delocalization (values of σ^- are 0.87 for $COCH_3$ and 0.68 for COOR).[26] On the other hand, values of σ^* (1.65 for $COCH_3$ and 2.00 for COOR)[27] suggest the diminished resonance effect should be partially compensated by a higher degree of inductive stabilization.

Studies of the kinetics of enolization demonstrate that **1** is deprotonated at a significantly faster rate than structurally analogous ketones. Although **1** is 2.1 pK units less acidic than 6-nitro-2-tetralone (**2**, k_1 = 6650 M^{-1} s^{-1}),[18] the ester is deprotonated by hydroxide at a ca. 2-fold faster rate. As shown in Figure 4, the rate constant for enolization of **1** deviates upward (Δlog k_1 = 1.06) from the Brønsted correlation for 2-tetralones. (Bunting[4] has reported comparable results for β-ketoesters; Brønsted plots for deprotonation by hydroxide of β-ketoesters and open chain ketones/aldehydes[2] have similar α values (0.43 and 0.40, respectively), but the β-ketoesters react at ca. 20-fold faster rates than ketones/aldehydes of equal acidity.) Moreover, due to the aberrant behavior of the *p*-nitro substituent, this factor of 11 (Δlog k_1 = 1.06) may substantially underestimate the inherent difference in the reactivities of isochroman-3-ones and 2-tetralones. The negative deviation of **2** from the correlation has previously been interpreted to indicate that only 55% of the resonance stabilization of the enolate by the *p*-nitro group is proportionally reflected, with respect to the inductive effect, in the transition state for enolization.[8] Similar behavior in the isochroman-3-one system would lead to a ca. 25-fold difference in rates of deprotonation for isochroman-3-ones and 2-tetralones of equal thermodynamic acidity.

(23) Agreement of the K_a values obtained from studies of hydrolysis (pH dependence of k_{hyd}) and enolization (pH dependence of k_{ion}) does not enable distinction between mechanisms I and II since both mechanisms predict the same pH dependence of k_{hyd}.

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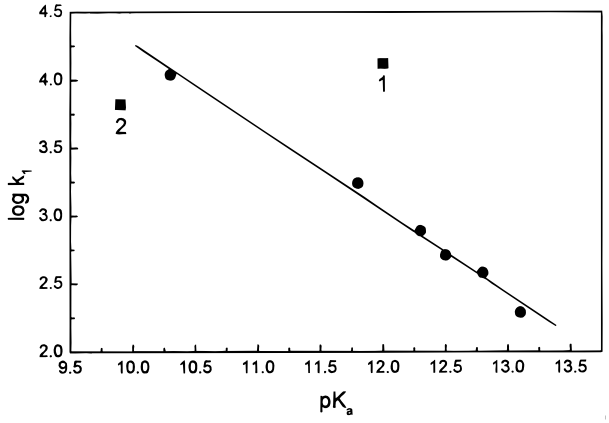

Figure 4. Brønsted plot for deprotonation by hydroxide ion of 7-nitroisochroman-3-one (**1**), 6-nitro-2-tetralone (**2**), and other 2-tetralones (circles (left to right): 5,7-dinitro-, 5-nitro-, 5-chloro-, 6-chloro-, unsubstituted, 6-methoxy-). With the exception of **1**, all data is from ref 8.

The rapid rate of deprotonation of **1** compared to that of the 2-tetralones can be attributed to differences in resonance stabilization provided by the carbonyl and alkoxycarbonyl groups. According to the principle of nonperfect synchronization, a product-stabilizing feature (e.g., resonance) that develops late along the reaction coordinate with respect to the main process (e.g., C−H bond cleavage) will increase the intrinsic kinetic barrier to the reaction.[28] If, relative to the carbonyl group, the alkoxycarbonyl group provides less efficient resonance stabilization of the enolate, the diminished demand for resonance stabilization should be manifest in the transition state, resulting in a larger intrinsic rate constant for enolization of the ester. That is, greater imbalance in the transition state for deprotonation of ketone **2** than for deprotonation of lactone **1** would lead to a higher intrinsic kinetic barrier for deprotonation of **2**. In addition, Richard has noted that deprotonation of carboxylate esters should involve a relatively small loss of ground-state resonance stabilization (eq 7) at the transition state, which will also contribute to a lower intrinsic kinetic barrier.[6]

Experimental Section

Materials. Except as noted below, all reagents and solvents were used without further purification. Merck silica gel (230−400 mesh, 60 Å (Aldrich)) was used for column chromatography. 2-Indanone (Aldrich, 98%) was purified by column chromatography (5:1 petroleum ether/ethyl acetate) followed by recrystallization from 2:1 petroleum ether/ethyl ether. 3-Chloroperoxybenzoic acid (Aldrich, 57−86%) was dissolved in ethyl ether and extracted with of phosphate buffer (pH 7.5, 1 M) to remove chlorobenzoic acid.[29] Isochroman-3-one was prepared by Baeyer−Villiger oxidation of 2-indanone with 3-chloroperoxybenzoic acid using a previously published procedure.[30]

Water used for the preparation of all aqueous solutions was purified by reverse osomosis, boiled for 15 min to remove dissolved CO_2,[31] and stored under nitrogen. Standard aqueous sodium hydroxide (1.000 ± 0.005 M) was purchased from Fisher Scientific. All other sodium hydroxide solutions were prepared by dilution of the above. Except where otherwise noted, all solutions for kinetic experiments had an ionic strength of 1.00 M (adjusted with NaCl). Deuterated solutions for solvent isotope effect experiments were prepared from deuterium oxide (Aldrich, 99.9 atom % D), sodium deuteroxide (Aldrich, 40 wt % solution in D_2O, 99.9 atom % D), and methanol-*d* (CH_3OD, Aldrich, 99.5+ atom % D).

7-Nitroisochroman-3-one (1). Nitronium tetrafluoroborate[7] (NO_2BF_4, Aldrich, 1.25 g, 0.0094 mol) was dissolved in 20 mL of acetonitrile. This solution was added dropwise, with stirring, to a cold solution (0 °C) of isochroman-3-one (1.0 g, 0.0067 mol) in acetonitrile (20 mL). The reaction mixture was stirred for 6 h at 0 °C while monitoring formation of product by GC/MS. The reaction mixture was poured onto 30 g of ice and extracted with three 20 mL portions of ethyl ether. After drying over anhydrous $MgSO_4$, evaporation of the solvent gave a yellow oil. Column chromatography (2:1 petroleum ether/ethyl acetate) followed by recrystallization (3:1 petroleum ether/ethyl acetate) gave 0.5 g (39% yield) of 7-nitroisochroman-3-one (mp 130−131 °C) ^{1}H NMR ($CDCl_3$, TMS): δ 3.85 (s, 2H), 5.42 (s, 2H), 7.44 (d,1 H, J = 8.2 Hz), 8.14 (s, 1 H), 8.22 (d,1 H, J = 8.2 Hz). MS: *m*/*z* (%) 193 (M, 17.8), 149 (100), 103 (16.8), 77 (16.8). IR (Nujol): includes 1750, 1525, 1355, 1025 cm^{-1}. Anal. Calcd for $C_9H_7NO_4$: C, 55.96; H, 3.66; N, 7.25. Found: C, 56.19; H, 3.93; N, 7.12.

UV/vis Spectrum of 7-Nitroisochroman-3-one in Aqueous Sodium Hydroxide. A solution of 7-nitroisochroman-3-one (**1**) in 10% methanol−water was rapidly mixed (Hi-Tech SFA-12 Rapid Kinetics Accessory) with an equal volume of aqueous sodium hydroxide in the sample chamber of a Hewlett-Packard 89532 UV/vis spectrophotometer (final conditions: [**1**] = 26 μM, [NaOH] = 0.500 M, 5% MeOH). Absorption spectra (200−800 nm) were recorded immediately after mixing and at ca. 1−3 s intervals after the initial scan (Figure 1).

Hydrolysis of 7-Nitroisochroman-3-one in Aqueous Sodium Hydroxide. Equal volumes of solutions of **1** (10% methanol−water; μ = 1.00 (NaCl); [**1**] = 52 μM) and aqueous sodium hydroxide (0.0100−1.000 M; μ = 1.00 (NaCl)) were rapidly mixed (Hi-Tech SFA-12 Rapid Kinetics Accessory) in the sample chamber of a Cary 1 UV/VIS spectrophotometer. The subsequent reaction was monitored at 532 nm for at least 10 half-lifes. Fitting the absorption data for the first-order decay by nonlinear least-squares regression gives the pseudo-first-order rate coefficients (k_{hyd}) for hydrolysis of **1** (Table 1). In all cases, the standard deviation of the absorbance data from the theoretical curve was less than 0.25%.

Ionization of 7-Nitroisochroman-3-one in Aqueous Sodium Hydroxide. Solutions of **1** (0.30 mM in 5% MeOH, μ = 1.00 M (NaCl)) and aqueous sodium hydroxide (5.00−75.0 mM, μ = 1.00 M (NaCl), 5% MeOH) were mixed in a 1:5 ratio in the observation cell of a Hi-Tech PQ/SF-53 stopped-flow spectrophotometer. Formation of the enolate of **1** was monitored at 532 nm. Fitting the absorption data to a first-order rate equation by nonlinear least-squares regression gives the pseudo-first-order rate coefficients (k_{ion}) for ionization of **1** (Table 2). In all cases, the standard deviation of the absorption data from the theoretical curve was less than 0.50%.

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