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Kinetics and Mechanism of the Isomerization of 1*H*-Indene-1-carboxylic Acid to 1*H*-Indene-3-carboxylic Acid in Aqueous Solution and Determination of Their Keto-Enol Equilibrium Constants and Acid Dissociation Constants of the Keto and Enol Forms. Implication on the Photolysis of Diazonaphthoquinones

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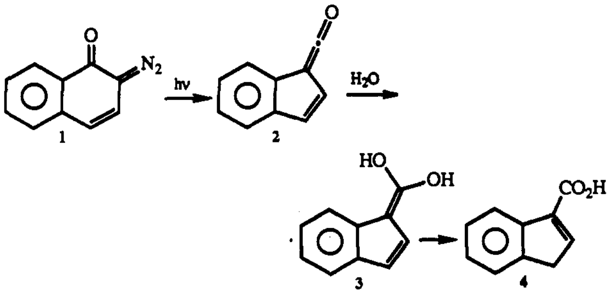
Abstract: Rates of isomerization of 1*H*-indene-1-carboxylic acid to 1*H*-indene-3-carboxylic acid were measured in dilute aqueous solutions of $HClO_4$, NaOH, and CH_3CO_2H and $H_2PO_4^-$, $(CH_3)_3CPO_3H^-$, and HCO_3^- buffers. This gave a rate profile which, together with the occurrence of general base catalysis and sizable primary kinetic isotope effects, indicates that the isomerization takes place through an enolization–reketonization reaction sequence. The equilibrium constant of the isomerization reaction is K = [indene-3-carboxylic acid]/[indene-1-carboxylic acid] = 200 in aqueous acid solution and K = 100 in base. The ratio of products formed by ketonization of the indenecarboxylic acid enol intermediate generated in the photolysis of 2-diazo-1(2*H*)-naphthalenone is R = [indene-3-carboxylic acid]/[indene-1-carboxylic acid] = 0.47 in aqueous acid solution and R = 20 in base. The failure of previous investigations of the photolysis reaction to detect any indene-1-carboxylic acid as the product is attributed to the facile isomerization of this substance to indene-3-carboxylic acid and the preponderance of the latter at equilibrium. The enol intermediate of this isomerization reaction was also generated by flash photolysis of 2-diazo-1(2*H*)-naphthalene and rates of its ketonization were measured in dilute aqueous $HClO_4$ solutions. Analysis of the data gave the enol acidity constant $pK_a^E = 2.09$. The results, in combination with those for the isomerization reaction, also provided carbon acid acidity constants (K_a^K) and keto–enol equilibrium constants (K_E) for the two acids: $pK_a^K = 9.35$ and $pK_E = 7.26$ for indene-1-carboxylic acid and $pK_a^K = 11.69$ and $pK_E = 9.60$ for indene-3-carboxylic acid.

The photolysis of diazonaphthoquinones such as **1** is of interest for its commercial application in photolithography[1] and also for the rich chemistry of reactive intermediates that this reaction affords.[2] The process in aqueous solution occurs through ketene, **2**, and dienol, **3**, intermediates[2b] and gives 1*H*-indene-3-carboxylic acid, **4**, as the ultimate reaction product, eq 1. This product was originally formulated as the isomeric 1*H*-indene-1-carboxylic acid,[3] but it was later discovered that what was once believed to be the 1-acid actually is the 3-acid,[4] and it is now generally accepted that the final product of this reaction is indeed indene-3-carboxylic acid.[2a]



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It was not clear from previous reports, however, whether indene-3-carboxylic acid is the only substance formed by ketonization of the dienol intermediate, or whether some indene-1-carboxylic acid is formed as well and this then isomerizes to the 3-acid. Isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid is known to be a facile process, and the 3-acid is known to be the more stable substance.[5] The ketonization of other conjugated dienols, moreover, generally gives mixtures of both possible isomeric products.[6]

In order to clarify this issue, we have examined the products formed immediately upon photolysis of the diazonaphthoquinone **1** in aqueous solution. We have found that both isomeric indenecarboxylic acids are indeed products, in proportions that vary with the acidity of the medium, but that isomerization takes place readily to give indene-3-carboxylic acid as essentially the only final product. Before we could carry out this product study, however, we had to know the lifetime of indene-1-carboxylic acid in aqueous solution under various conditions of acidity. We consequently determined the acidity-rate profile for the isomerization reaction. The information so obtained, together with some isotope effect determinations, has enabled us to elucidate the mechanism of the isomerization as an enolization–reketonization

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[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1994.

(1) See, *e.g.*: Reichmanis, E. In *Polymers for Electronic and Photonic Applications,* Wong, C. P., Ed.; Academic Press: New York, 1993; pp 67–117. Reichmanis, E.; Thompson, L. F. *Chem. Rev.* **1989,** *89,* 1273–1289.

(2) (a) For brief reviews and references to previous literature, see: Gill, G. B. In *Comprehensive Organic Synthesis*: Trost, B. M., Ed.; Pergmanon Press: New York, 1991; Vol. 3, pp 891–892. Vollenbroek, F. A.; Nijssen, W. P. M.; Mutsaers, C. M. J.; Goemani, M. J. H. J.; Reuhman, M. E.; Visser, R. J. *Polymer Eng. Sci.* **1989,** *29,* 928–936. (b) See, also: Andraos, J.; Chiang, Y.; Huang, C. G.; Kresge, A. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1993,** *115,* 10605–10610.

(3) Süs, O. *Justus Liebigs Ann. Chem.* **1944,** *556,* 65–84.

(4) (a) Melera, A.; Claesen, M.; Vanderhaeghe, H. *J. Org. Chem.* **1964,** *29,* 3705–3706. (b) Meth-Cohn, O.; Gronowitz, S. *J. Chem. Soc., Chem. Commun.* **1966,** 81–82.

(5) Friedrich, E. C.; Taggart, D. B. *J. Org. Chem.* **1975,** *40,* 720–723.

(6) Pollack, R. M.; Bounds, P. L.; Bevins, C. L. In *The Chemistry of Enones;* Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; Chapter 13. Capon, B. In *The Chemistry of Enones;* Patai, S., Rappoport, Z., Ed.; Wiley: New York, 1989; Chapter 20. Weedon, A. C. In *The Chemistry of Enols;* Rappoport, Z., Ed.; Wiley: New York, 1990; Chapter 9.

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reaction sequence. We have also measured rates of the ketonization of enol **3** and have combined these with rates of the 1-acid to 3-acid isomerization to obtain the acidity constants for indene-1-carboxylic acid and indene-3-carboxylic acid ionizing as carbon acids as well as the keto–enol equilibrium constants of these substances.

Experimental Section

Materials. Diazonaphthoquinone **1** (2-diazo-1(2*H*)-naphthalenone) was prepared from 1,2-naphthoquinone via its tosylhydrazone,[7] 1-*H*-Indene-1-carboxylic acid was synthesized by treating indenyllithium with carbon dioxide at low temperature,[4b] and indene-3-carboxylic acid was obtained by heating the 1-acid above its melting point.[4b] The ^{1}H NMR spectra of all of these materials were consistent with their structures and were similar to those reported in the literature.

Indene-1-carboxylic acid-1,3,*O*-d_3 was synthesized from indene-1,1,3-d_3, which was made by allowing indene to exchange with methanol-*O*-*d* using sodium methoxide as the catalyst.[8] Isotopic analysis performed by ^{1}H NMR showed deuterium contents at the indicated positions of 94% for the indene and 89% for the acid. The mass spectrum of the acid confirmed the presence of three atoms of deuterium.

All other materials were best available commercial grades.

Equilibrium Constant Determination. Equilibrium constants for the isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid were obtained by using ^{1}H NMR signal intensities to determine the relative amounts of the two acids. Signals at δ/ppm = 7.0 (H_3), 6.6 (H_2), and 4.5 (H_1) for indene-1-carboxylic acid and δ/ppm = 8.1 (H_7) and 3.6 ppm (H_1) for indene-3-carboxylic acid were employed. The amount of indene-1-carboxylic acid present at equilibrium was small, and its signals were consequently weak; allowance for signal integral drift was therefore made by measuring the drift immediately before and after the integral recording and then correcting the integral using the average of the two drift values.

Determinations were made in aqueous 0.01 M $HClO_4$ and 0.01 M NaOH solutions at times that corresponded to 100 isomerization half-lives (7 h for the acid solutions and 20 min for the basic solutions); indenecarboxylic acid concentrations were *ca.* 0.001 M. Fifty milliliter aliquots of the solutions were extracted with 1-mL portions of $CDCl_3$, the extracts were dried with $MgSO_4$, and their NMR spectra were recorded.

Product Ratio Determinations. Ratios of indene-1-carboxylic acid to indene-3-carboxylic acid formed immediately upon photolysis of diazonaphthoquinone **1** were determined by NMR analysis as described above for equilibrium constant measurements. Determinations were made in aqueous 0.001 M $HClO_4$ and aqueous 0.01 M $H_2PO_4^-/HPO_4^{2-}$ and 0.02 M HCO_3^-/CO_3^{2-} buffers, both at buffer ratio = 1.0; diazonaphthoquinone concentrations were 0.0005–0.001 M. Aliquots of these solutions cooled to 0 °C were irradiated with 10 pulses from our conventional flash photolysis apparatus.[9] The irradiated solutions were then immediately extracted with dichloromethane, the extracts were dried with Na_2SO_4, and their NMR spectra were recorded; before the buffer solutions were extracted their pH was quickly adjusted to 3–4 by the addition of cold $HClO_4$. These operations, from the first flash to drying of the extracts, were all performed at 0 °C and were completed in 1.5 min; control experiments in which the solutions were left at 0 °C for an additional 1 min showed no change in product ratios.

Kinetics. Rates of isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid were determined spectroscopically, using the difference in UV absorbance of the two acids (*vide infra*) to monitor the process. Measurements were made either with a Cary Model 2200 spectrometer, whose cell compartment was thermostatted at 25.0 ± 0.1 °C, or, for the faster reactions in sodium hydroxide solutions, with a Hi-Tech SF-S1 stopped-flow spectrometer operating at 25.0 ± 0.1 °C. Reactions monitored by the Cary spectrometer were initiated by injecting 20–50 μL of indene-1-carboxylic acid stock solution into a cuvette containing 3 mL of reaction solution that had been allowed to come to temperature equilibrium with the spectrometer cell compartment. Reactions monitored by stopped-flow spectrometry were initiated by 1:1 mixing of sodium hydroxide solution with a solution of indenecarboxylic acid in water that had been prepared immediately before, again by injection 5–10 μL of indenecarboxylic acid stock solution into *ca.* 3 mL of water. Substrate concentrations in the reaction mixtures were of the order of 1 × 10^{-4} M. It was found that, unless care was exercised to exclude impurities from the solvent used to prepare substrate stock solutions, isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid took place readily; HPLC grade methanol proved to be satisfactory, but even this had to be stored at −70 °C.

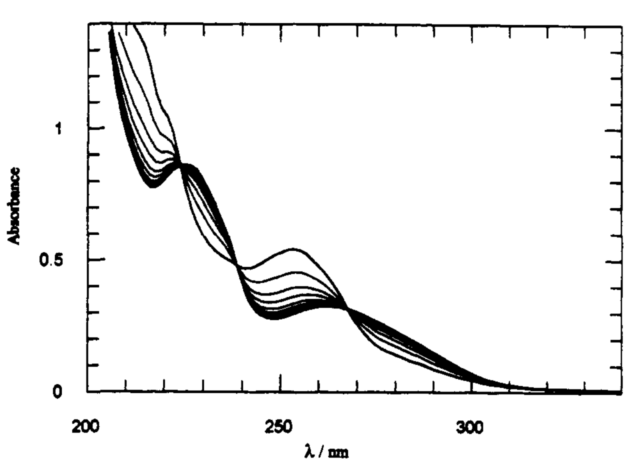

Figure 1. Ultraviolet spectral changes accompanying the isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid in 0.001 M aqueous $HClO_4$; successive spectra were recorded at 3-min intervals.

The kinetic data obtained in this way, except for that from systems in which the isotope of hydrogen present in the solvent was different from that at the reacting position of the substrate (*vide infra*), obeyed the first-order rate law well, and observed first-order rate constants were determined by least squares fitting to an exponential function.

Flash photolysis experiments were carried out using an excimer laser system that has already been described.[2b] Excitation was provided with light of wavelength λ = 308 nm, and the transients were monitored at λ = 330 nm.

Results and Discussion

The UV absorption spectrum of indene-1-carboxylic acid in aqueous solution consists of a band with λ_{max} = 252 nm plus end absorbance beginning at λ = 230 nm, while that of indene-3-carboxylic acid consists of two bands with λ_{max} = 225 and 262 nm. As Figure 1 shows, isomerization of one acid into the other occurs with the development of several clean isosbestic points, indicating tht the reaction takes place without significant buildup of any reaction intermediate. Proton NMR examination of the reaction mixture after the UV spectroscopic change is finished shows that the isomerization goes to completion, i.e., no more than 1% of indene-1-carboxylic acid is present at equilibrium (*vide infra*); the reaction is therefore essentially nonreversible. The UV spectral change accompanying isomerization is greatest at λ = 252 nm, and this wavelength was therefore used to perform the kinetic measurements whose results are described below.

Rate Profile. Rates of isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid were determined in dilute aqueous

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[7] Hacker, N. P.; Turro, N. J. *Tetrahedron Lett.* **1982**, *23*, 1771–1774.

[8] Berson, J. A.; Aspelin, G. B. *Tetrahedron* **1864**, *20*, 2697–2700.

[9] Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000–4009.

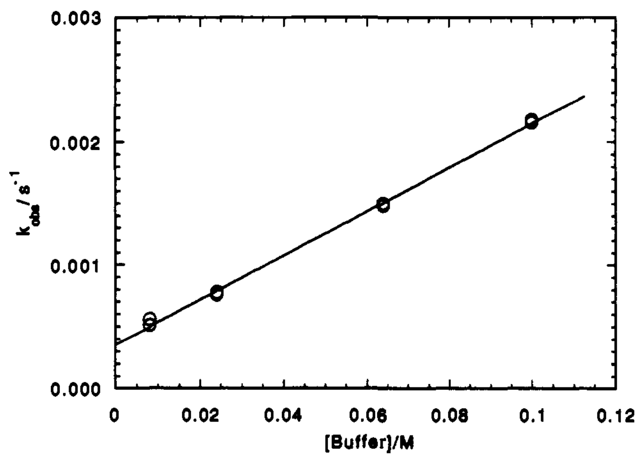


Figure 2. Rates of isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid in aqueous acetic acid buffer solutions, buffer ratio = 1.00, at 25 °C.

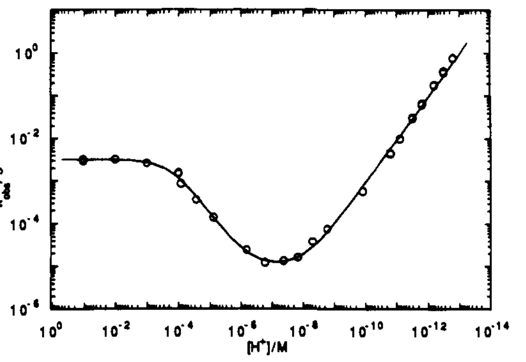


Figure 3. Rate profile for the isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid in aqueous solution at 25 °C.

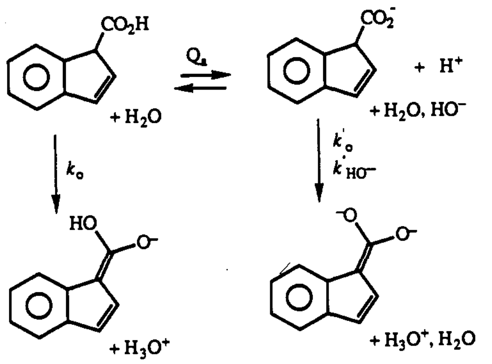
solutions of perchloric acid and sodium hydroxide and in acetic acid, biphosphate ion, hydrogen *tert*-butylphosphonate ion, and bicarbonate ion buffers. The concentrations of perchloric acid, sodium hydroxide, and the buffers were varied over appropriate ranges, and replicate determinations (usually three) were made at each concentration. The ionic strength of the reaction solutions was maintained at μ = 0.10 M through the addition of sodium perchlorate, as required. The data obtained are summarized to Tables S1–S3.[10]

The isomerization reaction proved to be strongly catalyzed by all of the buffers examined. Measurements were consequently performed in series of solutions of varying buffer concentration but constant buffer ratio, which at the constant ionic strength employed, served to hold hydrogen ion concentrations constant along a buffer series. As Figure 2 illustrates, observed first-order rate constants determined under these conditions proved to be accurately proportional to buffer concentration in a given buffer series, and buffer-independent rate constants, k_u, were obtained by least-squares fitting to eq 2.

$$k_{obs} = k_u + k_{cat}[\text{buffer}] \tag{2}$$

These buffer-independent rate constants, together with observed rate constants determined in perchloric acid and sodium hydroxide solutions, are shown as the rate profile of Figure 3. Hydrogen ion concentrations of the buffer solutions needed for this purpose were obtained by calculation using pK_a values of the buffer acids from the literature and activity coefficients recommended by Bates.[11]

This rate profile shows two horizontal regions where the rate is independent of the acidity of the medium, one above [H$^+$] = *ca.* 0.01 M and another, somewhat shorter, about [H$^+$] = 10^{-7} M; there is also an area of apparent acid catalysis connecting these horizontal regions and an area of base catalysis at [H$^+$] below *ca.* 10^{-8} M. These features can be accommodated by a reaction scheme, shown as eq 3, in which isomerization occurs through base-catalyzed enolization of either carboxylic acid or carboxylate forms of indene-1-carboxylic acid, with either water or hydroxide ion serving as the base that removes a proton from the α-position of the substrate; this is followed by reprotonation of the enolate ion intermediate on γ-carbon to give the isomerized product. The apparent acid catalysis seen from [H$^+$] = *ca.* 10^{-4}–10^{-6} M then represents conversion of the carboxylate ion to the more reactive carboxylic acid in a region where carboxylate is the predominant form of the substrate. The greater reactivity of carboxylic acid over carboxylate ion is consistent with the fact that base-catalyzed enolization puts a negative charge on the substrate, and this will be less favorable in the case of the already negatively charged carboxylate ion.



(3)

The rate law that corresponds to this reaction scheme is shown as eq 4.[12]

$$k_{obs},k_u = (k_0[H^+] + k'_0Q_a + k'_{HO^-}Q_a[HO^-])/([H^+] + Q_a) \tag{4}$$

Nonlinear least-squares fitting of the data to this expression produced the following results: $k_0 = (3.13 \pm 0.20) \times 10^{-3}$ s^{-1}, $k'_0 = (1.01 \pm 0.14) \times 10^{-6}$ s^{-1}, $k'_{HO^-} = 5.77 \pm 0.21$ M^{-1} s^{-1}, and $Q_a = (1.79 \pm 0.24) \times 10^{-4}$ M. The line shown in Figure 3 was drawn using these parameters; it may be seen that they reproduce the data well.

The parameter Q_a is the concentration dissociation constant of the substrate, indene-1-carboxylic acid, at the ionic strength of the kinetic measurements, μ = 0.10 M. The result obtained may be converted into a thermodynamic acidity constant by applying appropriate activity coefficients. Use of the value for H$^+$ recommended by Bates,[11] together with his value for benzoate ion[11] as a surrogate for the indene-1-carboxylate ion, gives pK_a = 3.92 ± 0.06, which is in remarkably good agreement with pK_a = 3.93 predicted for indene-1-carboxylic acid by a Hammett σ–ρ correlation for carboxylic acids.[13]

Buffer Catalysis. Use of eq 2 to obtain buffer-independent rate constants for the construction of a rate profile also produced buffer catalytic coefficients, k_{cat}. They were partitioned into contributions from the acidic and basic components of the buffers according to eq 5

$$k_{cat} = k'_B + (k'_{HA} - k'_B)f_A \tag{5}$$

in which k'_B and k'_{HA} are general base and general acid catalytic coefficients, respectively, and f_A is the fraction of buffer present in the acidic form.

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(10) Supplementary material: see paragraph at the end of this paper regarding availability.

(11) Bates, R. G. *Determination of pH. Theory and Practise*; Wiley: New York, 1973; p 49.

(12) Loudon, G. M. *J. Chem. Ed.* **1991**, *68*, 978–984.

(13) Perrin, D. D.; Boyd, D.; Serjeant, E. P. *pK_a Predictions for Organic Acids and Bases*; Chapman and Hall: New York, 1981; p 127.

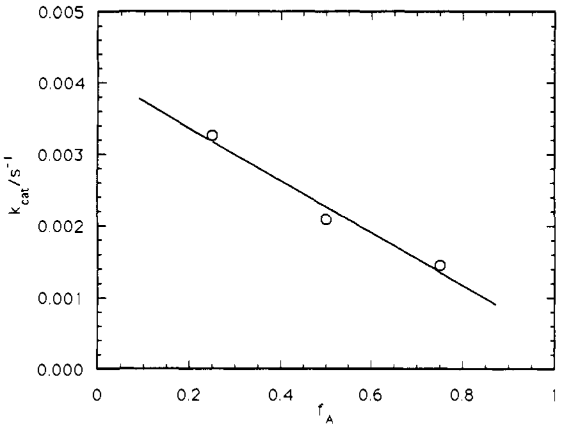
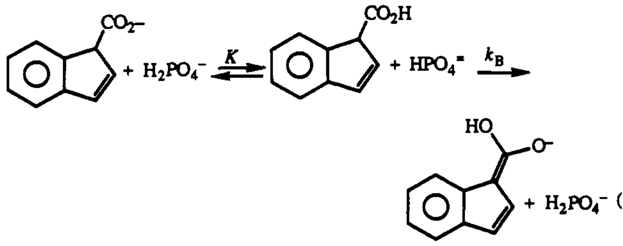


Figure 4. Analysis of buffer catalysis of the isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid in aqueous hydrogen *tert*-butylphosphonate ion buffers at 25 °C.

Figure 4 illustrates the application of this method to isomerization in hydrogen *tert*-butylphosphonate ion buffers. Least-squares fitting gave the results $k'_B = (4.08 \pm 0.33) \times 10^{-3}$ M^{-1} s^{-1} and $k'_{HA} = (4.57 \pm 3.31) \times 10^{-4}$ M^{-1} s^{-1}, which show the buffer catalysis in these solutions to be essentially completely of the general base type with no significant contribution from general acid catalysis. This is in keeping with the rate profile of Figure 3, as interpreted by the reaction scheme of eq 3, which shows only base catalysis in the region of acidity of these buffer solutions, $[H^+] = 10^{-8}$–10^{-9} M.

Similar analysis of the data for isomerization in biphosphate ion buffers, on the other hand, gave comparable contributions from general base catalysis, $k'_B = (3.56 \pm 0.06) \times 10^{-3}$ M^{-1} s^{-1}, and general acid catalysis, $k'_{HA} = (4.06 \pm 0.06) \times 10^{-3}$ M^{-1} s^{-1}. This again is consistent with expectation, for these buffers had $[H^+] = 10^{-6}$–10^{-7} M, which the rate profile shows to be the region of the transition from base catalysis to apparent acid catalysis.

This general acid catalysis in biphosphate buffers may be attributed, just as was the apparent acid catalysis of the rate profile, to conversion of the indene-1-carboxylate ion to the more reactive indene-1-carboxylic acid followed by α-proton removal by general base, eq 6. This corresponds to specific hydrogen ion



(6)

catalysis followed by general base catalysis, which is operationally equivalent to general acid catalysis. The rate law that applies to this situation is shown as eq 7,

$$k'_{HA} = Kk_B \tag{7}$$

and, since K is equal to the ratio of acidity constants of $H_2PO_4^-$ and indene-1-carboxylic acid, both of which are known (the latter from analysis of the rate profile), k'_{HA} may be converted into k_B. The results is $k_B = 4.38 \pm 0.59$ M^{-1} s^{-1}.

Application of this treatment to buffer catalysis in acetic acid buffers required allowance for the fact that not all of the substrate was in the carboxylate form in these solutions, but rather some (5–30%) remained as undissociated indene-1-carboxylic acid. This was done by adjusting observed values of k_{cat} up to what they would be in the presence of completely ionized substrate through division by the fraction of substrate ionized: $k_{adj} = k_{cat}/Q_a/([H^+] + Q_a)$. Use of eq 5 with k_{adj} replacing k_{cat} then gave $k'_B = -(1.16 \pm 0.45) \times 10^{-3}$ M^{-1} s^{-1} and $k'_{HA} = (4.37 \pm 0.05) \times 10^{-2}$ M^{-1} s^{-1}. These results show general base catalysis of isomerization through enolization of the carboxylate ion to be absent in these solutions, which again is consistent with the fact that their acidity, $[H^+] = 10^{-1}$–10^{-5} M, lies in the region of the rate profile showing only apparent acid catalysis. Conversion of k'_{HA} into the catalytic constant for reaction of the carboxylic acid form of the substrate using eq 7 then gives $k_B = (2.88 \pm 0.39) \times 10^{-1}$ M^{-1} s^{-1}.

Table 1. Summary of Rate Constants for Base-Catalyzed Isomerization of Indene-1-carboxylic Acid to Indene-3-carboxylic Acid in Aqueous Solution at 25 °C[a]

base	pK_a(BH)	k_B,[b] M^{-1} s^{-1}	k'_B,[c] M^{-1} s^{-1}
HO^-	15.74		5.77
CO_3^{2-}	10.33		0.0152
t-$BuPO_3^{2-}$	8.71		0.00408
HPO_4^{2-}	7.20	4.38	0.00356
OAc^-	4.76	0.288	
H_2O	−1.74	0.00313[d]	0.0000101[d]

[a] Ionic strength = 0.10 M ($NaClO_4$). [b] Reaction of indene-1-carboxylic acid. [c] Reaction of indene-1-carboxylate ion. [d] Units are s^{-1}.

This treatment could not be applied to catalysis in bicarbonate buffers because rate measurements there were made at only one buffer ratio. The acidity of these buffers, however, was very low, $[H^+] = 10^{-10}$ M, and, in view of the fact that general acid catalysis was found to be hardly significant in the more acidic hydrogen *tert*-butylphosphonate ion buffers $(H^+] = 10^{-8}$–10^{-9} M), it seems safe to assume that general acid catalysis was absent in these bicarbonate buffers. The whole of k_{cat} may then be assigned to general base catalysis of isomerization through enolization of indene-1-carboxylate ion, with $k'_B = (1.52 \pm 0.28) \times 10^{-2}$ M^{-1} s^{-1}.

The rate constants for buffer catalysis obtained by this analysis are summarized in Table 1. It may be seen that they form a sensible pattern showing increasing reactivity with increasing basic strength of the catalyst, as expected for general base catalyzed reactions. These rate constants also show indene-1-carboxylate ion to be about three orders of magnitude less reactive than indene-1-carboxylic acid, which again is consistent with the carbanion-forming nature of this reaction and the increased difficulty of putting a negative charge onto a substrate that is already negatively charged.

These observations of general base catalysis in the isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid require a reaction mechanism in which proton transfer is taking place in the rate-determining step. This, of course, is what is happening in the scheme of eq 3, and these observations thus provide additional support for that scheme.

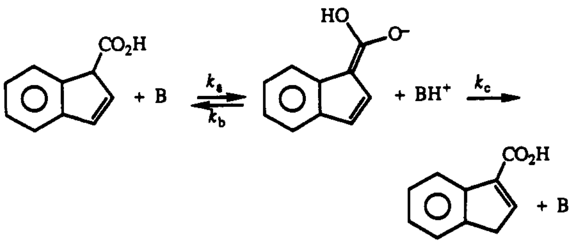
Isotope Effects. Still further support for a reaction mechanism involving rate-determining proton transfer was obtained from kinetic isotope effects. Simple substrate isotope effects comparing normal and deuterated indene-1-carboxylic acid in the same solvent could not be readily obtained because isomerization of the deuterated substrate in H_2O or the undeuterated substrate in D_2O did not follow first-order kinetics. Isomerization of the deuterated substrate in H_2O produced deviations from first-order behavior in the form of too slow a change at the beginning of the reaction and too fast a change at the end. This suggests that isomerization was being accompanied by isotope exchange which converted a more slowly reacting deuterated substrate into a more rapidly reacting protio substrate. This supposition was confirmed by the behavior of the undeuterated substrate in D_2O which gave deviations in the opposite directions suggesting that now a more rapidly reacting protio substrate was being converted into a more slowly reacting deuterated substrate.

These deviations from first-order behavior in themselves substantiate the reaction mechanism of eq 3. This follows from the fact that the product studies of the photolysis of diazonaphotoquinone **1**, described below, show that the enol intermediate ketonizes to form both indenecarboxylic acids. Some of the enol formed in the scheme of eq 4 will consequently revert to indene-1-carboxylic acid, and that reformed substrate will have incorporated in it hydrogen from the solvent, thus effecting isotope exchange if the hydrogen isotope initially in the substrate is different from that in the solvent. It is significant that these deviations from first-order bvehavior occurred earlier in the course of the reaction under acidic conditions than under basic conditions, for the product studies show more indene-1-carboxylic acid is formed from the enol in acid solutions than in basic solutions.

The isomerization of deuterated indene-1-carboxylic acid in D_2O solution, on the other hand, did conform to first-order kinetics, and kinetic isotope effects could be obtained by comparing these reactions with those of the protio substrate in H_2O. Rates of isomerization of the deuterated substrate in D_2O were consequently measured under two sets of conditions: in hydrochloric acid solutions with [DCl] = 0.01 and 0.1 M, which corresponds to the first horizontal portion of the rate profile of Figure 3, and in sodium hydroxide solutions with [NaOD] = 0.003–0.08 M, which corresponds to the upper region of base catalysis of the profile. These data are summarized in Tables S4 and S5.[10] Comparison of these results with the corresponding rate constants for isomerization of the protio substrate in H_2O gives the isotope effect $k_H/k_D = 9.52 \pm 0.13$ for acid solutions and $k_H/k_D = 4.37 \pm 0.23$ for basic solutions.

Both of these isotope effects are of substantial magnitude, and they consequently imply that the isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid involves rate-determining cleavage of the isotopically substituted bond. This, of course, is implied by the reaction mechanism of eq 3, and these isotope effects therefore provide strong support for that reaction scheme.

This reaction scheme requires these isotope effects to be composite rate ratios consisting of several single-step rate constants for the two-step enolization–ketonization process, eq 8. The rate law for this process, given as eq 9, leads to eq 10, which shows



(8)

$$k_{obs} = k_a/(1 + k_b/k_c) \tag{9}$$

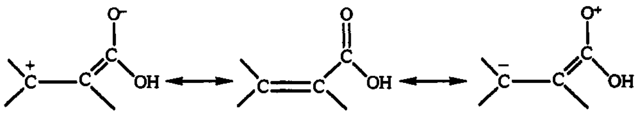
$$\frac{k_{obs}{}^{H}}{k_{obs}{}^{D}} = \frac{k_a{}^{H}}{k_a{}^{D}} \times \frac{1 + k_b{}^{D}/k_c{}^{D}}{1 + k_b{}^{H}/k_c{}^{H}} \tag{10}$$

that isotope effects on observed rate constants are products of isotope effects on the first, hydrogen-removal step, $k_a{}^H/k_a{}^D$, and terms involving rate constants for partitioning of the reaction intermediate in the forward and reverse dirction, k_b/k_c. The product studies of the photolysis of diazonaphthoquinone **1** (*vide infra*) indicate that in basic solution the intermediate partitions mainly to indene-3-carboxylic acid and the ratio k_b/k_c is small, 0.05. Acidic solutions give a more substantial partitioning ratio, $k_b/k_c = 2.2$, but its value is unlikely to be affected much by isotopic substitution, and $k_b{}^H/k_c{}^H$ will consequently be similar to $k_b{}^D/k_c{}^D$. It would appear reasonable to assume, therefore, that the second fraction on the right in eq 10 makes little contribution to $k_{obs}{}^H/k_{obs}{}^D$ and that the latter provides a reasonable estimate of the isotope effect on the proton removal step $k_a{}^H/k_a{}^D$.

Since observed isotope effects were determined by making isotopic substitution in the solvent as well as in the substrate, they consist of secondary (solvent) effects in addition to primary effects on substrate carbon–hydrogen bond breaking. In acid solution the proton acceptor is a water molecule, and the secondary effect here stems from conversion of this molecule into a hydronium ion; this is a bond-loosening process that will give a secondary isotope effect in the normal direction ($k_H/k_D > 1$).[14] In basic solution, on the other hand, the proton acceptor is a hydroxide ion and the secondary effect stems from conversion of this ion into a water molecule; this is a bond-tightening process that will give an inverse ($k_H/k_D < 1$) secondary effect.[14] It is difficult to estimate the magnitude of these secondary effects, but $k_H/k_D = 1.5$ for the acid and $k_H/k_D = 1/1.5$ for the basic solutions might not be unreasonable values.[14] This then leads to primary effects slightly greater than $k_H/k_D = 6$ for both acid and basic solutions. These effects are clearly large enough to leave no doubt that carbon–hydrogen bond breaking is taking place in the rate determining step of the indene-1-carboxylic acid to indene-3-carboxylic acid isomerization reaction.

Equilibrium. The relative amounts of indene-1-carboxylic acid and indene-3-carboxylic acid present at equilibrium in aqueous solution were determined under both acidic and basic conditions. Four separate measurements made in 0.01 M perchloric acid gave the average equilibrium constant K_{isom} = [indene-3-carboxylic acid]/[indene-1-carboxylic acid] = 220 ± 30, and two measurements made in 0.01 M sodium hydroxide gave $K_{isom} = 97 \pm 20$. These results are consistent with a previous study conducted in pyridine solution in which no indene-1-carboxylic acid could be detected at equilibrium, and its amount was consequently estimated at 1% or less.[5]

The preponderance of indene-3-carboxylic acid at equilibrium is consistent with the fact that in this isomer the carboxylic acid group is conjugated with a carbon–carbon double bond, whereas in the 1-isomer it is not. This conjugative stabilization is likely to be of the type in which carboxyl is an electron acceptor, **5**,



5 **6**

rather than an electron donor, **6**, because oxygen is more electronegative than carbon. The stabilization should then be stronger for an un-ionized carboxylic acid group than for a carboxylate ion, because conjugation in the latter case puts a negative charge on an already negatively charged substituent, and that is consistent with the fact that the equilibrium lies further on the side of the 3-isomer in acidic than in basic solution.

Photolysis Product Ratios. The relative amounts of indene-1-carboxylic acid and indene-3-carboxylic acid formed immediately upon photolysis of diazonaphthoquinone **1** were obtained by determining the ratio of products before isomerization of the acids could take place. Replicate measurements were made in aqueous solution under three different conditions of acidity. The results gave the ratios *R* = [indene-3-carboxylic acid]/[indene-1-carboxylic acid] = 0.47 ± 0.03 in 0.001 M perchloric acid, $R = 1.6 \pm 0.5$ in biphosphate buffer at $[H^+] = 2 \times 10^{-7}$ M, and $R = 20 \pm 4$ in bicarbonate buffers at $[H^+] = 1 \times 10^{-10}$ M. These determinations show that indene-1-carboxylic acid is the principal product formed in acidic solution and that a significant amount of this acid is formed even in base. The failure of previous investigations to detect this product must be due to its ready isomerization to the considerably more stable indene-3-carboxylic acid.

The predominant formation of indene-1-carboxylic acid in acid solution is consistent with the fact that ketonization under these

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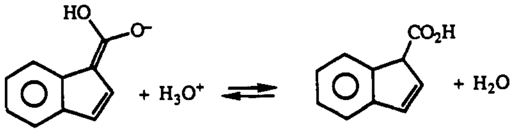
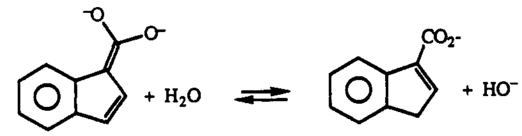
[14] Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. in *Isotopes in Organic Chemistry*; Buncel, E.; Lee, C. C., Eds.; Elsevier: New York; 1987; Vol. 7, Chapter 4.

conditions occurs through protonation of the enolate monoanion by hydronium ion, eq 11. This follows from the present identification of un-ionized carboxylic acid and water as the reaction partners for the enolization of indene-1-carboxylic acid in acid solution, and the requirement that ketonization be the microscopic reverse of enolization. Electrostatic attraction between the oppositely charged enolate and hydronium ions will then lead to preferential protonation at the α-position and a predominant formation of indene-1-carboxylic acid. In basic solution, on the other hand, the proton acceptor for reaction in the enolization direction is hydroxide ion and the proton donor for enolization is consequently water, eq 12. Electrostatic repulsion between the enolate dianion and the partial negative charge forming on the water-molecule proton donor, on its way to becoming a hydroxide ion in the transition state of the ketonization reaction, will direct protonation to the γ-position and lead to preferential formation of indene-3-carboxylic acid.

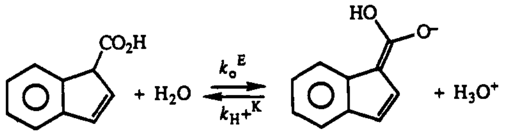


(11)



(12)

Carbon Acid Acidity. Identification of the reaction mechanism for isomerization of indene-1-carboxylic acid to indene-3-carboxylic acid as the enolization–reketonization scheme of eq 3 presents the opportunity of determining the equilibrium constants for ionization of these substances as carbon acids, as illustrated in eq 13 for the 1-acid. These equilibrium constants, K_a^K, which represents ionization of the keto tautomer, are equal to the ratio of enolization to ketonization rate constants: $K_a^K = k_0^E/k_{H^+}^K$. The enolization rate constant k_0^E is available from the presently determined rates of isomerization. In order to evaluate K_a^K, we have determined the requisite ketonization rate constant, $k_{H^+}^K$, by measuring rates of ketonization of enol generated through photolysis of diazonaphthoquinone **1**.



(13)

Nanosecond flash photolysis of this diazonaphthoquinone gave an immediate increase in absorbance at λ = 330 nm, followed by a slower rise and subsequent decay that took place on a microsecond time scale. In accord with recent definitive studies,[2b,15] we attribute these absorbance changes to the series of reaction shown in eq 1, *i.e.*, formation of the ketene **2**, its hydration to the enol **3**, and ketonization of that to indenecarboxylic acids. The lifetime of the ketene in H_2O with no acid or base added was $\tau = 0.9\ \mu s$, the solvent isotope effect on its hydration was k_{H_2O}/k_{D_2O} = 1.4, and the hydration was catalyzed by hydroxide ion with $k_{HO^-} = 4.6 \times 10^7\ M^{-1}\ s^{-1}$; these parameters are typical of ketenes derived from diazonaphthoquinones,[2b] and the lifetime in H_2O and the hydroxide ion catalytic coefficient are consistent with other determinations of these quantities for this ketene: $\tau = 0.9\ \mu s$ and $k_{HO^-} = 3.8 \times 10^7\ M^{-1}\ s^{-1}$.[15b]

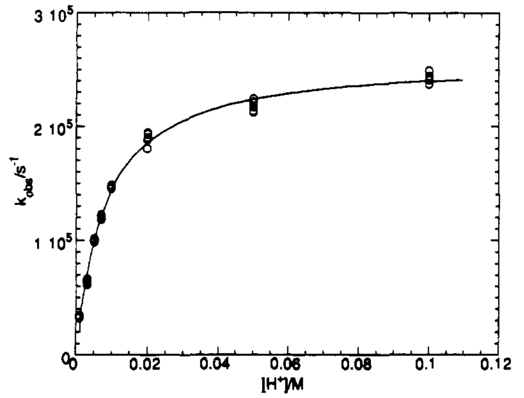
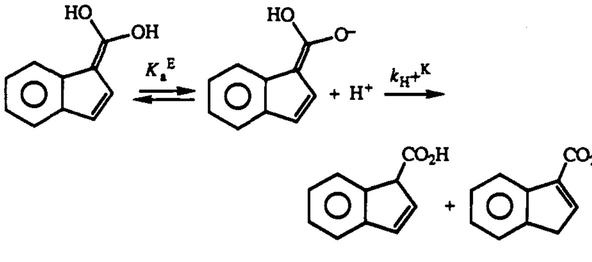


Figure 5. Relationship between perchloric acid concentration and rates of ketonization of indenecarboxylic acid enol in aqueous solution at 25 °C.

Rates of ketonization of enol **3** were measured in aqueous perchloric acid solutions over the concentration range [$HClO_4$] = 0.001–0.1 M at constant ionic strength (0.10 M). The data are summarized in Table S6[10] and are displayed in Figure 5. The relationship between observed first-order rate constants of ketonization and acid concentration shown by this figure is typical of enols of indenecarboxylic acids.[2b,15b] It has been interpreted in terms of the reaction scheme of eq 14. Ketonization takes place through carbon protonation of the enolate ion, and, at low acidities with $[H^+] < K_a^E$ and enolate ion as the predominant enol species, this leads to hydrogen ion catalysis; at higher acidities, however, the enolate ion is converted to the much less reactive un-ionized enol, and acid catalysis becomes saturated. The rate law that applies to this situation is shown in eq 15,

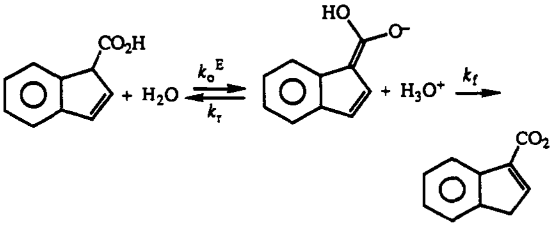


(14)

$$k_{obs} = k_{H^+}^K K_a^E [H^+]/(K_a^E + [H^+]) \qquad (15)$$

and least-squares fitting of the data to this expression gave $k_{H^+}^K = (3.21 \pm 0.07) \times 10^7\ M^{-1}\ s^{-1}$ and $K_a^E = (8.07 \pm 0.22) \times 10^{-3}$ M, $pK_a^E = 2.09 \pm 0.01$.[16] The line shown in Figure 5 was drawn using these parameters; it may be seen that they represent the experimental results well. The values of $k_{H^+}^K$ and pK_a^E obtained are typical of enols of indenecarboxylic acids[2b] and are consistent with other determinations of these quantities for the present enol: $k_{H^+}^K = 2.2 \times 10^7\ M^{-1}\ s^{-1}$ and $pK_a^E = 1.90$.[15b]

When enolate ion is formed from indene-1-carboxylic acid in the isomerization reaction, only part of it goes on to isomerized product: some enolate reverts to starting material, eq 16. The rate constant for enolization, k^E_0, is therefore not simply equal



(16)

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[15] (a) Urwyler, B.; Wirz, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 790–792. Barra, M.; Fisher, T. A.; Cernigliaro, G. J.; Santa, R.; Scaiano, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 2630–2634. (b) Almstead, J.-I.; Urwyler, B.; Wirz, J., preceding paper in this issue.

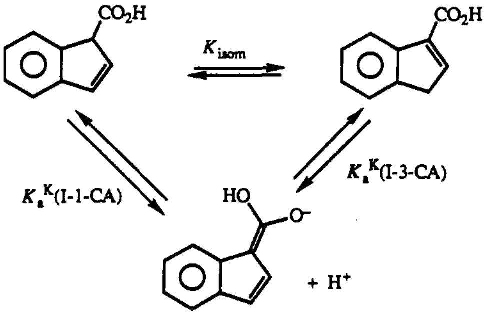
[16] This is a concentration equilibrium constant that applies at the ionic strength (0.10 M) of the present determinations.

to that for isomerization, but rather the two are related through the ratio of rate constants for reverse to forward partitioning of the enolate ion, as shown in eq 17.

$$k_{\text{isom}} = k_0^{\text{E}}/(1 + k_r/k_f) \tag{17}$$

This partitioning ratio is known from our determination of *R*, the ratio of indene-3-carboxylic acid to indene-1-carboxylic acid present in a photolysis reaction mixture before isomerization has had a change to take place: $R = 0.47 = k_f/k_r$. Combination of this with the rate constant for isomerization then gives $k_0^{\text{E}} = (9.80 \pm 0.76) \times 10^{-3}\ \text{M}^{-1}\,\text{s}^{-1}$, and that together with $k_{\text{H}^+}{}^{\text{K}}$, modified by the fraction of enolate that ketonizes to indene-1-carboxylic acid (0.68), then leads to K_a^{K} (I-1-CA) = $(4.48 \pm 0.39) \times 10^{-10}$ M, $\text{p}K_a^{\text{K}}$(I-1-CA) = 9.35 ± 0.04.[16]

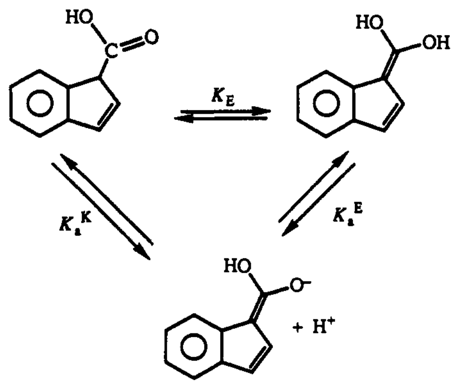
This result refers to indene-1-carboxylic acid ionizing to its enolate anion. Since the same anion is produced by the ionization of indene-3-carboxylic acid, eq 18, this acidity constant may be converted to that for indene-3-carboxylic acid by applying the equilibrium constant for the isomerization reaction: K_a^{K}(I-3-CA) = K_a^{K}(I-1-CA)/K_{isom}. The result is K_a^{K}(I-3-CA) = (2.04 ± 0.33) × 10^{-12} M, $\text{p}K_a^{\text{K}}$(I-3-CA) = 11.69 ± 0.07.



(18)

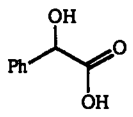
These acidity constants show indenecarboxylic acids to be unusually strong carbon acids: the values obtained here are some 20 pK units more acidic than the $\text{p}K_a$ of phenylacetic acid in a hexamethylphosphoramide-tetrahydrofuran solvent.[17] This remarkable increase in acid strength attests to the ability of the cyclopentadiene moiety of indenecarboxylic acids to stabilize the negative charge generated when these substances ionize as carbon acids, as is aptly illustrated by the unusual carbon acidity of cyclopentadiene itself: $\text{p}K_a$ = 16.[18]

Keto–Enol Equilibria. These acidity constants for indene-1-carboxylic acid and indene-3-carboxylic acid ionizing as carbon acids are related to keto–enol equilibrium constants connecting the carboxylic acid (keto) and enol isomers of these substances, K_{E}, through the acid ionization constant of the enol, K_a^{E}, as illustrated in the thermodynamic cycle of eq 19. Since K_a^{E} has been determined by our ketonization rate measurements in acid solution, K_{E} may be calculated using the relationship $K_{\text{E}} = K_a^{\text{K}}/K_a^{\text{E}}$. The results are K_{E}(I-1-CA) = (5.55 ± 0.50)10^{-8}, $\text{p}K_{\text{E}}$(I-1-CA) = 7.26 ± 0.04 and K_{E}(I-3-CA) = (2.53 ± 0.41) × 10^{-10}, $\text{p}K_{\text{E}}$ (I-3-CA) = 9.60 ± 0.07. The latter value agrees well with another determination of this quantity by a different method; $\text{p}K_{\text{E}}$ (I-3-CA) = 9.3 ± 0.3.[15b]



(19)

These keto–enol equilibrium constants are unusually large for carboxylic acid systems, where the presence of a hydroxyl group next to the carbonyl function lowers the energy of the keto (carboxylic acid) isomer and makes K_{E} much smaller than it would otherwise be. For example, $\text{p}K_{\text{E}}$ = 15.4 for mandelic acid,[19] **7**, whereas $\text{p}K_{\text{E}}$ = 2.9 for phenylacetaldehyde, **8**,[20] and $\text{p}K_{\text{E}}$ = 21



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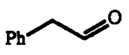

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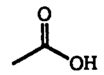

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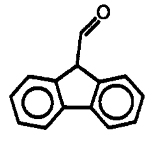

11

has been estimated for acetic acid,[21] **9**, whereas $\text{p}K_{\text{E}}$ = 6.2 for acetaldehyde.[9] This remarkable increase in enol content in indencarboxylic acids may also be attributed to their cyclopentadiene moiety and the consequent fulvenoid structure of the enol; the effect is seen as well in the keto–enol equilibrium of 9-formylfluorene, **11**, which, at $\text{p}K_{\text{E}} = -1.2$,[22] represents an enol content 7 pK units greater than that of acetaldehyde.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada, the Petroleum Research Fund administered by the American Chemical Society, and the U.S. National Institutes of Health for financial support of his research.

Supplementary Material Available: Tables S1–S5 of kinetic data (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(17) Renaud, P.; Fox, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 5705–5709.

(18) Streitwieser, A., Jr.; Nebenzahl, L. L. *J. Am. Chem. Soc.* **1976**, *98*, 2188–2190.

(19) Chiang, Y.; Kresge, A. J.; Pruszynski, P.; Schepp, N. P.; Wirz, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 792–794.

(20) Chiang, Y.; Kresge, A. J.; Walsh, P. A.; Yin, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 869–871.

(21) Guthrie, J. P. *Can. J. Chem.* in press.

(22) Harcourt, M. P.; More O'Ferrall, *Bull. Chim. Soc. Fr.* **1988**, 407–414.