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Kinetics and Mechanism of Ionization of the Carbon Acids 4'-Substituted 2-Phenyl-1,3-indandiones

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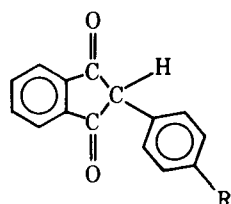
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Abstract □ The ionization kinetics of 1,3-diketone carbon acids are slow relative to those of classical acids and bases. The ionization kinetics of three 4'-substituted 2-phenyl-1,3-indandiones, 4'-chloro-, 4'-methoxy-, and 2-phenyl-1,3-indandione itself, were studied at 25° and ionic strength 0.1 using stopped-flow spectrometry and a pH jump technique. A log k'_{obs} -pH profile for the approach to the ionization equilibrium was consistent with a reaction scheme postulated earlier for the ionization of another carbon acid, phenylbutazone. The percent enol *versus* diketo form of the acids and the $pK_{a, enol}$ and $pK_{a, diketo}$ were calculated from the kinetic data. Hammett plots of the various kinetic and equilibrium constants supported a mechanism for acid deprotonation consistent with proton abstraction being the predominant process when very weak bases such as water were the proton acceptors. Desolvation effects and the work required to get the two reacting molecules together in the correct configurations predominated when the proton abstraction was by stronger proton acceptors.

Keyphrases □ Carbon acids—ionization kinetics, stopped-flow spectrophotometric and pH jump analysis □ Ionization kinetics—carbon acids, anisindione, phenindione, clorindione □ Anticoagulants—anisindione, phenindione, clorindione, ionization kinetics

The objective of this study was to compare the kinetics and ionization of the 1,3-diketone carbon acids anisindione (I), phenindione (II), and clorindione (III). All three compounds are used clinically as anticoagulants. The ionization kinetics of phenindione and phenylbutazone, two carbon acids of pharmaceutical interest, were reported previously (1, 2). Kinetic data for the deprotonation of various carbon acids have appeared in the chemical literature, but few studies of the effects of electron-withdrawing and electron-donating groups on the ionization kinetics and mechanism have been reported. The reported chemical studies have concerned acids of fairly high pK_a (3, 4) or substituted nitromethane carbon acids (3, 5-12).

The objectives of this work were to study the effects of electron-withdrawing and electron-donating substituents



on ionization kinetics of I-III and to determine whether the results supported a model proposed previously for phenindione ionization (1).

EXPERIMENTAL

Phenindione¹ and anisindione² were used as received. Clorindione was prepared by the reaction of phthalide and *p*-chlorobenzaldehyde in a sodium ethoxide-ethanol solution using a literature procedure (13) for the synthesis of various 2-phenyl-1,3-indandiones. All other materials, kinetic procedures, conditions, and methods of pK_a determination were identical to those described previously (1).

RESULTS AND DISCUSSION

The macroscopic dissociation constants for I-III, determined spectrophotometrically in aqueous solution at 25° and $\mu = 0.1$, are given in Table I. These values compare favorably with the literature values for the pK_a 's when solvent differences are considered.

Figure 1 is a plot of $\log k'_{obs}$ versus pH for the approach to ionization equilibrium for I-III. The rate constant k'_{obs} is the pseudo-first-order observed rate constant for the approach to ionization equilibrium extrapolated to zero buffer concentration. A possible model for the ionization kinetics of I-III is given in Scheme I. This model is identical to the scheme postulated previously for phenylbutazone ionization (2).

The predominant neutral form of I-III in aqueous solution is the diketo species, K, rather than the enol species, E (14). The dissociated form of I-III is the so-called mesomeric anion, E⁻ (17). The macroscopic dissociation constant K_a , the percent enol, and k'_{obs} for the approach to ionization equilibrium in the absence of buffers are best described by Eqs. 1-3 (2):

$$\frac{1}{K_a} = \frac{1}{K_{a, enol}} + \frac{1}{K_{a, diketo}} \quad (\text{Eq. 1})$$

$$\% \text{ enol} = \frac{K_{a, diketo}}{K_{a, enol} + K_{a, diketo}} \left(\frac{100}{1} \right) \quad (\text{Eq. 2})$$

$$k'_{obs} = k_1 + k_3[\text{OH}^-] + \frac{k_2[\text{H}^+]K_{a, enol}}{K_{a, enol} + [\text{H}^+]} + \frac{k_4K_{a, enol}}{K_{a, enol} + [\text{H}^+]} \quad (\text{Eq. 3})$$

Table I—Macroscopic Ionization Constants for Anisindione, Phenindione, and Clorindione Determined Spectrophotometrically at 25 ± 0.1° and $\mu = 0.1$ with Sodium Chloride

Compound, Wavelength Used, nm	pK_a	Literature pK_a Values
Anisindione, 330	4.13	4.09 (14), 4.25 (15), 5.6 (16)
Phenindione, 326	4.09	4.10 (14), 4.13 (15), 5.4 (16)
Clorindione, 284	3.59	3.54 (14), 3.72 (15), 4.8 (16)

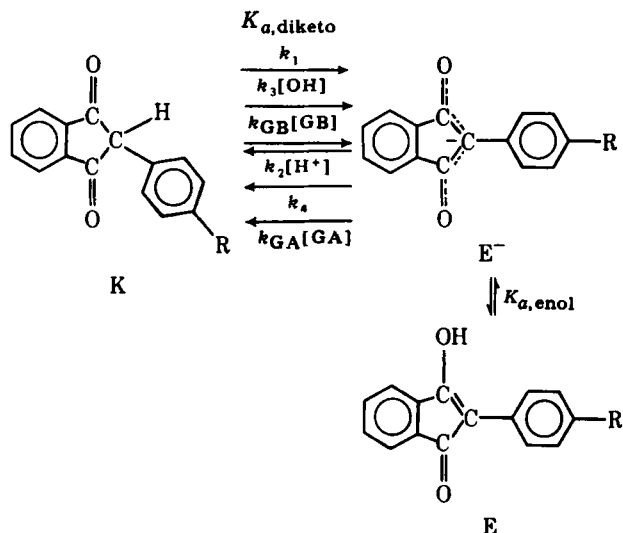
¹ Pfaltz and Bauer, Flushing, N.Y.

² Schering Corp., Bloomfield, N.J.

Table II—Kinetic and Equilibrium Constants for the Ionization of I–III at 25° and $\mu = 0.1$ with Sodium Chloride

Parameter	I	II	III	ρ^a
σ^b	-0.11	0	+0.23	
k_1, sec^{-1}	5	6.9	13	1.22
$k_2, M^{-1} \text{sec}^{-1}$	6.7×10^4	6.5×10^4	3.5×10^4	-0.88
$k_3, M^{-1} \text{sec}^{-1}$	10^6-10^7	10^6-10^7	10^6-10^7	— ^c
k_4, sec^{-1}	$10^{-3}-10^{-4}$	$10^{-3}-10^{-4}$	$10^{-3}-10^{-4}$	— ^c
$K_{a,\text{enol}}$	7.1×10^{-3}	4.2×10^{-3}	1.2×10^{-2}	1.77
$K_{a,\text{diketo}}$	7.5×10^{-5}	1.1×10^{-4}	3.7×10^{-4}	2.08
$\text{pK}_{a,\text{enol}}$	2.52	2.34	1.92	—
$\text{pK}_{a,\text{diketo}}$	4.12	3.96	3.43	—
$\text{pK}_{a,\text{calc}}$	4.14	3.97	3.44	—
$\text{pK}_{a,\text{exp}}$	4.13	4.09	3.59	—
% enol	2.4	2.6	3.0	—

^a The ρ value refers to the slope of $\log k$ versus σ for I–III and is a measure of the relative sensitivity of the parameter k to electron-donating and electron-withdrawing groups. ^b The σ value refers to the Hammett σ value for the various substituents, R. The σ values used were those for the ionization of phenols. G. B. Barlin and D. D. Perrin, *Q. Rev.*, 20, 75 (1966). ^c Because of the inaccuracy in the values of these two rate constants, Hammett σ plots were not attempted.



Scheme I

Treatment of the k_{obs} data as previously described (1) allows estimates of the constants $k_1, k_2, k_3, k_4, K_{a,\text{diketo}}$, and $K_{a,\text{enol}}$ as well as k_{GB} and k_{GA} for those buffers used in the study. Table II summarizes the calculated buffer-independent kinetic and equilibrium constants. The values for the constants placed into Eq. 3 were used to generate the solid lines in Fig. 1. Apparently, Eq. 3 and Scheme I adequately describe the observed values, although, as discussed previously (1, 2), alternative mechanisms and schemes may be possible. The pK_a values determined from the kinetic data compare favorably to those determined experimentally.

Unfortunately, little confidence can be placed on the k_3 values given in Table II since the pH range where the hydroxide-ion-catalyzed proton abstraction begins to be significant is also the region where stronger bases, buffers of high pK_a , must be used to control the pH. Normally the buffer concentration is varied while the pH is maintained constant and plots of k_{obs} versus buffer concentration are extrapolated to zero buffer concentration to obtain k_{obs} . The constant k_{GB} can be calculated from the slopes (1). With stronger bases like morpholine, the plots have such a large slope that intercept values become very inaccurate. The use of lower buffer concentrations is not possible because the desired final pH cannot be maintained. All k_3 values appear to be between 10^6 and $10^7 M^{-1} \text{sec}^{-1}$ for I–III. Similarly, the accuracy of the k_4 values, which are calculated from k_3 and $K_{a,\text{diketo}}$, is limited by the accuracy of the k_3 values.

Although Eq. 3 appears to describe adequately the protonation and deprotonation kinetics of I–III in the absence of acids and bases other than water, analysis of kinetic data in the presence of general acids (GA) and bases (GB) (buffer components) requires a more complex equation. The observed pseudo-first-order rate constant for the approach to ionization equilibrium at constant pH could be described by Eq. 4 (1):

$$k_{\text{obs}} = k'_{\text{obs}} + k_{\text{GB}}[\text{GB}] + k_{\text{GA}}[\text{GA}] \quad (\text{Eq. 4})$$

The constants k_{GA} and k_{GB} can be determined for various buffer

Table III—Values of k_{GB} for Various General Bases as well as Water and Hydroxide Ion for the Deprotonation at 25° and $\mu = 0.1$ for I–III

General Base (pKa')	$k_1, k_3,$ or $k_{\text{GB}}, M^{-1} \text{sec}^{-1}$			ρ^a
	I	II	III	
H ₂ O (-1.74)	9.0×10^{-2} ^b	1.24×10^{-1} ^b	2.34×10^{-1} ^b	1.22
Pyridine (5.28)	2.7×10^3	3.6×10^3	3.8×10^3	0.39
3-Methylpyridine (5.75)	4.6×10^3	5.2×10^3	7.1×10^3	0.56
4-Methoxypyridine (6.64)	5.7×10^3	6.5×10^3	1×10^4	0.73
Imidazole (7.10)	5.2×10^3	5.7×10^3	8.0×10^3	0.56
Morpholine (8.53)	5.0×10^4	4.8×10^4	7.6×10^4	0.59
OH ⁻ (15.74)	10^6-10^7	10^6-10^7	10^6-10^7	— ^c

^a The ρ values have the same meaning as that described in Table II. The σ values used for substituents R also were the same. ^b These numbers are equal to $k_1/55.5 = k_1$; i.e., k_1 is a pseudo-first-order rate constant that has to be corrected for the water concentration, 55.5 M, to convert it to the second-order rate constant k_1 . ^c Because of the k_3 inaccuracy, Hammett plots were not attempted.

species if the ionization kinetics of I–III are determined at various buffer concentrations and pH values (1). Table III is a compilation of some calculated k_{GB} values for all buffer and water species studied for I–III. The conjugate acids of these bases did not show any significant general acid catalysis.

The effects of various electron-donating or electron-withdrawing substituents on any kinetic or equilibrium constant are best quantitated by linear free energy relations such as the Hammett equation:

$$\log k/k_0 = \rho \sigma \quad (\text{Eq. 5})$$

Equation 5 assumes that a free energy difference in any rate or equilib-

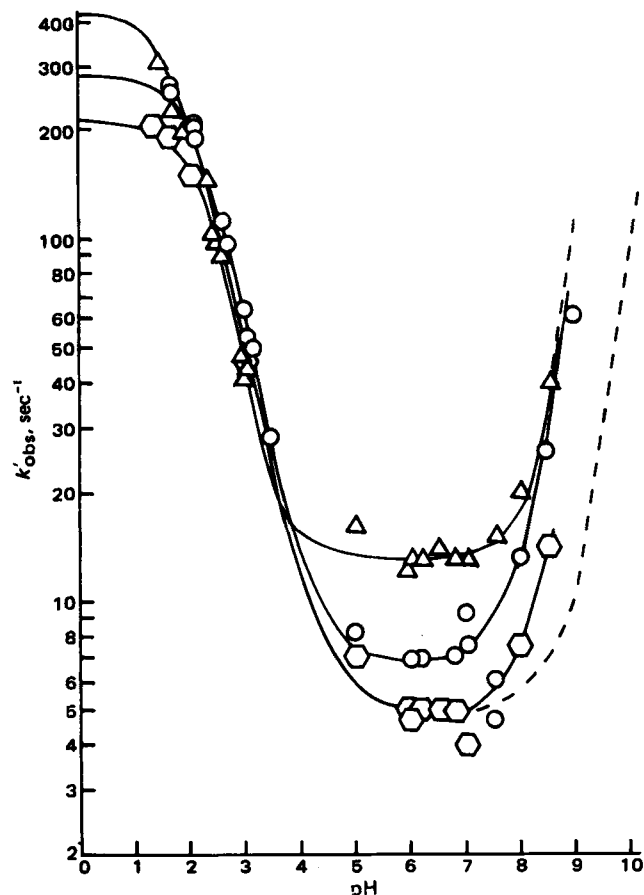


Figure 1—Log k'_{obs} versus pH for the establishment of the ionization equilibrium for anisindione (O), phenindione (□), and clorindione (Δ). The broken lines at pH > 7 represent k_3 having the limits of $10^6-10^7 M^{-1} \text{sec}^{-1}$. The lack of reproducibility of the data at pH > 8 precludes placing an accurate value on k_3 . The solid lines drawn at pH > 7–8 are simply the best eyeball fit.

rium process (given by $\log k/k_0$) between two compounds that differ only by a substituent is a linear function of some property of that substituent group. In Eq. 5, σ , the substituent constant, refers to the relative electron-donating (negative) or electron-withdrawing (positive) power of the substituent and ρ , the reaction constant, is a measure of the sensitivity of the constants, k , to changes in σ values of the substituents (18). The constant k_0 refers to the constant (rate or equilibrium constant) where the substituent is a hydrogen atom, *e.g.*, II.

In the present case, any proton abstraction reaction leading to a buildup of negative charge on the 2-position of the phenylindandiones will be stabilized by electron-withdrawing groups in the 4'-position (R), while electron-donating groups in the 4'-position will destabilize the transition state by increasing electron density at the 2-position. For example, k_1 of Scheme I refers to the pseudo-first-order rate constant for proton abstraction by the base, water. A plot of $\log k_1$ versus σ was linear with a slope, ρ , equal to 1.22. The reverse reaction, proton donation to the 2-position by hydronium ion, H_3O^+ , represented by k_2 gave a ρ value of -0.88 . This finding suggests that the R groups on the 4'-position of the phenylindandiones were having a greater effect on k_1 than on k_2 .

The effects of the substituents on $K_{a, \text{enol}}$ and $K_{a, \text{diketo}}$ are also interesting. The $K_{a, \text{diketo}}$ term describes the equilibrium acidity constant associated with proton abstraction from the 2-position of the phenylindandiones. It would be expected to be more sensitive to substituent effects than $K_{a, \text{enol}}$, which represents proton abstraction from the enol form of the phenylindandiones, because the enol proton is further removed from the substituent. The measured ρ values of 2.08 for $K_{a, \text{diketo}}$ versus 1.77 for $K_{a, \text{enol}}$ are consistent with this hypothesis.

In an earlier paper (1), it was hypothesized from Brønsted data that the deprotonation rate of phenindione (II) was determined largely by the free energy of the proton abstraction step when weak bases were the proton acceptors, while with the stronger bases the deprotonation was significantly affected by the work necessary to get the molecules into the correct configuration and solvation state for reaction. If this were the case, these effects should be seen in the ρ value of a Hammett plot. Table III lists the ρ values for proton abstraction by various bases. The rate constant for proton abstraction by a weak base like water ($pK_a' = -1.74$), $\rho = 1.22$, was more sensitive to substituent effects than the rate constants for proton abstraction by various other stronger bases, pyridine through morpholine ($pK_a' = 5.28-8.53$), $\rho = 0.39-0.74$. The rather small ρ values for this latter group suggest that a smaller negative charge was formed on the 2-carbon of the phenylindandiones in the rate-determining proton abstraction transition state, which supports the hypothesis that the work required to desolvate and bring the two reacting species together probably contributes significantly to the free energy of reaction.

Eigen (17) and others (19) have suggested that proton abstraction from strong carbon acids should be relatively insensitive to pK_a differences

between the carbon acids. The present study supports this hypothesis when the proton abstracting base is a relatively strong base, *i.e.*, ρ is small. However, if the proton abstracting base is very weak, *e.g.*, water, the proton abstraction step can be sensitive to the pK_a differences between the carbon acids; *i.e.*, substituent effects are significant, as measured by larger ρ values.

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