Kinetics of Proton Transfer Reactions in Aqueous Solution. Alkyl Structural Effect on CH Acids Systems[1]

Raymond Brouillard and Jacques-Emile Dubois*

Laboratoire de Chimie Organique Physique de l'Université Paris VII, associé au Centre National de la Recherche Scientifique, 1, rue Guy de la Brosse, 75005 Paris, France

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The position of the tautomeric keto–enol equilibrium in aqueous solution was studied for the compounds $CH_3COCHRCO_2C_2H_5$ (R = H, CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, i-C_3H_7, s-C_4H_9) by the T-jump relaxation technique under alkaline conditions of catalysis: $EH + OH^- \rightleftharpoons E^- + H_2O \rightleftharpoons CH + OH^-$. The kinetics is characterized by two relaxation times, one in the microsecond range, corresponding to the enol reactivity, and the other in the millisecond range, corresponding to the ketone reactivity. In all cases, the slow relaxation time has been measured. Only for R = H and a substituted compound presenting a similar enol structure (ethyl 2-hydroxycyclohexenecarboxylate) is there a sufficiently high enol content to allow the measurement of the fast relaxation time. Results show that the alkyl substituent effect on the enol content and the ketone acidity and deprotonation rate is large. The α-alkyl substituent effect on the enol form is often explained as being steric in nature. Although we do not completely reject this hypothesis, we present a number of arguments in favor of an electronic effect on the keto form.

Our knowledge of the keto–enol interconversion in aqueous media of β-keto esters bearing alkyl groups in the α position is particularly limited. These compounds ($CH_3COCHRCO_2C_2H_5$ series), which exist in both keto and enol forms, are weak acids dissociating according to the following scheme.

$$\text{Ketone (CH)} + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{Enolate } (E^-) + H_3O^+ \quad K_{CH} = k_1/k_2$$
$$\text{Enol (EH)} + H_2O \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \text{Enolate } (E^-) + H_3O^+ \quad K_{EH} = k_3/k_4 \qquad (1)$$

The overall change may be represented as follows.

$$\text{Ketone} \overset{K_T}{\rightleftharpoons} \text{Enol} \qquad K_T = \frac{[EH]}{[CH]} = K_{CH}/K_{EH} \qquad (2)$$

The equilibrium constant (K_T = 0.0039 at 20 ± 1°) for the first member of the series, R = H, was measured by Schwarzenbach and Felder.[2] In this case the keto–enol equilibrium strongly favors the keto form. By an indirect method these authors determined the acidity constants of this same compound at 20 ± 1°: pK_{CH} = 10.49 and pK_{EH} = 8.09. Their method, generally applicable to β-dicarbonyl compounds, allows a calculation of K_{EH} and K_{CH} from the overall acidity ($K_g = [E^-][H_3O^+]/[EH] + [CH]$) and the enol content, according to the following equations.

$$K_{CH} = K_g(1 + K_T) \cong K_g(\text{for } K_T \ll 1) \qquad (3)$$
$$K_{EH} = K_g(1 + 1/K_T) \qquad (4)$$

Rumpf and Reynaud,[3] identifying the overall acidity with that of the keto form, determined the K_{CH} acidity constants at ambient temperature for R = H, CH_3, C_2H_5, and n-C_4H_9. These values are given in the last column of Table I. They demonstrate an attenuation of the degree of ionization of the keto form as the chain length of R increases. Owing to experimental difficulties the authors were unable to measure the acidity constants for secondary R groups.

From the reactivity of enol toward bromine, Eidinoff[4] as well as Pearson and Mills[5] has measured k_1 for R = H and C_2H_5 (1.2×10^{-3} and 7.5×10^{-6} sec^{-1}, respectively). From determination of K_{CH}, these authors were able to calculate k_2 (5.8×10^7 and 3.8×10^7 M^{-1} sec^{-1}, respectively). These results show that the k_2 constant is not sensitive to the structural effect produced by replacing H by C_2H_5. On the other hand, the ionization constant (k_1) is considerably diminished by the same structural change.

Apart from their structures, the keto form belongs to the class of CH acids while the enol form belongs to that of acids possessing an intramolecular hydrogen bond. From observation of acid reactivity toward bases, Eigen[6] has shown that it is possible to classify the former either in terms of the two classes cited above or as normal acids. We may represent the acid–base transformation as follows.

$$AH + B \underset{k_r}{\overset{k_f}{\rightleftharpoons}} A^- + BH^+ \qquad (5)$$

When the equilibrium lies far to the right, it is possible to use the k_f value to classify acids according to these three categories (Figure 1). The order of magnitude of k_f for normal acids is 10^{10} M^{-1} sec^{-1}. This corresponds to the diffusion limit. For acids with an internal hydrogen bond, the ionization reaction is rendered more difficult by the fact that the proton is bound up in this bond. A measurement of k_f constitutes a kinetic means of evaluating the strength of the internal hydrogen bond. In certain cases (*e.g.*, the presence of electron-attracting groups in the vicinity of the acidic hydrogen) the reactivity of CH acids extends into the range of rapid reactions, but does not reach the diffusion limit. There are relatively few kinetic studies of CH acids by fast kinetics methods. However, this area is of great importance since it concerns carbanion formation, vital to organic synthesis.

A complete kinetic study of the keto–enol interconversion of β-dicarbonyls would be very difficult using classical methods but becomes possible using the fast kinetics methods (Figure 1); and this can be a good indirect method to derive in turn the K_T values not easily attainable by direct measurements. Such a study will be carried out on a series of β-keto esters $CH_3COCHRCO_2C_2H_5$ (where R = alkyl) so as to specify the influence of the alkyl groups on the degree of enolization in aqueous media, and to discuss the thermodynamic stabilities of the tautomeric forms.

Experimental Section

Solvent and Reagents. Rate and equilibrium constants have been determined in doubly distilled water. The salts used to adjust the ionic strength, NaBr and $NaClO_4$, were recrystallized, dried, and stored in a desiccator. The β-keto esters were purified by glpc (DEGS and XF 1150 columns) at very low injection temperatures, in order to avoid any decomposition. The final purity was checked by the same method and in every case was better than 99.5%.

Rate Constant Measurement. The stock solutions were pre-

Table I
Rate Constants for the Acid–Base Equilibrium of the Keto Form $CH_3COCHRCO_2C_2H_5$. Ketone Acidity

Init concn, M^{-1}	pH	τ_{32}, sec^{-1}	k_{32}, M^{-1} sec^{-1}	k_{23}, sec^{-1}	pK_{CH}
		I. $CH_3COCH_2CO_2C_2H_5$			
	12.01	87.5			
	12.02	80			
	11.92	67			
	11.82	64			
~4 ×	11.57	29.5			
10^{-5}	11.53	33.5	6.7 ×	3.0	10.65[a]
	11.36	18	10^3		10.49[b]
	11.36	16			10.68[c]
	11.33	16			10.81[d]
	10.52	5.5			10.90[e]
	10.00	4			10.64[f]
		II. $CH_3COCH(CH_3)CO_2C_2H_5$			
	12.92	12.8			
	12.83	10.5			
~1.4	12.72	9.1			
×	12.58	6.25	1.07 ×	1.8	12.25[a]
10^{-4}	12.52	5.6	10^2		12.59[e]
	12.26	4.2			12.42[f]
	11.96	3.0			
		III. $CH_3COCH(C_2H_5)CO_2C_2H_5$			
	13.06	11.1			
	12.97	9.5			
	12.90	8.35			
	12.78	5.9			
	12.74	7.1			
~1.3	12.70	4.65	6.4 ×	1.9	12.50[a]
×	12.53	4.3	10^1		12.93[e]
10^{-4}	12.27	3.5			12.87[f]
	12.16	2.2			13.01[f]
					12.74[g]
		IV. $CH_3COCH(n\text{-}C_3H_7)CO_2C_2H_5$			
	12.84	6.30			
	12.81	5.90			
	12.75	5.55			
~2.4	12.68	4.00			
×	12.56	3.30	5.3 ×	1.3	12.40[a]
10^{-4}	12.42	2.40	10^1		12.98[e]
	12.31	2.30			
	12.24	2.20			
	12.07	2.00			
		V. $CH_3COCH(n\text{-}C_4H_9)CO_2C_2H_5$			
	12.94	4.50			
	12.85	3.45			
~2.2	12.72	3.20			
×	12.65	2.90	3.1 ×	1.45	12.70[a]
10^{-4}	12.50	2.60	10^1		13.04[e]
	12.25	2.20			13.20[f]
	12.09	2.05			
		VI. $CH_3COCH(i\text{-}C_3H_7)CO_2C_2H_5$			
	13.08	12.3			
	12.84	9.35			
~1.7	12.71	9.8			
×	12.58	9.1			
10^{-3}	12.40	7.15	2.2 ×	8	13.5[a]
	12.23	8.0	10^1		13.24[e]
	12.06	8.35			>15[f]
		VII. $CH_3COCH(sec\text{-}C_4H_9)CO_2C_2H_5$			
	12.90	4.35			
~1.6	12.72	3.60			
×	12.50	3.10	1.95 ×	2.7	13.1[a]
10^{-3}	12.39	3.20	10^1		13.31[e]
	12.16	3.30			

[a] Our values. [b] See ref 2. [c] See ref 4. [d] W. Walisch and H. A. Ruppersberg, *Chem. Ber.*, **92**, 2622 (1959). [e] These values have been calculated from the equation $pK_{CH} = 12.59 - 3.44\sigma^*$; see ref 17. [f] See ref 3. [g] See ref 5.

pared by injecting, with a microsyringe, a small quantity of pure β-keto ester in an aqueous solution. The ionic strength was adjusted by using $NaClO_4$; 100 ml of each stock solution was prepared in a graduated flask in order to perform five to six kinetic runs.

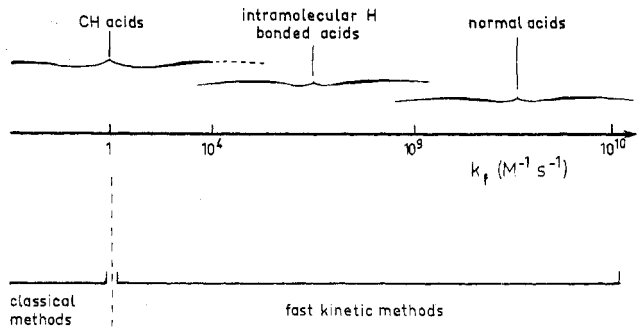


Figure 1. Types of acids according to their rates of ionization, k_f (OH^- as base).

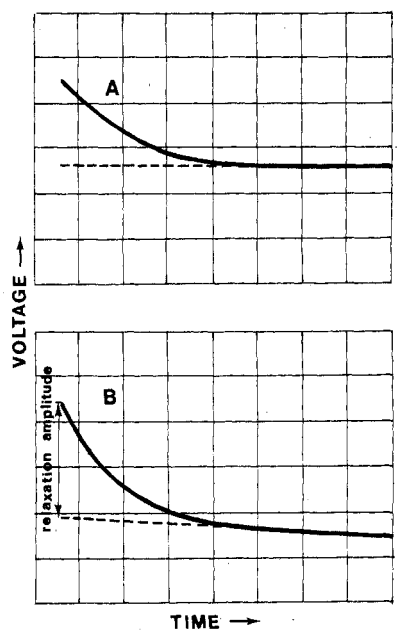


Figure 2. Slow relaxation time (compound III): A, scope 50 × 10^{-3} V and 0.2 sec, pH 12.27; B, scope 20 × 10^{-3} V and 0.2 sec, pH 12.70.

For each kinetic run the pH was adjusted to the desired value by injecting with a microsyringe a predetermined amount of a 1 *N* alkali solution. The pH was measured with a Beckman Research type pH meter at 25°. The alkaline glass electrode used operates in the range 0–14 without correction. All solutions were 0.1 *M* in $NaClO_4$. In this way relaxation times have been determined at different ionic strength varying from about 0.1 (pH lower than 12) to about 0.2 (pH near 13). The effect of this ionic strength variation on the rate constant was experimentally found to be extremely weak and to lie within the experimental error.

The solution to be investigated was then transferred into the T-jump cell. In order to prevent any carboxylation the cell was hermetically sealed by use of a plastic film.

After the T-jump experiment, the final pH was checked again directly in the cell. pH variations during the relaxation experiment did not exceed 0.05 pH unit.

Relaxation experiments were carried out using a commercial T-jump apparatus[7] (Messanlagen Studiengesellschaft, Göttingen, Germany). Unexpected oscillations due to the light source instability (Osram lamps XBO and HBO) were suppressed by using a second photomultiplier between the cell and the monochromator. Satisfactory reproducibility was obtained in the millisecond range. The final temperature after the T-jump was 25°. The kinetic analysis was performed at a wavelength corresponding to the maximum absorption of the enolate ion, 280 nm. The given relaxation times represent the average of five to six values.

At high pH (pH > 12.5), the decomposition of the keto ester was observed in competition with the slow chemical relaxation time. This produces a continuous decrease of the enolate ion absorbance. The hydroxide ion concentration does not vary, since the overall β-keto ester concentration is much smaller. The calculation of the relaxation time takes account of this by a graphical method shown in Figure 2B. In this way the measured relaxation

times and the rate constants are not affected by the decomposition.

Equilibrium Constant Measurement. The enol content was determined by the enol reactivity toward bromine. This method is based on the assumption that bromination is much more rapid than the keto–enol transformation. The bromine concentration was electrochemically measured by means of a couloamperometric apparatus described elsewhere.[8] Experiments were performed at 25°, in acidic aqueous solution at a 0.1 constant ionic strength by use of NaBr. The experimental error reaches 10%, essentially owing to the imprecise determination of the titration end point.

Spectroscopic Data. Nuclear magnetic resonance spectra of the pure liquids were recorded, at 27°, on a JEOL JNM PS 100 spectrometer. The high sensitivity of this apparatus allowed the detailed analysis of the enol signal. Tetramethylsilane was used as internal standard.

Calculation of Relaxation Times

The keto–enol transformation catalyzed by the hydroxide ion is shown in the following equation.

$$\underset{1}{\text{Enol} + \text{OH}^-} \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \underset{2}{\text{Carbanion-Enolate} + \text{H}_2\text{O}} \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} \underset{3}{\text{Ketone} + \text{OH}^-} \quad (6)$$

Equation 6 is generally characterized by two relaxation times, τ_{12} and τ_{32}.[7] If one of these equilibria is much more rapid than the other, a simple analytical expression can be derived for τ_{12} and τ_{32} from the kinetic and equilibrium data.

If the enol content is very small, the acidity of the enol form is much stronger than that of the keto form and eq 3 and 4 reduce to

$$pK_{EH} \ll pK_g \text{ and } pK_{CH} \cong pK_g \quad (7)$$

Thus the relaxation time τ_{12} is related to the fast enol–enolate equilibrium.

$$\tau_{12}^{-1} = k_{21} + k_{12}([\overline{OH^-}] + [\overline{EH}]) \quad (8)$$

This classical result means that the rapid equilibrium is not disturbed by the slow one.

τ_{32} is given by considering the rate equation of the keto form CH.

$$\frac{d[CH]}{dt} = -k_{32}[CH][OH^-] + k_{23}[E] \quad (9)$$

Instantaneous concentrations are expressed by

$$[CH] = [\overline{CH}] + \delta[CH] \quad (10)$$

$$[E] = [\overline{E}] + \delta[E] \quad (11)$$

$$[OH^-] = [\overline{OH^-}] + \delta[OH^-] \quad (12)$$

$[\overline{CH}]$, $[\overline{E}]$, and $[\overline{OH^-}]$ being equilibrium concentrations.

Equation 9 becomes

$$\frac{d\delta[CH]}{dt} = -k_{32}([\overline{CH}] + \delta[CH])([\overline{OH^-}] + \delta[OH^-]) + k_{23}([\overline{E}] + \delta[E]) \quad (13)$$

By considering the fast equilibrium constant K_1 from eq 6, one obtains for eq 13

$$\frac{d\delta[CH]}{dt} = -\delta[CH][k_{32}([\overline{OH^-}] + \alpha[\overline{CH}]) + k_{23}\alpha] \quad (14)$$

$$\alpha = \frac{K_1[OH^-]}{1 + K_1([\overline{EH}] + [\overline{OH^-}])}$$

In eq 14, the term between brackets corresponds to the relaxation time τ_{32}.

$$\tau_{32}^{-1} = k_{23}\alpha + k_{32}([\overline{OH^-}] + \alpha[\overline{CH}]) \quad (15)$$

α takes into account the influence of the fast equilibrium. Typical experimental data concerning compound II allow the determination of α.

$[\overline{OH^-}] = 2 \times 10^{-2}\,M$ $[\overline{EH}] = 4 \times 10^{-7}\,M$ $[\overline{E}] = 7 \times 10^{-5}\,M$

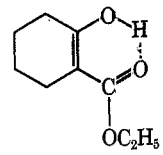
$\alpha = 0.995$

Taking α equal to 1, with an approximation better than 1%, eq 15 becomes eq 16.

$$\tau_{32}^{-1} = k_{23} + k_{32}([\overline{CH}] + [\overline{OH^-}]) \quad (16)$$

This unexpected result leads to the interesting conclusion that both relaxation times are dependent solely on the corresponding equilibrium.

Unfortunately, the observation of the rapid phenomenon is extremely difficult when compounds have a low enol content. In this series τ_{12} could only be measured for acetoacetic ester.[9] We also obtained τ_{12} for a β-keto ester showing a highly analogous enolic structure: ethyl 2-hydroxycyclohexenecarboxylate (enol content about 2%).[10]



Rate constants were obtained by plotting τ_{32}^{-1} (or τ_{12}^{-1}) *vs.* hydroxide ion concentration. The slope gives k_{32} (or k_{12}) and the intercept k_{23} (or k_{21}). Experimental error is of the order of 10% for k_{12} and k_{32} and 20% for k_{21} and k_{23}.

Results

A typical example of the slow relaxation curve is shown in Figure 2A. In strong alkaline solutions the enolate ion and the ketone concentrations decrease continuously because of decomposition. This phenomenon is accompanied by a decrease of the total amplitude of the relaxation curve. For instance, after a delay of about 10 min, decomposition of compound III is so important that observation of the relaxation curve is no longer possible. Rate constants are shown in Table I.

For compounds VI and VII, the observed relaxation times show poor sensitivity to hydroxide ion concentration. In fact, by varying this concentration by a factor of 10, τ_{32}^{-1} decreases from 9.35 to 8.35 sec^{-1} (VI) and from 4.35 to 3.30 sec^{-1} (VII). This is related to a continuous decrease of the difference between k_{32} and k_{23} which makes k_{23} no longer negligible with respect to k_{32}.

The keto form acidity (pK_{CH}) is given by

$$K_{CH} = 10^{-14}\frac{k_{32}}{k_{23}} \quad (17)$$

This equation is derived by setting

$$\frac{k_{32}}{k_{23}} = \frac{[E]}{[CH][OH^-]} = \frac{a_E a_{H^+}}{[CH]} \frac{1}{[OH^-][H^+]\gamma_E\gamma_{H^+}}$$

where a_E and a_{H+} are activities and γ_E and γ_{H+} are the corresponding activity coefficients. By assuming $\gamma_E = \gamma_{OH-}$, which is a very good approximation, one obtains $[OH^-][H^+]\gamma_E\gamma_{H+} = 10^{-14}$ at 25°.

The values obtained here are reported in Table I together with the literature data. Rumpf[3] has pointed out the difficulty of measuring this acidity by conventional techniques because of the rapid hydrolysis of the ester function in alkaline solution. These studies are so difficult that the determination is quite impossible for secondary R substituents. Thus it appears that the high instability of the chemical systems studied requires a fast observation time technique, such as T-jump relaxation.

The enol content obtained for dilute aqueous solution is presented in Table II. Each value has been averaged from at

Table II
Determination of the Enol Content (K_T) by Bromination. Enol Acidity

Compd	Expt	$[Br_2]$, $\times 10^7$, M^{-1}	[β-keto ester] $\times 10^5$, M^{-1}	$K_T \times 10^2$	pK_{EH}
I				0.39[a]	8.24
II	1	4.02	2.43		
	2	4.13	3.01		
	3	2.27	1.69		
	4	4.40	3.79	0.29	9.70
	5	2.08	2.38		
	6	2.91	2.95		
III	1	2.04	1.93		
	2	2.14	2.85		
	3	1.99	1.85	0.17	9.70
	4	2.12	2.65		
	5	4.07	3.68		
IV	1	3.45	2.95		
	2	3.45	3.65		
	3	5.70	5.45		
	4	3.42	2.86	0.13	9.60
	5	3.62	4.07		
	6	4.33	4.05		
	7	5.8	5.05		
V	1	3.62	4.53		
	2	3.73	4.88		
	3	5.9	8.7		
	4	3.72	4.83	0.09	9.65
	5	3.65	5.25		
	6	6.15	8.96		
	7	6.28	10.10		
VI	1	2.24	0.675		
	2	4.22	1.69		
	3	4.45	2.48		
	4	2.26	0.68	0.05	10.20
	5	2.23	0.905		
	6	4.30	1.78		
	7	4.38	2.35		
VII	1	1.68	4.50		
	2	1.64	6.6		
	3	3.08	11.1		
	4	3.22	13.8	0.04	9.70
	5	1.63	4.34		
	6	3.06	8.5		

[a] See ref 2.

Table III
Chemical Shifts and Coupling Constants of the Enolic Protons

	$\delta_{O(H)}$, ppm		Coupling constant, Hz
	Measured	Literature[a]	
I	12.16	12.17	0.6
II	12.70	12.63	0.6
III	12.70	12.73	0.6
IV	12.80	12.80	0.6
V	12.75	12.85	
VI	12.97	12.98	
VII	13.09	13.1[b]	

[a] J. L. Burdett and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 2105 (1964). [b] S. T. Ioffe, E. I. Fedin, P. V. Petrovskii, and M. I. Kabachnik, *Tetrahedron Lett.*, 2661 (1966).

least five experimental runs. The calculated enol acidity constants (pK_{EH}) are tabulated in the same table.

The chemical shifts and coupling constants of the enolic proton are presented in Table III. The value of the chemical shift expresses the strength of the intramolecular H bond,[11] which appears to be weaker than for the symmetric β-diketones $CH_3COCHRCOCH_3$.[9] Compounds I–IV present a sufficiently high enol content to allow a fine structure analysis of the enolic peak (Figure 3). It exhibits a quartet with a single coupling constant of 0.6 Hz.

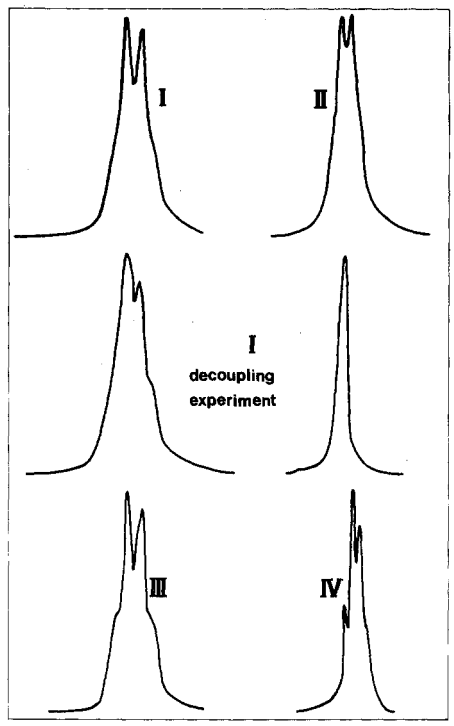
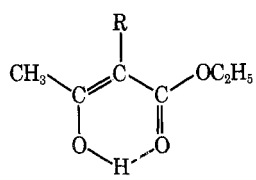


Figure 3. Nuclear magnetic resonance spectra of the enolic proton.

The possibility of coupling with the vinylic proton has been proposed by Burdett.[12] However, it should result in a doublet and not in a quartet. Moreover, for R ≠ H this coupling should disappear. From a decoupling experiment (Figure 3), it is seen that coupling takes place with the methyl group. This coupling shows that the enolic proton is closer to the carbonyl oxygen than to the ester oxygen, whereas for the above-mentioned β-diketones it is equidistant from these two oxygen atoms.[13] This result leads us to propose the following structure for the enolic forms of our β-keto esters.



Discussion

It is generally accepted that the carbanion–enolate anion is an intermediate species in the base-catalyzed keto–enol transformation. This anion is at the same time the conjugate base of both the ketone and the enol, and is produced by the abstraction of the acidic proton by a base in the reacting medium. Equation 6 represents catalysis by the hydroxide ion occurring in our kinetic experiments. If now the medium is slightly acidic (in order to avoid any protonation of the carbonyl function), the concentration of the carbanion–enolate intermediate will decrease and become very low compared with that of the un-ionized species. This is the case for the water-catalyzed transformation occurring in our equilibrium constant determinations.[14]

Enol–Enolate Equilibrium. Some 30 years ago, Schwarzenbach and Felder measured the acidity of both tautomers of acetoacetic ester.[2] They observed a higher acidity for the enol than for the keto form. Our results show that the introduction of R = alkyl leads to a significant constant decrease in the enol acidity. All the substituted keto esters present a pK_{EH} value of about 9.7, without

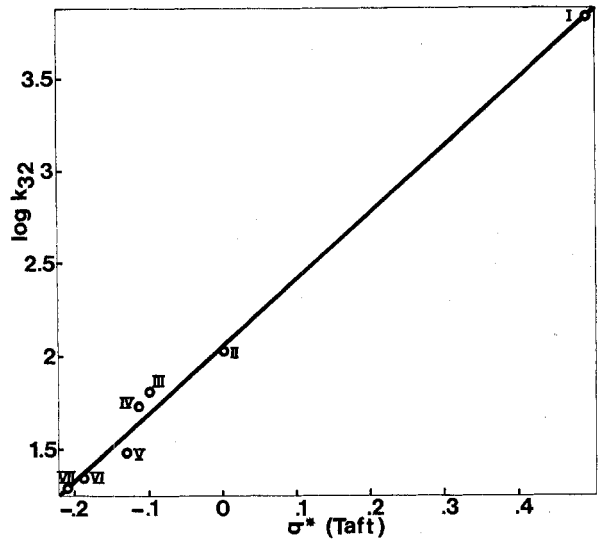


Figure 4. The relationship between the σ^* constants and the deprotonation rate constants k_{32} of the keto form.

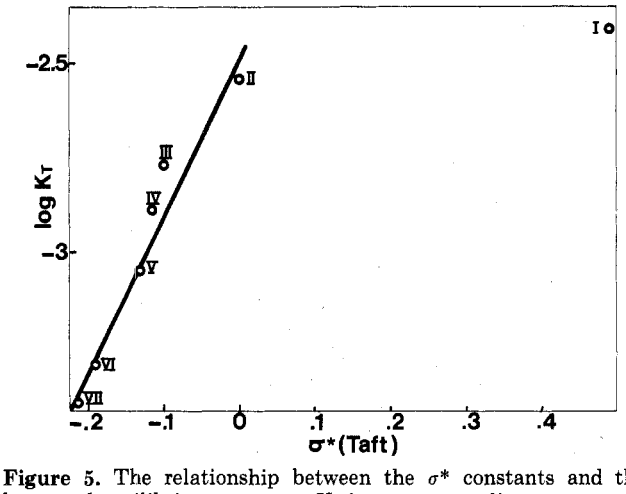
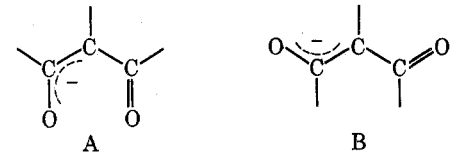


Figure 5. The relationship between the σ^* constants and the keto-enol equilibrium constants K_T in aqueous media.

any marked difference for primary or secondary alkyl substituents.

The enol deprotonation rate constant of I, $k_{12} = 2.5 \times 10^8\ M^{-1}\ sec^{-1}$,[9] lies significantly under the diffusion-controlled value accepted for aqueous solution ($k_{12} \cong 10^{10}\ M^{-1}\ sec^{-1}$), which argues for the existence of an intramolecular hydrogen bond in the enol form in aqueous solution. *This hydrogen bonding is essentially responsible for the stability of the enol and any modification of its conformation should result in a variation of k_{12} and enol content.* k_{12} being unknown for compounds II–VII, we investigated the deprotonation rate of ethyl 2-hydroxycyclohexenecarboxylate, which may be taken as a model for alkyl-substituted β-keto esters. The rate constant obtained, $k_{12} = 2.4 \times 10^8\ M^{-1}\ sec^{-1}$, is very close to that of I. For the chemical shift of the enolic proton of this compound, we obtained 12.24 ppm, a value extremely close to that found for ethyl acetoacetate (12.16 ppm). Thus k_{12} and δ_{OH} appear to be two independent estimates of the intensity of intramolecular hydrogen bonding. Considering the larger chemical shift for compounds II–VII (~12.8 ppm) it would appear that representative value of k_{12} is slightly less than $2.4 \times 10^8\ M^{-1}\ sec^{-1}$. This has been demonstrated directly for β-dicarbonyl compounds of the form $CH_3COCHRCOCH_3$.[9] This result tends to show that the hydrogen bond is only slightly modified by R substitution.

A possible explanation is that our results can be accommodated within the currently accepted framework that alkyl structural effects are exerted on the enol form.[3,15] According to this view, if one assumes that there is no difference in the steric requirements of the enol and enolate (a reasonable assumption, since they are both flat), then a lack of variation of pK_{EH} with alkyl subtitution is expected. The lower pK_{EH} for R = H would be the consequence of an inductive effect. This hypothesis assumes that the nature of the effect is necessarily steric. In our opinion the fact that the two forms are planar does not require that the steric effect be identical in each case; a more complete knowledge of their structures is necessary. The geometry of the enol form is quite well known (cyclic planar structure, enolization toward the carbonyl) but that of the enolate is less evident. There are two possibilities which may be drawn as follows.



A B

If structure A corresponds to the real situation a similarity of steric effects between enol and enolate appears quite probable, while this is not the case if structure B is operating. From an analysis of the infrared and Raman spectra of the anion corresponding to penta-2,4-dione, Ernstbrunner[16] has shown that in organic solvents structure A prevails while in aqueous solution B is by far the more important. Thus one can reasonably assume this same structure for the anion of ethyl acetoacetate, and consequently reject the hypothesis that steric effects are equally important for the enol and enolate forms. Moreover, a destabilization of the enol form seems incompatible with the invariable intensity of hydrogen bonding, considering that this bonding is probably the most important factor determining enol stability. It seems to us that the hypothesis of a very weak effect on the ionization equilibrium of the enol is more consistent with the factors we have just discussed.

Ketone–Enolate Equilibrium. The ketone acidity is more sensitive to structural effects than the enol acidity. It decreases significantly as the number of carbon atoms increases for primary alkyl substituents, and as the degree of branching of a substituent increases. Barlin and Perrin[17] showed for these β-keto esters the existence of a linear free energy relationship between the overall acidity, which may be identified with the ketone acidity in view of the very weak enol content, and the Taft σ^* constants: $pK_{CH} = 12.59 - 3.44\sigma^*$.

In order to carry out a more accurate analysis of the structural effect on the equilibration step $2 \rightleftharpoons 3$ from eq 6, we shall examine the rate constants k_{23} and k_{32}. We find that, while k_{23} is remarkably constant, k_{32} varies, by a factor of 350, in the same direction as pK_{CH}. Thus α-alkyl substitution affects the ketone reactivity tremendously. A thorough investigation of the k_{32} variation in relation to the structure shows a linear relationship between log k_{32} and the Taft σ^* constants (Figure 4). Furthermore, the same analysis on the keto-enol equilibrium constant K_T shows a similar relationship between log K_T and σ^* (Figure 5), with the exception of the point corresponding to R = H, which is ruled out without any doubt.[18] Consequently there exists, for alkyl groups, a linear free energy relationship between the rate constant of ketone deprotonation and the enol content. In a strictly formal sense, this is compatible with the two limiting hypotheses under discussion: a steric effect on the enol or an electronic ef-

fect on the ketone. We will now consider the arguments in favor of the first hypothesis. The increase of pK_{CH} with the degree of branching is expected since the enolate has greater steric requirements than the ketone. The constancy of k_{23} and the variation of k_{32} with pK_{CH} are explicable if the steric requirements of the enolate are the same as those of the transition state. This is expected, since only a flat transition state will allow conjugation with the carbonyl oxygens. Unfortunately, we have practically no knowledge of the structure of the keto form (all we know is that the dipole moment is greater for the ketone than for the enol) and it does not seem certain to us that the effect, if it is steric, would be more important on the enolate than on the ketone. Moreover, the probability of an isosteric effect on the enol, enolate, and ketonic transition state appears difficult to accept; the condition of simultaneous coplanarity is not sufficient to reach such a conclusion. The following considerations lead us to believe that an electronic effect operating principally on the keto form is the most probable.

(1) The correlations pK_{CH}, log K_T, and log $k_{32} = f(\sigma^*)$ do not support a steric effect interpretation.

(2) Ingold,[19] quoting Hughes, concludes that the +I effect of alkyl groups would lead to an increase in the thermodynamic stability of the ketone.

(3) The coupling constant between the methyl and acidic protons is not affected by alkyl substitution, probably indicating a constant planar geometry for the enol form.

(4) The variation of the enol content with respect to R = H corresponds to a decrease for electron-donating substituents and an increase for electron-withdrawing substituents.

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References and Notes

(1) This work is taken from the Doctoral Thesis of R. Brouillard, Université Paris VII.
(2) G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, **27**, 1701 (1944).
(3) P. Rumpf and R. Reynaud, *C. R. Acad. Sci.*, 1501 (1960).
(4) M. L. Eidinoff, *J. Amer. Chem. Soc.*, **67**, 2072 (1945).
(5) R. G. Pearson and J. M. Mills, *J. Amer. Chem. Soc.*, **72**, 1692 (1950).
(6) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(7) M. Eigen and L. de Maeyer in "Technique of Organic Chemistry," Vol. 8, A. Weissberger, Ed., Interscience, New York, N. Y., 1963.
(8) J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, **8**, 359 (1964).
(9) P. Alcais and R. Brouillard, *J. Chem. Soc., Perkin Trans. 2*, 1214 (1972).
(10) R. P. Bell and D. C. Vogelsong, *J. Chem. Soc.*, 243 (1958).
(11) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, London, 1967.
(12) J. L. Burdett, Ph.D. Thesis, Michigan State University, 1963.
(13) A. H. Lowrey, C. George, P. D'Antonio, and J. Karle, *J. Amer. Chem. Soc.*, **93**, 6399 (1971).
(14) The direct determination of such a low enol content is only possible by means of the enol reactivity toward bromine. This technique cannot be used in alkaline solution for the following reasons: (1) bromine undergoes dismutation; (2) the carbanion–enolate anion reactivity toward bromine is similar to that of the enol.
(15) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, pp 446–447; E. S. Gould in "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp 377–378; R. Jacquier, C. Petrus, F. Petrus, and J. Verducci, *Bull. Soc. Chim. Fr.*, 3694 (1969); S. Forsén and M. Nilsson in "The Chemistry of the Carbonyl Group," Vol. 2, Interscience, London, 1970, p 202; A. I. Kol'tsov and G. M. Kheifets, *Russ. Chem. Rev.*, **40**, 773 (1971).
(16) E. E. Ernstbrunner, *J. Chem. Soc. A*, 1558 (1970).
(17) G. B. Barlin and D. D. Perrin, *Quart. Rev., Chem. Soc.*, **20**, 75 (1966).
(18) Although the parameter σ^*, as a measure of the polar effect of alkyl group, has been controverted [C. D. Ritchie, *J. Phys. Chem.*, **65**, 2091 (1961)], the two correlations which we have observed show that the same effect is responsible for the variation of both k_{32} and K_T. It would be interesting to have some information on the validity of the relationship $pK_{CH} = 12.59 - 3.44\sigma^*$ for groups other than alkyl. Unfortunately, sufficient data are not available.
(19) C. K. Ingold in "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1969, p 818.

A Study of Acetate Participation in Acyclic Epoxide Systems. Acid-Catalyzed Rearrangements of *trans*- and *cis*-1-Acetoxy-3,4-epoxypentanes, -4,5-epoxyhexanes, and -5,6-epoxyheptanes

James M. Coxon,* M. P. Hartshorn, and W. H. Swallow

Department of Chemistry, University of Canterbury, Christchurch, New Zealand

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Acid-catalyzed rearrangements of *trans*- and *cis*-1-acetoxy-3,4-expoypentanes gave, respectively, *cis*- and *trans*-2-methyl-3-acetoxytetrahydrofuran. Similar reaction of *cis*- and *trans*-1-acetoxy-4,5-epoxyhexane gave *threo*- and *erythro*-2-(1-acetoxyethyl)tetrahydrofuran. In the course of these rearrangements the configuration at the epoxide carbons is retained. The mechanism of these rearrangements, elucidated by ^{18}O-labeling experiments, is consistent with the intermediacy of ortho esters. When the ester group is further removed from the epoxide moiety no participation is observed.

The present investigation, as part of a general study of the chemistry of epoxides, was prompted by the possibility of forming bicyclic ortho esters 2 by intramolecular hydroxyl attack on 1,3-dioxolenium ions 1.

Neighboring-group participation by ester groups to give 1,3-dioxolenium ions is now well established.[1] In 1942 Winstein and Buckles[2] found that solvolysis of 2-acetoxy-3-bromobutanes in dry acetic acid–silver acetate takes place with retention of configuration, threo bromo acetate giving the *dl* diacetate and the erythro bromo acetate giving meso diacetate. The postulated 1,3-dioxolenium ion intermediate 4 was later observed[3] by nmr spectroscopy whan 3-acetoxy-2-chloro-2,3-dimethylbutane (3) was dissolved in SbF_5–SO_2 or SbF_5–FSO_3H–SO_2 at −60°. Meer-