JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 9, 545–551 (1996)

AN UNEXPECTED LINEAR BRØNSTED CORRELATION

KLAUS D. BAUMANN, INÊS M. C. BRIGHENTE, MOACIR G. PIZZOLATTI AND ROSENDO A. YUNES*
Departamento de Química, Universidade Federal de Santa Catarina, Campus Universitário, Trindade, 88040-970, Florianópolis, SC, Brazil

The reaction of barbiturate and 1,3-dimethylbarbiturate ions with *o*-, *p*- and 2,4-dinitrobenzaldehyde was studied. The reactions of barbiturate anion with *o*- and *p*-nitrobenzaldehyde exhibit a pH–rate profile different to that the corresponding to the reactions of barbiturate and 1,3-dimethylbarbiturate ions with 2,4-dinitrobenzaldehyde. The dependence of the rate constant on the viscosity of the medium in the pH range 2–4, for all the reactions, indicates the contribution of a diffusion-controlled proton transfer from the hydronium ion to an addition intermediate, T^-, in the rate-determining step. Surprisingly, in the reaction of 2,4-dinitrobenzaldehyde with barbiturate and 1,3-dimethylbarbiturate anions, the Brønsted plot for general acid catalysis for carboxylic acids of pK_a between 2 to 5 gives a linear relationship with $\alpha = 0{\cdot}707$ ($r = 0{\cdot}991$), whereas $\alpha = 0$ is expected, considering the pK_a of the addition intermediate T^-. On the other hand, the point for the rate constant, considering water as a general acid catalyst, falls approximately 10^5 times above the corresponding Brønsted line. The tautomerism existing in the intermediate T^- permits these surprising facts to be explained.

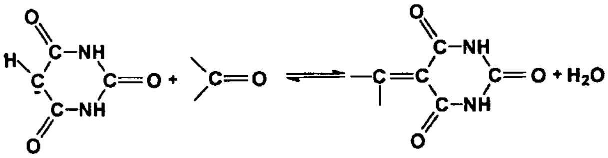
INTRODUCTION

Reactions of carbonyl compounds are important in synthetic chemistry and in biochemical processes. Thus, the reactions between nitrogen bases and carbonyl compounds were considered as simple models for enzymatic reactions involving the formation of imine intermediates, as in the case of aldolases, decarboxylases, etc.[1]

Barbituric acid derivatives are a well known class of compounds having different pharmacological activities. The ionization of barbituric acids is thought to influence their conformational and biological properties.[2]

The kinetics, mechanism and catalysis of the reactions of nitrogen nucleophiles and some carbonyl compounds have been widely studied.[3] The mechanisms involved in product formation are complex, involving different rate-determining steps under different conditions: nucleophilic attack, proton transfer and dehydration.[4,5] However, the reaction of barbiturates as nucleophiles with carbonyl compounds has been little studied. Nikolov and Poneva,[6] on the basis of spectroscopic data, suggested a simple two-step mechanism. More recently, Girgis and El-Shahawy[7] suggested a mechanism with rate-determining attack of the barbiturate on the protonated benzaldehyde.

In the light of these observations, we studied the reaction of barbiturate and 1,3-dimethylbarbiturate ions with *o*-, *p*- and 2,4-dinitrobenzaldehydes to give benzylidenebarbituric acid, as shown in Scheme 1.



Scheme 1

---

* Author to whom correspondence should be addressed.

CCC 0894–3230/96/080545–07

Received 31 October 1995
Revised 8 March 1996

EXPERIMENTAL

Materials. The organic reagents employed were commercially available products and were either redistilled or recrystallized. Inorganic chemicals and carboxylic acids used in buffers were of reagent grade and were used without further purification.

Kinetics. The reaction of the carbonyl compounds with barbituric acid and 1,3-dimethylbarbituric acid in water at 25·0 °C, ionic strength 1·0 M (NaCl), was observed on a Varian DMS 80 spectrophotometer, equipped with a thermostated cell holder, by monitoring the formation of the product at 355 nm. A sufficient excess of barbiturate ions ($6{\cdot}0 \times 10^{-3}$ M) was employed to ensure pseudo-first-order kinetic behaviour. The concentration of aldehyde did not exceed $3{\cdot}33 \times 10^{-4}$ M.

The determinations of the rate constants were carried out using established procedures.[4] Reactions were followed for three half-lives ($t_{1/2}$) and first-order rate constants (k_{obs}) were calculated by computer. Second order rate constants (k_2) were calculated by dividing the first-order rate constants by the concentration of the free nucleophile ($k_2 = k_{obs}/[\mathrm{Nu}^-]$), and the concentration of the free nucleophile was calculated using the Henderson–Hasselbalch equation ($\mathrm{p}K_a = \mathrm{pH} + \log[\mathrm{NuH}]/[\mathrm{Nu}^-]$).

Third-order rate constants were obtained from the slopes of plots of second-order rate constants (k_2) against the concentration of catalytic species.

To determine the nature of the buffer catalysis, third-order rate constants, using acetic acid–acetate buffer, were determined and plotted against the molar fraction of free acid for several different concentrations and a least-squares fit was made (plots not shown). The right-hand intercept gives the value of the catalytic constant for the acid component of the buffer (k_{cat}, see Table 2) whereas the left-hand intercept (where the fraction of free acid is zero) is zero.

General acid catalysis for these reactions was determined for cyanoacetic acid, chloroacetic acid, formic acid and acetic acid, working at a pH corresponding to the pK_a of the catalyst [pK_a' = pK_a determined previously[3–5] under the experimental conditions of this study: water, ionic strength 1·0 M (NaCl), 25 °C]. The pK_a' values are 2·33, 2·70, 3·63 and 4·60, respectively.[4,5]

The Brønsted correlation coefficient was obtained from the plot of catalytic rate constants vs pK_a' of the acids, using statistical correction.

The pK_as of barbituric acid and 1,3-dimethylbarbituric acid are 3·98 and 4·69, respectively.[8]

The method of Sayer and Edman[9] was used to determine rate constants at apparent pHs and the pK_a of barbituric acid in 50% aqueous glycerol and ionic strength 1·0 M (pK_a' = 3·86).

pK_a Calculation. The pK_a of the negatively charged oxygen of the T^- intermediate can be calculated considering that it is the conjugate base of an alcohol. Alcohols can be regarded as being derived from carboxylic acids by replacement of an oxygen atom by two hydrogen atoms, so alcohols and acids would be expected to show similar effects of substituents on pK_a values.

The pK_a of the T^- intermediate based on the pK_a of 15·9 for ethanol[10] can be calculated using the correction for the C_6H_3-2,4-$(NO_2)_2$ ($\sigma^* = 1{\cdot}88$)[11] and for the complex barbiturate nucleus ($\sigma^* = 1{\cdot}92$)[11] that is calculated from CHO ($\sigma^* = 2{\cdot}15$)[11] and from –NHCONH$_2$ ($\sigma^* = 1{\cdot}31$),[11] which should contribute in a similar way to – NHCONH – of the barbiturate ion. The total effect would be $2{\cdot}15 + 2{\cdot}15 + 0{\cdot}52 = 4{\cdot}82$ (0·52 is the effect of the – NHCONH – group considering the attenuation factor for the carbonyl group of 0·4). The attenuation effect of one carbonyl group on the other carbonyl group is not considered because it should introduce a negligible error. The attenuation effect of C-2 with respect to C-1 gives $4{\cdot}82 \times 0{\cdot}4 = 1{\cdot}92$. As the acidities of substituted alcohols have been satisfactorily correlated with a value of $\rho^* = -1{\cdot}32$,[10] then p$K_a = 15{\cdot}9 - 1{\cdot}32\,(1{\cdot}88 + 1{\cdot}92) = 10{\cdot}89$.

The pK_a of the hydroxy group as an acid for the hydroxydioxo structure is estimated to be similar to that of dimedone (pK_a = 5·23).[12]

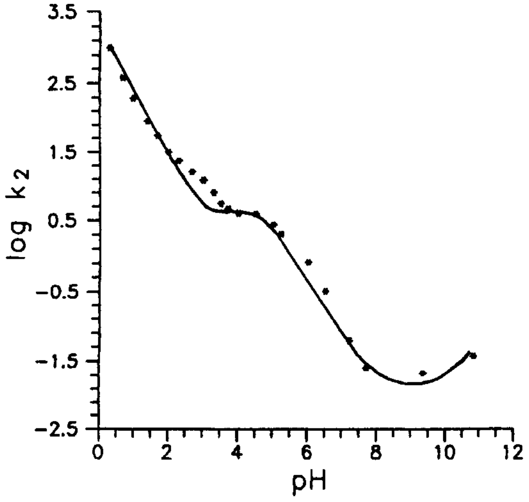


Figure 1. pH dependence of the logarithms of second-order rate constants for the reaction between barbituric acid and *p*-nitrobenzaldehyde in water at 25 °C and ionic strength 1·0 M. The reaction of barbiturate anion with *o*-nitrobenzaldehyde, which has a similar profile, is not shown

RESULTS AND DISCUSSION

Reaction of barbiturate anions with *o*- and *p*-nitrobenzaldehydes

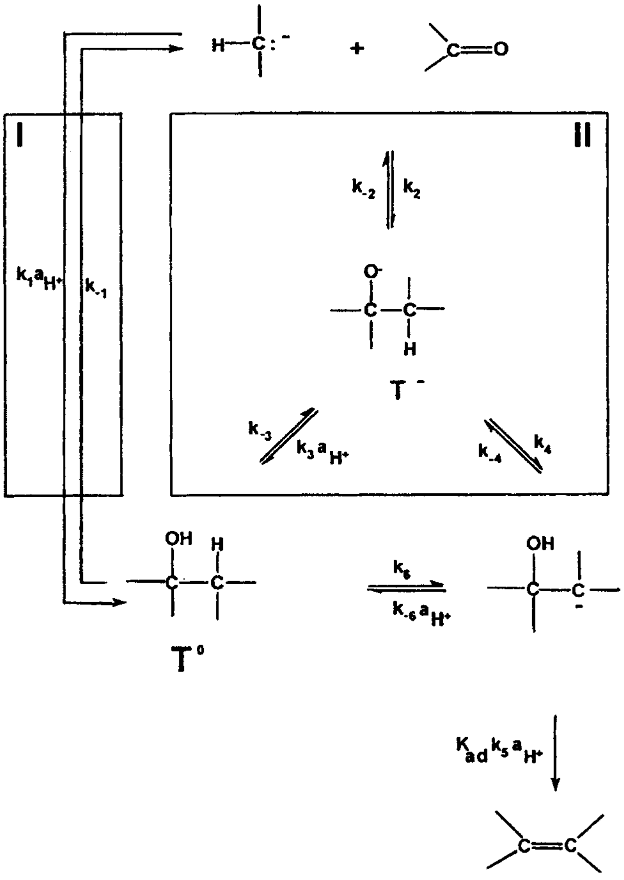
The pH–rate profile for the reactions of barbiturate anion with *o*- and *p*-nitrobenzaldehyde shows complex behavior between pH 0 and 6, as indicated in Figure 1. The presence of a break at pH 5·5 is clear, but there is no definitive break at low pH. A similar kind of pH–rate profile is observed in the mechanism for the formation of a neutral tetrahedral addition intermediate from carbonyl compounds and nitrogen nucleophiles[5] when a concerted process (I) is favourable with respect to a stepwise pathway (II) according to Scheme 2, where the nitrogen nucleophile was substituted by a carbanion, considering that their behaviour should be similar.

In this case, the profile exhibits only one negative break corresponding to the transition from the rate-limiting attack of the nucleophile on the carbonyl compound at low pH to the hydronium ion-catalysed dehydration of the addition intermediate at moderate pH. It was demonstrated[5] that the pH-independent reaction occurs by a stepwise mechanism involving rate-limiting solvent-catalysed isomerization of T^- (see Scheme 2).

In the case of the reaction of barbiturate anion with *p*-nitrobenzaldehyde, the solid curve was calculated employing equation (1) on the basis of Scheme 2,[4] with the assistance of the rate constants in Table 1 (Figure 1).

$$k_2 = \frac{(k_1 aH^+ + K_n k_4) K_{ad} k_5 aH^+}{k_1 aH^+ + K_n k_4 + K_{ad} k_5 aH^+} \qquad (1)$$

where k_2 = the observed second-order rate constant (in terms of carbanion free base) for the benzylidenebarbituric acid formation at zero buffer concentration. It involves the second-order rate constant for the addition



Scheme 2

Table 1. Rate and equilibrium constants for benzylidenebarbituric acid formation from substituted benzaldehydes[a,b]

Reaction	k_1[c] ($dm^6\,mol^{-2}\,s^{-1}$)	k_2 ($dm^3\,mol^{-2}\,s^{-1}$)	K_nk_3 ($dm^6\,mol^{-2}\,s^{-1}$)	K_nk_4 ($dm^3\,mol^{-2}\,s^{-1}$)	K_n (mol^{-1})
2,4-Dinitrobenzaldehyde with barbituric acid	$5{\cdot}62\times10^{2}$	$1{\cdot}00\times10^{2}$	$1{\cdot}78\times10^{4}$	1.12	$1{\cdot}78\times10^{-6}$
2,4-Dinitrobenzaldehyde with 1,3-dimethylbarbituric acid	$5{\cdot}62\times10^{3}$	$6{\cdot}31\times10^{2}$	$1{\cdot}00\times10^{5}$	2.51	$1{\cdot}00\times10^{-5}$
2-Nitrobenzaldehyde with barbituric acid	$5{\cdot}62\times10^{2}$			3·16	
4-Nitrobenzaldehyde with barbituric acid	$1{\cdot}99\times10^{3}$			3·84	

[a] Water, 25 °C, ionic strength 1·0 M (NaCl).
[b] In most cases the data agree to within 3%.
[c] See Scheme 2.

step ($k_{ad} = k_1aH^+ + K_nk_4$) and the second-order rate constant for the dehydration of the addition intermediate step ($k_{deh} = k_5aH^+K_{ad}/1 + k_5aH^+K_{ad}$).

The term K_nk_4 which corresponds to the solvent-catalysed proton transfer in the tetrahedral addition intermediate T^- (see Scheme 2), was calculated taking into consideration the small pH-independent region existing between pH 4·0 and 4·5. It is observed that the experimental values do not correspond to the theoretical curve between pH 2 and 6.

Considering that this difference might be caused by the participation of a rate-determining proton transfer from the hydronium ion to the addition intermediate T^-, formed from the attack of barbiturate ion on the carbonyl compound (see Scheme 2), the effect of the solvent viscosity (50% aqueous glycerol) was studied in this region. Water and glycerol form relatively ideal mixtures[13] and it has been demonstrated that the increase in viscosity, increasing with proportion of glycerol, decreases the rate of diffusion-controlled reactions but has little effect on non-diffusion-limited reactions.[14] The retardation expected can be calculated from the relation $k_{H_2O}/k_{glyc} = \eta_{glyc}/\eta_{H_2O}$, which is 6·03 in 50% aqueous glycerol without added salt.[15] The relation $k_{H_2O}/k_{glyc} = 3{\cdot}56$ obtained at pH 1·51 in the reaction of 4-nitrobenzaldehyde and barbiturate ion indicates clearly that some contribution of a diffusion-limited step exists in the mechanism of this reaction.

The importance of pathway II relative to I is determined by the stability of the intermediate T^- relative to the transition state for the 'concerted' mechanism of pathway I. The contribution of the hydronium ion proton transfer to the intermediate T^- in the rate-determining step of the above mentioned reactions indicates that the intermediate T^- is relatively stable with respect to the transition state of the 'concerted' mechanism. For this reason, the reaction between 2,4-dinitrobenzaldehyde and barbiturate ions was studied, assuming that the two nitro groups should stabilize the intermediate T^- more than the transition state of the 'concerted' mechanism, considering both polar and electronic effects.

Reaction of barbiturate ions with 2,4-dinitrobenzaldehyde

The profiles of the reactions of barbiturate and 1,3-dimethylbarbiturate anions with 2,4-dinitrobenzaldehyde are similar to those of methoxyamine and *p*-nitrobenzaldehyde,[4] showing clearly the presence of two breaks at *ca* pH 2·0–3.0 and 5·0–7·0 approximately, as shown in Figure 2. This kind of profile with two negative breaks is also observed with amines of moderate basicity and moderate equilibrium constants (K_{ad}) for addition intermediate formation[5] (Scheme 2).

The profile exhibits two negative breaks and five kinetically significant regions which correspond to major contributions from the observed rate constants k_1, k_2, K_nk_3, K_nk_4 and $K_{ad}k_5$ (see Scheme 2). The five regions are (i) at pH lower than 2·0, the concerted pathway for the hydronium ion-catalysed attack of the barbiturate ion on the carbonyl group (k_1), (ii) between pH 2·0 and 3·0, the uncatalysed attack (k_2), (iii) between *ca* pH 3·0 and 5·0, the proton transfer from the hydronium ion to the T^- intermediate (K_nk_3), (iv) between pH 5·0 and 7·0, the solvent-catalysed intramolecular proton transfer in the intermediate (K_nk_4), and (v) above pH 6, the region of hydronium-catalysed elimination of the hydroxide ion.

Steady-state treatment of the mechanism in Scheme 2 yields equations (2) and (3) for product formation in the regions where the addition intermediate formation and elimination of the hydroxide ion, respectively, are the rate-determining steps. The theoretical curves were calculated with the assistance of the rate constants in

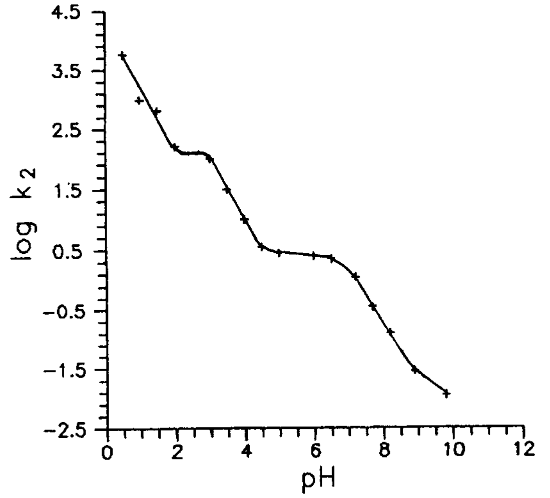


Figure 2. pH dependence of the logarithms of second-order rate constants for the reaction between 1,3-dimethylbarbituric acid and 2,4-dinitrobenzaldehyde in water at 25 °C and ionic strength 1·0 M. The reaction of barbiturate anion with 2,4-dinitrobenzaldehyde, which has a similar profile, is not shown

Table 1, and the experimental values correspond to the calculated curve (Figure 2).

$$k_2 = k_{ad}K_{ad}k_5aH^+/k_{ad} + K_{ad}k_5aH^+ \qquad (2)$$

where k_2 = observed second-order rate constant (for free carbanion), and

$$k_{ad} = k_1aH^+ + k_2(K_nk_4 + K_nk_3aH^+)/k_2 + K_nk_4 + K_nk_3aH^+ \qquad (3)$$

Consequently, according to this mechanism in the region of the hydronium-catalysed proton transfer to the intermediate T^- (between pH 3 and 5), the effect of the viscosity gives $k_{H_2O}/k_{glyc} = 6{\cdot}2$, which is the value expected for a diffusion-controlled process.[9]

In this region, experimental general acid catalysis is observed. If a simple proton transfer is rate determining, it was predicted[12] that the Brønsted slope will give an 'Eigen curve' with $\alpha = 0$ when this proton transfer is in a thermodynamically favourable direction and α approaching -1 as the reaction becomes thermodynamically unfavourable with increase in the pK_a of the acid catalyst.

In this case, considering the pK_a of the intermediate T^- formed by the attack of the barbiturate ion on the carbonyl compound (pK_a calculated = 10·89), it is surprising to observe that the Brønsted plot among the logarithms of the catalytic rate constants as a function of the pK_a of the carboxylic acids gives a linear relationship with $\alpha = 0{\cdot}707$ and $r = 0{\cdot}991$ for the barbiturate anion and $\alpha = 0{\cdot}846$ and $r = 0{\cdot}975$ for the 1,3-dimethylbarbiturate anion (Table 2). Further, two particular aspects should be noted.

(i) First, the points corresponding to the catalytic rate constant for the hydronium ion show a negative deviation of 14-fold for the reaction of barbiturate anion with 2,4-dinitrobenzaldehyde and a negative deviation of 53-fold for the reaction between 1,3-dimethylbarbiturate anion and 2,4-dinitrobenzaldehyde (Figure 3). On the other hand, it is known that the proton exhibits a positive deviation of 10–50-fold from the line of diffusion-limited proton transfer.[16] This indicates that the negative deviation of the hydronium ion catalytic rate constant from the Brønsted line corresponding to the carboxylic acid is significant, suggesting that the carboxylic acid catalytic effect must take place via a different mechanism to that indicated for the hydronium ion, which is for diffusion-controlled proton transfer to the intermediate T^-.

(ii) Second, the rate constants corresponding to a mechanism where water is considered as the general acid show a positive deviation of $2{\cdot}05 \times 10^5$-fold from the corresponding point in the Brønsted line for the reaction of the barbiturate anion with 2,4-dinitroben-

Table 2. General acid catalysis of benzylidenebarbituric acid formation from 2,4-dinitrobenzaldehyde in proton transfer step.[a,b]

		Log k_{cat}/p	
Catalyst	$pK_a + \log p/q$	Barbituric acid	1,3-Dimethylbarbituric acid
Hydronium	−1·26	3·77	4·52
Cyanoacetic acid	2·03	2·68	3·68
Chloroacetic acid	2·40	2·21	2·99
Formic acid	3·33	1·74	2·21
Acetic acid	4·30	0·98	1·67

[a] Water, 25 °C, ionic strength 1·0 M (NaCl).
[b] In most cases the data agree to within 3%.

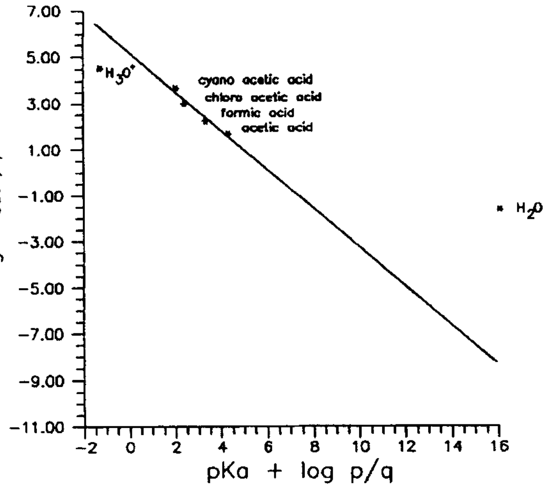


Figure 3. Brønsted plot for general catalysis (in the region of pH ≈ 3–5) of the reaction between 1,3-dimethylbarbituric acid and 2,4-dinitrobenzaldehyde in water at 25 °C and ionic strength 1·0 M. The reaction between barbituric acid and 2,4-dinitrobenzaldehyde, which has a similar plot, is not shown

zaldehyde and $5{\cdot}55 \times 10^6$-fold from the Brønsted line for the reaction of 1,3-dimethylbarbiturate anion with 2,4-dinitrobenzaldehyde.

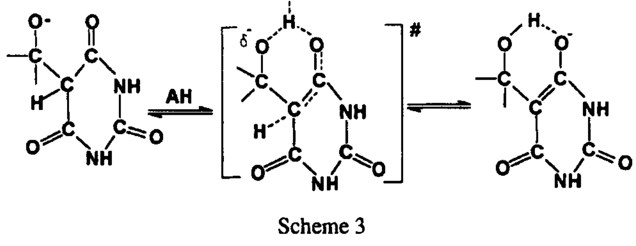
How is it possible to explain this remarkable positive deviation? Millefiori and Millefiori[17] have shown that in the case of the 5-nitro derivative of barbituric acid, the tautomeric dioxo-hydroxy form prevails over the trioxo form, and that in the dioxo-hydroxy form there should exist an intramolecular hydrogen bond between the hydroxy and the nitro groups.

In the case of the T^- addition intermediate of the reaction under study, the large deviation observed of the value of the rate constant that would correspond to a mechanism of water-catalysed reaction could be explained by a mechanism in which the intermediate T^- tautomerizes to the predominant dioxo-hydroxy form, permitting strong hydrogen bonding in a six-membered ring between the hydroxy group of the barbiturate group and the negatively charged oxygen atom of the benzaldehyde as a first step for a subsequent rapid intramolecular proton transfer. This idea is supported by consideration of the pK_a values of the hydroxy group and the negatively charged oxygen atom, which were calculated to be 5–6 and 10·89, respectively. This mechanism may also give some insight into the mechanism of some enzymes, e.g. the general acid–base catalysis by imidazole of His-57 of chymotripsin.[1]

The fact that $\alpha \neq 0$ in the region of pH 3–5 of the Brønsted plot for carboxylic acids, which would be expected from the pK_a of the addition intermediate T^- ($pK_a \approx 10{\cdot}89$), could be explained if the proton transfer were not diffusion controlled. It seems probable that the proton transfer from the carboxylic acids to the intermediate T^- occurs together with the tautomerization of the intermediate in same kind of 'concerted' mechanism. Eigen[12] has established that 'if the acid and its conjugate base differ in their electron distribution and molecular structure, i.e. if the recombination with H^+ or OH^- is associated with a resonance or tautomeric transformation, then the reaction rates may be relatively slow'. Hence this explains why the proton transfer is not diffusion controlled and why the 'Eigen curve' is not observed in the Brønsted correlation as in other cases.

The proton transfer of the carboxylic acid to the addition intermediate T^- could be similar to that for the addition of a proton of HBr to 2-methyl-1,3-diphenylpropane-1,3-dione and to 2,2-dimethyl-1,3-diphenylpropane-1,3-dione, where the proton is first located between the keto groups in a very strong intramolecular hydrogen bond.[18] This implies that some break of the carbonyl double bond and some double bond formation between the carbon atoms should exist in the transition state, as is indicated in Scheme 3.

The present studies have the following implications: (a) they show the importance of the study of differences and similarities in the reactions of nitrogen bases and carbanion ions with carbonyl compounds; (b) the existence of a special behaviour of the Brønsted relationship that indicates that its analysis is not trivial; and (c) The notable effectiveness of the tautomeric catalysis in the spontaneous reaction region. This leads to the consideration that a detailed study of its mechanism may give an insight into why enzymes are such effective catalysts.



Scheme 3

ACKNOWLEDGEMENTS

We thank the Conselho Nacional de Pesquisas (CNPq) and Financiadora de Estudos e Projetos (FINEP) for financial support.

REFERENCES

1. H. L. Fink, in *Enzyme Catalysis*, edited by M. I. Page and A. Williams, Chapt. 17 and 18. Royal Society of Chemistry, London (1987).
2. F. I. Carroll, A. Phillip and C. G. Moreland, *J. Med. Chem.* **19**, 521–525 (1976).
3. W. P. Jencks, *Prog Phys. Org Chem.* **2**, 63–129 (1964).
4. S. Rosemberg, S. M. Silver, J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.* **96**, 7986–7998 (1974).
5. J. M. Sayer, B. Pinsky, A. Schonbrunn and W. Washtien, *J. Am. Chem. Soc.* **96**, 7998–8009 (1974).
6. M. N. Nikolov and M. V. Poneva, *Spectrosc. Lett.* **20**, 821–834 (1987).
7. M. M. Girgis and A. S. El-Shahawy, *Indian J. Chem.* **30A**, 21–24 (1991).
8. A. E. Martell and R. M. Smith, *Critical Stability Constants*, Vol. 2, p.342. Plenum Press, New York (1975).
9. J. M. Sayer and C. Edman, *J. Am. Chem. Soc.* **101**, 3010–3016 (1979).
10. (a) J. P. Fox and W. P. Jencks, *J. Am. Chem. Soc.* **96**, 1436–1449 (1994); (b) S. Takahashi, L. H. Cohen, H. K. Miller and E. G. Peake, *J. Org Chem.* **36**, 1205–1207 (1971).
11. D. D. Perrin, B. Dempsey and E. P. Serjeant, *pK_a Prediction for Organic Acids and Bases*, p. 23. Chapman and Hall, London (1984).
12. M. Eigen, *Angew. Chem. Int. Ed. Engl.* **3**, 1–14 (1964).
13. L. L. Schaleyer and C. N. Richards, *J. Am. Chem. Soc.* **92**, 5565–5570 (1971).
14. C. Cerjean and R. E. Barnett, *J. Phys. Chem.* **76**, 1192–1195 (1972).
15. S. S. Hall, A. M. Doweyko and F. Jordan, *J. Am. Chem. Soc.* **100**, 5934–5939 (1978).
16. M. L. Bender, R. J. Bergeron and M. Komiyama, *Biorganic Chemistry in Enzymatic Catalysis*. Wiley, new York (1984).
17. S. Millefiori and A. Millefiori, *J. Heterocycl. Chem.* **26**, 639–643 (1989).
18. D. R. Clark J. Emsley and F. Hibbert, *J. Chem. Soc., Perkin Trans. 2* **9**, 1299–1301 (1989).