

REACTION KINETICS OF 1,2-DIAMINO BENZENE WITH ETHYL 2-OXOPROPANOATE AND 2,3-BUTANEDIONE

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The reaction of 1,2-diaminobenzene with 2,3-butanedione is subject to general acid catalysis in acetate and phosphate buffers (pH 4–7). The rate-limiting step of formation of 2,3-dimethylquinoxaline consists in the protonation of dipolar tetrahedral intermediate. In the case of the reaction of 1,2-diaminobenzene with ethyl 2-oxopropoate, the dehydration of carbinolamine gradually becomes rate-limiting with increasing pH in acetate buffers, whereas in phosphate buffers a new reaction pathway makes itself felt, viz. the formation of amide catalyzed by the basic buffer component and by hydroxide ion.

The cyclization reaction of aromatic *ortho* diamines with α -dicarbonyl compounds, known under the name quinoxaline reaction, is used to prove either of the reaction components¹ and to prepare a number of quinoxaline derivatives^{2–4}. Kinetics of this reaction has not yet been studied in detail, and there exists no comprehensive treatment of its mechanism. This present report gives results of kinetic measurements of the reaction of 1,2-diaminobenzene with ethyl 2-oxopropoate and 2,3-butanedione in aqueous acetate and phosphate buffers and discusses the respective reaction mechanisms.

EXPERIMENTAL

All the reagents used were commercial chemicals. 1,2-Diaminobenzene m.p. 104–105°C was used as such; ethyl 2-oxopropoate was distilled before use, b.p. 74–76°C/15 kPa; 2,3-butanedione was purified by fraction distillation at 87–88°C. For the kinetic measurements a fresh solution of 0.01 mol l⁻¹ 1,2-diaminobenzene in 0.02 mol l⁻¹ hydrochloric acid was prepared every day. The solution of 0.2 mol l⁻¹ ethyl 2-oxopropoate in redistilled water was mixed with 1 : 1 acetate buffer to make its final concentration c. $2 \cdot 10^{-3}$ mol l⁻¹, and this solution was used for two days at most. The solution of 2,3-butanedione ($1 \cdot 10^{-2}$ mol l⁻¹) in redistilled water was stable. The solutions of acetate and phosphate buffers were prepared from the p.a. chemicals and redistilled water. Their ionic strength 0.5 mol l⁻¹ was adjusted with KCl, and their

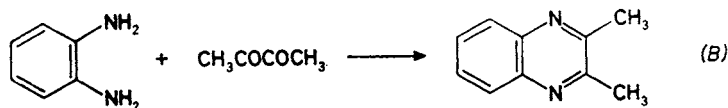
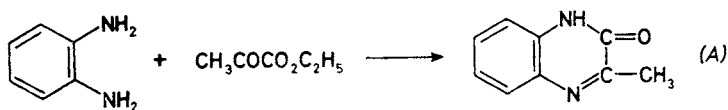
pH was measured with a Precision Digital pH meter Radelkis using the combined glass and saturated calomel electrodes at 25°C.

The ratio of 1,2-diaminobenzene to its conjugated acid in acetate buffers of 0.5 mol l^{-1} ionic strength was determined spectrophotometrically (Specord UV-VIS, Zeiss). In a 1 cm cell, $0.4 \text{ ml } 8 \cdot 10^{-4} \text{ mol l}^{-1}$ 1,2-diaminobenzene was added to 1.6 ml buffer, and the spectrum was recorded in the range of 250–330 nm. The proportion of the base to the overall concentration of 1,2-diaminobenzene was determined from the ratio $(A - A_{\text{BH}})/(A_{\text{B}} - A_{\text{BH}})$, where A is the absorbance value in the buffer, and A_{BH} and A_{B} are the absorbances in 0.1 mol l^{-1} HCl and in 4 : 1 phosphate buffer, respectively, always measured at 294 nm. The ratio values 0.14, 0.41, and 0.70 were found for the acetate buffers 4 : 1, 1 : 1, and 1 : 4, respectively.

The kinetic measurements were carried out spectrophotometrically (Specord UV-VIS, Zeiss) at 25°C at the ionic strength of 0.5 mol l^{-1} . 1,2-Diaminobenzene (20 μl) was injected into a 1 cm cell containing the buffer, KCl, and 2,3-butanedione ($(1 \text{ to } 4) \cdot 10^{-3} \text{ mol l}^{-1}$) or ethyl 2-oxopropanoate ($(2 \text{ to } 8) \cdot 10^{-2} \text{ mol l}^{-1}$) and the absorbance increase was measured at 316 or 334 nm, respectively. The rate constants were calculated from the relation $k_{\text{exp}}t = -\ln(A_{\infty} - A_t) + \text{const}$. In the case of ethyl 2-oxopropanoate, a slow absorbance increase was observed even after the reaction examined was finished. The reaction was followed up to c. four half-lives, and the A_{∞} value was determined by the method of stepwise approximation in such way that the time dependence of $\ln(A_{\infty} - A_t)$ were linear throughout the measurement range. The stoichiometric rate constants were obtained by dividing k_{exp} by the concentration of carbonyl compound, and the rate constants k related to the free base were obtained by dividing the stoichiometric constant by the molar proportion of the free base.

RESULTS AND DISCUSSION

The reaction of 1,2-diaminobenzene with ethyl 2-oxopropanoate⁵ (*A*) and with 2,3-butanedione⁶ (*B*) was followed at a great excess of the carbonyl compound, hence the reaction kinetics was pseudo-first order. At the reversed ratio of the reacting components the k_{exp} values were not reliable due to the high absorbance of 1,2-diaminobenzene.



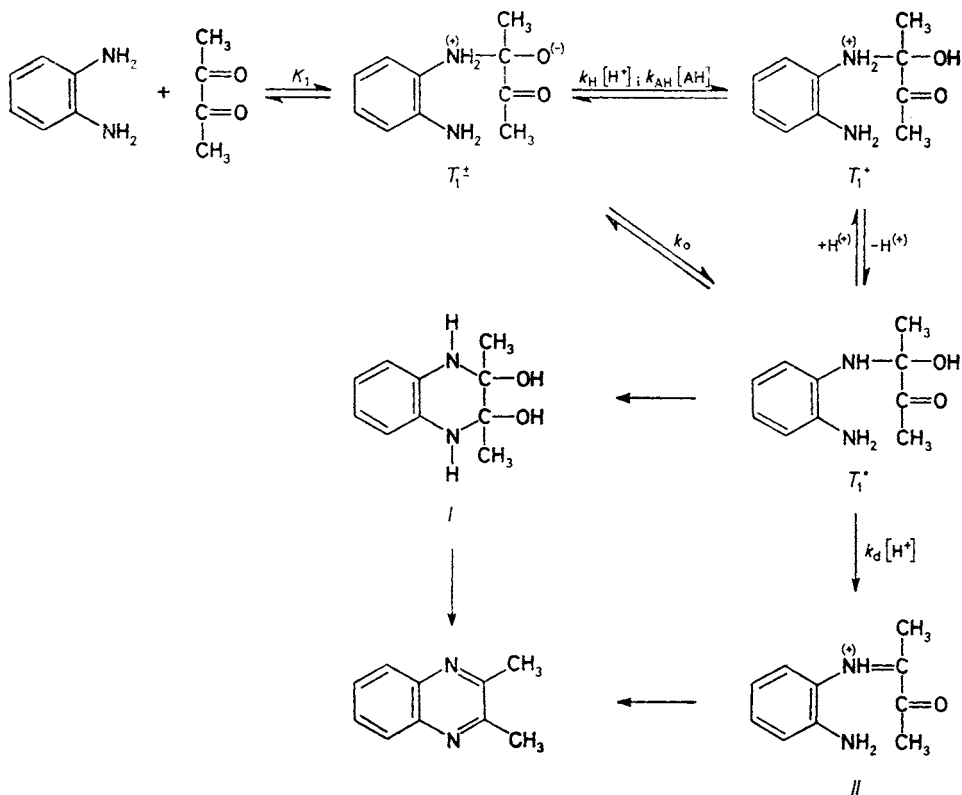
The dependence of the rate constants k of reaction (*B*) on concentration of the acid buffer component are given in Fig. 1, and that of k of reaction (*A*) on concentration of potassium hydrogen phosphate in Fig. 2. The dependence of k of reaction

(*B*) on the buffer composition and concentration is defined by the empirical equation (*I*) where $[HA]$ means concentration of the acidic buffer component.

$$k = a + b[H^+] + c[HA] \quad (I)$$

The proton concentration is so small in phosphate buffers, that the expression $b[H^+]$ can be neglected as compared with the other terms of the equation, hence practically all the points of the dependence of k on $[HA]$ lie at a single straight line for all the phosphate buffers used.

Taking into account the available knowledge about the reactions of amines with carbonyl compounds⁷⁻¹², we can describe the reaction mechanism by Scheme 1.



SCHEME 1

The reaction rate constant for the second amino group and the second carbonyl group of 2,3-butanedione must be several orders higher than that of formation of T_1^* or the protonated Schiff base *II* (an intramolecular process¹³), hence the rate-limiting

step must consist in the protonation of the intermediate T_1^\pm to give T_1^+ and in the simultaneous water-assisted proton transfer $T_1^\pm \rightarrow T_1^0$ (Eq. (2)).

$$k = K_1(k_0 + k_H[H^+] + k_{HA}[HA]) \quad (2)$$

The dependence of k on $[HA]$ is linear in the whole range of buffer concentration and composition, hence the cyclization goes via $T_1^0 \rightarrow I$ and not via the Schiff base *II*. If the Schiff base were one of the reaction intermediates, its formation would become rate-limiting with increasing pH and increasing buffer concentration, and the slope value of the k vs $[HA]$ dependence should gradually decrease¹⁴. The K_1k_{HA} values are given by the slope of the dependence of k on $[HA]$. The values K_1k_0 and K_1k_H were determined by plotting the intercepts at the y axis (Fig. 1) against the proton concentration* (Table I). As the protonation of the negatively charged oxygen atom of the T_1^\pm intermediate by the hydroxonium ion is considerably thermodynamically

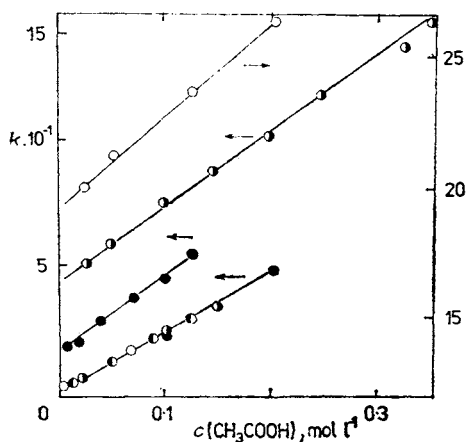


FIG. 1

Dependence of the rate constant k (in $1 \text{ mol}^{-1} \text{ s}^{-1}$) of the reaction of 2,3-butanedione with 1,2-diaminobenzene on the concentration c of acetic acid and hydrogenphosphate in acetate buffers 4:1 (○), 1:1 (○●), 1:4 (●), and in phosphate buffers 4:1 (●), 2:1 (●●), 1:1 (●○), and 1:2 (○), respectively

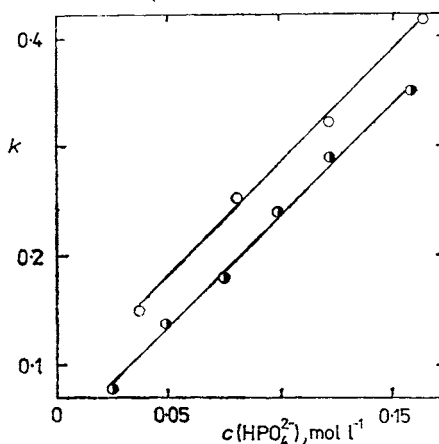


FIG. 2

Dependence of the rate constants k (in $1 \text{ mol}^{-1} \text{ s}^{-1}$) of the reaction of ethyl 2-oxopropanoate with 1,2-diaminobenzene on the concentration c of hydrogenphosphate in phosphate buffers 1:1 (○) and 1:4 (●)

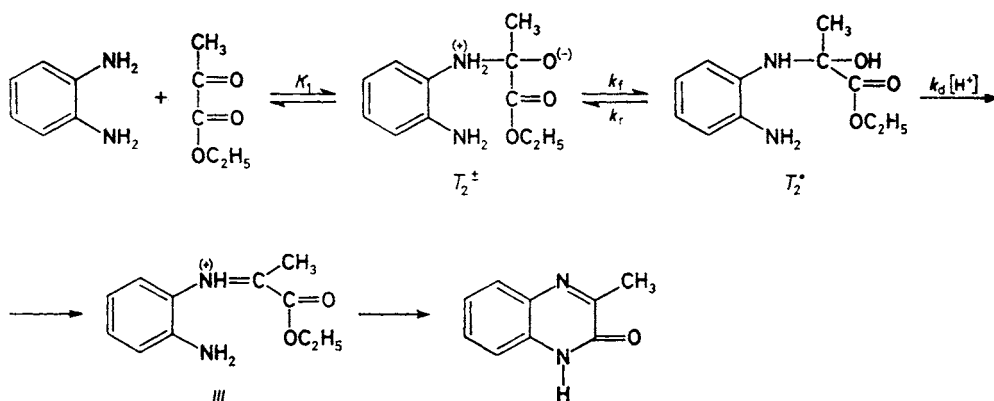
* The proton concentration was calculated from the dependence $[H^+] = -\text{antilog pH}$; the activity coefficient of the proton is close to 1 at the ionic strength of 0.5 mol l^{-1} (see e.g. ref.¹⁵), but its precise value cannot be found¹⁶.

favourable, it can be presumed that the rate of this reaction is diffusion-controlled, and the k_H value is $(4 \pm 1) \cdot 10^{10} \text{ l mol}^{-1} \text{ s}^{-1}$ (ref.¹⁷). Using this value and the $K_1 k_H$ value experimentally found ($1.5 \cdot 10^6 \text{ l}^2 \text{ mol}^{-2} \text{ s}^{-1}$) we obtain $K_1 \approx 4 \cdot 10^{-5} \text{ l mol}^{-1}$.

The dependence of the stoichiometric rate constant of the reaction (A) on the acetic acid concentration decreases with decreasing proton concentration (Fig. 3). The course of the dependence in Fig. 3 is typical of the change in the rate-limiting step from the protonation of the T_2^\pm intermediate (and its direct transformation into T_2°) (Scheme 2) to the dehydration of the carbinolamine T_2° (ref.¹⁴). The rate constant k is defined by Eq. (3)

$$k = K_1 k_f k_d [\text{H}^+] / (k_r + k_d [\text{H}^+]), \quad (3)$$

where $k_f = k_0 + k_H [\text{H}^+] + k_{\text{HA}} [\text{HA}]$ is the overall rate constant of the transformation $T_2^\pm \rightarrow T_2^\circ$, and k_r means the overall rate constant of the reverse reaction $T_2^\circ \rightarrow T_2^\pm$; the ratio k_f/k_r is equal to the equilibrium constant of the reaction $T_2^\pm \rightleftharpoons T_2^\circ$ and is independent of both pH and buffer concentration; k_d means the rate constant of dehydration of the carbinolamine T_2° into the Schiff base III (Scheme 2).



SCHEME 2

Equation (3) can be rewritten to the form (4) which can be transformed to Eq. (5).

$$k^{-1} = k_r / (K_1 k_f k_d [\text{H}^+]) + (K_1 k_f)^{-1} = (K_{\text{CA}} k_d [\text{H}^+])^{-1} + (K_1 k_f)^{-1} \quad (4)$$

$$(k^{-1} - (K_{\text{CA}} k_d [\text{H}^+])^{-1})^{-1} = K_1 (k_0 + k_H [\text{H}^+] + k_{\text{HA}} [\text{HA}]) \quad (5)$$

K_{CA} is the equilibrium constant of formation of the carbinolamine T_2^0 from the starting components, and the expression $K_{CA}k_d[H^+]$ represents the k value at such a high $[HA]$ concentration (experimentally inaccessible) that $k_r \gg k_d[H^+]$, hence the carbinolamine stands in a rapid pre-equilibrium with the starting components

TABLE I

The rate and equilibrium constants of the reaction of 1,2-diaminobenzene with 2,3-butanedione (B) and ethyl 2-oxopropanoate (A)

Quantity	Units	(A)	(B)
$K_1 k_0$	$l \text{ mol}^{-1} \text{ s}^{-1}$	0.25 ± 0.05	2.0 ± 0.5
$K_1 k_H$	$l^2 \text{ mol}^{-2} \text{ s}^{-1}$	$(2.2 \pm 0.3) \cdot 10^4$	$(1.5 \pm 0.2) \cdot 10^6$
$K_1 k_{HA}^a$	$l^2 \text{ mol}^{-2} \text{ s}^{-1}$	15.5 ± 2.0	300 ± 3.0
$K_1 k_{HA}^b$	$l^2 \text{ mol}^{-2} \text{ s}^{-1}$	—	240 ± 10
K_1	$l \text{ mol}^{-1}$	$5 \cdot 10^{-7}$	$4 \cdot 10^{-5}$
k_0	s^{-1}	$5 \cdot 10^5$	$5 \cdot 10^4$
k_H	$l \text{ mol}^{-1} \text{ s}^{-1}$	$4 \cdot 10^{10}$	$4 \cdot 10^{10}$
k_{HA}^a	$l \text{ mol}^{-1} \text{ s}^{-1}$	$3.1 \cdot 10^7$	$7.5 \cdot 10^6$
k_{HA}^b	$l \text{ mol}^{-1} \text{ s}^{-1}$	—	$6 \cdot 10^6$
$K_{AC}k_d$	$l^2 \text{ mol}^{-2} \text{ s}^{-1}$	$(1.50 \pm 0.15) \cdot 10^5$	—
$K_T k_A^c$	$l^2 \text{ mol}^{-2} \text{ s}^{-1}$	23 ± 3	—
$K_T k_{OH}$	$l^2 \text{ mol}^{-2} \text{ s}^{-1}$	$(4 \pm 1) \cdot 10^5$	—

^a HA = CH₃COOH; ^b HA = H₂PO₄⁻; ^cA = HPO₄²⁻.

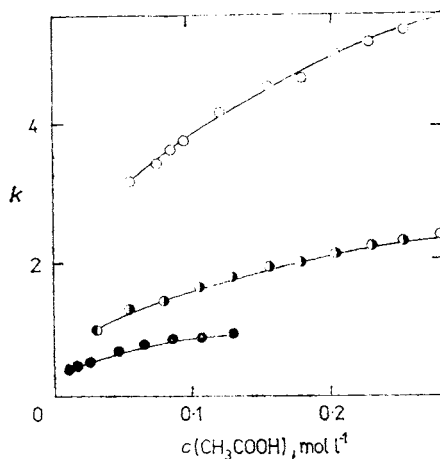


FIG. 3

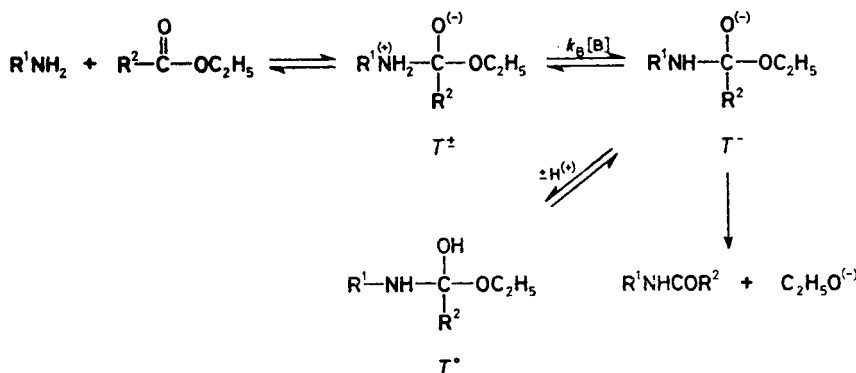
Dependence of the rate constant k (in $l \text{ mol}^{-1} \text{ s}^{-1}$) of the reaction of ethyl 2-oxopropanoate with 1,2-diaminobenzene on the concentration c of acetic acid in acetate buffers 4 : 1 (○), 1 : 1 (◐), and 1 : 4 (●)

and its dehydration is rate-limiting. The values corresponding to the acetate buffer ratios used were calculated by optimization from Eq. (5) and the k values found.

Figure 4 presents the dependence of the values from the left-hand side of Eq. (5) on the acetic acid concentration for the used ratios of acetate buffers. The K_1k_0 , K_1k_H , and K_1k_{HA} values found from slopes and intercepts in the same way as in the reaction with 2,3-butanedione are given in Table I. Using the value $k_H = 4 \cdot 10^{10} \text{ l mol}^{-1} \text{ s}^{-1}$ we calculated the value $K_1 = 5 \cdot 10^{-7} \text{ l mol}^{-1}$ which is almost two orders lower than the corresponding equilibrium constant of the reaction of 1,2-diaminobenzene with 2,3-butanedione.

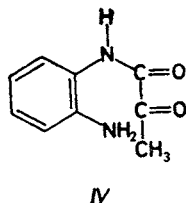
Whereas in the reaction with 2,3-butanedione the cyclization of the carbinolamine T_1^0 is presumed (on the basis of the k vs $[\text{H}^+]$ dependences found) to be the main reaction pathway, in the reaction with ethyl 2-oxopropanoate we presume that the carbinolamine T_2^0 is, at first, dehydrated to the protonated Schiff base *III* which is cyclized faster than the carbinolamine itself is. A similar conclusion was arrived at by Cocivera^{11,12} who studied the cyclization reactions of pentanedione and ethyl 2-oxobutanoate with hydroxylamine and explained this fact by a far greater reactivity of keto group (as compared with ester group) towards nucleophiles: in these cases he presumed a reactivity difference of 6 orders of magnitude.

In phosphate buffers (Fig. 2) the reaction is catalyzed by OH^- ions and the basic buffer component, which indicates a new reaction pathway to operate¹⁸. The general base catalysis in neutral and mildly basic media is typical of aminolyses of esters^{19,20} (Scheme 3). The rate-limiting step consists in splitting off of the proton from the T^\pm

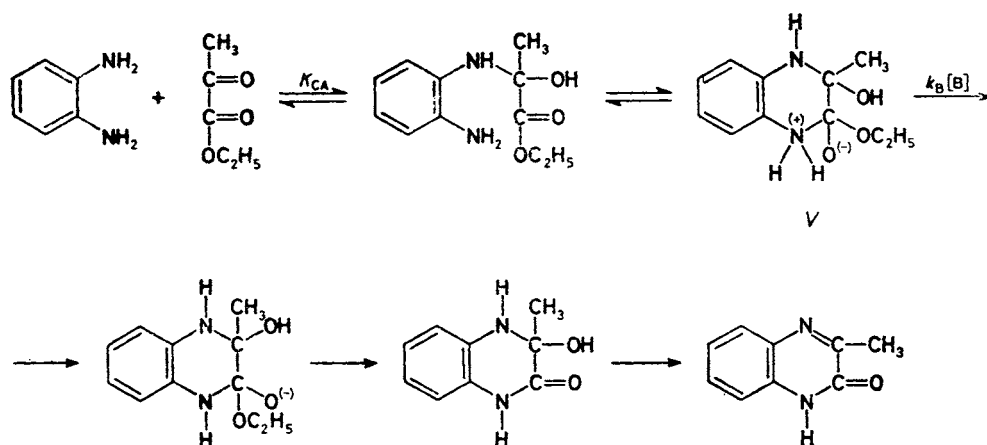


SCHEME 3

intermediate to give T^- which is either decomposed to amide and ethoxide ion or reversibly transformed into the T_0 intermediate. The generally base-catalyzed reaction of NH_2 group of 1,2-diaminobenzene with the ester group of ethyl 2-oxopropanoate to give amide *IV* and its subsequent cyclization can hardly be a new,



faster reaction pathway because of the large difference between the reactivities of carbonyl and ester groups¹¹.



SCHEME 4

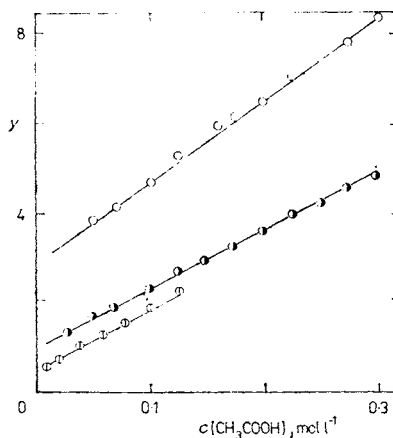


FIG. 4

Dependence of the rate constant $y = (k^{-1} - (K_{CA}k_d[\text{H}^+])^{-1})^{-1}$ (in $1 \text{ mol}^{-1} \text{ s}^{-1}$) of the reaction of ethyl 2-oxopropanoate with 1,2-diaminobenzene on the concentration c of acetic acid in acetate buffers 4:1 (○), 1:1 (⊙), and 1:4 (⊕). The calculated values $K_{CA}k_d[\text{H}^+]$ (in $1^2 \text{ mol}^{-2} \text{ s}^{-1}$) for the buffers used are 18, 4.5, and 1.33, respectively

A more likely reaction mechanism is given in Scheme 4. The rate of acid-catalyzed formation of the protonated Schiff base decreases and, on the other hand, the rate of base-catalyzed transformation of the cyclic intermediate *V* to cyclic amide (see Schemes 2 and 4) increases with decreasing proton concentration, hence in phosphate buffers the latter pathway becomes faster than that via the Schiff base. The rate constants of the reactions catalyzed by hydrogenphosphate (k_B) and hydroxyl ion (k_{OH}) (multiplied by the equilibrium constant K_T of formation of the cyclic intermediate) (Table I) were determined from the slope and intercept of the dependence of k on $[HPO_4^{2-}]$ (Fig. 2).

The pK_A value of the equilibrium $T^+ \rightleftharpoons T^\pm + H^+$ calculated from the extrathermodynamic relations²¹ is 6–6.5, i.e. the reaction of T^\pm with acetic acid should be thermodynamically favourable and the k_{HA} value should be near to the rate constant of diffusion-controlled reactions, $(0.5-1) \cdot 10^{10} \text{ l mol}^{-1} \text{ s}^{-1}$ (refs^{17,22}). The really calculated k_{HA} values are by 2–3 orders lower (Table I), hence the pK_A of T^+ intermediates are far smaller. From the published^{17,23} dependences of k_{HA} on ΔpK_A we can consider a value about 4 for the pK_A of the T^+ intermediate. Such a large difference between the pK_A values calculated from the extrathermodynamic relations and those estimated from the previous discussion can possibly be explained as follows: In usual protonated amines the positive charge of the nitrogen atom is largely dispersed through hydrogen bonds with the solvating water molecules²⁴. In the intermediates T^+ and T^\pm the NH_2 group is considerably "hidden" in the centre of the molecule, and formation of hydrogen bonds is sterically hindered. The resulting greater positive charge of nitrogen atom strongly attracts the electrons of adjacent groups, which increases the acidity of OH group.

The sterically hindered access to the NH_2 hydrogen atoms is also indicated by the k_0 values of the water-assisted proton rearrangement $T^\pm \rightarrow T^0$ which usually vary within the limits 10^6-10^8 (refs^{25,26}), but the values found by us are c. one order smaller than the lower limit mentioned.

The k_{HA} value of the reaction with 2,3-butanedione catalyzed with dihydrogenphosphate is almost the same as that of the reaction catalyzed with acetic acid, although the pK_A value of dihydrogenphosphate is two orders higher. Dibasic acids of this type can undergo a considerably concerted proton transfer, similar to that in the reaction catalyzed by water, hence the k_{HA} values are 2–3 orders greater than those corresponding to the respective pK_A value²⁷.

REFERENCES

1. Jureček M.: *Organická analýza I*, p. 300. Publishing House ČSAV, Prague 1955.
2. Pratt Y. T.: *Heterocyclic Compounds* (R. C. Elderfield, Ed.), Vol. 6, Chap. 10. Wiley, New York 1957.
3. Cheeseman G. W. H.: *Advances in Heterocyclic Chemistry* (A. R. Katritzky, Ed.), Vol. 2, p. 204. Academic Press, New York 1963.

4. Cheeseman G. W. H.: *Advances in Heterocyclic Chemistry* (A. R. Katritzky, Ed.), Vol. 22, p. 368. Academic Press, New York 1978.
5. Hinsberg O.: *Justus Liebigs Ann. Chem.* 292, 249 (1896).
6. Lundquist J. K.: *J. Chem. Soc.* 1953, 2825.
7. Sayer J. M., Jencks W. P.: *J. Am. Chem. Soc.* 94, 3262 (1972).
8. Diebler H., Thorneleg R. N. F.: *J. Am. Chem. Soc.* 95, 896 (1973).
9. Sayer J. M., Edman C.: *J. Am. Chem. Soc.* 101, 3010 (1979).
10. Jencks W. P.: *Chem. Soc. Rev.* 10, 345 (1981).
11. Cocivera M., Effio A., Chen H. E., Vaish S.: *J. Am. Chem. Soc.* 98, 7362 (1976).
12. Cocivera M., Woo K. W.: *J. Am. Chem. Soc.* 98, 7366 (1976).
13. Kirby A. J.: *Advances in Physical Organic Chemistry* (V. Gold and D. Bethell, Eds), Vol. 17, p. 183. Academic Press, London 1980.
14. Rosenberg S., Silver S. M., Sayer J. M., Jencks W. P.: *J. Am. Chem. Soc.* 96, 7986 (1974).
15. Schwabe K.: *pH-Messung*, p. 130. Akademie Verlag, Berlin 1980.
16. Bates R. G.: *Determination of pH*, 2nd ed., p. 47. Wiley, New York 1973.
17. Eigen M.: *Angew. Chem., Int. Ed.* 3, 1 (1964).
18. Štěřba V., Panchartek J.: *Kinetické metody při studiu reakcí organických sloučenin*, p. 96. SNTL, Prague 1985.
19. Satterthwait A. C., Jencks W. P.: *J. Am. Chem. Soc.* 96, 7018 (1974).
20. Cox M. N., Jencks W. P.: *J. Am. Chem. Soc.* 103, 572 (1981).
21. Fox J. P., Jencks W. P.: *J. Am. Chem. Soc.* 96, 1436 (1974).
22. Ridd J. H.: *Advances in Physical Organic Chemistry* (V. Gold and D. Bethell, Eds), Vol. 16, p.1. Academic Press, London 1978.
23. Ahrens M. L., Maass G.: *Angew. Chem., Int. Ed.* 7, 818 (1968).
24. Meot-Ner (Mautner) M.: *J. Phys. Chem.* 91, 417 (1987).
25. Luz Z., Meiboom S.: *J. Am. Chem. Soc.* 85, 3923 (1963).
26. Grunwald E., Fong D. W.: *J. Am. Chem. Soc.* 94, 7371 (1972).
27. Cox M. M., Jencks W. P.: *J. Am. Chem. Soc.* 103, 580 (1981).

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