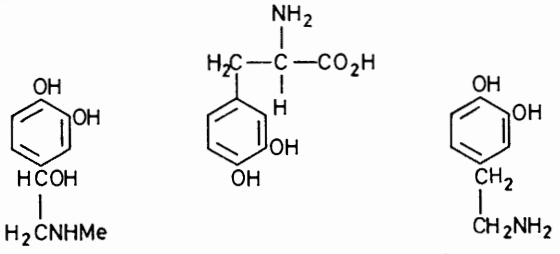
Kinetics and Mechanism of Oxidation Pathways of Some Catecholamines with Periodic Acid

By **Ezio Pelizzetti,* Edoardo Mentasti,** and **Edmondo Pramauro,** Istituto di Chimica Analitica dell'Università, Via P. Giuria 5, Torino, Italy

The kinetics and mechanism of oxidation of adrenalin, L-dopa, and dopamine to the corresponding open-chain *o*-benzoquinones with periodic acid have been investigated in the pH range 0—7, at different temperatures. The reactions are of the first order in each reagent and are strongly dependent on pH. Possible mechanisms are discussed with reference to previous work on oxidation with periodic acid and the variation of the rate as a function of pH has been explained in terms of differently protonated reagent couples. At pH >4, the substituted *o*-benzoquinones rearranged with cyclization of the side-chain into the corresponding leuco-aminochromes (5,6-dihydroxy-2,3-dihydroindoles), which are then rapidly oxidized to aminochromes (2,3-dihydroindole-5,6-quinones). The rate law is, in the pH range 4—8, in the form $k_{obs} = k_0K'_1/(K'_1 + [H^+])$, where K'_1 is the acid dissociation constant of the ammonium group of the side-chain, thus predicting that for pH >9 only the cyclization rates are nearly independent of pH. The cyclization rates have been found to decrease significantly in the order adrenalin ≫ L-dopa > dopamine.

WE have begun a systematic investigation of the oxidation of catecholamines in aqueous solution in order to obtain information about the reaction rates and mechanism of oxidation of these compounds which are of biological interest. In previous papers the oxidation of catecholamines to the corresponding substituted *o*-benzoquinones was examined for aqueous acidic perchlorate media (pH < 1), the oxidizing agent being an



(I) (II) (III)

aquametal ion (Tl^{III}, Mn^{III}, V^{V}, Co^{III}).[1] The cyclization of open-chained quinones to leuco-aminochromes (5,6-dihydroxy-2,3-dihydroindoles), further oxidized to aminochromes (2,3-dihydroindole-5,6-quinones),[2] takes place at higher pH (>4) and has been investigated by different techniques.[3]

In order to establish the mechanism and the rate constants of the single steps of formation of aminochromes, the oxidation of adrenalin {(—)-4-[1-hydroxy-2-(methylamino)ethyl]benzene-1,2-diol} (I), L-dopa [3-(3,4-dihydroxyphenyl)-2-aminopropionic acid] (II), and dopamine [4-(2-aminoethyl)benzene-1,2-diol] (III) with periodic acid in the pH range 0—8 was followed by means of a stopped-flow spectrophotometric technique.

EXPERIMENTAL

Reagents.—Catecholamine (Merck) solutions were prepared daily. Reagent grade materials were used for preparing periodate and buffer solutions. Sodium perchlorate was used for adjusting the ionic strength (μ 1.0M). Twice distilled water was used.

Procedure.—Kinetic runs were performed with a Durrum–Gibson stopped-flow spectrophotometer. A 564 Tektronix memory oscilloscope stored the traces of each run; these were photographed when traces of at least three runs were in satisfactory agreement. The data were then treated by a least-squares method. The formation of *o*-quinones was recorded at 390 nm with periodic acid in excess thus avoiding the intervention of iodate; the cyclization reactions were followed at 480 nm, the maximum absorbance of aminochromes (for comparison purposes some runs were

[1] E. Pelizzetti, E. Mentasti, E. Pramauro, and M. E. Carlotti, *Gazzetta*, 1975, **105**, 307; E. Mentasti, E. Pelizzetti, and E. Pramauro, *ibid.*, p. 551; E. Pelizzetti, E. Mentasti, and G. Saini, *ibid.*, in the press; E. Pelizzetti, E. Mentasti, and E. Pramauro, *J.C.S. Dalton*, 1976, 23.

[2] R. A. Heacock, *Chem. Rev.*, 1959, **59**, 181; *Adv. Heterocyclic Chem.*, 1965, **5**, 205; *Prod. Probl. Pharm.*, 1972, **27**, 107.

[3] (*a*) P. A. Malachesky, L. S. Marcoux, and R. N. Adams, *J. Phys. Chem.*, 1966, **70**, 4068; (*b*) R. N. Adams, M. D. Hawley, and S. W. Feldberg, *ibid.*, 1967, **71**, 851; (*c*) M. D. Hawley, S. V. Tatawawadi, S. Piekarsky, and R. N. Adams, *J. Amer. Chem. Soc.*, 1967, **89**, 447; (*d*) A. Brun and R. Rosset, *Electroanalyt. Chem. Interfacial Electrochem.*, 1974, **49**, 287; (*e*) T. E. Young, J. R. Griswold, and M. H. Hulbert, *J. Org. Chem.*, 1974, **39**, 1980; (*f*) S. Senoh, C. R. Creveling, S. Underfriend, and B. Witkop, *J. Amer. Chem. Soc.*, 1959, **81**, 6236.

followed at both wavelengths). pH Measurements of the buffer solutions were made with a Metrohm potentiometer, and were found to vary within 0.05 units during reactions. In the pH range 0—4 no buffers were used (perchloric acid was added to bring solutions to the proper acidity). In the pH range 4—6 acetate and >6 phosphate buffers were used. Details are given in Supplementary Publications No. SUP 21803 (6 pp.).*

RESULTS AND DISCUSSION

Stoicheiometry.—At pH < 3 the spectra of the products did not differ significantly from those previously recorded for open-chain *o*-benzoquinones.[1] Moreover spectrophotometric titrations supported the expected stoicheiometry (1) where Cat and Per represent cate-

$$\text{Cat} + \text{Per} \longrightarrow o\text{-quinone} + \text{iodate} \qquad (1)$$

cholamine and periodic acid respectively, whatever the ionic form. In the pH range 4—8, the spectra of the products were characteristic of aminochromes. The reported overall reaction is an oxidation involving four electrons per molecule.[3]

Kinetics and Mechanism of o-Benzoquinone Formation.—The formation of the open-chain *o*-benzoquinone was of the first order with respect to the reagent in deficit (catecholamine) and plots of $\ln(A_\infty - A_t)$ *vs.* time were linear for at least three half-lives with correlation coefficients >0.997. The observed rate constants were found to increase linearly with [Per] (Table 1). Second-order rate constants at various pH values and temperatures are collected in Table 2. Plots of $1/k_{obs}$ *vs.*

TABLE 1

Pseudo-first-order rate constants for the oxidation of adrenalin [a] at different pH values

pH 1.00 [b]		pH 3.45 [c]	
10^3[Per]/M	k_{obs}/s^{-1}	10^3[Per]/M	k_{obs}/s^{-1}
2.0	0.28	2.0	1.49
5.0	0.78	5.0	3.31
10.0	1.66	10.0	6.6
50	8.4	15.0	9.6
100	16.3	25.0	16.2

[a] [Adr] = 2×10^{-4}M, 25°. [b] Perchloric acid added. [c] Acetate buffer added.

1/[Per] showed good linearity with intercepts that did not differ significantly from zero over a large range of periodic acid concentrations.

In the present investigations, kinetic runs were carried out at different pH values, wavelengths, and reagent concentrations in order to investigate the formation of intermediates. At very low pH (<1) the reactions give rise to stable end products whose absorption spectra indicate the formation of *o*-benzoquinones. At intermediate pH (1—4), there is a rapid decrease in transmittance followed by an increase of *ca.* 2% units (with a half-life of *ca.* 2—3 s) as previously found by Weidman and Kaiser for catechol oxidation.[4] This fact was considered by these authors as due to the formation of an intermediate, although no definitive conclusions about its structure were advanced.

TABLE 2

Second-order rate constants (1 mol^{-1} s^{-1}) for oxidation of adrenalin (15.0°), L-dopa (25.0°), and dopamine (25.0°) at different pH values

pH	Adrenalin	L-Dopa	Dopamine
0.10 [a]	0.34×10^2		
0.70 [a]	0.68×10^2	1.32×10^2	1.28×10^2
1.00 [a]	1.05×10^2	1.86×10^2	1.83×10^2
1.30 [a]	1.55×10^2	2.5×10^2	2.3×10^2
1.53 [a]	1.95×10^2		
1.70 [a]	2.3×10^2		
1.90 [a]	2.2×10^2	3.2×10^2	2.95×10^2
2.00 [a]	2.7×10^2		
2.50 [a]	2.8×10^2	3.7×10^2	3.35×10^2
2.75 [a]	2.9×10^2	3.85×10^2	3.6×10^2
3.45 [b]	5.3×10^2		
3.50 [a]	5.25×10^2	5.05×10^2	4.95×10^2
3.75 [b]	7.3×10^2		
3.91 [b]		1.35×10^3	1.22×10^3
4.10 [b]	1.42×10^3		
4.23 [b]	1.73×10^3		
4.33 [b]		1.95×10^3	1.80×10^3
4.73 [b]	3.6×10^3		
4.88 [b]	5.6×10^3		
5.06 [c]	1.30×10^4		
5.12 [b]	1.23×10^4		
5.56 [c]		3.0×10^4	2.2×10^4
5.64 [c]	7.2×10^4		
6.05 [c]		7.5×10^4	5.7×10^4
6.16 [c]	4.0×10^5		
6.45 [c]		2.05×10^5	1.41×10^5
6.65 [c]	1.05×10^6		
6.82 [c]	2.3×10^6		

[a] Perchloric acid added. [b] Acetate buffer added. [c] Phosphate buffer.

For the present compounds, at higher pH, where cyclization occurs at a considerable rate, the formation of the product with an absorbance maximum at 390 nm was followed immediately by its decomposition. The rate of this last reaction was found to be the same as the rate of formation of aminochromes, determined at 480 nm. Because cyclization occurs only for *o*-quinonoid derivatives, it seems reasonable to suggest a reaction involving the formation of products of similar structure in the first stage. Moreover, the values of the rate constants for the decomposition of the compound with absorption maximum at 390 nm to give an *o*-quinone, as proposed by Weidman and Kaiser, should be slower than our cyclization rate constants, and an induction period or more complex kinetics should be observed. In conclusion the hypothesis that no formation of an intermediate occurs and that the product of the first transmittance decrease is a quinonoid structure seems more probable.

pH *Dependence.*—The data reported in Table 2 indicate that the rate constants for the first oxidation step are much affected by pH. This pH dependence can be explained by taking into account the different status of protonation of the reagents, *i.e.* for periodic acid, equation (2) applies and for adrenalin, equation (3). K_1 and K_2 are the apparent first and second dissociation constants of periodic acid. For catecholamines, the first acid

* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue. Items less than 10 pp. are supplied as full-size copies.

[4] S. W. Weidman and E. T. Kaiser, *J. Amer. Chem. Soc.*, 1966, **88**, 5820.

dissociation constant K_1 was assigned to the ammonium deprotonation and K_2 to the first phenolic group dissociation. Recently Boggess and Martin [5] suggested

$$H_5IO_6 \underset{+H^+}{\overset{K_1}{\rightleftharpoons}} Per^- \underset{+H^+}{\overset{K_2}{\rightleftharpoons}} H_3IO_6^{2-} \quad (2)$$

$$H_3Adr^+ \underset{+H^+}{\overset{K_1}{\rightleftharpoons}} H_2Adr \underset{+H^+}{\overset{K_2}{\rightleftharpoons}} HAdr^- \quad (3)$$

that these dissociation constants represent competitive deprotonations and consequently they cannot be assigned to the ammonium or phenolic group. The second order rate constants k_0 can be expressed as in

$$-d[Cat]/dt = k_0[Cat]_t[Per]_t \quad (4)$$

equation (5) where k_{ij} is the specific rate constant

$$k_0 = \sum_{i=0}^{m} \sum_{j=0}^{n} k_{ij}\alpha_i\alpha'_j \quad (5)$$

corresponding to the reacting species, i for adrenalin and j for periodic acid (*i.e.*, k_{12} for H_2Adr and $H_3IO_6^{2-}$), and α_i and α_j' represent the molar fraction of the corresponding species. For (I) and (III), $m = 2$ and for (III), $m = 3$. Thus in the case of (I) equation (6) holds. From the values of the dissociation constants of

$$k_0 = k_{00}\alpha_0\alpha_0' + k_{01}\alpha_0\alpha_1' + k_{02}\alpha_0\alpha_2' + k_{10}\alpha_1\alpha_0' + k_{11}\alpha_1\alpha_1' + k_{12}\alpha_1\alpha_2' + k_{20}\alpha_2\alpha_0' + k_{21}\alpha_2\alpha_1' + k_{22}\alpha_2\alpha_2' \quad (6)$$

equilibria (2) [6] and (3) [7] it is possible to evaluate $\alpha_j\alpha_j'$ at different pH values. At pH 0—2, it is reasonable to take into account only H_3Adr^+, H_5IO_6, and Per^- (the more deprotonated species are present in very low concentrations and should give specific rate constants higher than the diffusion-controlled limit) to give a good estimate of k_{00} and k_{01}; similarly in the pH range 4—7, only the paths described by $\alpha_0\alpha_2'$, $\alpha_1\alpha_1'$, and $\alpha_1\alpha_2'$ need to be considered; by taking into account the pH effect on $\alpha_0\alpha_2'$ and $\alpha_1\alpha_1'$ these two paths cannot be differentiated.

Figure 1 shows a comparison between the experimental points (adrenalin at 15°) and a curve calculated with the parameters given in the Figure caption. Because the paths involving $\alpha_0\alpha_2'$ and $\alpha_1\alpha_1'$ are indistinguishable, k_{02} represents a combination of both paths. A minimization technique, previously described, has been adopted.[8] The agreement of experimental and calculated rate constants is within 15%; it should be noted that larger deviations occur at the highest pH, where small deviations in the experimental pH give rise to large variations in the reaction rates.

[5] R. K. Boggess and R. B. Martin, *J. Amer. Chem. Soc.*, 1975, **97**, 3076.

[6] G. J. Buist, C. A. Bunton, and J. Lomas, *J. Chem. Soc.* (*B*), 1966, 1094; G. J. Buist, W. C. P. Hipperson, and J. D. Lewis, *J. Chem. Soc.* (*A*), 1969, 307.

[7] L. G. Sillen and A. E. Martell, 'Stability Constants of Metal-Ion Complexes,' Chem Soc. Special Publication Nos. 17 (1964) and 25 (1971).

[8] E. Pelizzetti, E. Mentasti, and G. Saini, *Ber. Bunsengesellschaft Phys. Chem.*, 1973, **77**, 1126.

Even taking into account this agreement and the lack of any experimental evidence for formation of intermediates, the oxidation mechanism of catecholamines with periodic acid cannot be definitely assigned. In fact Buist and Bunton reported in their papers [9] on glycol oxidation that the reaction proceeds through various steps (monoester, cyclic ester, decomposition into products) and that the rate-determining step varies with the substrates and pH. On the other hand it must be noted that the oxidation of aromatic diols does not need

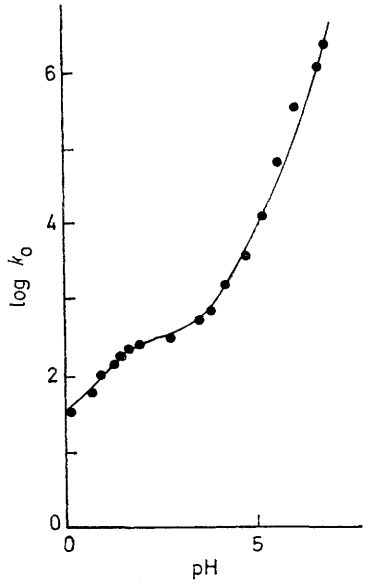
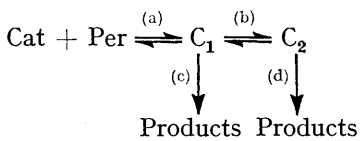


FIGURE 1 pH Dependence of k_0 for the oxidation of adrenalin with periodic acid at 15.0°. The points are experimental data and the curve was computed, according to equation (6), with the following values: $k_{00} = 25$, $k_{01} = 3.6 \times 10^2$, $k_{02} = 3.0 \times 10^6$, $k_{12} = 4.6 \times 10^9$ l mol^{-1} s^{-1} (other k_{ij} were taken zero, see text); $K_1 = 5.5 \times 10^{-10}$, $K_2 = 6.8 \times 10^{-11}$, $\bar{K}_1 = 3.2 \times 10^{-2}$, $\bar{K}_2 = 2.7 \times 10^{-8}$ mol l^{-1}

the formation of a cyclic ester intermediate (quinol,[10] guaiachol,[4] and quinol monoesters [11]). Then Scheme 1 can be considered. C_1 and C_2 represent the monoester



SCHEME 1

and the cyclic ester, whatever their ionic form. The pH dependence, the lack of necessity of cyclic ester intermediate, the small base catalysis observed (acetate buffer), and comparison with data for propane-1,2-diol,[9] suggest that step (a) is kinetically relevant. The

[9] G. J. Buist and C. A. Bunton, *J. Chem. Soc.* (*B*), 1971, 2117; G. J. Buist, C. A. Bunton, and W. C. P. Hipperson, *ibid.*, p. 2128; G. J. Buist, 'Comprehensive Chemical Kinetics,' eds. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1972, vol. VI, ch. 5.

[10] E. T. Kaiser and S. W. Weidman, *J. Amer. Chem. Soc.*, 1964, **86**, 4354.

[11] C. A. Bunton and J. M. Hellyer, *J. Amer. Chem. Soc.*, 1967, **89**, 6252; R. J. Brooks, C. A. Bunton, and J. M. Hellyer, *J. Org. Chem.*, 1973, **38**, 2151.

hypothesis that step (c) is rate limiting is also consistent with experiment and in this instance the pH dependence could be explained by taking into account the various protonated species of monoester. However the possibility that for different pH ranges, different steps are rate limiting or partly rate limiting, cannot be ruled out. Comparison of the oxidation data for the three catecholamines shows that for the pair $H_3Cat^+ + H_5IO_6$ the order of reactivity is (III) ~ (II) > (I) (according to the formal redox potentials of the pair *o*-benzoquinone–catecholamine),[12] as previously observed for the oxidation of several catechols with periodic acid in highly acidic media; [13] the specific rate constants for the pair $H_3Cat^+ + Per^-$ is independent of the nature of the organic substrate; at higher pH (>4), various pairs are consistent with observed dependence and the comparisons do not yield much useful information.

TABLE 3

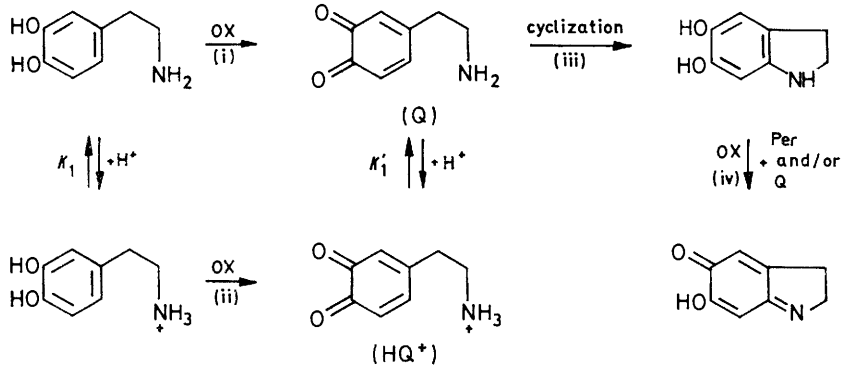
Effect of buffer concentration on oxidation of adrenalin (k_0/l mol^{-1} s^{-1}, 15.0°)

pH 4.07 ± 0.03		pH 4.93 ± 0.05	
10^2[AcO$^-$]/M	10^{-3} k_0	10^2[AcO$^-$]/M	10^{-3} k_0
0.60	1.42		
1.2	1.45	1.2	6.2
2.4	1.61	2.4	6.6
3.6	1.75		
4.8	1.93	4.8	5.9
6.0	2.05	9.6	6.5
pH 5.06 ± 0.04		**pH 6.06 ± 0.03**	
10^2[$H_2PO_4^-$]/M	10^{-4} k_0	10^2[$H_2PO_4^-$]/M	10^{-5} k_0
1.2	1.25	1.2	2.01
2.4	1.40	2.0	1.83
3.6	1.42	4.0	1.67
4.8	1.43	6.0	1.65
		8.0	1.55

Temperature and Salt Effects.—Kinetic data at different temperatures showed a larger increase of reaction rates at lower pH. The effect of the concentration of buffer was investigated at 15.0° and at pH 4.07 and 4.93 (acetate) and 5.06 and 6.06 (phosphate); the data are reported in Table 3 and show that only for acetate buffer at lower pH is there a slight catalytic effect. Moreover kinetic runs performed at pH 3.7 with and without acetate buffer ([Ac$^-$] + [HAc] = 7 × 10^{-2}M) showed only a slight increase in the rate constants. The addition of $NaClO_4$ from 0.05 to 0.30M, decreases the reaction rate of 20%.

Cyclization Reaction.—The open-chain *o*-benzoquinones rearrange to give leuco-aminochromes, further oxidized to aminochromes,[2,3] as shown by cyclic voltammetry over narrow ranges of pH [up to 5 for (I), 6 for (II), and 7 for (III)].[3c,e]

The present technique allows investigations to be carried out up to pH 8. Moreover there is the possibility of evaluating reliable values of reaction rates by following both the formation of aminochromes and the decomposition of *o*-quinones at different wavelengths. Scheme 2 can be proposed (*e.g.* dopamine). Step (iii) is rate determining if the experiments are made for a large excess of periodic acid (up to 2 × 10^{-2}M for *ca.* 5 × 10^{-6}M of catecholamine) (see Table 4). The



SCHEME 2

TABLE 4

Effect of periodic acid concentration on cyclization rate ([Adr] = 6 × 10^{-5}M, 25.0°)

10^3[Per]/M	k_{obs}/s^{-1}	
	pH: 3.76 [a]	5.64 [b]
1.0	0.087	4.8_5
2.0	0.105	6.4
5.0	0.114	7.7
10.0	0.119	7.6_5
20.0	0.119	7.9

[a] Acetate buffer added. [b] Phosphate buffer added.

kinetic runs at pH > 7, owing to the unavailability of an anaerobic system, were performed by mixing a catecholamine solution at pH < 7 with the oxidant buffered at the desired pH (the final pH was tested potentiometrically). At pH > 8 the spectra of the reaction products showed that in addition to the aminochromes, other side-products are formed, probably due to condensation reactions of *o*-benzoquinones.[14] The rate constants evaluated under these conditions cannot be assigned only to cyclization, so that the rate-limiting

[12] W. M. Clark, 'Oxidation-Reduction Potentials of Organic Systems,' Williams and Wilkins, Baltimore, 1960.

[13] E. Mentasti, E. Pelizzetti, and G. Giraudi, *Z. phys. Chem (Frankfurt)*, 1976, **100**, 71.

[14] H. Musso, 'Oxidative Coupling of Phenols,' eds. W. I. Taylor and A. R. Battersby, Dekker, New York, 1967, ch. 1.

condition cannot be experimentally achieved. Data are reported in Table 5.

TABLE 5

First-order rate constants (s^{-1}) for cyclization reaction at different pH (25.0°)

pH	Adrenalin	pH	L-Dopa	pH	Dopamine
3.50 [a]	0.060	4.31 [a]	0.008 1	5.56 [b]	0.009 1
3.75 [a]	0.098	4.62 [a]	0.022	6.05 [b]	0.026
4.23 [a]	0.29	5.56 [b]	0.155	6.42 [a]	0.066
4.55 [a]	0.62	6.05 [b]	0.495	6.73 [b]	0.083
5.12 [a]	2.5	6.42 [b]	1.21	6.95 [b]	0.133
5.62 [b]	7.1	6.73 [b]	2.6	7.35 [b]	0.42
6.07 [b]	19.2	6.95 [b]	3.85	7.85 [b]	1.02
6.47 [b]	46	7.30 [b]	7.0	8.07 [b]	1.55
6.61 [b]	69	7.38 [b]	7.5	8.40 [b]	3.95
6.80 [b]	97	7.82 [b]	12.2		
		8.04 [b]	19		

[a] Acetate buffer added. [b] Phosphate buffer added.

From Scheme 2, by assuming that the oxidation and protonation reactions are fast with respect to step (iii), expression (7) holds where k_c is the specific rate constant

$$k_{obs} = k_c K'_1/(K'_1 + [H^+]) \qquad (7)$$

for cyclization and K'_1 the acid dissociation constant of the ammonium group in the side chain of the *o*-benzoquinone. In previous papers,[3] the assumption that $K'_1 = K_1$ was made in order to evaluate k_c. In the light of ref. 5 this hypothesis is uncorrect because after oxidation to *o*-benzoquinone, no phenolic group is available to dissociate competitively with the ammonium group. From equation (7), it follows that when $K'_1 \ll [H^+]$, $k_{obs} = k_c K'_1 [H^+]^{-1}$ and when $K'_1 \gg [H^+]$, $k_{obs} = k_c$; hence equation (7) predicts that for pH > 9 only the cyclization rates become independent of pH. Figure 2 shows plots of experimental data with the lines calculated according to equation (7); the values of $k_c K'_1$ are collected in Table 6. The data show that the reactivity decreases in the order (I) $\gg$ (II) > (III), which accords with previous findings.[3c] In previous work [3c,e] the rate-limiting step at higher pH was assumed to be deprotonation of HQ^+ to Q. This rate constant, with $K'_1 = k'_1/k'_{-1}$ *ca.* 10^{-9} mol l^{-1}, and by assuming the rate corresponding to k'_{-1} to be diffusion-controlled, should have a value *ca.* 10^2 s^{-1}. Then for (II) and (III) cyclization is rate determining even at higher pH (*ca.* 9) where in addition the oxidation proceeds largely through step (i) giving Q directly. In the case of (I), deprotonation of HQ^+ may become kinetically relevant but this catecholamine is so reactive that no data are available above pH 7. Up to this value plots of log k_{obs} *vs.* pH are linear.

TABLE 6

Specific rate constants $k_c K'_1$ (mol l^{-1} s^{-1}) and overall activation parameters for cyclization reactions

	Adrenalin			
T/°C	15.0	25.0		35.0
$k_c K_1'$	5.6×10^{-6}	1.85×10^{-5}		5.5×10^{-5}
	$\Delta H^{\ddagger}$ 19.7 ± 1.2 kcal mol^{-1}			
	$\Delta S^{\ddagger}$ −14.5 ± 3.8 cal mol^{-1} K^{-1}			
	L-Dopa			
T/°C	6.0	25.0	32.0	40.0
$k_c K_1'$	1.78×10^{-8}	4.0×10^{-7}	1.62×10^{-6}	4.6×10^{-6}
	$\Delta H^{\ddagger}$ 28.3 ± 1.0 kcal mol^{-1}			
	$\Delta S^{\ddagger}$ 6.9 ± 3.4 cal mol^{-1} K^{-1}			
	Dopamine			
T/°C	6.0	25.0	32.0	40.0
$k_c K_1'$	1.25×10^{-9}	1.71×10^{-8}	4.2×10^{-8}	1.04×10^{-7}
	$\Delta H^{\ddagger}$ 22.2 ± 0.7 kcal mol^{-1}			
	$\Delta S^{\ddagger}$ −20.1 ± 2.4 cal mol^{-1} K^{-1}			

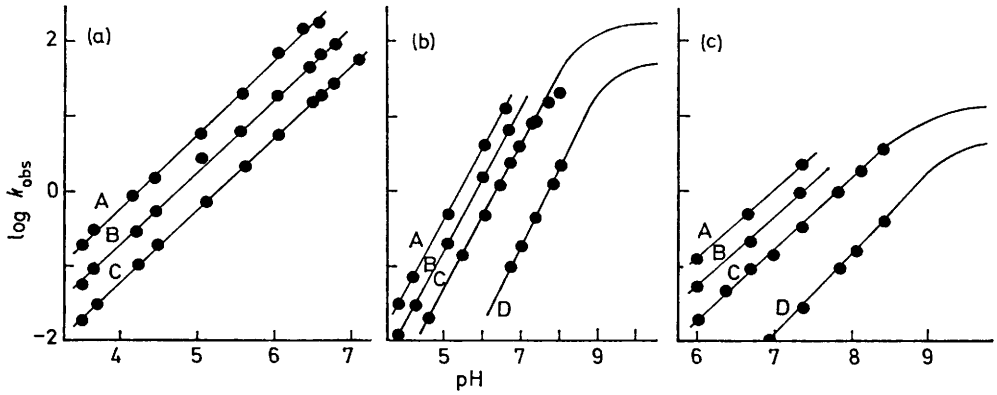


FIGURE 2 Analysis of pH dependence of cyclization reaction. The points are the experimental data and the curves were computed according to equation (7) with the values of $k_c K_1'$ reported in Table 6: (a) adrenalin, A, 15.0°; B, 25.0°; C, 35.0°; (b) L-dopa, A, 6.0°; B, 25.0°; C, 32.0°; D, 40.0°; (c) dopamine, A, 6.0°; B, 25.0°; C, 32.0°; D, 40.0°

Salt Effects.—A four-fold variation of buffer concentration did not produce a significant effect on the observed cyclization rate. Similarly kinetic runs performed at pH 3.7 in the absence or presence of acetate buffer as well as at pH 5.2 with acetate or phosphate did not exhibit significant differences. However the addition of $NaClO_4$ causes variations (at pH 6.06 the rate is reduced to one third by addition of 1.5M-$NaClO_4$); this could be accounted for by variation of K'_1 with ionic strength.

[5/2110 *Received*, 28*th October*, 1975]