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Complexes of 3,4-Dihydroxyphenyl Derivatives*. IV. Equilibrium Studies on some Transition Metal Complexes formed with Adrenaline and Noradrenaline

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The stoichiometries and stability constants of the complexes formed in the manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II)–L-adrenaline and noradrenaline systems were determined pH-metrically at 25 °C and 0.2 mol/dm³ ionic strength.

It was proved that when there is an excess of ligand only the ortho *phenolic hydroxy groups take part in the coordination, and that the participation of the side-chain in the complex formation is subordinate.*

From an ESR spectral study of the copper(II)–adrenaline system it was assumed that at a metal ion/ligand ratio of 1:1 and at higher pH (pH > 10) a polynuclear complex may also be formed. In this species the mode of bonding is mixed, with the participation of the side-chain donor groups.

It was found that the complex-forming properties of adrenaline and noradrenaline towards the transition metal ions studied are very similar, this being a consequence of the small difference between the structures of these ligands.

Introduction

Metal ions play a significant role in the storage and transport of adrenaline, noradrenaline and other biogenous amines. A review [1] has appeared on the results obtained so far relating to the transition metal–biogenous amine–ATP complexes formed in these biological processes.

Detailed studies have been made of the protonation processes of adrenaline and noradrenaline [2–4]. Martin [3] reported the microscopic dissociation constants for the side-chain ammonium and the first phenolic hydroxy groups by recalculating some earlier published spectrophotometric data. He found that the phenolic hydroxy group is more acidic than the side-chain ammonium group.

Adrenaline and noradrenaline each contain two separate chelate-forming groups within the molecule. Hence, the *ortho* phenolic hydroxy groups may form catechol-like O,O-coordinated, and the side-chain donor atoms ethanolamine-like O,N-coordinated complexes with metal ions. Because of the significant difference between the complex-forming tendencies of ethanolamine and catechol, it is to be expected that the participation of the side-chain in complex formation, at least at lower pH, is insignificant.

A pH-metric equilibrium study of transition metal complexes of adrenaline and noradrenaline, among others those of nickel(II), copper(II) and zinc(II), has been performed by Weber *et al.* [4]. Their measurements were evaluated in a very narrow pH interval with the assumption of only O,O-coordination. In the case of the zinc(II)–ligand interaction, they observed only the formation of a 1:1 protonated complex. The manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II) complexes of adrenaline and noradrenaline have been investigated by Jameson and Neillie [5, 6]. In the presence of an excess of ligand, mainly O,O-coordinated complexes were assumed in all systems. In the nickel(II) and copper(II)–ligand systems at a metal/ligand ratio of 1:1, however, the fomation of mixed-bonded complexes (containing both O, O and O, N bonds) and only O,N-coordinated complexes could not be excluded. On the basis of spectroscopic measurements, Bogges and Martin [7] concluded that copper(II) forms mainly O, O complexes with adrenaline. At a ligand/metal ratio of 1:1, and at higher pH, however, the complex-forming role of the side-chain increases, and thus the possibility arises for the formation of polynuclear complexes containing mixed bonding. From ESR spectral studies Smith *et al.* [8, 9] concluded that only monomeric complexes are present in the copper(II)–adrenaline and copper(II)–noradrenaline systems at room temperature. In frozen solutions at 77 K, however, the formation of a dimeric complex was also proved. Jarke and Rajan [10] carried out

*Part III, ref. [13].

TABLE I. Macroconstants of Deprotonation of Adrenaline and Noradrenaline.

	pK_1	pK_2	pK_3	I [mol/dm^3]	T [°C]	Ref.
Adrenaline	8.64 ± 0.01	9.84 ± 0.01	13.1 ± 0.2	0.2 KCl	25	this work
	8.66 ± 0.01	9.95 ± 0.05	13.0	0.1 KCl	25	2
	8.71	9.90	–	0.1	20	3
	8.52 ± 0.02	10.04 ± 0.03	11.99 ± 0.03	0.5 $NaNO_3$	20	4
Noradrenaline	8.58 ± 0.01	9.53 ± 0.01	12.9 ± 0.2	0.2 KCl	25	this work
	8.64 ± 0.01	9.70 ± 0.05	13.0	0.1 KCl	25	2
	8.73	9.78	–	0.1	20	3
	8.73 ± 0.02	9.59 ± 0.02	11.56 ± 0.02	0.5 $NaNO_3$	20	4

NMR spectral studies on the copper(II)–noradrenline system, and from a slight broadening of the α-methylene proton resonance they assumed the coordination of the ethanolamine side-chain even at pD ~ 4.

The aim of the present work is to establish the stoichiometric compositions and stability constants of the species formed in the manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II)–adrenaline and noradrenaline systems. In addition, an attempt is made to obtain information on the bonding modes in the complexes formed, on the participation of the side-chain in complex formation, and on the possibility of the formation of polynuclear species, by means of ESR and visible spectral studies.

Experimental

Chemicals

The chemicals used were commercially-available products of Fluka and Reanal. Stock solutions were prepared from metal chlorides of the highest analytical purity and their concentrations were checked gravimetrically in the form of the oxinate and for manganese(II) in the form of the ammonium phosphate.

pH-metric and Spectral Measurements

The stability constants of the manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II) parent complexes were determined by pH-metric titration. The ionic strength was adjusted to 0.2 mol/dm^3 with KCl. In all systems the titrations were carried out at eight ligand/metal ratios. The ligand concentration was 6×10^{-3}, 4×10^{-3} or 2×10^{-3} mol/dm^3 and the metal ion concentration was 1×10^{-3}, 2×10^{-3} or 4×10^{-3} mol/dm^3. The ligand/metal ratio was varied from 6:1 to 1:1. At a ratio of 1:1, precipitation was observed at pH ~ 8.5. For the same reason the cobalt(II), nickel(II) and zinc(II)–noradrenaline systems were titrated only to pH ~ 9.5 at 3:1 or lower ratios. In other cases titrations were performed in the pH range 5–11. The pH-metric measurements were made in the manner described earlier [11], with a Radiometer PHM 64 instrument, a G 202 B glass electrode and a K 404 calomel electrode. The temperature of the measurements was 25 ± 0.1 °C.

The dissociation microconstants of the ligands were determined as described in our earlier paper [13], using the method of Edsall *et al.* [12]. A Beckman ACTA MIV double-beam recording spectrophotometer was used for these examinations.

ESR spectra were recorded with a JES-ME-1X ESR spectrometer. The experimental conditions were the same as those described earlier [11].

Calculations

The species of various compositions formed in the systems studied can be characterized by the following general equilibrium process:

$$nA + qM + pH \rightleftharpoons A_nM_qH_p \quad (1)$$

The stability constants of the species are given by:

$$\beta_{nqp} = \frac{[A_nM_qH_p]}{[A]^n[M]^q[H]^p} \quad (2)$$

The stability constants defined by eqn. (2) were calculated in the usual manner from the pH-metric titration data [11].

Results and Discussion

The pH-metrically determined protonation constants of adrenaline and noradrenaline are given in Table I, together with some literature data.

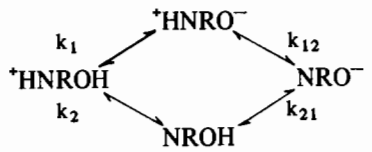
Comparison of the deprotonation constants determined in the present work and by others reveals good agreement, with the exception of the value of pK_3, which characterizes the deprotonation of the

TABLE II. Microconstants of Deprotonation of Adrenaline and Noradrenaline.

	pk_1	pk_2	pk_{12}	pk_{21}	k_1/k_2	$pk_{21} - pk_1$	I [mol/dm^3]	T [°C]	Ref.
Adrenaline	8.67	9.38	9.81	9.10	5.1	0.43	0.2 KCl	25	this work
	8.81	9.39	9.80	9.22	3.8	0.41	0.1	20	3
	8.75	9.42	9.82	9.16	4.7	0.40	0.1 KNO_3	25	14
Noradrenaline	8.69	9.11	9.42	9.00	2.6	0.31	0.2 KCl	25	this work
	8.84	9.37	9.67	9.14	3.4	0.30	0.1	20	3

second phenolic hydroxy group. For pK_3 Weber *et al.* [4] obtained a value which is more than one order of magnitude smaller than the constant determined in our work. The possible cause of this difference was explained in our previous paper [13] in connection with dopamine.

The dissociation processes of the first phenolic hydroxy group and the ammonium group of adrenaline and noradrenaline overlap one another, and thus the values of pK_1 and pK_2 cannot be ascribed unambiguously to one or the other process; they rather arise from the superposition of the constants of the following microprocesses:



The UV spectral procedure elaborated by Edsall *et al.* [12] was employed for the complete elucidation of the deprotonation processes. The microconstants obtained by this method are listed in Table II, together with some literature data.

It can be seen from the data in Table II that, allowing for the differing ionic strengths and temperatures, there is reasonably good agreement between our values and those determined by other authors. This is true especially for adrenaline where the agreement is excellent with the pk values determined by the NMR method [14]. The k_1/k_2 values (characterizing the molar ratio of the two forms of HA), which depend to only a slight extent on the ionic strength, show even better agreement. It can be stated from these data that the phenolic hydroxy group of these ligands is more acidic than the side-chain ammonium group. For adrenaline the difference in acidity between the two groups is significantly higher than for noradrenaline: the electron-repelling effect of the methyl group in adrenaline causes a decrease in the acidity of the ammonium group as compared with noradrenaline.

The $pk_{21} - pk_1 = pk_{12} - pk_2$ values, characterizing the effects of a protonated and a deprotonated ammonium group on the phenolic dissociation and of a protonated and a deprotonated phenolic hydroxy group on the ammonium dissociation, also show good agreement with the literature data. Because of the similar structures of adrenaline and noradrenaline, these values differ only slightly from one another.

The titration data on the metal ion–adrenaline and the metal ion–noradrenaline systems were evaluated by the assumption of complex formation *via* the phenolic hydroxy groups and deprotonation of the side-chain terminal $-NH_3^+$ group. Therefore, we assumed the formation of species of compositions MAH, MA, MA_2H_2, MA_2H and MA_2. With this assumption the titration could be fitted within the limits of experimental error in all systems (depending on the meral ion and the ligand, in some cases the assumption of fewer species also gave good fits). The stability constants obtained, together with some derived equilibrium constants, are listed in Table III.

It is clear from the data in Table III that stability constants for the 1:3 complexes could not be obtained from the pH-metric data in these systems. Since the two chelate-forming donor groups are separated within the molecule, only one of them can be bound to the metal ion in monomeric complexes, and thus there is a possibility for the coordination of a third ligand molecule. It could be assumed, therefore, that the binding of a third ligand is hindered because of the size of the ligand molecule and the electrostatic repulsive effect between the coordinated phenolate groups. The latter effect actually hinders the binding of the second molecule too, which is reflected in the log $K_{MAH}/K_{MA_2H_2}$ values.

The stability data for the complexes of adrenaline and noradrenaline correspond to those of dopamine [13]. Accordingly, coordination of the ethanolamine side-chain can be excluded. The slightly higher stabilities of the adrenaline complexes as compared with the noradrenaline complexes originates from the difference in the protonation macroconstants of the ligands. When the pK_3 and pK_1 values characterizing the dissociation of the phenolic hydroxy groups are taken into consideration, the relative stability

TABLE III. Stability and Derived Equilibrium Constants of the Metal Complexes of Adrenaline and Noradrenaline, t = 25 °C, I = 0.2 mol/dm^3 KCl.

	Adrenaline					Noradrenaline				
	Mn(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)	Mn(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)
MAH	17.56 ± 0.01	18.60 ± 0.01	18.84 ± 0.01	23.57 ± 0.05	19.75 ± 0.01	16.93 ± 0.01	17.98 ± 0.01	18.26 ± 0.01	23.00 ± 0.02	19.12 ± 0.01
MA	7.69 ± 0.03	9.23 ± 0.03	9.43 ± 0.03	15.6 ± 0.3	–	7.44 ± 0.02	8.69 ± 0.04	9.07 ± 0.04	15.4 ± 0.3	–
MA_2H_2	–	35.07 ± 0.03	34.5 ± 0.1	44.0 ± 0.2	37.99 ± 0.02	–	34.01 ± 0.04	–	43.4 ± 0.1	36.78 ± 0.01
MA_2H	22.5 ± 0.2	25.25 ± 0.03	24.7 ± 0.1	34.2 ± 0.2	28.35 ± 0.02	22.0 ± 0.17	24.61 ± 0.04	–	34.1 ± 0.1	27.48 ± 0.03
MA_2	12.46 ± 0.02	15.15 ± 0.02	14.2 ± 0.03	24.0 ± 0.2	18.19 ± 0.01	12.07 ± 0.02	14.76 ± 0.02	14.53 ± 0.06	24.4 ± 0.1	17.82 ± 0.02
MA_2H_{-1}	–	–	–	–	6.74 ± 0.08	–	–	–	–	6.38 ± 0.08
$MAH + AH \rightleftharpoons MA_2H_2$	–	16.47	15.6	20.4	18.24	–	16.03	–	20.4	17.66
$MAH \rightleftharpoons MA + H$	9.87	9.37	9.41	8.0	–	9.49	9.29	9.19	7.6	–
$MA_2H_2 \rightleftharpoons MA_2H + H$	–	9.82	9.8	9.8	9.64	–	9.40	–	9.3	9.30
$MA_2H \rightleftharpoons MA_2 + H$	10.1	10.10	10.5	10.2	10.16	9.9	9.85	–	9.7	9.66
$MA_2 \rightleftharpoons MA_2H_{-1} + H$	–	–	–	–	11.4	–	–	–	–	11.14
$\log K_{MAH}/K_{MA_2H_2}$	–	2.13	3.2	3.1	1.51	–	1.95	–	2.6	1.46
$\log K_{MA}/K_{MA_2}$	2.92	3.31	4.66	7.2	–	2.81	2.62	3.61	6.5	–
$M + H_2AH \rightleftharpoons MAH + 2H$	5.38	4.34	4.10	–0.63	3.19	5.45	4.40	4.12	–0.62	3.26

increase, expressed by the equilibrium constant of the process

$$M^{2+} + H_2AH^+ \rightleftharpoons MaH^+ + 2H^+$$

is nearly the same for both ligands. This meets the expectations because of the similar structures of the ligands and the identical bonding mode in their complexes. Such calculations can also be made for the other species. The data obtained support the similar complex-forming behaviours of the two ligands.

It is noteworthy that some of the protonated species, with compositions MAH, MA_2H_2 and MA_2H, cannot be detected in each system. This can be explained by the overlapping processes of metal complex formation and the dissociation of the ammonium group, and by the extent of steric hindrance of coordination of the second ligand molecule. In accordance with the Irving–Williams series [15], the metal–ligand interaction is the weakest in the case of the manganese(II) complexes, and thus overlap with the dissociation process is the largest here. Hence, MnA_2H_2 is formed in a non-detectable amount, and MnA_2H in a very small concentration, *i.e.* 1:2 complexes are formed by the interaction of metal(II) with the HA form of the ligand (in which the side-chain ammonium group is deprotonated). In the case of the nickel(II) complexes, because of the difference in the microconstants characterizing the dissociation of the ammonium group of adrenaline and noradrenaline, the species NiA_2H_2 and NiA_2H are formed with adrenaline, but are not formed in measurable concentration with noradrenaline. This is proved by our model calculations. Similar stability relations were assumed in the nickel(II)–noradrenaline system as in the nickel(II)–adrenaline system, *i.e.* $\log K_{MAH}/K_{MA_2H_2} = 3.2$, the stability constant for the species NiA_2H_2 was fixed and the concentration distribution of species formed in the nickel(II)–noradrenaline system was calculated. The highest concentration for NiA_2H_2 was only 2 Ni%, which is indeed too small for pH-metric detection.

In the cases of the cobalt(II) and zinc(II) complexes the coordination of a second ligand molecule is less hindered sterically ($\log K_{MAH}/K_{MA_2H_2} \sim 2$), and thus the overlap between the complex formation and the ligand dissociation processes is smaller. For this reason, with a ligand excess the formation of the 1:2 complexes takes place at lower pH and there is therefore no possibility for deprotonation of the complex ZnAH. At a ligand/metal ratio of 1:1, where the experimental conditions are favourable for the formation of 1:1 complexes, a precipitation process occurs before the dissociation of the ZnAH.

The deprotonation constants for the 1:1 and 1:2 complexes of adrenaline and noradrenaline are approximately the same and correspond to the microconstants characteristic of the dissociation of the

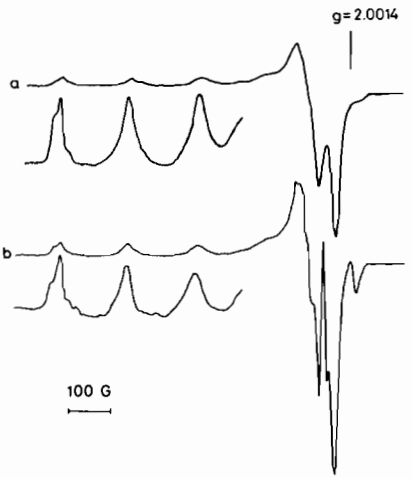


Fig. 1. ESR spectra of the copper(II)–adrenaline (a) and copper(II)–catechol (b) systems at a 1:1 ligand/metal ratio in a 1:1 methanol–water mixture at pH 7.5 at 77 K.

$-NH_3^+$ group of the ligand. These values for the MAH complexes are slightly smaller than the pk_{12} values fo the ligands, which can be explained by the fact that the coordination of a metal ion causes an electron shift extending to the side-chain too. In the case of CuAH, however, similarly as in the copper(II)–dopamine system [13], this electron shift is more significant, and the pK value for the species CuAH is more than one order of magnitude smaller than the pk_{12} value of the ligand. From statistical considerations a difference of 0.6 log unit is to be expected between the two stepwise deprotonation constants of the species MA_2H_2. In some systems this value is smaller than 0.6 log unit, and therefore the possibility arises that deprotonation of the ammonium group and formation of mixed hydroxo complexes take place simultaneously. This is supported by the fact that a complex of composition ZnA_2H_{-1} is among those formed in the zinc(II)–ligand systems. Because of its stoichiometric composition, this species can be ascribed only to a mixed hydroxo complex. A similar complex is also formed in the zinc(II)–pyrocatechol system [16].

During the pH-metric study of the copper(II)–adrenaline and copper(II)–noradrenaline systems it was observed that the copper(II) ion has a very strong catalytic effect on the autoxidation of the ligands, especially that of adrenaline. Because of the presence of oxygen traces, the pH-metric samples became pale pink at pH 6–7; this was caused by the formation of aminochromes, which are intense red ($\epsilon = 10^3$–10^4 mol^{-1} cm^{-1}). The slight colouration during the titrations did not make measurements impossible, but did decrease the accuracy of the stability constants calculated from the pH-metric data.

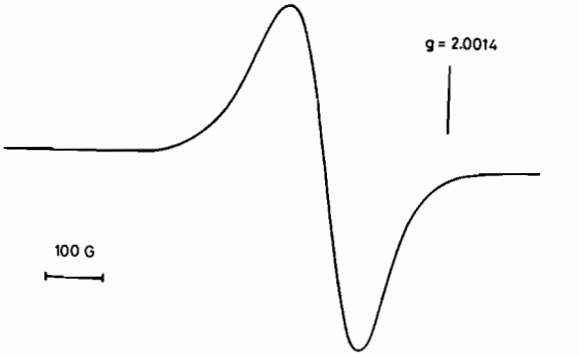


Fig. 2. ESR spectrum of the copper(II)–adrenaline system at a 1:1 ligand/metal ratio in a 1:1 methanol–water mixture at pH 10.5 at 77 K.

As regards the complex-forming properties of copper(II) with adrenaline and noradrenaline, it may be stated that the two ligands show a behaviour similar to that of dopamine in the pH range 5–11 with a ligand excess, and up to pH ~ 9 (where precipitation starts) at a ligand/metal ratio of 1:1. Under these conditions the participation of the side-chain donor atoms in the coordination is negligible.

This assumption is supported by our visible spectral measurements, which are in full agreement with the results of Bogges and Martin [7]. The ESR spectral examinations led to similar results: ESR spectra recorded at ligand/metal ratios of 1:1 and 1:2 at various pH values and at 77 K correspond to those of the copper(II)–catechol system. The spectra recorded at 77 K for the copper(II)–adrenaline and copper(II)–catechol systems with a ligand/metal ratio of 1:1 at pH 7.5 are presented in Fig. 1.

It is noteworthy, however, that at a ligand/metal ratio of 1:1 the sample containing precipitate became clear at pH > 10. The ESR spectrum recorded under these conditions is presented in Fig. 2.

This broad, poorly-resolved signal points to a strong copper(II)–copper(II) interaction. The possibility arises of the formation of a hydroxo-bridged dimeric species, which is ESR-inactive, however, due to spin–spin exchange interaction via the OH bridges. It may be assumed, therefore, that the spectrum can be ascribed to a polynuclear species in which the ethanolamine side-chain is also coordinated to the copper(II). According to Jameson and Neillie [5] this species is a cyclic tetramer in contrast with the dimeric complex of dopa. From our results we cannot draw conclusions on the number of ring atoms, but on the basis of earlier examinations and findings [7, 11, 17] the mixed binding mode is probable (one ligand coordinates in catechol-like O,O way, and the other in an ethanolamine-like O,N way to each metal ion). The coordination of the alcoholic hydroxy group is supported by the

fact that in the copper(II)–dopamine system with a ligand/metal ratio of 1:1 the precipitate did not dissolve at high pH.

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