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# Complexes of 3,4-Dihydroxyphenyl Derivatives, III.* Equilibrium Study of Parent and some Mixed Ligand Complexes of Dopamine, Alanine and Pyrocatechol with Nickel(II), Copper(II) and Zinc(II) Ions

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*The equilibrium constants of the parent complexes of nickel(II), copper(II) and zinc(II) with dopamine, and of the mixed ligand complexes with alanine or pyrocatechol as ligand B, were determined pH-metrically at 25 °C and 0.2* M *ionic strength.*

*As regards the parent complexes, it was found that only the* ortho *phenolic hydroxy groups take part in the coordination. The 1:1 complexes MHA and MA, and the 1:2 complexes $MH_2A_2$, $MHA_2$ and $MA_2$ are formed.*

*It was demonstrated that the stability relations of the mixed complexes formed with pyrocatechol as ligand B correspond to the statistical case, as a consequence of the values of $\log K_1/K_2$ of the parent complexes being almost the same. An increased stability compared to the statistical case was observed for mixed complexes with alanine. This was interpreted by the different stability relations of the parent complexes and by the role of neutralization of charge for complexes of all three metal ions.*

## Introduction

A detailed survey was recently made of the interaction between the biogenous amines and metal ions and of the biological importance of this [1]. It is assumed that the formation of mixed ligand complexes involving the participation of ATP and metal ions (among others copper(II) and zinc(II)) must be reckoned with in the transport and storage of these amines. Friedman and Kaufman [2] confirmed that the enzyme dopamine-β-hydroxylase, which catalyzes the hydroxylation reaction of dopamine, contains copper(II). It is justified above all, therefore, to study the interaction of dopamine with transition metal ions and with other ligands.

Dopamine is a decarboxylated derivative of 3,4-dihydroxyphenylalanine (DOPA) and in contrast with the latter ligand, therefore, only the phenolic hydroxy groups are suitable for chelate formation. Hence, the equilibrium conditions of metal–dopamine systems are essentially simpler than that of metal–DOPA, and it probably displays similarities to the other pyrocatechol derivatives.

Extensive studies have been made of the equilibrium relations of the complexes of nickel(II), copper(II) and zinc(II) ions with pyrocatechol and certain of its ring-substituted derivatives [3–7]. For the parent complexes, only the formation of the simple complexes MA and $MA_2$ has been suggested. In addition, it was established that binding of the second ligand is less favoured in the case of the nickel(II) and copper(II) complexes. This has been interpreted by the occurrence of an electrostatic repulsion effect between the negatively-charged oxygen atoms coordinated in the plane [3–7], and by the interaction between the π-electron system of the pyrocatechol and the *d* orbital of the metal ion [8].

The equilibrium relations of the transition metal complexes of dopamine (3,4-dihydroxyphenylethylamine) have been investigated by Weber *et al.* [9]. It was concluded that in the copper(II)–dopamine and nickel(II)–dopamine systems complexes of various compositions are formed, involving (O,O) bonds and containing the chain-terminal amino group in the protonated or the deprotonated form. Of the 1:2 complexes, however, it is surprising that only the species $MH_2A_2$ and $MA_2$ were taken into consideration. The zinc(II)–dopamine system was studied only in a very narrow pH interval, up to pH ~ 7.6, and thus the establishment of the equilibrium relations was very limited.

Sigel *et al.* made a detailed study of the mixed ligand complexes of pyrocatechol with various aliphatic and aromatic B ligands containing (N,N) donor atoms [10–12]. They found that besides the neutralization of the charges, the interaction between the metal ion and the π-electron system of the ligand also plays a role in the stabilities of the mixed ligand complexes.

In agreement with the above, in this work we carry out detailed studies to determine the stoichiometric

*Part II, ref. [14].

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compositions and stabilities of the species formed in the nickel(II)–dopamine, zinc(II)–dopamine and copper(II)–dopamine systems. A study is also made of the equilibrium relations of the formation of the mixed ligand complexes of metal–dopamine with the B ligands alanine and pyrocatechol, containing (N,O) and (O,O) donor atoms.

## Experimental

*Compounds Used and Experimental Conditions*

The alanine and pyrocatechol used were Reanal products of the highest analytical purity, while the dopamine was a Fluka product of *puriss.* quality. The alanine was purified by recrystallization from an ethanol–water mixture, and the pyrocatechol by distillation at reduced pressure. The dopamine was used without further purification. Metal chloride stock solutions were prepared from chemicals of the highest analytical purity, and their concentrations were checked gravimetrically via the oxinate. The pH-metric measurements were performed at 25 °C at an ionic strength of 0.2 *M* KCl, as described elsewhere [13, 14].

In order to determine the dissociation constants of the second phenolic hydroxy group of dopamine, two samples were measured in the presence and absence of the ligand. In the first case the concentration of dopamine·HCl was $6 \times 10^{-2}$ *M* and the ionic strength was adjusted to 0.2 *M* with KCl, while in the second case in the absence of the ligand the concentration of HCl was 0.12 *M* and the ionic strength was also adjusted to 0.2 *M*. Both solutions were titrated with 4.5 *M* KOH solution until pH 13.1. The dissociation constant was calculated pointwise from the data of the first titration, and the 'actual' $pK_w$ values obtained from the points of the second titration curve were used in each point in order to take into account the changes in ionic strength and the electrode correction factor [20] during the titration. Even if this method is used the $pK_3$ can be obtained only with appreciable inaccuracy because its value lies close to the ionic product of water $pK_w$.

Spectrophotometric titrations were carried out to determine deprotonation micro constants of the dopamine. The dissociation of the phenolic hydroxy groups of the ligand was followed in the pH range 8.5–11.4 in the absorbance interval 250–330 nm. A Beckman ACTA MIV double-beam recording spectrophotometer was used for these examinations.

## Calculations

The complexes formed can be characterized by the following general equilibrium process:

$$qM + pH + nA + rB \rightleftharpoons M_qH_pA_nB_r \quad (1)$$

where A and B mean the fully deprotonated form of the ligands.

The stability constants of the species can be given by the formula

$$\beta_{qpnr} = \frac{[M_qH_pA_nB_r]}{[M]^q[H]^p[A]^n[B]^r} \quad (2)$$

The corresponding stability constants defined by eqn. (2) were calculated in the usual manner from the pH-metric titration data [13].

The equilibrium constants relating to the mixed ligand complexes can be defined on the basis of the following equations:

$$M + H + A + B \rightleftharpoons MHAB \quad (3)$$

and

$$M + A + B \rightleftharpoons MAB \quad (4)$$

The stabilization constants $\Delta\log\beta_{1111}$ and $\Delta\log\beta_{1011}$ arise from the differences between the measured values and those calculated in accordance with statistical considerations:

$$\Delta\log\beta_{1111} = \log\beta_{1111}^{exp} - \frac{1}{2}(\log\beta_{1220} + \log\beta_{1002} + \log 4) \quad (5)$$

and

$$\Delta\log\beta_{1011} = \log\beta_{1011}^{exp} - \frac{1}{2}(\log\beta_{1020} + \log\beta_{1002} + \log 4) \quad (6)$$

The value $\Delta\log K$, expressing the relation of the stepwise stability constants, is obtained as follows:

$$M + MHAB \rightleftharpoons MHA + MB \quad (7)$$

$$\Delta\log K = \log\beta_{1110} + \log\beta_{1001} - \log\beta_{1111}$$

The equilibrium constants $K_{HAB}$ and $K_{BHA}$ relating to the binding of the second ligand can be derived from the following two equations:

$$CuHA + B \rightleftharpoons CuHAB \quad (8)$$

$$CuB + HA \rightleftharpoons CuHAB \quad (9)$$

## Results and Discussion

The pH-metrically determined protonation constants of dopamine are given in Table I together with some literature data.

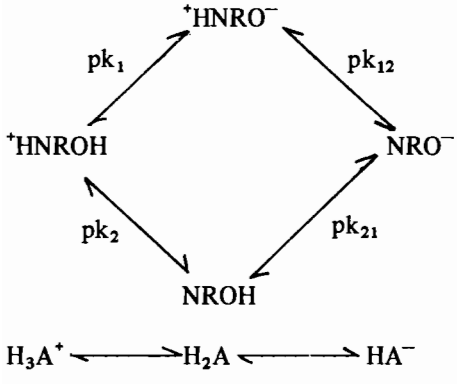
Because of the uncertainty in the $pK_3$ value given in Table I, the protonation constant was determined at 2.0 *M* (KCl) ionic strength too, and a value of 13.4 ± 0.2 was obtained. By extrapolation from this data to 0.2 *M* ionic strength also a value of 13.1 could be estimated for $pK_3$.

TABLE I. Macroconstants of Deprotonation of Dopamine.

| $pK_1$ | $pK_2$ | $pK_3$ | I(*M*) | °C | Ref. |
|---|---|---|---|---|---|
| 8.89 ± 0.01 | 10.41 ± 0.01 | 13.1 ± 0.2 | 0.2 KCl | 25 | this work |
| 9.06 ± 0.01 | 10.60 ± 0.01 | 12.05 ± 0.01 | 0.37 $NaNO_3$ | 20 | 9 |
| 8.96 | 10.50 | 11.2 | 1.0 $KNO_3$ | 25 | 19 |

Comparing the deprotonation constants determined in the present work and by others a good agreement is found with the exception of the value of the second phenolic hydroxy group. It is surprising that for $pK_3$ Weber *et al.* [9] obtained a value which is about one order of magnitude smaller than the constant determined in this work. This can presumably be attributed to the fact that, since the value of this dissociation constant lies close to the ionic product of water, the concentration of $1 \times 10^{-2}$ *M* that they employed is not sufficiently high for accurate pH-metric determination [15]. The value of $pK_3$ found in this work is in good agreement with the corresponding values determined earlier for pyrocatechol and certain of its derivatives [13].

The dissociation processes of the first phenolic hydroxy group and the $-NH_3^+$ group of dopamine overlap one another [16], and thus the values of $pK_1$ and $pK_2$ cannot be ascribed unambiguously to one or the other process; they rather arise as the superposition of the constants of the following microprocesses:




The UV spectral procedure elaborated by Edsall *et al.* [17] was employed for the complete elucidation of the deprotonation processes. The microconstants obtained by joint evaluation of the pH-metric and spectrophotometric titration data are listed in Table II, together with the macroconstants calculated from them.

It can be seen from the data in Table I and II that the pH-metrically and spectrophotometrically obtained macroconstants agree approximately. There is fairly good agreement between our constants and those earlier reported by Martin [16]. From a comparison of the microconstants and the macroconstants it may be stated that the acidity of the phenolic hydroxy group is essentially higher than that of the $-NH_3^+$ group; there is a difference of ~1 order of magnitude between $pk_1$ and $pk_2$. This can also be seen in Fig. 1 where the concentration distribution of the proton complexes is plotted as a function of pH. This figure shows that the ratio of the concentrations of the two forms of $H_2A$ is >10. On this basis, the macroconstant $pK_1$ can be ascribed to a first approximation to the dissociation of the first phenolic hydroxy group, and $pK_2$ to that of the chain-terminal amino group.

TABLE II. Spectrophotometrically Determined Microconstants and Macroconstants of Deprotonation of Dopamine.

| $pk_1$ | $pk_2$ | $pk_{12}$ | $pk_{21}$ | $pK_1$ | $pK_2$ | Ref. |
|---|---|---|---|---|---|---|
| 8.87 | 9.95 | 10.36 | 9.39 | 8.82 | 10.40 | this work |
| 8.90 | 10.06 | 10.60 | 9.44 | 8.87 | 10.63 | 16 |

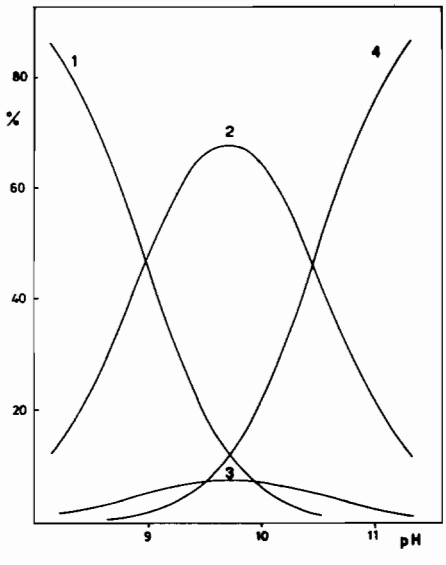



Fig. 1. pH-dependence of the concentration distribution of the proton complexes of dopamine. 1) $^+HNROH$, 2) $^+HNRO^-$, 3) NROH, 4) $NRO^-$.

The titration data on the nickel(II)–dopamine, copper(II)–dopamine and zinc(II)–dopamine systems were evaluated by the assumption of complex formation processes via the phenolic hydroxy groups and

TABLE III. Stability and Derived Equilibrium Constants of Nickel(II)–Dopamine, Copper(II)–Dopamine and Zinc(II)–Dopamine Complexes.

$\beta_{qpn} = \frac{[M_qH_pA_n]}{[M]^q[H]^p[A]^n}$ t = 25 °C, I = 0.2 *M* KCl.

| | Composition qpn | M = Ni(II) | M = Cu(II) | M = Zn(II) |
|---|---|---|---|---|
| MHA | 111 | 19.37 ± 0.04 | 24.22 ± 0.04 | 20.21 ± 0.04 |
| MA | 101 | 9.42 ± 0.08 | 16.60 ± 0.10 | – |
| $MH_2A_2$ | 122 | 35.66 ± 0.04 | 45.83 ± 0.04 | 38.93 ± 0.04 |
| $MHA_2$ | 112 | 25.61 ± 0.05 | 35.66 ± 0.04 | 28.67 ± 0.05 |
| $MA_2$ | 102 | 14.81 ± 0.06 | 24.78 ± 0.04 | 18.05 ± 0.06 |
| $MHA \rightleftharpoons MA + H^+$ | | −9.96 | −7.6 | – |
| $MH_2A_2 \rightleftharpoons MHA_2 + H^+$ | | −10.05 | −10.17 | −10.26 |
| $MHA_2 \rightleftharpoons MA_2 + H^+$ | | −10.81 | −10.62 | −10.88 |
| $\log K_{MHA}/K_{MH_2A_2}$ | | 3.09 | 2.60 | 1.49 |

the deprotonation of the chain-terminal $-NH_3^+$ group. Therefore, we assumed the formation of the species of composition $MHA^+$ and MA, containing one metal ion and one ligand, and the 1:2 complexes $MH_2A_2$, $MHA_2^-$ and $MA_2^{2-}$. With this assumption, the titration data could be fitted within the limits of experimental error in all systems. The stability constants obtained, together with some derived equilibrium constants, are listed in Table III.

On evaluation of the titration data in the case of the copper(II)–dopamine system, it was found that the complex CuA could be replaced in the calculations by the species $CuH_3A_2^+$, in which the second ligand would be coordinated via the chain-terminal amino group. To make a decision in connection with the existence of this species of mixed bonding type, we studied a model system in which the donor groups of dopamine are present in separate ligands. The copper(II)–pyrocatecholate–tyramine (4-hydroxyphenylethylamine) system was found suitable for this, and a study was made as to whether a mixed ligand complex is formed. The experimental titration points of this system in the pH range of 5–10 could be well fitted within the limits of experimental error by the assumption of the pyrocatechol parent complexes CuA and $CuA_2^{2-}$ and the proton complexes of the ligands. Accordingly, it may be stated that mixed complex formation need not be assumed in the system. With regard to this, formation of the complex $CuH_3A_2^+$ in addition to CuA is not to be expected in the copper(II)–dopamine system.

It can be seen from Table III that the deprotonated complex ZnA is not formed in the zinc(II)–dopamine system; this may be explained by the considerable difference in the $\log K_1/K_2$ values between the nickel(II)–dopamine and the zinc(II)–dopamine complexes. In these two systems, where the processes of complex formation and of deprotonation of the chain-terminal $-NH_3^+$ group take place in almost the same pH interval, binding of the second ligand is hindered only in the case of the nickel(II) complex, and there is therefore a possibility for deprotonation of the species NiHA. On the other hand, in the zinc(II)–dopamine system the two complex formation processes overlap one another to an appreciable extent and they also take place in a lower pH range; as a consequence, only the deprotonation of $ZnH_2A_2$ takes place. In the case of the copper(II) complex, on the other hand, although the value of $\log K_1/K_2$ is large, a possibility for the deprotonation is given by the fact that the electron transfer process in the direction $O \rightarrow Cu^{2+}$ causes an electron shift extending to the side-chain too. Consequently, there is a considerable decrease in electron density on the chain-terminal $-NH_3^+$ group, and hence the deprotonation may proceed even in the complex formation pH range. This also shows up in the pK value for the species $CuHA^+$, which, in contrast with the nickel(II) complex, is more than two orders of magnitude smaller than the value of the microconstant ($pk_{12}$ = 10.36) of the deprotonation of the $-NH_3^+$ group of the ligand. At the same time, the deprotonation constants of the complex $CuH_2A_2$ approximately agree with the microconstant values, since this electron shift towards the metal ion is much more hindered because of the electrostatic repulsion effect between the O atoms in the plane [3].

The above arguments relating to the parent complexes were supplemented with investigations of the mixed ligand complexes formed with alanine or pyrocatechol. In the case of the mixed ligand systems of the copper(II) and zinc(II) ions, the experimental titration curves could be well fitted with the assumption of the complexes MHAB and MAB. In the nickel(II)–alaninate–dopamine system, however, the formation of the species $NiHAB_2^-$ and $NiAB_2^{2-}$, containing

TABLE IV. Equilibrium Constants of Nickel(II), Copper(II) and Zinc(II) Mixed Ligand Complexes; t = 25 °C, I = 0.2 *M* KCl.

| | | $\log\beta_{1111}$ | $\Delta\log\beta_{1111}$ | $\log\beta_{1011}$ | $\Delta\log\beta_{1011}$ | $pK_{1111}^{1011}$ | $\log K_1^B/K_2^B$ | $\Delta\log K$ | $\log K_{HAB}$ | $\log K_{BHA}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Alaninate | Ni(II) | 23.68 | 0.66 | 13.32 | 0.73 | 10.36 | 0.90 | 1.04 | 4.31 | 18.36 |
| | Cu(II) | 31.06 | 0.48 | 20.62 | 0.56 | 10.44 | 1.35 | 1.20 | 6.84 | 23.02 |
| | Zn(II) | 24.39 | 0.37 | 13.96 | 0.38 | 10.43 | 0.61 | 0.38 | 4.18 | 19.38 |
| Pirocatecholate | Ni(II) | 25.52 | 0.05 | 15.10 | 0.06 | 10.42 | 2.77 | 2.62 | 6.10 | 16.75 |
| | Cu(II) | 35.63 | 0.07 | 25.08 | 0.05 | 10.55 | 2.96 | 2.41 | 11.41 | 21.81 |
| | Zn(II) | 28.69 | 0.05 | 18.26 | 0.06 | 10.43 | 1.69 | 1.24 | 8.48 | 18.97 |

two alanines and one dopamine, was also demonstrated. However, it was not necessary to assume the formation of the complexes containing two dopamines and one alanine. This corresponds to the expectations based on the results obtained for similar systems [14]. Namely, as was already discussed, the formation even of the nickel(II)–dopamine parent complex $NiH_2A_2$ is sterically hindered ($\log K_{NiHA^+}/K_{NiH_2A_2}$ = 3.06). Table IV contains the stability constants calculated for the mixed ligand complexes, the deprotonation constants for the species MHAB, and the previously-defined equilibrium constants.

Table IV does not include the stability constants of the complexes $NiHAB_2$ and $NiAB_2^{2-}$ formed in the nickel(II)–dopamine–alanine system. The values of these are as follows: $\log\beta_{1112}$ = 26.68 ± 0.08 and $\log\beta_{1012}$ = 16.07 ± 0.10.

As regards the six mixed equilibrium systems investigated in the present work, Figs. 3 and 4 illustrate the pH-dependences of the concentration distributions of the complexes formed at a metal ion–ligand A–ligand B ratio of 1:2:2 in the copper(II)–dopamine–alaninate and copper(II)–dopamine–pyrocatecholate systems.

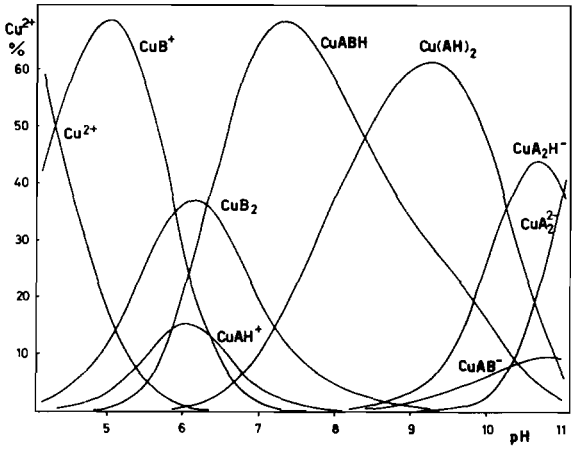



Fig. 2. pH-dependence of the concentration distribution of the complexes formed in the copper(II)–dopamine (A)–alaninate (B) system at a metal ion–ligand–ligand ratio of 1:2:2.

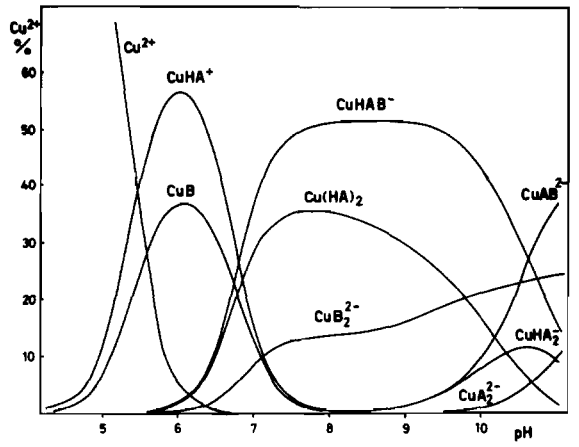



Fig. 3. pH-dependence of the concentration distribution of the complexes formed in the copper(II)–dopamine (A)–pyrocatecholate (B) system at a metal ion–ligand–ligand ratio of 1:2:2.

It can be seen from Fig. 2 that with alanine as ligand B the concentration of CuHAB increases considerably up to pH ~ 7, but with further increase of the pH the alaninate is displaced from the coordination and the 1:2 complexes of dopamine become predominant. The situation is similar when the central metal ion is zinc(II). In the nickel(II)–dopamine–alaninate system, however, there is practically no formation of 1:2 dopamine complexes; instead, the mixed ligand complexes are present in large quantities. This experimental fact can be explained by the findings made earlier for the formation conditions of the parent complexes. It is noteworthy that for all three metal ions mainly the mixed ligand complex is present in the physiological pH range. This supports the assumption [1, 2] that mixed complex formation may play a significant role in the biochemical reactions of catecholamines and in their transport and storage.

With pyrocatechol as ligand B (as in the case of the copper(II)–dopamine–pyrocatecholate system, (see Fig. 3)) for all three metal ions the mixed ligand complexes are formed in maximum concentration from pH ~ 7.5.

From the data listed in Table IV the following conclusions may be drawn:

(*i*) In agreement with our earlier findings [18] the value of the stabilization constant is the larger, the greater the difference between the values of $\log K_1/K_2$ for the parent complexes. Thus, in the systems containing pyrocatechol as ligand B, where the $\log K_1/K_2$ values for the parent complexes differ from each other to only a slight extent, the stability constant of the mixed ligand complex exceeds the statistical value to only a slight extent. On the other hand, since there is a great difference between the two $\log K_1/K_2$ values when alanine is ligand B, the stability increase also is considerable.

(*ii*) It was argued earlier [18] that instead of the stabilization constants $\Delta\log\beta_{1111}$ and $\Delta\log\beta_{1011}$ defined by eqns. (5) and (6), it is more suitable to draw conclusions on the stability relations of the mixed ligand complexes from comparisons of the $\Delta\log K$ and the $\log K_{HAB}$ and $\log K_{BHA}$ values. Changes in the latter data compared to the corresponding data for the parent complexes are in fact characteristic only of mixed complex formation. If this is taken into consideration, it may be stated that, in the cases of both alanine and pyrocatechol as ligand B, the $\Delta\log K$ values agree approximately in most cases with the $\log K_1/K_2$ values of the parent complexes of ligand B. That is, dopamine binds with almost the same probability to its own complex of composition $MHA^+$ and to the parent complex MB. Thus, in the case of alaninate as ligand B the extensive mixed ligand complex formation can primarily be attributed to the fact that the formation of MHAB in contrast with that of the complex $M(HA)_2$ is not hindered sterically. With pyrocatecholate as ligand B, on the other hand, in accordance with the above the mixed ligand complex is formed to an extent nearly corresponding to the statistical case.

(*iii*) From a comparison of the $\log K_{HAB}$ and $\log K_{BHA}$ values with the $\log K_2$ values of the parent complexes it may be stated that in mixed complexes with alanine as ligand B the value of $\log K_{BHA}$ is substantially larger than the $\log K_{MH_2A_2}$ values of the dopamine parent complexes. Dopamine entering as second ligand is therefore bound with higher stability to the alanine complex $MB^+$ than to the corresponding dopamine complex. This phenomenon can be attributed to the role of the charge change. This appears to be in contradiction with the fact that both species $MHA^+$ and $MB^+$ are unipositively charged. However, the charge of the $MHA^+$ complex of dopamine results from the side-chain $-NH_3^+$ group, which does not participate in the coordinate bonding, while in the case of alanine the charge can be ascribed to the metal ion. Consequently, as regards the coordination sphere the species $MHA^+$ appears to be neutral and $MB^+$ to be unipositively charged.

Our findings for the mixed ligand complexes in the present work are supported by the results for the nickel(II)–alanine–pyrocatechol, the copper(II)–alanine–pyrocatechol and the zinc(II)–alanine–pyrocatechol systems [14].

It may also be stated that in the copper(II)–dopamine–alaninate system the stability of the mixed ligand complex is not marked compared to the zinc(II) and nickel(II) complexes. This supplements the previous results of Sigel *et al.* [10]. In the copper(II)–ethylenediamine–pyrocatecholate system these authors observed a significant increase in the stability of the mixed complex compared to the copper(II)–ethylenediamine–oxalate complex. They interpreted this by an interaction between the $\pi$-electron system of the pyrocatechol and the *d* orbitals of the copper(II) ion. Our present investigations indicate that the effect of the $\pi$-electron system of the dopamine or the pyrocatechol is of subordinate importance as regards the stabilities of the mixed complexes with alanine. The electron transfer O → metal results in a considerable increase in the stability of the mixed ligand complex only when ligand B is a $\pi$-acceptor in nature.

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