Computer simulated approach to the formation of mixed coordinated complexes of DOPA with toxic metal ions

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ABSTRACT

The potentiometric method is adopted to determine formation constants of complexes and used with a new numerical scheme. This study deals with the coordination behaviour of L-DOPA (3,4-dihydroxyphenylalanine) in Hg(II)/Pb(II)/Cd(II)–DOPA–L-alanine/glycine/L-phenylalanine (1:1:1) systems. DOPA is recognized as a neurotransmitter, and used in the treatment of Parkinson’s disease. All the selected ligands are biologically active and play a vital role in the physiological processes. All the systems were investigated pH-metrically at 20 ± 1°C and 30 ± 1°C at three different ionic strengths in aqueous medium. Stability Constants of Generalized Species’ computer program was used to obtain refined values of formation constants. Thermodynamic parameters (log \( \Delta G \), \( \Delta H \), \( \Delta S \)) for biligand systems were calculated. The speciation of different species in mixed coordinated systems was obtained up to a specific pH in particular system. High values of formation constants support the formation of stable ternary complexes. Biligand complexes involving alanine were found to be the most stable, while those of phenylalanine were the least with lowest concentration at a particular pH in specific conditions. Results obtained are helpful in understanding the physiological behaviour of these systems.

1. Introduction

Bioaccumulation and detoxification of heavy metals involve metal chelation [1]. Such complexation reactions in biological relevance have promoted various research investigations [2–5], which are helpful in designing therapeutic methodologies. Few monoligand and biligand systems of DOPA and related neurotransmitters have been investigated by different groups of researchers [6–9]. Nair et al. carried out work on the mixed coordinated systems of DOPA with nickel and zinc in an aqueous medium and adopted a computer-aided approach for finding the results [6]. The speciation of ternary complexes of lead(II), cadmium(II) and mercury(II) with L-dopa and phenanthroline in propandiol–water mixtures was obtained by Padmaja et al. [7]. Potentiometric investigations on catecholamine and catechol were reported by R. Nair (Ahuja) et al., in an aqueous medium [8,9]. Interesting results of these researchers prompted computer-simulated investigations on the selected systems in an aqueous medium.

To understand the compatibility and toxic interference of heavy metals in the central nervous system, studies were done on nutrient and toxic metal ions and biologically potential ligands, including DOPA. Results obtained for Ni(II), Co(II) and Cd(II) with DOPA, dopamine and tyrosine were reported earlier [10–16].

The present study deals with the thermodynamic stabilities of Hg(II)/Pb(II)/Cd(II)–DOPA–Ala/Gly/Phe complexes (where, DOPA = L-(3,4-dihydroxyphenyl)alanine, Ala = L-alanine, Gly = glycine, Phe = L-phenylalanine).

All the selected ligands are structurally related and directly or indirectly play a vital role in physiology and Central Nervous System (CNS) [17]. These are synthesized in the body according to the following sequence:

- Glycine → Alanine → Phenylalanine
- Phenylalanine → Tyrosine → DOPA → DOPM

DOPA acts as a precursor to DOPM (Dopamine) in CNS and is involved in nerve transduction [18]. Lack of DOPM causes Parkinson’s disease, in which a person loses its ability to move controlled and smooth actions [19]. DOPA is now being used to treat Parkinson’s disease and manganese poisoning [20–22].

2. Material and method

All the reagents used were of the highest purity Merck/Aldrich products. Solutions were prepared in doubly distilled CO2-free water having pH ≈ 6.8 by using a standard method. All the titration mixtures were prepared in the same manner as published elsewhere.
Figure 1. Representative pH vs. “a” curves, where Curve 1 represents ligand “A” (DOPA) titration curve, Curve 2 represents ligand “B” (Ala/Gly/Phe) titration curve, Curve 3 represents metal–ligand “A” (1:1) titration curve, Curve 4 represents metal–ligand “B” (1:1) titration curve, Curve 5 represents mixed-ligand (1:1:1) titration curve, and Curve “T” represents theoretical composite curve.

Table 1. Protonation/dissociation constants of Ligands (log $\beta_{\mu\rightarrow 0}$) and thermodynamic formation constants of binary complexes in equimolar systems.

| Ligand | Parameter | DOPA | Ala | Gly | Phe |
|--------|-----------|------|-----|-----|-----|
|        | 20°C | 30°C | 20°C | 30°C | 20°C | 30°C | 20°C | 30°C |
| log $\beta_{HA}$ | – | – | 10.25 | 10.01 | 9.9 | 9.68 | 9.31 | 9.12 |
| pK$_{HA}$ | 8.88 | 8.79 | – | – | 9.1 | 9.02 | 8.9 | 8.78 |
| log $K_{M_{Hg}AH_2}$ | 6.66 | 6.49 | – | – | – | – | – | – |
| log $K_{M_{Pb}AH_2}$ | – | – | 7.39 | 7.14 | 7.05 | 6.77 | 6.83 | 6.5 |
| log $K_{M_{Cd}AH_2}$ | – | – | 6.85 | 6.56 | 6.42 | 6.07 | 6.14 | 5.88 |
| log $\beta_{HA}$ | – | – | 5.1 | 4.85 | 4.89 | 4.63 | 4.55 | 4.2 |

Notes: 1. Thermodynamic formation constants were obtained by extrapolating the log $\beta$ vs. $\sqrt{\mu}$ plot to zero ionic strength. 2. Ala, Gly and Phe become the ligand “B” in biligand systems.

[11] and titrated against 0.10 M NaOH solution. Studies were carried out at three different ionic strengths ($\mu = 0.05M, 0.10M, 0.15M$ (NaNO$_3$)) using an Elico digital pH-meter model LI-127 with the ATC probe and combined electrode type (CL-51B-Glass Body; range 0–14 pH unit; 0–100°C Automatic/Manual) with an accuracy of ±0.01. To find out thermodynamic parameters, titrations were done at two randomly selected temperatures (at 20 ± 1°C and 30 ± 1°C).

For each system pH was plotted against “a” to obtain titration curves (where “a” is the moles of alkali added per mole of metal/ligand). Figure 1 shows representative titration curves at 30 ± 1°C. A Theoretical Composite Curve was obtained by the theoretical addition of metal–ligand B titration curve with a ligand A titration curve.

Experimental data were subjected to the algebraic method of Chaberek and Martell [23,24] as modified by Dey et al. [25] to calculate formation constants. These values were refined by the SCOGS computer program [26–28] extrapolated to zero ionic strength in log K and $\sqrt{\mu}$ (square root of the ionic strength) plot to obtain thermodynamic formation constants. Values of $\Delta G^\circ$, $\Delta H^\circ$ and $\Delta S^\circ$ for mixed coordinated complexes were calculated using Gibb’s Helmholtz equation, van’t Hoff isotherm and van’t Hoff isochore. All these results are depicted in Tables 1 and 2.

3. Results and discussion

Protonation constants of ligands and the thermodynamic formation constants of binary complexes are given in Table 1.

The plot of experimental data is given in Figure 1. Titration curves for Hg$^{II}$ and Pb$^{II}$ follow the same trend (Figure 1), and the pattern of curves for Cd$^{II}$ systems is similar to those of Co$^{III}$-DOPA-Ala/Phe systems [11], as shown in Figure 1.

The nature of titration curves supports the formation of all the mixed coordinated complexes simultaneously (Scheme 1), as was predicted using the method of Carey and Martell [29]. Furthermore, the predictions are
Table 2. Thermodynamic parameters for biprotonated M(II)-DOPA-ligand ’B’ biligand complexes in equimolar systems.

| System          | 20 ± 1°C | 30 ± 1°C |
|-----------------|----------|----------|
|                 | log $K_{u-o}$ | $\Delta G^\circ$ kJ mol$^{-1}$ | log $K_{u-o}$ | $\Delta G^\circ$ kJ mol$^{-1}$ | $\Delta H^\circ$ kJ mol$^{-1}$ | $\Delta S^\circ$ JK$^{-1}$ mol$^{-1}$ |
| Hg$^{II}$-DOPA-Ala | 14.98     | 84.04    | 14.55     | 84.41    | 73.09     | 37.36     |
| Hg$^{II}$-DOPA-Gly | 14.23     | 79.83    | 13.91     | 80.70    | 54.39     | 86.81     |
| Hg$^{II}$-DOPA-Phe | 13.43     | 75.34    | 13.12     | 75.54    | 69.69     | 19.28     |
| Pb$^{II}$-DOPA-Ala | 13.71     | 76.91    | 13.36     | 77.22    | 67.70     | 30.44     |
| Pb$^{II}$-DOPA-Gly | 13.44     | 75.40    | 13.12     | 76.12    | 54.40     | 71.69     |
| Pb$^{II}$-DOPA-Phe | 12.97     | 72.76    | 12.59     | 73.04    | 64.60     | 27.88     |
| Cd$^{II}$-DOPA-Ala | 9.92      | 55.65    | 9.63      | 54.59    | 49.30     | 21.69     |
| Cd$^{II}$-DOPA-Gly | 9.63      | 54.02    | 9.41      | 54.59    | 37.40     | 56.75     |
| Cd$^{II}$-DOPA-Phe | 9.21      | 51.67    | 8.93      | 51.81    | 47.60     | 13.90     |

Scheme 1. Simultaneous complexation in biligand systems.

$$
\begin{align*}
M + B & \overset{0 \leq a \leq 1}{\rightleftharpoons} MB \\
M + H_2A & \overset{0 \leq a \leq 1}{\rightleftharpoons} MAH_2 \\
M + H_2A + B & \overset{0 \leq a \leq 2}{\rightleftharpoons} MABH_2 \\
MAH_2 + B & \overset{0 \leq a \leq 2}{\rightleftharpoons} MABH_2 \\
MB + H_2A & \overset{0 \leq a \leq 2}{\rightleftharpoons} MABH_2 
\end{align*}
$$

The complexation behaviour of DOPA is supported by spectroscopic studies done by Boggess and Martin [30]. Boggess et al. explained the displacement of bound glycinate site (aminocarboxylic end) to catecholate locus above pH 8.0 on the basis of absorption spectra. At a higher pH, DOPA is likely to form polymeric species [30,31]. Hence, the calculations for the monoligand and biligand complexes of DOPA were confined below pH 7.0 in the systems involving Hg$^{II}$ and Pb$^{II}$ and up to pH 9.0 in the systems of Cd$^{II}$, to avoid errors. The speciation of various monoligand and biligand species is also given to the confined pH in the respective systems (Figures 2 and 3).

Speciation curves obtained for Pb$^{II}$/Hg$^{II}$-DOPA systems show the formation of the mixed coordinated complex above pH 5.0 (Figure 2). The concentration of monoligand species is low in the systems of lead. While in Hg$^{II}$ and Cd$^{II}$ systems, the monoligand and biligand species exist at the initial pH of complex formation. Both these complexes are formed up to pH 5.5 in Hg$^{II}$ systems and up to pH 7.0 in the systems of Cd$^{II}$. Above this pH in respective systems, a biligand complex is formed by simultaneous coordination of metal and ligands as well as by the combination of monoligand complexes with other ligands (Scheme 1).

$$
\begin{align*}
M + B & \overset{0 \leq a \leq 1}{\rightleftharpoons} MB \\
M + H_2A & \overset{0 \leq a \leq 1}{\rightleftharpoons} MAH_2 \\
M + H_2A + B & \overset{0 \leq a \leq 2}{\rightleftharpoons} MABH_2 \\
MAH_2 + B & \overset{0 \leq a \leq 2}{\rightleftharpoons} MABH_2 \\
MB + H_2A & \overset{0 \leq a \leq 2}{\rightleftharpoons} MABH_2 
\end{align*}
$$

where $M = \text{Metal ion, } A = \text{L-DOPA, } B = \text{L-alanine/glycine/L-phenylalanine.}$

Species distribution of metal in the systems of phenylalanine show the percentage of maximal formation of $\text{MAH}_2B$ complex is lower than other systems due to the repulsion between bulky phenyl rings of DOPA and phenylalanine.

Results obtained for biligand systems are incorporated in Table 2. These results show that the order of stability of complexes is

$$
M - \text{DOPA} - \text{Ala} > M - \text{DOPA} - \text{Gly} > M - \text{DOPA} - \text{Phe}
$$

This can be explained on account of the structure of these ligands. The highest stability of complexes of alanine is due to the positive inductive effect of the methylene group of the ligand. While a lower stability of biligand complexes of phenylalanine is attributed to

![L-DOPA](image)

Aminocarboxylic end

Catecholic end

$\text{L-DOPA}$
the electron withdrawing nature of phenyl ring of a particular ligand and to the steric hindrance between two bulky ligands.

The stability order of complexes with respect to metal ions is in the sequence of their hydrolysis, which is given as follows:

\[
\text{Hg}^{II} - \text{DOPA} - \text{Ala/Gly/Phe} \\
> \text{Pb}^{II} - \text{DOPA} - \text{Ala/Gly/Phe} \\
> \text{Cd}^{II} - \text{DOPA} - \text{Ala/Gly/Phe}
\]

This order can be explained on the basis of the charge to radius ratio.

4. Conclusion

Results show that the ternary complexes of alanine are most stable, and those of phenylalanine are least stable. As far as metal ions are concerned, complexes of mercury are most stable, and those of the cadmium are least stable.

The present work is helpful in understanding the in vivo stability and biochemical behaviour of selected ligands with the selected metal ions. All the selected ligands play a vital role in the Central Nervous System. Hence this study is helpful for biochemists to understand the compatibility and toxic interference of selected heavy metal ions in the Central Nervous System. These data are useful in designing...
complexo-therapeutic treatment for such metal toxicity. An alternative model for the species distributions from potentiometric data, in thermodynamic equilibrium, based on the models used for HySS or Hyperquad, and titration curve has also a bottle neck [32] and is expected to be recognized shortly.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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