Study of the Mixed Ligand Complexes of Cadmium(II) with the Antidepressant Drug Imipramine and Glutamic Acid or Histidine Using Polarography

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The stability constants of binary and ternary complexes of Cd(II) with glutamic acid (Glu) or histidine (His) as a primary ligand and imipramine (Imip) as a secondary one have been determined polarographically. The reduction process of both simple and mixed systems is reversible and diffusion-controlled. For the system Cd—Glu—Imip, two mixed complexes were formed: $Cd(Glu)(Imip)_2$ and $Cd(Glu)_2(Imip)$ with stabilities log $\{\beta_{12}\}$ = 11.45 and log $\{\beta_{21}\}$ = 10.26, respectively. But the system Cd—His—Imip forms three mixed complexes, Cd(His)(Imip), $Cd(His)(Imip)_2$, and $Cd(His)_2(Imip)$. The calculated stability constants of these complexes are log $\{\beta_{11}\}$ = 7.17, log $\{\beta_{12}\}$ = 10.39, and log $\{\beta_{21}\}$ = 9.7, respectively.

The study is devoted to the polarographic investigation of MA_iL_j ternary systems where M are the Cd(II) ions, A is the glutamic acid or histidine, and L is the antidepressant drug imipramine. The method of *DeFord—Hume* [1] and its extention [2] have been used to determine the stability constants of the binary and ternary systems, respectively.

The binary and some ternary complexes of histidine and glutamic acid have been studied using electrochemical techniques [3—5], but there are no available data concerning the mixed complexes involving imipramine. On the other hand, it has been established that Cd(II) has a toxic effect in the form of Cd^{2+} ions [6]. Fortunately most of the Cd^{2+} ions do not exist in the free form but form complexes with the biological ligands *in vivo* [7]. Therefore, such study is of a particular importance.

EXPERIMENTAL

Imipramine (5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine monohydrochloride) was obtained from Sigma and used without further purification. All the other chemicals used were of anal. grade and were dissolved in double-distilled water. The total concentration of imipramine, glutamic acid or histidine was recalculated taking into consideration their pK_a's values, these being 9.50, 9.47, and 9.05 for imipramine [8], glutamic acid [9], and histidine [10], respectively. The polarograms were recorded with a Sargent—Welch model 5001 after deaeration of the test solution with purified nitrogen. Saturated calomel electrode (SCE) was used as a reference electrode and a wire of Pt as an auxiliary one. The dropping mercury electrode (DME) had the following characteristics: $m' = 1.76$ mg s^{-1}, $t = 3.4$ s in 0.1 M-KCl (open circuit) at the mercury height 60 cm. All the measurements were carried out at 25 °C, pH 7.4, and ionic strength $I(NaNO_3)$ = 0.1 mol dm^{-3}

The stability constants of the formed binary complexes were calculated using the *DeFord—Hume* method [1]. They may be expressed as follows

$$F_{0(X)} = \sum \beta_j [X]^j \; (j = 1, 2, 3) = \\ = \text{antilog}\,[(0.434nF/RT)\,\Delta E_{1/2} + \log I_s/I_c] \qquad (1)$$

where [X] is the analytical concentration of the ligand and $\Delta E_{1/2}$ is the half-wave potential shift. I_s and I_c are diffusion currents of the free and complexed metal ions, respectively. The other symbols have their usual meaning.

For the ternary systems, the DeFord—Hume expression was extended by *Schaap* and *McMasters* [2] and became as follows

$$F_{\infty(XY)} = \text{antilog}\,[(0.434nF/RT)\,\Delta E_{1/2} + \log I_s/I_c] \qquad (2)$$

where

$$F_\infty = A + B[X] + C[X]^2 + D[X]^3 \qquad (2a)$$

and

$$A = \beta_{01}[Y] + \beta_{02}[Y]^2 + \beta_{03}[Y]^3 \qquad (2b)$$
$$B = \beta_{10} + \beta_{11}[Y] + \beta_{12}[Y]^2 \qquad (2c)$$
$$C = \beta_{20} + \beta_{21}[Y] \qquad (2d)$$
$$D = \beta_{30} \qquad (2e)$$

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The values *A, B, C,* and *D* were obtained from the plots of F_{i0} *vs.* [X] by the extrapolation of F_{00}, F_{10}, F_{20}, and F_{30} to [X] equal to zero. The values of F_{i0} were calculated from the following relations

$$F_{10} = (F_{00} - A)/[X] \quad (3)$$
$$F_{20} = (F_{10} - B)/[X] \quad (4)$$
$$F_{30} = (F_{20} - C)/[X] \quad (5)$$

RESULTS AND DISCUSSION

The binary systems of Cd(II) with imipramine, glutamic acid or histidine were investigated under the experimental conditions mentioned above. The plots of $\log i/(i_d - i)$ *vs.* *E* of the waves of the Cd—imipramine system proved that the reduction process is reversible and diffusion-controlled. Also it was observed that the half-wave potential is shifted to the more negative values with increasing imipramine concentration. The plots of $E_{1/2}$ against log {[ligand]} for the investigated ligands gave a smooth curve and consequently the method of DeFord—Hume was used to treat the polarographic data. The obtained results are presented in Table 1.

Table 1. Stability Constants of the Formed Binary Complexes pH = 7.4, I($NaNO_3$) = 0.1 mol dm^{-3}, [Cd] = 1 × 10^{-4} mol dm^{-3}

System	log {β_1}	log {β_2}	log {β_3}
Cd—Imip	4.29	5.77	9.31
Cd—Glu	4.47	6.47	10.03
Cd—His	4.00	6.69	10.81

The Cd—Glu—Imip and Cd—His—Imip mixed systems were studied at constant concentration of imipramine, *viz.* 0.001 mol dm^{-3} and 0.002 mol dm^{-3} and varying concentrations of glutamic acid or histidine ranged from 0.0005 mol dm^{-3} to 0.0026 mol dm^{-3} (six points were registered). In all cases, the single well-defined and diffusion-controlled wave was obtained. The logarithmic analysis plots of the waves proved that the reduction process is reversible and involves two electrons. In each of the mixed systems, a shift in the half-wave potential to the more negative side was observed with increasing glutamic acid or histidine concentration. This shift is in the presence of imipramine greater than in its absence indicating the formation of mixed complexes. Following the method of Schaap and McMasters, the functions F_{00}, F_{10}, F_{20}, and F_{30} were obtained as described above for each of the systems under investigation. The values of *A, B, C,* and *D* were abstracted from the intercept of F_{00}, F_{10}, F_{20}, and F_{30} with the [X] axis at [X] equal to zero, respectively. Using eqns (*2c*) and (*2d*) and the values of *B* and *C* the stability constants β_{11}, β_{21}, and β_{12} for the ternary systems MAL, MA_2L, and MAL_2, respectively, were determined. The collected data are given in Table 2.

Table 2. The Polarographic Data of the Studied Systems I($NaNO_3$) = 0.1 mol dm^{-3}, pH = 7.4, [Imip] = *a*) 0.001 mol dm^{-3}; *b*) 0.002 mol dm^{-3}

System		log {*A*}	log {*B*}	log {*C*}	log {*D*}	log {β_{ij}}
Cd—Glu—Imip	*a*	1.7	5.69	7.00	11.57	log {β_{12}} = 11.45
	b	2.69	5.84	8.00	11.75	log {β_{21}} = 10.26
Cd—His—Imip	*a*	1.39	4.84	7.00	10.68	log {β_{11}} = 7.17
	b	1.69	5.00	7.18	10.86	log {β_{12}} = 10.39
						log {β_{21}} = 9.70

For the Cd—Glu—Imip system, the value of β_{11} is negative, *i.e.* the Cd(Glu)(Imip) does not exist in the solution under our experimental conditions and the value of log {β_{12}} was calculated to be 11.45. The two values of *C* gave two values for log {β_{21}} and the average value is 10.26.

For the Cd—His—Imip system, the stability constants log {β_{11}} and log {β_{12}} were calculated from the two values of *B* and were found to be 7.17 and 10.39, respectively. And the two values of *C* gave two values for log {β_{21}} (average value is 9.7).

The binary and ternary complexes have been compared. The mixing constant (K_m) [11] was used to compare the stabilities of the binary and ternary complexes. For the following reactions

$$1/2\,[Cd(A)_2] + 1/2\,[Cd(L)_2] \rightleftharpoons [Cd(A)(L)] \quad (A)$$
$$1/3\,[Cd(A)_3] + 2/3\,[Cd(L)_3] \rightleftharpoons [Cd(A)(L)_2] \quad (B)$$
$$2/3\,[Cd(A)_3] + 1/3\,[Cd(L)_3] \rightleftharpoons [Cd(A)_2(L)] \quad (C)$$

the mixing constants could be calculated from the relations

$$\log\{K_m(A)\} = \log\{\beta_{11}\} - 1/2\,(\log\{\beta_{20}\} + \log\{\beta_{02}\})$$
$$\log\{K_m(B)\} = \log\{\beta_{12}\} - (1/3\log\{\beta_{30}\} + 2/3\log\{\beta_{03}\})$$
$$\log\{K_m(C)\} = \log\{\beta_{21}\} - (2/3\log\{\beta_{30}\} + 1/3\log\{\beta_{03}\})$$

The values of log {K_m} of the Cd—Glu—Imip system are: log {$K_m(B)$} = 1.66 and log {$K_m(C)$} = 0.24. For the Cd—His—Imip system, values of 0.94, 0.58, and – 0.61 were obtained for log {$K_m(A)$}, log {$K_m(B)$}, and log {$K_m(C)$}, respectively. These values show that the mixed complexes are more stable than the simple ones except for the $Cd(His)_2$(Imip) complex in which a negative value is obtained (– 0.61) indicating that the complex is less stable than the binary one.

The equilibria between various species existing in solution for the Cd—Glu—Imip and Cd—His—Imip

Table 3. Equilibria Involved in the Formation of Ternary Complexes for the Cd—Glu—Imip System

	Equilibria		log {*K*}
1	Cd + 2 Glu + Imip	$Cd(Glu)_2(Imip)$	10.26
2	Cd + Glu + 2 Imip	$Cd(Glu)(Imip)_2$	11.45
3	$Cd(Glu)_2$ + Imip	$Cd(Glu)_2(Imip)$	3.79
4	$Cd(Glu)_3$ + Imip	$Cd(Glu)_2(Imip)$ + Glu	− 0.23
5	$Cd(Imip)_2$ + Glu	$Cd(Imip)_2(Glu)$	5.68
6	$Cd(Imip)_3$ + Glu	$Cd(Imip)_2(Glu)$ + Imip	2.14
7	$Cd(Imip)_2(Glu)$ + Imip	$Cd(Imip)_3$ + Glu	− 2.14
8	$Cd(Imip)(Glu)_2$ + Glu	$Cd(Glu)_3$ + Imip	0.23

Table 4. Equilibria Involved in the Formation of Ternary Complexes for the Cd—His—Imip System

	Equilibria		log {*K*}
1	Cd + His + Imip	Cd(His)(Imip)	7.17
2	Cd + 2 His + Imip	$Cd(His)_2(Imip)$	9.70
3	Cd + His + 2 Imip	$Cd(His)(Imip)_2$	10.39
4	Cd(His) + Imip	Cd(His)(Imip)	3.17
5	$Cd(His)_2$ + Imip	$Cd(His)_2(Imip)$	3.01
6	$Cd(His)_3$ + Imip	$Cd(His)_2(Imip)$ + His	1.11
7	Cd(His)(Imip) + Imip	$Cd(His)(Imip)_2$	3.22
8	$Cd(His)_2(Imip)$ + Imip	$Cd(His)(Imip)_2$ + His	0.69
9	Cd(Imip) + His	Cd(His)(Imip)	2.78
10	$Cd(Imip)_2$ + His	$Cd(Imip)_2(His)$	3.92
11	$Cd(Imip)_3$ + His	$Cd(Imip)_2(His)$ + Imip	1.08
12	$Cd(Imip)_2(His)$ + His	$Cd(Imip)(His)_2$ + Imip	− 0.69

systems with the equilibrium constants (log {*K*}) values are given in Tables 3 and 4, respectively.

From Table 3 it was found that Glu can replace Imip in the complex $Cd(Imip)_3$ while Imip cannot replace Glu in the complex $Cd(Glu)_3$ (equilibria *6* and *4*). Also it can be observed that the equilibria *3*, *5*, and *6* favour the formation of mixed complexes over the simple ones. The same table shows also that the addition of Glu to Cd(Imip) is more easier than the addition of Imip to Cd(Glu) (*cf.* equilibrium *3* and *5*).

From the values of log {*K*} in Table 4 one can observe that the equilibria *4*, *5*, *6*, *9*, *10*, and *11* favour the ternary complexes over the binary ones. Also it was found that the addition of Imip to Cd(His) is more easier than the addition of His to Cd(Imip) (equlibria *4* and *9*) and Imip can replace His readily (equilibrium *6*).

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