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IONIZATION OF PERLNDOPRIL PERMADIOL AND AMINEPTINE – HCL AS PHARMACEUTICAL LIGANDS AND THEIR COMPLEXES WITH DIVALENT CATIONS AND LANTHANONS.

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IONIZATION OF PERLNDOPRIL PERMADIOL AND AMINEPTINE – HCL AS PHARMACEUTICAL LIGANDS AND THEIR COMPLEXES WITH DIVALENT CATIONS AND LANTHANONS.

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Abstract

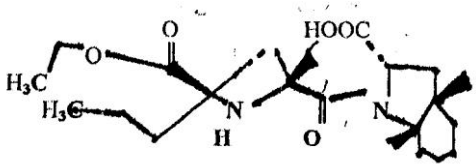
Proton – constants of Per (I) and Amin (II) ligands and the formation constants of their complexes with some transition metal ions (Zn(II) and Cu(II)) and some trivalent lanthanides (Ce(III), Pr(III), and Er(III)) ions have been determined potentiometrically in aqueous methanol medium. The effect of temperature was studied at 20, 30, and 40ºC. The thermodynamic parameters (ΔH^o, ΔG^o, ΔS^o) were evaluated and discussed. The formation curves for the metal complexes were obtained and the formation constants were determined.

Key words: potentiometry, complexes; thermodynamic

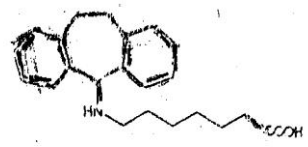
Experimental

Reagents and Materials: Metal ion solutions (0.01M) were prepared from Analar metals nitrate in bidistilled water. Standardization of metal ions were performed by complexometric titration using standard solution of EDTA (1). The ligand solutions (0.01M) were prepared by dissolving the accurate weight of the solid in aqueous methanol medium. Solutions of 0.1M HCl and 0.1M of nitric acid and potassium nitrate were prepared by dissolving A.R. grade chemicals in bidistilled water. The acids were standerdized by using primary standard base.

Potentiometric Measurements: pH – measurements were carried out using Fisher scientific equipment pH meter model 825 mp.



(I)



(II)

Method of calculation: The proto-ligand stability constants were calculated using the linear least - square computer program (2).

Results and Discussion

Dissociation constants of Perlndopril (Per) and Amineptine – HCl (Amin) Ligands.

The dissociation constants of Per and Amin were determined by titrating 10 ml of the ligand (0.001M) with 0.0035M KOH at different temperatures and ionic strength 0.1 using KNO_3. The pKa´s values are shown in table (1).

Effect of temperature:

The effect of temperature on the ionization constants of ligands are shown in Figs.(1-2). It is clear that pKa values increase in order 20 > 30 > 40ºC and this may be due to the fast deprotonation process at high temperature.

Ionization constants and thermodynamic functions:

The values of ΔH^o are shown in table (1) indicate that endothermic ionization process is enhanced with temperature in addition to the positive values of ΔH^o and the positive values of ΔG^o making the ionization process nonspontaneous and ΔS^o values suggest solvation of the ligands in aqueous – methanol medium(3).

Potentiometric studies:

The titration curves of the metal-ligand mixtures were plotted and the pH - reading depressed relative to that of the titration curves of the free ligand. The formation constants for (Per-Zn(II) complex) and (Per- Cu(II) complex) were determined by using the linear least- square computer program. According the average values are represented in table (2) the following general remarks can be pointed:

1- The maximum values of n was = 1 indicating the formation of 1:1(metal:ligand) complexes(4).
2- The metal titration curves indicating the large decrease in pH for metal titration curves relative to ligand titration curve are shown in Fig.(3).
3- The metal ions solutions used in the present study were dilute (10^{-4}M), hence there were no possibility of formation of polynuclear complexes(5).
4- The formation constants of (Per-Zn (II)) complex are relative small compared with those of (Per-Cu (II)) complex where the d orbital of Zn (II) is fully(6).

Thermodynamic functions:

Thermodynamic parameters ΔG^o, ΔH^o and ΔS^o for the complexes were calculated from the stability constants obtained at various temperatures (20, 30 and 40ºC). The values of the thermodynamic parameters associated with complexes formation are indicated in table (3). The stepwise stability constants of complexes increase with increasing the temperature. The positive values of ΔG^o for complexation process suggests the nonspontaneous process. It was suggested (3) that the ions in aqueous solution, order the water molecules around them and during complex formation between oppositely charged ions (ligand $-L^{2-}$ and metals M^{n+}) will lead to the breakdown of metal-water arrangement resulting in positive entropy and enthalpy changes. Qualitativly, the data in table (3) do not agree well with this picture. The negative values of ΔH^o could be explained by the increase of solvent basicity (7) which causes exothermic behavior for the transfer of metal ion from the aqueous state to methanol solvent. The ΔH^o dependence on solvent can be ascribed primarily to different hydration-solvation condition of the metal ions (2). Such negative entropy change can be attributed to the extensive solvation of metal chelates in aqueous-methanol medium.

Table (1) Thermodynamic functions for the dissociation of Per and Amin in (1/10) of methanol : water and 0.lM KNO_3 at different temperatures.

Temp. K	Dissociation constant pK^H		Enthalpy Chang ΔH^o		Free energy change ΔG^o		Entropy Chang ΔS^o	
	Per	Amin	Per	- Amin	Per	- Amin	Per	- Amin
293	9.4593	5.5543	63.097	15.9674	12.684	7.4474	0.1720	29
303	9.3021	5.5143	63.097	15.9674	12.899	7.6485	0.16567	27
313	9.145	5.4793	63.097	15.9674	13.099	7.848	0.1597	25

ΔG^o units are (kcal. mol^{-1}).
ΔH^o units are (kcal. mol^{-1}).
ΔS^o units are (cal. $mol^{-1}.K^{-1}$).

Table (2) Stepwise stability constants for the complexation of Per with Cu^{2+}, and Zn^{2+} in (1/10) methanol-water medium and 0.1 M $KN0_3$ at different temperatures.

M	293K Log Kf	303K Log Kf	313K Log Kf
Cu(II)	5.1264	5.154	5.3004
Zn(II)	3.608	3.6764	3.784

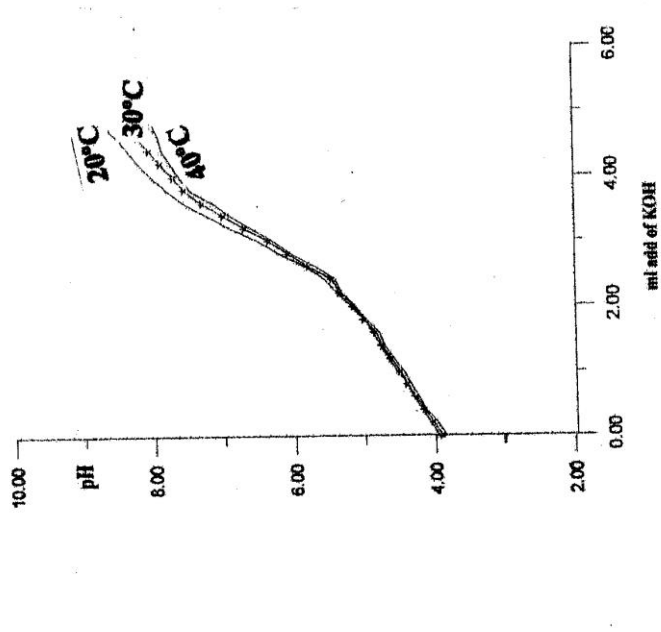


Fig.(2) Effect of temperature on ionization constant of Amin, [KNO3] = 0.1M, [KOH] = 0.0035M, [Amin] = 0.001M

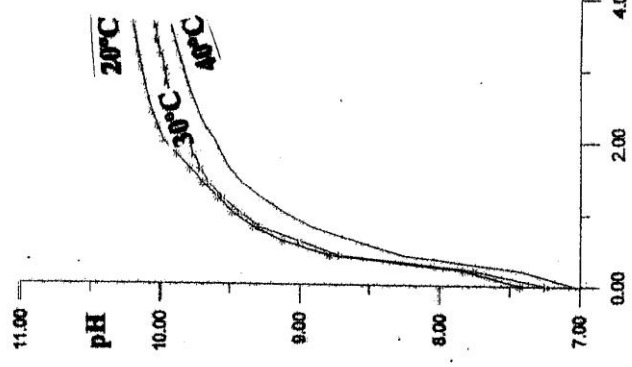


Fig.(1) Effect of temperature on ionization constant of Per, [KNO3] = 0.1M, [KOH] = 0.0035M, [Per] = 0.001M

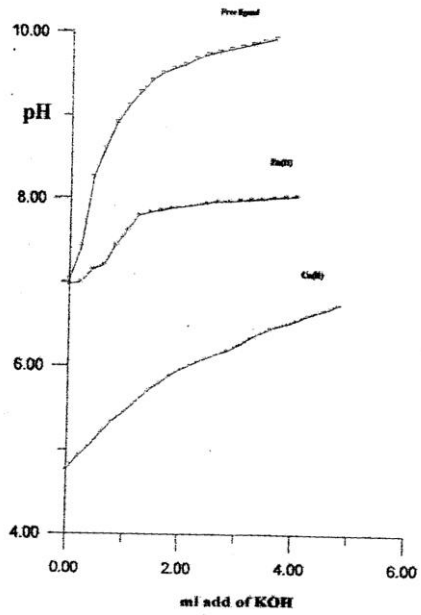


Fig.(3) pH-titration curves of Per and its complexes Cu(II) –complex, and Zn(II) –complex at T=30°C and the ratio of (metal-ligand) = 1:1, [KNO_3] = 0.1M, [Per] = 0.001 M and [KOH] = 0.0035M

Table (3) Thermodynamic functions for the complexation of Per with Cu^{2+}, and Zn^{2+} (1/10) methanol-water medium and 0.lM KNO_3 at different temperatures.

M	ΔG°	ΔH°	ΔS°
Cu(II)	6.874	-11.2137	-0.1113
	7.1469		-.1085
	7.5925		-0.1061
Zn(II)	4.838	-27.7907	-0.0617
	5.0979		-0.0607
	5.4203		-0.0600

Complexes of lanthanides with ligands:

1- pH – metric study:

The lanthanide ions (Er^{3+}, Ce^{3+}, Pr^{3+}) with Per and Amin ligands (1×10^{-3} M) were titrated against KOH at (20, 30, and 40 °C) and ionic strength of 0.1 M KNO_3 in methanol aqueous medium. The titration curves of the metal-ligand mixtures were

plotted and the pH – reading depressed relative to that of the titration curves of the free ligand. The formation constants for (Per-Er(III) complex), (Amin- Er(III) complex), (Amin-Pr(III))complex and (Amin-Ce(III)) complex were determined by using the linear least- square computer program. According the average values are represented in table (4) the following general remarks can be pointed:

1- The maximum values of $\bar{n}$ was = 1 indicating the formation of 1:1(metal:ligand) complexes(4).
2- The metal titration curves indicating the large decrease in pH for metal titration curves relative to ligand titration curve are shown in Fig.(5).
3- The metal ions solutions used in the present study were dilute (10^{-4}M), hence there were no possibility of formation of polynuclear complexes(5), that agree with Fig. (6)

Thermodynamic functions

Thermodynamic parameters ΔG^o, ΔH^o and ΔS^o for the chelate compounds were calculated from the stability constants obtained at various temperatures (20, 30 and 40 ºC). The values of the thermodynamic parameters associated with complexes formation are indicated in tables (4), and (5). The stepwise stability constants of complexes increase with increasing the temperature. The positive values of ΔG^o for complexation process suggests the nonspontaneous nature and the negative values of ΔH^o meaning that these processes are exothermic and clearly reflect the increasing metal-ligand strength. The large negative ΔS^o values attributed to the extensive solvation of metal chelates in aqueous – methanol medium. The positive ΔS^o values confirming that the complex formation is entropically favourable.

Table (4) Stepwise stability constants for the complexation of Amin and Per with Pr^{3+}, $Ce^{3+}$and Er^{3+} in (1/10) methanol-water medium and 0.1 M $KN0_3$ at different temperatures.

M	293K Log Kf		303K Log Kf		313K Log Kf	
Ce(III)	Amin	per	Amin	Per	Amin	Per
	6.602	------	6.6324	------	6.6628	-------
Pr(III)	6.617	------	6.601	---------	6.6465	-------
Er(III)	6.5465	5.288	6.6028	5.458	6.6374	5.6292

Table(5) Thermodynamic functions for the complexation of Per and Amin with Pr^{+3}, $Ce^{3+}$and Er^{3+} in (1/10) methanol-water medium and 0.lM KNO_3 at different temperatures.

M	ΔGº		ΔHº		ΔSº	
	Amin	Per	Amin	Per	Amin	Per
Ce(III)	8.8537	----	-12.188	----	-71.8	----
	9.1988	-----			-70.5	----
	9.544	----			-69.4	-----
Pr(III)	8.9	-----	75.733	-----	228	----
	8.9455	-----			220.4	----
	9.3775	----			211.9	----
Er(III)	8.778.3	7.0911	19.1934 - 71.5389		95.4	-0.2199
	9.155	7.3418			93.5	- 0.2683
	9.507	7.5925			91.6	-0.2603

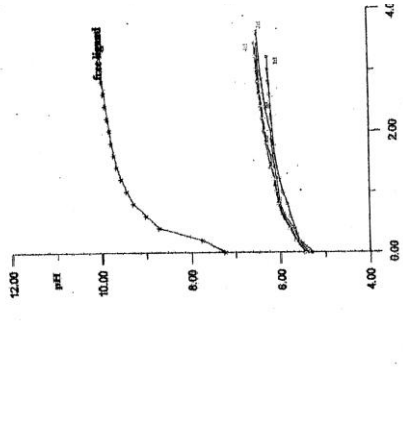


Fig.(6) pH-titration curves of Per and its Er(III)-complex at T=30°C and different ratio of (metal-ligand), [KNO3] = 0.1M, [Per] = 0.001 M and [KOH] = 0.0035M

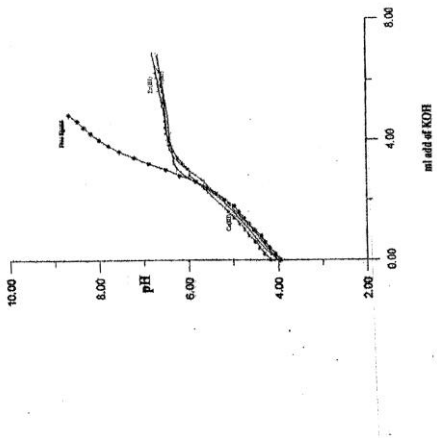


Fig.(5) pH-titration curves of Amin and its complex Er(III), Pr(III), and Ce(III) at T= 30°C the ratio of (metal-ligand) = 1:1, [KNO3] = 0.1M, [Amin] = 0.001 M and [KOH] = 0.0035M

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الملخص العربى

ان صناعة الدواء تعتبر من أهم الصناعات المؤثرة فى حياة البشر فلا غنى عن الدواء لآى منا ولكن أصبح سعر الدواء يمثل قضية هامة نظرا لكونه سلعة استراتيجية ومن البديهى أن سعر الدواء يتوقف على عدة عوامل من بينها التكلفة الخا صة بمعامل الجودة و الرقابة الموجودة داخل مصانع الأدوية لذا بات من الضرورى ايجاد طرق تحليلية رخيصة ودقيقة لتعين ثوابت التأين لهذه الأدوية ودراسة امكانية هذه الأدوية على تكوين متراكبات مع بعض العناصر الموجودة فى جسم الأنسان مثل النحاس والزنك وكذلك دراسة امكانية تكوين بعض المتركبات مع بعض اللنثيدات وذلك لأمكانية استخدامها كمصدر بيولوجى(biosensor) لتعرف على بعض الأنزيمات الموجودة فى الجسم وعلى هذا الأساس تم اختيار نوعين من الأدوية

Perlndorpil(I) and Amineptine – HCl(II)

فكانت النتائج تدل على ان كل منهم له ثابت تأين (5.5543) وذلك للمركب(II) و (9.4593) وذلك للمركب (I) وذلك عند درجة 20درجة سليزية وتم حساب ثابت التأين ايضا عند درجة حرارة40 و 30 درجة سيليزية . وتم حساب قيم كل من ΔG^o, ΔH^o, ΔS^o لكل من العقارين اثناء عملية التأين وايضا للمتراكبات المتكونة فاسفرت النتائج عن الأتى:

*انه كلما زادت درجة الحرارة كلما قل ثابت التأين لكل منهما

*كما ان الدراسة اثبتت ان عملية التأين تفاعل ماص للحرارة وايضا غير تلقائية

*وان البريمادويل يكون متراكبات مع كل من الزنك والنحاس بنسبة1:1 وان هذا التفاعل غير تلقائى وانه تفاعل طارد للحرارة

*كما وجدا ان هذة المرتبطات تكون متراكبات مع Pr(III), Er(III),Ce(III) بنسبة 1:1 وان هذا التفاعل غير تلقائى وانه طارد للحرارة

*تم حساب ثوابت التكوين لهذة المتراكبات عند درجات الحرارة 20و 30 و 40 درجة سيلزية

التوصية :

1- نو صى بان العقار (I) يؤثر على عنصر الزنك والنحاس الموجودين داخل الجسم وكذلك يمكن استخدامه عند حالت التسمم بالزنك او مركبات النحاس

2- ان كل من العقارين يمكن استخدامهم كا (biosensor)