



# Ionization of Perindopril Permadiol and Amineptine-HCl as Pharmaceutical Ligands and Their Complexes with Divalent cations and Lanthanons

## KEYWORDS

Potentiometry, complexes, thermodynamic

**N. Abdel-Ghany**Suez Canal University, Department of Chemistry,  
Faculty of Education, El-Arish, Egypt**Adel S. Orabi**Department of Chemistry, Faculty of Science, Suez  
Canal University, Ismailia, Egypt**N.B. El-Assy**Suez Canal University, Department of Chemistry,  
Faculty of Education, El-Arish, Egypt**Sawssan M. Abu El-Hassan**Suez Canal University, Department of Chemistry,  
Faculty of Education, El-Arish, Egypt

**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 2°, 3° and 40°C. The thermodynamic parameters ( $\Delta H^\circ$ ,  $\Delta G^\circ$ ,  $\Delta S^\circ$ ) were evaluated and discussed. The formation constants for the investigated metal complexes were calculated.

**Aim of the works:**

The aim of the present work is to optimize the various experimental conditions for the preparation of complexes of Zn(II), Cu(II) and some trivalent lanthanides Ce(III), Pr(III) and Er(III). Also the calculation of the formation constants and thermodynamic parameters of such complexes.

The dissociation constants of perindopril and amineptine-HCl have been calculated at different temperatures and the associated thermodynamic parameters have been determined. The complexing ability of these compounds with some transition elements and lanthanides via a new, fast, simple, sensitive, precise and cheap procedures based on the potentiometric method. Also thermal analysis (DTA and TG) has been carried out for some complexes.

**Introduction:**

The spectrophotometric determination of perindopril has been reported<sup>1</sup>. Solutions containing per were reacted with 2,3-dichloro-5,6-dicyano-p-benzo-quinone (DDO), 7,7,8,8-tetracyanoquinodimethane (TCNQ), chloranil (CL) and p-chloranilic acid (P-CA) and the absorbance of the solutions were measured at 419-843 nm. The colours were stable for at least 1h.

Another method for the determination of perindopril by spectrophotometry was done<sup>2</sup>. Ground Coversyl and trtace tablets were dissolved in H<sub>2</sub>O, or portions of perindopril standard solutions were diluted to 10 ml with H<sub>2</sub>O. The absorbance of the combined organic layers was measured at 535 nm.

The analysis of chiral drugs with enantioselective biosensors was carried out previously<sup>3</sup>. The opportunity to use amperometric biosensors based on L-amino acid oxidase in enantioselective analysis of chiral drugs was discussed.

A new, sensitive, simple, rapid and precise reversed-phase HPLC and two spectrophotometric methods have been developed for resolving binary mixture of perindopril and indapamide in the pharmaceutical dosage forms<sup>4</sup>.

A new, sensitive, simple, rapid and precise flow-injection procedure based on the formation of copper complexes with some angiotensin converting enzyme (ACE) inhibitors was developed and evaluated for the determination of perindopril<sup>5</sup>.

The ion-pair formation of bismuth (III)-iodide with amineptine HCl by spectrophotometry has been reported<sup>6</sup>. The absorbance was measured at 490 nm.

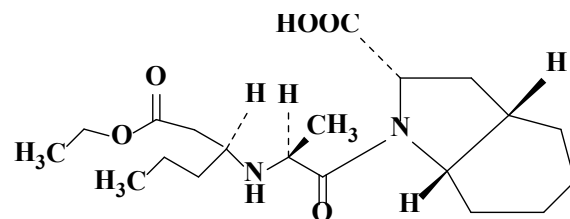
The determination of amineptine HCl in plasma by high-performance liquid chromatography after solid-phase extraction was described<sup>7</sup>.

**Experimental:****Reagents and materials:**

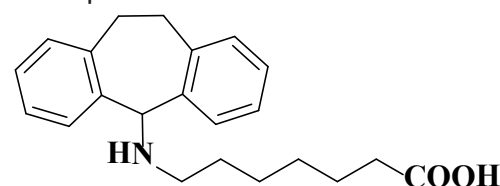
Metal ion solutions (0.01M) were prepared from Analar metals nitrate in bidistilled water. Standardization of metal ions were performed by complexometric titration using standard solution of EDTA<sup>8</sup>. The ligand solutions (0.01M) were prepared by dissolving the accurate weight of the solid in 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 standardized by using primary standard base.

**Potentiometric measurements:**

pH-measurements were carried out using Fisher scientific equipment pH meter model 825 mp.



(I)

**Perindopril**

(II)

Amineptine-HCl

**Method of calculation:**

The proto-ligand stability constants were calculated using the linear least-square computer program<sup>9</sup>.

**Results and Discussion:****Dissociation constants of perindopril (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<sub>3</sub>. The pK<sub>a</sub>'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 pK<sub>a</sub> values increase in order 20 > 30 > 40°C and this may be due to the fast deprotonation process at high temperature.

**Ionization constants and thermodynamic functions:**

The values of  $\Delta H^\circ$  are shown in table (1) indicate that endothermic ionization process is enhanced with temperature in addition to the positive values of  $\Delta H^\circ$  and the positive values of  $\Delta G^\circ$  making the ionization process nonspontaneous and  $\Delta S^\circ$  values suggest solvation of the ligands in aqueous-methanol medium<sup>10</sup>.

**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 to the average values 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, Fig. (3)<sup>11</sup>.
2. The metal titration curves indicate a large decrease in pH for metal titration curves relative to ligand titration curve, Fig. (4).
3. The metal ions solutions used in the present study were dilute (10<sup>-4</sup>M), hence there were no possibility of formation of polynuclear complexes<sup>12</sup>.
4. The formation constants of (Per-Zn(II) complex) are relatively small compared with those of (Per-Cu(II) complex) where the d-orbital of Zn(II) is completely with electrons<sup>13</sup>.

**Thermodynamic functions:**

Thermodynamic parameters  $\Delta G^\circ$ ,  $\Delta H^\circ$  and  $\Delta S^\circ$  for the complexes were calculated from the stability constants obtained at various temperatures (20, 30 and 40°C). 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  $\Delta G^\circ$  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<sup>2-</sup> and metals M<sup>n+</sup>) will lead to the breakdown of metal-water arrangement resulting in positive entropy and enthalpy changes. Qualitatively, the data in table (3) do not agree well with this picture. The negative values of  $\Delta H^\circ$  could be explained by the increase of solvent basicity<sup>14</sup> which causes exothermic behavior for the transfer of metal ion from the aqueous state to methanol solvent. The  $\Delta H^\circ$  dependence on solvent can be ascribed primarily to different hydration-solvation condition of the metal ions<sup>9</sup>. 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 0.1M KNO<sub>3</sub> at different temperatures.

Temp. K	Dissociation constant pK <sub>a</sub>		Enthalpy change $\Delta H^\circ$		Free energy change $\Delta G^\circ$		Entropy change $\Delta S^\circ$	
	Per	Amin	Per	Amin	Per	Amin	Per	Amin
293	9.4593	5.5543	63.097	5.9674	12.684	7.4474	0.1720	29
303	9.3021	5.5143	63.097	5.9674	12.899	7.6485	0.16567	27
313	9.145	5.4793	63.097	15.967	13.099	7.848	0.1597	25

$\Delta G^\circ$  units are (kcal.mol<sup>-1</sup>)

$\Delta H^\circ$  units are (kcal.mol<sup>-1</sup>)

$\Delta S^\circ$  units are (cal. mol<sup>-1</sup>.K<sup>-1</sup>)

Table (2). Stepwise stability constants for the complexation of perindopril with Cu<sup>2+</sup>, and Zn<sup>2+</sup> in (1/10) methanol : water medium and 0.1M KNO<sub>3</sub> at different temperatures.

M	293K Log K <sub>f</sub>	303K Log K <sub>f</sub>	313 K Log K <sub>f</sub>
Cu(II)	5.1264	5.154	5.3004
Zn(II)	3.608	3.6764	3.784

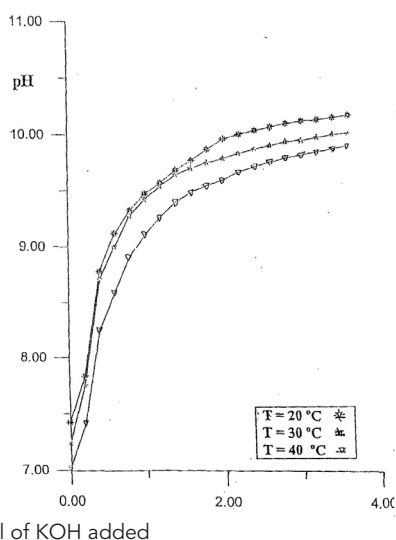


Fig.(1). Effect of temperature on ionization constant of Per, (KNO<sub>3</sub>) = 0.1M, (KOH) = 0.0035M, (Per) = 0.001M.

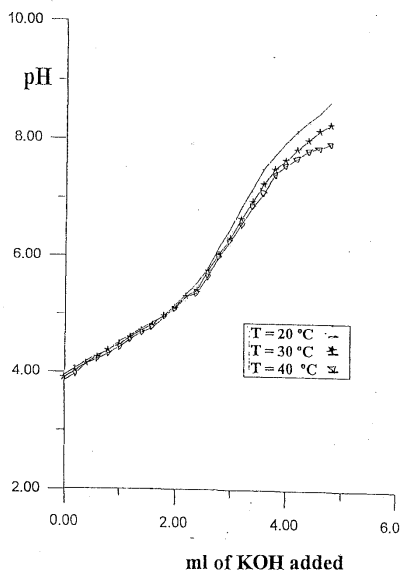


Fig. (2). Effect of temperature on ionization constant of Amin. (KNO<sub>3</sub>) = 0.1M, (KOH) = 0.0035M, (Amin) = 0.001M.

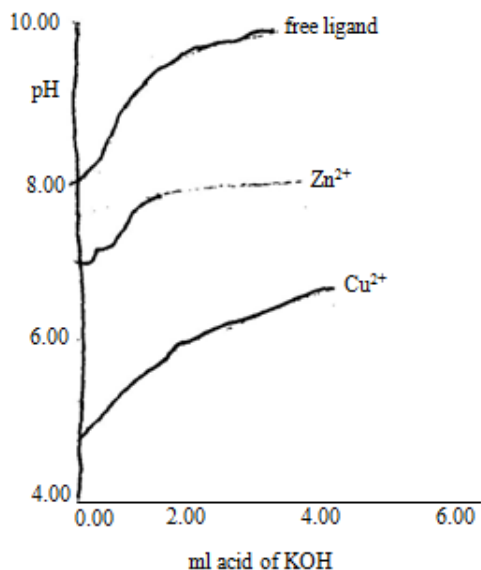


Fig. (3). pH-titration curves of Per and its complexes with Cu(II) and Zn(II) ions at  $t = 30^{\circ}\text{C}$  and the ratio of (metal-ligand) = 1:1, ( $\text{KNO}_3 = 0.1\text{M}$ , (Per) = 0.01M and (KOH) = 0.0035M.

Table (3). Thermodynamic functions for the complexation of perindopril with  $\text{Cu}^{2+}$ , and  $\text{Zn}^{2+}$  (1/10) methanol-water medium and 0.1M  $\text{KNO}_3$ , at different temperatures.

$\text{M}^{n+}$	$\Delta\text{G}^{\circ}$	$\Delta\text{H}^{\circ}$	$\Delta\text{S}^{\circ}$
Cu(II)	6.874	-11.2137	-0.1113
	7.1469		-0.1085
	7.5925		-0.1061
Zn(II)	4.838	-27.7907	-0.0617
	5.0979		-0.0607
	5.4203		-0.0600

$\Delta\text{G}^{\circ}$  units are (kcal.mol<sup>-1</sup>)

$\Delta\text{H}^{\circ}$  units are (kcal.mol<sup>-1</sup>)

$\Delta\text{S}^{\circ}$  units are (cal.mol<sup>-1</sup>.K<sup>-1</sup>)

**Complexes of lanthanides with ligands:**

**1- pH-metric study:**

The lanthanide ions ( $\text{Er}^{3+}$ ,  $\text{Ce}^{3+}$ ,  $\text{Pr}^{3+}$ ) with Per and Amin ligands ( $1 \times 10^{-3}\text{M}$ ) were titrated against 0.0035M KOH at (20, 30, and 40°C) and ionic strength of 0.1M  $\text{KNO}_3$  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 to the average values, represented in table (4) the following general remarks can be pointed:

- 1) The metal titration curves indicating the large decrease in pH for metal titration curves relative to ligand titration curve, Fig. (4).
- 2) The maximum values of n was = 1 indicate the formation of 1:1 (metal : ligand) complexes Fig. (4).
- 3) The metal ions solutions used in the present study were dilute ( $10^{-4}\text{M}$ ), hence there were no possibility of formation of polynuclear complexes<sup>12</sup>, that agree with Fig. (5)

**Thermodynamic functions:**

Thermodynamic parameters  $\Delta\text{G}^{\circ}$ ,  $\Delta\text{H}^{\circ}$  and  $\Delta\text{S}^{\circ}$  for the chelate complexes compounds were calculated from the stability

constants obtained at various temperatures (20, 30 and 40°C). The values of the thermodynamic parameters associated with complexes formation are collected in tables (4), and (5). The stepwise stability constants of complexes increase with increasing the temperature. The positive values of  $\Delta\text{G}^{\circ}$  for complexation process suggests the nonspontaneous nature of the processes. The negative values of  $\Delta\text{H}^{\circ}$  mean that these processes are exothermic and clearly reflect the increasing of metal-ligand strength. The large negative  $\Delta\text{S}^{\circ}$  values attributed to the extensive solvation of metal chelates in aqueous-methanol medium. The positive  $\Delta\text{S}^{\circ}$  values confirm that the complex formation is entropically favourable.

Table (4). Stepwise stability constants for the complexation of aminoptine-HCl and perindopril with  $\text{Pr}^{3+}$ ,  $\text{Ce}^{3+}$  and  $\text{Er}^{3+}$  in (1/10) methanol : water medium and 0.1M  $\text{KNO}_3$  at different temperatures.

M	293K Log $K_f$		303K Log $K_f$		313K Log $K_f$	
	Amin	Per	Amin	Per	Amin	Per
Ce(III)	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 amineptine-HCl and perindopril with  $\text{Pr}^{3+}$ ,  $\text{Ce}^{3+}$  and  $\text{Er}^{3+}$  in (1/10) methanol : water medium and 0.1M  $\text{KNO}_3$  at different temperatures.

$\text{M}^{n+}$	$\Delta\text{G}^{\circ}$		$\Delta\text{H}^{\circ}$		$\Delta\text{S}^{\circ}$	
	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)	8.7783	7.0911	9.1934-71.5389		95.4	-0.219
	9.155	7.3418			93.5	-0.268
	9.507	7.5925			91.6	-0.260

$\Delta\text{G}^{\circ}$  units are (kcal.mol<sup>-1</sup>)

$\Delta\text{H}^{\circ}$  units are (kcal.mol<sup>-1</sup>)

$\Delta\text{S}^{\circ}$  units are (cal.mol<sup>-1</sup>.K<sup>-1</sup>)

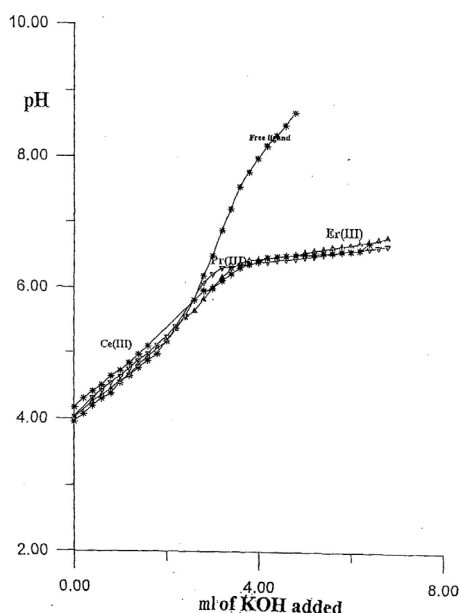


Fig. (4). pH-titration curves of amineptine-HCl and its complex at  $T = 30^{\circ}\text{C}$  the ratio of (metal-ligand) = 1:1

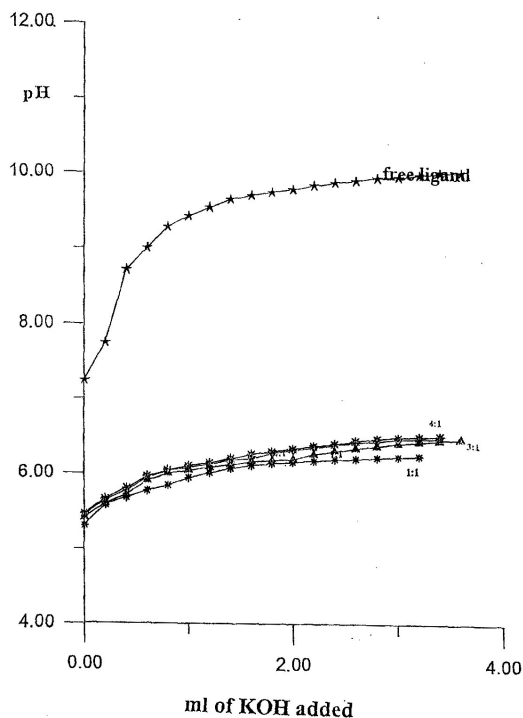


Fig. (5). pH-titration curves of perindopril and its Er(III)-complex at  $T=30^{\circ}\text{C}$  and different ratio of (metal-ligand), ( $\text{KNO}_3$ ).

#### REFERENCE

1. Abdellatef, H.E. J. Pharm. Biomed-Anal. 17, (1998) 1267-1271. | 2. Abdellatef, H.E., Ayad, M.M. and Taha, E.A., J. Pharm. Biomed. Anal. 18, (1999) 1021-1027. | 3. Stefan, R., Van-Staden, J.F. and Aboul-Enein, H.Y., J. Chirality (1999) 11, 631-34. | 4. Erk, N. J. Pharm.Biomed. Anal. 26 (2001)43-52. | 5. Emara, S., El-Gindy, A., and Hadad, G. J. Anal. Chim. Acta 489, (2003) 115-123. | 6. Abdel-Gawad, F.M. J. Pharm.Biomed. Anal. 16, (1998) 793-799. | 7. Rop, P.P., Spinazzola, J. and Viala, A. J. Chromatogr. Biomed. Appl., 97, (1990) 351-361. | 8. A.J.Vogel, Text Book of Quantitative Inorganic Analysis, 4th ed., Longman, London, (1978). | 9. Adel S.Orabi, Ph.D. Thesis, Suez Canal University, Egypt (1994). | 10. Hyoung-Ryun Park. Bull. Korean Chem. Soc. 21, (2000) 9. | 11. El-Bindary A., A., El-Sonbati, A.Z., and Kera H.M. J. Chem. 77, (1999), 1305. | 12. El-Bindary, A. A. and El-Sonbati, A.Z., J. Chem. 49, (2001) 1312. | 13. Sanyal, P., Sengupta, G.P. J. Ind. Chem. Soc., 67, (1990) 342. | 14. Offiong E. Offiong, J. Transition Met. Chem. 23,(1998) 553-555.