A Study on complexation behavior of Lanthanides (III) with Pregabalin

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Abstract
Lanthanide(III)-Pregabalin complexes were formed by interaction between Pregabalin and Sm(III), Gd(III), Tb(III), Dy(III) & Ho(III) nitrates in aqueous medium. Stability of binary complexes was studied in detail by using Irving Rossotti titration technique at temperatures (30±0.1, 40±0.1 and 50±0.1°C) and ionic strength (0.1, 0.2, 0.3 and 0.4M). Protonation constants of Pregabalin have been evaluated using three different methods PKAS, BEST and point wise calculation method with Fortran IV computer program. Stability constants of Pregabalin lanthanide complexes have been obtained by BESTFIT program with consideration of systematic errors.

ΔG^0, ΔH^0 and ΔS^0 values were obtained to evaluate stability order of binary complexes which were further investigated with the aid of speciation curves (SPEPLOT) plotted. The value of overall stability constant of each complex obtained is relatively high, indicating good stability for the complexes in the pH range 2-12. Critical analysis of stability constant and their thermodynamic parameter indicate that stability order is Sm(III) < Gd(III) < Tb(III) < Dy(III) < Ho(III).

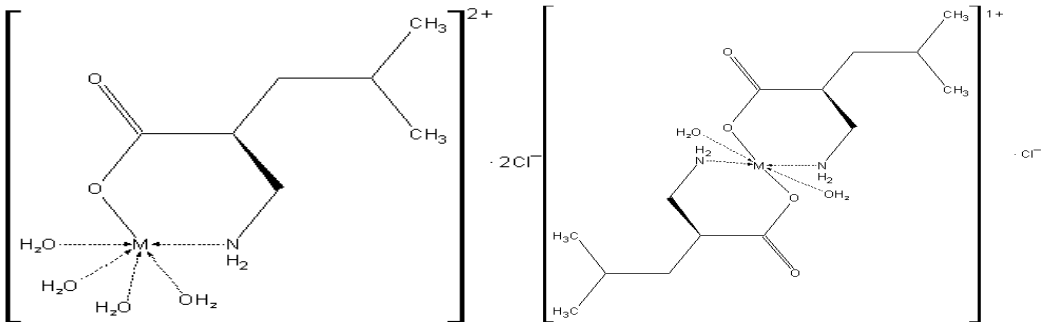
Keywords: Lanthanides, Stability constant, Binary complex, SPEPLOT, Irving-Rossotti technique.

Introduction

Metal-based compounds are rapidly emerging as an alternative to organic drugs, as they have the ability to kill pathogens via metal-specific modes of action[21]. Lanthanide complexes, similar to organic molecules, have a small size, clear structure and good reproducibility, securing their production and quality[4]. Metals especially lanthanides due to their chemical and magnetic properties find huge number of implementations in various fields like medical analysis and treatment as well[19]. The applications of Gd(III) complex-based responsive probes *in vivo* and *in vitro* MRI are much researched today[15].

The complexation behavior and luminescent properties of terbium Tb(III) complexes containing bi-dental ligands were studied for nitrogen - 1,10-phenanthroline and oxygen – trifluoroacetylacetone. Acetylacetone ligands were studied with ibuprofen in aqueous and alcohol microheterogeneous solutions were used as media[17]. Samarium(III), Gadolinium(III) and Dysprosium(III) complexes with coumarin-3-carboxylic acid (HCCA) were tested for antiproliferative activitiy on the chronic myeloid leukemia-derived K-562, over expressing the BCR-ABL fusion protein[10]. The trivalent holmium(III) and gadolinium(III) metal complexes of thymoquinone (TQ) were synthesized to conduct investigations on toxicities and other bioactivities with existing drug combinations and to establish more effective tumor models[3].

Certain metal complexes of pregabalin derivatives have been verified as strong anti-inflammatory and anti-cancer agents than pregabalin alone[1]. Pregabalin is an anti-epileptic, anticonvulsant drug that also treats nerve pain, fibromyalgia and restless leg syndrome[6-8]. The selectivity of pregabalin for an alpha-2-delta subunit of voltage-gated calcium channels[1,6,7] proves it to be effective for the treatment of neuropathic pain. It is highly soluble in water. The essential component that further qualifies any lanthanide compounds for analytical methods is its water solubility. Aqueous medium has been used to study a large number of binary and ternary complexes of lanthanide(III) pH metrically method[2,11,18].



Graphical Abstract

Biological significance lanthanide of pregabalin and lanthanide (II) drug has encouraged us to study their complexation with pregabalin in detail. This research study focuses on the formation of binary complexes of Pregabalin with Sm(III), Gd(III), Tb(III), Dy(III) and Ho(III) and their ΔG, ΔH and ΔS thermodynamic parameters.

Material and Methods

Materials: All chemicals used in this experiment were of analytical grade having 99 to 99.9 % purity. The materials utilized in the experiment include pregabalin, sodium perchlorate, double-distilled water, perchloric acid, Samarium, Gadolinium, Terbium, Dysprosium and Holmium nitrates. Metal solutions prepared in doubly distilled CO_2 - free water were standardized complexometrically[20].

Apparatus: Systronics digital 361 µ-pH systems (readability ±0.01 pH unit) having a combined glass electrode and a temperature probe (readability ±0.1°C) was used for pH measurements. A thermostatic water bath (readability ±0.1°C) was used to maintain constant temperature throughout the experiment.

Methods: These experiments have been carried out by using a modified version of the Irving and Rossotti method[9]. Following pH metric titration sets were carried out:

1. Acid Titration
2. Ligand Titration
3. Metal-Ligand Titration

All sets were titrated against a standardized 0.2 $mol.L^{-1}$ NaOH solution pH metrically. The experiment carried out at 30±0.1, 40±0.1 and 50±0.1°C temperature and various range of concentration (0.1, 0.2, 0.3 and 0.4M) and their effects are reported herewith. Total volume of each set was kept 50ml by maintaining particular ionic strength.

Model Strategy: The PKAS and BEST programs were used to find out pK_1^H and pK_2^H values shown in table 1[9,16]. Calculations were conducted on PC with a Pentium IV processor. The BEST FIT model was selected to calculate metal ligand stability constants.

Table 1 illustrates, similarity in data of pregabalin obtained from PKAS, BEST and pointwise calculations when compared with literature values. The amount of proton released during titration with standard NaOH solution was used to calculate the stability constant of binary complexes of metal ions with pregabalin. The findings of the BEST FIT model are given in table 2 and include the two species types, ML and ML_2, as well as the formation constants logβ with pH range, S_{min} and number of data points[5,14].

Minor values of S_{min} in this table suggest that the BEST FIT model is appropriate for determining the formation constants of lanthanide-pregabalin complexes. From pregabalin structure, it is anticipated that there is just one protonable site and one is ionisable site. In this investigation, the metal to ligand ratio is maintained at 1:10 to achieve the greatest coordination of ligand to metal ion throughout the experiment. Two β values were obtained which can be contributed by coordination of two pregabalin molecules to metal ions. The representative titration curve of Gd(III)-Pregabalin metal complexes for the current set of experimental conditions is shown in figure 1.

Results and Discussion

Stability constants: The study investigated the interaction of metal salts, namely Sm (III), Gd (III), Tb (III), Dy (III) and Ho (III), with pregabalin by pH-metric titration. The formation constants were determined by measuring the magnitude of proton released when the ligand was titrated against a standardized NaOH solution both in the presence and absence of metal. The formation constant values of the lanthanide (III) complexes are presented in table 3.

Table 1
Protonation constants of Pregabalin at Temperature 0±0.1°C and Ionic Strength 0.2M ($NaClO_4$)

Temperature	Protonation constant	Point Wise calculation method	PKAS	BEST	Literature value
30±0.1°C	pK_1^H	10.4777	10.4154	10.6012	10.6000
	pK_2^H	4.0495	4.2055	4.2211	4.2000

Table 2
Parameters of BESTFIT model of Lanthanide (III) Pregabalin binary complexes at Temperature 30±0.1°C and Ionic Strength 0.2M ($NaClO_4$)

Parameters	Sm(III)	Gd(III)	Tb(III)	Dy(III)	Ho(III)
$\log\beta_1$	7.7366	7.7718	7.9853	8.2619	8.4028
$\log\beta_2$	11.1317	11.3911	11.6846	11.9812	12.3128
pH range	1.93-9.13	1.96-9.69	1.96-11.42	1.96-9.26	1.95-8.84
S_{min}	0.2395	0.5455	0.2624	0.2619	0.1726
Number of data points	111	92	85	85	91

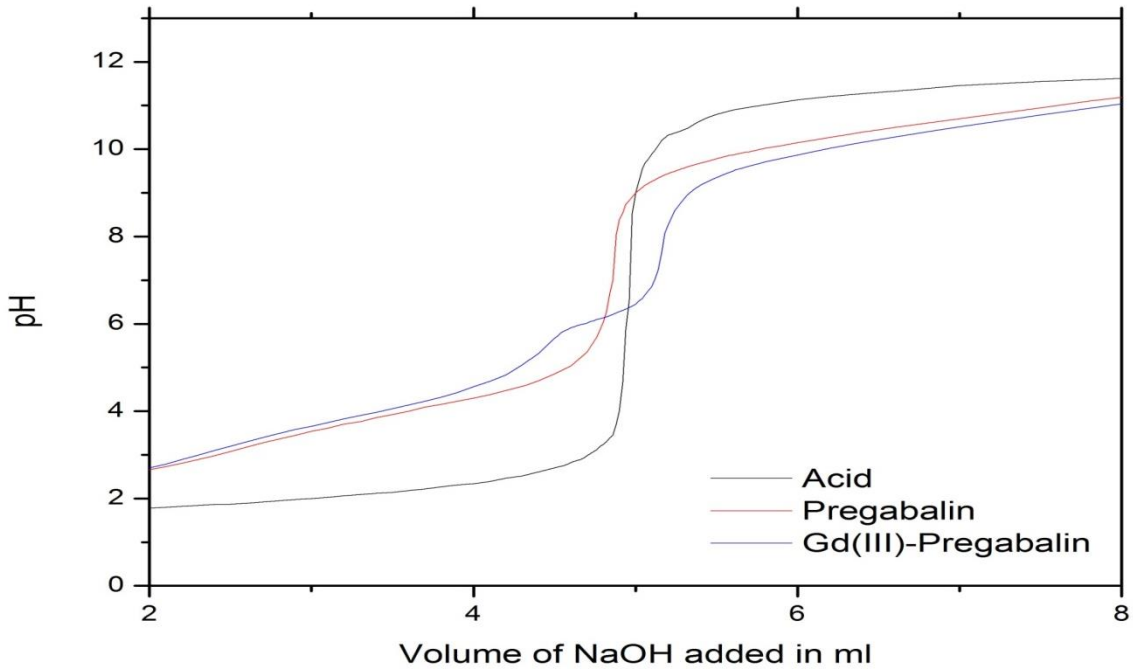


Figure 1: Titration curve of Gd(III)-Pregabalin metal complexes

Table 3
Formation constants of Lanthanide- Pregabalin complexes at different Temperatures and Ionic Strength μ 0.2 mol.L^{-1} ($NaClO_4$)

Temperature	$logk_1$	$logk_2$	S_{min}
Sm(III)			
30±0.1°C	7.7366	3.3950	0.2395
40±0.1°C	7.6500	3.2789	0.1156
50±0.1°C	7.5678	3.1678	0.2145
Gd(III)			
30±0.1°C	7.8718	3.5193	0.5455
40±0.1°C	7.6544	3.4211	0.4217
50±0.1°C	7.4356	3.3210	0.2256
Tb(III)			
30±0.1°C	7.9853	3.6993	0.2624
40±0.1°C	7.8120	3.5443	0.2147
50±0.1°C	7.6500	3.4120	0.1654
Dy(III)			
30±0.1°C	8.2619	3.7193	0.2619
40±0.1°C	8.1245	3.5890	0.3257
50±0.1°C	8.0012	3.4567	0.2189
Ho(III)			
30±0.1°C	8.4028	3.9100	0.1726
40±0.1°C	8.2415	3.7890	0.1245
50±0.1°C	8.1109	3.6760	0.2136

Both the ligand and metal characteristics affect binary complexes stability. Other variables that also have an impact on the stability of the binary metal complex are ionic strength, temperature, pressure, thermodynamic effects and kinetic impacts. The stability order observed is Sm(III) < Gd(III) < Tb(III) < Dy(III) < Ho(III).

Effect of Temperature: The stability of the complexes under examination with regard to temperature was assessed by conducting all sets of experiments at three distinct temperatures (30±0.1, 40±0.1 and 50±0.1°C) while maintaining ionic strength at 0.2M. The values of the stability constants of the lanthanide(III)-pregabalin metal complexes decrease as the temperature rises as indicated by the results shown in table 3. The sequence of stability constants in relation to temperature was found to be in the following order: 30±0.1°C > 40±0.1°C > 50±0.1°C. These findings are fairly consistent with Pitzer's[12,13].

Effect of ionic strength: A concentration range of 0.1 to 0.4 M at constant temperature 30±0.1°C was considered in order to check the influence of concentration on stability of the Lanthanide (III) complexes. It is discovered that when the ionic strength increases, the value of these stability of metal complexes' decreases. Table 4 also shows the thermodynamic stability constant ($logK_0$), which is determined by drawing the linear plot logK vs $\sqrt{(\mu)}$ and extrapolated to zero ionic strength. The constants were found in the following order based on ionic strength: 0.1M > 0.2M > 0.3M > 0.4M

Effect of systematic error: The BEST FIT model uses minor variations in many components to explain the effect of various errors as percentages but cannot explicitly calculate systematic error on stability constants. It is required to introduce systematic error in terms of concentration of alkali, ligand, dissolved carbon dioxide, acid and metal content in order to obtain accuracy in the evolution of stability constants using the BEST FIT model to understand the effect of systemic error. Systematic error has impact on the proportion of ML and ML_2 species. In given set of experimental conditions, the order of effect of systematic error that was determined, is found to follow following order:

carbon dioxide > alkali > acid > ligand > metal.

SPEPLOT: The data obtained was applied in various models to create a species distribution curve, yielding stoichiometric species such as HL, HL_2, ML, ML_2 and MLH_{-1}. According to the results of the species diagram shown in table 5 and figure 2, the pH range is from 5.2–5.6 and 9.5–9.6 for ML species (98%) and ML_2 species (78–92%) respectively. The species that is most stable for the current set of experiments, is ML as per the results of the species distribution curves. The formation of both species ML and ML2 is supported by the species distribution curve. For each of these lanthanide (III)- pregabalin complexes, the percentage of observed species and pH range are almost identical. This provide the evidence for the view that in the solution state, complex formation process follows the same mechanism. MLH_{-1} species are seen in all binaries in pH range of ~12.7.

Table 4
Formation constants of Lanthanide (III)- Pregabalin complexes at different Ionic Strength at Temperature 30±0.1°C

Ionic Strength(μ)	$logk_1$	$logk_2$	S_{min}
Sm(III)			
0.1M	7.7469	3.4055	0.4328
0.2 M	7.7366	3.3950	0.2395
0.3 M	7.7278	3.3867	0.2985
0.4 M	7.7190	3.3799	0.1622
$logk_0$	7.7752	3.4312	
Gd(III)			
0.1M	7.9423	3.5334	0.6323
0.2 M	7.8718	3.5193	0.5455
0.3 M	7.7701	3.5078	0.4421
0.4 M	7.6901	3.4978	0.2369
$logk_0$	8.0109	3.5692	
Tb(III)			
0.1M	7.9999	3.7123	0.2345
0.2 M	7.9853	3.6993	0.2624
0.3 M	7.9789	3.6888	0.5233
0.4 M	7.9699	3.6791	0.1542
$logk_0$	8.0297	3.7457	
Dy(III)			
0.1M	8.2731	3.7294	0.3546
0.2 M	8.2619	3.7193	0.2619
0.3 M	8.2515	3.7094	0.4200
0.4 M	8.2421	3.6998	0.1555
$logk_0$	8.3047	3.7598	
Ho(III)			
0.1M	8.4156	3.9212	0.2395
0.2 M	8.4028	3.9100	0.1726
0.3 M	8.3922	3.9011	0.3317
0.4 M	8.3812	3.8934	0.1487
$logk_0$	8.4503	3.9491	

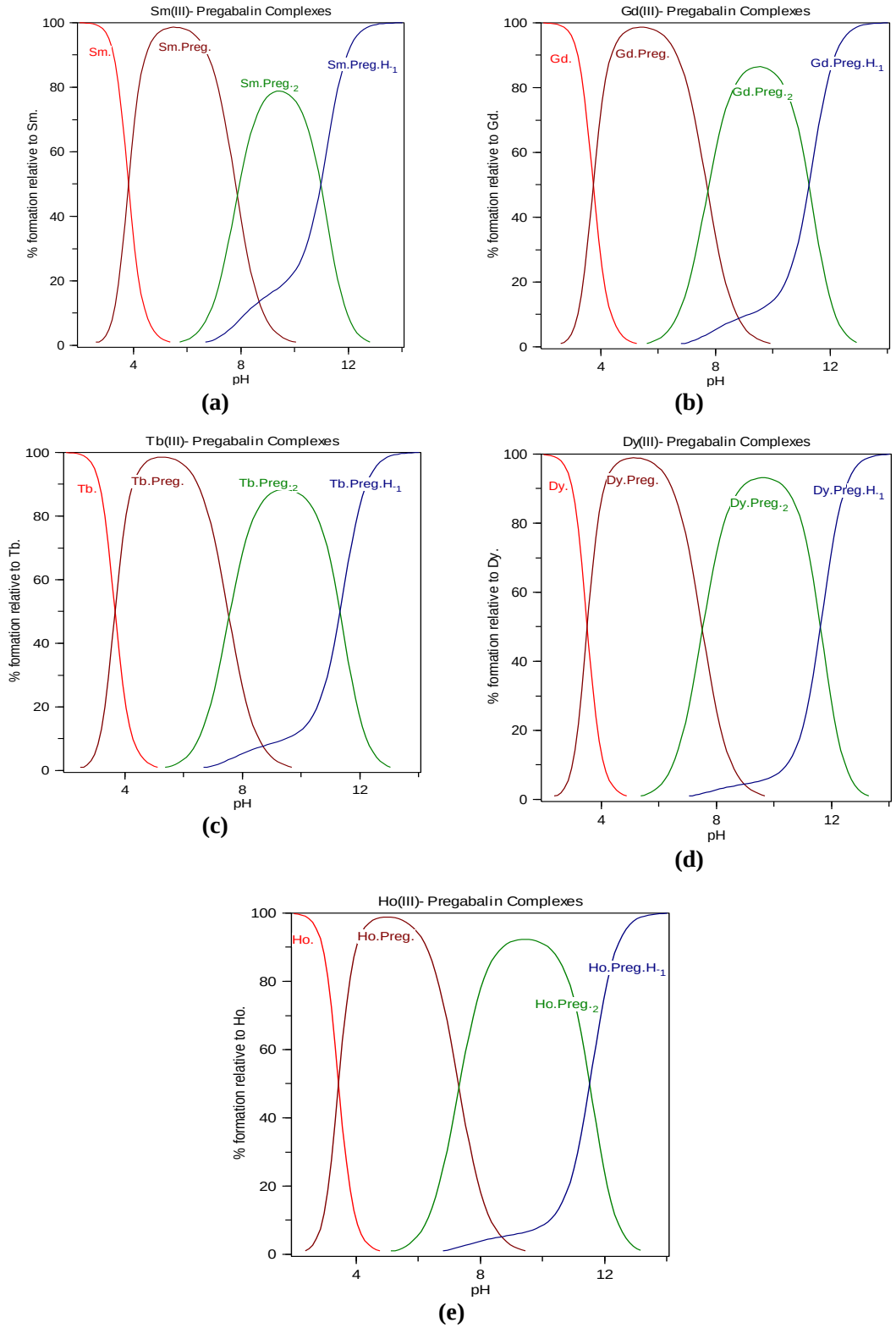


Figure 2: Distribution diagrams(curve) for (a) Sm(III)-Pregabalin (b) Gd(III)-Pregabalin (c) Tb(III)-Pregabalin (d) Dy(III)-Pregabalin (e) Ho(III)-Pregabalin at Temperature 30±0.1°C and Ionic Strength 0.2M ($NaClO_4$)

Thermodynamic parameters: The energy difference between metal-ligand and metal-water bonding is indicated by the enthalpy change during the experiment. The strong metal-ligand bindings are demonstrated by negative enthalpy change, which are the outcome of this experimental effort. From table 6, It is evident that when logK increases, ΔG and ΔS both become more negative and positive respectively. Therefore higher ΔS results in higher ΔG, which denotes more stable complex formation. The complexation behavior of binary complexes is favored by both entropy and enthalpy factors as demonstrated by the negative values of ΔH and ΔG. The order of ΔG values for the binary complexes is Sm(III) < Gd(III) < Tb(III) < Dy(III) < Ho(III).

Table 5
Species distribution in Lanthanide(III)- Pregabalin metal complexes at Temperature 30±0.1°C and Ionic Strength 0.2M ($NaClO_4$)

% Species Distribution (pH)	Sm(III)	Gd(III)	Tb(III)	Dy(III)	Ho(III)
ML	98 (5.6)	98 (5.5)	98 (5.3)	98 (5.3)	98 (5.2)
ML_2	78 (9.6)	85 (9.6)	87 (9.5)	92 (9.6)	92 (9.5)
$ML(OH)_2$	99 (12.6)	99 (12.7)	99 (12.8)	99 (12.8)	99 (12.8)

Table 6
Thermodynamic parameters of Lanthanide (III)- Pregabalin metal complexes at different Temperature and Ionic Strength 0.2M ($NaClO_4$)

M(III)-Pregabalin Complexes		ΔG K. Cal.mole^{-1}			ΔH K. Cal.mole^{-1}		ΔS K. Cal.mole^{-1}		Ea Cal.
		30±0.1°C	40±0.1°C	50±0.1°C	30±0.1°C	40±0.1°C	30±0.1°C	40±0.1°C	
Sm(III)	$logk_1$	-10.7325	-10.9624	-11.1909	-3.7620	-3.8065	0.0230	0.0229	-1642.76
	$logk_2$	-4.7097	-4.6986	-4.6844	-5.0435	-5.1447	-0.0011	-0.0014	-2211.02
Gd(III)	$logk_1$	-10.9199	-10.9687	-10.9954	-9.4398	-10.1320	0.0049	0.0020	-4242.80
	$logk_2$	-4.8821	-4.9024	-4.9109	-4.2659	-4.6353	0.0027	0.0009	-1923.19
Tb(III)	$logk_1$	-11.0775	-11.1945	-11.3125	-7.5285	-7.5018	0.0017	-0.0053	-3263.41
	$logk_2$	-5.1318	-5.0790	-5.0455	-6.7334	-6.1269	0.0118	-0.0033	-2797.58
Dy(III)	$logk_1$	-11.4612	-11.6424	-11.8318	-5.9688	-5.7097	0.0181	0.0189	-2537.89
	$logk_2$	-5.1595	-5.1430	-5.1116	-5.6604	-6.1264	-0.0017	-0.0031	-2554.71
Ho(III)	$logk_1$	-11.6566	-11.8100	-11.9940	-7.0071	-6.0477	0.0153	0.0006	-2843.16
	$logk_2$	-5.4241	-5.4296	-5.4359	-5.2564	-5.2327	0.0184	0.0006	-2277.49

Conclusion

From SPEPLOT data, it is observed that both ML and ML_2 type of binary lanthanide (III)-pregabalin complexes are formed. Binary metal complexation behavior is favourably influenced by negative ΔG, negative ΔH and positive ΔS values. Low temperature and low ionic strength are found to enhance the formation of these complexes. It was discovered that the stability value for these complexes follows the order: Sm(III) < Gd(III) < Tb(III) < Dy(III) < Ho(III).

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