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Thermodynamics Studies of a Novel Calix[4]arene Derivative Designed to Bind Herbicides

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I. Introduction

The use of pesticides can cause problems to the environment because 98% of insecticides and 95% of herbicides can spread through the air to contaminate other areas. Herbicides can cause water pollution and soil contamination [1]; some are persistent organic pollutants and as such they contribute to soil contamination. Of all the classes of herbicides, chlorophenoxy acids have been selected for this investigation (Table 1) [2, 3]. Chlorophenoxy acids are known to be hazardous substances and their use as herbicides has been banned in many countries. These substances can pose a serious threat to human health and the environment, mainly contaminating groundwater and drinking water [4, 5]. The development of novel technological approaches for their removal from water and soil by the use of efficient extracting agents is a challenging task.

Investigations on the capacity of macrocycles to respond to the presence of herbicides in different media are very limited .The prevalent research studies concentrate on the binding between calixarenes and toxic metals and pay little attention to the interaction between the calixarene derivatives and organic compounds such as herbicides. It is important to explore the potential offered by calixarene based receptors for the removal of these pollutants from contaminated sources. Thus efforts have been made to produce calixarene derivatives which are able to interact selectively with these pollutants.

Although the procedures used to synthesize these macrocycles are established, the design of calixarene-based receptors able to interact selectively with a given guest is a challenging area of research.

A great deal of effort has been focused on the design of selective macrocyclic extracting agents for the removal of these species from water and soil. Particular attention is paid to herbicides due to the toxicological impact of these species on human health.

Calix[4]arenes are strong size-selective receptors for a variety of substrates, in particular, for inorganic and organic cations [6]. Calixarenes can be used as ion selective electrodes or sensors [7], optical sensors [8], chiral recognition devices for solid phase extraction, as a stationary phase and modifiers [9]. In the ' cone ' conformation of *p-tert*-butylcalix[4]arene is characterised by a hydrophobic cavity which can complex neutral guest molecules, such as toluene [10]. Upon functionalization, calixarenes have become versatile hosts for cations, anions, and neutral molecules. They are used widely in chemical separations, ion-selective electrodes, chromatography, phase transfer catalysis, and as catalytic platforms [11].

Calix[4] arene derivatives bind weakly with herbicides. In order to modulate the anion binding behavior, the core size of calix [4]arene was extended through the induction of suitable spacer units as a rigid wall . Thus, this study concerns the design of receptor which is able to interact with these pollutants. Fully substituted calixarene with different lower rim functionalities have been prepared for the detection of herbicides (Fig. 1). A good response to herbicides was obtained by full functionalisation of the lower rim with ether-amine groups.

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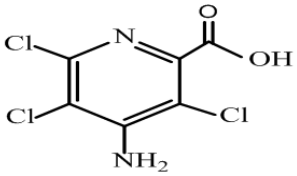
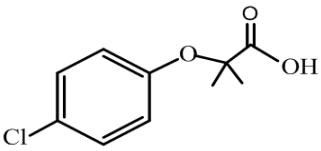
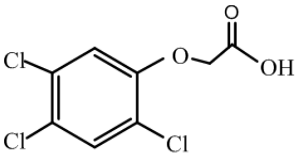
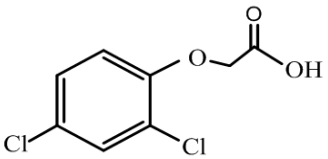
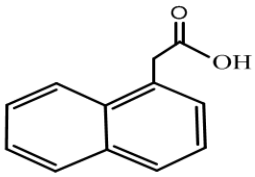
Table 1 : Group of pesticides selected to perform this investigation

Pesticides	pKa values at 20 °C in water
 **Picloram (P1)**	**2.3**
 **Clofibric acid (P2)**	**2.84**
 **2,4,5-Trichlorophenoxyacetic acid(P3)**	**2.88**
 **2,4-dichlorophenoxyacetic acid (P4)**	**2.73**
 **1-Naphthaleneacetic acid (P5)**	**4.23**

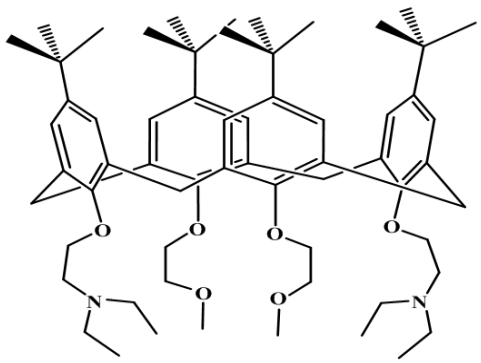


Figure 1 : Structure 5,11,17,23-*tetra-butyl* 25,27bis(diethylamino)ethoxy-26,28-(bis methoxyethoxy)calix[4]arene(L2)

Calix(4)arenes containing ether and amine functional groups at the lower rim have shown pronounced selectivity for herbicides in different media, particularly acetonitrile. It can be observed that the presence of the amino groups (basic) in the lower rim for calix[4]arene makes these ligands attractive to explore their complexation with herbicides. This receptor is capable of binding phenoxy acid molecules through hydrogen- bonding interaction. The interaction of the calix[4]arene amine derivative and a pesticide is shown in Fig. 2.

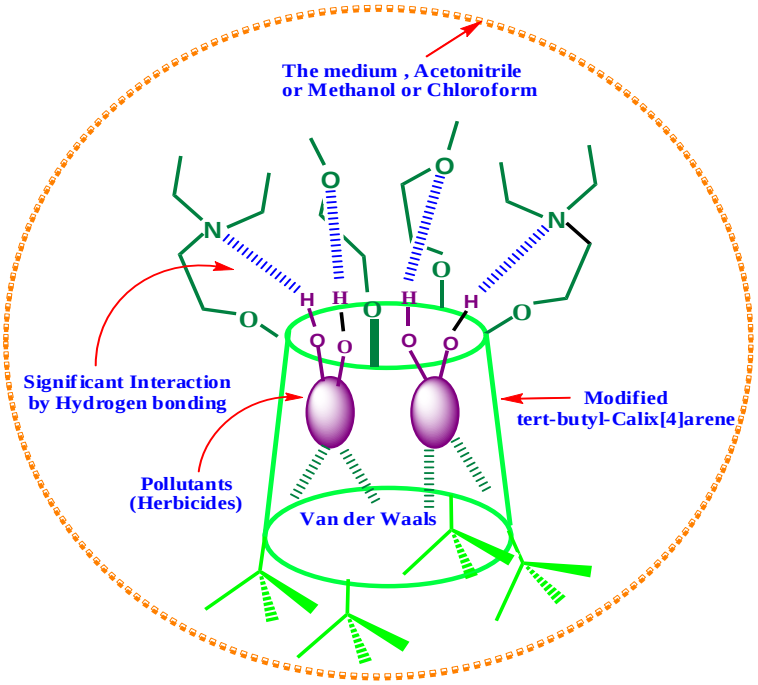


Figure 2 : The interaction model of the calix[4]arene based receptor for herbicides

The conformational changes that the calix[4]arene ligand undergoes upon complexation with ionic or neutral species can be assessed from ^{1}H NMR investigations [12]. Gutsche and co-workers [13] established that the conformations of calixarenes and their derivatives can be established by observing the resonance of the methylene protons (axial and equatorial) in the ^{1}H NMR spectrum. In the ' cone ' conformation $\Delta\delta_{ax\text{-}eq}$ is about 0.90 ppm while values of 0.50 ppm and higher than 0.90 ppm are found for calixarenes in their flattened and distorted conformation respectively.

A detailed investigation on the complexation of L2 with herbicides in a wide variety of solvents (methanol, acetonitrile and chloroform) using a variety of techniques such as ^{1}H NMR (to establish the binding sites and the conformational changes that these ligands undergo upon complexation with herbicides), conductance measurements (to establish the composition and the type and strength of the host-guest complexes) , nano ITC to derive the thermodynamics of complexation (stability constant, log *K*s, hence standard Gibbs energy, $\Delta_c G°$; enthalpy, $\Delta_c H°$; and entropy, $\Delta_c S°$ of complexation). Stability constants are used to assess quantitatively the selective behavior of this ligand for one herbicide relative to another.

II. Experimental Section

a) Chemicals

All chemicals were obtained from Sigma-Aldrich, Fluka and Fisher UK Scientific and were either analytical or reagent grade. Solid chemicals were used as received without further purification. All solvents were dried and purified as described in the literature [14].

b) ^{1}H NMR measurements

^{1}H NMR measurements were recorded at 298 K on A Bruker DRX-500 pulse Fourier Transform NMR Spectrometer. The operating conditions involved pulse or flip angle of 30°, spectra width (SW) of 15 ppm, spectral frequency (SF) of 500.150 MHz, delay time of 0.3 s, acquisition time (AQ) of 3.17s, and line broadening of 0.3 Hz. Solutions of the samples of interest (1×10^{-3} mol.dm^{-3}) were prepared in the appropriate deuterated solvent. These were placed in 5 mm NMR tubes using TMS (tetramethylsilane) as the internal reference.

c) Conductometric measurements

A Wayne-Kerr Autobalance Universal Bridge type B642 was used for conductometric measurements. The Wayne-Kerr is connected to a platinum glass bodied electrode housed in a cylindrical glass vessel where the reaction takes place. A thermostated bath circulating water in the vessel jacket was used to maintain the temperature of the vessel at 298.15 K. A magnetic stirrer was used to keep homogeneous the solutions throughout the time of the experiment.

d) Determination of the constant of the conductivity cell

The cell constant was determined by titrating a solution of KCl (0.1 mol dm^{-3}) in deionised water (25 cm^3) **[15]**. The cell was immersed in a thermostated bath at 298.15 K. The conductance of the solution was recorded after addition of KCl once the stability of the system was ensured.

e) Nano ITC (Isothermal Titration Calorimetry)

ITC measurements were performed in a Nano Isothermal Titration Calorimeter, models 5300 (TA Instruments). All measurements were carried out in acetonitrile solvent at a fixed temperature of 298.15 K. The basic principle of ITC is simply to measure the heat released or absorbed in a liquid sample after the addition of another liquid sample. This heat is proportional to the total amount of binding that occurs within the calorimeter cell. The instrument has a pair of identical cells (1.4 ml), denoted as the reference and sample cells. These cells, along with access stems, are enclosed in a temperature-controlled thermal jacket. The reference cell was filled with acetonitrile. The ligand solution (1 m M) placed in the sample or reaction cell. The herbicides (20 m M) loaded in the syringe. The interval time between two readings was set at 240 s. The experiments were designed for a total of 25 consecutive injections. The power (or heat) difference between the sample and reference cells is used to determine reaction stoichiometry or number of binding sites (n), stability constant (K_a), and the enthalpy (ΔH^o) **[16, 17]**. The first data point was removed from the data set prior to curve fitting. The data was analyzed to determine the heat of interaction by using Origin 7.0 and Nano Analyzer data analysis softwares supplied by Microcal and TA Instruments, respectively with the 'independent sites' model.

i *Calibration of the Equipment*

To determine the accuracy of measurements carried out in the Nano ITC, a chemical calibration should be performed. The following equilibrium is established upon the addition of barium chloride to 18-crown-6 ether in water at 298.15 K **[18]**. The sample cell was filled with an aqueous solution of 18-Crown-6 (1×10^{-3} mol dm^{-3}) and titrated incrementally from the burette stirring system with $BaCl_2$ (0.015 mol dm^{-3}).

f) Synthesis

i *Synthesis 5, 11, 17, 23 -p- ter t- butyl -25 ,27 dihydroxy 26, 28- bis (2-ethoxymethoxy) Calix(4) arene, L1*

The preparation of this derivative was achieved by procedure reported in the literature **[19]**.

ii *Synthesis of 5, 11, 17, 23- tetra- butyl 25, 27- bis (diethyl amino) ethoxy- 26, 28- (bis- methoxy ethoxy) calix[4] arene, L2*

5, 11, 17, 23- *p- tetra*- butyl- 25,27- dihydroxy- 26, 28- bis- (2-ethoxy) calix[4] arene, **L1** (1.6 g, 1.75 mmol), sodium hydride (1.7 g, 60 mmol) were suspended in 150 ml mixture of freshly refluxed THF and 30 ml of DMF dried on molecular sieves. Then 2-chlorotriethylamine hydrochlorid (1.5 g, 11.05 mmol) in 10 ml of DMF was syringed to the reaction mixture. Then the reaction was stirred and refluxed for 6 h. The reaction was monitored by TLC using DCM/Methanol (9:1) as the developing solvent mixture. After cooling down the reaction, the solvent was filtered through filter paper and removed under vacuum, to give an oily product which was broken by acetonitrile. **L2** was obtained in 80 % yield. The compound was characterized by ^{1}H-NMR in $CDCl_3$ at 298 K and microanalysis. ^{1}H-NMR ($CDCl_3$, 500 MHz) ; δ(ppm) = 6.61 (s, 1H, Ar-**H**); 6.95 (s, 1H, Ar-**H**); 4.41 (d, 2H, Ar-**CH_2(ax)**-Ar); 4.19 (t, 2H, Ar-O-**CH_2**$CH_2N(CH_2CH_3)_2$); 3.95 (t, 2H, Ar-O-**CH_2**CH_2-O-CH_3); 3.44 (s, 3H, Ar-O-CH_2CH_2-O-**CH_3**); 3.15 (d, 2H, Ar-**CH_2(eq)**-Ar); 3.0798 (t, 2H,Ar-CH_2-**CH_2**-O-CH_3);2.65 (Ar-O CH_2CH_2N(**CH_2**$CH_3)_2$));1.08 (s, 9H, -C-**$(CH_3)_3$**); 0.9482 (s, 9H, -C-**$(CH_3)_3$**). ^{13}C NMR ($CDCl_3$, 500 MHz) ; δ(ppm) = 30.95 (C1), 32.15 (C2), 33.17 (C3), 33.90 (C4), 134.01 (C5), 122.15 (C6),127.80 (C7),155.48 (C8),30.87 (C9), 128.55 (C10),122.25 (C11),135.90 (C12),157.17 (C13), 72.88 (C14),72.62 (C15),15.12 (C16),58.72(C17), 52.56 (C18),47.61 (C19), 11.96 (C20). Elemental analysis ;($C_{62}H_{94}O_6N_2$), Mw. (963.56). % calculated, C, 77.28, H, 9.85 and N, 2.91. % found for C, 77.36, H, 9.09 and N, 2.83.

III. Results and Discussion

a) ^{1}H NMR characterization of L1 and L2

The NMR spectra of these receptors in non-aquous deuterated solvents were recorded **(Appendix A)**.

b) ^{13}C NMR of L2 in $CDCl_3$ at 298.15 K

^{13}C NMR spectrum of L2 in $CDCl_3$ at 298.15 K is shown in **(Appendix A).**

c) ^{1}H NMR complexation studies of calix[4]arene derivative at 298 K

^{1}H NMR spectra of the herbicides - receptor complexes at 298 K in CD_3CN, CD_3OD and $CDCl_3$ were recorded **(Appendix A)**. The relevant ^{1}H NMR chemical shift changes of the protons observed by the addition of

acid pesticides (P1, P2, P3, P4, P5) to the receptor L2, in deuterated solvent at 298 K are listed in Tables 2 - 4.

Tables 2- 4 shows the chemical shift changes of the ligand protons after addition of the appropriate excess of herbicides in different solvents at 298 K. These chemical shift changes ($\Delta\delta$) were calculated by subtracting the chemical shift of the free ligand (δ_{FL}) from that of the ligand- pesticides (δ_{LP}).

The receptor L2 with herbicides was investigated in acetonitrile, methanol and chloroform at 298 K with the aim of assessing the medium effect in the interaction of this receptor with herbicides. It is well established that calix [4]arene derivative are able to form inclusion complexes with some solvents due to the hydrophobic nature of the upper cavity of the receptor, which hosts small organic molecules [20]. Therefore, the effect of the solvent on the free ligand, L2 was investigated through ^{1}H NMR measurements in acetonitrile, methanol and chloroform at 298 K.

Table 2 : Chemical shift changes ($\Delta\delta$) for L2 after addition of an excess amount of appropriate herbicides in CD_3CN at 298 K (0.09 mol of L2 + 0.9 mol of herbicides)

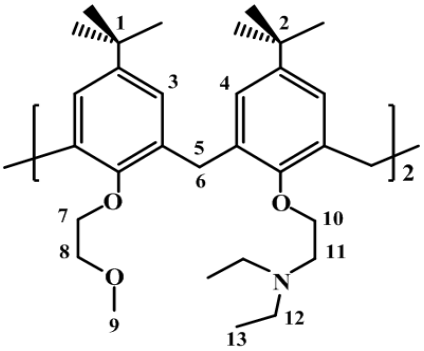
Receptor L2	$\Delta\delta$ in CD_3CN	L2	L2 + P1	L2 + P2	L2 + P3	L2 + P4	L2 + P5
	H-1	1.17	-0.10	-0.34	-0.1	-0.09	-0.09
	H-2	1.10	0.11	0.07	0.12	0.1	0.07
	H-3	6.99	0.14	0.08	0.15	0.13	0.11
	H-4	7.09	-0.17	-0.16	-0.16	-0.16	-0.14
	H-5(eq)	3.22	-0.07	-0.07	-0.06	-0.07	-0.01
	H-6(ax)	4.46	0.07	0.09	0.11	0.12	0.16
	$\Delta\delta_{(ax-eq)}$	1.24	1.39	1.41	1.42	1.43	1.41
	H-7	3.94	0.15	-0.07	-0.05	-0.05	0.02
	H-8	3.03	-0.44	-0.41	-0.44	-0.44	-0.37
	H-9	3.41	0.11	-0.30	0.08	0.07	0.13
	H-10	4.14	0.11	-0.19	-0.24	-0.23	-0.09
	H-11	3.90	0.11	0.17	0.17	0.17	0.33
	H-12	2.62	-0.63	-0.51	-0.60	-0.60	-0.27
	H-13	1.04	-0.29	-0.24	-0.26	-0.25	-0.05

Table 3 : Chemical shift changes (Δδ) for L2 after addition of an excess amount of appropriate herbicides in CD_3OD at 298 K (0.09 mol of L2 + 0.9 mol of herbicides)

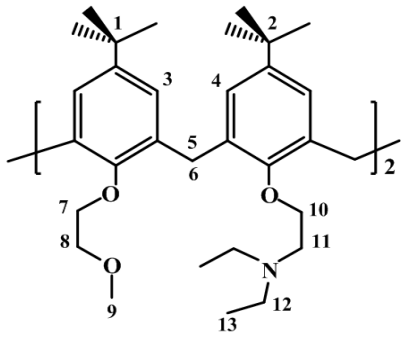
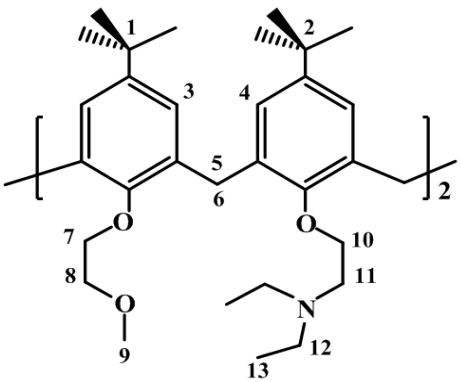
Receptor L2	Δδ in CD_3OD	L2	L2 + P1	L2 + P2	L2 + P3	L2 + P4	L2 + P5
	H-1	1.14	0.15	0.13	0.15	0.16	0.16
	H-2	1.09	-0.25	-0.17	-0.20	-0.20	-0.21
	H-3	6.83	-0.29	-0.18	-0.23	-0.23	-0.25
	H-4	6.90	0.28	0.25	0.27	0.28	0.28
	H-5(eq)	3.19	0.04	0.06	0.10	0.04	0.02
	H-6(ax)	4.48	-0.09	0.08	-0.09	-0.09	-0.14
	$\Delta\delta_{(ax\text{-}eq)}$	1.28	1.15	1.30	1.08	1.14	1.11
	H-7	4.08	0.42	0.31	0.37	-0.08	0.23
	H-8	3.15	-0.17	-0.31	-0.20	-0.21	-0.36
	H-9	3.47	0.10	-0.06	-0.05	-0.07	-0.09
	H-10	4.14	-0.15	-0.11	-0.13	0.31	-0.20
	H-11	3.92	0.43	0.55	0.48	0.46	0.36
	H-12	2.72	0.6	0.49	0.56	0.55	0.18
	H-13	1.15	0.18	0.16	0.18	-0.02	-0.04

Table 4 : Chemical shift changes (Δδ) for L2 after addition of an excess amount of appropriate herbicides in $CDCl_3$ at 298 K (0.09 mol of L2 + 0.9 mol of herbicides)

Receptor L2	Δδ in $CDCl_3$	L2	L2 + P1	L2 + P2	L2 + P3	L2 + P4	L2 + P5
	H-1	1.21	-0.07	0.08	-0.07	-0.07	-0.06
	H-2	0.94	0.07	-0.08	0.08	0.08	0.00
	H-3	6.61	0.08	-0.12	0.09	0.10	0.04
	H-4	6.95	-0.12	0.08	-0.12	-0.10	0.00
	H-5(eq)	3.15	-0.02	0.03	-0.01	-0.02	0.12
	H-6(ax)	4.41	0.14	0.14	0.14	0.02	0.25
	$\Delta\delta_{(ax\text{-}eq)}$	1.25	1.41	1.36	1.41	1.31	1.38
	H-7	3.95	0.00	-0.06	0.01	-0.09	0.22
	H-8	3.08	-0.45	-0.47	-0.46	-0.55	-0.23
	H-9	3.44	0.11	0.12	0.10	0.07	0.31
	H-10	4.19	-0.18	-0.03	-0.19	-0.33	0.05
	H-11	3.92	0.29	0.28	0.28	0.26	0.58
	H-12	2.65	-0.49	-0.48	-0.53	-0.61	-0.12
	H-13	1.08	-0.15	-0.10	-0.17	-0.28	0.17

The results in Tables 2- 4, show that L2 interact with the acid herbicides in protic and dipolar aprotic media. Gutsche [13] suggested that the difference between the chemical shift of axial and equatorial protons ($\Delta\delta_{ax\text{-}eq}$) of the methylene bridge of calix[4]arene derivatives provides information regarding the conformation adopted by these ligands in solution. Based on this suggestion, $\Delta\delta_{ax\text{-}eq}$ values were calculated and these data are also included in Tables 2- 4. It can be observed that $\Delta\delta_{ax\text{-}eq}$ values for L2 are 1.24, 1.28 and 1.25 ppm in CD_3CN, CD_3OD and $CDCl_3$ respectively. These results indicate that in these solvents, L2 adopt a distorted 'cone' conformation. This might be due to the steric and electrostatic effects between the pendent arms at the lower rim. Thus, these groups try to move away as possible from each other to reduce the steric and electrostatic effects.

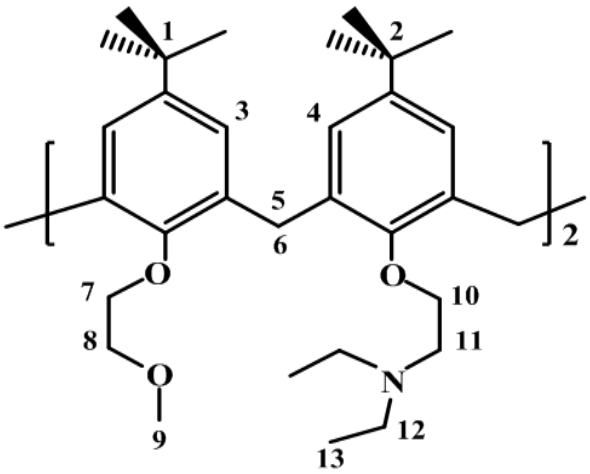
The results show that the conformation of L2 is not altered in moving from one solvent to another, indicating that no specific ligand-solvent interaction are taking place in these solvents at 298 K.

As can be seen from Tables 2- 4, the chemical shift changes of the ligand (L2) after addition of an excess amount of the herbicides are very significant in CD_3CN, CD_3OH and CD_3Cl , suggesting that interaction between this receptor and the herbicides are taking place. It can be seen that L2 has a slight change in the conformation in these solvents.

Approximately, all protons for ligand L2 have been affected upon the addition of the herbicides in CD_3CN, CD_3OD and $CDCl_3$ at 298 K. Some protons have shielding effects and others have deshielding effects. Deshielding effects were observed for protons (H-4, H-5(equatorial), H-7, H-11 and H-12). Shielding effects were observed for protons (H-3, H-6(axial), H-8 and H-10). It can be noted that the protons closest to the nitrogen and the oxygen atoms such as H-7, H-8, H-11 and H-12 have considerable chemical shift changes relative to others. This is an indication that the lower rim groups of the receptors interact with the pesticides. Protons such as H-1, H-2, H-3 and H-4 have been also affected as a result of this interaction.

^{1}H NMR titrations provide useful information regarding of active sites of the receptor interacting with the pesticides. ^{1}H NMR spectra for L2 with herbicides are shown in Fig. 3.

Fig. 4 shows ^{1}H NMR titration curves (plots of $\Delta\delta$(in ppm) for the titration of L2 with acid herbicides in CD_3CN at 298 K vs. [P]/ [L2] concentration ratio). These Figs shows the plot of the chemical shift changes observed upon an increase in the concentration of herbicides in CD_3CN at 298 K. The plot may illustrate that one ligand unit interacts with two units of herbicides but this will be confirmed more accurately by conductance measurements.



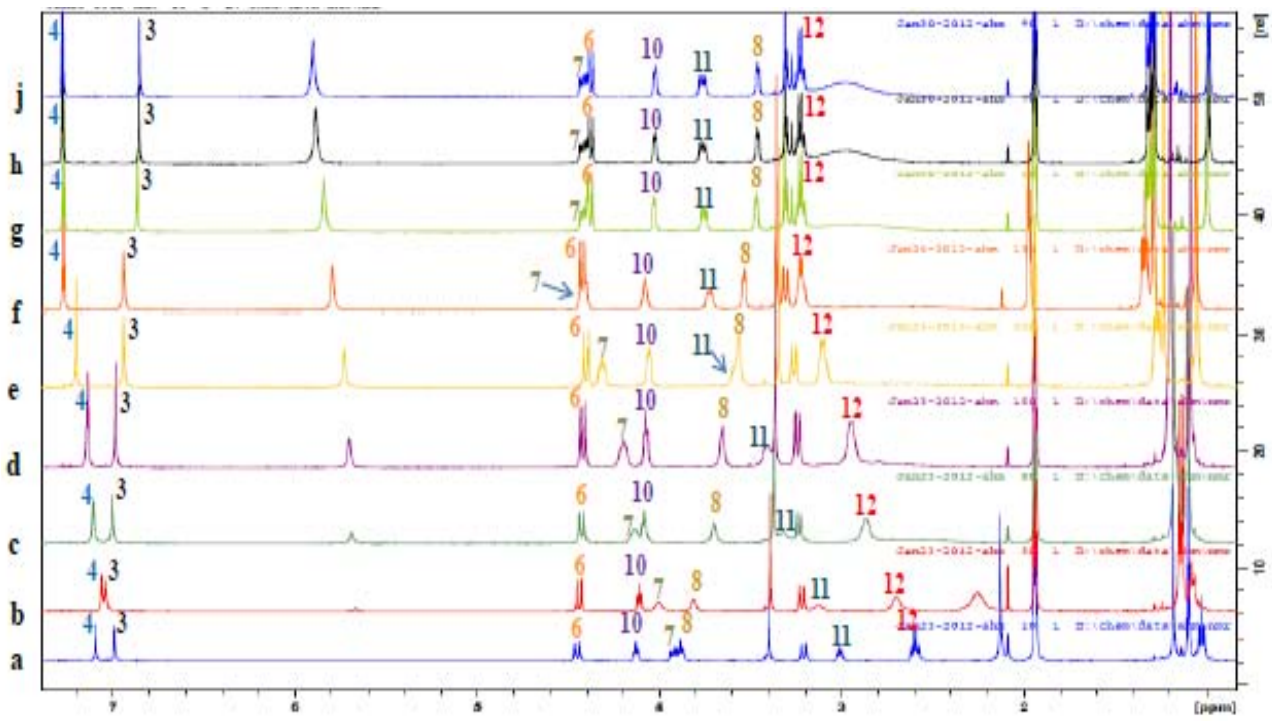


Figure 3 : Partial ^{1}H NMR (CD_3CN, 500 MHz) spectra showing the shift of the protons in L2 upon the addition of P1(4.14E-02 M), (a) L2 receptor(1.56E-02 M), (b) [P1]/[L2]=0.16, (c) [P1]/[L2]= 0.96, (d) [P1]/[L2] = 1.92, (e) [P1]/[L2] = 2.72, (f) [P1]/[L2] = 3.52, (g) [P1]/[L2] = 4.31, (h) [P1]/[L2]=5.11, (j) [P1]/[L2] = 5.43

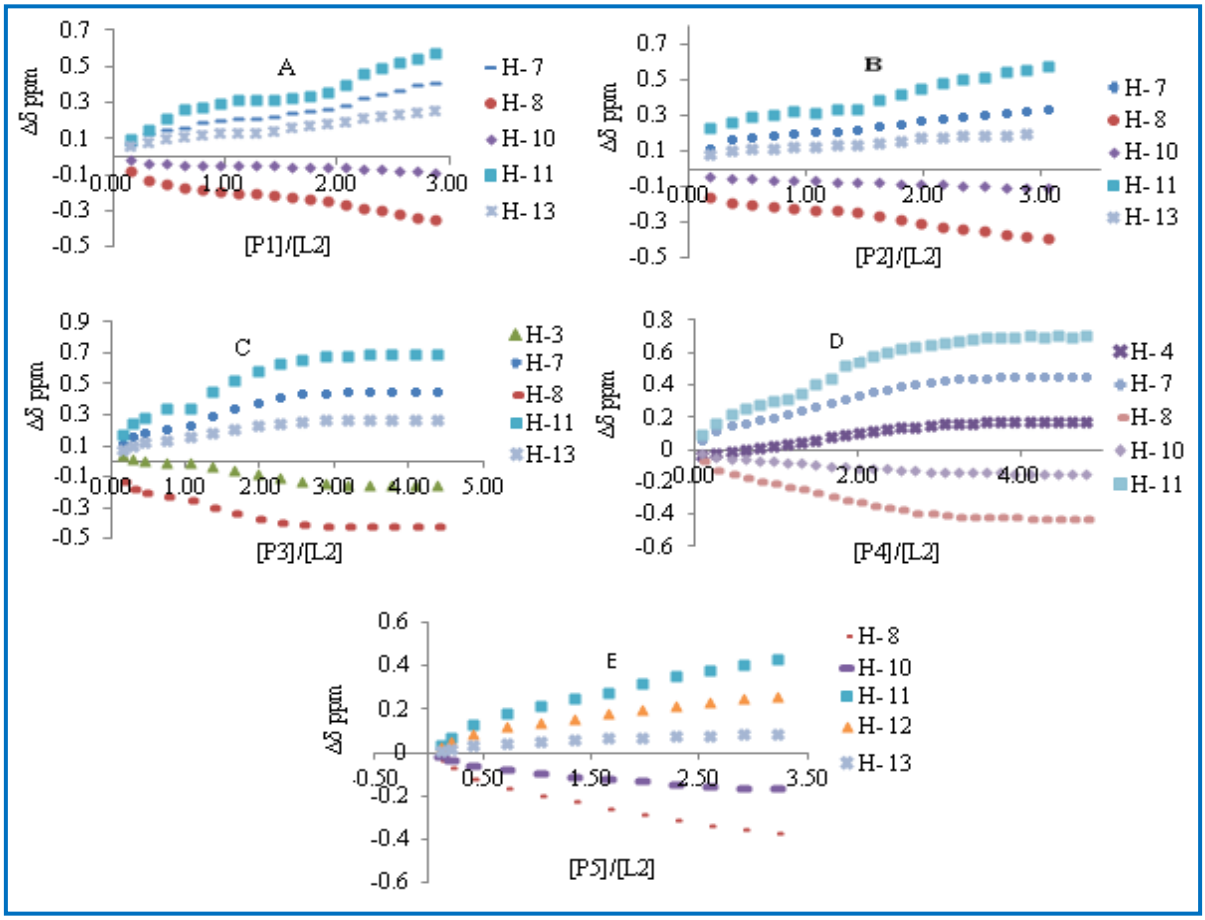


Figure 4 : ^{1}H NMR titration curves for the titration of Pesticides with the receptor L2 in acetonitrile at 298.15 K, (a) P1+ L2, (B) P2 + L2, (C) P3 + L2, (D) P4 + L2, (E) P5 + 5

d) Conductometric measurements

Fig. 5 shows the conductomeric curves (plots of Λ_m vs [L]/ [P]) for the titration of herbicides in acetonitrile at 298 K. From these Figs, It can be seen that all herbicides are likely to be strongly associated in acetonitrile as observed from the very low molar conductance value before starting the titration. Then the molar conductance increases. This is because there is a proton transfer reaction from acid pesticide to the amine group of the receptor. The conductomeric titration curves of P1 with L2 given in Fig.5, A shows an increase in molar conductance of the complexes throughout the titration, until the ligand/ P1 concentration ratio reaches 1: 2. Then the molar conductance remains almost constant until the end of the experiment. This increase in conductance reflects that the addition of the macrocycle (non electrode) to these herbicides substantially increases ion formation in solution. This may be attributed to a proton transfer reaction from the acid to the calixarene amine derivative. The conductomeric curve of L2 with P2 (Fig. 5, B) does not show significant changes in the curvature suggesting that the interaction of these ligand with P2 are weak in this solvent. This may be attributed to the steric hindrance effects because these acid herbicides contain two methyl groups which prevents or reduce formation hydrogen bonding. While significant shift changes were found for this herbicides in the ^{1}H NMR (Table 2). Conductometric curves for the titration of P3 and P4 with L2 in acetonitrile at 298.15 K are shown in Fig.5, C and D. Inspection of these titration curves shows that there is a marked increase in Λm values as the titration proceeds with a clear break at the molar conductance ratio of (0. 5) indicating that each ligand unit takes up four protons.

No changes in the molar conductance were observed by the addition receptor 5 to P5 (Fig. 5, E). This suggests the absence of interaction of this ligand and this pesticide in this solvent while significant chemical shift changes were found in ^{1}H NMR. This may be P5 are unable to transfer the proton that it strongly associated but may able to interact through hydrogen bond formation and this may be observed in the ^{1}H NMR spectra. These findings are in agreement with ^{1}H NMR measurements where significant chemical shift changes were observed by the addition of P1, P2, P3, P4 and P5 to the ligand in CD_3CN.

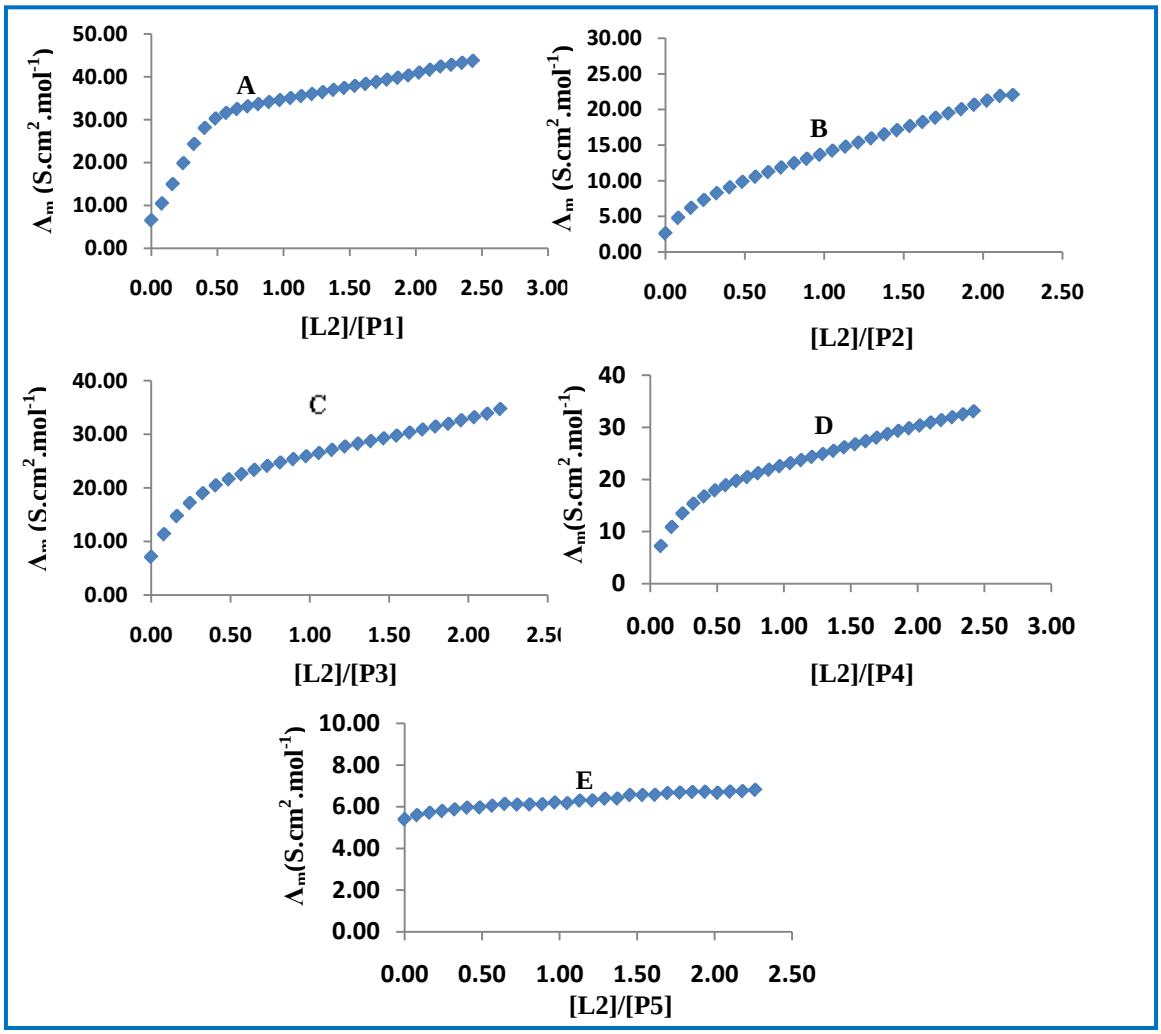


Figure 5 : Conductomeric curves for the titration of herbicides with the receptor 5 in acetonitrile at 298.15 K. (a) P1+ L2, (B) P2 + L2, (C) P3 + L2, (D) P4 + L2, (E) P5 + L2

e) Thermodynamics of complexation

Standard thermodynamics parameters of complexation (log K_s, ΔH°_c, ΔS°_c, ΔG°_c) of L2 with different herbicides in acetonitrile were determined using the Nano ITC. For this purpose the instruments were electrically and chemically calibrated prior to measurements. Calorimetric titration curves for the titration of herbicides with the receptor L2 in acetonitrile at 298 K were recorded (Appendix B).

i *Calibration of the Nano ITC instrument*

The reaction of complexation of 18-C-6 and Ba^{2+} in aqueous medium was used as a standard reaction to check the accuracy and reliability of the Nano ITC instrument following the procedure described in the Experimental Part [18]. Calorimetric titration curves for the titration of Ba^{2+} with 18-C-6 in water at 298 K were recorded (Appendix B).

The stability constant (expressed as log K_s), standard Gibbs energy, $\Delta_c G^\circ$, enthalpy, $\Delta_c H^\circ$ and entropy $\Delta_c S^\circ$ of complexation of 18-C-6 with Ba^{2+} in aqueous medium obtained at 298.15 K from nanocalorimetric titrations are summarized in Table 5. For comparison purposes, values reported in the literature are also included .The thermodynamic parameters for the complexation of Ba^{2+} with 18-C-6 in aqueous medium show a good agreement with the values reported in the literature by Briggner and Wadso [18].

Table 5: Thermodynamic parameters of $BaCl_2$ binding to 18-crown-6 by Nano-ITC in aqueous medium (deionized water) at 298.15 K

Log K_s	$\Delta_c H^\circ$(k J. mol^{-2})	$\Delta_c G^\circ$(KJ. mol^{-2})	$\Delta_c S^\circ$(J. mol^{-1}.K^{-1})	Ref.
3.63	-30.82	-20.73	-33.8	This work
3.77	-31.39	-21.49	-33	[18]

ii *Thermodynamic parameters of complexation of L2 with herbicides in acetonitrile at 298.15 K*

Titration calorimetry was used to obtain the log Ks and the enthalpy of complexation of L2 with herbicides in acetonitrile. Combination of Gibbs energies and enthalpies led to the calculation of the entropies associated to the complexation process. Calorimetric titration curves for the titration of the herbicides with the receptor L2 in acetonitrile at 298 K were recorded **(Appendix B)**. Thermodynamic data for the complexation of L2 with the herbicides in acetonitrile are summarized in **Table 6**.

Table 6: Thermodynamics of complexation of L2 and herbicides in acetonitrile at 298.15 K

Complexes	Log K_s	$\Delta_c H^\circ$(kJ. mol^{-2})	$\Delta_c G^\circ$(kJ. mol^{-2})	$\Delta_c S^\circ$(J. mol^{-1}.K^{-1})	n
L2 + P1	4.49	-41.04	-25.65	-51.6	2. 18
L2 + P2	3.81	-21.37	-20.47	-16.4	2.12
L2 + P3	4.18	-38.90	-23.86	-50.45	2.17
L2 + P4	4.14	-32.42	-23.64	-29.43	2.21
L2 + P5	3.42	- 17.51	-19.53	6.77	2.07

Inspection of stability constant data (expressed as log K_s) shows that this ligand interacts selectively with herbicides in acetonitrile following the sequence

P1> P3 > P4 > P2

This decrease may be attributed to the presence of the phenol groups which may either (i) lead to steric effects by which the phenol units may form rigid walls restricting the easy access of the herbicides to interact with the the amino groups and ethoxy protons in the lower rim for calix[4]arene or (ii) to electronic effects, since the aromatic phenol rings may form an induced magnetic field which may act as a repulsive force for these anionic guests. It can be observed that the selective behaviour of L2 for P1 relative to other acid pesticides in this solvent. This is corroborated by the ^{1}H NMR data where significant chemical shift changes were found in H-2, H-3, H-4, H-5, H-7, H-8, H-10 and H- 11 upon complexation of L2 with these acid pesticides.

A general analysis of the thermodynamic parameters shows that the complexation process is favored in terms of enthalpy $\Delta H^\circ < 0$) but not in terms of entropy ($\Delta S^\circ < 0$) in all the above systems. Therefore, the complexation process is enthalpically controlled. The only exception is P5 which shows the opposite behaviour (entropy controlled). This may be attributed to the higher desolvation that the pesticide undergoes upon complexation. The data in **Table 6** show the ΔG° values are obtained for the L2 and the different herbicides studied in acetonitrile are close to each other.

IV. Conclusions

From the above discussion on the calix[4]arene derivative, the following conclusion can be drawn. The ligand under investigation (L2) were successfully synthesised in good yields and characterized by ^{1}H NMR. From ^{1}H NMR studies, it is concluded that L2 interact with herbicides. Therefore, in this study, it is essential to investigate the factors why other receptors did not interact with these herbicides. The presence of the amino groups (basic) in the lower rim for calix[4]arenes makes these ligands attractive for exploring their complexation with herbicides. The ^{1}H NMR technique was successfully used for establishing the binding sites and the conformational changes that these ligands undergo upon complexation with the herbicides.

The interaction of 5, 11, 17, 23- tetra- butyl- 25, 27-bis(diethylamino)ethoxy-26, 28- (bis- methoxyethoxy) calix[4] arene (L2) with several acid herbicides were carried out in different solvents at 298 K.

From **Tables 2 - 4**, the results obtained seem to indicate that the sites of interaction of this ligand with the acid herbicides are amine group and ethoxy group. Indeed significant chemical shift changes in the proton close to the amine group and ethoxy group were observed. Stoichiometries of 2:1 (acid herbicides:ligand) were found in CD_3CN , CD_3OD and CD_3Cl.

Conductomeric measurements were carried out with the aim of determining the composition of the receptor-acid herbicides interaction and gaining information regarding the type and strength of interaction of these receptors with acid herbicides in acetonitrile at 298 K. From the conductance measurements of the acid herbicide at different concentration, it was concluded that these acids are highly associated in non-aqueous solvents.

Nano isothermal titration calorimetry is the most powerful tool to determine the enthalpies of binding of various reactions, including herbicides-ligand binding. Isothermal titration calorimetry (ITC) provides the most accurate and direct measurement of the enthalpy of any reaction under isothermal and isobaric conditions. It is also the only method capable of determining the enthalpy, entropy, and the Gibbs free energy of a reaction in a single titration experiment. Future work will

involve the attachment of the receptor to a solid support to generate recyclable materials for herbicides removal.

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Author Contributions

Author contributions designed and performed experiments, prepared figures, analysed data and wrote the paper.

Conflicts of Interest

The author declares no conflict of interest.

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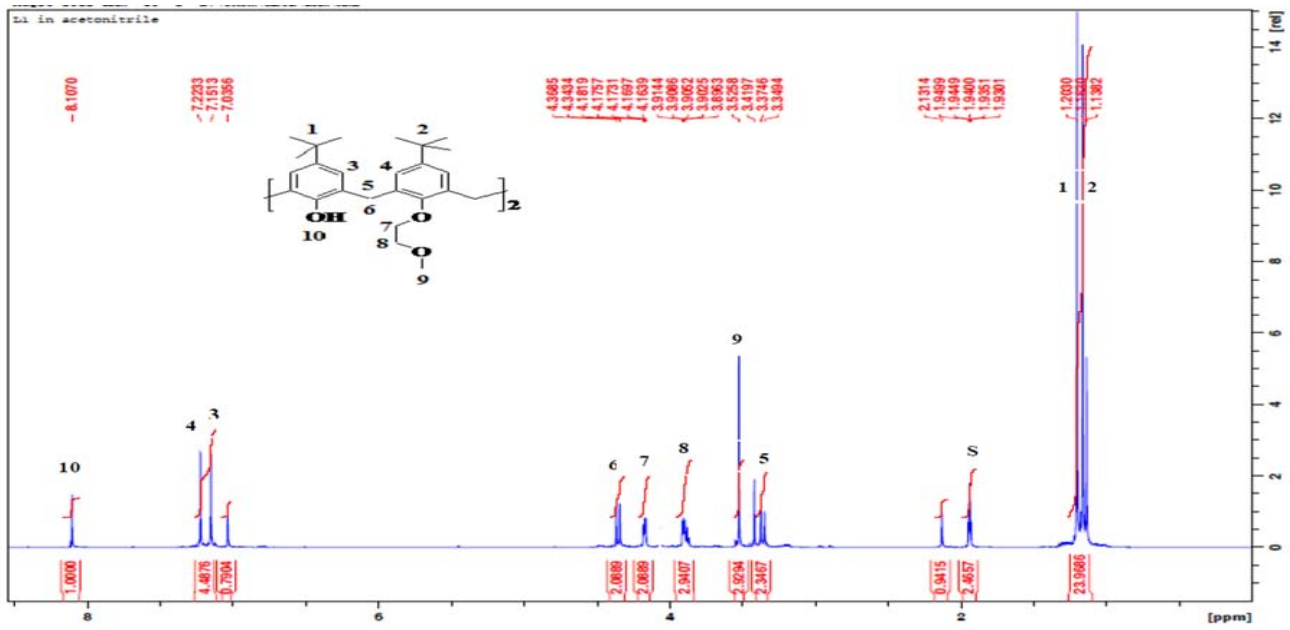
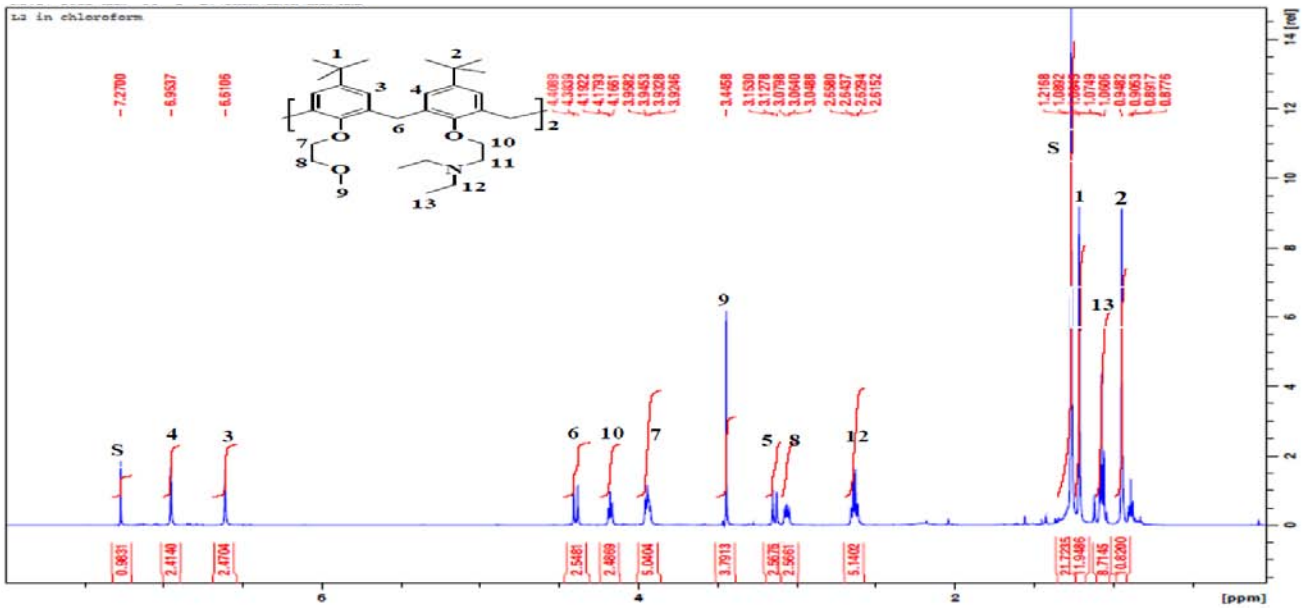
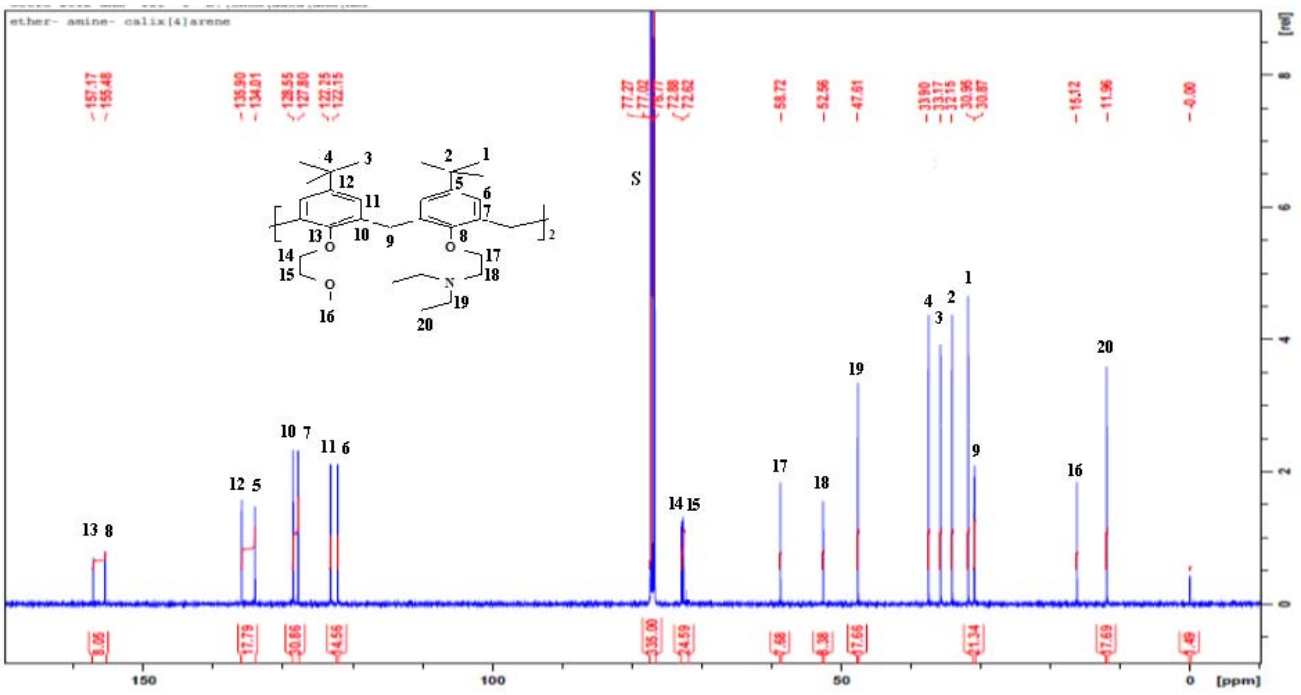
(Appendix A)



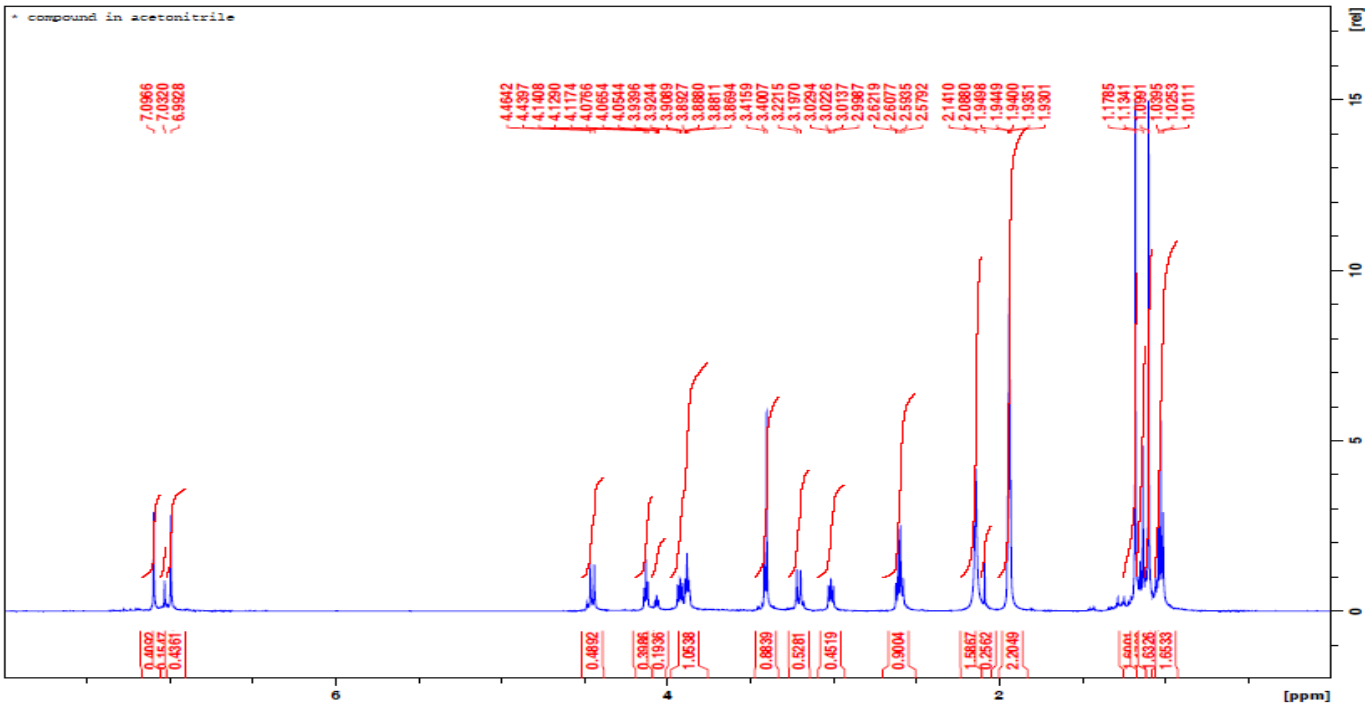
^{1}H NMR spectrum of L1 in CD_3CN at 298 K



^{1}H NMR spectrum of L2 in $CDCl_3$ at 298 K



^{13}C NMR spectrum 5,11,17,23-tetra-butyl 25,27-bis(diethylamino)ethoxy-26,28-(bis-methoxyethoxy)calix[4]arene, L_2 in $CDCl_3$ at 298 K



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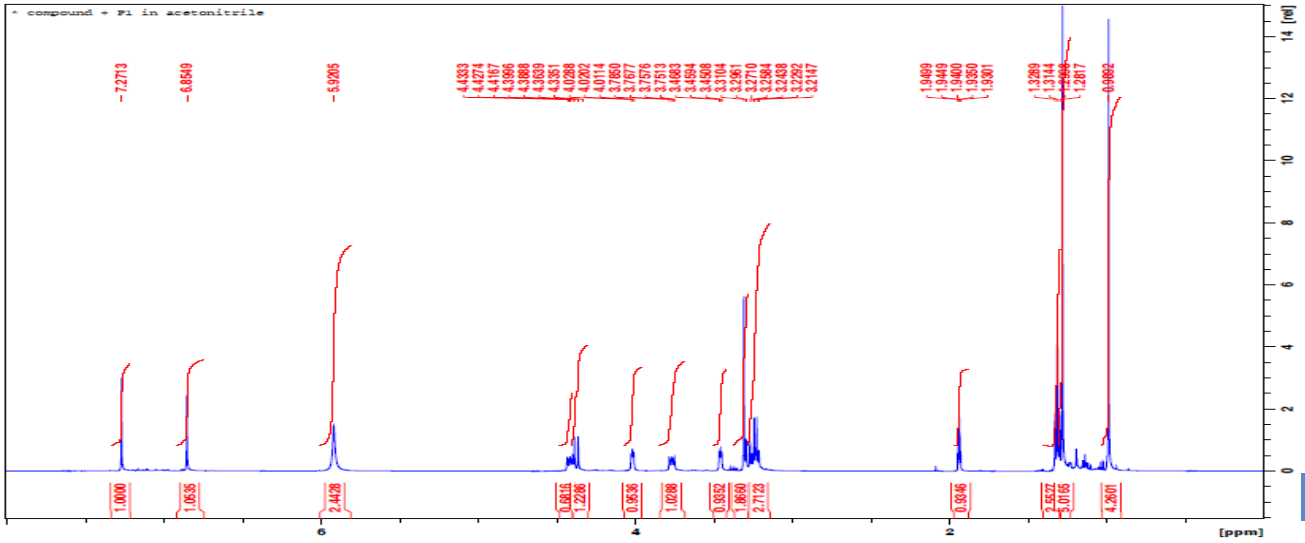
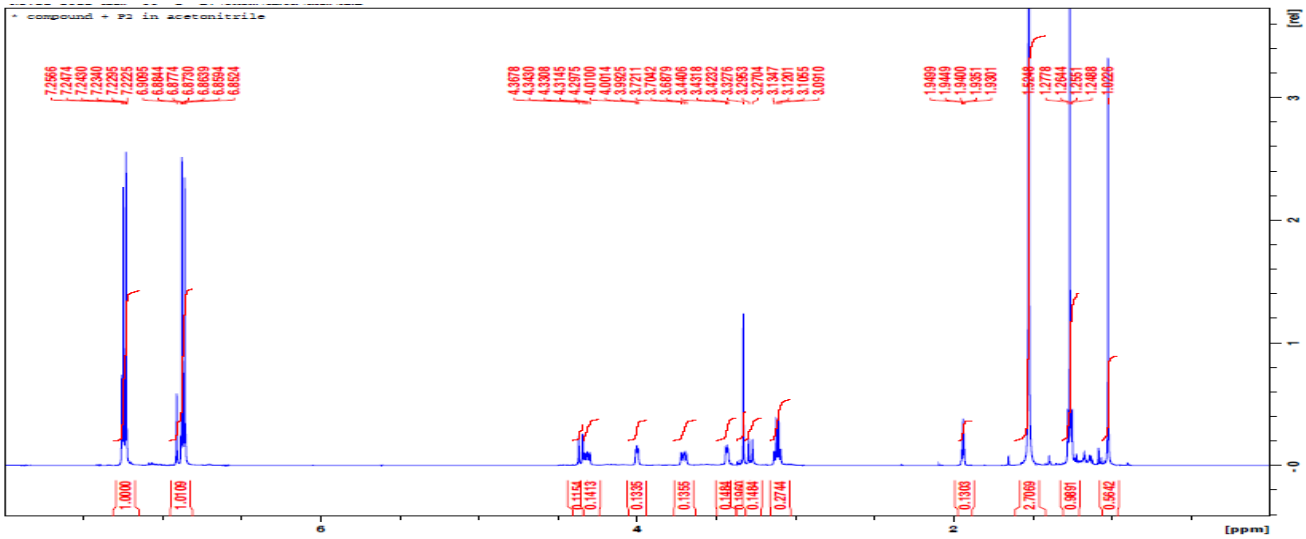


^1H NMR spectrum of L2 + P1 in CD_3CN at 298 K



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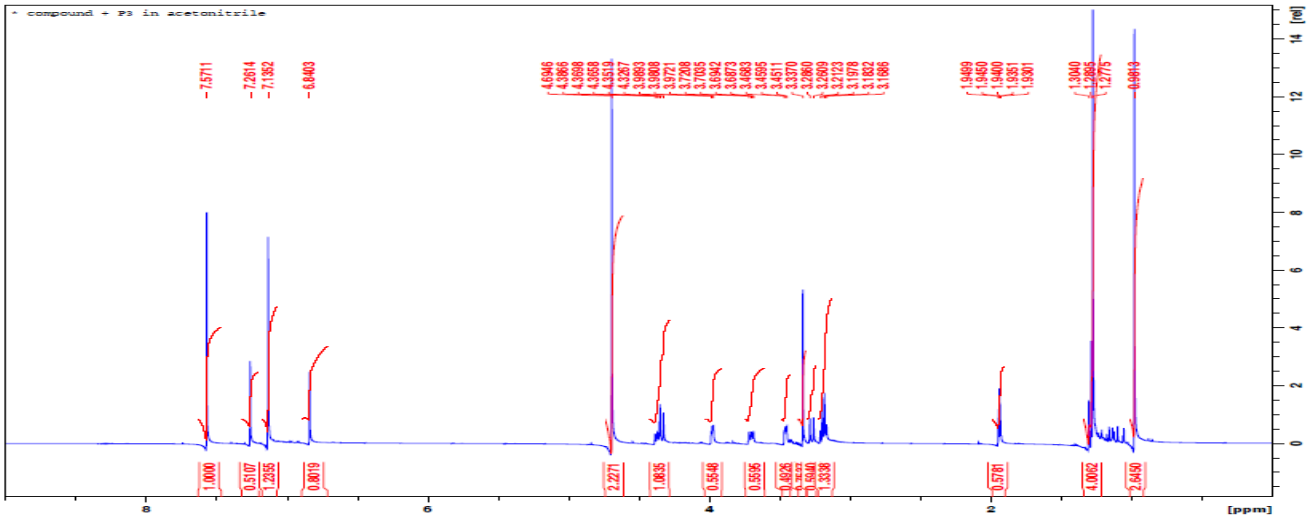
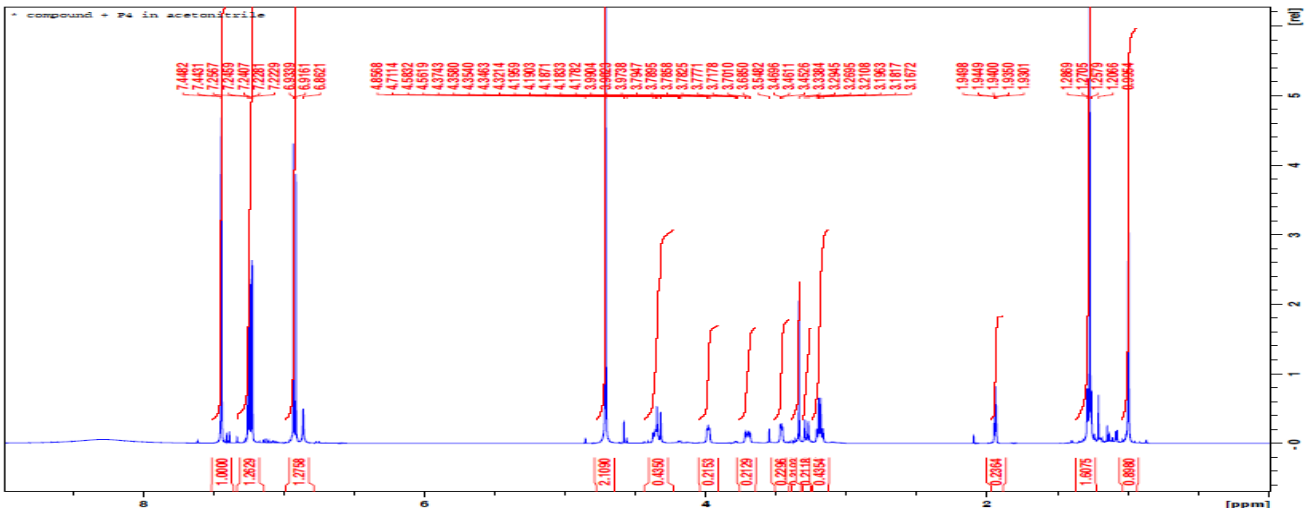


^1H NMR spectrum of L2 + P3 in CD_3CN at 298 K



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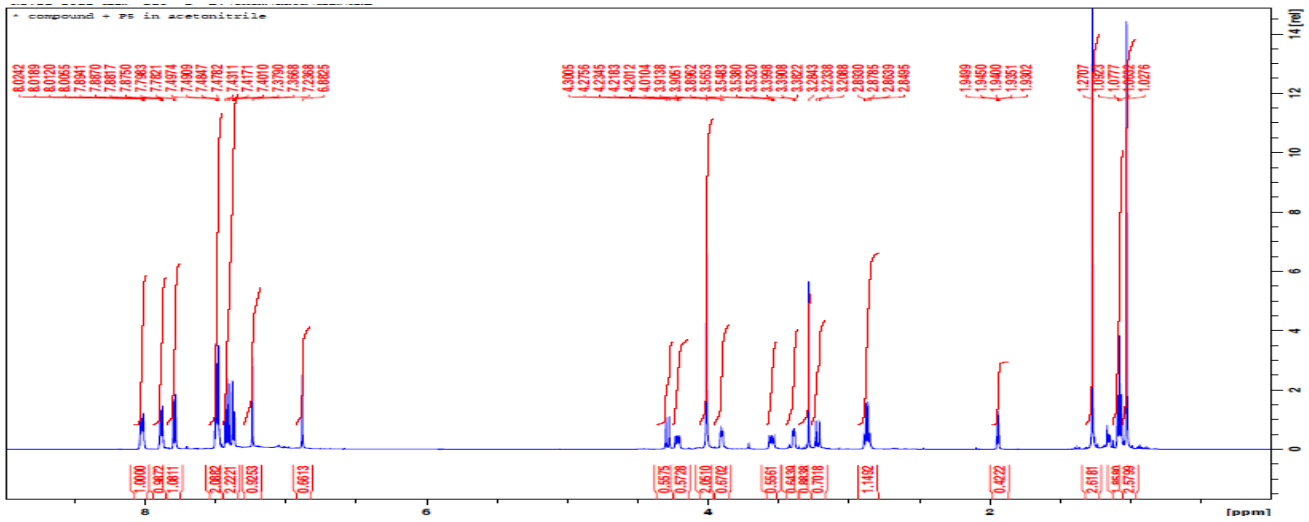
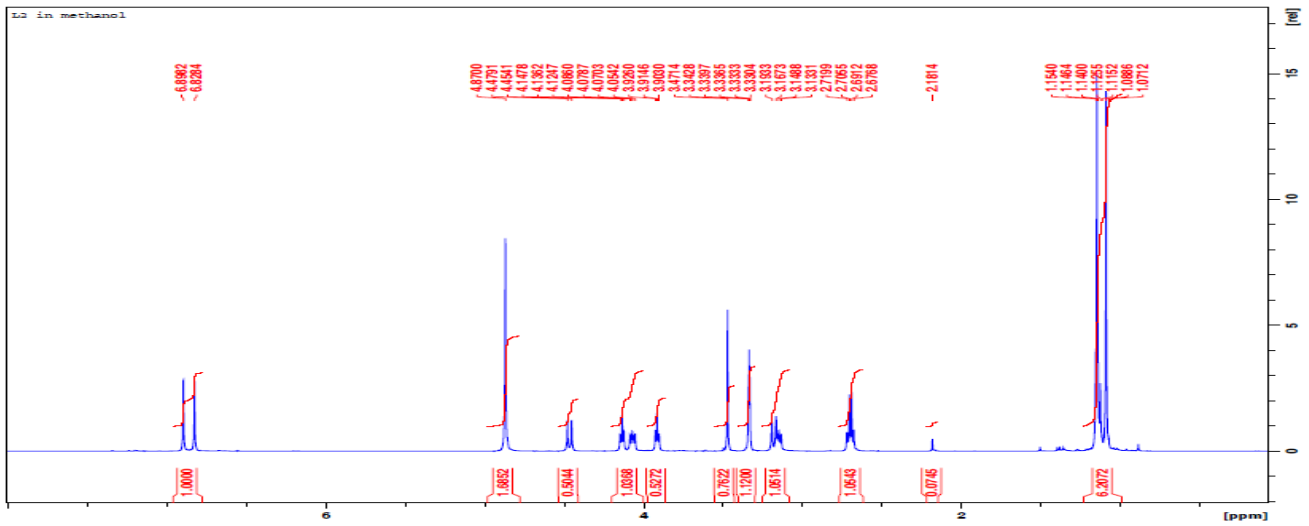
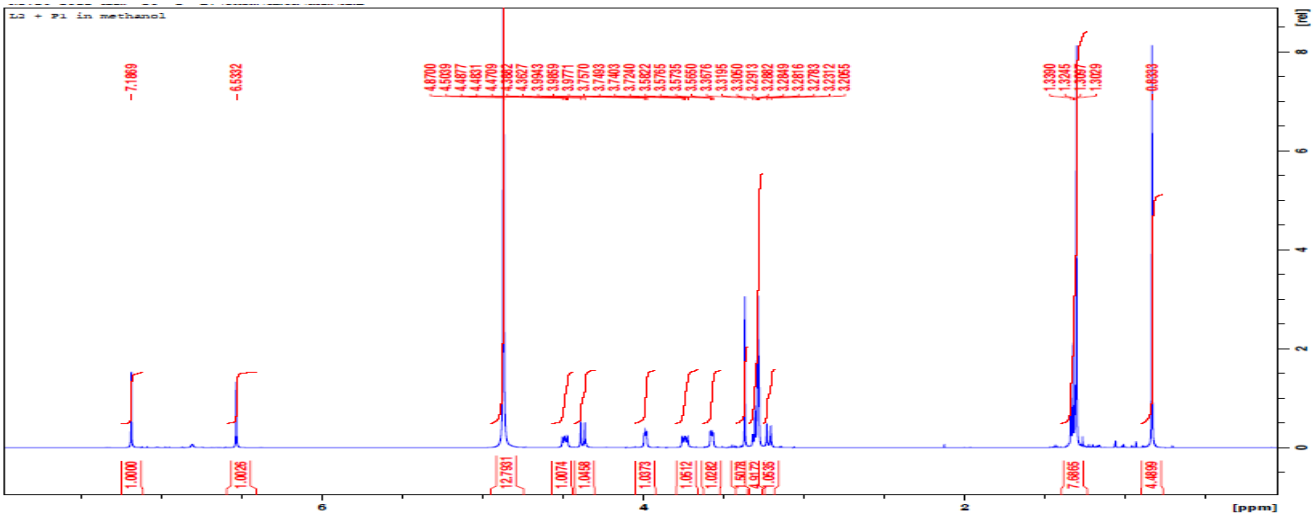


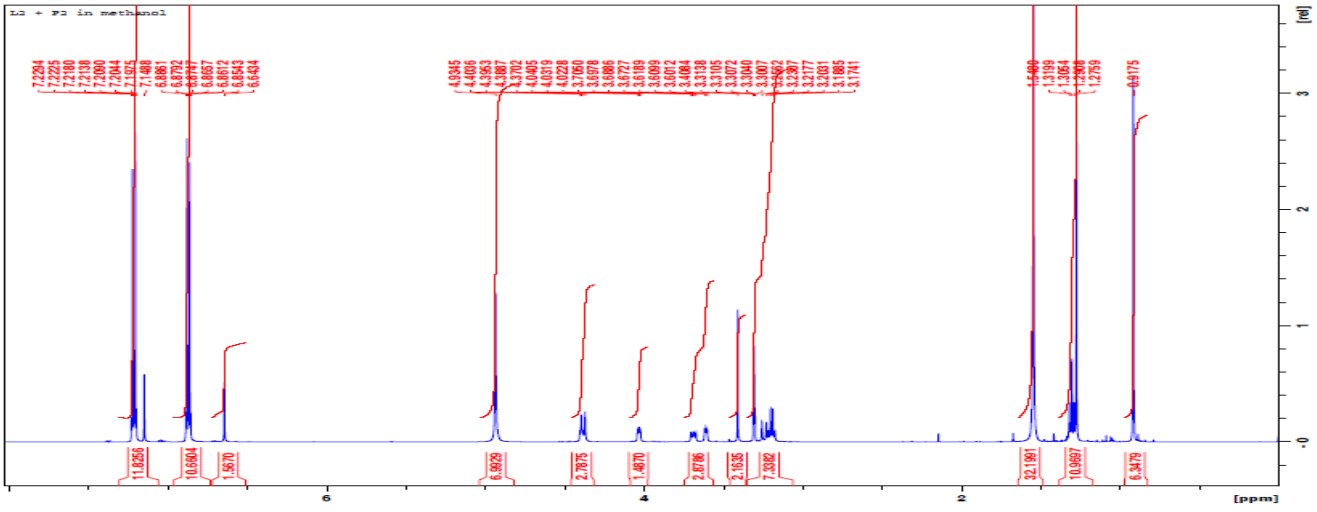
^{1}H NMR spectrum of L2 + P5 in CD_3CN at 298 K



^{1}H NMR spectrum of L2 in CD_3OD at 298 K



^{1}H NMR spectrum of L2 + P1 in CD_3OD at 298 K



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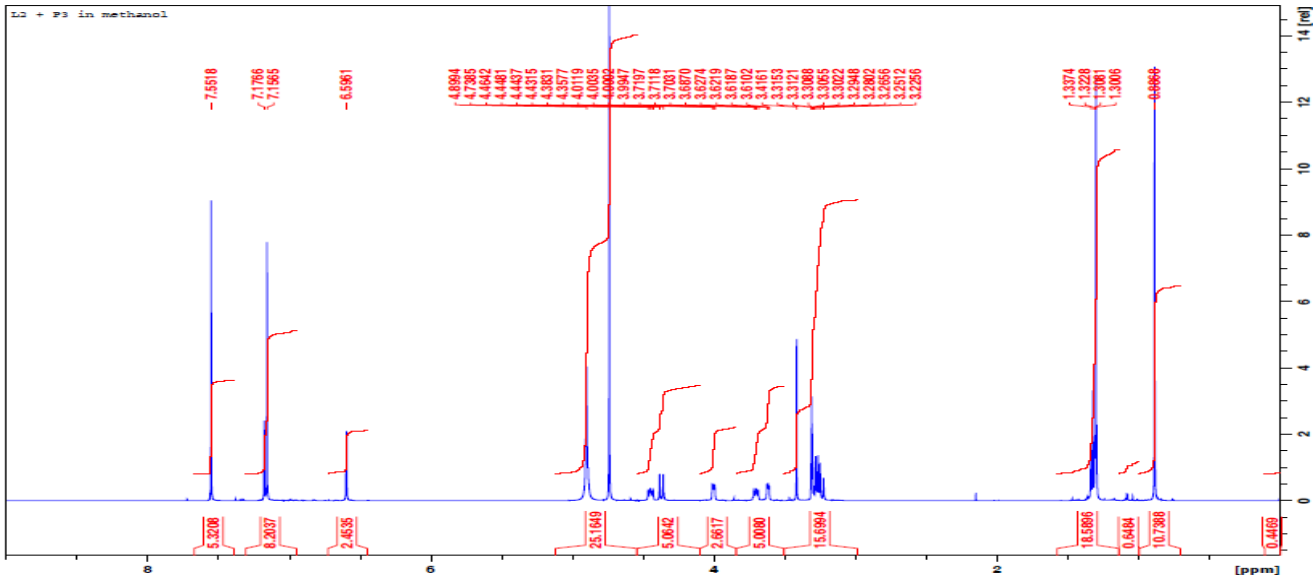

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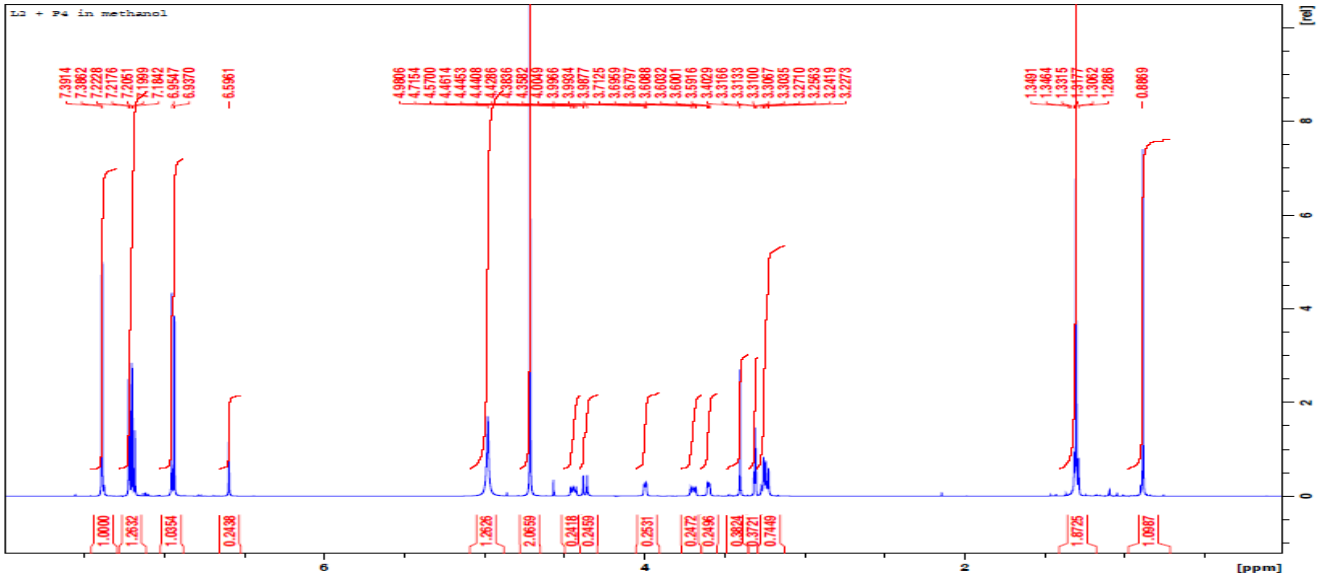
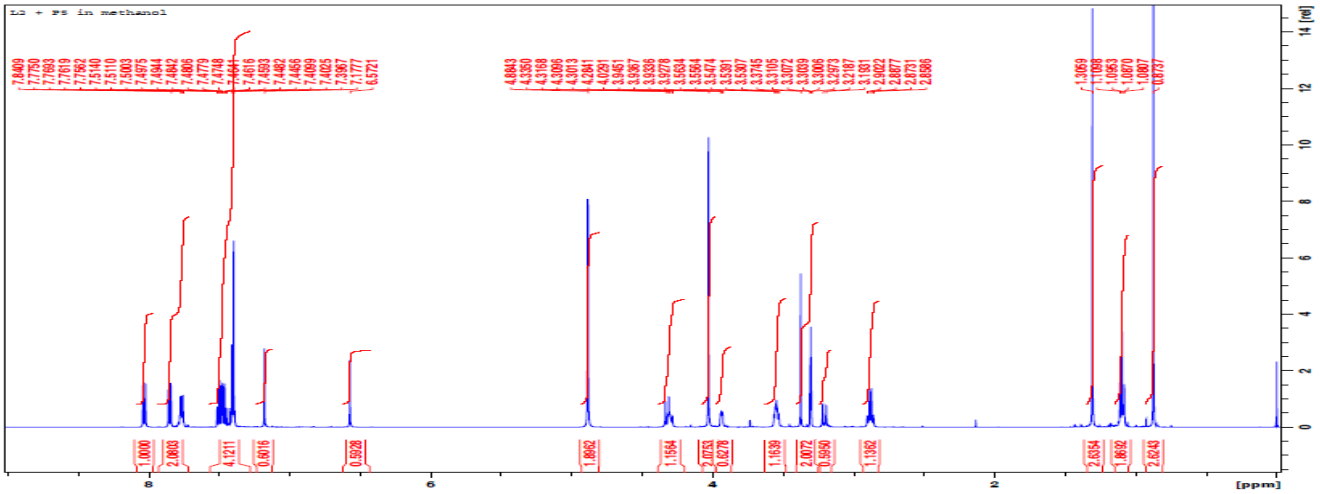
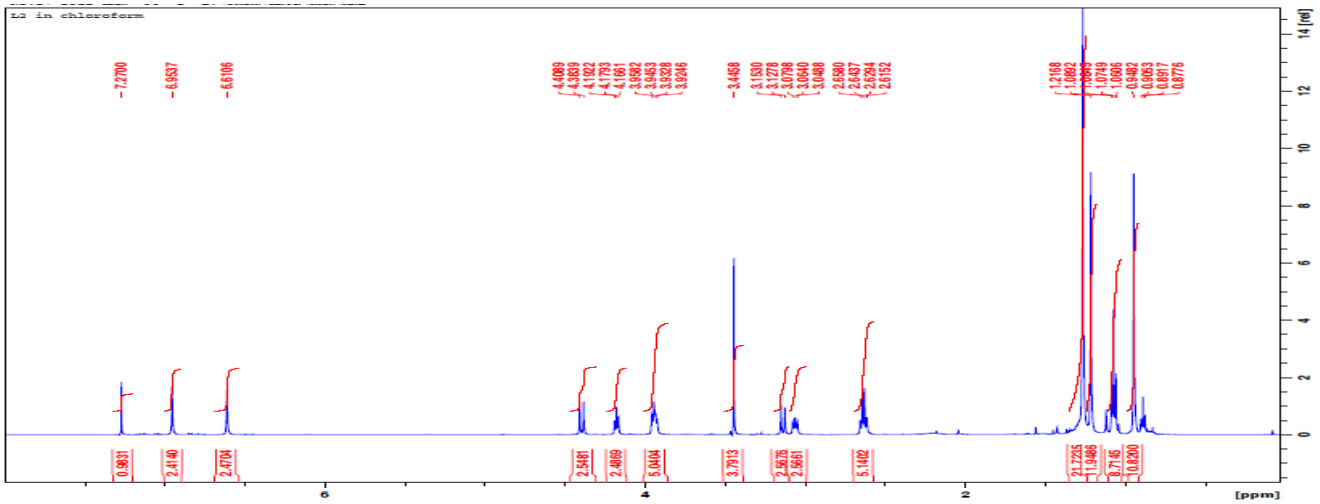


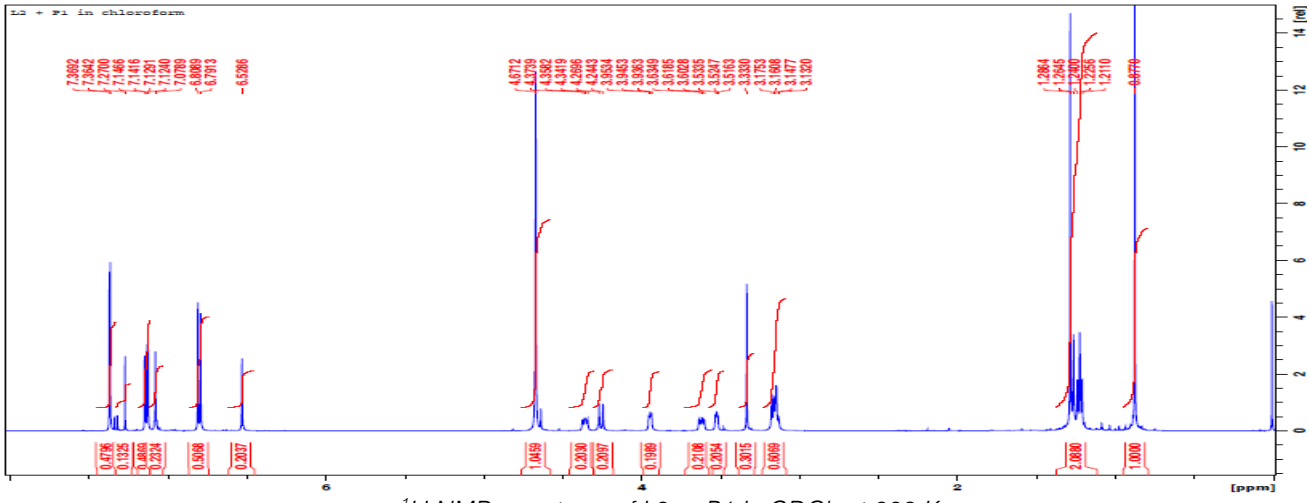
^{1}H NMR spectrum of L2 + P4 in CD_3OD at 298 K



^{1}H NMR spectrum of L2 + P5 in CD_3OD at 298 K



^{1}H NMR spectrum of L2 in $CDCl_3$ at 298 K



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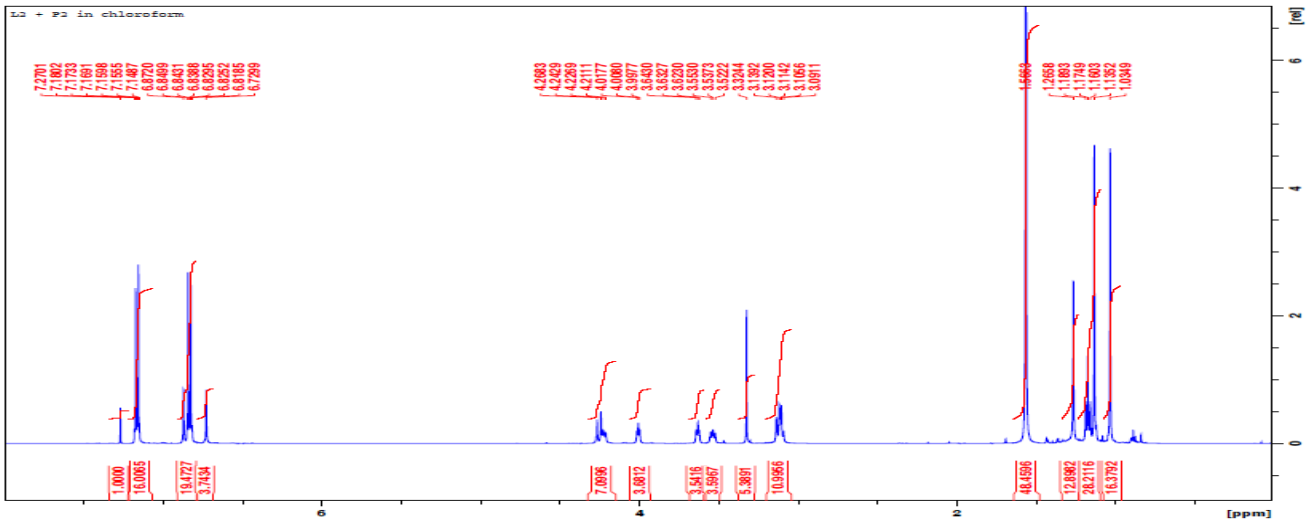
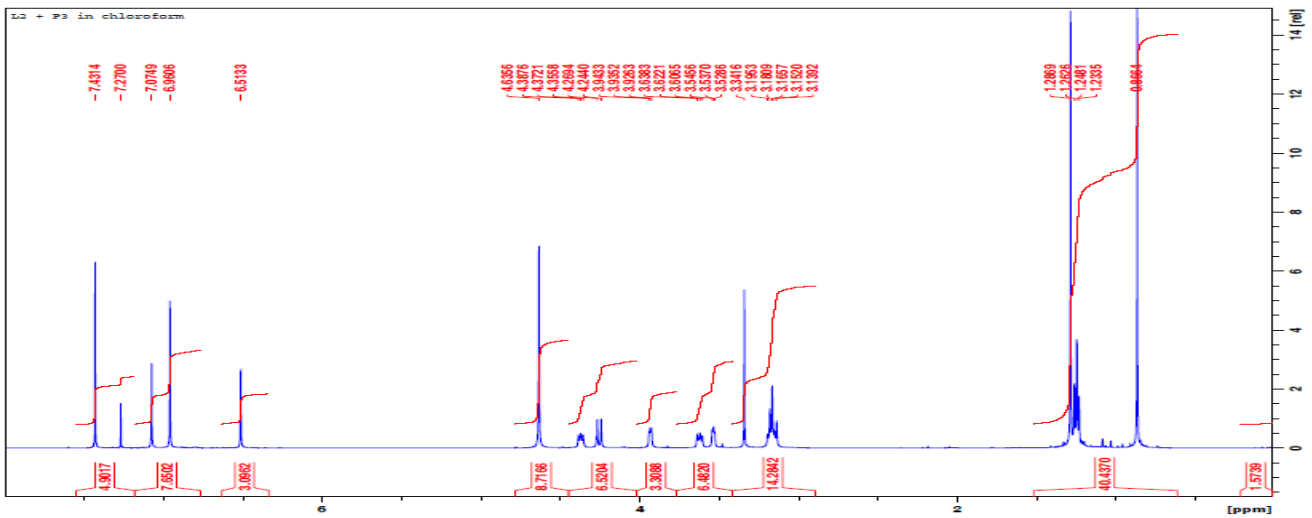
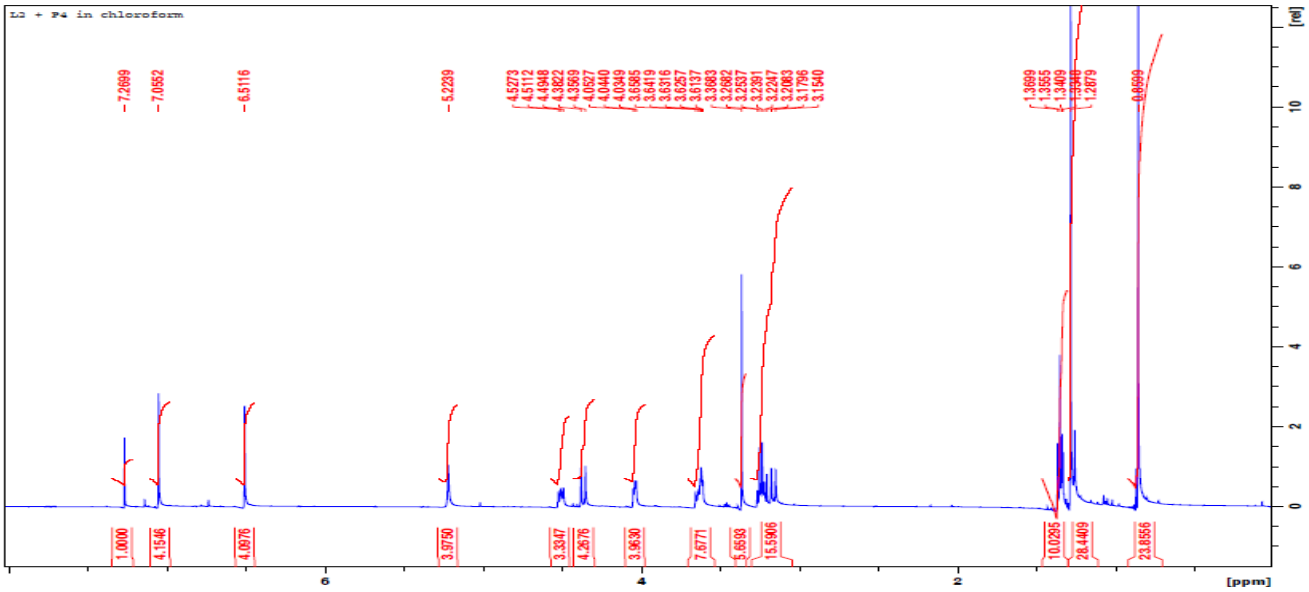


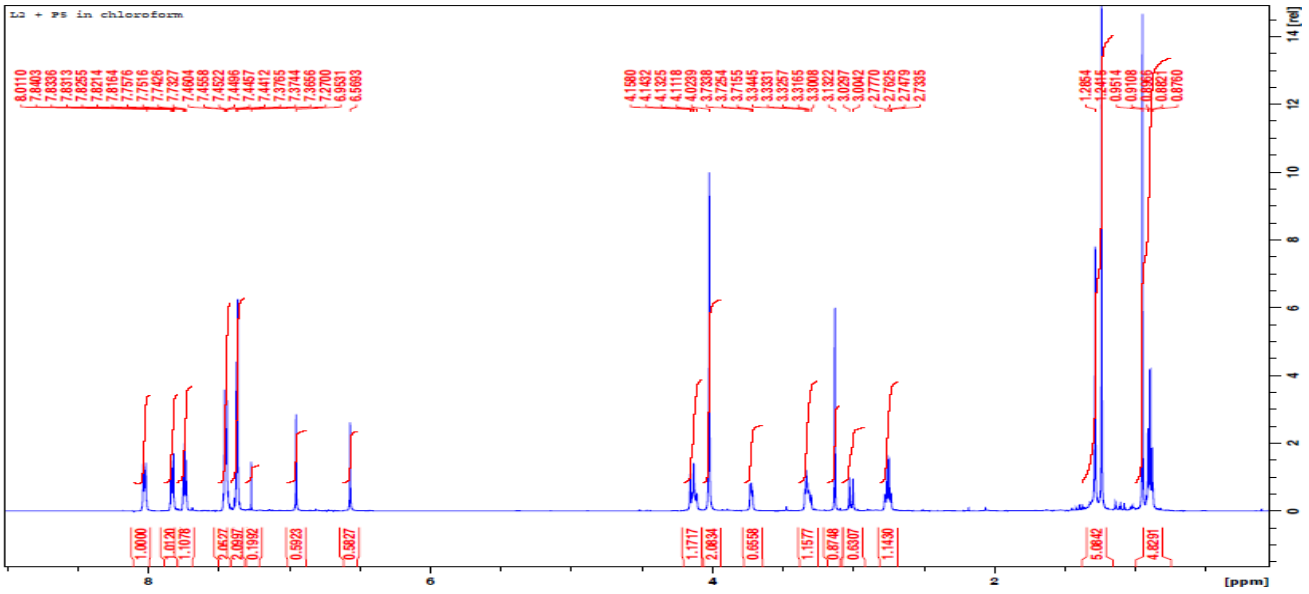
^{1}H NMR spectrum of L2 + P2 in $CDCl_3$ at 298 K



^{1}H NMR spectrum of L2 + P3 in $CDCl_3$ at 298 K

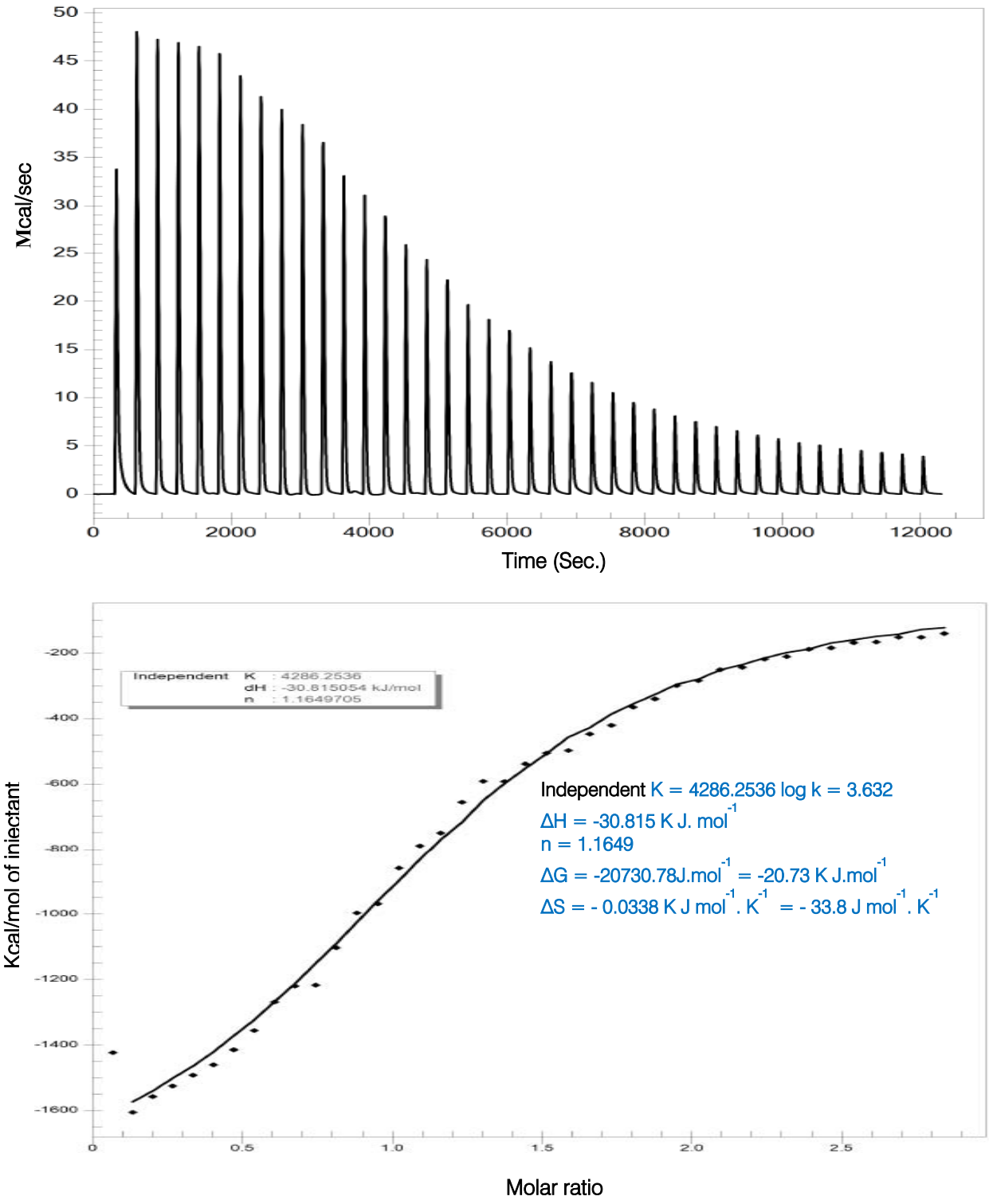


^1H NMR spectrum of L2 + P4 in $CDCl_3$ at 298 K

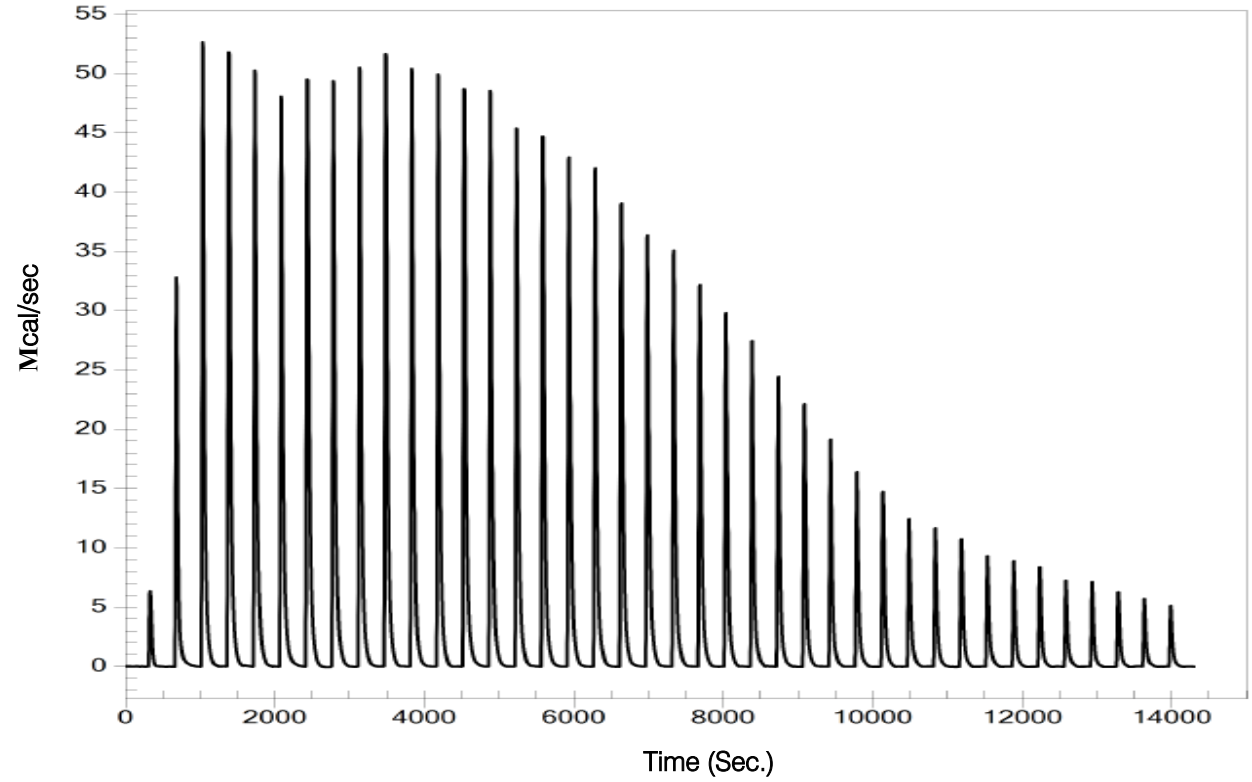


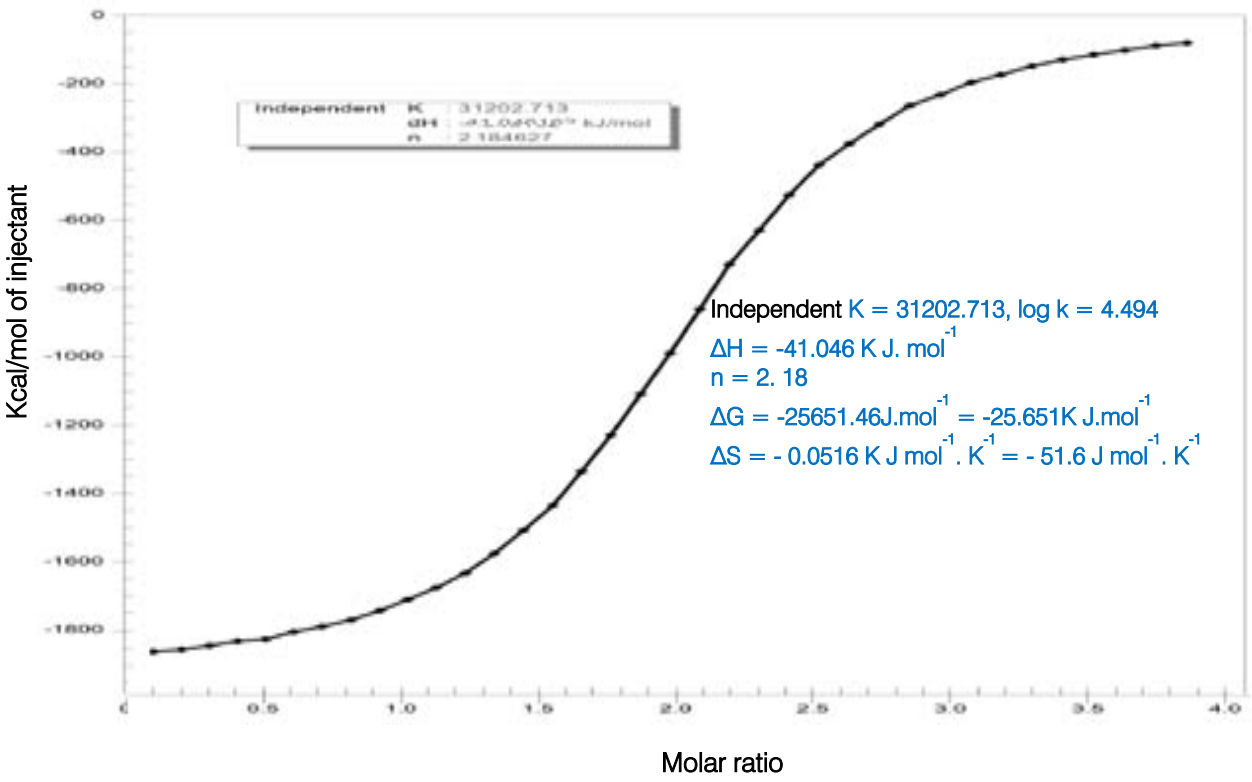
^1H NMR spectrum of L2 + P5 in $CDCl_3$ at 298 K

(Appendix B)

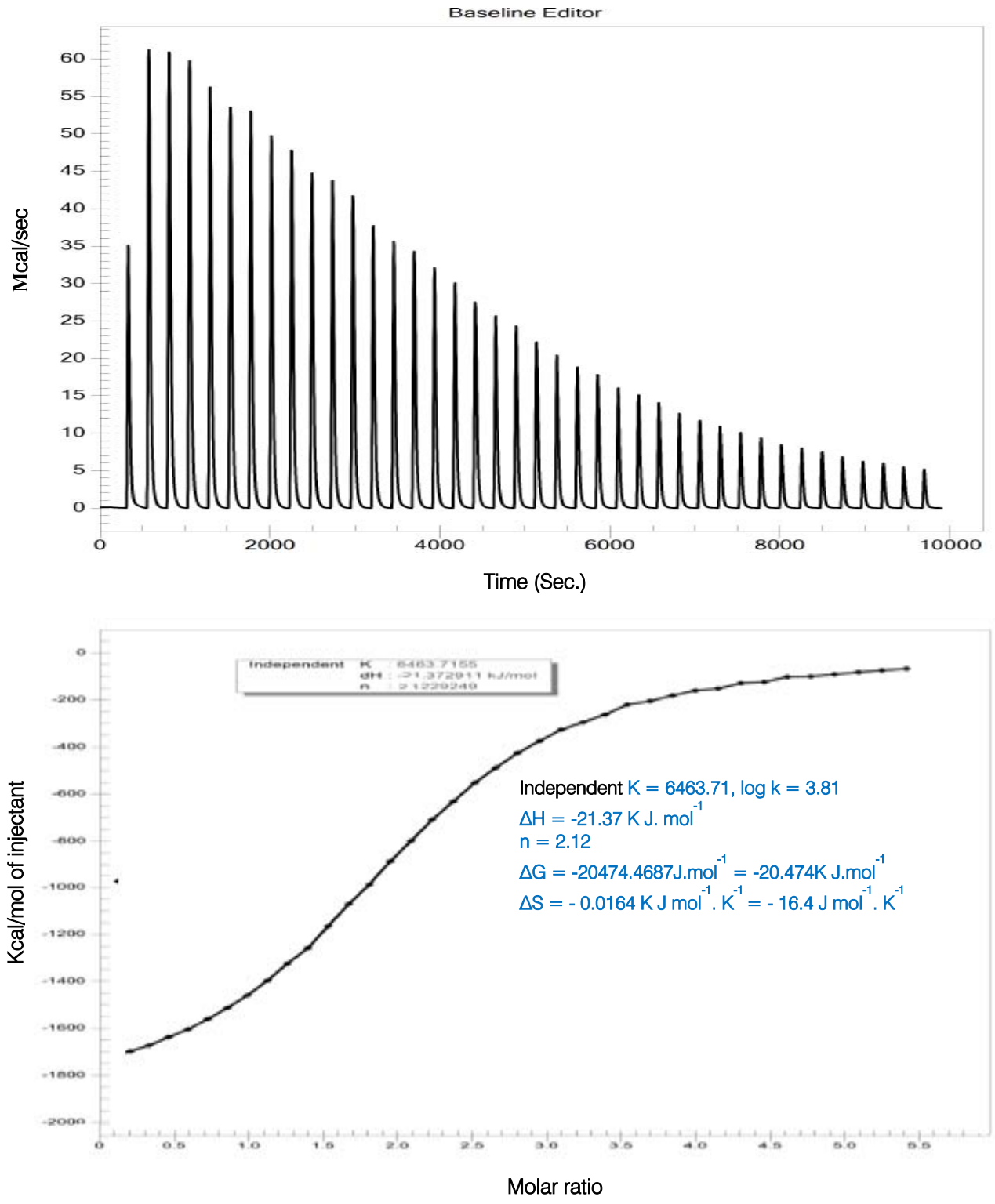


Representative calorimetric titration curves. The upper curve was obtained by titrating 18-crown-6 with Ba^{+2} in deionized water.

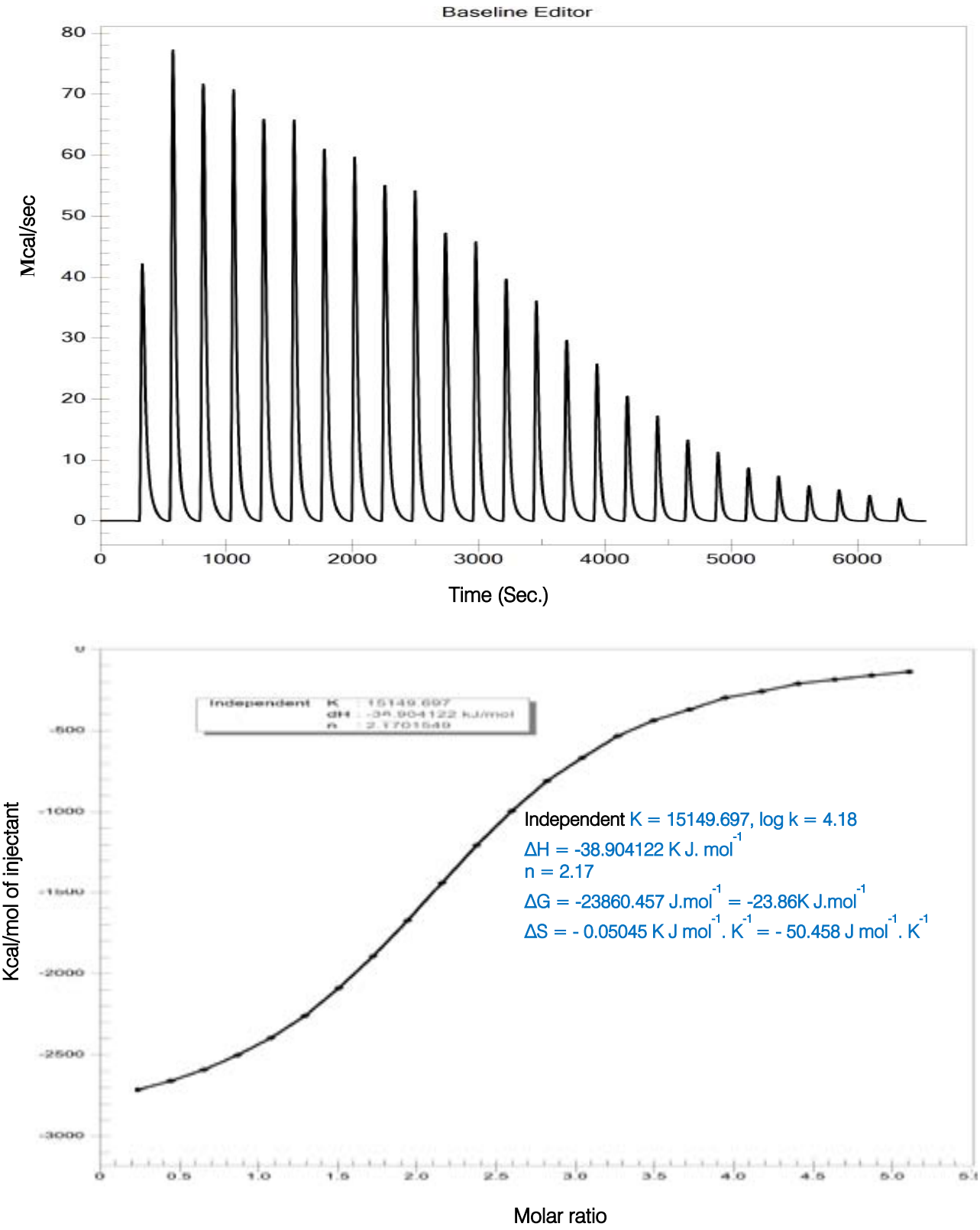




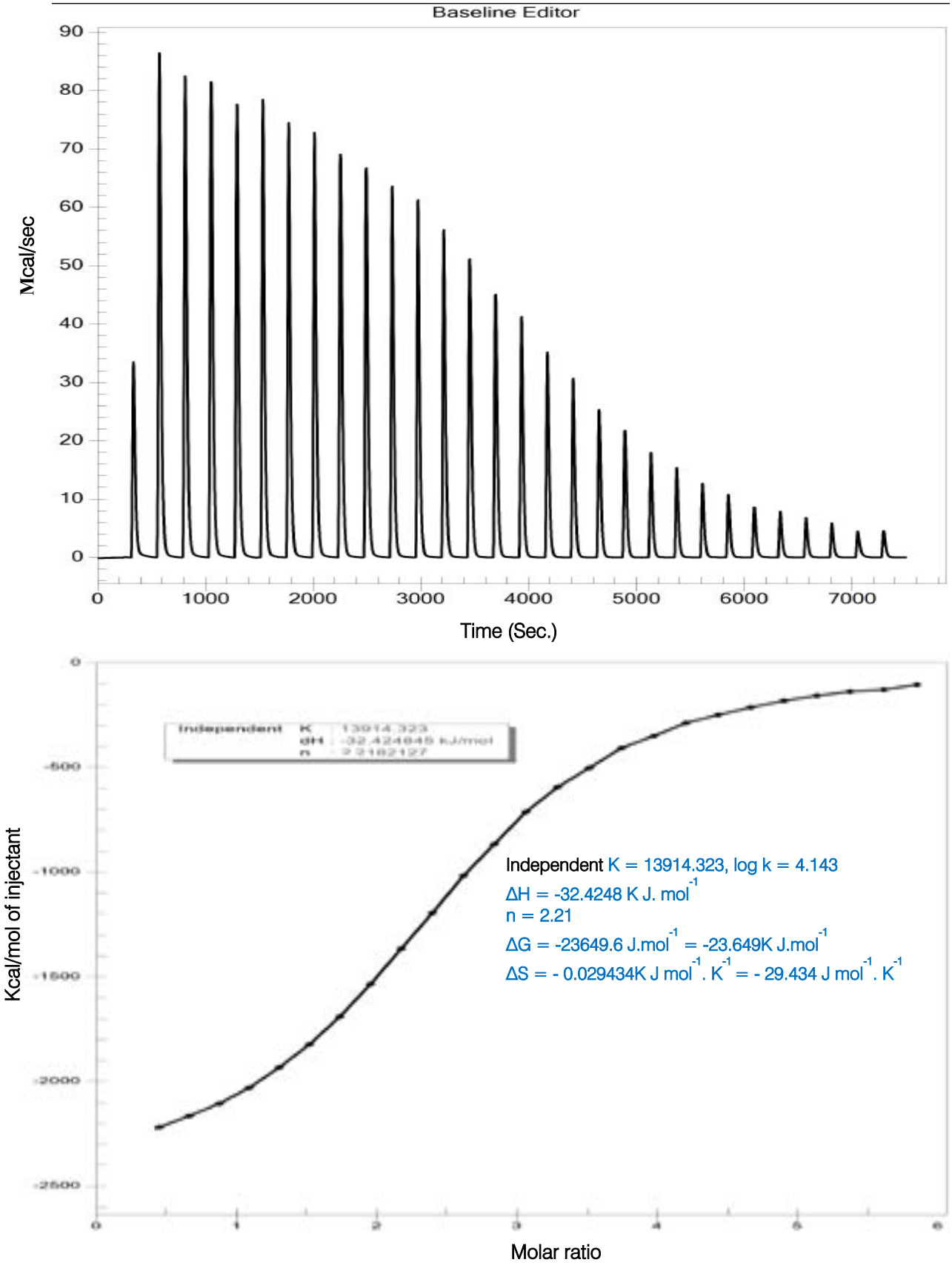
Representative calorimetric titration curves. The upper curve was obtained by titrating receptor 5 withP1 [Picloram].



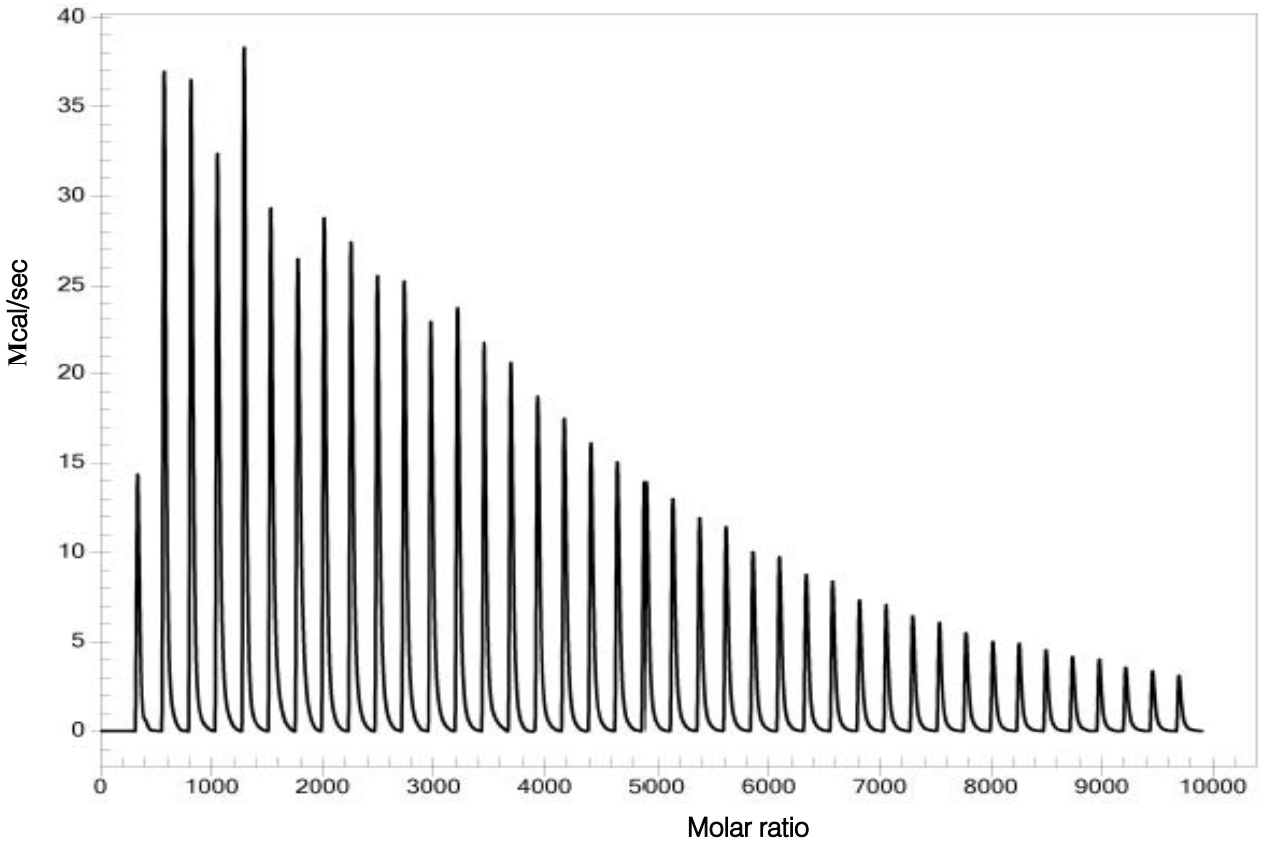
Representative calorimetric titration curves. The upper curve was obtained by titrating receptor 5 with P2 [Clofibric acid].

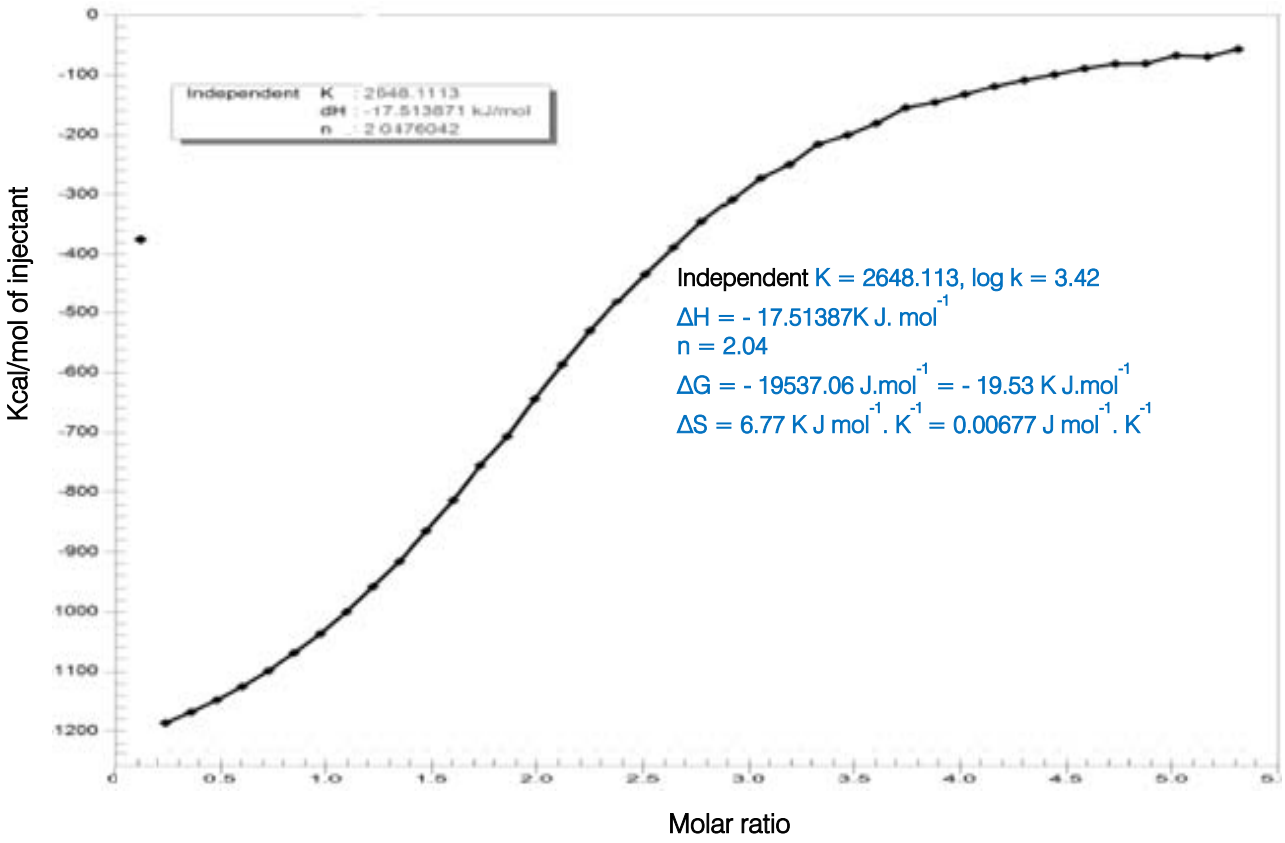


Representative calorimetric titration curves. The upper curve was obtained by titrating receptor 5 with P3 [2, 4, 5 - T].



Representative calorimetric titration curves. The upper curve was obtained by titrating receptor 5 with P4 [2,4, - T].





Representative calorimetric titration curves. The upper curve was obtained by titrating receptor 5 with P5.

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