Supplementary Section

New aspects of coordination chemistry and biological activity of NTMP-related diphosphonates equipped in heterocyclic ring

J. Gałęzowska[a]*, H. Czapor-Irzabek[b], R. Janicki[c], E. Chmielewska[d], T. Janek[a]

Content:

Comment S1. Potentiometric data evaluation additional details

Both L^1 and L^2 were synthesized in the form of diammonium salts ($(NH_4)_2L^{1,2}$) in order to improve the solubility of molecules in water. Therefore ammonium cations were also considered in the overall model of acid – base equilibrium. The determined values of the protonation constants fall in the region 8.57-9.50 and are very close to those reported in literature. [1,2,3]

Since ammonium and L^1/L^2 ligand may form mixed complexes with metal cations[1,4] the formation of such species was taken into consideration. No tertiary complexes were detected in studied systems. The $[Cu(NH_3)_2]^{2+}$ complex is the only detected species in which ammonia molecules are coordinated, however it is formed at pH as high as 9 and its molar fraction is less than 15%.

The metal ion hydrolysis was considered,[5,6,7,8] however no hydrolytic species were detected.

No precipitation occurred in any of studied systems in studied pH range (2-11).

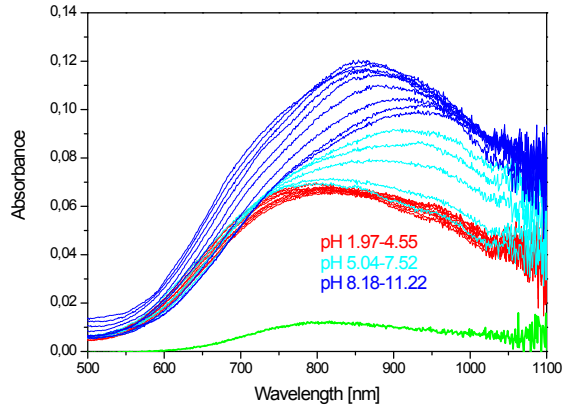
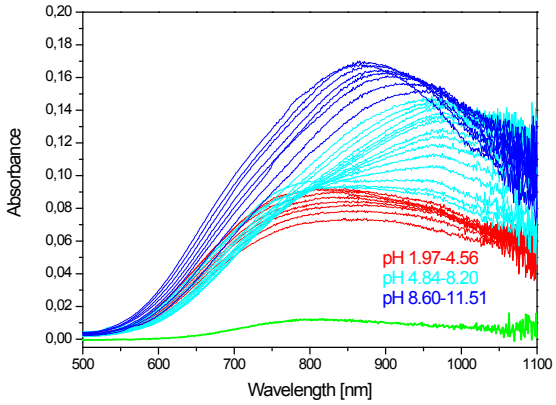
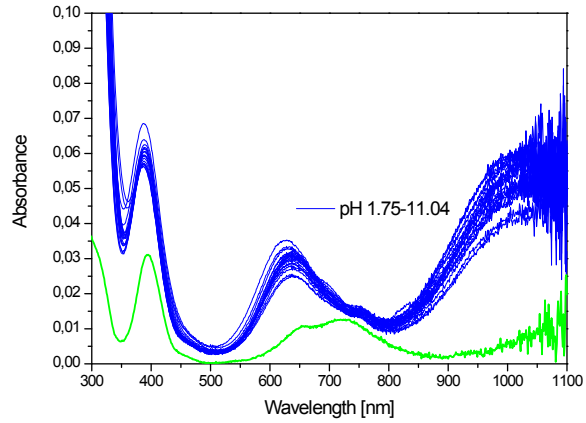
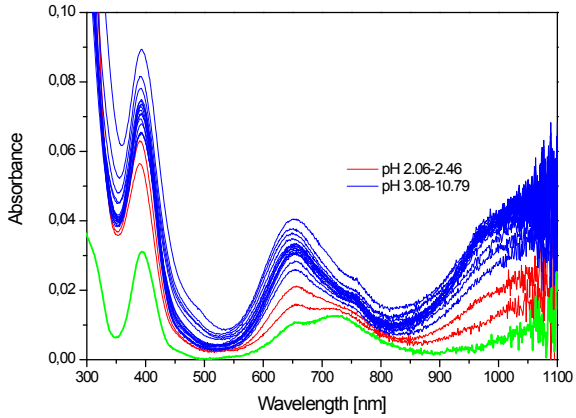
L^1:Cu^{2+}	L^2:Cu^{2+}
	
L^1:Ni^{2+}	L^2:Ni^{2+}
	

Figure S1. UV-vis spectra for Cu^{2+} and Ni^{2+} complexes on a broad pH range. For Cu^{2+} measurements: [L]=1×10^{-3}M, [Cu^{2+}]=1×10^{-3}M, for Ni^{2+}; [L]=5×10^{-3}M, [Ni^{2+}]=5×10^{-3}M. Spectra of Cu_{aq}^{2+} and Ni_{aq}^{2+} (green) under the same conditions ware additionally shown for comparison purposes.

Table S1. ESI-MS data for **L¹**/Cu^{2+}, Zn^{2+}, Ni^{2+}, Ca^{2+} and Mg^{2+} complexes.

L¹ : Cu^{2+}				
complex	calc.[a]	found [b]	err [ppm]	relative intensity [%]
$[L+H]^+$	297.04	297.0407	2.36	3
$[L+Cu-H]^+$	357.9539	357.9546	1.96	92
$[L+Cu-H+H_2O]^+$	375.9645	375.9648	0.80	46
$[L+Cu+Na-2H]^+$	379.9359	379.9364	1.32	100
$[2L+2Cu-3H]^+$	714.9006	714.9005	-0.14	8
$[2L+2Cu+Na-4H]^+$	736.8825	736.8820	-0.68	8
L¹ : Ni^{2+}				
$[L+Ni-H]^+$	352.9597	352.9577	-5.67	54
$[L+Ni-H+H_2O]^+$	370.9702	370.9687	-4.04	70
$[L+Ni+Na-2H]^+$	374.9416	374.9411	-1.33	31
$[2L+2Ni-3H]^+$	704.9121	704.9084	-5.25	6
L¹ : Zn^{2+}				
$[L+H]^+$	297.0400	297.0402	0.67	38
$[L+Zn-H]^+$	358.9535	358.9539	1.11	100
$[L+Zn-H+H_2O]^+$	376.9640	376.9640	0.00	40
$[2L+2Zn-3H]^+$	716.8997	716.8994	-0.42	7
L¹ : Ca^{2+}				
$[L+Ca-H]^+$	334.9869	334.9878	2.69	4
$[L+Ca-H+H_2O]^+$	352.9975	352.9984	2.55	5
[L+Ca+Na-2H]+	356.9689	356.9698	2.52	36
[L+Ca+2Na-3H]+	378.9508	378.9518	2.64	100
[L+Ca+3Na-4H]+	400.9328	400.9343	3.74	17
[2L+2Ca+2Na-5H]+	712.9305	712.9304	-0.14	6
L¹ : Mg^{2+}				
$[L+Mg-H]^+$	319.0094	319.0093	-0.31	3
$[L+Mg-H+H_2O]^+$	337.0199	337.0181	-5.34	6
$[L+Mg+Na-2H]^+$	340.9913	340.9896	-4.99	33
$[L+Mg+2Na-3H]^+$	362.9733	362.9729	-1.10	100
$[L+Mg+2Na-3H+H_2O]^+$	380.9838	380.9812	-6.82	79
$[2L+2Mg+2Na-5H]^+$	680.9754	680.9730	-3.52	9
$[2L+2Mg+3Na-6H]^+$	702.9573	702.9576	0.43	8

[a] monoisotopic mass of the indicated ion formed by the ligand calculated by Compass DataAnalysis 4.2

[b] monoisotopic mass found experimentally on a compact™ mass spectrometer (Bruker Daltonics. Bremen. Germany)

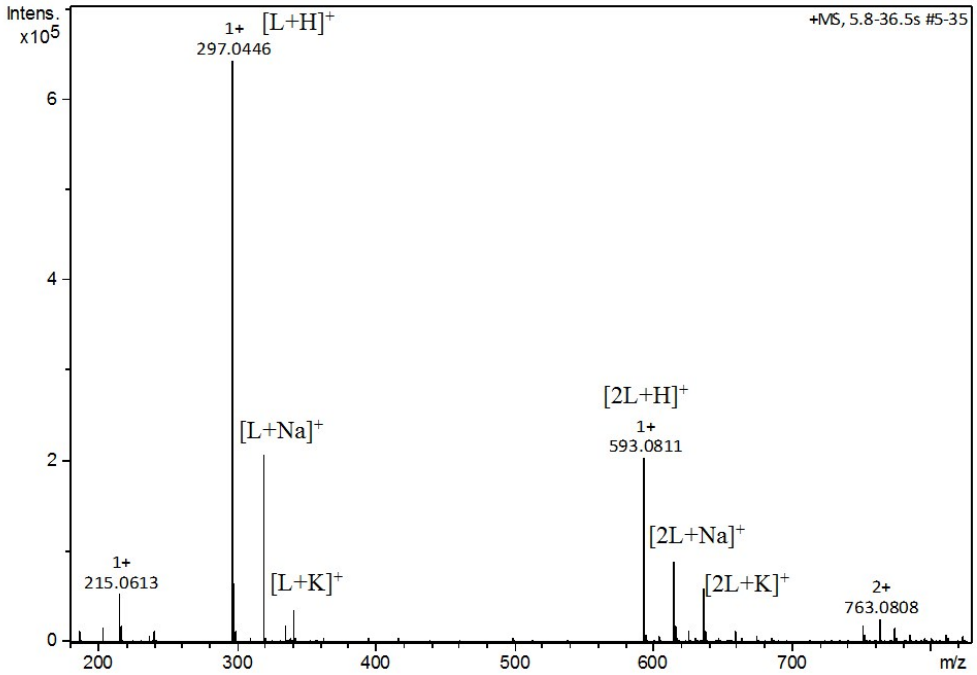
Table S2. ESI-MS data for **L²**/Cu^{2+}, Zn^{2+}, Ni^{2+}, Ca^{2+} and Mg^{2+} complexes.

complex	calc.[a]	found [b]	err [ppm]	relative intensity [%]
L^2 : Cu^{2+}				
$[L+H]^+$	336.0509	336.0509	0.00	11
$[L+Cu-H]^+$	396.9648	396.9650	0.50	100
$[L+Cu+Na-2H]^+$	418.9468	418.9468	0.00	95
$[2L+2Cu-3H]^+$	792.9224	792.9220	-0.50	3
L^2 : Ni^{2+}				
$[L+Ni-H]^+$	391.9706	391.9715	2.30	90
$[L+Ni-H+H_2O]^+$	409.9811	409.9818	1.71	43
$[L+Ni+Na-2H]^+$	413.9525	413.9532	1.69	85
L^2 : Zn^{2+}				
$[L+H]^+$	336.0509	336.0522	3.87	21
$[L+Zn-H]^+$	397.9644	397.9658	3.52	100
$[L+Zn+Na-2H]^+$	419.9463	419.9482	4.52	89
$[2L+2Zn-3H]^+$	794.9215	794.9243	3.52	10
L^2 : Ca^{2+}				
$[L+2Na-H]^+$	380.0148	380.0139	-2.37	9
$[L+3Na-2H]^+$	401.9967	401.9953	-3.48	33
$[L+4Na-3H]^+$	423.9787	423.9760	-6.37	22
[L+Ca+Na-2H]+	395.9798	395.9786	-3.03	21
[L+Ca+2Na-3H]+	417.9617	417.9606	-2.63	100
[L+Ca+3Na-4H]+	439.9437	439.9425	-2.73	25
L^2 : Mg^{2+}				
$[L+Mg+Na-2H]^+$	380.0022	380.0017	-1.32	5
$[L+Mg+2Na-3H]^+$	401.9842	401.9848	1.49	100
$[L+Mg+2Na-3H+H_2O]^+$	419.9947	419.9936	-2.62	54
$[L+Mg+3Na-4H+H_2O]^+$	441.9767	441.9762	-1.13	22

[a] monoisotopic mass of the indicated ion formed by the ligand calculated by Compass DataAnalysis 4.2

[b] monoisotopic mass found experimentally on a compact™ mass spectrometer (Bruker Daltonics. Bremen. Germany)

L^1


Intens.
x10^5
+MS, 5.8-36.5s #5-35
1+
297.0446
[L+H]+
[L+Na]+
[L+K]+
1+
215.0613
[2L+H]+
1+
593.0811
[2L+Na]+
[2L+K]+
2+
763.0808
0
2
4
6
200
300
400
500
600
700
m/z

L²

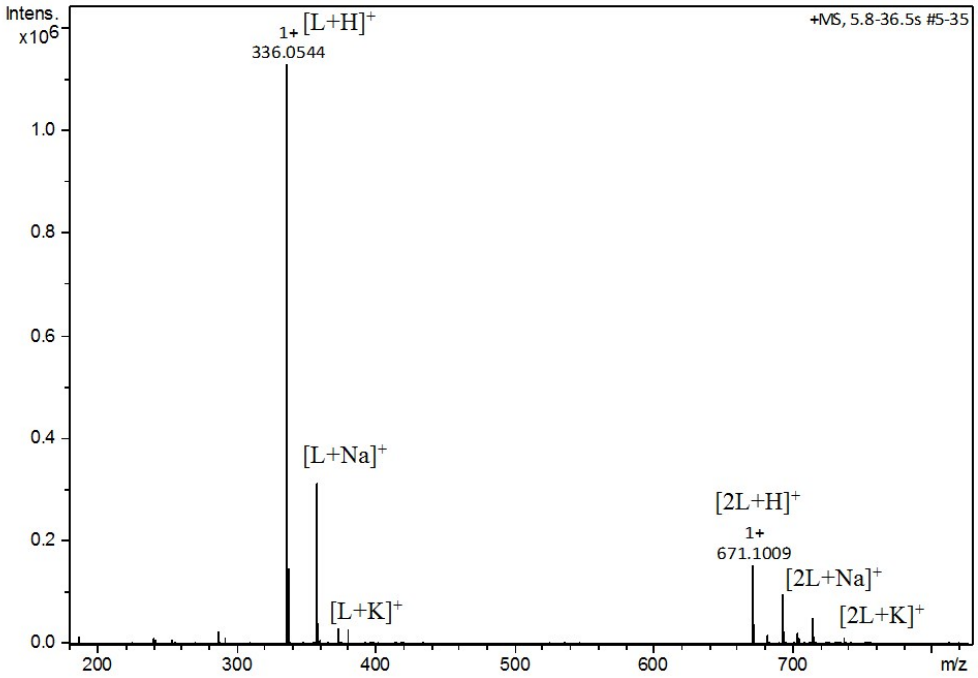
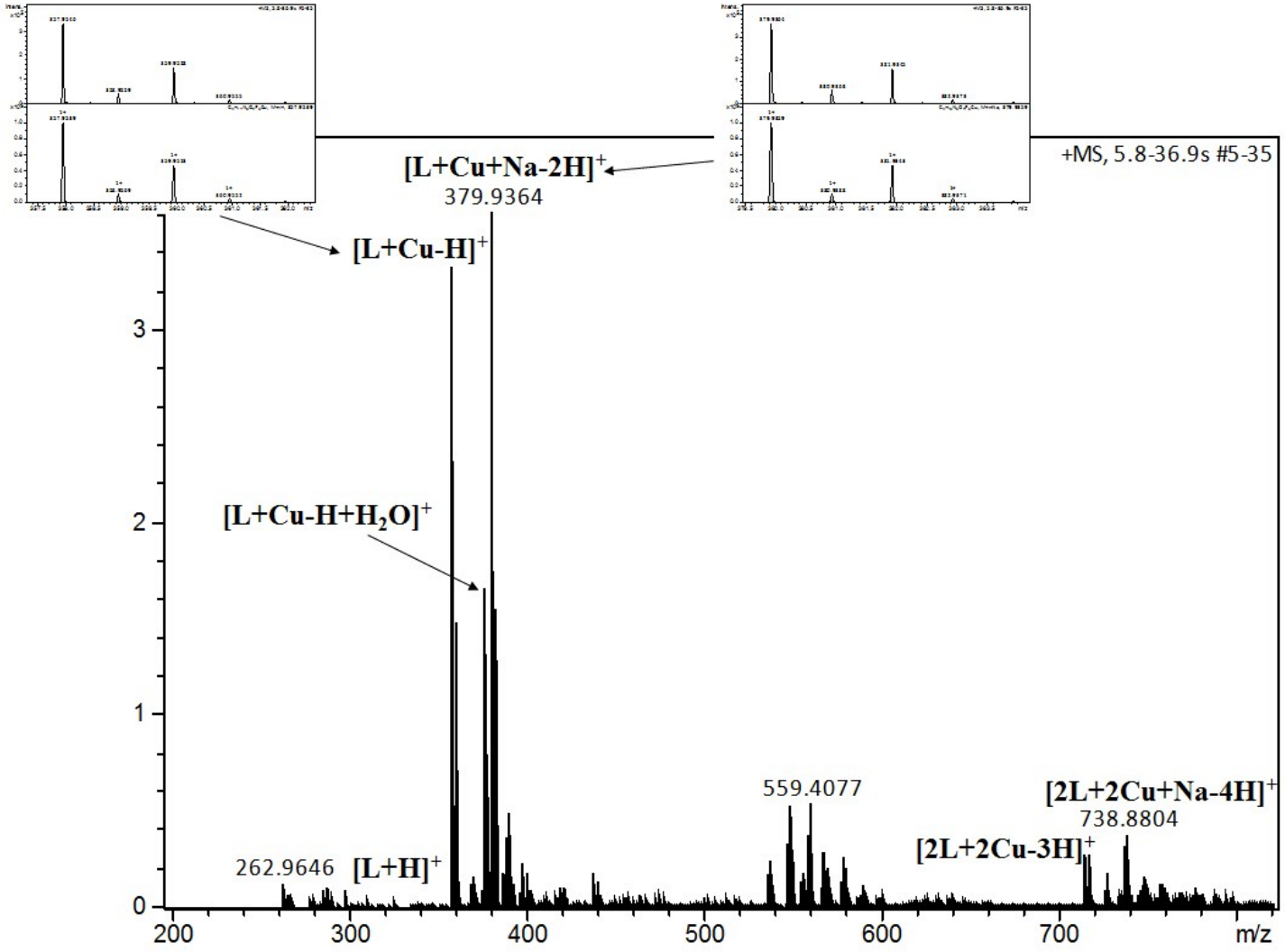
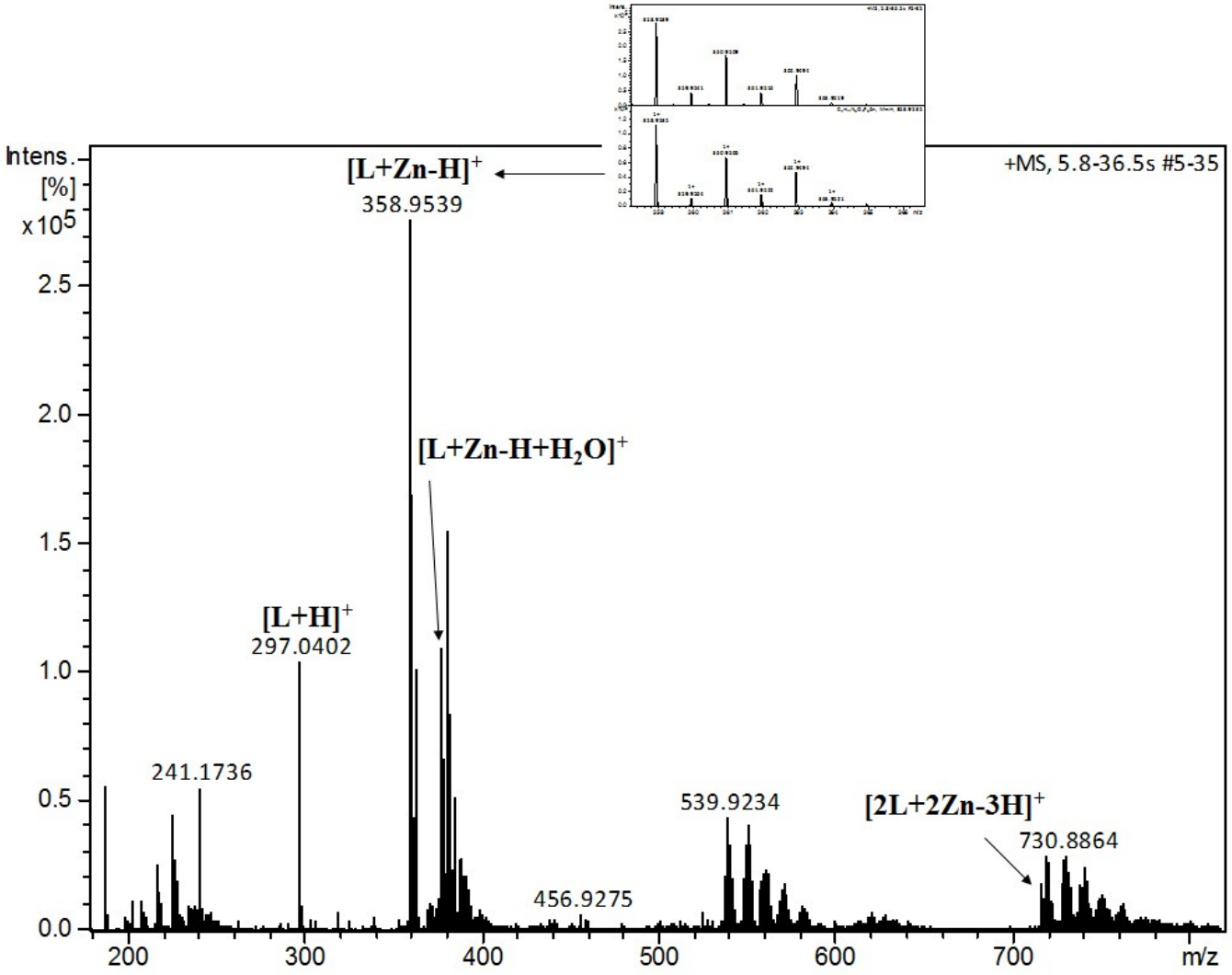


Figure S2. ESI-MS data for ligands alone

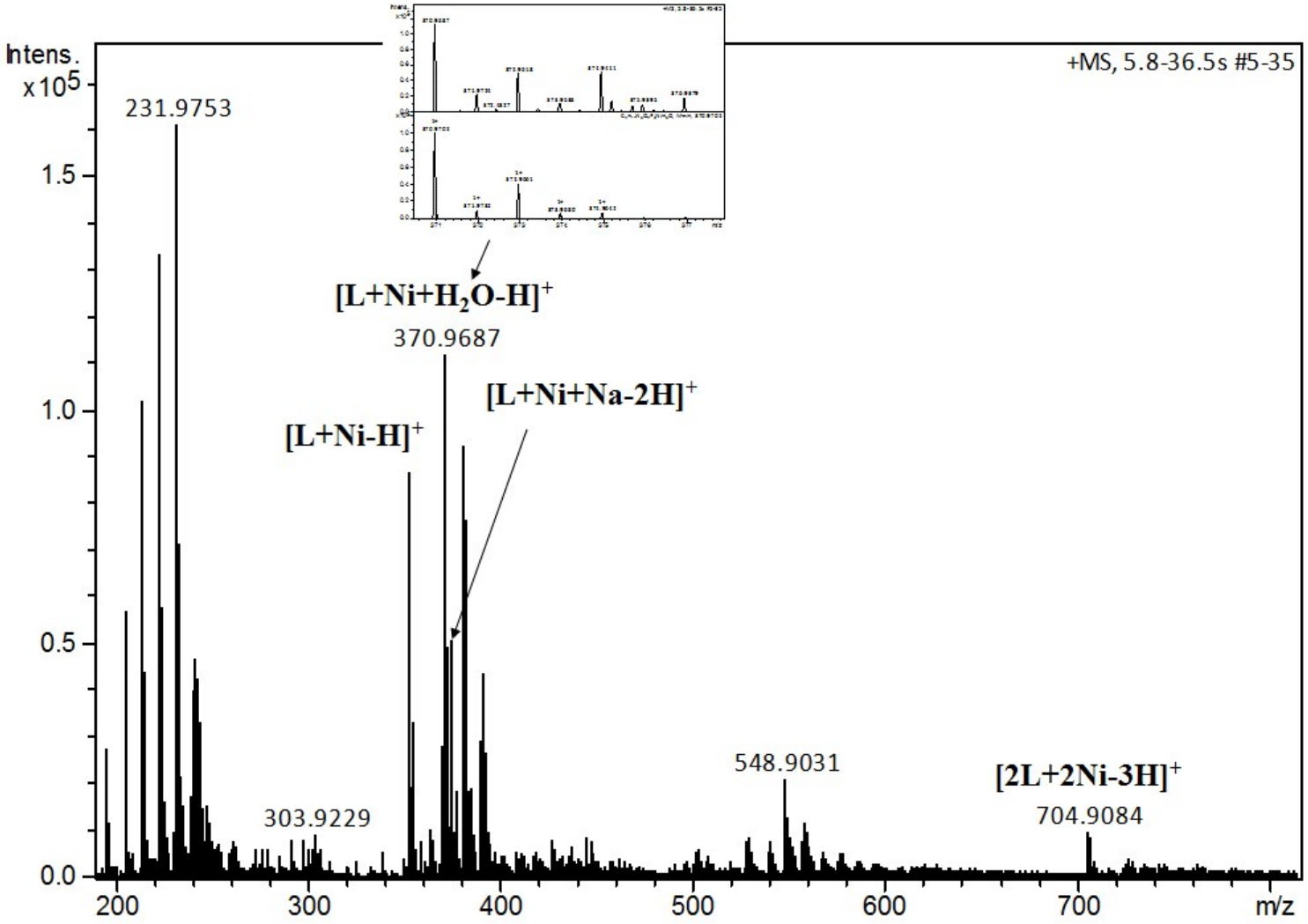
Cu^{2+}/**L**[1] (1:1)


+MS, 5.8-36.9s #5-35
[L+Cu+Na-2H]+
379.9364
[L+Cu-H]+
[L+Cu-H+H2O]+
559.4077
[2L+2Cu+Na-4H]+
738.8804
[2L+2Cu-3H]+
262.9646
[L+H]+
0
1
2
3
200
300
400
500
600
700
m/z

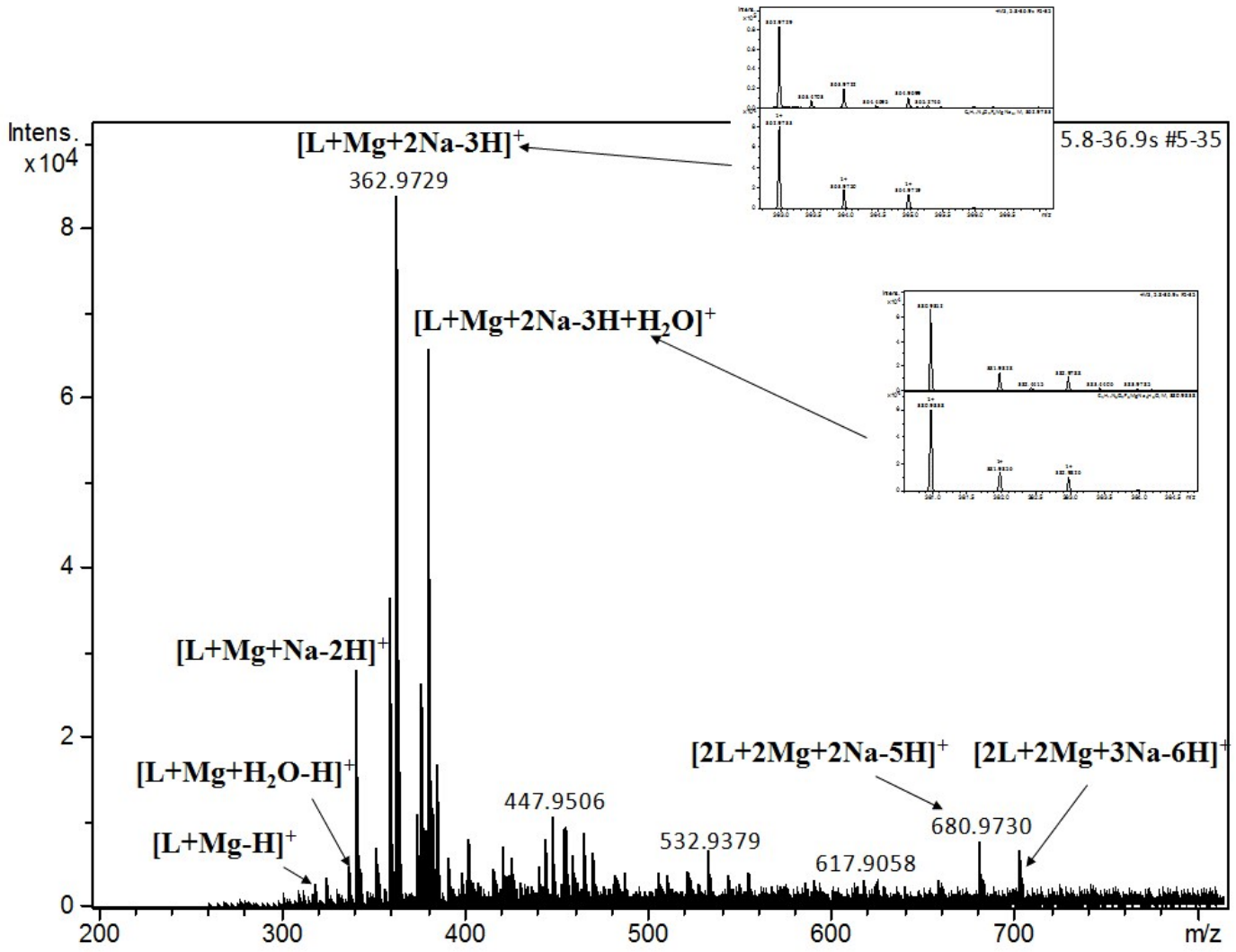
Zn^{2+}/**L**^{1} (1:1)


Intens.
[%]
x10^5
2.5
2.0
1.5
1.0
0.5
0.0
[L+Zn-H]+
358.9539
[L+Zn-H+H2O]+
[L+H]+
297.0402
241.1736
539.9234
[2L+2Zn-3H]+
730.8864
456.9275
+MS, 5.8-36.5s #5-35
200
300
400
500
600
700
m/z

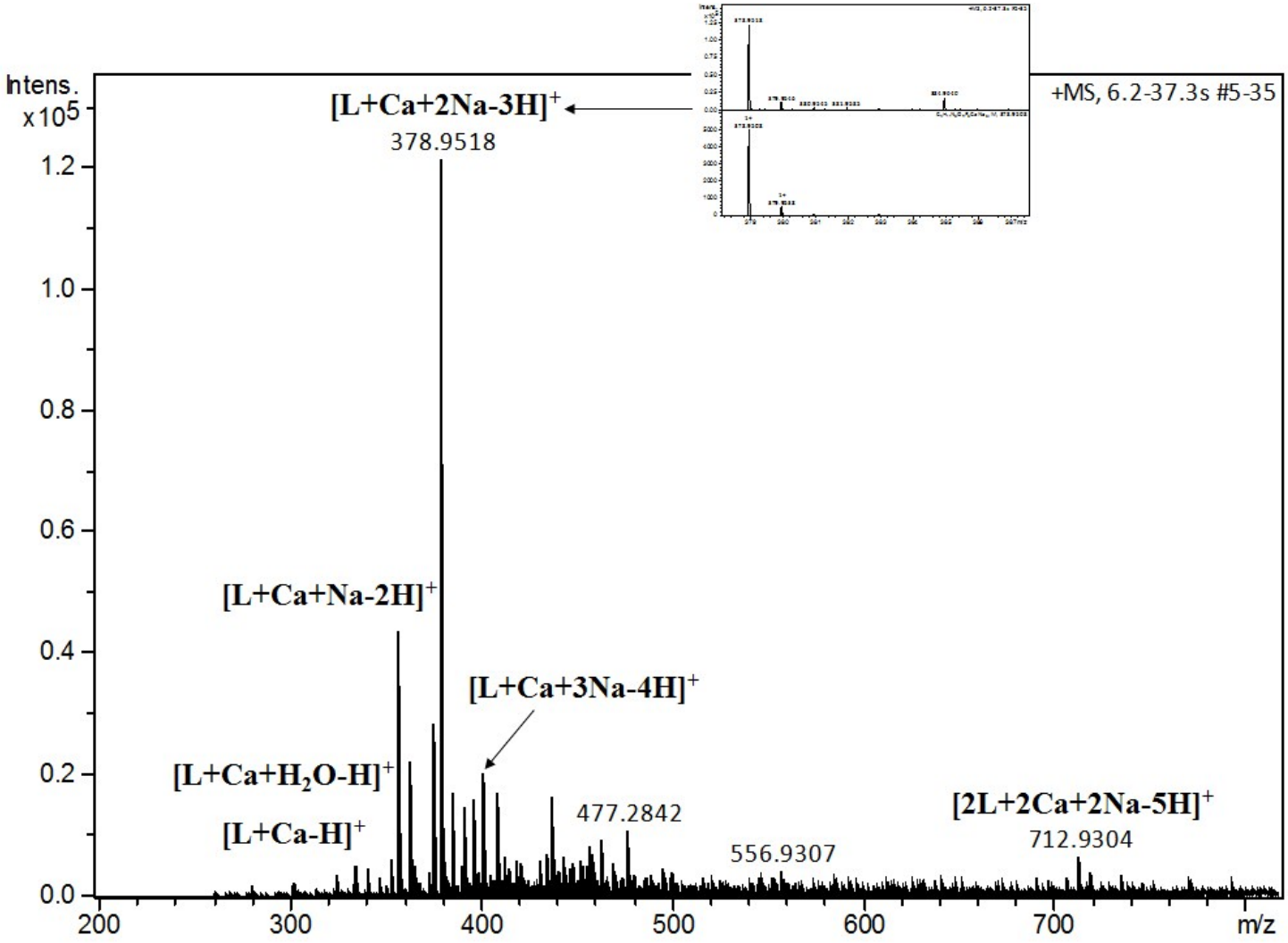
Ni^{2+}/**L**^{1} (1:1)


Intens.
x10^5
1.5
1.0
0.5
0.0
+MS, 5.8-36.5s #5-35
231.9753
[L+Ni+H2O-H]+
370.9687
[L+Ni+Na-2H]+
[L+Ni-H]+
303.9229
548.9031
[2L+2Ni-3H]+
704.9084
200
300
400
500
600
700
m/z

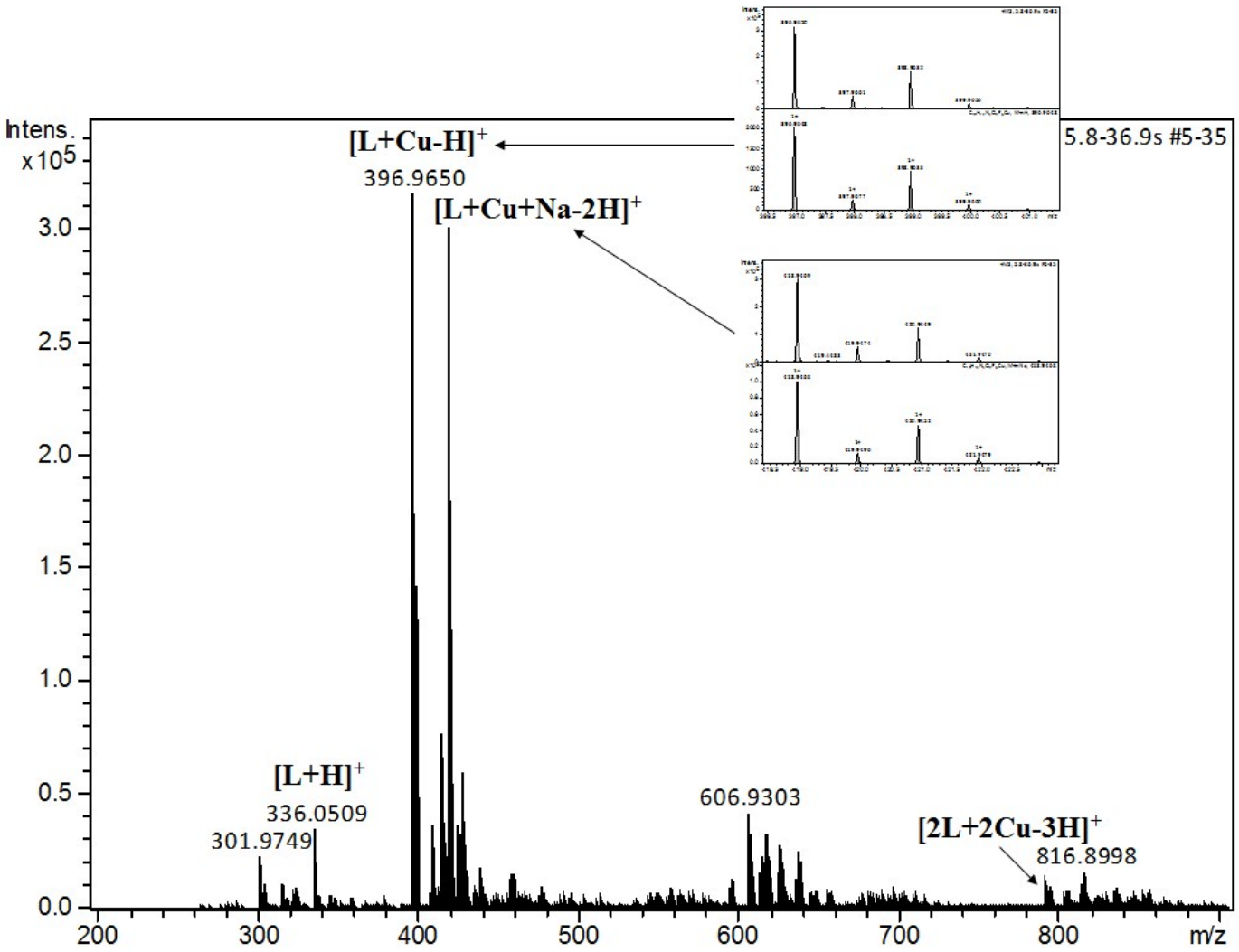
Mg^{2+}/**L**[1] (1:1)


Intens.
x10^4
8
6
4
2
0
200
300
400
500
600
700
m/z
[L+Mg+2Na-3H]+
362.9729
[L+Mg+2Na-3H+H2O]+
[L+Mg+Na-2H]+
[L+Mg+H2O-H]+
[L+Mg-H]+
447.9506
532.9379
617.9058
680.9730
[2L+2Mg+2Na-5H]+
[2L+2Mg+3Na-6H]+
5.8-36.9s #5-35

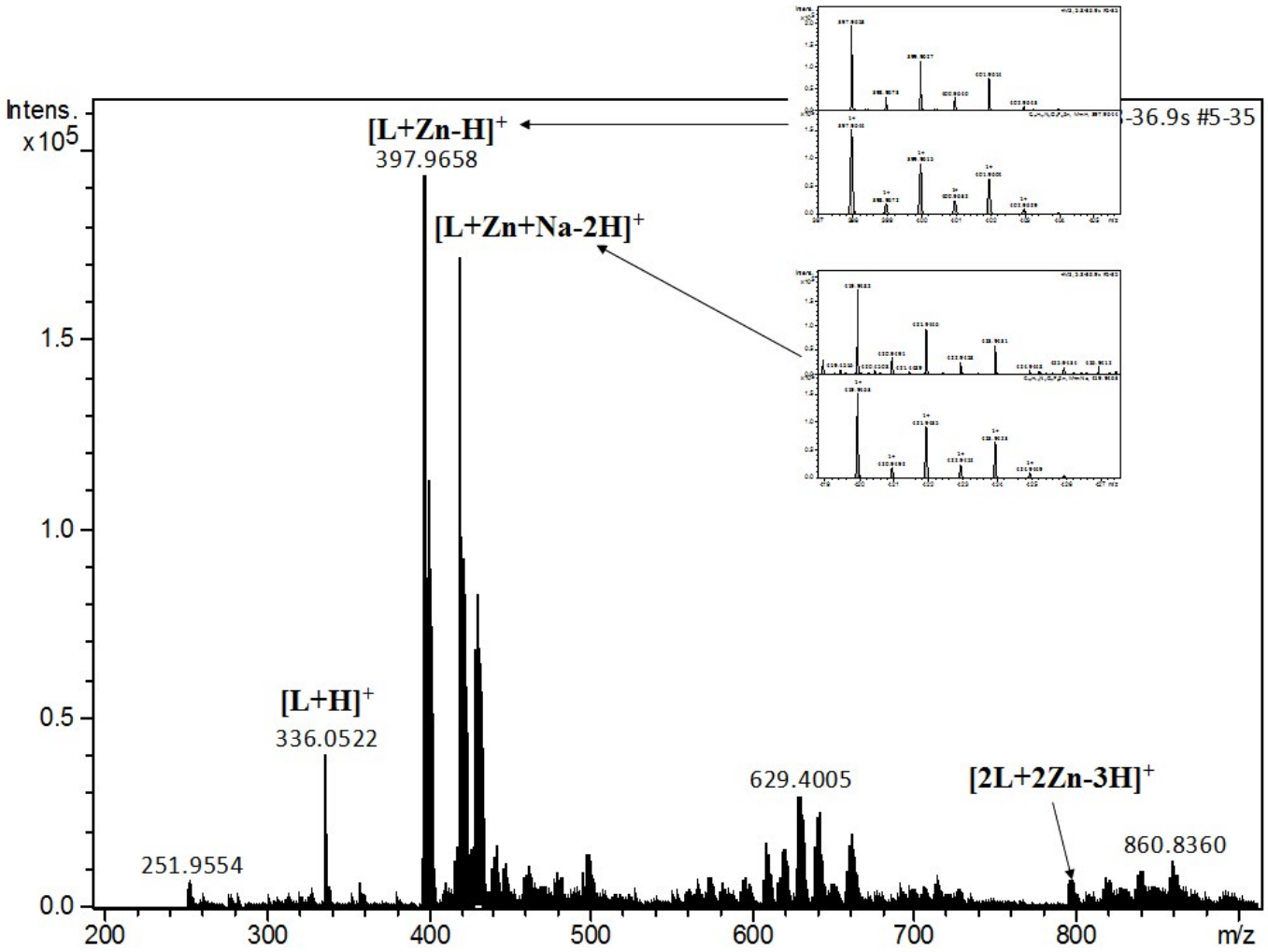
Ca^{2+}/**L**[1] (1:1)


Intens.
x10^5
1.2
1.0
0.8
0.6
0.4
0.2
0.0
200
300
400
500
600
700
m/z
+MS, 6.2-37.3s #5-35
[L+Ca+2Na-3H]+
378.9518
[L+Ca+Na-2H]+
[L+Ca+3Na-4H]+
[L+Ca+H2O-H]+
[L+Ca-H]+
477.2842
556.9307
[2L+2Ca+2Na-5H]+
712.9304

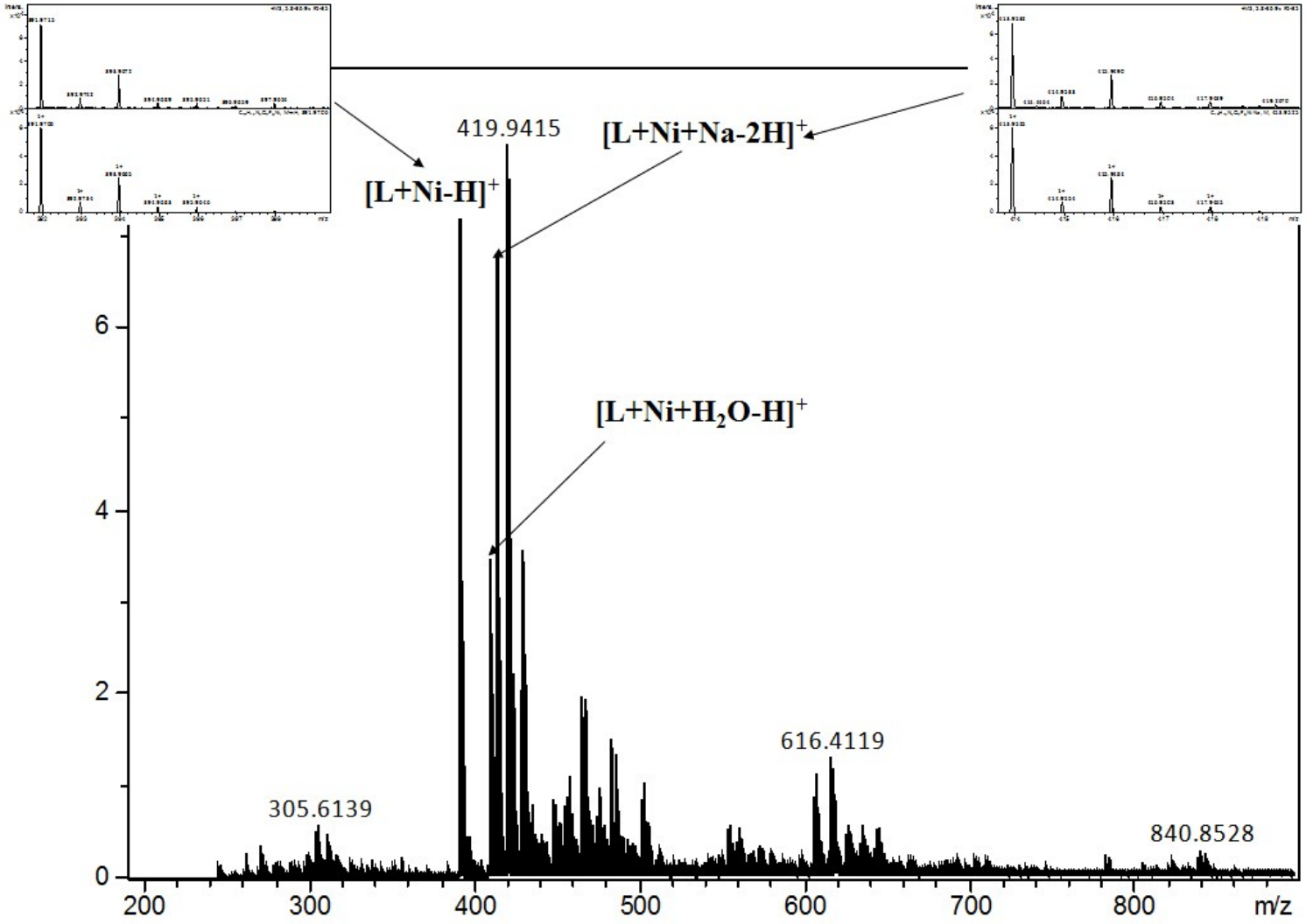
Cu^{2+}/**L²** (1:1)


Intens.
x10^5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
200
300
400
500
600
700
800
m/z
[L+Cu-H]+
396.9650
[L+Cu+Na-2H]+
5.8-36.9s #5-35
[L+H]+
336.0509
301.9749
606.9303
[2L+2Cu-3H]+
816.8998

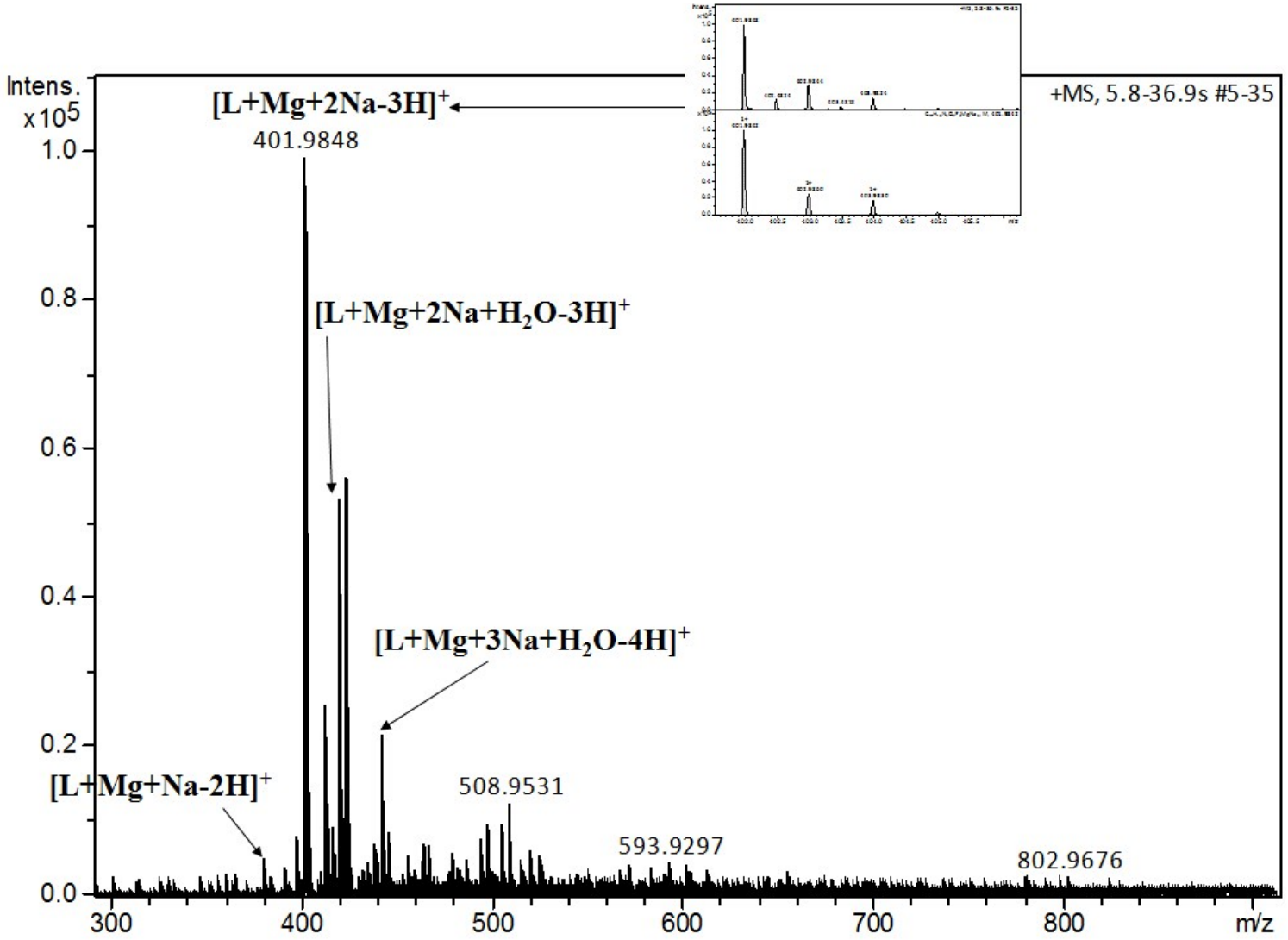
Zn^{2+}/**L²** (1:1)


Intens.
x10^5
[L+Zn-H]+
397.9658
[L+Zn+Na-2H]+
[L+H]+
336.0522
251.9554
629.4005
[2L+2Zn-3H]+
860.8360
-36.9s #5-35
0.0
0.5
1.0
1.5
200
300
400
500
600
700
800
m/z

Ni^{2+}/**L²** (1:1)


419.9415
[L+Ni+Na-2H]+
[L+Ni-H]+
[L+Ni+H2O-H]+
616.4119
305.6139
840.8528
0
2
4
6
200
300
400
500
600
700
800
m/z

Mg^{2+}/**L²** (1:1)


Intens.
x10^5
1.0
0.8
0.6
0.4
0.2
0.0
[L+Mg+2Na-3H]+
401.9848
[L+Mg+2Na+H2O-3H]+
[L+Mg+3Na+H2O-4H]+
[L+Mg+Na-2H]+
508.9531
593.9297
802.9676
+MS, 5.8-36.9s #5-35
300
400
500
600
700
800
m/z

$Ca^{2+}/\mathbf{L^2}$ (1:1)

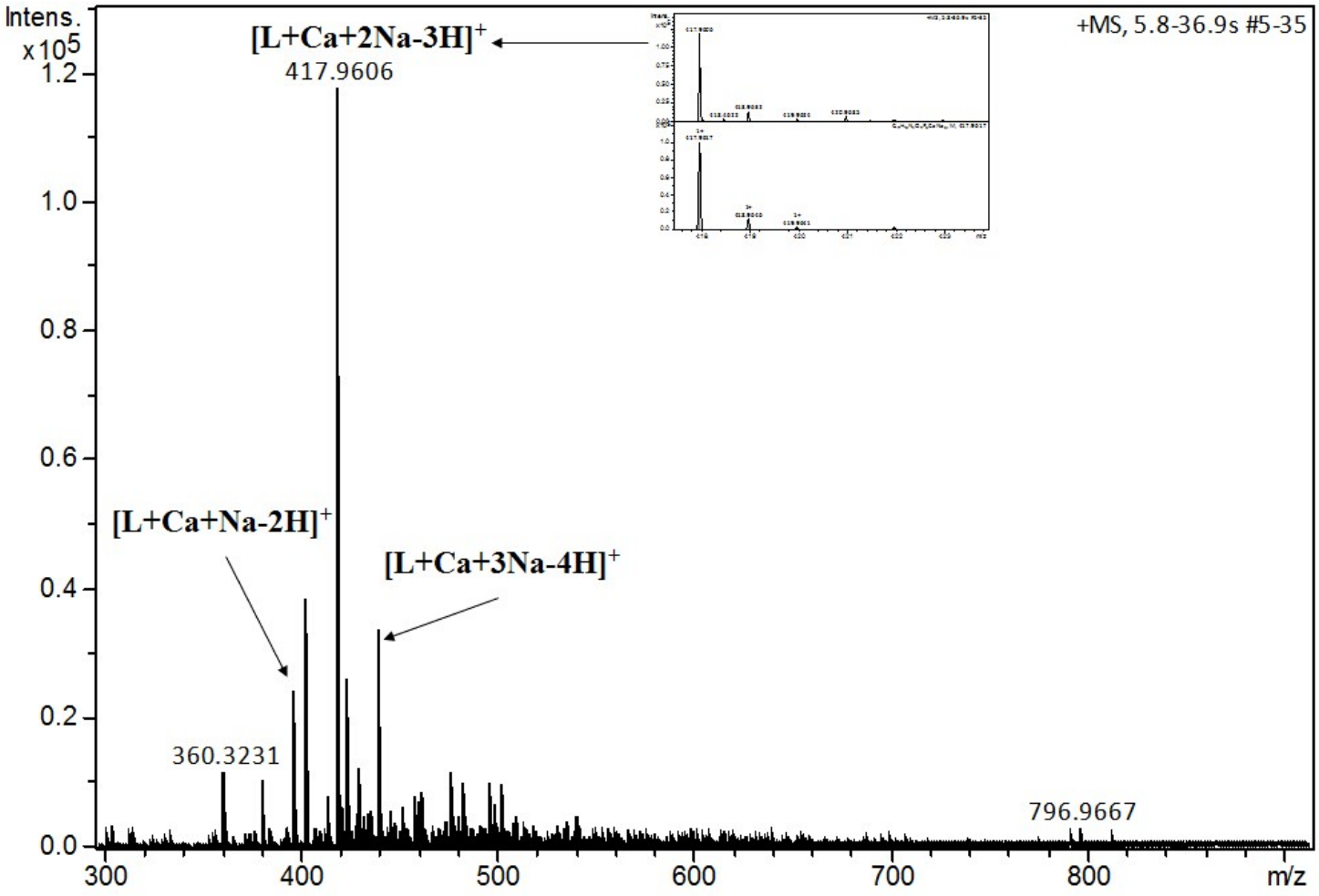


Figure S3. ESI-MS data for $M^{2+}/\mathbf{L^{1-2}}$ complexes. Enlarged pictures: experimental (higher panel) *vs* simulated (lower panel) isotopic pattern of the complexes; shown only for main species.

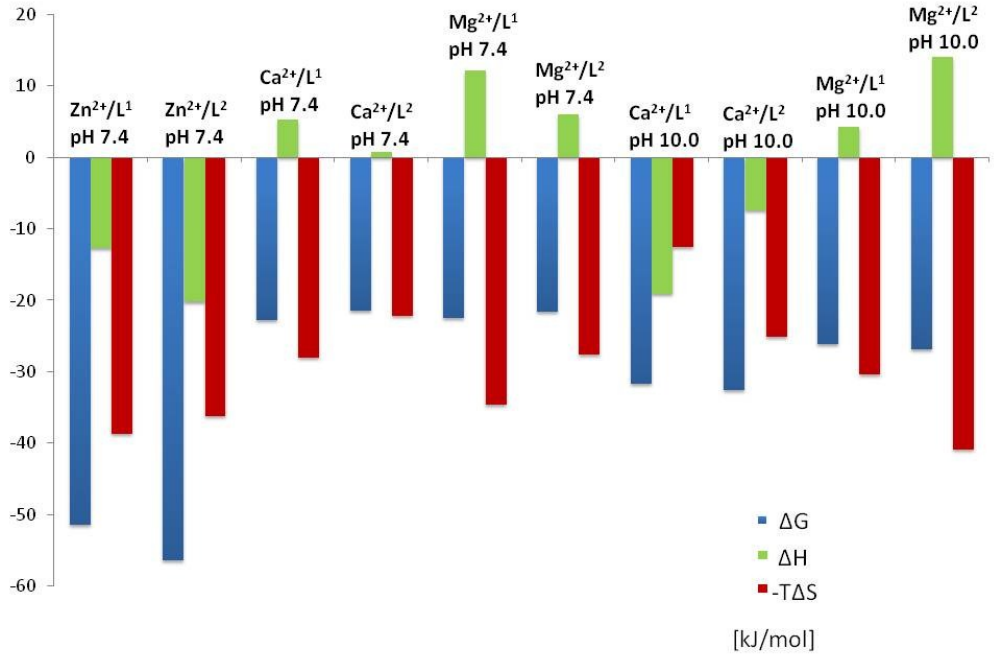
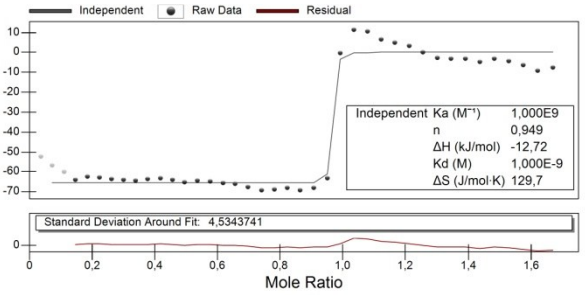
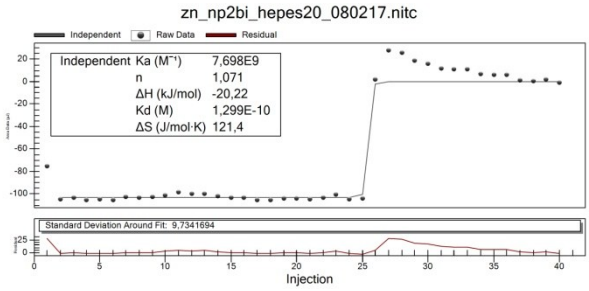


Figure S4. The contribution of particular thermodynamic forces into the binding events for studied systems.

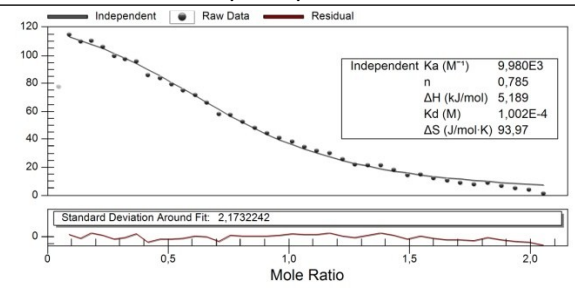
L¹/Zn²⁺ /HEPES



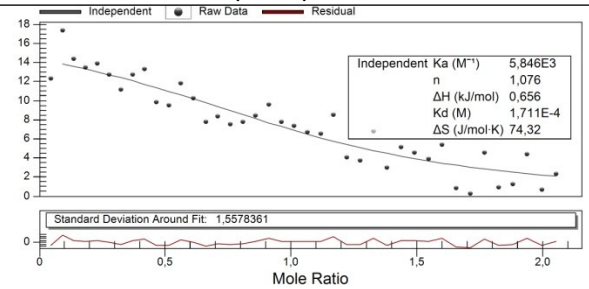
L²/Zn²⁺ /HEPES



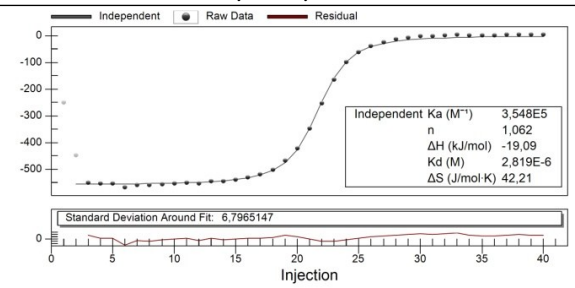
L¹/Ca²⁺ /HEPES



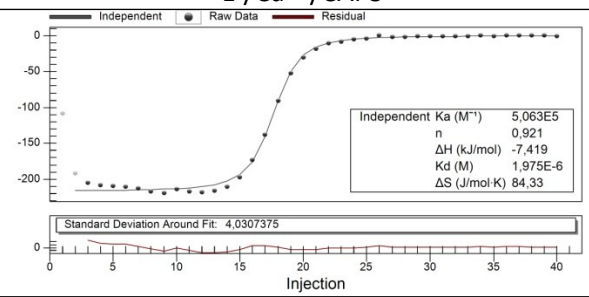
L²/Ca²⁺ /HEPES



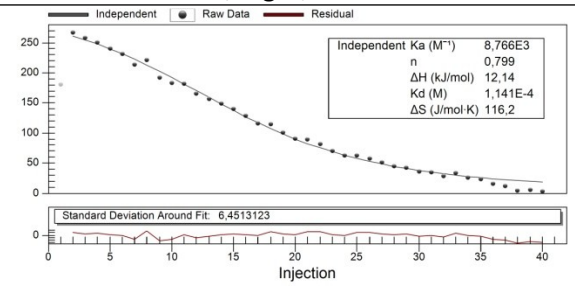
L¹/Ca²⁺ /CAPS



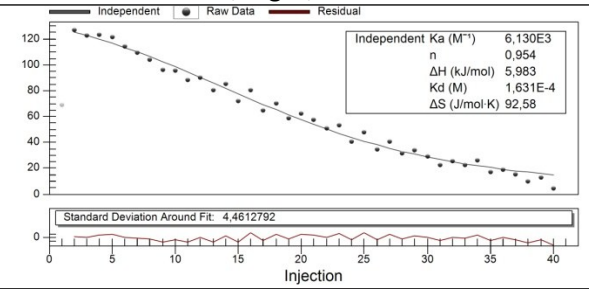
L²/Ca²⁺ /CAPS



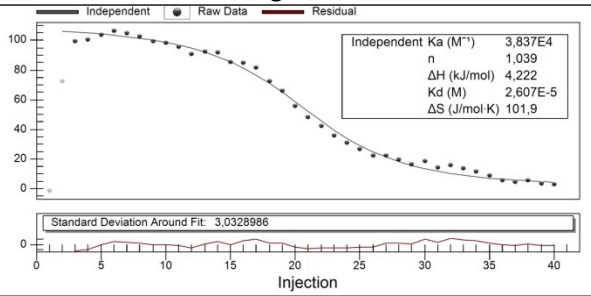
L¹/Mg²⁺ /HEPES



L²/Mg²⁺ /HEPES



L¹/Mg²⁺ /CAPS



L²/Mg²⁺ /CAPS

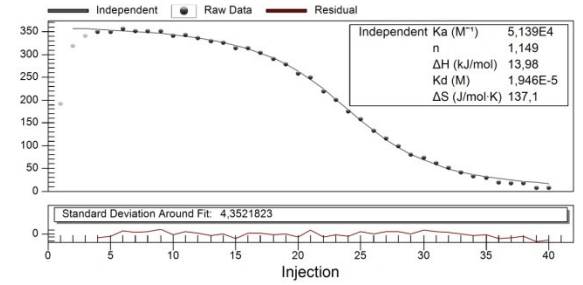


Figure S5. Standard deviation around ITC fit for studied systems.

[1] N. Saha and H. Sigel, *J. Am. Chem. Soc*., 1982, **104**, 4100.

[2] S. Kim and R. Martin, *J. Am. Chem. Soc*, 1984, **106**, 1707.

[3] W. N. Perera and G. Senanayake, *Inorg. Chem*., 2004, **43**, 3048.

[4] L. N. Trevani, J. C. Roberts and P.R. Tremaine, *J Sol. Chem,* 2001,**30**, 585.

[5] K.J. Powell, P. L. Brown, R.H. Byrne, T. Gajda, G. Hefters, S. Sjöberg, and H. Wanner, *Pure Appl. Chem*., 2007, **79**, 895, part 2

[6] Kipton J. Powell, P. L. Brown, R. H. Byrne, T. Gajda, G. Hefter, A-K. Leuz, S. Sjöberg and H.Wanner *Pure Appl. Chem*., 2013, **85**, 2249, part 5.

[7] Alkaline Earth Hydroxides in Water and Aqueous Solutions, A volume in IUPAC Solubility Data Series, Elsevier, 1992, Pages 49–111 and Pages 112–247.

[8] S. Bandyopadhyay, A. Das, G.N. Mukherjee, A. Cantoni, G. Bocelli, S. Chaudhuri and J. Ribas, *Inorg. Chim. Acta*, 2004, 357, 3563.