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Electron Impact and Electrospray Mass Spectral Study of $ZnCl_2$ Complexes with Nicotinoids

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Abstract: Mass spectrometric decomposition of $ZnCl_2$ complexes of anabasine (neonicotine), nicotine and its chalcogens (O, S, Se) was investigated by positive-ion electrospray ionization. The most abundant product ions for all complexes correspond to the protonated molecule of alkaloid. The proposed fragmentation pathways in the ESI spectra of complexes with nicotine, neonicotine (structural isomer of nicotine) and cotinine is slightly different from that proposed for complexes of thionicotine and selenonicotine. Moreover, the EI MS and ESI MS mass spectra of selenonicotine are also discussed and general fragmentation routes of its molecular ions are proposed.

Keywords: nicotine alkaloids, chalcogens, EI MS spectra, ESI MS spectra, $ZnCl_2$ complexes.

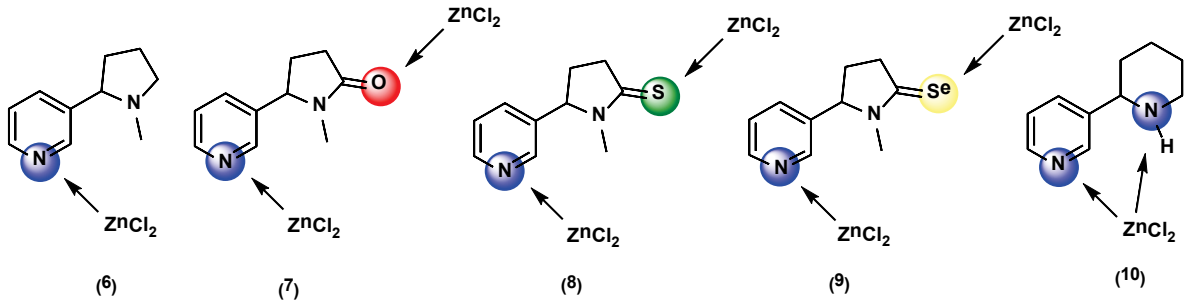
INTRODUCTION

RECENTLY, there has been a growing interest in the study of interactions of metal cations with organic and bioorganic compounds. Complexes of metal and biological compounds are at the core of numerous biological processes. It is known that some metal complexes can modulate biological activity of organic ligands.[1] Of particular importance are Zn(II) complexes because of the role this element plays in biological systems for example in the metabolism of RNA, DNA, in gene expression and in zinc fingers which helps recognize DNA base sequences during its replication.[2]

(*S*)-Nicotine (**1**), 3-[(2*S*)-1-methylpyrrolidin-2-yl]pyridine (Figure 1), the prototypical nAChR ligand, has attracted much attention because of its important pharmacological effects on central nervous system (CNS) diseases.[3–7] It is the principal pyridine alkaloid in widely used tobacco products and it is the main cause of tobacco addition. In human body, nicotine is metabolized to lactam - cotinine (**2**), which constitute a marker molecule for tobacco smoke exposure.[8] Recent studies have demonstrated that thiolactam or selenolactam analogues of bioactive compounds show important therapeutic activity, for example replacement of the lactam with thiolactam pharmacophore in thiocytisine resulted in a change in affinity at nACHR.[9] This properties have led to increased interest in their complexation characteristics with metal ions.

In view of the above, thioanalog (**3**)[10] and selenoanalog (**4**)[11] (Figure 1) of nicotine have been synthesized. The mass spectral behavior of nicotine and its oxo- and tioanalogs has been studied.[12] However, the fragmentation of new selenonicotine has not been reported. Furthermore, in the literature no work has been published on the mass spectra of Zn(II) complexes with nicotine and its derivatives. Moreover, it was interesting to investigate whether the replacement of the pyrrolidine ring (nicotine) to a piperidine ring of neonicotine (anabasine, **5**) influences the complexing properties of compounds and affect their fragmentation patterns.

In this paper we present the mass spectral study of complexes of nicotine, its chalcogens (O, S, Se) as well as anbasine with zinc chloride. Particular attention was paid to their formation in relationship with ions performed in solution. Additionally, the mass spectral behavior of new selenonicotine is also studied. Figure 1 presents $ZnCl_2$ coordination centres for complexes of nicotine, its chalcogens and anabasine.



(6) (7) (8) (9) (10)

Figure 1. $ZnCl_2$ coordination centres for complexes of nicotine (**6**), cotinine (**7**), thionicotine (**8**), selenonicotine (**9**) and anabasine (**10**).

EXPERIMENTAL

Selenonicotine was synthesized following a procedure described in [11]. $ZnCl_2$ complexes of nicotine, its chalcogens and anabasine were obtained according to literature.[13,14] Low-resolution and high-resolution mass spectra were recorded using a model 432 two-sector mass spectrometer [AMD-Intectra GmbH D-27243 Harpstedt, Germany] ionizing voltage 70 eV, accelerating voltage 8 kV, mass resolution 10 000 at 10 % valley. Samples were introduced by a direct insertion probe at a source temperature of ~150 °C. The elemental compositions of the ions were determined by peak matching method relative to perfluorokerosene. The spectra from the first field-free region were recorded using linked scans at constant *B* / *E*, with helium as collision gas at an indicated pressure of 1.75×10^{-5} Pa with an ion source temperature of 180 °C, ionizing energy of 70 eV and an accelerating voltage of 8 KV. The positive mode ESI mass spectra were recorded on a ZQ mass spectrometer (Water/Micromass) equipped with a Harvard Apparatus syringe pump. The sample solutions were prepared in methanol in a concentration 5×10^{-5} M. The samples were infused into the ESI source using a Harvard multipump at a flow rate of 40 mL min^{-1}. The ESI source potential was 3 kV on the capillary, 0.5 kV on the lens, 4 V on the extractor, and the cone voltage was 60 V. The source and desolvation temperatures were 120 and 300 °C, respectively. Nitrogen was used as neutralizing and desolvation gas at a flow rates of 100 and 30 L h^{-1}, respectively.

RESULTS AND DISCUSSION

On the basis of the low-resolution EI mass spectra, exact mass determinations (Table 1) and *B* / *E* linked scan spectra, as well as ESI mass spectra (Table 2), the principal mass spectral fragmentation routes of investigated selenonicotine (**4**) are explained as shown in Schemes 1 and 2, respectively. In the EI MS spectrum of **4**, the peak of molecular ion **a** was observed at *m* / *z* 240 (100 %). The main features of the EI mass spectrum fragmentation of the molecular ion **a** of selenonicotine are the cleavages of C7-N8, C9-C10, C10-C11 and C7-11 bonds of the pyrrolidine ring (Scheme 1). The even-electron fragment ion **b** resulted from the loss of H• radical from the molecular ion. Similar ion was formed in electron impact mass fragmentation of nicotine,[12] and the presence of selenium atom did not affect the location of the positive charge on the quaternary nitrogen atom. The opening of the *N*-methylpyrrolidine ring and $OE^{+\bullet}$ ion formation followed by rearrangement causing the formation of the bicyclic ion **c** (see Supplementary Information). This even-electron ion corresponds to the loss of the ethylene molecule and the H• radical from molecular ion **a**. The even-electron ions **d** and **e** are the ions formed directly from the molecular ion of **4** by the abstraction of the •SeH and H–C•=Se radicals, respectively. Furthermore, in the EI spectrum of selenonicotine, three other characteristic peaks appear at *m* / *z* 118, 106, and 92. They can be assigned to the EE^{+} fragment ions **f**, **g**, and **h**, respectively. Elimination of selenoformaldehyde and simple inductive cleavage of $C(7)sp^3$–$C(3)sp^2$ from molecular ion of **4** gave even-electron ion **i**.

Table 1. The relative abundances of characteristic ions in the EI spectra of **4**.

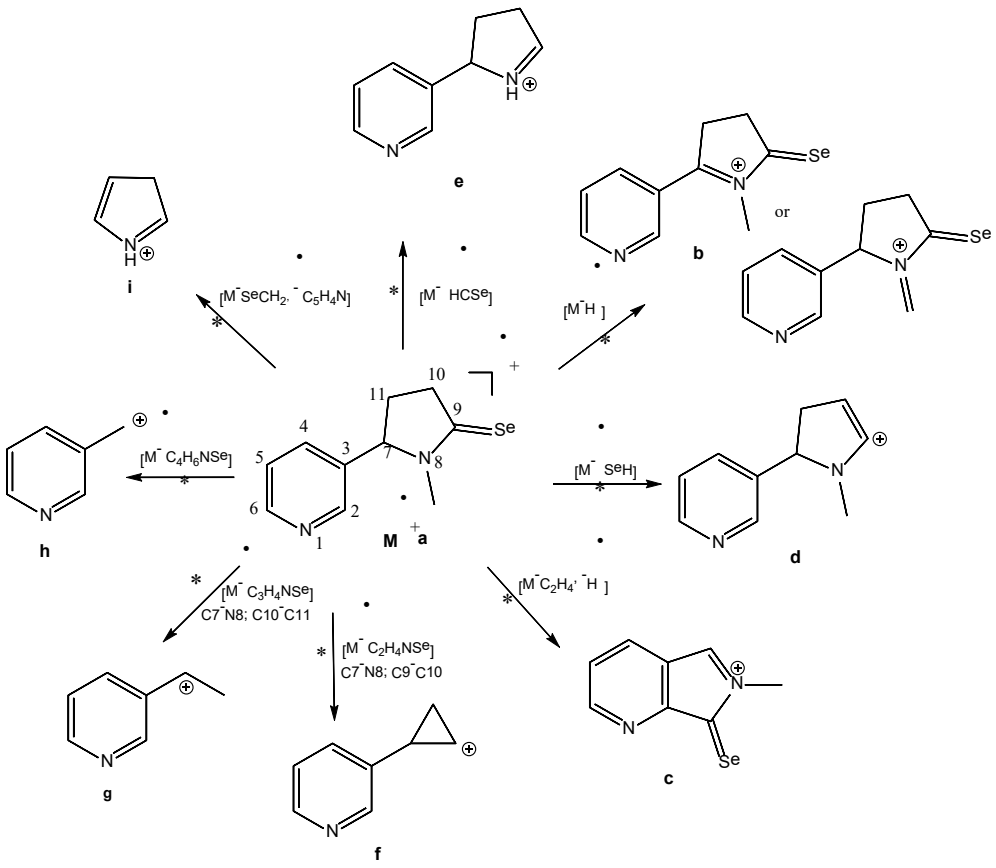
Ion	Elemental composition	*m* / *z*	Relative abundances [RA %]
a	$C_{10}H_{12}N_2Se$	240	100
b	$C_{10}H_{11}N_2Se$	239	49
c	$C_8H_7N_2Se$	211	25
d	$C_{10}H_{11}N_2$	159	18
e	$C_9H_{11}N_2$	147	10
f	C_8H_8N	118	28
g	C_7H_8N	106	48
h	C_6H_6N	92	13
i	C_4H_6N	68	18

Selenonicotine, under ESI MS conditions, gave a pro tonated ion $[M+H]^+$ at *m* / *z* 241. The major product ions were ions **b** and **d**. The ion **b** $[C_5H_7NSe+K]$ at *m* / *z* 199 was formed as a result of the elimination of C_5H_6N neutral molecule and next addition of potassium cation, whereas the ion **d** at *m* / *z* 177 was formed as a result of the elimination of C_4H_9N molecule and next addition of lithium cation. Furthermore, in the ESI-MS spectrum of **4** the ion **c** at *m* / *z* 193 and a less abundant ion **e** at *m* / *z* 169 are present (Scheme 2).

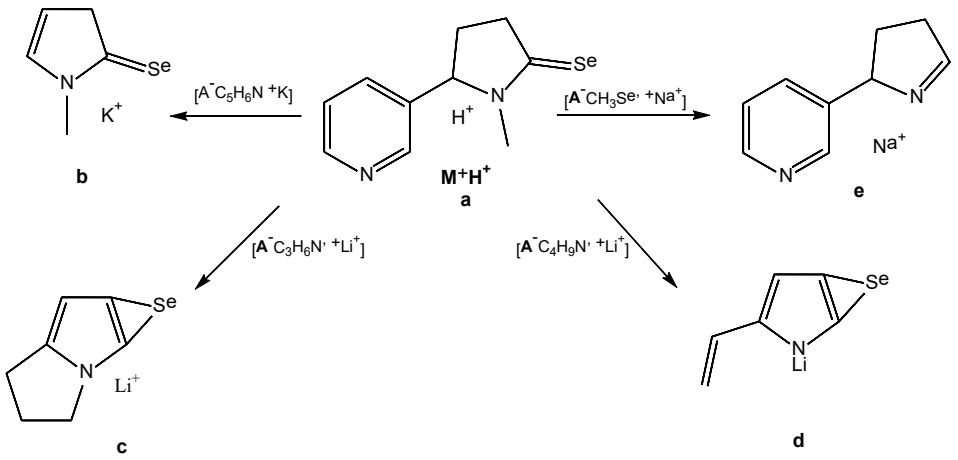
Table 2. The relative abundances of characteristic ions in the positive mode ESI spectra of **4**.

Ion	Elemental composition	*m* / *z*	Relative abundances [RA %]
a	$C_{10}H_{13}N_2Se$	241	5
b	C_5H_7NSeK	199	95
c	C_7H_7NSeLi	192	35
d	C_6H_4NSeLi	177	100
e	$C_9H_{10}N_2Na$	169	15

Comparison of known structures of nicotine complexes reveals that **1** acts mainly as a monodentate ligand utilizing for this purpose the pyridine nitrogen atom. In the $ZnCl_2$/Nicotine system the $ZnCl_3^-/^+$H-Nicotine type complex is formed in 1 : 1 metal:ligand ratio.[13] Spectroscopic and X-ray diffraction data showed that cotinine and its thio- and selenoanalogs with $ZnCl_2$ can acts as a bridging bidentate ligand through both pyridine nitrogen and chalcogen (O, S, Se) atoms.[13] Although anabasine is a structural isomer of nicotine, in contrast to nicotine, can complexing by both pyridine and piperidine nitrogen atom.[14] The dominant fragmentation pathways of $ZnCl_2$ complexes of nicotine (**6**), cotinine (**7**), thionicotine (**8**), selenonicotine (**9**) and anabasine (**10**) were investigated in the positive ESI mode. The ESI MS data are collected in Table 3. The proposed fragmentation pathways are given in Supplementary Information. The most abundant product ions for all complexes correspond to the protonated molecule of alkaloid. The next most abundant ions were those attributed to $[Zn(C_{10}H_{14}N_2)_2Cl]^+$ (*m* / *z* 423), $[Zn(C_{10}H_{11}N_2O)]^+$ (*m* / *z* 239), $[Zn(C_{10}H_{12}N_2S)_2Cl]^+$ (*m* / *z* 483), $[Zn(C_{10}H_{11}N_2Se)]^+$ (*m* / *z* 303) and $[(C_{10}H_{14}N_2)_2\text{-}H]^+$ (*m* / *z* 325) for complexes **6**–**10**, respectively.



Scheme 1. The proposed fragmentation pathways in the EI spectrum of selenonicotine (**4**).



Scheme 2. The proposed fragmentation pathways in the ESI spectrum of selenonicotine (**4**).

In the molecular ions of complex **6** $[Zn(C_{10}H_{14}N_2)_3Cl_2\text{-}H]^+$, **7** $[Zn(C_{10}H_{12}N_2O)_3Cl]^+$ and **10** $[Zn(C_{10}H_{14}N_2)_3Cl_2\text{-}H]^+$, zinc cations were complexed by three ligands of alkaloid and two or one chloride anion. Ions **a** for **6** and **7** after elimination of H^+ and chloride anion led to ions **b** $[Zn(C_{10}H_{14}N_2)_3Cl]^+$ at *m* / *z* 586 and $[Zn(C_{30}H_{35}N_6O_3)]^+$ at *m* / *z* 591, respectively. Ions **c** $[Zn(C_{10}H_{14}N_2)_2Cl_2\text{-}H]^+$, $[Zn(C_{10}H_{12}N_2O)_2Cl]^+$ and $[Zn(C_{10}H_{14}N_2)_2Cl_2\text{-}H]^+$ are formed from ions **a** after the elimination of alkaloid molecule nicotine, cotinine or anabasine, respectively.

The key fragments detected for **6** were *m* / *z* 423 $[Zn(C_{10}H_{14}N_2)_2Cl]^+$ (ion **d**), 387 $[Zn(C_{20}H_{27}N_4)]^+$ (ion **e**) and 325 $[(C_{10}H_{14}N_2)_2\text{-}H]^+$ (ion **f**) (Table 2). The peak at 423 resulted from the loss of Cl^- anion and proton from the ion **c**. Further elimination of another H^+ and Cl^- anion leads to ion **e**, which gave ion **f**.

Ion **c** of complex **7** after elimination of $ZnCl^+$ ion and addition of proton gave ion **f** $[(C_{10}H_{14}N_2)_2\text{-}H]^+$, which form ion **g** $[(C_{10}H_{14}N_2)\text{-}H]^+$ due to loss of cotinie molecule.

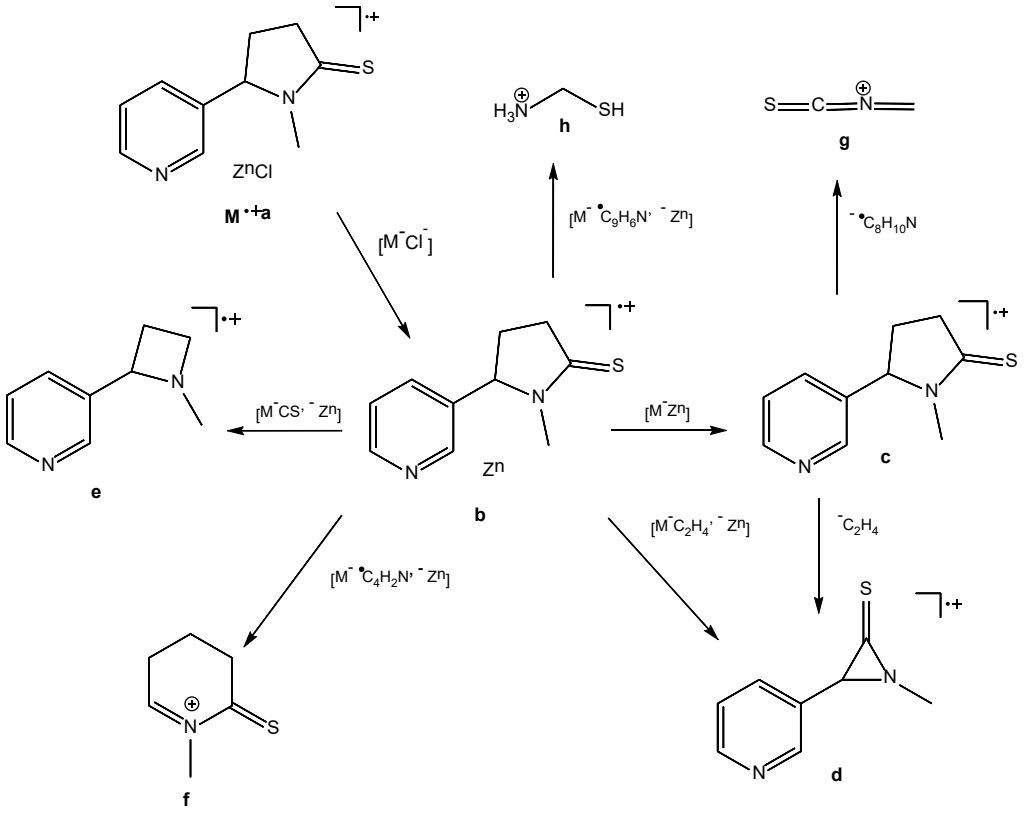
On the other hand for complex **7** ion **k** $[Zn(C_{10}H_{14}N_2)Cl]^+$ at *m* / *z* 275 is created by elimination of two molecules of cotinine from ion **a**. Further elimination of Cl^- anion and proton gave ion **l** $[Zn(C_{10}H_{11}N_2O)]^+$ at *m* / *z* 239.

Ion **c** of complex **10** after elimination of $ZnCl^+$ and addition of proton led to the ion **h** $[H_2(C_{10}H_{14}N_2)_2Cl]^+$ at *m* / *z* 361. Further loss of proton and Cl^- anion gave ion **f** which after elimination of anabasine molecule is converted in ion **g** correspond to the protonated molecule of alkaloid.

It is known that, in contrast to nicotine, anabasine readily forms zinc complexes in alkaline solution.[14] In the ESI MS spectrum of **10** we can see key fragments consist of molecule of anabasine and hydroxide ions at *m* / *z* 423 $[Zn(C_{10}H_{14}N_2)_2(OH)_2\text{-}H]^+$, *m* / *z* 261 $[Zn(C_{10}H_{14}N_2)(OH)_2\text{-}H]^+$ and *m* / *z* 243 $[Zn(C_{10}H_{14}N_2)(OH)]^+$.

Table 3. The relative abundances of characteristic ions in the positive mode ESI spectra of complexes **6**–**10**.

Ion	Elemental composition	*m* / *z*	Relative abundances [RA %]				
			6	**7**	**8**	**9**	**10**
a	$C_{30}H_{43}N_6Cl_2Zn^+$	623	22	–	–	–	20
	$C_{30}H_{36}N_6O_3ClZn^+$	627	–	10	–	–	–
	$C_{20}H_{24}N_4S_2ClZn^+$	483	–	–	40	–	–
	$C_{20}H_{24}N_4Se_2ClZn^+$	579	–	–	–	45	–
b	$C_{30}H_{43}N_6ClZn^+$	586	60	–	–	–	–
	$C_{30}H_{35}N_6O_3Zn^+$	591	–	15	–	–	–
	$C_{10}H_{13}N_2SCl_2Zn^+$	329	–	–	22	–	–
	$C_{10}H_{13}N_2SeCl_2Zn^+$	377	–	–	–	78	–
c	$C_{20}H_{29}N_4Cl_2Zn^+$	461	70	–	–	–	18
	$C_{20}H_{24}N_4O_2ClZn^+$	451	–	50	–	–	–
	$C_{10}H_{12}N_2SClZn^+$	291	–	–	18	–	–
	$C_{10}H_{12}N_2SeClZn^+$	339	–	–	–	52	–
d	$C_{20}H_{28}N_4ClZn^+$	423	90	–	–	–	–
	$C_{10}H_{11}N_2SeZn^+$	303	–	–	–	95	–
e	$C_{20}H_{27}N_4Zn^+$	387	15	–	–	–	–
	$C_{10}H_{13}N_2S^+$	193	–	–	–	100	–
	$C_{10}H_{13}N_2Se^+$	241	–	–	100	–	–
f	$C_{20}H_{29}N_4^+$	325	35	–	–	–	25
	$C_{20}H_{25}N_4O_2^+$	353	–	18	–	–	–
g	$C_{10}H_{15}N_2^+$	163	100	–	–	–	100
	$C_{10}H_{13}N_2O^+$	177	–	100	–	–	–
h	$C_{20}H_{30}N_4Cl^+$	361	–	–	–	–	10
k	$C_{10}H_{12}N_2OClZn^+$	275	–	63	–	–	22
l	$C_{10}H_{11}N_2OZn^+$	239	–	85	–	–	15



Scheme 3. The proposed fragmentation pathways in the EI spectrum of thionicotine complex of $ZnCl_2$.

In the molecular ion of complex **8** $[Zn(C_{10}H_{12}N_2S)_2Cl^+]$ zinc cation is coordinated by two alkaloid ligands and one chloride anion. Ion **b** is created by elimination of thionicotine ligand and addition of H^+ and Cl^- ions. Furthermore, elimination of Cl^- and H^+ from ion **b** led to the ion **c** $[Zn(C_{10}H_{12}N_2S)Cl]^+$ at *m* / *z* 291. Further loss of $ZnCl^+$ and addition of proton gave ion **e** correspond to the protonated molecule of alkaloid. A similar fragmentation pathway was observed for complex **9** with one exception. Ion **c** after the loss of proton and the Cl^- anion gave ion **d** $[Zn(C_{10}H_{11}N_2Se)]^+$ (*m*/*z* 303), which is further converted in ion **e** $[(C_{10}H_{12}N_2Se)\text{-}H]^+$.

Table 4. The relative abundances of characteristic ions in the EI spectra of complex **7**.

Ion	Elemental composition	*m* / *z*	Relative abundances [RA %]
a	$C_{10}H_{12}N_2S$+ZnCl	291	25
b	$C_{10}H_{12}N_2S$+Zn	256	100
c	$C_{10}H_{12}N_2S$	192	15
d	$C_8H_8N_2S$	164	20
e	$C_9H_{12}N_2$	148	26
f	$C_6H_{10}NS$	128	20
g	C_2H_2NS	72	10
h	CH_6NS	64	25

Moreover, the fragmentation of complex **8** can be analysis also by EI MS spectrometry. In its EI mass spectrum we can see the molecular ion **a** formed from the thionicotine as a ligand and a coordinated $ZnCl^+$ ion ($C_{10}H_{12}N_2S$+ZnCl) at *m*/*z* 291 (25 %) as well as the ion **b** formed from the alkaloid molecule and coordinated zinc cation at *m*/*z* 256 (100 %) (Table 4, Scheme 3). The odd-electron ion **c** was formed from the odd-electron ion **b** by the abstraction of the zinc atom. The odd-electron ion **d** and even-electron ion **g** were formed from the odd-electron ion **c** by the abstraction of the ethylene molecule and $^{\bullet}C_8H_{10}N$ radical, respectively. The $OE^{+\bullet}$ ion **d** may also arise from ion **b** by elimination ethylene molecule and zinc. In turn elimination neutral molecule C=S and zinc from ion **b** led to the even-electron fragment ion **e**. It should be pointed out that the formation of fragment ion **f** in the processes of mass decomposition of ion **b** was mainly determined by the rearrangement of *N*-methylpyrrolidine ring and elimination of $^{\bullet}C_4H_2N$ radical and zinc. In the EI mass spectra of **8**, the even-electron ion **h** (H_3N^+–CH_2–SH,

m/*z* 64, 25%) was formed from ion **b** by elimination of zinc and $^{\bullet}C_9H_6N$ radical.

To conclude, our results demonstrate that electrospray ionization is an efficient method for study of $ZnCl_2$ complexes of anabasine, nicotine and its chalcogens in solution. The most abundant product ions for all complexes correspond to the protonated molecule of alkaloid.

The change of the pyrrolidine ring to a piperidine ring generally does not influence on the fragmentation route. Because anabasine readily forms zinc complexes in alkaline solution, in its ESI MS spectrum key fragments consist of molecule of alkaloid and hydroxide ions can be seen. Moreover, we found that thionicotine complex with $ZnCl_2$ showed fragmentation in the EI mass spectra.

Supplementary Information. Supporting information to the paper is attached to the electronic version of the article at: http://doi.org/10.5562/cca3244.

REFERENCES

[1] F. M. Alberti, J. J. Fiol, A. Garcia-Raso, M. T. Torres, A. Terron, M. Barcelo-Oliver, M. J. Prieto, V. Moreno, E. Molins, *Polyhedron* **2010**, *29*, 34.

[2] N. N. Greenwood, A. Earnshaw, *Chemistry of the Elements*, 2nd edition, Oxford: Butterworth-Heinemann, Oxford, **1997**.

[3] E. D. Levin, W. Wilson, J. E. Rose, J. McEvoy, *J. Neuropsychopharmacol*. **1996,** *15*, 429.

[4] P. A. Newhouse, M. Kelton, *Pharm. Acta Helv*. **2000**, *74*, 91.

[5] G. K. Lloyd, M. Williams, *J. Pharmacol. Exp. Ther*. **2000**, *292*, 461.

[6] M. I. Debay, W. Glassco, M. Dukat, E. L. May, R. A. Glennon, B. R. Martin, *Drug Dev. Res.* **1996**, *38,* 177.

[7] B. Latli, K. D'Amour, J. E. Casida, *J. Med. Chem.* **1999**, *42*, 2227.

[8] S. E. Murphy, L. M. Johnson, D. A. Pullo, *Chem. Res. Toxicol.* **1999**, *12*, 639.

[9] P. Imming, P. Klaperski, M. T. Stubbs, G. Seitz, D. Gundish, *Eur. J. Med. Chem.* **2001**, *36*, 375.

[10] M. Wojciechowska-Nowak, W. Boczoń, B. Warżajtis, U. Rychlewska, B. Jasiewicz, *J. Mol. Struct.* **2011,** *989*, 51.

[11] B. Jasiewicz, K. Malczewska-Jaskóła, I. Kowalczyk, B. Warżajtis, U. Rychlewska, *Spectrochim. Acta* A **2014**, *128*, 773.

[12] B. Jasiewicz, M. Wojciechowska-Nowak, W. Boczoń, E. Wyrzykiewicz, *Eur. J. Mass Spectrom*. **2011**, *17*, 227.

[13] K. Malczewska-Jaskóła, W. Jankowski, B. Warżajtis, B. Jasiewicz, M. Hoffmann, U. Rychlewska, *Polyhedron* **2015**, *100*, 404.

[14] R. Bregier-Jarzębowska, K. Malczewska-Jaskóła, W. Jankowski, B. Jasiewicz, M. Hoffmann, A. Gąsowska, R. Jastrząb, *Polyhedron* **2015**, *85*, 841.