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INVESTIGATION OF ALKALOID N-OXIDES BY SECONDARY-ION MASS SPECTROMETRY

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An advantage of the SIMS method for investigating alkaloid N-oxides has been shown. In the case of N-oxides of steroid, diterpene, tropane, and pyrrolizidine alkaloids, fragments including the oxygen of the N-oxide group are revealed. The protonation of N-oxide molecules in a glycerol matrix takes place mainly through the negatively polarized oxygen atom of the N-oxide function. On fragmentation, the MH^+ ions of N-oxides of monoester tropane and pyrrolizidine alkaloids tend to form fragmentary ions of the protonated forms of the aminoalcohols (A^+). The energies of the metastable transitions $MH^+ \rightarrow A^+$ have been calculated for the N-oxides of the pyrrolizidine alkaloids viridiflorine, trachelanthamine, and echinatine.

In the majority of cases, the N-oxide forms of alkaloids are isolated from plant material in parallel with the bases, which can also be obtained easily from the initial alkaloids [1]. One of the N-oxides of a synthetic base of the benzodiazepine series — élenium — is used in medical practice as a tranquilizer [2]. From the chemical point of view, a N-oxide bond can be assigned to the donor–acceptor type in which the unshared pairs of electrons of the nitrogen and oxygen atoms participate [3].

There are a number of reports of the chemical stability of the N-oxide group and of its participation in the synthesis of organic compounds. The fragmentation of the N-oxides of individual groups of bases under the conditions of electron-impact (EI) mass spectrometry has been considered in [5-7]. We may note that, in the EI regime, N-oxides of pyridine and quinoline derivatives show intense peaks of the molecular ions [5], while for N-oxides with N-alkyl chains the intensities of the peaks of the $M^{+\cdot}$ ions are appreciably less [8]. Up to the present, there has been no literature information on the behavior of N-oxide molecules in the regime of secondary-ion mass spectrometry (SIMS).

The existence of a collection of N-oxides in the alkaloid chemistry laboratory of IKhRV AN RUz, including alkaloids of various groups, has created the prerequisites for the study of these compounds under SIMS conditions. The aim of the present investigation was, in the first place, to evaluate the stabilities of the protonated molecular ions; in the second place, to determine the degree of participation of the oxygen of the N-oxide group in fragmentation; and, in the third place, to consider the process of fragmentation of the protonated forms of the molecular ion, MH^+.

Among steroid alkaloids we have analyzed the N-oxides of imperialine (1) and sevedine (2) [1], belonging to the cevane series. In the SIMS regime, the peaks of the MH^+ ions of (1) and (2) had the maximum intensity, and, together with them, we detected ions resulting from a clusterization process (Table 1). So far as concerns the fragmentation of the MH^+ ions, it may be mentioned that bombardment with high-energy cesium ions Cs^+ of the liquid matrix led to the transfer to the molecules of the substance under investigation of sufficient energy for the formation of a series of primary fragmentary ions. Since the MH^+ ions possess an even-electron nature, it is possible to detect in the SIMS spectrum fragments corresponding to the ejection of neutral particles. In this case, the triplet of peaks of the $(M-16)^+$, $(M-17)^+$, and $(M-18)^+$ ions that is characteristic for EI is converted into a doublet consisting of the peaks of the $(MH-16)^+$ and $(MH-18)^+$ ions, although the peak of the ion corresponding to the ejection of the atom of oxygen of the N-oxide group does not possess a high intensity. In the metastable defocusing (MD) spectrum of the $(MH-16)^+$ ion of substance (2) the $MH^+ \rightarrow (MH-16)^+$ transition is recorded in the form of a low-intensity peak.

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TABLE 1. Main Ions of Alkaloid N-Oxides in the SIMS Regime (*m/z*, I, %)

Compound	Forms of the molecular ions detected				MH^+	$(MH-16)^+$	$(MH-18)^+$	Characteristic fragmentary ions
	$(2M+Na)^+$	$(2M+H)^+$	$(MH+GL)^+$	$(M+Na)^+$				
1	-	891(1)	538(1)	-	446(100)	430(10)	428(30)	128(22), 124(30), 114(50), 112(44) 111(30), 98(70)
2	-	895(2)	-	-	448(100)	432(8)	430(30)	128(20), 124(20), 114(35), 112(44), 111(18), 98(45)
3	-	751(0.5)	-	-	376(100)	360(4)	358(20)	344(3), 342(6), 340(5)
4	773(1)	-	-	398(90)	376(100)	360(5)	358(20)	342(7), 340(5)
5	-	863(1)	-	-	432(100)	416(7)	414(5)	775(0.5), 360(6), 344(10), 324(3), 322(4)
6	665(1)	643(15)	-	344(3)	322(100)	306(14)	304(15)	292(13), 290(5), 182(1), 165(20), 158(1), 156(1), 140(8), 124(15)
7	-	603(5)	-	324(0.5)	302(100)	286(4)	284(10)	268(2), 258(3), 256(7), 242(3), 240(2), 238(2), 158(30), 156(7), 140(10), 124(15), 122(16), 83(8)
8	-	603(0.5)	-	324(0.5)	302(100)	286(2)	284(5)	268(1), 258(1.5), 256(3), 242(1.5), 240(0.5), 238(0.5), 158(25), 156(5), 140(5), 124(5), 122(5), 83(3)
9	653(1)	631(8)	-	-	316(100)	300(5)	298(8)	272(2), 270(3), 256(1), 246(1), 172(21), 170(2), 156(7), 154(2), 138(7), 136(12)
10	-	739(4)	462(1)	-	370(100)	354(8)	352(5)	136(50), 120(55), 119(30), 118(50)

TABLE 2. Mass Numbers of the Daughter Ions in the Linked Scanning Spectra (*B/E* = const.) of the Main Parental Ions of N-Oxides in the SIMS Regime

Compound	Parental ion, *m/z*	Daughter ions, *m/z*
2	MH^+ 448	432, 430, 418, 416, 402, 398, 396, 168, 164, 128, 124, 114, 112, 106, 98, 86
	$(MH-H_2O)^+$ 430	412, 402, 394, 168, 164, 129, 128, 114, 112, 106, 98, 86
6	MH^+ 322	306, 304, 292, 290, 266, 254, 240, 220, 182, 165, 156, 140
7	MH^+ 302	286, 284, 258, 256, 242, 240, 158, 140
	$(MH-16)^+$ 286	268, 266, 262, 242, 240, 238, 142, 124, 122
	$(MH-H_2O)^+$ 284	266, 264, 240, 238, 142, 124, 122
	158	140, 124, 122, 108, 83
8	MH^+ 302	286, 284, 258, 256, 242, 240, 158, 140
	158	140, 124, 122, 108, 83
9	MH^+ 316	300, 298, 272, 270, 256, 224, 222, 172, 156, 138, 137, 136
	172	156, 154, 136, 111, 106, 80

TABLE 3. Mass Numbers of the Parental Ions in the MD Spectra of Protonated Fragmentary Ions of Amino Alcohols in SIMS Regime

Compound	Daughter ion, *m/z*	Parental ions, *m/z*
7	158	242, 256, 268, 284, 302 (MH^+)
8	158	242, 256, 268, 284, 302 (MH^+)
9	172	256, 270, 282, 298, 316 (MH^+)

The series of characteristic fragmentary ions of the quinolizidine part of the molecule that was obtained is a consequence of rearrangement processes in the breakdown of the MH^+ and $(MH-18)^+$ ions (Table 1). The method of formation and the structures of these ions obtained in the EI spectra of the free bases have been given in the literature [9]. Among them, only the peaks of ions with *m/z* 114 and 128 are unusual for this group of compounds. Although they have also been recorded in the EI spectra of compounds (**1**) and (**2**), no attention has been devoted to their origin. The results of measurements of the elementary compositions of these ions that we have obtained in the SIMS and EI regimes (114.0920 — $C_6H_{12}NO$ — and 128.1075 — $C_7H_{14}NO$) indicate that they are oxygen analogs of the ions with *m/z* 98 and 112 that include the oxygen of the N-oxide group.

In the linked scanning spectrum (*B/E* = const.) of the MH^+ ion of compound (**2**), together with other metastable transitions we recorded transitions to ions with *m/z* 114 and 128. Analogous transitions were recorded in the *B/E* spectrum of the $(MH-H_2O)^+$ ion (Table 2). This phenomenon shows the equal claims of the N-oxide and hydroxy groups of the molecule to participation in the appearance of the $(MH-18)^+$ ions.

Peaks of stable MH^+ ions are also characteristic for the SIMS spectra of the diterpenoid alkaloids napelline (**3**) [1], lepenine (**4**) [10], and 2-isobutyryl-14-hydroxyhetisine (**5**) [11], while in the case of compound (**4**), together with MH^+ we detected a cationized form of the molecular ion $(M + Na)^+$ and its dimeric cluster with *m/z* 773. The fragmentation of the first two compounds is completed by the ejection of a molecule of water and of the side chains. The ester grouping present in the (**5**) molecule makes its own contribution to fragmentation, which lead to the appearance of the peak of an ion with *m/z* 344 $(MH-AcylOH)^+$. It was found that the dimeric cluster ion $(2M + H)^+$ underwent a similar decomposition.

The SIMS spectrum of the N-oxide of the esterified tropane alkaloid convolamine (**6**) [12] was characterized by tropane and acyl fragments. Although the (**6**) molecule lacks functional groups with mobile hydrogen atoms, its spectrum contained a weak peak of a protonated fragment of the N-oxide of the amino alcohol, with *m/z* 158 $(140 + 16 + 2H)^+$

Then, from the series of pyrrolizidine alkaloids we considered the N-oxides of viridiflorine (**7**), trachelanthamine (**8**), echinatine (**9**), and trichodesmine (**10**) [1]. The intensities of the M^+ peaks of the first two compounds in the EI regime amounted to only 1-2%, while in the spectra of the last two, even with intensified injection of the sample, no M^+ peaks were recorded, and they were identified indirectly — from the presence of the triplet of ion peaks $(M-16)^+$, $(M-17)^+$, and $(M-18)^+$ that is characteristic for the majority of N-oxides. Since the MH^+ peaks are the maximum ones for the compounds concerned under SIMS conditions, this method has proved to be the most useful for investigating this group of substances.

In addition to MH^+, dimeric cluster ions and a series of pyrrolizidine fragmentary ions coinciding in mass numbers with those in EI spectra were detected. So far as concerns fragments including the oxygen atoms of the N-oxide groups, we must mention the clearer picture in the case of compounds (**7**)-(**9**), in the spectra of which a whole series of peaks of ions corresponding to the elimination of the elements of the side-chain from MH^+ were obtained. The *B/E* spectra completely confirmed this direction of breakdown of the MH^+ ions, while in the *B/E* spectra of the $(MH-H_2O)^+$ ion, naturally, the fractional participation of ions with the oxygen of the $N \rightarrow O$ group in the formation of secondary fragmentary ions was far less.

In the EI regime, we have previously [8] established an increase in the fractional contribution of the acid moieties of these N-oxides to the total ion current in comparison with the initial bases. However, in the SIMS spectra the peaks of the ions of the acid moiety were weak. This fact may be evidence that the protonation of N-oxide molecules takes place mainly through the negatively polarized oxygen atoms of the N-oxide functions, with the formation of N^+-OH groups. A confirmation of this is the formation in the spectra of monoesters of N-oxides of intense fragmentary ions of the protonated forms of the N-oxides of the amino alcohols (A^+), with *m/z* 158 in the case of compounds (7) and (**8**), and *m/z* 172 in the case of compound (**9**). The formation of these ions is favored by the presence in the acid moiety of the molecule of hydrogen atoms that are fairly mobile and are located in positions sterically favorable for rearrangements. As a result, this direction of fragmentation took place ten times more intensively in compounds (7)-(**9**) than in convolamine N-oxide (**6**). An interesting and, for us, unexpected pattern was shown by the MD spectra of the ions with *m/z* 158 and 172 of substances (7)-(**9**); in addition to the intense $MH^+ \rightarrow A^+$ transition, they contained transitions of fragmentary ions formed from MH^+ on the ejection of fragments of the side-chain, and this phenomenon basically confirms the above-mentioned law of the protonation of the oxygen of the N-oxide group under SIMS conditions. We may also note that in the *B/E* spectra of the A^+ fragments we traced their further breakdown, leading to fragmentary pyrrolizidine ions (Table 3).

Since the structures of the N-oxides of (7) and (**8**) differ only by the stereochemistry of the acid moieties, and (**9**) by the presence of an additional OH group at the C_7 atom and a double bond at $C_1=C_2$ of the pyrrolizidine nucleus, we resolved to estimate the energy of the metastable transition $MH^+ \rightarrow A^+$ in the MD regime, using Beynon's formula [13]. The results obtained proved to be comparable, and amounted to 0.44 eV for the first two compounds and 0.48 eV for echinatine N-oxide (**9**). These values show that, in the formation of these ions, monotypical energy processes of hydrogen atom rearrangement take place that do not depend on the presence of a double bond in the pyrrolizidine nucleus.

EXPERIMENTAL

The general secondary-ion mass spectra of the N-oxides and the recording of metastable ions were carried out by the procedure described in [14].

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