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Product ion distributions for the reactions of NO^+ with some N-containing and O-containing heterocyclic compounds obtained using SRI-TOF-MS

Paweł Mochalski[a,*], Karl Unterkofler[a,b], Patrik Španěl[d], David Smith[e], Anton Amann[a,c,1]

[a] Breath Research Institute of the University of Innsbruck, Rathausplatz 4, A-6850 Dornbirn, Austria
[b] Vorarlberg University of Applied Sciences, Hochschulstr. 1, A-6850 Dornbirn, Austria
[c] Univ.-Clinic for Anesthesia and Intensive Care, Innsbruck Medical University, Anichstr. 35, A-6020 Innsbruck, Austria
[d] J. Heyrovský Institute of Physical Chemistry, Academy of Sciences of the Czech Republic, Dolejškova 3, 18223 Prague 8, Czech Republic
[e] Institute for Science and Technology in Medicine, Medical School, Keele University, Thornburrow Drive, Hartshill, Stoke-on-Trent ST4 7QB, UK

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ABSTRACT

Product ion distributions for the reactions of NO^+ with nine O-containing and six N-containing heterocyclic compounds present in human volatilome have been determined under the conditions of a Selective Reagent Ionization Time of Flight Mass Spectrometer (SRI-TOF-MS) at E/N values in the drift tube reactor ranging from 90 to 130 Td. This study was undertaken to provide the kinetics data by which these heterocyclic compounds could be analyzed in biogenic media using SRI-TOF-MS. The specific heterocyclic compounds are furan, 2-methylfuran, 3-methylfuran, 2,5-dimethylfuran, 2-pentylfuran, 2,3-dihydrofuran, 1,3-dioxolane, 2-methyl-1,3-dioxolane, γ-butyrolactone, pyrrole, 1-methylpyrrole, pyridine, 2,6-dimethylpyridine, pyrimidine, and 4-methylpyrimidine. Charge transfer was the dominant mechanism in the majority of these NO^+ reactions generating the respective M^+ parent cation, but in the pyridine, pyrimidine, and 4-methylpyrimidine reactions, stable NO^+M adduct ions were the major products with M^+ ions as minor products. The reactions of dioxolanes with NO^+ proceeded by hydride ion transfer only producing $(M-H)^+$ ions. Fragmentation of the excited nascent product ions $(M^+)^*$ did not occur for the majority of these reactions under the particular chosen conditions of the SRI-TOF-MS reactor, but partial fragmentation did occur in the 2,3-dihydrofuran and 2-pentylfuran reactions. However, lowering of the E/N in the drift tube suppresses fragmentation of $(M^+)^*$ ions and promotes the formation of NO^+M adduct ions, whereas increasing E/N has the opposite effect, as expected. The product ion distributions were seen to be independent of the humidity of the sample gas.

1. Introduction

Volatile heterocyclic compounds are commonly reported constituents of the human volatilome. Members of this chemical family have been detected in human breath [1–3], urine [3–6], blood [2] and skin emanations [7–9]. In vitro studies evidenced the production of heterocyclic compounds by pathogenic organisms responsible for several diseases and thereby revealed the potential of these volatile organic compounds (VOCs) for non-invasive diagnosis and therapy monitoring [10–12]. For instance, 2-pentylfuran was shown to be a biomarker for lung colonization/infection by fungal pathogens [12,13], whereas pyrrole and 3-methylpyrrole were suggested to be chemical indicators of *Pseudomonas aeruginosa* infections [11]. Several heterocyclics in urine were also suggested as potential indicators of prostate cancer [14]. Thus, the analysis of volatile heterocyclic compounds in exhaled breath and the headspace of other biogenic fluids could be a valuable diagnostic tool.

The human volatilome consists of hundreds of VOCs representing different chemical families [15]. Reliable identification and quantification of compounds/biomarkers in such a complex matrix can pose a number of analytical challenges and problems. Real-time mass spectrometric analytical techniques [16], such as proton-transfer reaction mass spectrometry (PTR-MS) and selected ion

* Corresponding author. Tel.: +43 512 503 24636; fax: +43 512 504 6724636.
E-mail address: pawel.mochalski@uibk.ac.at (P. Mochalski).

[1] It is with deep sadness that we record the untimely passing of our dear friend and co-author Anton Amann who contributed very much to the research described in this paper and indeed initiated the project. In addition to being a great friend to all of us and an exceptional human being, Anton was variously a mentor and highly respected colleague and excellent scientist who will be greatly missed.

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flow tube mass spectrometry (SIFT-MS) [17,18], are particularly attractive analytical methods for detecting and quantifying VOCs in biological, medical and environmental matrices. This is due to their versatility, excellent sensitivity and real-time response. In particular, the last feature opens up a new fascinating opportunity of tracking rapid short-time changes in the human volatilome, which can provide invaluable information on normal and abnormal processes occurring in the body [19–22]. Moreover, real-time analysis improves the quality and reliability of the results, since sample collection, storage and pre-concentration that can result in loses of trace compounds and contamination are avoided. Recently, the analytical power of the classic PTR-MS instruments has been notably improved by the exploiting time-of-flight (TOF) mass spectrometry and by allowing precursor (reagent) ions such as NO^+, O_2^+, and Kr^+ to be used as alternatives to the usual H_3O^+ ions, thus creating a Selective Reagent Ionization Time of Flight Mass Spectrometry (SRI-TOF-MS) [23,24]. In particular, the TOF mass filter provides higher mass (m/z) resolving power (up to 5000 $m/\Delta m$), which facilitates the separation of isobaric analyte ions that are sometimes formed during the analysis of the human volatilome.

The main goal of the present study was to determine the product ion distributions for the reactions of NO^+ ions with some selected N-containing and O-containing heterocyclic compounds using an SRI-TOF-MS instrument. The reactions of NO^+ with several S-containing heterocyclic compounds were the subject of our recent articles [25,26], where the true value of NO^+ reagent ions was demonstrated. A valuable characteristic of NO^+ reactions with VOCs is the diversity of reaction mechanisms that occur under thermal energy conditions, as revealed by numerous SIFT-MS studies [17]. These include charge (electron) transfer, hydride ion (H^-) transfer, hydroxide ion (OH^-) transfer, alkoxide ion (OR^-) transfer and NO^+ ion-molecule association. Interestingly, different chemical classes of VOCs undergo characteristic reaction processes with NO^+, which is analytically very useful and in some cases helps to identify structural isomers of compounds [16–18]. The product ion distributions of the reactions of NO^+ with most VOCs under the suprathermal energy conditions of SRI-TOF-MS reactors [24] are poorly known. This situation limits the applicability of SRI-TOF-MS instruments for trace gas analysis. The present study and our previous studies of NO^+ reactions with aldehydes and organosulphur compounds [24,25] are intended to partially fill this literature data gap and thus to facilitate analyses of these classes of VOCs in biogenic media.

2. Experimental

2.1. Materials and standard mixtures

Single-compound calibration mixtures were prepared from the pure liquid heterocyclic compounds, which were purchased from Sigma–Aldrich (Austria), SAFC (USA), and Alfa Aesar (USA). The purity of each liquid compound is given in Table 1 to assist interpretation of the observed product ion distributions of the reactions. All purities are seen to be better than 97% with the majority at 99%.

Gaseous standard mixtures were prepared using the procedure described in our recent article [26]. It should be stressed that the product ion distributions were investigated using 3 distinct concentrations of each analyte in high purity air at partial pressures ranging from approximately 20 to 230 ppbv and at two different absolute humidity levels of <0.1% and 4.9%, the latter approximately corresponding to that of exhaled breath.

2.2. SRI-TOF-MS analysis

The NO^+ reactions were studied using an Ionicon Analytik (Innsbruck, Austria) type 8000 SRI-TOF-MS instrument and the analytical procedure outlined in Mochalski et al. [26]. The settings of the ion source were chosen as follows: ion source current 5 mA, source voltage (Us) 20 V, source-out voltage (Uso) 70 V, and source valve opening 40%. The levels of the major "impurity ions" relative to that of the NO^+ precursor ion for these conditions were H_3O^+ (0.2–0.3%), O_2^+ (0.3–0.4%) and NO_2^+ (1.3–1.5%). The NO^+/heterocyclic compound reactions occurred in the drift tube at a total pressure of 2.3 mbar and at a gas temperature of 60 °C. The product ion distributions were investigated for five distinct E/N ratios in the reaction tube ranging from 90 to 130 Td with incremental changes of 10 Td, as adjusted by changing the voltage difference along the drift section over the range of 400–600 V. The ion mass (m/z) calibration was regularly checked using the presence of the impurity ions of known m/z values: H_3O^+ (19.0178), $^{15}NO^+$ (30.9945), and NO_2^+ (45.9924).

The instrument-specific ion mass-dependent discrimination functions ("transmission") was determined using a standard gas mixture containing 14 compounds having molecular masses ranging from 21 to 180 (Restek TO-14A Aromatics Mix), in accordance with the procedure recommended by the instrument manufacturer (Ionicon Analytik) [27]. The transmission factors for the observed ions were calculated using an algorithm implemented in the software provided by the manufacturer (PTR-MS Viewer 3.1.0).

The standard mixtures of heterocyclic compounds, which act as both the sample and carrier gas, were introduced into the drift tube of the SRI-TOF-MS instrument at a steady flow rate of 20 mL/min via a 2-m long, heated (40 °C) Teflon transfer line, which minimizes the surface adsorption of water vapour and the heterocyclic compounds under study.

The spectral scans of the TOF analyzer ranged from approximately m/z 2.7 to 500 and were acquired in a time of 30 s by co-adding 750 000 single 40-μs long TOF-MS extractions recorded at a sampling frequency of $1/\Delta t$ = 10 GHz. The actual mass resolution obtained from the detected peaks was ≈4000 at m/z 100. The total duration of a single measurement was 5 min, which corresponds to 10 mass spectra acquired per reactant gas concentration level. The average of the ion signal levels at each m/z value from these 10 spectra was used to calculate the percentages of the product ions for each of the NO^+/heterocyclic reactions.

3. Results and discussion

Table 1 shows the percentage product ion distributions for the reactions of NO^+ with the 15 heterocyclic compounds. These percentages refer to the ion signal intensities corrected for the transmission factors referred to above and are the averages of intensities obtained for 3 distinct mean concentrations (of 10 spectra) for each heterocyclic compound. Only product ions with abundance exceeding 2% of the total signal were included in Table 1, recognizing that signals at this low level might originate from reactions of the injected "impurity ions" with the heterocyclic compound and/or reactions of the NO^+ ions with any impurities that are present in the liquid heterocyclic compounds and appear in the sample mixture.

Scrutiny of Table 1 reveals that charge (electron) transfer producing stable M^+ parent ions is the dominant mechanism in most of the reactions; it is the single product ion channel in most of the furan reactions and in both pyrroles reactions. The small fractions of other product ions in the 2-pentylfuran reaction is probably related to the lower purity of this compound (see Table 1) and the possibility that the liquid impurities are more volatile than the majority 2-pentylfuran. The dominance of charge transfer in these heterocyclic compound reactions is surely due to their ionization energies (IE) being lower than the IE of the NO molecule (9.26 eV), equivalent to the recombination energy of ground vibronic state NO^+ [28], which energetically allows charge transfer to occur [17].

Table 1
Product ion distributions for the reactions of NO^+ with 15 heterocyclic compounds under dry and humid (AH 4.9%) air sample/carrier gas in the SRI-TOF-MS instrument at E/N ranging from 90 to 130 Td. Uncertain neutral products for the reactions are indicated by bracketing. Ionization energies (IE) are taken from [34]. The reactions occurred in the drift tube at a total pressure of 2.3 mbar and at a gas temperature of 60 °C.

Compound Formula Purity	CAS	IE [eV]	Reaction channel	Dry air (0% AH) [%]					Humid air (4.9% AH) [%]			Measured m/z [Th]	Expected m/z [Th]	Error [mTh]
				90 [Td]	100 [Td]	110 [Td]	120 [Td]	130 [Td]	90 [Td]	110 [Td]	130 [Td]			
Furan C_4H_4O 99%	110-00-9	8.89	$C_4H_4O^+ + NO$			100				100		68.0263	68.0257	0.6
2-Methylfuran C_5H_6O 99%	534-22-5	8.41	$C_5H_6O^+ + NO$			100				100		82.0421	82.0413	0.8
3-Methylfuran C_5H_6O 99%	930-27-8	8.64	$C_5H_6O^+ + NO$			100				100		82.0421	82.0413	0.8
2,5-Dimethylfuran C_6H_8O 99%	625-86-5	8.03	$C_6H_8O^+ + NO$			100				100		96.0583	96.0570	1.3
2-Pentylfuran	3777-69-3	n.a.	$C_9H_{14}O^+ + NO$	93	92	91	88	80	93	91	83	138.1060	138.1039	2.1
$C_9H_{14}O$			$C_9H_{12}^+ + H_2O + NO$	2	3	–	2	4	–	–	4	120.0962	120.0934	2.8
97%			$C_5H_6O^+ + (C_4H_8 + NO)$	3	–	3	5	8	2	3	7	82.0426	82.0413	1.3
			$C_6H_9^+ + (C_3H_5NO_2)$	–	3	2	3	5	–	2	4	81.0707	81.0699	0.8
			$C_5H_5O^+ + (C_4H_9NO)$	–	–	3	3	4	2	3	3	81.0343	81.0335	0.8
2,3-Dihydrofuran	1191-99-7	n.a.	$C_4H_6O^+ + NO$	98	98	96	91	77	98	97	79	70.0420	70.0413	0.7
C_4H_6O			$C_3H_6^+ + CO + NO$	2	2	3	8	18	2	3	18	42.0467	42.0469	0.2
99%			$C_3H_5^+ + CO + HNO$	–	–	–	–	4	–	–	3	41.0389	41.0386	0.3
Pyrrole C_4H_5N 98%	109-97-7	8.20	$C_4H_5N^+ + NO$			100				100		67.0424	67.0416	0.8
1-Methylpyrrole C_5H_7N 99%	96-54-8	8.10	$C_5H_7N^+ + NO$			100				100		81.0584	81.0573	1.1
Pyridine	110-86-1	9.45	$C_5H_5N{\cdot}NO^+$	79	72	70	65	58	78	68	56	109.0415	109.0396	1.9
C_5H_5N			$C_5H_5N^+ + NO$	21	28	30	35	42	22	32	44	79.0428	79.0417	1.1
99.8%														
2,6-Dimethylpyridine	108-48-5	9.02	$C_7H_9N{\cdot}NO^+$	9	8	5	4	2	10	6	2	137.0707	137.0709	0.2
C_7H_9N			$C_7H_9N^+ + NO$	91	92	95	96	98	90	94	98	107.0722	107.0729	0.7
98%														
Pyrimidine	289-95-2	9.45	$C_4H_4N_2{\cdot}NO^+$	87	81	76	62	48	88	78	51	110.0364	110.0349	1.5
$C_4H_4N_2$			$C_4H_4N_2^+ + NO$	13	19	24	38	52	12	22	49	80.0381	80.0369	1.2
99%														
4-Methylpyrimidine	3438-46-8	n.a.	$C_5H_6N_2{\cdot}NO^+$	70	62	55	42	25	72	57	28	124.0510	124.0505	0.5
$C_5H_6N_2$			$C_5H_6N_2 + NO$	30	38	45	58	75	28	43	72	94.0535	94.0525	1.0
97%														
1,3-Dioxolane $C_3H_6O_2$ 99%	646-06-0	10.00	$C_3H_5O_2^+ + HNO$			100				100		73.0282	73.0284	0.2
2-Methyl-1,3-dioxolane $C_4H_8O_2$ 98%	497-26-7	n.a.	$C_4H_7O_2^+ + HNO$			100				100		87.0451	87.0440	1.1
γ-Butyrolactone $C_4H_6O_2$ 99%	96-48-0	10.26	$C_4H_6O_2{\cdot}NO^+$			100				100		116.0346	116.0342	0.4

n.a., not available.

The reactions of NO^+ with pyridine, 2,6-dimethylpyridine, pyrimidine, and 4-methylpyrimidine are more complicated since, in addition to M^+ products, significant fractions of $M{\cdot}NO^+$ adduct ions are produced via ion-molecule association. Adduct ion production becomes more efficient when IE(NO) approaches IE(M), as has been shown by a detailed study of NO^+ with a series of ketones [29], and this phenomenon is operative in the present NO^+/heterocyclic compound reactions, as can be seen in Table 1. Note that the IE of both pyridine and pyrimidine are only 0.19 eV greater than that of NO, which allows for only a small fraction of M^+ production in parallel with NO^+M production, whereas the IE of 2,6-dimethylpyridine is 0.24 eV smaller than that of NO and so M^+ production dominates.

The adjustment of the E/N ratio in the drift tube considerably influences the relative fractions of the M^+ and NO^+M product ions; lowering E/N promotes the fraction of $M{\cdot}NO^+$ ions, and increasing E/N increases the fraction of M^+ ions. For instance, the abundance of the NO^+/pyrimidine adduct ion is only 48% at an E/N of 130 Td, whilst at 90 Td it is 87%. This is in accordance with some mechanistic considerations that indicate an increase of lifetimes of the $(M{\cdot}NO^+)^*$ complexes decrease with increasing ion/molecule interaction energy [30]. Thus, the probability of detecting stabilized $M{\cdot}NO^+$ adduct ions in the drift reactor is higher at the lower E/N. A similar phenomenon has been observed in the reactions of NO^+ with aldehydes [26]. Consequently, by varying E/N either M^+ or NO^+M can be made the dominant product (analyte) ion, thus providing additional analytical information and less ambiguity in identification and quantification of the neutral reactant heterocyclics. For instance, by lowering the E/N when analyzing pyridine and pyrimidine the adduct ion product becomes the dominant analyte ion. Conversely, in the 2,6-dimethylpyridine reaction, higher E/N suppresses the formation of the $M{\cdot}NO^+$ ion and the M^+ ion is essentially the only product. It is also worthy of note that the SRI-TOF-MS instrument used for the present studies operates at a reactor gas temperature of 60 °C; increasing temperature inhibits, to some extent, adduct ion formation and decreases the lifetime against collisional dissociation of adduct ions [30].

Both dioxolanes included in this study react with NO^+ via hydride ion transfer generating $(M-H)^+$ ions; see Table 1. This is probably due to the relatively high IE of these compounds (relative to that of NO; IE of dioxolane is 10 eV), which prevents charge transfer, inhibits adduct ion formation and leaves hydride ion transfer as the only exothermic reaction process available. Hydride ion transfer commonly occurs in the reactions of NO^+ with aldehydes and esters [17]. These findings are essentially in agreement with earlier studies carried out under the thermalized condition of the SIFT-MS [31]. It should also be noticed that the γ-butyrolactone reaction with NO^+ proceeds via adduct ion formation only. This compound has the highest IE of all the compounds included in this study, and because of the large energy deficit, IE(NO) – IE(γ-butyrolactone), it is to be expected that the efficiency of the association reaction will be relatively small and thus the rate coefficient for this reaction will be small. On this issue, it is important to note that for trace gas analysis by either SIFT-MS or PTR-MS the rate coefficients for the analytical reactions must be known. Numerous measurements have been made, and reported, for the thermal energy reaction occurring in SIFT-MS [32], but fewer measurements have been made under the suprathermal conditions of PTR-MS. Note that competitive association and charge transfer in the reactions of NO^+ with some ketones have also been observed in a selected ion flow drift tube study [33]. Thus, to achieve accurate analyses by PTR-MS, either the rate coefficients should be measured under the specific conditions of the particular instrument (buffer gas pressure and E/N) or calibration procedures should be used. These procedures are especially important when association reactions forming adduct ions are exploited as analyte ions.

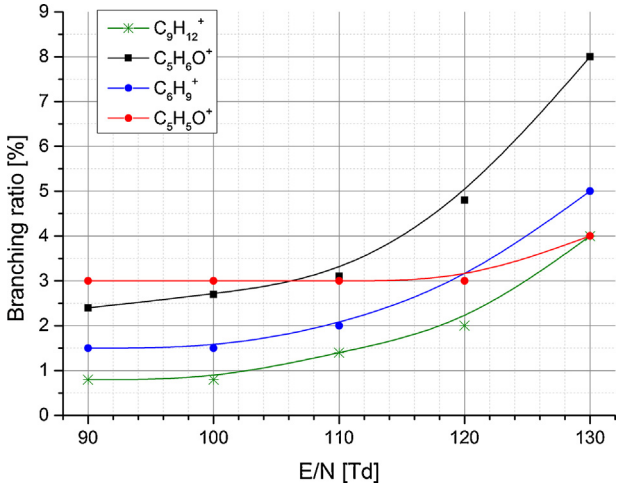

Fig. 1. The influence of increasing E/N in the drift region of the SRI-TOF-MS instrument on the fragmentation of 2-pentylfuran parent cations $C_9H_{14}O^+$ formed in the NO^+/2-pentylfuran reaction.

A glance at the data in Table 1 shows that fragmentation of the nascent $(M^+)^*$ ion is rare in these heterocyclic molecules reactions with NO^+. This can be attributed to the small energy deficits indicated above, which leave little excess energy for bond breaking in the nascent $(M^+)^*$ ions. Also, there are few long aliphatic chains in these particular heterocyclic compounds. The reactions of NO^+ with several volatile organosulphur and aldehydes compounds possessing long aliphatic chains were shown to result in considerable fragmentation in SRI-TOF-MS reactors [25,26]. Indeed, fragmentation is seen in just one of the heterocyclic compounds – 2-pentylfuran – that has a pentyl chain, as can be seen in the data in Table 1 and the plots in Fig. 1. However, these fragment channels represent very small fractions of the total ion products and, if ignored, would not greatly affect quantification in the SRI-TOF-MS analytical instrument. In short, lower E/N simplifies the product ion distributions, reduces the chance of m/z overlaps and improves analytical sensitivity for those reactions for which fragmentation is prone to occur in SRI-TOF-MS instruments. Lack of physicochemical data on the reactants and products of the 2-pentylfuran reaction does not allow positive identification of the neutral products of these fragmentation channels and this is indicated by the bracketing in Table 1.

It is always important to check the influence on the products of the reactions of the humidity of the sample gas, which can vary widely in biogenic samples. So such checks were carried out in these experiments involving both ostensibly dry sample gas and sample gas at an absolute volume mixing ratio of water vapour of 4.9%. It was seen that the presence of water molecules in the samples had a little or no effect on the product ion distributions; see Table 1. This greatly simplifies the analysis of these heterocyclic compounds by SRI-TOF-MS in the NO^+ reagent ion mode.

4. Concluding remarks

The rationale behind this study was to identify the major product ions of the reactions of NO^+ ions with 15 heterocyclic compounds in SRI-TOF-MS instrument, and thus to prepare the way for their analysis in biomedical and environmental matrices. The findings are that exothermic charge transfer generating parent M^+ ions is the dominant ionization mechanism in these reactions. However, in the pyridine, 2,6-dimethylpyridine, pyrimidine, and 4-methylpyrimidine reactions, considerable fractions of stable adduct ions NO^+M appear in parallel with charge transfer parent ions M^+. In contrast, the NO^+/1,3-dioxolane and NO^+/2-methyl-1,

3-dioxolane reactions occur via hydride ion transfer resulting in $(M-H)^+$ product ions. In most of the reactions, no fragmentation of the nascent $(M^+)^*$ ions occurred (as formed by the initial charge transfer) under the conditions of a SRI-TOF-MS reactor. The two exceptions are 2,3-dihydrofuran and 2-pentylfuran reactions in which partial fragments of the $(M^+)^*$ ions were seen to occur. Predictably, variation of E/N in the drift tube modifies the product ion distribution. Lower E/N suppresses fragmentation and promotes adduct ion formation, whereas increasing E/N increases the fraction of charge transfer parent cations. This facility allows the investigation of the influence of ion–molecule interaction energy over a wider range than is possible by varying the temperature in either PTR-MS or SIFT-MS instruments. Increased humidity had no effect on the product ion distributions. The findings of this study will facilitate the analysis by SRI-TOF-MS of heterocyclic compounds in complex biomedical or environmental matrices.

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