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TECHNICAL REPORT

Stability and alignment of MCC/IMS devices

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Introduction

There are numerous analytical detection methods available for human breath investigations. The major spectrometric methods used are proton transfer reaction mass spectrometry (PRT-MS) [1–5], selected ion flow tube mass spectrometry (SIFT-MS) [6–10], solid phase micro extraction-gas chromatography coupled to mass spectrometry (SPME-GC/ MS) [11–14], and multi-capillary column coupled to ion mobility spectrometry (MCC/IMS) [15–20]. In all cases mentioned, a non–invasive and an easy method for early diagnosis or therapy monitoring are developed by identifying disease-specific biomarkers in the breath of patients.

Obviously, if the results of these studies are to be valid, consideration of sampling techniques, and the comparison of the inhaled and the exhaled air are some fundamental requirements. Small changes within the room air can affect the difference between room air and exhaled breath depending on the method selected, for example, patients suffering lung cancer and healthy volunteers. Therefore, in the present paper a study of the stability of two volatiles present in room air ion mobility spectrometry measurements over 6 months is reported, and also the variability of these two volatiles for different MCC/IMS devices is also described.

The present paper considers the influence of temperature and other parameters with small variations in the instrumentation. General remarks could be found in [21, 22], the influence of temperature in [23–32], pressure in [33], electric field in [34, 35], carrier gas flow [23, 31], geometrical parameters [36, 37]. Therefore, we discuss the inter-comparison of different instruments. Theoretical aspects and in-depth explanations regarding the operating conditions of the MCC/IMS were discussed in the literature mentioned above. The present paper deals with practical points that are to be considered while intercomparing different instruments and show, that a proper alignment is really needed for such purpose.

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Table 1 Main MCC-IMS parameters

Ionization source ß-radiation (^{63}Ni)	550 MBq
Drift length	12 cm
Diameter of drift region	15 mm
Length of ionization chamber	15 mm
Electric field strength	330 V/cm
Drift and carrier gas	Synthetic air, (20.5% O_2 (4.5), 79.5% N_2 (5.0)) purity 99,999%
Drift gas flow	100 mL/min
Carrier gas flow	150 mL/min
Shutter grid opening time	300 µs
Spectra length/sample interval	100 ms
Spectra resolution	40 kHz
Sample loop	10 mL
MCC length	20 cm
Temperature MCC	40 °C-adjusted

Material and methods

The multi-capillary column—ion mobility spectrometer (MCC/IMS) used for this study was a BreathDiscovery (B&S Analytik, Dortmund, Germany). The major measurement parameters are summarized in Table 1. The multi-capillary column (MCC) is an OV-5 type (Multichrom, Novosibirsk, Russia) and is used as the pre-separation unit. In this MCC, the analytes of the sample are sent through 1,000 parallel capillaries, each with an inner diameter of 40 µm and a film thickness of 200 nm. The total diameter of the separation column is 3 mm. Once pre-separated, the analytes present in the sample of 10 mL and the carrier gas reach the ion mobility spectrometer where they are ionized with a 555 MBq ^{63}Ni β-radiation.

Once the analytes are ionized, when the shutter opens they can pass through the drift region where they are differentiated by mobility and then they are detected using a Faraday plate. In this study only the ions in positive mode were considered.

The signals/peaks were characterized using the software Visual Now (B&S Analytik, Dortmund Germany), which is described elsewhere [19, 38–40]. All analytes are characterized

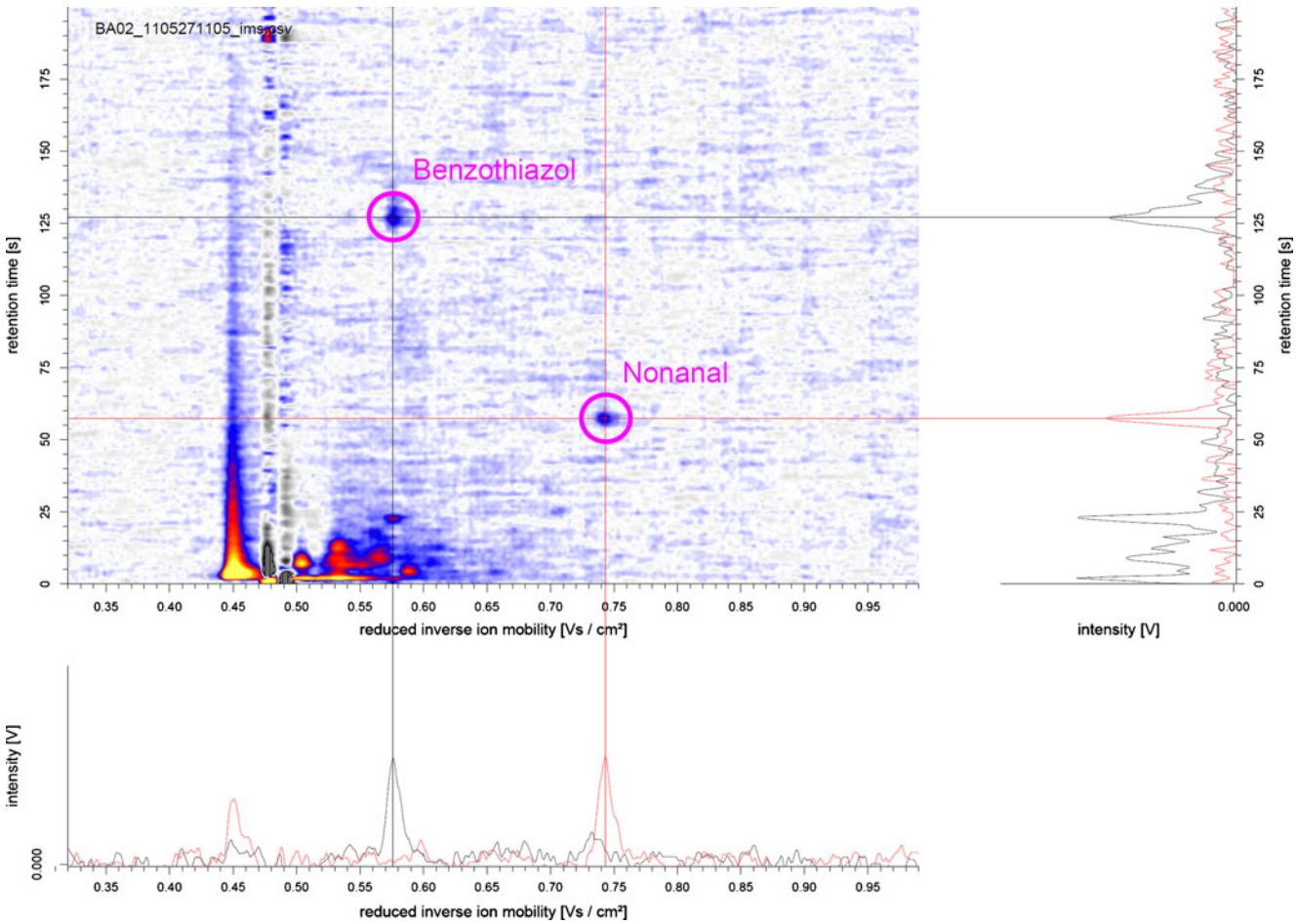

Fig. 1 MCC/IMS chromatogram for a measurement of room air using IMS-1 device. The studied compounds are highlighted inside purple circles: Benzothiazol and Nonanal

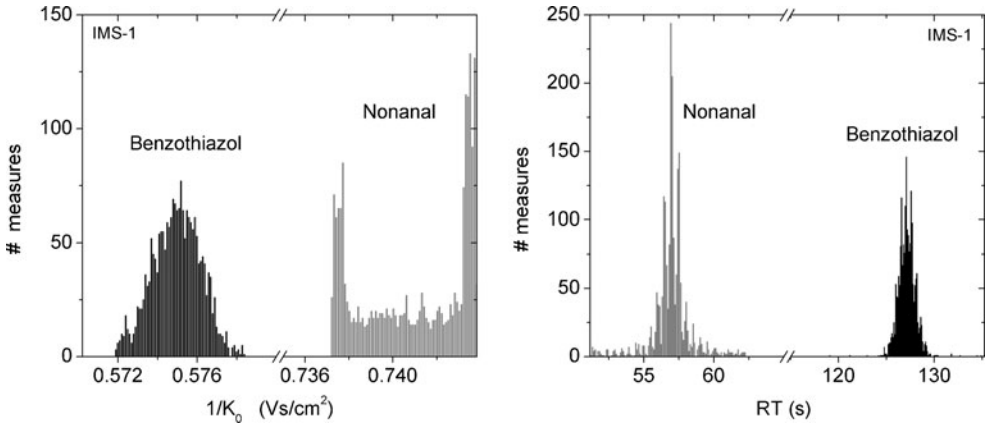

Fig. 2 $1/K_0$ and RT distributions for Benzothiazol and Nonanal for IMS-1 device

by their position (in the chromatograms) with the inverse reduced mobilities ($1/K_0$-value) and retention time (RT-value) and no peak height intensity was considered.

Results and discussion

Stability—MCC/IMS peaks variations

Studies of Room Air with MCC/IMS show a wide variety of peaks depending on the location of the device and the day and time. So, to compare different Chromatograms, there is a need to have at least one peak that is always in the chromatogram to align the different measurement data. In this line, we have found two analytes that are always in the room air chromatograms analyzed: Benzothiazol and Nonanal as can be seen in Fig. 1.

To assure that both compounds are found in all room air chromatograms, measurements over 6 months giving up to more than 2000 measurements for IMS-1 device have been analyzed. Figure 2 shows the histograms of the inverse of the reduced mobility and the retention time distributions for Benzothiazol and Nonanal. It can be easily seen that Benzothiazol follows a Gaussian curve for both $1/K_0$ (R^2= 0.95) and RT (R^2=0.93). While, Nonanal does not follow this behavior. This is due to the fact that Benzothiazol evaporates from the plastic compounds of the MCC/IMS, while Nonanal

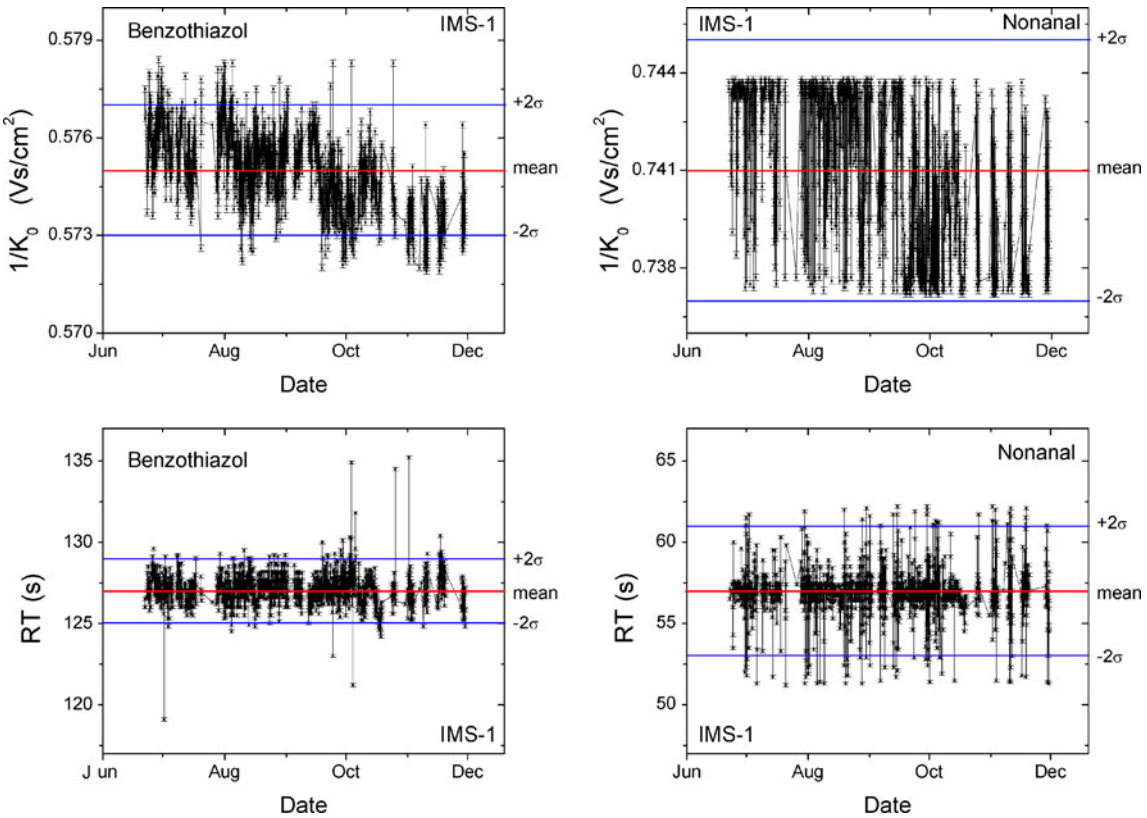

Fig. 3 $1/K_0$ and RT distributions along the time for Benzothiazol and Nonanal for IMS-1 device

Table 2 Mean values of RT and $1/K_0$ of the studied MCC/IMS devices

	Benzothiazol		Nonanal		
	$1/K_0$ (Vs/cm^2)	RT (s)	$1/K_0$ (Vs/cm^2)	RT (s)	
IMS-1	0.575±0.001	127±1	0.741±0.002	57±2	2066 files
IMS-2	0.571±0.001	144±2	0.734±0.002	61±1	127 files
IMS-3	0.574±0.002	148±3	0.734±0.002	64±1	43 files
mean	0.573		0.739		

comes from the air-conditioning system and it can be present in the room air sometimes or not.

Furthermore, we can take a look into the distribution of the $1/K_0$ and RT over time (Fig. 3), where the mean values can be found in Table 2 for IMS-1 where is also showed with the standard deviation range. The analysis for Benzothiazol and Nonanal shows that for the $1/K_0$, there is a declining linear tendency of the inverse reduced mobility value, while for the RT there is a constant linear tendency and almost all results are within the range of standard deviation. Variations in the mobility can be explained due to the appearance of $M(H_2O)_nH^+$ like cluster ions formed from small variations of humidity content of the carrier gas. The standard deviation for Nonanal is the double that of Benzothiazol for both $1/K_0$ and RT, as can be seen in Fig. 3.

Alignment—MCC/IMS devices variations

Once considered the stability of the devices, we focused on the alignment between three different MCC/IMS devices for Benzothiazol and Nonanal. The box-and-whisker plots have been used to show the variation in the inverse reduced mobility and also in the RT for the studied devices (Fig. 4). The results are summarized in Table 2. The expected $1/K_0$ values have to be similar for all three devices, as it is obtained. However for the retention time, it is expected that for different devices with different oldness the RT values may vary more sustainably. Thus, the way to adjust the temperature of the MCC will be different. Small changes in the temperature adjustment and place of measurement of the temperature (IMS-1 and IMS-2/IMS-3 are different in that point of measurement) will affect the retention time scale. So, the results show the importance to align the data of different devices especially for the RT. In addition, more sensitive regulation of temperature over the MCC should be considered. As shown in Fig. 4, linear alignment on the Retention time scale is possible.

From the analyzed VOC's, Benzothiazol has a Gaussian behavior in RT-values and a linear tendency over time. The older the device, (i.e. multi-capillay column) the sooner the analytes elute out from the MCC, i.e., the lower RT for the analytes. Also Benzothiazol is from the materials of which the MCC/IMS is built, so we will have it in all the chromatograms either from Room Air or from Breath Analysis, so all these properties make Benzothiazol a suitable peak for the alignment of different devices in positive mode.

It should be noted, that the software package of B&S Analytik, VisualNow includes functionality for alignment on both the inverse reduced mobilitiy and the retention time scales.

Summary

The present paper shows, that for investigations of time series using a single instrument and multi-centric studies including the comparison of spectra and IMS-chromatograms from different instruments a real need exists for alignment on the inverse reduced mobilitiy and the retention time scales. By comparison of three different instruments the influence of measuring and adjusting the temperature as well as the temperature range allowed by the regulation circle was observed to be small but considerable. On the retention time scale a linear alignment is sufficient. For the drift time scale further investigations are needed, but the variations were rather small in this dimension.

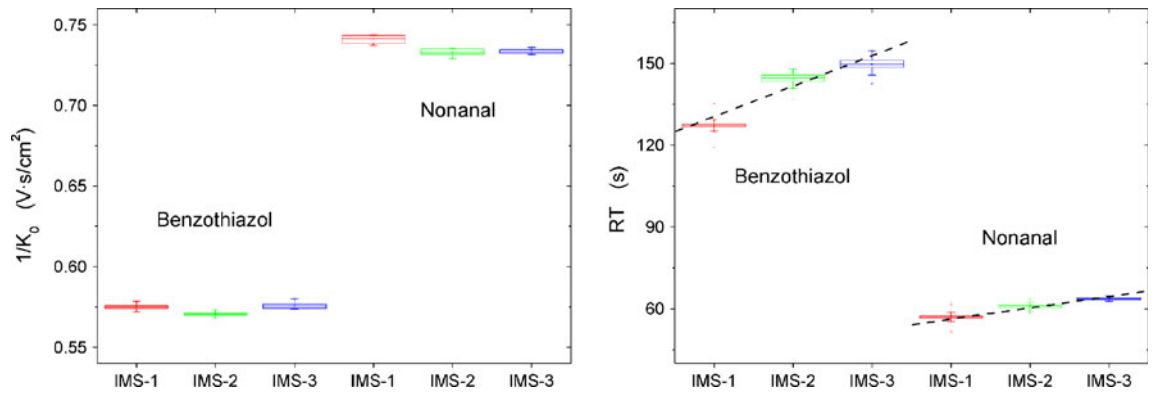

Fig. 4 Box-and-whisker plots of the $1/K_0$ and RT of Benzothiazol and Nonanal for three studied MCC/IMS devices

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