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Analyte and matrix evaporability – key players of low-temperature plasma ionization for ambient mass spectrometry

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Abstract
The introduction of ambient ionization at atmospheric pressure for mass spectrometry (AI-MS) attracted the interest of many researchers in the field and various ionization techniques have been described in recent years that allow a quick and easy-to-handle analysis of samples under ambient conditions without or with only minor sample preparation. Among those, plasma-based techniques including the low-temperature plasma probe require very little resources thereby providing great potential for implementation in mobile analytical devices. However, systematic studies on signal responsiveness with this technique, such as the influence of the analyte and matrix characteristics on relative signal intensity, are still rare. Therefore, we used a low-temperature plasma source based on dielectric barrier discharge with helium as process gas to assess influencing factors on signal intensity in mass spectrometry. Among 12 tested molecular descriptors, in particular a low vaporization enthalpy and a large molecular nonpolar surface area improve the relative signal intensity. In addition, we show that the impact of compound characteristics strongly outperforms the influence of simple sample matrices such as different organic solvents and water, with a weak trend that volatile solvents tend to decrease the signal responsiveness of the analytes. However, several specific solvent-analyte interactions occurred, which have to be considered in targeted applications of this method. Our results will help further in improving the implementation and standardization of low-temperature plasma ionization for ambient mass spectrometry and understanding the requirements and selectivity of this technique.

Keywords Low-temperature plasma ionization · Ambient mass spectrometry · Optimal signal intensity · Aromatic amines · Molecular descriptors

Introduction

Soft ionization under ambient conditions allows direct analysis of samples employing mass spectrometers with an atmospheric pressure inlet. These techniques use a variety of desorption and ionization methods, e.g., by interaction with charged droplets [1–3], photons [4–6], or plasma [7–9]. Common to all "ambient" mass spectrometry (MS) techniques is the minimal to no sample preparation, as well as the operation exposed to the environment. Therefore, they offer an enormous potential in saving time and resources. Since the works of Takats et al. [1] about desorption electrospray ionization (DESI) and Cody et al. [7] about direct analysis in real time (DART), many papers described different varieties of ambient ionization for mass spectrometry. In principle, ambient techniques can be subdivided in direct desorption/ionization techniques and two-stage ionization techniques. In direct desorption/ionization techniques, desorption and ionization are accomplished in a concerted action. For DESI as an example of direct desorption/ionization techniques, charged droplets hitting the sample surface fulfill the task of desorption as well as ionization [1, 10].

Most of the techniques developed for the ionization of analytes directly from sample surfaces under ambient conditions are essentially based on slight changes or extensions of DESI and DART. Plasma sources, for example, also employ the

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direct desorption/ionization strategy; in comparison to other techniques, they offer the advantage of a very simple construction and the potential in saving further resources, since no solvent is needed. The plasma ionization techniques in particular were often modified and innumerable variations of the geometrical arrangement are found in the literature. Other differences are related to whether the ionic plasma species are removed by additional electrodes, as in DART, or not, as in dielectric-barrier discharge ionization, DBDI [11], low-temperature plasma ionization, LTPI [9], plasma-assisted desorption/ionization, PADI [8], or atmospheric pressure glow discharge, APGD [12], and the corresponding flowing atmospheric pressure afterglow, FAPA [13]. In addition, it is possible to enhance the temperature of the plasma gas either by an additional heater (DART), Joule-heating (APGD, FAPA), or to ionize without additional heating (PADI, LTPI, DBDI). Furthermore, the kind of voltage applied to produce the plasma, and therefore the type of the generated plasma, is a distinctive feature: there are DC (DART, APGD, FAPA) or AC (PADI, LTPI, DBDI) voltages applied. Only few reviews are available attempting to systemize the different approaches that have been published so far [14–16]. Table 1 presents characteristics for a small selection of the most commonly employed techniques.

For our research, we chose the easy-to-build and cost-efficient design of a DBDI source in probe configuration with two parallel outer electrodes [17]. In dielectric barrier discharge, the use of a dielectric between the electrodes and the plasma gas (helium) limits the current, resulting in non-equilibrium, low-temperature plasma [18] enabling the direct ionization and subsequent mass spectrometric analysis of compounds at a very low process gas flow rate, with high signal intensity and minimal fragmentation. Here, we studied the impact of analyte and matrix characteristics on signal responsiveness in LTPI-MS using a set of aromatic amines, primarily anilines, a class of compounds of high interest for both synthetic organic and pharmaceutical chemistry.

Materials and methods

Chemicals

3-Aminophenol, 2-fluoroaniline, 3-fluoroaniline, 4-fluoroaniline, 2-methoxyaniline (o-anisidine), 3-methoxyaniline (m-anisidine), 4-methoxyaniline (p-anisidine), 2-nitroaniline, 3-nitroaniline, 4-nitroaniline, 3-methylaniline (m-toluidine), 3-aminoaniline (m-phenylenediamine), 4-aminoaniline (p-phenylenediamine), 2-aminobenzonitrile, 3-aminobenzonitrile, 4-aminobenzonitrile, N,N-dimethylaniline, 4,N,N-trimethylaniline, N,N-dimethyl-4-nitroaniline and pyridine were purchased from Sigma Aldrich (Taufkirchen, Germany). 2-methylaniline (o-toluidine), 4-methylaniline (p-toluidine) from Fluka (Buchs, Switzerland) and aniline from Acros (Geel, Belgium). Acetonitrile (ACN), 1,4-dioxane and ethanol were purchased from VWR (Dresden, Germany). Acetone, methanol and tetrahydrofuran (THF) were from Carl Roth (Karlsruhe, Germany), water from BIOSOLVE (Valkenswaard, Netherlands), 1-butanol and 1-propanol from J.T.Baker (Griesheim, Germany). 2-aminoaniline (o-phenylenediamine), 2-aminopyridine, 3-aminopyridine, 4-aminopyridine, 2-aminophenol, 4-aminophenol, 2-aminobenzoic acid, 3-aminobenzoic acid, 4-aminobenzoic acid, sulfanilic acid and 4-chloroaniline were kindly provided by Prof. em. S. Berger (Institute of Analytical Chemistry, University of Leipzig, Germany).

The detailed structures of all analytes are summarized in the Electronic Supplementary Material (ESM) Fig. S1. The analytes were selected for a systematic study of the influence of the molecular descriptors such as polarity and vapor pressure on the response with DBDI-MS. They provide a very broad structural variety, importance in biological contexts and many compounds of interest contain structural units that are similar to our analytes. In addition, these analytes are already well characterized in the literature and publicly available databases and all are amenable to LTP ionization.

Plasma source parts and configuration

The plasma source has already been described in detail [19]; a picture of the physical appearance is provided as ESM Fig. S2. Briefly, it consisted of an ignition transformer (EBI4 CM S, Danfoss, Nordborg, Denmark) and a glass tube (GC liner, Thermo Scientific, Waltham, MA, USA) with two surrounding outer electrodes made of copper foil tape (Noll GmbH, Wörrstadt, Germany). The electrodes were isolated by a homemade Teflon housing. The ignition transformer converted 230 V at 50/60 Hz to a peak-to-peak voltage (V_{PP}) of 2 ×

Table 1 Common characteristics of plasma sources

	DART	APGD/FAPA	PADI	DBDI/LTPI
Plasma species selection	Yes	No	No	No
Heating	Yes (additional heater)	Yes (by discharge)	No	No
Voltage	DC	DC	RF AC	AC
Type of plasma	Corona glow discharge	Glow arc discharge	Glow discharge	Dielectric barrier discharge

7.5 kV at a frequency of 25 kHz. Helium 5.0 (Air Liquide, Düsseldorf, Germany) was used as plasma gas. The flow was adjusted with an Ellutia 7000 GC Flowmeter (Ellutia Ltd., Ely, UK).

Plasma source configuration was optimized based on the signal intensities of model compounds and ionized air species [19], produced by the plasma after coupling the source to a Bruker Esquire 3000+ ESI-ion trap MS (Bruker Daltonics, Bremen, Germany) operated by Bruker esquire control 5.3 software.

LTPI responsiveness of anilines

A set of 31 anilines was prepared as 1 mM solutions in ACN/H$_2$O 1:1 for each aniline. The plasma source was placed in an angle of 30° towards the sample (ESM Fig. S2), in a distance of 0.5 cm to the MS inlet and the plasma source outlet, respectively. Mass spectra were acquired on an Esquire 3000+ MS with the following instrumental parameters: high voltage off, dry gas (nitrogen) 1.5 mL/min with a temperature set to 0 (readback 42 °C), scan range: m/z 50–300, target mass: 120. The number of ions per scan was limited to 20,000 with a maximum accumulation time of 200 ms and a rolling average of three scans. After spotting 1 μL of the solutions on a paper target, data acquisition was immediately started at least for 2 min and the average response of each analyte was calculated from triplicate analysis. Optimized parameters for plasma ionization were used: process gas flow 20 mL/min, dielectric thickness 2 mm, width and distance of the electrodes 10 mm each, and distance of the electrode to the outlet 20 mm [19]. Solvent blanks were run on a frequent basis to ensure the absence of cross-contamination.

Prior to the measurement of the complete set of aromatic amines after plasma ionization, dynamic behavior was successfully confirmed with three analytes in the concentration range of 1 μM to 5 mM aniline, 2-fluoroaniline and 4-methoxyaniline. For assessing the impact of different solvents on signal responsiveness, a set of six anilines was prepared as 1 mM solutions in acetone, acetonitrile, butan-1-ol, 1,4-dioxane, ethanol, methanol, propan-1-ol, tetrahydrofuran, and water, respectively, resulting in 54 samples. Three replicates of the freshly prepared solutions were analyzed by LTPI-MS.

Data evaluation

Responsiveness of the anilines was assessed as the average intensity (cps, peak height) of the corresponding peak for the [M + H]$^+$ ion of the analyte of interest and for chloroaniline as the sum of the two most abundant isotope peak signal intensities.

Characteristic chemical constants (negative decadic logarithm of the acid dissociation constant, pKa, molecular polar surface area, solvent accessible molecular surface area, logarithmic measure of the partition and distribution coefficients,

logP and logD, respectively, proton affinity, gas phase basicity, boiling point, vapor pressure, vaporization enthalpy, and surface tension) were retrieved from public databases, namely ChemSpider by the Royal Society of Chemistry, London, UK [http://www.chemspider.com/], chemicalize.org by ChemAxon, Budapest, Hungary [http://www.chemicalize.org/], Scifinder by the Chemical Abstracts Service, Columbus/Ohio, USA [https://scifinder.cas.org/], and the NIST Chemistry WebBook by The National Institute of Standards and Technology (NIST), Gaithersburg, USA [http://webbook.nist.gov/chemistry/]. Further information about the characteristic chemical constants and their calculation can be found in the ESM.

The molecular volume was calculated using the Spartan software package (Spartan 14, Wavefunction Inc., Irvine, CA, USA). The settings for calculation were DFT (density functional theory) B3LYP with a 6–31G* basis set.

Correlation analysis of peak signal intensities with physicochemical characteristics (Pearson's product-moment correlation coefficient and significance) was carried out using the Analysis ToolPak in MS Excel 2013 (Microsoft Corp., Redmond, USA). Before correlation analysis, a visual inspection of appropriate data distribution was carried out using scatter plots (ESM Fig. S4). Multivariate linear regression analysis was performed using IBM SPSS Statistics Version 24 (IBM, Armonk, New York, USA).

Results and discussion

Selective cluster formation between the target analyte and solvent

Ambient ionization methods for mass spectrometry were found earlier prone to produce cluster ions with appropriate gas phase molecules such as water [7, 20]. Indeed, protonation as observed in DART positive ionization mode was suggested to be effected by interaction with hydronium ion-water clusters in the plasma plume. In agreement, with most of the solvents we used during our experiments, we indeed observed protonation. However, we also experienced cluster formation not only with (ambient) water but also with the solvents THF and dioxane. In Fig. 1, a full scan spectrum for LTPI-MS analysis of aniline in THF is shown. However, cluster formation was rather specific for this solvent-analyte combination; with dioxane and toluidine it was less pronounced, and with other analytes not abundant at all.

Unlike Song et al. [21] using DART, in LTPI, THF was not ionized by protonation but appeared as [2 THF-H]$^+$ and a very small [THF-H]$^+$. Both species and the solvent cluster with aniline, [M + THF-H]$^+$, were also detected using ESI-MS (not shown). A hydride-ion leave after LTPI was already observed earlier for 4-methyl-1,3-dioxolane [22]. Concerning

Fig. 1 LTPI mass spectrum of
1 mM aniline in THF
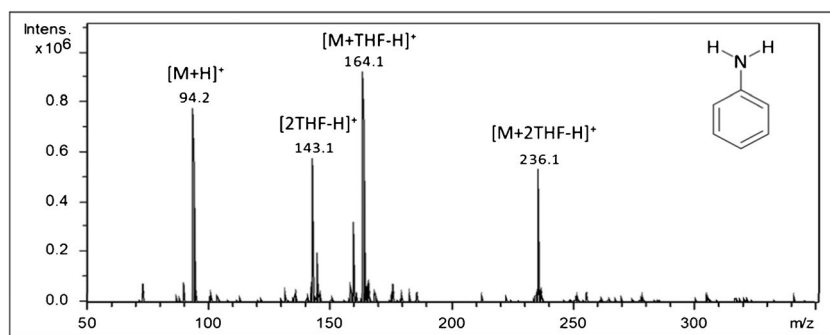
the solvents under investigation, dioxane showed a similar, but less pronounced behavior. In conclusion, the potential formation of clusters should be taken into account when choosing solvents for analysis, since they can complicate the obtained spectra unnecessarily and hamper sensitive detection of ions. The use of solvent-free ionization at the chosen conditions, on the other hand, was not successful in our hands and obtained signals were considerably smaller. Here, heating may be an indispensable precondition to DBDI to enable vaporization of the analyte and establishment of a balance between thermal stability and ionization efficiency of the target analytes might be required.

Volatility and polarity are the main compound characteristics determining signal intensity with LTPI

For the selection of a particular analytical technique, responsiveness is one of the critical parameters for quantitation of chemical compounds [23]. Therefore, we investigated the influence of the analyte characteristics on the corresponding signal intensity. During our experiments, 2-aminobenzoic acid, 3-aminobenzoic acid and sulfanilic acid were not detected, while amino-, nitro-, and hydroxyanilines were generally found to have the lowest response to low-temperature plasma ionization. In contrast, methoxy- and methylanilines showed the highest signal intensity, except *p*-methoxyaniline. Compared to our results from ESI [23], there was a big difference in the obtained signal intensities and reproducibility. Whereas plasma ionization of 1 mM *o*-anisidine produced the highest signal intensity of 1.6 million cps, ESI showed the highest signal intensity of 4.6 million cps for *p*-anisidine at a concentration of only 10 μM (50 μL/min flow rate). On the other hand, plasma ionization showed maximal signal differences between the analytes by a factor of about 90 compared to 320 with ESI measurements at pH 7 and factor 140 with ESI at pH 3 of the same analytes, indicating a lower selectivity of LTPI compared to ESI.

Concerning reproducibility, it is clear that there is still need for improvement of plasma ionization. Over all analytes, an average standard deviation of 46% for plasma ionization contrasting to 19% for ESI at pH 7 and 9% for ESI at pH 3 was observed (not shown). This difference may be reasoned by the

open construction of an ambient source resulting in much more variable conditions with respect to, e.g., fluctuations of sample flow, temperature, or moisture. Moreover, the prototypic nature of our plasma setup could contribute to this observation as well. The geometric arrangement of individual parts is not yet permanently fixed in place, greatly increasing flexibility and adaptability of the source but, unfortunately, at the possible expense of interday reproducibility. At the current stage, a comparison to commercial ESI equipment, which manufacturing is standardized, needs to consider that small variations in the *manually* adjusted distances between plasma source, analyte and MS inlet might influence signal intensity.

The logarithmized signal responses were subjected to analysis of covariance with the values of available molecular descriptors by Pearson correlation coefficient. The results showed a negative correlation for surface tension (very strong, ESM Fig. S3a), vaporization enthalpy (strong, Fig. 2a), and the second substituents electronegativity (weak, ESM Fig. S4) of the anilines. A positive correlation was found for the polarity descriptors molecular nonpolar surface area (very strong, Fig. 2b), logP (strong, ESM Fig. S3b) and the molar volume (moderate, ESM Fig. S3c). (Note: strength of correlation was evaluated according to Evans (1996) [24]: (a) very weak 0.00–0.019, (b) weak 0.20–0.39, (c) moderate 0.40–0.59, (d) strong 0.60–0.79, (e) very strong 0.80–1.0.)

The course of the plotted data (Fig. 2a) imply an S-shape with a linear range rather than strict linear dependency, with a particularly steep behavior in a narrow window between 45 and 50 kJ/mol, which may suggest the existence of thresholds near that values. In general, a lower vaporization enthalpy results in easier evaporation, and thus, the number of desorbed analyte molecules available for ionization in the gas phase is enhanced. In agreement, the supply of heat would promote ionization by improved evaporation and desorption of the analyte, and the use of higher temperatures has indeed already been described in the literature to improve LODs with LTPI [25–28] but was not the scope of our investigation of the behavior at native conditions (room temperature and humidity). Thus, we would expect the vaporization enthalpy—window to shift to the right (to higher values) for setups employing heat during ionization. Compounds with

Fig. 2 Log signal intensity in dependency on the **a** vaporization enthalpy and **b** nonpolar surface area of the analytes
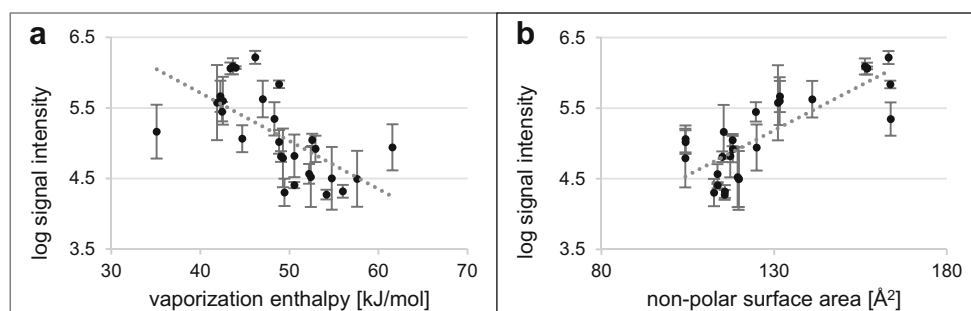
vaporization enthalpies below a certain, temperature-dependent threshold for ionization (as ~40 kJ/mol in our set-up) will presumably not show this correlation, as they are easily vaporized under ambient conditions already, while compounds above a certain threshold are hardly desorbed.

Multivariate linear regression analysis with stepwise backward elimination (Table 2) of non-significant variables suggested that 81% of the variance of logarithmized signal intensity is explained by the description factors vaporization enthalpy and molecular nonpolar surface area.

According to these results, six of the 12 molecular descriptors significantly influence signal responsiveness. In particular, nonpolar surface area and vaporization enthalpy show strong correlations. Consequently, in agreement with the literature [29], we consider an analyte's volatility and polarity the most influential factors in LTPI.

In addition to that, we observed a very strong correlation with the surface tension of the analytes. Surface tension is a result of the enhanced cohesive intermolecular forces between molecules at air-liquid interfaces. For many liquids, vaporization enthalpy changes linearly with the macroscopic surface tension [30, 31]. Consequently, surface tension and vaporization enthalpy of the analytes strongly correlate with each other ($R = 0.86$, ESM Fig. S4). In agreement with this relationship, we found higher signals with lower surface tension values of the analytes. In conclusion, surface tension might also be among the key players in LTPI under the chosen conditions.

Less volatile and less polar solvents improve LTPI signal responsiveness of substituted anilines

For investigations on the influence of the solvent on the signal response of analytes after LTPI, six analytes were analyzed in nine solvents as described above (LTPI responsiveness of anilines). The analytes were selected in order to compare electron donating and withdrawing effects, as well as the influence of the methylated or non-methylated amino group (e.g., its polarity). Solvents were selected to cover a series of increasing polarity (butanol to water) and boiling point (acetone to butanol) and to compare different polarities at the same boiling points (e.g., THF and methanol). Results are illustrated in Fig. 3.

Clearly, with LTPI-MS, the signal response is rather dominated by the influence of the analyte characteristics in comparison to the influence of the solvent. Furthermore, while N,N-dimethylaniline and 4,N,N-trimethylaniline exhibit a similar behavior in all solvents ($R = 0.92$), this does not apply for the other analytes indicating specific solvent-analyte interactions. The analogous signal intensity pattern of N,N-dimethylaniline and 4,N,N-trimethylaniline may be a consequence of similar molecular descriptors important for plasma ionization, e.g., nonpolar surface area, vaporization enthalpy, and logP. Thus, within this context, our results are in agreement with Petucci et al. [32], who obtained similar signal intensities for warfarin in six different solvents, apart from DMSO in which it had the lowest signal response. DMSO had the highest boiling point among the tested solvents.

Therefore, we reduced the impact of analyte characteristics on signal response by normalization to the corresponding maximum value among all solvents for a given analyte, in order to isolate the influence of the solvent on responsiveness. These normalized response patterns were subsequently subjected to correlation analysis with the molecular descriptors for the solvents under investigation. Unfortunately, we mostly obtained only inconsistent and non-significant patterns, even for the polarity of the solvent, so that we consider the influence of the

Table 2 Pearson's correlation coefficient and significance (p value) between log signal intensity and molecular descriptors of anilines from multivariate linear regression with stepwise backward elimination

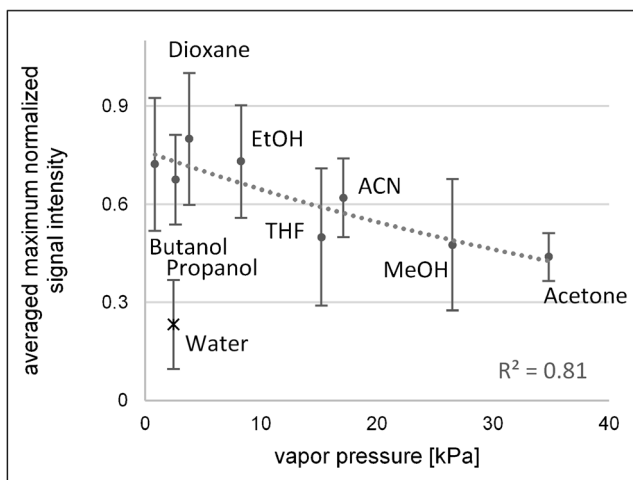| Log signal intensity	Nonpolar surface area	logP	Molar volume	Surface tension	Vaporization enthalpy	Substituents electronegativity
Pearson's correlation coefficient R	0.803	0.614	0.49	-0.859	-0.642	-0.39
Significance	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.05$

Fig. 3 Signal intensity of six analytes (from left to right: 4-nitroaniline, aniline, 4-methylaniline, N,N-dimethyl-4-nitroaniline, N,N-dimethylaniline, and 4,N,N-trimethylaniline) in nine different solvents
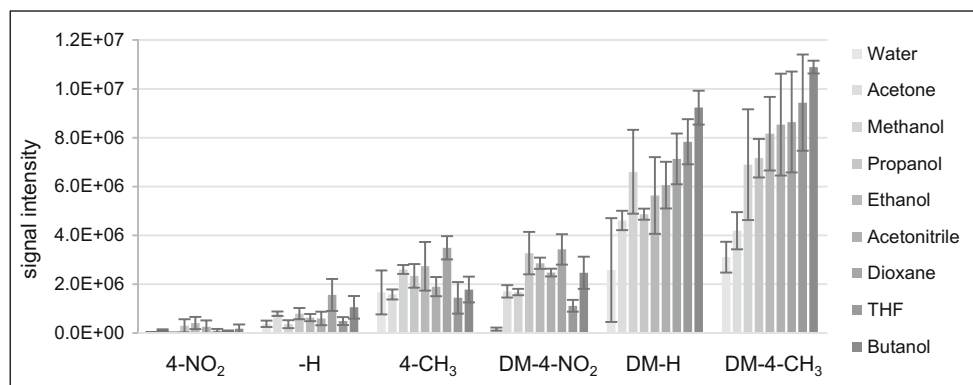
solvent characteristics again small and dominated by specific interactions between analytes and solvent, indicating that unpredictable matrix effects will interfere with signal response in applications of this technique. An exception was the boiling point ($R = 0.77$) and the related vapor pressure ($R = 0.84$) as represented in Fig. 4. For this presentation, the averaged normalized responses over the six analytes ($n = 6$) in the nine solvents (9 levels/data points) were plotted over the solvents vapor pressure. The RSD of the data points illustrates the variance within the response pattern of the analytes in a particular solvent, hence the extent of differences in relative signal responses caused by specific solvent-analyte interactions. The size of the error bars in Fig. 4 are therefore a measure for the appearance of selective matrix effects with a particular solvent.

As can be concluded from Fig. 4, correlation analysis of the signal intensities of the analytes with the available molecular descriptors for the solvents showed a negative correlation for the calculated vapor pressure of the solvents and consequently a positive correlation for the boiling point (not shown), i.e., a less volatile matrix seemed to enhance the analyte signal

intensity. The extracted correlation is very strong with a correlation factor (R) of 0.84 and a significance of $p = 0.017$. Unlike in Shelley et al. [33], the proton affinity of the solvents (matrix) had no influence in our case. In contrast, our results are rather in agreement with Song et al., who suggested that when the plasma reaches the sample, a transient microenvironment (TME) may be generated and the desorbed solvent would cause shielding effects hampering direct ionization of the analytes, i.e., causing ionization suppression [21]. However, on the other hand, signal intensity dropped dramatically when the solvent was completely consumed, so that we consider the mere presence of a solvent critically beneficial for LTPI-MS analysis and a threshold may exist for signal improvement by the solvents or matrix, respectively, vapor pressure.

Since the influence of the solvent still plays a minor role compared to the analyte characteristics, it may be particularly considered when sensitive analysis is required. Our findings showed that most of the solvents are suitable for plasma ionization, water, however, with limitations (Figs. 3 and 4). In contrast to the other tested solvents, water has a very high surface tension. Therefore, instead of the TME effect [21], desorption of analyte molecules into the gas phase might rather be hampered due to the strong intermolecular interactions at the air-liquid interface within this solvent [34, 35]. Finally, different solvent-analyte interactions impeded the general identification of an optimal solvent for LTPI as indicated by the large deviations of signal responses for the selected analytes dissolved in a particular solvent.

Conclusion

The influence of molecular characteristics of analytes and their solvents on signal response with low-temperature plasma ionization was investigated using a set of aromatic amines in common organic solvents and water. Typically, analytes were detected as [M + H]+, only in exceptional cases clusters were observed (e.g., with THF and aniline). The analysis of the amines demonstrates the already well-documented fact that

Fig. 4 Average maximum normalized signal intensity of the analytes as a function of the solvents vapor pressure (water as outlier is highlighted). R^2 was calculated excluding water (exponential fit). Standard deviation of each data point represents the response variance within the six analytes. EtOH … ethanol; MeOH … methanol

cold plasma ionization is a relatively soft ionization method since no fragmentation of the analytes occurred. It was further found that a low vaporization enthalpy and low polarity of the analyte are advantageous for achieving high signal intensities. Conversely, this means that for substances with a boiling point beyond 200 °C, the supply of additional energy, e.g., in the form of heat, might be recommended in order to achieve improved signal intensities.

Compared to the impact of the analyte's molecular characteristics such as volatility and polarity, the solvent exerts much less impact with respect to relative and absolute signal intensity. Thus, in our experiments, the use of a less appropriate solvent led to a signal reduction up to 50% for a given analyte. This could suggest that matrix effects with this technique might be less related with the sample composition per se but more detailed investigations of this behavior are required in the future. In general, a better signal intensity of the analyte was obtained with higher boiling solvents; however, except water, most of the solvents appeared to be almost equally suitable when using LTPI for mass spectrometry.

In summary, howbeit LTPI is an ideal technique to be implemented in mobile analytical devices in a way that conserves resources and requires little equipment, ionization of low-boiling and less polar substances is particularly favored. Though signal intensity seems to benefit from embedding the analyte in an organic matrix with a relatively low vapor pressure with low surface tension, specific analyte-matrix effects as well as a high variation in replicate analyses still hamper quantitative analyses and further investigation is required to address this bottleneck.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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