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RESEARCH ARTICLE

Rapid Screening of Carboxylic Acids from Waste and Surface Waters by ESI-MS/MS Using Barium Ion Chemistry and On-Line Membrane Sampling

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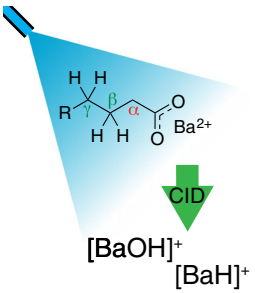

Abstract. Negative ion tandem mass spectrometric analysis of aliphatic carboxylic acids often yields only non-diagnostic ($[M - H]^-$) ions with limited selective fragmentation. However, carboxylates cationized with Ba^{2+} have demonstrated efficient dissociation in positive ion mode, providing structurally diagnostic product ions. We report the application of barium adducts followed by collision induced dissociation (CID), to improve selectivity for rapid screening of carboxylic acids in complex aqueous samples. The quantitative MS/MS method presented utilizes common product ions of $[M - H + Ba]^+$ precursor ions. The mechanism of product ion formation is investigated using isotopically labeled standards and a series of structurally related carboxylic acids. The results suggest that hydrogen atoms in the β and γ positions yield common product ions ($[BaH]^+$ and $[BaOH]^+$). Furthermore, the diagnostic product ion at *m/z* 196 serves as a qualifying ion for carboxylate species. This methodology has been successfully used in conjunction with condensed phase membrane introduction mass spectrometry (CP-MIMS), with barium acetate added directly to the methanol acceptor phase. The combination enables rapid screening of carboxylic acids directly from acidified water samples (wastewater effluent, spiked natural waters) using a capillary hollow fiber PDMS membrane immersion probe. We have applied this technique for the direct analysis of complex naphthenic acid mixtures spiked into natural surface waters using CP-MIMS. Selectivity at the ionization and tandem mass spectrometry level eliminate isobaric interferences from hydroxylated species present within the samples, which have been observed in negative electrospray ionization.

Keywords: Tandem mass spectrometry, Condensed phase membrane introduction mass spectrometry, Rapid screening, Bioanalytical chemistry, Environmental chemistry, Naphthenic acids, On-line analysis, Oil sands process water

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Introduction

Rapid screening methodologies offer researchers the option of surveying large numbers of samples prior to comprehensive targeted analysis (e.g., GC-MS or LC-MS). Further, with the advent of field portable miniature mass spectrometers [1–3] and ambient ionization sources [4, 5], mass spectrometry is a viable option for the direct analysis of environmental and/or bioanalytical samples. Many biomolecules and organic pollutants contain carboxylic acid functional groups [6]. In particular, naphthenic acids (NAs) have emerged as persistent environmental contaminants [7, 8]. NAs are classically defined as aliphatic carboxylic acids with the general formula $C_nH_{2n+z}O_x$, where *n* represents the number of carbon atoms, *z* the hydrogen deficiency, and *x* the number of oxygen atoms. Moreover, they exist as complex mixtures of hundreds to thousands of different molecules within contaminated samples [9, 10]. These analytes are often readily ionized by electrospray ionization (ESI) to yield predominantly $[M - H]^-$ ions. While an abundant deprotonated molecule is beneficial for tandem MS, many aliphatic carboxylic acids (e.g., fatty acids and naphthenic acids) generate very few or no structurally diagnostic product

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ions, which makes developing selective tandem MS methods virtually impossible [10, 11]. Consequently, selective direct MS analysis of aliphatic carboxylic acids remains difficult, in particular without the use of chromatography. In addition, negative mode electrospray ionization is effective at ionizing both hydroxylated and carboxylated analytes.

The use of metal ions for the cationization of carboxylated analytes facilitates analysis by positive ion MS [12]. In conjunction with collision induced dissociation (CID), cation adducts fragment via charge remote fragmentation mechanisms to form structure-specific product ions [12]. Examples of metal-carboxylate adducts used for mass spectrometry in the literature include di-lithium [13, 14], copper [15], and alkaline earth metal complexes [12]. In particular, several studies have focused on the cationization of fatty acids with barium [14, 16, 17]. Zehethofer et al. were able to screen 29 free fatty acids (saturated, unsaturated, and polyunsaturated) using unique tandem mass spectrometric transitions [17]. Interestingly, each mass spectrum that was displayed in their study had common product ions at *m/z* 139 and 155, attributed to and $[BaH]^+$ and $[BaOH]^+$, respectively. We exploit the use of this barium chemistry for the online complexation of carboxylates for subsequent mass spectral analysis. We report the utilization of these product ions for rapid screening of carboxylated analytes directly from complex aqueous samples using condensed phase membrane introduction mass spectrometry (CP-MIMS).

CP-MIMS is a direct sampling mass spectrometric method that utilizes a membrane interface to separate an aqueous sample from a flowing solvent acceptor phase. Several recent studies establish CP-MIMS as a relevant method for the rapid quantitative analysis of pharmaceuticals, environmental contaminants, and biomolecules from real-world matrices (e.g., surface water, wastewater effluent, and artificial urine) [18–21]. The membrane precludes transport of ionized species within the sample (e.g., salts), whereas hydrophobic analytes partition into the membrane, diffuse through it, and are solvated by a flowing acceptor solvent. The signal to noise ratio is increased over direct infusion methods by reducing the noise and ionization suppression related to ionized matrix species in the sample [18]. In general, both the selectivity and sensitivity of CP-MIMS can be affected at the membrane (permselectivity), ion source (ionization efficiency), and mass spectrometry level.

We report the combination of selective ionization and tandem mass spectrometry (via barium–carboxylate complexes) in positive ion mode with CP-MIMS for on-line rapid screening of carboxylated analytes in complex aqueous samples. A series of structurally related compounds were analyzed by direct infusion to identify the source of hydrogen present within the common $[BaOH]^+$ and $[BaH]^+$ product ions, to elucidate a mechanism, and establish structural criteria for carboxylic acid detection by this method. In addition, both carboxylated and hydroxylated analytes were examined to identify possible isobaric interferences. Direct calibration of several model analytes is presented, demonstrating method linearity and limits of detection. Lastly, we apply positive ion tandem MS methods for the screening of naphthenic acids with unknown molecular structures in spiked surface waters from northern Alberta. This method can be used for non-targeted screening, where selectivity for carboxylic acids in complex samples arises in part from the barium ion affinity [22] in the flowing acceptor as well as positive ion tandem MS to yield common product ions [16].

Experimental

Standard Solutions and Sample Preparation

All stock solutions were prepared gravimetrically in methanol using compounds with 99.99% purity (Sigma Aldrich, Oakville, ON, Canada), unless otherwise noted. Barium acetate (99.99%, Fisher Scientific, Ottawa, ON, Canada) stock solutions were prepared in deionized 18 MΩ water (Model MQ Synthesis A10; Millipore Corp., Billerica, MA, USA). Solutions used for obtaining CID spectra were prepared at 500 ppb of the desired analyte in methanol with 0.1 mM barium acetate (final water concentration of 2.5% v/v). Perfluoroctyl ethanoic acid was obtained as a 50 ± 2.5 μg/mL solution in isopropanol (Wellington Laboratories, Guelph, ON, Canada). Wastewater effluent was collected from a small municipality in British Columbia, and surface water was collected from a river in northern Alberta; both were stored at 4 °C, and raw samples were used without filtration for CP-MIMS analysis. Refined Merichem naphthenic acid standard (Merichem Company, Houston, TX, USA), a complex mixture of naphthenic acids, was supplied from Environment Canada and stored at 4 °C prior to dilution.

Mass Spectrometry Method Development

A syringe pump (Econoflow; Harvard Apparatus, St. Laurent, QC, Canada) was employed to directly infuse solutions at 200 μL/min (for direct comparison to CP-MIMS experiments) to a triple quadrupole mass spectrometer (Quattro LC; Waters, Altrincham, UK) with positive electrospray ionization. Desolvation gas was maintained at 700 L/h at 300 °C, with a 50 L/h curtain gas setting. Relatively high cone voltages were required to maximize the abundance of desired carboxylate-barium adduct species, with the entrance cone set at 50 V and the extractor cone set at 10 V. A high collision cell pressure was utilized (~8 mTorr) for CID (collision energy, 60 eV), which displayed the greatest intensity for desired product ions. Product ion scans with a 1 s scan time over *m/z* 100 to 500 in Q3 were used to obtain CID mass spectra, which were averaged for >30 scans.

Condensed Phase Membrane Introduction Mass Spectrometry

CP-MIMS experiments were conducted using polydimethylsiloxane (PDMS) hollow fiber membrane (HFM) (Dow Corning Silastic tubing, o.d. = 0.64 mm; i.d. = 0.30 mm; 170 μm thickness; Midland, MI, USA) membrane immersion probes constructed in-house as previously described [20, 21]. A

syringe pump was used to push acceptor phase solvent through the lumen of the HFM at 200 μL/min. The membrane interface probes were directly immersed into well-mixed aqueous samples acidified to pH < pKa (typically pH ~ 4), and rinsed with clean methanol (HPLC grade, Fisher Scientific) between samples. Aqueous sample pH was adjusted to < 4 via small additions of 6 M HCl (Fisher Scientific), and verified via pH test strips (Sigma Aldrich).

Both methanol and acetonitrile were evaluated as acceptor phase solvents, with methanol giving the lowest background intensities for peaks in the spectral region of interest (*m/z* 300–500). Barium acetate was added directly to the acceptor phase reservoir to a final concentration of 0.1 mM, as previously published [17]. Experiments were conducted with 0.05, 0.1, and, 0.2 mM barium acetate, with the greatest signal to noise resulting from 0.1 mM (data not shown). Data for CP-MIMS experiments were collected using multiple reaction monitoring for $[M - H + Ba]^+$ ions fragmenting to *m/z* 155 and 139 (0.5 s dwell time each). Signal intensities displayed in the figures correspond to the sum of intensities for both *m/z* 155 and 139 for each precursor ion. All experiments were conducted at room temperature and atmospheric pressure (~25 °C and 101 kPa).

Results and Discussion

Confirmation of Diagnostic Ions for Quantitative Screening Purposes

Previous work by Volmer and coworkers employing barium ions as cationization reagent for fatty acids by tandem MS displayed major product ions at *m/z* 155 and 139, attributed to $[BaOH]^+$ and $[BaH]^+$ [17]. To elucidate the source of hydrogen in these product ions, several model carboxylic acids were prepared in dilute methanol solution with 0.1 mM aqueous barium acetate (2.5% v/v). To establish whether α hydrogen transfer was taking place, lauric acid, 2,2-lauric acid-d_2, and perfluoro-octylethanoic acid solutions were directly infused into the mass spectrometer, and product ions *m/z* 139 and 155 produced from the precursor ion $[M - H + Ba]^+$ were monitored. Figure 1 displays the resulting CID mass spectra. The lauric acid CID spectrum (Figure 1a) exhibits several diagnostic ions and compares well with analogous spectra from the literature [17]. Interestingly, the spectra obtained for lauric acid-d_2 (Figure 1b) displays a strong signal for the same product ions at *m/z* = 139 and 155, as depicted in Scheme 1. However, the peak occurring at *m/z* 196 from lauric acid now appears at *m/z* 198. We attribute this ion to $[C_2H_2O_2Ba]^+$ (or $[C_2D_2O_2Ba]^+$ in case of lauric acid-d_2), which results from bond cleavage between the α and β carbons (Scheme 1). Secondly, the signal at *m/z* 209 has shifted to 210. The ion at *m/z* 209 has been previously attributed to charge remote fragmentation between β and γ carbons, resulting in the formation of an alkene after loss of H_2 [23]. This is further supported by the shift of *m/z* 209 to 210 for CID of lauric acid-d_2, where a deuterium atom is lost from the α position. We propose the ion to have the formula $[C_3H_2DO_2Ba]^+$. Since no mass shift was observed for *m/z* 155 or 139, the source of hydrogen in $[BaOH]^+$ and $[BaH]^+$ is not the α position. Furthermore, when perfluoro-octylethanoic acid (which only contains hydrogen atoms in α position) was directly infused under the same conditions (see Figure 1c), no signal was observed for *m/z*

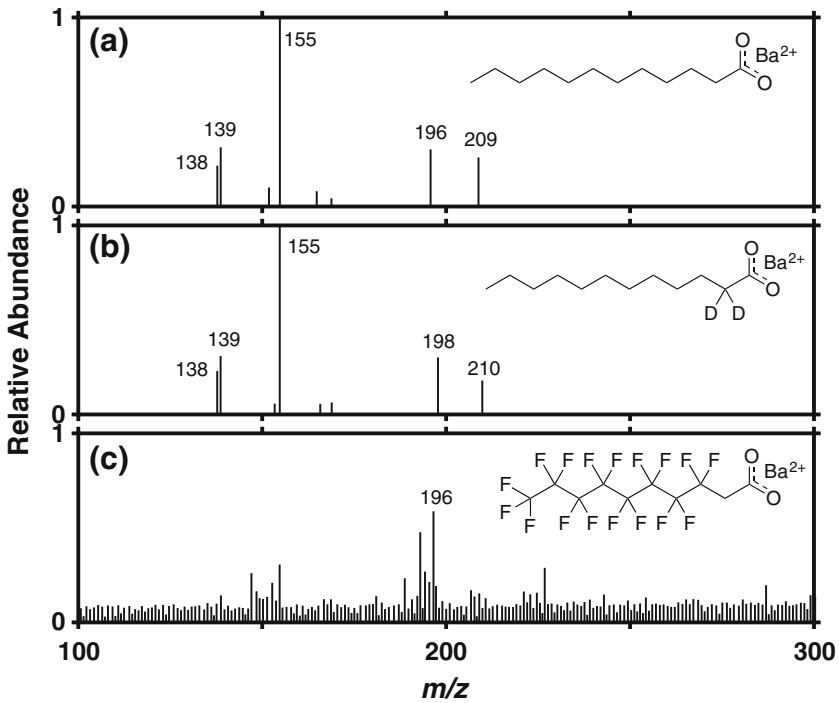
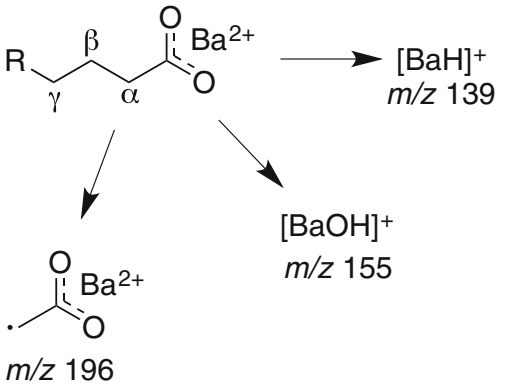


Figure 1. CID mass spectra for (**a**) lauric acid, (**b**) lauric acid-d_2, and (**c**) perfluoro-octylethanoic acid in the presence of barium acetate. The noise seen in panel (**c**) is the result of considerably lower absolute intensities



Scheme 1.

155 and 139. This observation confirms the hypothesis that hydrogen transfer from the α position was not responsible for formation of $[BaOH]^+$ and $[BaH]^+$ product ions.

A homologous series of phenyl-substituted aliphatic carboxylic acids were investigated to determine if the hydrogen atom from β or γ carbons was transferred to form the product ions at *m/z* 155 and 139. The CID spectra for 2-phenylethanoic acid, 3-phenylpropanoic acid, and 4-phenylbutanoic acid are displayed in Figure 2. As expected, no discernable signals were observed for *m/z* 155 and 139 for 2-phenylethanoic acid, which only has α carbon hydrogen atoms. Conversely, the desired product ions were readily observed by CID of 3-phenylpropanoic acid (Figure 2b), which has β carbon hydrogen atoms. Signal intensity for *m/z* 155 and 139 increased when hydrogen atoms were present on the γ carbon, as illustrated by CID of 4-phenylbutanoic acid (Figure 2c). The results suggest that hydrogen atoms on β and/or γ carbons can lead to formation of both $[BaOH]^+$ and $[BaH]^+$. Further, the increase of signal intensity observed for 4-phenylbutanoic acid could indicate a combination of two competing mechanisms. Thus, prospective carboxylic acids analyzed by this method must contain hydrogen atoms on either β or γ carbons in order to be detected. A proposed mechanism for formation of $[BaOH]^+$ and $[BaH]^+$ from $[M - H + Ba]^+$ precursor ions is shown in Scheme 2. It is conceivable that a similar mechanism exists for γ hydrogen transfer. However, as no compounds were available to us that contained exclusively γ hydrogens, we were unable to confirm this mechanistic variant. It should be noted that the final product structures in Scheme 2 are not directly observed, and their inclusion here is merely for reasons of completeness.

To evaluate method selectivity, several model compounds were directly infused into the ESI source, monitoring the product ions at *m/z* 139 and 155 from $[M - H + Ba]^+$. Figure 3 displays the resulting signal intensities from four different carboxylic acids (50 ppb) and four different alcohols (250 ppb). Strong signals were observed for the carboxylated analytes, except for perfluorodecanoic acid (which does not contain C–H bonds). Perfluorodecanoic acid was added as a control to ensure that *m/z* 155 and 139 were not products of

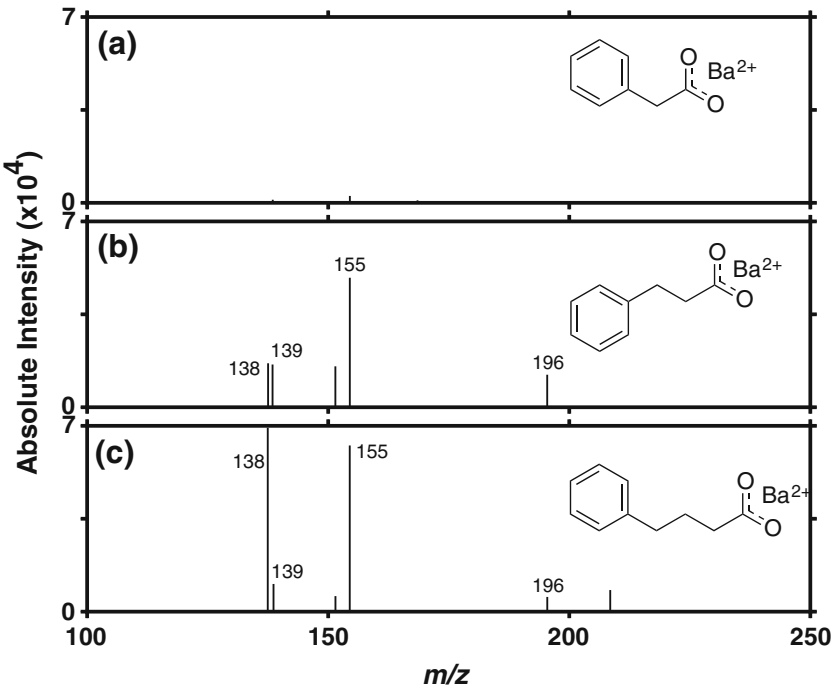
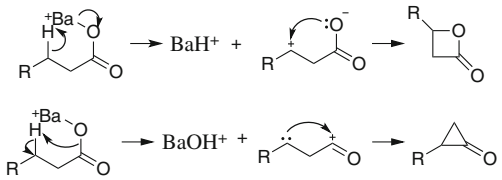


Figure 2. CID mass spectra of (**a**) 2-phenylethanoic acid, (**b**) 3-phenylpropanoic acid, and (**c**) 4-phenylbutanoic acid in the presence of barium acetate



Scheme 2.

hydrogen/hydride transfer from background moisture within the collision cell. It is quite apparent that no signal was observed from hydroxylated species, even at the higher concentrations tested. We attribute this to the much weaker affinity of barium ions for alcohols within the acceptor solvent phase and/or the liquid/gas phase of the ESI source.

Although no signals were observed for monohydroxylated molecules, we observed barium adducts for a 1,3-diol (2-ethyl-1,3-hexanediol), generating product ions at *m/z* 155 and 139 (CID spectrum given in Supplementary Figure S1). However, this compound did not give rise to the qualifier ion at *m/z* 196 (Scheme 1 and Supplementary Figure S1). Cleavage between the α and β carbon for 1,2-diol ions with the formula $[M - H + Ba]^+$ would result in *m/z* 197 product ions, and the same process for 1,3-diols would yield product ions with three carbon atoms (*m/z* >196). In summary, the tandem MS method used for subsequent experiments selects for a $[M - H + Ba]^+$ precursor ion and monitors the sum of $[BaOH]^+$ and $[BaH]^+$ product ions. Analytes with unknown molecular structures can be identified as carboxylic acids via this method, provided the CID spectrum also contains the qualifying ion at *m/z* 196.

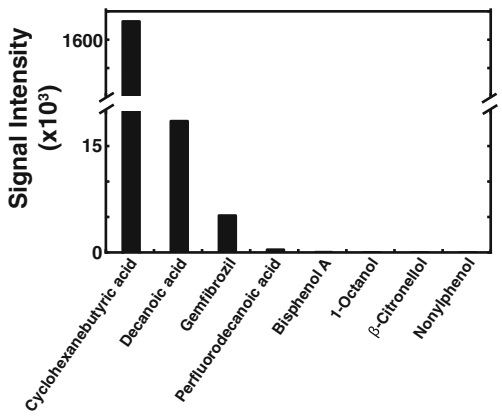


Figure 3. Direct infusion of several carboxylated and hydroxylated compounds. The signal intensity displayed represents the sum of the product ions *m/z* 139 and 155 for the CID analysis of each corresponding $[M - H + Ba]^+$ ion. The first three compounds also exhibit the qualifier ion at *m/z* 196

Direct Analysis in Wastewater Effluent

Combining the selectivity of barium adduct formation and tandem MS with CP-MIMS allowed for the continuous on-line direct measurement of carboxylic acids in complex aqueous samples. By simply adding barium acetate to the methanol acceptor phase solvent reservoir, CP-MIMS [21] was readily adapted. The addition of barium acetate facilitated both the complexation of barium to carboxylates in the acceptor phase solution (by raising the pH above the pK_a value of the carboxylic acids) and cationization of carboxylates during the ESI process. To demonstrate the utility of this method, a CP-MIMS probe was immersed directly into wastewater effluent spiked with increasing levels of lauric acid and gemfibrozil. Representative calibration curves plotting the sum of product ion intensities (*m/z* 139 and 155) versus concentration are presented in Figure 4. Excellent linearity was observed, with r^2 values for lauric acid and gemfibrozil at 0.997 and 0.999. Experiments in deionized water yielded a linear dynamic range (LDR) for gemfibrozil of three orders of magnitude with concentrations up to 1200 ppb. Although Zehethofer et al. observed considerably wider LDR for similar analytes using LC-MS with the same barium acetate concentrations [17], we attributed the smaller range observed here to ion suppression effects from co-permeating matrix molecules, particularly in complex 'dirty' samples. Although the membrane in CP-MIMS precluded any charged species from entering the acceptor phase, co-permeating matrix molecules have been previously demonstrated to contribute to ionization suppression in ESI [21]. In this earlier study, we presented several strategies for increasing the LDR for CP-MIMS-ESI, including: (1) using a continuously infused internal standard to provide correction factors to account for variations in ionization efficiency and ionization suppression; and (2) adjusting the flow of acceptor solvent to increase or decrease the effective concentration of permeating analyte species in the acceptor phase solvent. The same methods could also be employed here to extend the LDR, if necessary.

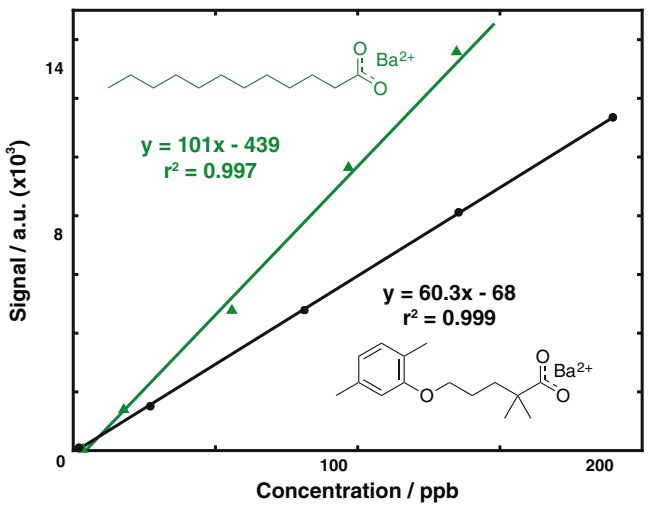


Figure 4. Calibration of model compounds in wastewater effluent. The signal displayed represents the sum of both *m/z* 139 and 155 product ions from each $[M - H + Ba]^+$ precursor ion

Table 1 summarizes calculated detection limits for gemfibrozil and lauric acid by CP-MIMS in both negative ion ESI mode using $[M - H]^-$ ions and tandem MS of barium adducts in positive ion mode. As can be seen, both model analytes exhibited detection limits of 1 ppb with the barium cationization method, which is ca. 10 times higher than for the negative ion experiments. Given that gemfibrozil has distinctive CID transitions in negative ion ESI (*m/z* 249 ➔ 121), barium cationization in a targeted screening method offers few advantages. However, lauric acid does not fragment to any diagnostic ions in negative ESI mode. The higher detection limits observed may therefore be an acceptable sacrifice for gaining improved selectivity of targeted tandem MS screening amenable to aliphatic carboxylated analytes. This is particularly important for fast, direct sampling methods that preclude chromatography such as CP-MIMS.

Non-targeted Tandem MS Screening of Naphthenic Acids

The analytical method presented here can be used for targeted or non-targeted screening of carboxylic acids in contaminated aqueous samples. Given that the product ions are common for the barium carboxylate adducts ($[M - H + Ba]^+$), unknown carboxylated analytes can be identified through CID spectra, and functional group confirmation can be ascertained through the presence of *m/z* 196 ($[C_2H_2O_2Ba]^+$). We have previously demonstrated CP-MIMS as a potential rapid screening methodology for naphthenic acids from contaminated aqueous samples [20, 24]. Further, recent work has shown that hydroxylated compounds contribute signal to CP-MIMS quantification of NAs using negative ion ESI (data not shown).

To demonstrate proof of concept, the method was used for on-line monitoring of naphthenic acids in a natural water sample. Figure 5 displays the time evolution (chronogram) of the MS/MS signal intensity from the continuous monitoring of a surface water from northern Alberta. At ~ 5 min, a spike of a Merichem NA mixture was added to yield a resulting total NA concentration of 1 ppm. While this sample is extremely complex, containing many individual NAs and other compounds [7, 25], we have exploited the barium ion adduct formation and the CID qualifier ion at *m/z* 196 to increase the specificity for

Table 1. Comparison of Detection Limits Between Negative Mode ESI and Positive Tandem MS Method or Analytes in Deionized Water

Analyte	Ionization method			
	Negative ESI CP-MIMS		Barium adduct CP-MIMS	
	MS	DL[a]/ ppb	MS	DL[a]/ppb
Lauric acid	SIM 199	0.1	MS/MS 337 ➔ 139 + 155	1
Gemfibrozil	MS/MS 249 ➔ 121	0.05 [21]	MS/MS 387 ➔ 139 + 155	1

[a]Detection limit based on S/N = 3

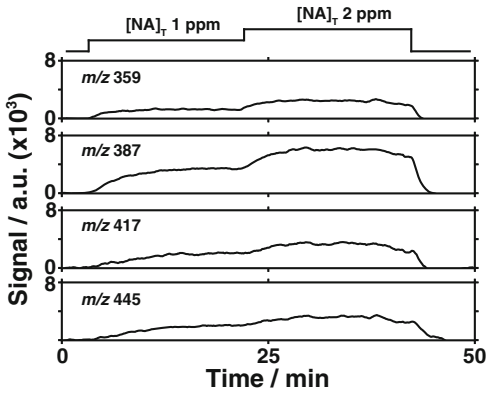


Figure 5. On-line tandem MS analysis of Merichem naphthenic acids spiked to a natural river water sample. The signals represent the sum of *m/z* 139 + 155 ions arising from $[M - H + Ba]^+$ precursor ions (indicated), with the qualifying ion at *m/z* 196 present in the CID spectrum

NAs. Figure 5 displays the signals at *m/z* 139 + 155 arising from four selected $[M - H + Ba]^+$ precursor ions at *m/z* 359, 387, 417, and 445, corresponding to NA isomer classes $C_{14}H_{22}O_2$ ($[M - H]^-$, *m/z* 221), $C_{16}H_{26}O_2$ ($[M - H]^-$, *m/z* 249), $C_{18}H_{32}O_2$ ($[M - H]^-$, *m/z* 279), and $C_{20}H_{36}O_2$ ($[M - H]^-$, *m/z* 307), respectively. Ions from negative ion ESI are included to facilitate comparisons with other studies [26]. At nominal mass resolution, only the NA isomer class is known (i.e., there will generally be several individual NAs at each *m/z* with varying chemical structure). The concentration of each monitored ion (isomer class) is in the low parts-per-billion range. In excellent work by Woudneh et al. using solid phase extraction, chemical derivatization and liquid chromatography-mass spectrometry, abundances for all naphthenic acid isomer classes present in a Merichem mixture were provided [26]. Using these data for the composition of Merichem, the estimated concentrations of each NA isomer class for each spike correspond to 53, 75, 15, and 4 ppb for the signals displayed in Figure 5 at *m/z* 359, 387, 417, and 445, respectively. This suggests that we were able to monitor trace levels of NAs with unknown molecular structures directly in surface waters. However, the authors note that the ionization efficiencies of individual analytes may vary, and in the case of non-targeted analysis, this method could suffer from inherent biases in quantitation. This challenge is not unique to the presented method, and is common whenever analytical standards for individual compounds are not available. This assay also excluded signals from hydroxylated species present in the contaminated samples, which could otherwise contribute to the signals in negative ion ESI, resulting in positive bias. Improved selectivity is particularly relevant for continuous online methods where sample clean-up and chromatographic separations are not possible or problematic. Further, with the growing interest for field portable ESI mass spectrometers [1, 2], this method could offer increased selectivity for in-field analysis of carboxylic acids, while maintaining the analytical robustness that is inherent to CP-MIMS.

Conclusions

We have demonstrated a method for selective ionization and tandem mass spectrometric identification of carboxylic acids directly in aqueous samples. The method employs common product ions for all barium complexed carboxylate precursor ions ($[M - H + Ba]^+$). Use of isotopically labeled standards and a homologous series of phenyl-substituted carboxylic acids suggests the source of hydrogen present within the common product ions $[BaOH]^+$ and $[BaH]^+$ is not from an α carbon, but rather from the β and/or γ positions. Possible method interferences including 1,3-diols can be eliminated by the use of *m/z* 196 ($[C_2H_2O_2Ba]^+$) as diagnostic qualifier ion, which only occurs for barium carboxylates. We have paired this new tandem MS method with CP-MIMS for direct analysis of carboxylated analytes in complex aqueous samples (e.g., wastewater effluent and northern Alberta surface water). The observed linear dynamic range is roughly two orders of magnitude and may be extended using corrections from a continuously infused standard and/or modulating the acceptor phase flowrate [21]. Detection limits calculated for model analytes are in the low ppb range, which is approximately 10 times higher than those observed for negative ESI. However, the lower sensitivity is offset by greater selectivity, which is particularly important for fast, direct sampling methods that preclude chromatography such as CP-MIMS. Lastly, we demonstrate the use of this method for non-targeted screening of naphthenic acids at the ppb level with directly spiked surface water samples. In combination with conventional techniques (e.g., LC-MS), rapid screening methods can be used to increase the number of samples analyzed, while minimizing the time and cost of analysis. The method described can be elaborated for both qualitative and quantitative screening of carboxylated analytes in bioanalytical and/or environmental samples, with the potential for in-field analysis.

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