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COMMUNICATION

Using differential ion mobility spectrometry to perform class-specific ion-molecule reactions of 4-quinolones with selected chemical reagents

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Abstract
Gas phase ion/molecule reactions are often used in analytical applications to support the analysis of isomers or to identify specific functional groups of organic molecules. Until now, deliberate chemical reactions have not been performed in differential ion mobility spectrometry (DMS) devices except for hydrogen exchange and cluster formation. The present work extends that of Colorado and Brodbelt (Anal Chem 66:2330–5, 1994) on ion/molecule reactions in an ion trap mass spectrometer. In this study, class-specific chemical reactions of 4-quinolone antibiotics with various chemical reagents were used to demonstrate the analytical utility of ion/molecule reactions in a DMS drift cell. For these reactions, dehydrated reactive precursor ions were initially formed and made to undergo annulation reactions with selected reagents within the timescale of the DMS separation. Careful study of the energies required for dissociation of the adducts confirmed the covalent nature of the newly formed bond; thus demonstrating the analytical utility of this approach.

Keywords Differential ion mobility spectrometry · Ion/molecule reactions · 4-Quinolone antibiotics · Protomer separation

Introduction

Ion mobility spectrometry (IMS) separates ions based on differences of mobilities in the gas phase. In the classical drift tube spectrometer, the ions move through a counter current gas flow in the drift cell driven by a potential difference. Different collision cross sections (CCS) of the molecules result in different drift times, which enable separation of ions. In field asymmetric waveform ion mobility spectrometry (FAIMS) and differential ion mobility spectrometry (DMS), differences of ion mobilities in a high (e.g., 20 kV cm^{-1}) and a low (e.g., 1 kV cm^{-1}) electric field are utilized for the separation [1]. Both FAIMS and DMS use an asymmetric separation voltage (AC) and superimpose a direct current voltage (compensation voltage) to prevent ions from discharging at the electrodes. Differences of the two techniques exist with respect to their electrode structures: FAIMS utilizes a cylindrical design, whereas DMS has two parallel, planar electrodes [1, 2]. These designs enable DMS and FAIMS to be used with a continuous ion beam, in contrast to IMS, where the ions must be pulsed into the drift tube. FAIMS and DMS are therefore ion filters, comparable to a quadrupole mass analyzer, whereas IMS operates similar to a time-of-flight mass spectrometer. There are numerous analytical applications for hyphenated IMS-MS, as CCS and drift times are directly related [3–5]. FAIMS and DMS are particularly suitable for hyphenation to LC-MS, to separate isobaric compounds [2], reduce chemical noise [6] or to separate charge isomers such as protomers [7–11]. The resolving power and specificity of DMS, especially for separation of chemically similar compounds such as isomers and protomers, can be influenced by addition of vaporized chemical modifiers (e.g., diethyl ether, methanol, or water) to the gas flow of the FAIMS or DMS cell. These modifiers trigger enhanced modifier/ion interactions during the low electric field phase of the separation and thus form ion/modifier clusters, which subsequently dissociate during the high electric field phase [12]. This effectively creates larger differences of ion mobilities between high and low electric fields, which is the essential working principle of FAIMS and DMS [1].

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In this study, modifier/ion cluster formation during the low field phase was utilized as a means of inducing ion/molecule reactions. Ion/molecule reactions are widely used in analytical applications such as identification of functional groups in organic molecules [13, 14], for studies of drug metabolism [15] and biomolecules [16], for distinction and identification of isomers as well as chiral [17] and achiral [18] compounds. For example, borates and boranes (e.g., trimethyl borate, tris(dimethylamino)borane, and diethylmethoxyborane) can be used for identification and differentiation of epoxides [19], phosphorylations [16], N-oxides [15], sulfoxides [15], and other oxygen-containing functional groups [13, 14, 20]. Ion/molecule reactions were also used for ion/molecule reactions of 4-quinolones after collision-induced dissociation (CID), as described by Colorado and Bordbelt [21]. The authors reacted dehydrated product ions formed from the protonated molecules with various compounds (acetone, methanol, 1,2-ethanediol, and 2- aminopropanol) in a modified ion trap mass spectrometer [21]. The analytical application of such reactions is not straightforward, however, as commercial mass spectrometers do not easily allow introduction of chemical reagents. On the other hand, a commercial DMS instrument can be easily used for this purpose without any modification, as it provides the possibility of introducing volatile chemical reagents for inducing cluster formation and enhanced separation. Here, we report the application of DMS for performing chemical modifications of ionized 4-quinolone antibiotics using a variety of different chemical reagents. To our knowledge, there has not been any previous report of deliberate chemical reactions within an ion mobility cell, except for H/D exchange reactions [22–27].

Material and methods

Chemicals

Ciprofloxacin, danofloxacin, flumequine, nalidixic acid, formic acid, diethyl ether, LC-grade acetonitrile, diethyl ether, LC grade absolute ethanol, 1-propanol, 2-propanol, and acetone were purchased from Sigma-Aldrich (Steinheim, Germany). LC-grade methanol was purchased from VWR International (Darmstadt, Germany). Organic-free water was generated by a Millipore (Bedford, MA, USA) Direct-Q8 purification system. Stock solutions of quinolones at 100 μM were prepared in methanol and diluted to 1 μM in 70/30 methanol/water $(v/v) + 0.1\%$ formic acid prior to the experiments.

Mass spectrometry and differential ion mobility spectrometry

All experiments were performed on an Sciex QTRAP 5500 quadrupole-quadrople-linear ion trap (QqLIT) MS equipped with a SelexIon differential ion mobility cell between electrospray ionization (ESI) source and orifice. The detailed instrumental setup is described elsewhere [28, 29]. Selected ion monitoring (SIM) and tandem (MS/MS) data were acquired in positive ESI mode at 5.5 kV; samples were infused continuously at 7 μL/min using an integrated syringe pump. The ion source and mass spectrometer were operated under the following parameters: source temperature, 80 °C; curtain gas, 23 psi; nebulizer gas (GS1), 25 psi; auxiliary gas (GS2), 0 psi; declustering potential, 65–115 V (optimized for each compound); entrance potential, 10 V; collision cell exit potential, 13 V; collision energy 5–50 V at 0.1 steps for break down curves; SIM dwell time, 100 ms, nitrogen as collision gas at medium setting. Parameters for the DMS cell were as follows: temperature, high (300 °C); resolution enhancement (DR), off; DMS offset (DMO), − 3 V; modifier compensation, high (3%); separation voltage (SV), 3500 V. The compensation voltages (CV) for CV chromatograms were scanned from − 50 to 25 V in 0.1 V steps; for the MS/MS experiments an optimized value was used. For comparison of stability and binding strength of the formed products, we compared the collision energies required for dissociation 90% of the precursor ion $[M+H]^+$ and $[M+H\text{-}H_2O+\text{reagent}]^+$.

Results and discussion

Class-specific ion/molecule reactions of activated 4-quinolone precursor ions in DMS cell after electrospray ionization with subsequent tandem mass spectrometric analysis of the reaction products were studied here. For this purpose, we utilized the gas phase ion/molecule reactions of 4-quinolones previously described by Colorado and Brodbelt [21], who used reactive product ions after CID as substrates for reaction with a variety of chemical reagents in a modified ion trap mass spectrometer.

We implemented similar ion/molecule reactions in our work, but transferred the reactions to a commercial DMS device, which was placed between the ESI source and mass analyzer of a quadrupole-quadrupole-linear ion trap mass spectrometer. We used the 4-quinolones nalidixic acid, flumequine, danofloxacin and ciprofloxacin, and acetone, ethanol, methanol, 1-propanol, 2-propanol, and acetonitrile as chemical reagents for the reactions in the DMS cell. These reagents were chosen because they were able to undergo nucleophilic substitutions with the substrate in the gas phase, analogous to well-known S_N1 reactions in organic chemistry. The initial step of the utilized ion/molecule reactions was the formation of dehydrated $[M+H\text{-}H_2O]^+$ product ions from the protonated 4-quinolones. These highly reactive, electrophilic acylium ions readily reacted with nucleophilic reagents via a six-membered ring, as shown in Fig. 1, exemplified for the

reaction of dehydrated protonated molecule of ciprofloxacin with ethanol, acetone, and acetonitrile.

Diethyl ether was used as a negative control reagent, as this compound cannot chemically react with the dehydrated $[M+H\text{-}H_2O]^+$ ions.

The yields of the initial dehydration reaction in the ion source depended strongly on the analyte structure, ranging from 6.5% for ciprofloxacin, 17.9% for danofloxacin, 25.4% for flumequine, to 53.4% for nalidixic acid. Importantly, the dehydration reaction can only occur from the protonated keto group at C-4, which is the major protonation site for nalidixic acid and flumequine. The proton affinity of this group is unusually high, which is due to partial aromatization of the six-membered ring upon protonation and formation of a hydrogen bond between the protonated keto and the adjacent carboxyl group. Ciprofloxacin with its basic piperazinyl and danofloxacin with a corresponding 2,5-diazabicyclo[2.2.1]heptyl group exhibit alternative protonation sides of similar proton affinity [7]. We have previously shown that 4-quinolones with two basic sites in the gas phase give two abundant protomers A and B, upon electrospray ionization (Fig. 2a) [7], which are readily separated by DMS. Importantly, the dissociation reactions of the two isomeric $[M+H]^+$ ions are entirely different: while isomer A's fragmentation proceeds via an initial charge-remote neutral loss of CO_2 from the carboxyl group, isomer B dissociates via an initial charge-mediated neutral loss of H_2O from the same carboxyl group. For our research, we utilized the reactive B species as precursor for the subsequent chemical reaction in the DMS cell. Figure 2 illustrates the DMS separation of the A and B protomers along with the corresponding CID spectra.

With the current experimental setup, only reagents with sufficiently high vapor pressure could be implemented. In practice,

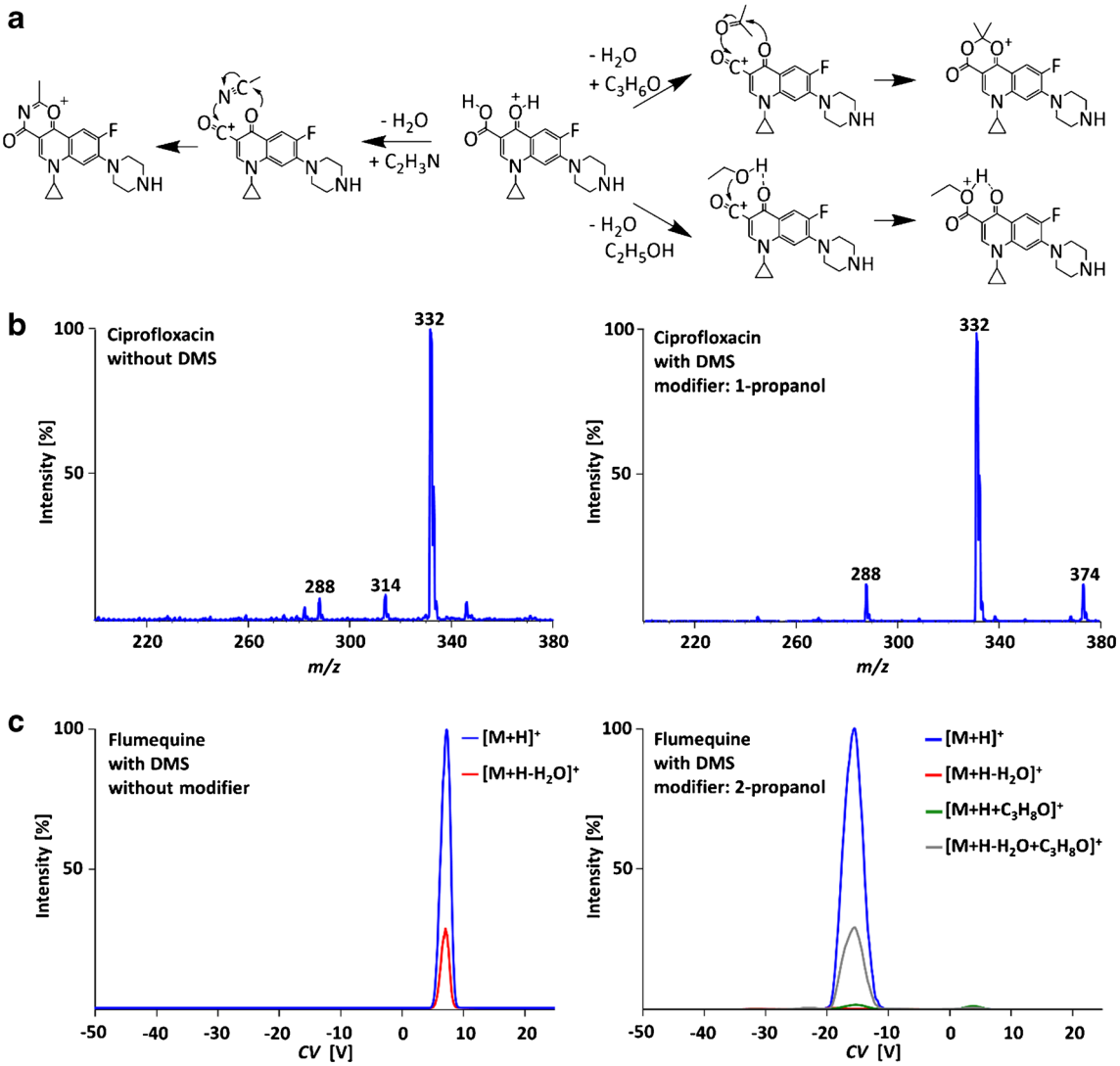


Fig. 1 Class selective ion/molecule reactions of 4-quinolones antibiotics. **a** Proposed reaction pathways of ion/molecule reaction (adapted from Colorado and Brodbelt [21]). **b** Full-scan mass spectra of ciprofloxacin (*m/z* 332; 314; 288) and of the reaction product $[M+H\text{-}H_2O+1\text{-propanol}]$ (*m/z* 372). **c** SIM CV chromatogram of flumequine without modifier and with 1-propanol as modifier

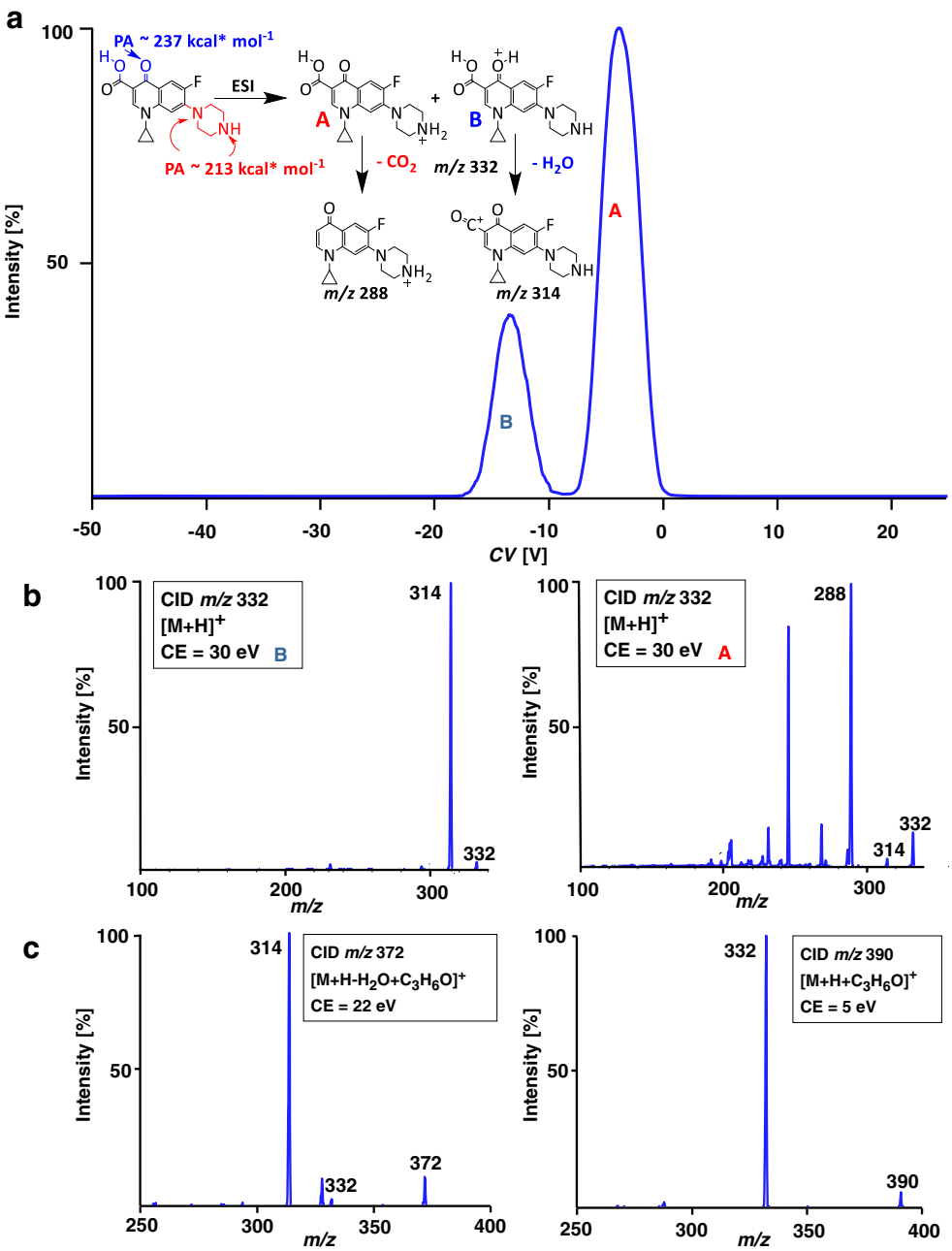


Fig. 2 **a** DMS separation of ciprofloxacin protomers A and B using acetone as chemical modifier. **b** CID spectra of the $[M+H]^+$ (*m/z* 332) ions clearly distinguish the isomers A and B, because charge-remote CO_2 loss is only possible from isomer A, whereas H_2O loss from isomer B is a charge-mediated process. **c** CID spectra of formed adducts and ion-clusters. The collision energies clearly identify the $[M+H\text{-}H_2O+C_3H_6O]^+$ ion as a chemical reaction product, whereas $[M+H\text{-}CO_2+C_3H_6O]^+$ is a weakly bound ion/molecule cluster

this limited the useful compounds to those with boiling points below 100 °C. Even for DMS temperature as high as 300 °C, compounds with high boiling points (e.g., water) condensed in the lower, cooler part of the ion source and triggered electrical discharges within the DMS ion source region.

The second limitation of the used DMS-MS instrument was the lack of an efficient ion activation step prior to DMS, which would maximize the initial formation of $[M+H\text{-}H_2O]^+$ ions from $[M+H]^+$. The design of the instrument did not provide in-source CID after ESI prior to DMS. As a result, we used the $[M+H\text{-}H_2O]^+$ formation during the ionization process, which gave $[M+H\text{-}H_2O]^+$ and $[M+H\text{-}CO_2]^+$ product ions at varying relative abundances for the analytes. Raising the source temperature did not provide higher yields for this dissociation, which was not unexpected considering the charge-mediated nature of the dehydration process.

For the actual ion/molecule reactions with acetone, ethanol, methanol, 1-propanol, 2-propanol, and acetonitrile, reaction

yields between 73 to 100% were obtained (Table 1). The reactions were highly reproducible with RSD values usually < 3.9%; only the reaction of ethanol with ciprofloxacin and 2-propanol with danofloxacin exhibited higher values of 7 and 11%, respectively, which was likely the result of instrumental problems due to air bubbles in the reagent inlet of the DMS cell during these experiments.

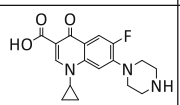
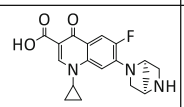
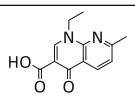
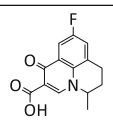
The products of the reactions and the nature of the chemical interaction of substrate and reagent in the formed products were further characterized by subsequent MS/MS experiments. The binding strength was assessed by the collision energy required for dissociation of 90% of the $[M+H-H_2O+reagent]^+$ ions (the 90% dissociation rate value was arbitrarily chosen to obtain comparable and meaningful energy values within the study for all species; this value provided reproducible collision energy conditions for the newly-formed products. A definition based on collision energy break down curves could not be implemented here because the weakly-bound ion/molecule clusters already dissociated at values ≤ 5 eV). CID of the newly-formed compounds primarily yielded $[M+H-H_2O]^+$ ions, accompanied by lower intensity $[M+H]^+$ product ions. The reverse reaction of the $[M+H-H_2O]^+$ ion—that is, back to the $[M+H]^+$ ion—can also occur, induced by the presence of water as contamination in the collision gas. This was previously described for quinolone antibiotics [30, 31] as well as for other compounds, which form similar reactive species, e.g., acylium and arylium ions [32, 33]. In our study, water was also present in the collision gas, as seen by the low-abundant signals for $[M+H]^+$ at *m/z* 332 in the CID spectra of the $[M+H-H_2O]^+$ ions (*m/z* 314) of ciprofloxacin at collision energies ≤ 20 eV.

The required collision energies for the newly-formed products ($[M+H-H_2O+reagent]^+$) were similar to the energies necessary for dissociation of the protonated 4-quinolone precursor molecules (again at 90% dissociation level). Because CID of the protonated quinolones also yielded primarily $[M+H-H_2O]^+$ ions, the CID data were directly comparable to assess the nature of the formed complex, whether it was a weak cluster ion or the result of a chemical reaction. The CE values were between 19 and 29 eV for the protonated quinolones, and between 13 and 32 eV for the products of the ion/molecule reactions (Table 1), readily demonstrating the formation of covalent bonds during the reactions.

The negative control reagent diethyl ether exhibited only minor cluster formation during DMS with very low yields (< 10%), because it could not undergo the reaction mechanism shown in Fig. 1. Consequently, the obtained cluster ions $[M+H-H_2O+C_2H_5OC_2H_5]^+$ were easily dissociated at collision energies of ≤ 5 eV, demonstrating the weak, non-covalent nature of the cluster formation.

Similarly, ion/molecule clusters of all investigated chemical reagents with other, non-reactive ions of the 4-quinolones, such as $[M+H]^+$ and $[M+H-CO_2]^+$, also required the very low collision energies of ≤ 5 eV for 90% dissociation rate (Fig. 2c provides an example for an $[M+H]^+$ ion and acetone).

Table 1 Reaction yield and corresponding collision energies for $[M+H-H_2O+reagent]^+$

		Ciprofloxacin	Danofloxacin	Nalidixic acid	Flumequine
					
$[M+H-H_2O]^+$	Relative intensity ± SD [%]	6.5 ± 0.1	17.9 ± 1.6	53.4 ± 1.1	25.4 ± 0.5
	CE [eV]	26	29	19	22
Acetone	Reaction yield ± SD [%]	93.1 ± 1.0	98.3 ± 0.1	76.5 ± 2.6	81.4 ± 3.9
	CE [eV]	22	20	13	15
Acetonitrile	Reaction yield ± SD [%]	95.7 ± 0.2	97.8 ± 0.1	98.5 ± 0.1	97.0 ± 0.1
	CE [eV]	15	17	11	13
Methanol	Reaction yield ± SD [%]	95 ± 0.6	99 ± 0.1	98 ± 0.2	98 ± 0.1
	CE [eV]	28	32	21	25
Ethanol	Reaction yield ± SD [%]	92.3 ± 7.0	95.5 ± 0.7	99.6 ± 0.02	98.1 ± 0.1
	CE [eV]	30	31	22	23
1-Propanol	Reaction yield ± SD [%]	90.5 ± 1.2	93.6 ± 0.5	87.7 ± 0.3	73.1 ± 0.7
	CE [eV]	29	29	21	24
2-Propanol	Reaction yield ± SD [%]	92.7 ± 0.2	83.3 ± 11.8	99.0 ± 0.2	97.9 ± 0.2
	CE [eV]	25	29	20	20
Diethyl ether	Reaction yield ± SD [%]	2.8 ± 0.3	2.4 ± 0.1	6.2 ± 0.5	8.9 ± 1.3
	CE [eV]	≤5	≤5	≤5	≤5

The latter again highlights the difference of covalent [M+H-H_2O+reagent]$^+$ products and non-reactive substrate ions, or reagents that cannot undergo the reaction in Fig. 1, which only enable weakly bound cluster formation.

We believe that these ion/molecule reactions are potentially very useful for the class-specific screening in complex samples, utilizing the "derivatized" products within the DMS cell as markers for 4-quinolone compounds. For example, after the DMS ion/molecule reaction, a workflow for the employed MS instrument could comprise a neutral loss scan using alternating low/high energy CID cycles in the collision cell of the instrument, with the neutral mass offset corresponding to the adduct mass. During the low energy CID cycle (e.g., at 5 eV), only the non-covalently-bound cluster ions are dissociated and removed, while the covalent new products stay intact, whereas during the higher energy CID step (30 eV), both species dissociate.

Conclusions

This study has demonstrated a new application for DMS by implementing ion/molecule reactions as an analytical tool. This was exemplified by the reaction of 4-quinolones antibiotics with various gas-phase chemical reagents within the DMS drift cell. We believe that the combination of ion/molecule reactions in the DMS cell and tandem mass spectrometry can provide novel analytical and structural tools, such as the class-specific screening of antibiotics proposed here. Importantly, the method does not require hardware changes and solely used a commercial DMS-MS/MS system. The present method was limited by the lack of an efficient in-source CID step prior to DMS, which would further increase the overall sensitivity if available.

Author contributions The manuscript was written through contributions of all authors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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