



RESEARCH ARTICLE

Laser-Induced Acoustic Desorption/ Atmospheric Pressure Chemical Ionization Mass Spectrometry

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Abstract

Laser-induced acoustic desorption (LIAD) was successfully coupled to a conventional atmospheric pressure chemical ionization (APCI) source in a commercial linear quadrupole ion trap mass spectrometer (LQIT). Model compounds representing a wide variety of different types, including basic nitrogen and oxygen compounds, aromatic and aliphatic compounds, as well as unsaturated and saturated hydrocarbons, were tested separately and as a mixture. These model compounds were successfully evaporated into the gas phase by using LIAD and then ionized by using APCI with different reagents. From the four APCI reagent systems tested, neat carbon disulfide provided the best results. The mixture of methanol and water produced primarily protonated molecules, as expected. However, only the most basic compounds yielded ions under these conditions. In sharp contrast, using APCI with either neat benzene or neat carbon disulfide as the reagent resulted in the ionization of all the analytes studied to predominantly yield stable molecular ions. Benzene yielded a larger fraction of protonated molecules than carbon disulfide, which is a disadvantage. A similar but minor amount of fragmentation was observed for these two reagents. When the experiment was performed without a liquid reagent (nitrogen gas was the reagent), more fragmentation was observed. Analysis of a known mixture as well as a petroleum cut was also carried out. In summary, the new experiment presented here allows the evaporation of thermally labile compounds, both polar and nonpolar, without dissociation or aggregation, and their ionization to predominantly form stable molecular ions.

Key words: LIAD, APCI, APCI reagents, Petroleum, Nonpolar hydrocarbons

Introduction

Mass spectrometry has long been recognized as a powerful analytical technique for volatile analytes [1, 2]. The development of two soft evaporation/ionization

methods, electrospray ionization (ESI) [3] and matrix-assisted laser desorption ionization (MALDI) [4], made it possible to evaporate and ionize (nearly simultaneously) large, thermally labile molecules, thus enabling a broader application of mass spectrometry for uses in biology and other life sciences. The ionization of analytes in ESI and MALDI is limited to protonation, deprotonation, or cation attachment (often involving ions preformed in solution for ESI). ESI suffers from severe ion suppression in the presence of impurities with higher proton affinity (PA) than

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the analyte [5, 6]. Neither method can ionize analytes without easily ionizable functional groups, such as saturated and unsaturated hydrocarbons, in the presence of basic or acidic analytes [7, 8]. In order to enable the analysis of polycyclic aromatic analytes, some investigators have derivatized them prior to ESI/mass spectrometry [9]. Other methods used to facilitate the analysis of polyaromatic hydrocarbons include using silver cationization or adding CHCl_3 into the ESI solvent. However, both approaches are limited to aromatic hydrocarbons and are not applicable to other nonpolar hydrocarbons [10].

Laser-induced acoustic desorption (LIAD) enables the evaporation of nonvolatile and thermally labile compounds as intact neutral molecules into the gas phase [11, 12]. This makes it possible to decouple the desorption and ionization processes, thus allowing the use of a variety of methods to ionize analytes, such as electron bombardment [13, 14] and chemical ionization (CI) [8, 15–17]. LIAD has been implemented with a Fourier-transform ion cyclotron resonance mass spectrometer [18, 19], a quadrupole ion trap [20], a linear quadrupole ion trap (LQIT) [21], and a quadrupole/time-of-flight mass spectrometer [22]. In these studies, the analyte was deposited onto either a thin titanium or aluminum foil or silicon wafer. LIAD was accomplished by irradiating the backside of the foil or wafer with high-intensity laser pulses. A laser-induced shock wave propagated through the foil or wafer and evaporated only neutral molecules from the other side of the foil into the gas phase. Because the laser pulses did not interact with the analytes directly, ions were not formed. The desorbed neutral molecules have been found to have low kinetic and internal energies [18]. LIAD/CI using $\text{CIMn}(\text{water})$ reagent ions has been demonstrated to allow the characterization of both polar and nonpolar organic compounds simultaneously without causing fragmentation at either the evaporation or ionization stage in an FT-ICR cell [15]. Furthermore, it appears to be the only mass spectrometric method that can be used to analyze large branched saturated hydrocarbons without fragmentation, including those present in petroleum [14]. Unfortunately, all these experiments were performed in high vacuum. Effective ionization of saturated hydrocarbons in atmospheric pressure is highly desired for practical analytical applications.

Recently, polar neutral compounds desorbed by LIAD were ionized by electrospray ionization (ESI) under ambient conditions before analysis by a quadrupole/time-of-flight (Q-TOF) mass spectrometer [22]. A sample droplet was first deposited onto an aluminum foil. After drying, the analyte was desorbed by LIAD into the ESI plume, resulting in singly and/or multiply charged ions. However, as the ionization step involves ESI, this method suffers from all the same limitations as ESI alone, which are discussed above.

Initially called atmospheric pressure ionization (API), APCI was developed in the 1970s [23, 24]. The chemical ionization process of APCI was initiated by a nickel-63 radiation source in the early applications; this was later replaced by a corona discharge electrode. The potential of

APCI was not realized until another API method, ESI, was developed and gained popularity for its ability to gently ionize large proteins [25]. In an APCI source, a corona discharge needle is used as the electron source to ionize gas molecules, such as N_2 (commonly used as a sheath gas for the inlet) and methanol/water (commonly used as a solvent mixture for the analyte), forming radical cations in the positive ion mode [23, 26, 27]. These ions collide with the vaporized solvent molecules to form secondary reactant ions, usually protonated methanol and cluster ions of the type $\text{H}^+(\text{H}_2\text{O})_n$ and $\text{H}^+(\text{CH}_3\text{OH})_n$ [23]. Protonation of the analyte molecules is usually observed in positive-mode APCI, although molecular ions and their fragments (including $\text{M}-\text{H}^+$) can also be formed [27, 28].

In this study, LIAD was coupled with APCI in a commercial linear quadrupole ion trap mass spectrometer to test whether this method allows for the analysis of analytes that are not amenable to LIAD/ESI experiments. Since APCI can be used to ionize compounds with low to medium polarity, this approach may be applicable to the analysis of hydrocarbon mixtures, such as petroleum. In order to facilitate ionization of hydrocarbons, and avoid fragmentation of ionized analytes, different ionization reagents were tested for APCI.

Experimental

All experiments were carried out using a linear quadrupole ion trap mass spectrometer (LQIT; specifically, LTQ of Thermo Fisher Scientific, Inc., San Jose, CA, USA), which was equipped with an APCI source. The APCI conditions were as follows: vaporizer temperature, about 375°C , nitrogen sheath gas, 40–50 (arbitrary units); nitrogen auxiliary gas, 5 (arbitrary units); capillary temperature, 275°C ; the MS scan range, m/z 50–500. The flow rate of APCI reagents (liquid) was 15–25 $\mu\text{L}/\text{min}$ for all solvents. The nitrogen gas was obtained from boil-off of a liquid nitrogen cylinder.

5 α -Cholestane (purity 97%), squalene (98%), androsterone (97%), coronene (97%), bathophenanthroline (97%), and carbon disulfide (99.9%) were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received. To prepare a sample foil, 5 α -cholestane, squalene, coronene, and bathophenanthroline were dissolved in 100% tetrahydrofuran, and coronene in 90:20 acetonitrile/methanol. A mixture of model compounds was prepared by dissolving equimolar amounts of the aforementioned compounds in 1:6 dichloromethane/methanol. By using electrospray deposition [29], a volume of 60–80 μL of each solution (~ 1 mM) was deposited on thin Titanium foils (12.5 μm). The solvent evaporated nearly instantaneously and the foil was placed onto the sample support stage of the LIAD probe. The back side of the foil was rested on a thin (200 μm) glass support. The petroleum cut sample was dissolved in toluene/methanol (75:25) and electrospray deposited onto the titanium foil for subsequent desorption by LIAD and ionization by APCI.

The LIAD probe employed in this study has been previously described [19]. The only difference between the

probe used here (10 in. length) and the one described in the literature is that the literature probe is longer. The glass window in the front of the source was removed so that the LIAD probe could be inserted into the APCI source. About 5 in. of the probe (from the front of a Cajon fitting adaptor) was inserted into the source, which placed the probe tip 5/8 in. away from the corona discharge needle and just underneath the back edge of the APCI probe. The side of the foil coated with sample was exposed to the ion transfer capillary entrance of the LQIT mass spectrometer. In the probe, the laser pulse generated by an Nd:YAG laser (Minilite II; Continuum Lasers, Santa Clara, CA, USA; 532 nm; 3 ns pulse width; 10 Hz) was directed by using silver mirrors (ThorLabs, Newton, NJ, USA) to an area of about 10^{-3} cm² on the back side of the foil surface. The output energy was 20 mJ/pulse, as measured by a pyroelectric meter (PE25-SH; OPHIR Laser Measurement, Logan, UT, USA). The outer cylinder of the LIAD probe, containing the sample foil, was rotated so that analytes were desorbed from multiple sites. Typically, one-fourth of a foil (90° area) was rotated during each experiment when 180 shots of the laser were fired. To prevent heating of the LIAD probe and analytes deposited on the Ti foil, the LIAD probe was inserted into the APCI source just before firing the laser and removed immediately after each experiment. Earlier studies have demonstrated that LIAD is the cause of evaporation of the analytes in these experiments, rather than thermal heating [18].

Results and Discussion

A schematic representation of a LIAD/APCI source is shown in Figure 1. To evaluate the performance of the

LIAD/APCI source, model compounds of different types (Table 1) were analyzed. These compounds are structurally similar to components commonly present in petroleum, ranging from saturated hydrocarbons to polar compounds. All analytes were successfully evaporated into the APCI source by using LIAD. Three different liquid APCI reagent systems were employed to ionize the analytes, a mixture of methanol and water (1:1, vol/vol), neat benzene, and neat carbon disulfide. APCI with no liquid reagent (hence, using nitrogen gas as the ionizing reagent) was also employed. The mass spectra measured for each analyte under the different ionization conditions are discussed below. After that, results obtained upon analysis of a mixture of these model compounds, as well as a petroleum cut, are discussed.

Bathophenanthroline

When a mixture of methanol and water (1:1, vol/vol) was introduced into the APCI source, only protonated methanol and its cluster ion, $\text{CH}_3\text{OH}_2^+(\text{CH}_3\text{OH})$, were observed. This ion mixture is the reagent mixture that will ionize any introduced analyte. Hence, it is not surprising that the production of only stable protonated molecules was observed for the nitrogen heteroaromatic analyte, bathophenanthroline (Supplemental Figure S1, top). However, when benzene was used as the reagent, the dominant reagent ions generated upon APCI were the benzene molecular ions (radical cations). These conditions lead to the initial formation of analyte molecular ions if the ionization energy (IE) of the analyte is lower than that of benzene (9.24 eV) [30]. For bathophenanthroline, both protonated molecules (branching ratio: 80%) and molecular ions (branching ratio: 20%) were observed. The protonated molecules are likely

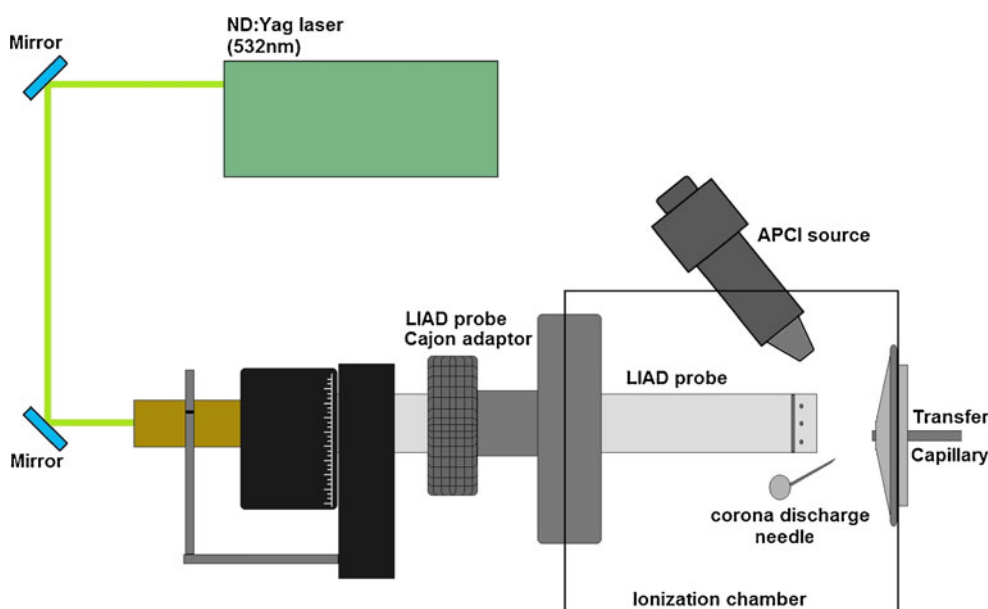
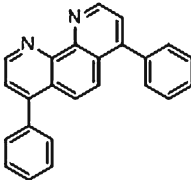

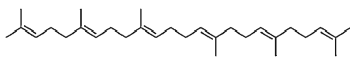
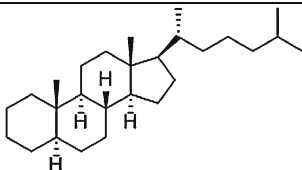
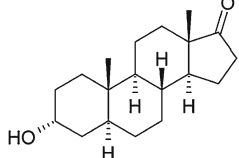


Figure 1. Schematic view of the LIAD/APCI source

Table 1. Ions (with their branching ratios, corrected for ^{13}C isotope; only ions with branching ratios $\geq 5\%$ are listed) formed upon LIAD/APCI of model compounds

Analyte \ Reagent	$\text{CH}_3\text{OH}/\text{H}_2\text{O}$ IE = 10.84 eV PA = 754.3 kJ/mol (methanol)	Benzene IE = 9.24 eV PA = 750.4 kJ/mol	CS_2 IE = 10.07 eV PA = 681.9 kJ/mol
 Bathophenanthroline (MW 332)	M+H ⁺ 100%	M+H ⁺ 80% M ²⁺ 20%	M+H ⁺ 30% M ²⁺ 70%
 Coronene (MW 300)	M+H ⁺ 100%	M+H ⁺ 48% M ²⁺ 52%	M+H ⁺ 9% M ²⁺ 91%
 Squalene (MW 410)	M+H ⁺ 95% m/z 329 5%	M+H ⁺ 7% M ²⁺ 76% m/z 341 17% (-(CH ₃) ₂ C=CH-CH ₂)	M+H ⁺ 8% M ²⁺ 92%
 5α-Cholestane (MW 372)	No ions detected	M ²⁺ 80% m/z 218 20%	M ²⁺ 81% M-H ⁺ 8% m/z 218 11%
 Androsterone (MW 290)	M+H ⁺ 46% M+H ⁺ -H ₂ O 45% M+H ⁺ -2H ₂ O 9%	M+H ⁺ 4% M ²⁺ 87% M+H ⁺ -H ₂ O 9%	M ²⁺ 73% M+H ⁺ -H ₂ O 19% M+H ⁺ -2H ₂ O 8%

formed in secondary reactions of the benzene or bathophenanthroline molecular ions either with bathophenanthroline or with adventitious water. These results are similar to those of a previous study on APCI of polycyclic aromatic compounds where both molecular ions and protonated

molecules were observed when using toluene as the APCI reagent [27]. APCI with no liquid reagent (i.e., N₂ molecular ions as the most likely ionization reagent ions) of this analyte yielded a mass spectrum similar to that obtained using benzene reagent (Supplemental Figure S1, bottom).

Carbon disulfide was tested as an APCI reagent to avoid proton transfer reactions and to make the method less energetic than when using nitrogen gas as the reagent but more widely applicable than when using benzene, as this reagent has a higher ionization energy (IE=10.07 eV) than benzene (IE=9.24 eV) but lower than nitrogen (IE=15.6 eV) [30]. This reagent was expected to lead to more efficient electron transfer, but possibly more fragmentation of the molecular ions, than APCI with benzene reagent. However, no fragmentation was observed for bathophenanthroline. As expected, the branching ratio for molecular ions was substantially greater than that for protonated molecules (70:30; Table 1).

Coronene

Upon methanol/water APCI, coronene, a polyaromatic analyte with no heteroatoms, only generated protonated molecules, as expected (Table 1). APCI with either benzene or carbon disulfide reagent, or no liquid reagent, resulted in the formation of both the protonated molecules and molecular ions. The relative abundance of the protonated molecules was less than for bathophenanthroline, a substantially more basic compound. Out of these three conditions, APCI with carbon disulfide yielded the most desirable mass spectrum for coronene, with the molecular ion dominating. This is likely due to the lack of hydrogens in carbon disulfide, as opposed to benzene.

Squalene

Squalene, a linear polyene hydrocarbon, yields predominantly protonated molecules upon LIAD/APCI when a mixture of methanol and water is used as the reagent system (Table 1). Only a small amount of fragmentation was observed. When benzene was used as the reagent, the molecular ions dominate the spectrum. Fragmentation was also observed and it occurred via the cleavage of the weakest, doubly allylic C-C bond. Again, APCI with carbon disulfide yielded the most desirable mass spectrum, with molecular ions dominating and no obvious fragmentation.

5 α -Cholestane

5 α -Cholestane, a saturated hydrocarbon containing three six-membered rings and one five-membered ring, yielded no detectable ions when a mixture of methanol and water were used as the APCI reagent. However, molecular ions dominated (branching ratio: 80%–81%) the APCI mass spectra obtained by using benzene or carbon disulfide (Supplemental Figure S2, top) as the reagent. About an equal amount of fragment ions were also observed in these experiments.

Interestingly, APCI with benzene resulted in a cleavage of the alkyl chain and most of the five-membered ring in 5 α -cholestane, while carbon disulfide also showed loss of a

hydrogen atom from the molecular ion (Table 1). APCI with no liquid reagent yielded a mass spectrum (Supplemental Figure S2, bottom) indicating more fragmentation than those obtained by using benzene or carbon disulfide as liquid reagents in APCI. Hence, detection of this hydrocarbon cannot be achieved using proton transfer APCI, and the carbon disulfide APCI method again yields the best results.

Androsterone

Androsterone is an interesting analyte since it is known, after protonation, to readily fragment by loss of water. Androsterone yields some stable protonated molecules (46%) upon LIAD/APCI using methanol/water, but fragmentation by losses of one and two water molecules also occurs readily (Table 1). In sharp contrast, when benzene was used as the reagent, the molecular ions dominate the spectrum. Only minor fragmentation took place. APCI with CS₂ also yielded an abundant molecular ion but more fragmentation than APCI with benzene (Figure 2). Hence, for this analyte, APCI with benzene reagent yielded the best results.

Mixture of Model Compounds

A mixture of all five model compounds (all in equimolar ratios) was analyzed by LIAD/APCI using CS₂ reagent. The mass spectrum (Figure 3) shows molecular ions for all five analytes, as well as their most abundant fragment ions (Table 1). While the relative abundances of the molecular ions do not exactly match the relative molar concentrations, all analytes were successfully detected in a single experiment, in spite of their widely varying ionization energies, compositions, structures, and volatilities. The same mixture was also analyzed using water/methanol as the APCI reagent mixture, as well as with no liquid reagent at all. Similar molecular ion branching ratios were observed when no liquid APCI reagent was used and

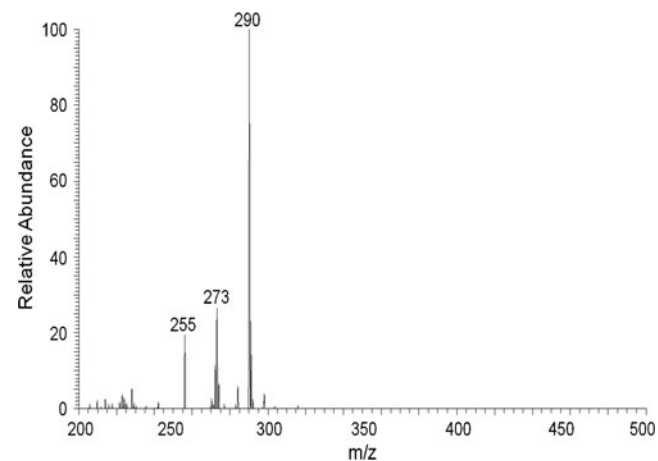


Figure 2. LIAD/APCI mass spectrum of androsterone in positive ion mode. The solvent was CS₂

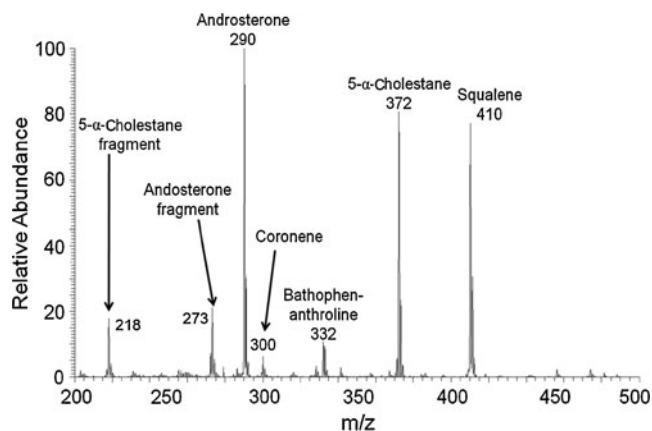


Figure 3. A mixture of 5- α -cholestane (MW 372), coronene (MW 300), squalene (MW 410), androsterone (MW 290), and bathophenanthroline (MW 332) (all in equimolar ratios) analyzed by LIAD/APCI using CS₂ as the reagent

when the CS₂ reagent was used. APCI using the water/methanol reagent mixture yielded protonated molecules for the analytes, with the exception of 5 α -cholestane, which cannot be detected under these conditions. Future research will focus on

improving the relative sensitivity of APCI using CS₂ reagent toward the aromatic analytes.

Petroleum Cut 800

Petroleum cut 800, a petroleum distillate provided by ExxonMobil, was analyzed by LIAD/APCI using nitrogen gas as the reagent (no liquid reagent). The mass spectrum (Figure 4, top) shows a bimodal distribution where the ions with the greater m/z ratios (m/z 400–950) appear to be comprised mostly of even mass ions. Hence, these ions are most likely hydrocarbon molecular ions formed by electron transfer. Some of them may also be protonated nitrogen compounds. Their true identities need to be resolved by ultra-high resolution mass spectrometry. The lower mass distribution has ions with mostly odd mass values, indicating that the lower mass distribution mostly consists of fragment ions formed from the molecular ions. This is as expected because ionization occurred via the high-energy process of electron abstraction by N₂⁺⁺ and this method caused fragmentation also for the model compounds discussed above. The high mass distribution correlates well with

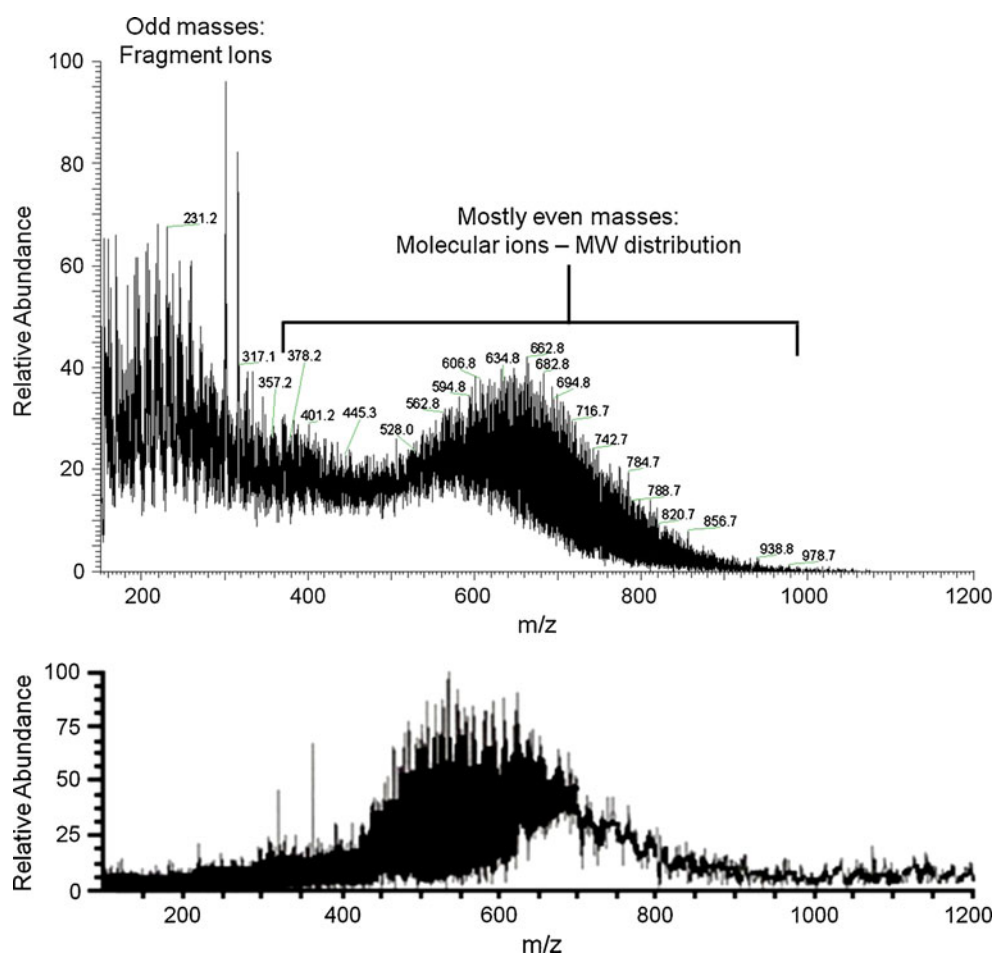


Figure 4. Top: LIAD/APCI (no liquid reagent) mass spectrum of petroleum cut 800 (MW~400–950). Bottom: LIAD/EI mass spectrum of the same sample measured in a 3 T FT-ICR spectrometer. The mass ranges for the molecular ions in the two spectra are similar

the MW distribution measured for the same sample (Figure 4, bottom) in an experiment wherein the sample was evaporated by high-power LIAD into high vacuum (10^{-9} Torr) and ionized by 30 eV electron impact (EI) in a 3 Tesla Fourier-transform ion cyclotron (FT-ICR) mass spectrometer [14].

Detection Limit

Finally, the detection limit for LIAD/APCI analysis of bathophenanthroline (MW 332 Da) by using methanol/water reagent system was determined to be 2.3 ng by depositing a known amount of the analyte on the foil, and estimating the amount of molecules evaporated when rotating the foil 90 degrees (if the foil is rotated the full 360 degrees, this number reduces to 0.6 ng). This value corresponds to a detectable solution concentration of about 100 pmol/mL (1×10^{-7} M) when the foil is rotated 360° (100 μ L spray volume). This value compares well with literature values. For example, 10^{-6} to 10^{-7} M solution was reported as the detection limit for LIAD/ESI mass spectrometric analysis of hemoglobin [22]. The LIAD/APCI detection limit for squalene with no liquid APCI reagent was determined to be 2.9 ng.

Conclusions

LIAD was successfully combined with the APCI source of a commercial linear quadrupole ion trap mass spectrometer. By changing (or omitting) the liquid reagent used in APCI, different mass spectra were obtained. A mixture of methanol and water was found to produce protonated molecules for polar compounds while saturated hydrocarbons produced no detectable ions. Both molecular ions and protonated molecules (likely formed in secondary reactions) were observed for polar compounds when benzene or carbon disulfide were used as the reagent, but carbon disulfide forms mostly molecular ions. Both of these reagents led to ionization of the nonpolar analytes studied, including saturated hydrocarbons. Carbon disulfide appears to be the best reagent among those studied since it forms predominantly molecular ions for both polar and nonpolar analytes. Only minor fragmentation of the molecular ions was observed, and this was found to be comparable in the carbon disulfide and benzene experiments, in spite of the different ionization energies of these two reagents. However, APCI with no liquid reagent led to more extensive fragmentation. The detection limit was determined to be about 7×10^{-7} M for bathophenanthroline. Finally, a known mixture containing all the model compounds, and a petroleum cut sample, were examined by LIAD/APCI using APCI with carbon disulfide or nitrogen as the reagent, respectively. All five analytes were successfully detected in a single experiment, in spite of their widely varying ionization energies, compositions, structures, and volatilities. On the other hand, the molecular weight distribution determined for the petroleum cut agrees

well with that determined by using another method, LIAD coupled with EI in a Fourier-transform ion cyclotron resonance mass spectrometer.

The LIAD/APCI experiment described here benefits from several advantages. As opposed to LIAD/ESI and other ESI- and MALDI-based methods, both polar and nonpolar compounds (including saturated hydrocarbons) can be analyzed simultaneously by using the carbon disulfide reagent. Only minimal fragmentation is observed, and predominantly stable molecular ions are formed for all analytes. The results presented here suggest no strong bias toward basic or acidic analytes. Further, any solvent can be used to deposit the analyte on the surface, as opposed to ESI. In fact, this can be performed without using a solvent at all [13]. Further, the analysis can be done on any mass spectrometer equipped with an APCI source. Finally, rastering the LIAD foil will be much more straightforward than using the traditional LIAD set-up due to the atmospheric pressure conditions, thus enabling rapid analysis of a large number of different samples deposited onto one LIAD foil and using LIAD as a novel imaging tool.

Acknowledgments

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