Desorption Ionization Mass Spectrometry: Sample Preparation for Secondary Ion Mass Spectrometry, Laser Desorption, and Field Desorption

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Abstract: Derivatization of neutral samples to produce nonvolatile ionic species enhances the analytical capabilities of secondary ion mass spectrometry and laser desorption mass spectrometry. Precharged species can be generated by using Brφnsted or Lewis acid/base chemistry or by employing specific organic functional group transformations. Mass spectrometry/mass spectrometry confirms that the fragments observed in desorption ionization occur as the result of gas-phase processes. Parallels with enhancement effects in field desorption mass spectrometry are drawn. The results obtained suggest that in desorption ionization mass spectrometry, the emission of covalently bonded preformed ions from surfaces is favored over a combination of ion and neutral moieties in the selvedge.

As currently practiced, derivatization in mass spectrometry achieves either of two objectives. First, it tailors the *physical* properties of the analyte to the requirements of the analytical method. For example, in conjunction with gas chromatography/mass spectrometry (GC/MS), derivatization produces enhanced volatility or stability; examples include trimethylsilylation and perfluoroacylation. Second, it introduces particular *chemical* features into the analyte. Examples include the introduction of a group with low ionization potential to increase molecular ion intensity (as in the flavazole derivatives of oligosaccharides[1]), a group with high electron affinity to promote formation of negative ions (as in the pentafluorobenzyl derivatives of amphetamines[2]), and the incorporation of isotopic labels at specific sites in the analyte.[3] Comprehensive surveys of these analytical derivatization reactions are available,[4,5] while reports have also appeared on ion/molecule reactions which can be considered as derivatization reactions of gaseous ions.[6,7]

Desorption ionization mass spectrometry is a general term describing those methods which sample directly from the condensed phase, be it liquid or solid. Included are the techniques of secondary ion mass spectrometry (SIMS), field desorption (FD), fast atom bombardment (FAB), laser desorption (LD), plasma desorption (PD), and electrohydrodynamic ionization (EHD). These methods have made possible the analysis of a wide range of thermally fragile and nonvolatile compounds, and similarities in the methods have been noted.[8–11]

These procedures are particularly suited to the analysis of preformed ionic species; for example, they have had conspicuous success in the analysis of quaternary ammonium salts.[12–24] (In SIMS, both picogram sensitivity[13] and the ability to desorb such ions directly from complex matrices[25] has been demonstrated.) Features common to all desorption ionization methods are the comparative rarity of molecular ions M[+·] and the lower yields of cationized molecules such as (M + H)[+] and (Ag + M)[+] relative to ammonium, sulfonium, and other intact cations. The former species must be generated through chemical reactions of the analyte; the latter need only be desorbed.

In conjunction with the development of desorption ionization mass spectrometry, a distinctive set of derivatization reactions is emerging which endow the analyte with the physical and chemical properties of nonvolatility and ionic character—characteristics which contrast with those traditionally sought in mass spectrometry derivatization. Succinctly stated, these chemical reactions are designed to produce preformed ions at the surface; energy input into the sample is then required only to effect a change in state, that is to effect desorption without any requirement for concurrent ionization.

This paper assembles available information on sample preparation for desorption ionization, tests the concept of facile emission of preexisting ions using both SIMS and LD, and relates these observations to procedures used to enhance atomic ion emission by SIMS.

Experimental Section

Positive and negative ion SIMS spectra were obtained with a Riber instrument (Model SQ 156L) utilizing an energy selector, a quadrupole mass filter, a Channeltron electron multiplier, and pulse counting electronics. A 5-keV argon ion beam was used to bombard the sample. Ion currents were held to 2×10^{-9} A/mm^2 or lower to avoid thermal or beam-induced reactions. Operating pressure in the main chamber of the instrument was typically 1×10^{-8} torr or less. Spectra were obtained with the quadrupole scanning at the rate of 3 s/amu. A solution of the analyte

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or the analyte mixed with the derivatizing reagent was deposited onto a silver or graphite planchette and evaporated under vacuum. Samples were obtained commercially or were available from a previous FD study.[26] The LD experiments were performed by using a 1.06 μm, 20-Hz pulsed Nd:YAG laser (Quanta Ray) to create a power density at the sample of about 10^7 W/cm².[11] For the LD runs made on the SIMS instrument, the ion gun was removed and the photon beam was set to collinear with the trajectory normally followed by the argon ion beam.[27] The same laser was also interfaced to a reverse geometry mass spectrometer, and this instrument was used to record MS/MS spectra by collision-induced dissociation of a mass-selected ion beam.[11]

Results and Discussion

Background. Derivatizing agents in desorption ionization react with the analyte in the condensed phase at its surface so as to impart to it a formal charge (reaction 1). The simplest such

$$M^0 + X^\pm \rightarrow MX^\pm \qquad (1)$$

reagents are those based on Brönsted acid/base chemistry, viz., proton donation to form $(M + H)^+$ and proton abstraction to form $(M - H)^-$. While widely applicable and easily accomplished, these reactions are not highly selective.

We can explain some previous results in terms of derivatization to form ionic species. Benninghoven[14] has observed that in the SIMS spectra of amino acids, the yield of the $(M + H)^+$ ion is enhanced when the initial solution of the analyte is acidified, and the $(M-H)^-$ ion yield is maximized when the solution is basified; these examples represent simple cases of derivatization via Brönsted acid/base reactions. Since the standard sample preparation procedure in some of these studies involved roughening a silver support with nitric acid prior to use, it is possible that residual nitric acid may also contribute to the formation of the $(M + H)^+$ ions.

Addition of Brönsted acids to samples or to the emitter surface prior to sample deposition is also reported to enhance $(M + H)^+$ intensities in FD. The increased FD sensitivity for adenine by using 1 M HCl as the solvent instead of water[28] is also rationalized by the formation of the protonated molecule in situ. Direct reaction with chemically modified surfaces to force protonation has been demonstrated in FD studies.[29,30] Alternatively, the emitter can be coated with polyphosphoric acid.[31]

More specificity, together with enhanced ion yields, may be obtained by using reagents, such as alkali or transition-metal ions, which can be considered as Lewis acids in their reactions with neutral organic molecules. The large number of metals known to be cationization reagents in SIMS[32] correspond to Lewis acids of precise but unknown strengths. For a few analytes such as 2,9-dimethyl-1,10-phenanthroline, metal ion selectivity has been demonstrated,[32] but such chemistry is still largely unexplored. It seems likely that steric factors will plan a role in providing a range of Lewis acid/base *responses*. Typically, in desorption ionization mass spectrometry, stable ions corresponding to cation attachment, for example, $(Na + M)^+$, can be formed by addition of alkali salts to the sample matrix. The practical importance of such reactions in providing FD spectra from simple untreated wire emitters, thus avoiding the complications of field ionization reactions, has been emphasized by Röllgen and co-workers.[33,34] Their work built upon recognition of the importance of preformed ions in the condensed phase suggested to exist at the surface under the heating conditions used in FD analyses.[35] Enhancement of FD spectra by addition
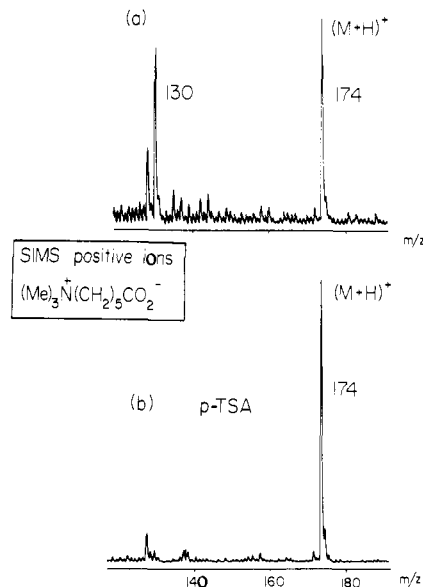

Figure 1. Enhancement of the positive ion SIMS spectrum of a zwitterionic ammoniohexanoate by *p*-toluenesulfonic acid as evidenced by enhanced $(M + H)^+$ abundance, reduced fragmentation, and greater spectrum durability.
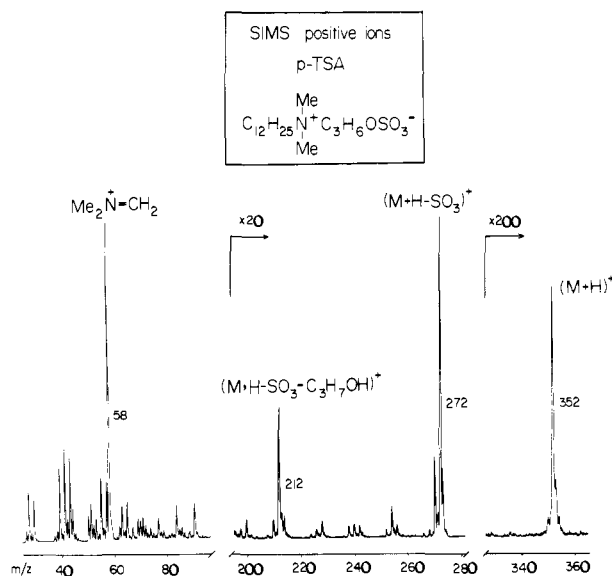

Figure 2. Analysis of the zwitterionic sulfate by SIMS in the presence of *p*-toluenesulfonic acid. Without the acid, an analytically useful spectrum is not obtained.

of alkali salts has now become a standard operating procedure.[36] Formation of $(Ba + M)^{2+}$ adducts has been shown to increase the mass range of FD mass spectrometry.[37]

A third and particularly flexible approach to derivatization employs functional group selective organic reactions. For example, aldehydes and ketones can be converted to immonium salts,[38] and exhaustive methylation provides a means of derivatizing many amines, phosphites, and sulfur-and arsenic- containing compounds (vide infra).

Present Results

Two zwitterionic compounds used in a previous FD study[26] were investigated by SIMS to test whether similar derivatization procedures might have value in both techniques. In the FD study, sensitivity for detection of the zwitterion as the $(M + H)^+$ ion

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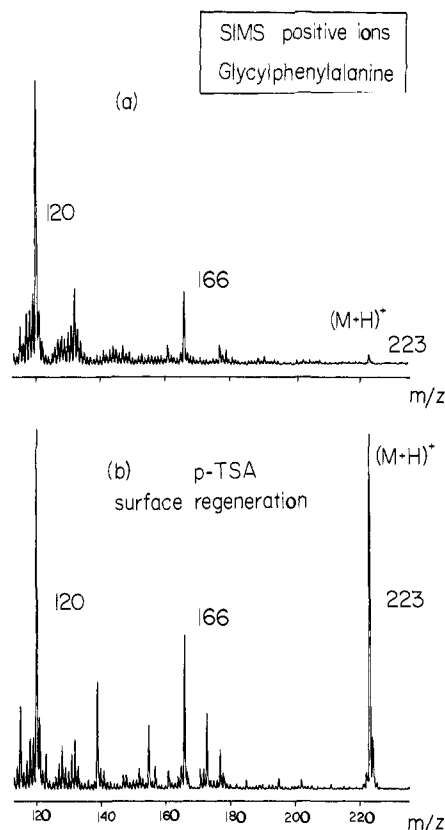(38) Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1963**, *28*, 3021.

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Figure 3. (a) Positive ion SIMS spectrum produced by the dipeptide glycylphenylalanine; (b) enhanced spectrum produced by the addition of acid to the same surface.

Figure 4. Increase in spectral quality for biological compounds by derivatization with hydrochloric acid. Shown here is the positive ion SIMS spectrum of 1-methyladenosine monophosphate.

was significantly increased by protonation, effected simply by adding p-toluenesulfonic acid (p-TSA) to a solution of the analyte prior to application to the field desorption emitter. This acid was chosen because of its high acid strength and its relative nonvolatility, reasons discussed more fully in the original paper.[26]

Figure 1 compares SIMS results for a simple zwitterionic ammoniohexanoate examined on a silver support both with and without the addition of p-TSA. In Figure 1a, the protonated zwitterion is observed as the highest mass ion in the spectrum. Decarboxylation to form the ion at m/z 130 is also observed. The $(M + H)^+$ ion decreased to both absolute and relative abundance as the analysis proceeded. Figure 1b shows the spectrum obtained after addition of an equimolar amount of p-TSA to the analyte solution. The S/N ratio of the $(M + H)^+$ ion is increased by a factor of about 5, and the spectrum remains constant while ion bombardment is continued over a period of several hours.

In Figure 2 the SIMS spectrum of a zwitterionic sulfate, again derivatized with p-TSA, is shown. The spectrum appears to consist of $(M + H)^+$, $(M + H - SO_3)^+$, and $(M + H - SO_3 - C_3H_7OH)^+$ ions, in addition to the base peak at m/z 58 corresponding to $(CH_3)_2N^+=CH_2$. The SIMS spectrum of this compound in the absence of the acid contained only the m/z 58 ion, and none of the higher mass ions whatsoever.

Field desorption spectra[26] of these zwitterionic compounds in the presence of p-TSA exhibited $(M + H)^+$ adduct ions of significantly greater abundance than in the absence of the acid. In general, the emitter heater currents required for the analyses also decreased, with concomitant reductions in fragment ions or ions formed by such intermolecular processes as methyl transfer. In FD, the simplification of the spectra in the presence of the acid is such that mixtures can be easily analyzed via the abundant $(M + H)^+$ ions. In each of these respects, a close parallel between the behavior in SIMS and FD is evident.

As in the case of the aminocarboxylic acids, spectral enhancement by acid treatment can be accomplished for many other compounds. For example, consider the SIMS spectrum of glycylphenylalanine on graphite (Figure 3). Before acid treatment,
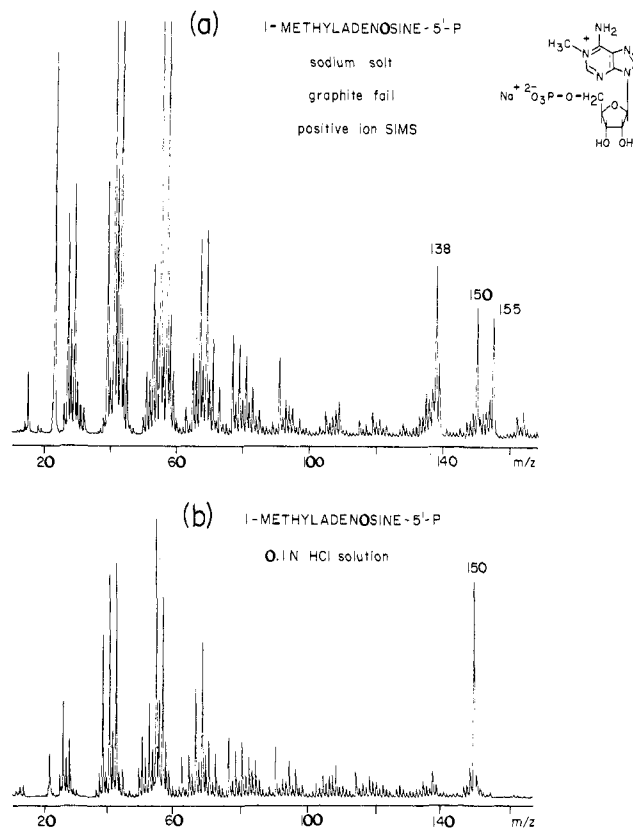
the $(M + H)^+$ ion at m/z 223 (Figure 3a) is barely observed above background while abundant fragments are observed at m/z 166 and 120. Addition of p-TSA to the *same* sample (Figure 3b) greatly enhanced the intensity of the $(M + H)^+$ ion of the peptide and increased its abundance relative to the intensities of the fragment ions. Addition of the more volatile acetic acid to the sample did not effect irreversible protonation, presumably as it is pumped away during sample introduction.

The SIMS spectrum of 1-methyladenosine mophosphate on graphite (Figure 4) contains an ion at m/z 150 which can be ascribed to the protonated base (Figure 4a). The spectrum is much simplified when the sample is deposited onto the graphite from a solution acidified with 0.1 N HCl (Figure 4b). In addition, the S/N ratio of the m/z 150 ion is much improved. A similar improvement in spectral quality was obtained when N^6-methyladenosine monophosphate was analyzed from an acidic solution. Under acidic conditions, the base–ribose bond is easily cleaved, resulting in formation in high yield of the ion at m/z 150 corresponding to the protonated adenine base. Similar results were observed in SIMS spectra of alkylated nucleosides. Nucleosides which exist as positively charged salts (e.g., 1-methyladenosine, 3-methylcytidine, and 7-methylguanosine) exhibit large intensities of the modified base as well as the intact methylated nucleoside.[39] Modified nucleosides which exist as neutral compounds (e.g., 3-methylthymidine) only show characteristic SIMS spectra when protonated by adding an acid such as hydrochloric acid.

Quaternization is a straightforward reaction that can be used for derivatization. Thus, tertiary amines react with methyl iodide to form the N-methyl quaternary salt (reaction 2). Inadvertent

$$R_3N + CH_3I \rightarrow R_3N^+CH_3 + I^- \qquad (2)$$
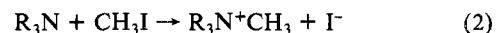
quaternization has been recognized as a possible source of error in normal mass spectrometric analyses of the amines,[40] but the

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(a) PYRIDINE-2-ALDOXIME / graphite
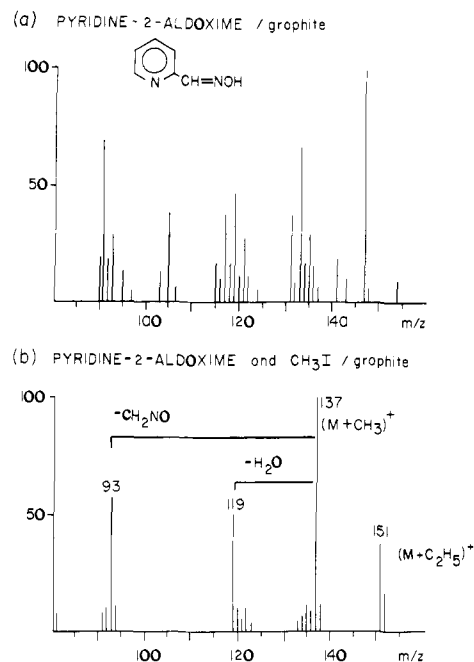
(b) PYRIDINE-2-ALDOXIME and CH$_3$I / graphite

Figure 5. (a) SIMS spectrum of pyridine 2-aldoxime on graphite; underivatized, the neutral compound is not successfully analyzed. (b) Product of quaternization of a tertiary amine by methyl iodide yields an analytically useful SIMS spectrum.

derivatization reaction should prove valuable as desorption ionization methods are increasingly applied to the identification of thermally fragile or nonvolatile amines. We have successfully applied this reaction to the analysis of tertiary amines by SIMS. An example is the methylation of pyridine 2-aldoxime; Figure 5a shows the SIMS spectrum of this compound on graphite. This spectrum is weak and is not analytically useful since essentially no M$^{+\cdot}$ or (M + H)$^+$ ions appear with abundances above background. The spectrum of the product of the oxime reaction with CH$_3$I (added directly to the surface in atmosphere) is shown in Figure 5b. Here, reaction with the methyl iodide has generated a prechanged quaternary species at m/z 137. Further reaction to replace hydrogen with a methyl group forms the dimethyl ion at m/z 151. The (M – CH$_3$)$^+$ parent ion appears to fragment by (i) loss of H$_2$O (m/z 119) and (ii) loss of HCNO to generate the methylpyridinium ion (m/z 93). Generation of the monomethyl oxime may be controlled by the addition of less CH$_3$I to the sample; however, for many biological amines, exhaustive methylation may provide the best procedure for reverse derivatization.

Properly designed derivatizations are flexible to allow for the needs of the analytical method. For instance, phenothiazine can be derivatized to either of the corresponding quaternary compounds (reaction 3).

$$m/z\ 214 \qquad (3)$$

$$m/z\ 228$$
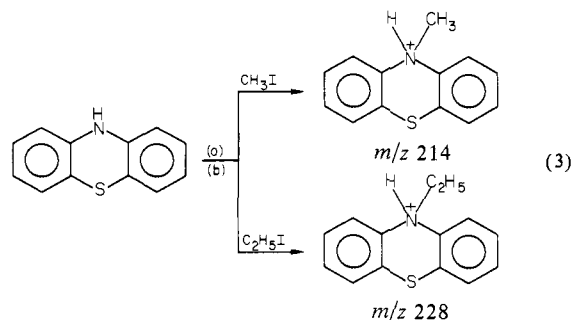
Since samples are typically supported on silver foil, the SIMS spectrum contains an isotope cluster for Ag$_2^+$, which includes an

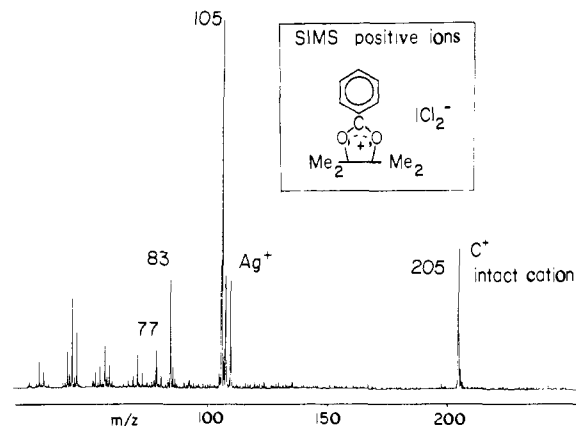(40) Vincze, A.; Gefen, L. *Isr. J. Chem.* **1978**, *17*, 326.

Figure 6. Positive ion SIMS spectrum of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolan-2-ylium dichloroiodate. Ion at m/z 205 corresponds to the intact cation which serves as a surrogate for the diol which is not itself readily examined by SIMS.

ion at m/z 214 (^{107}Ag$_2$). To avoid this interference, derivatization reaction b is chosen, and the ethylated ion at m/z 228 is observed. Similarly, labeled reagents can be used to shift important ions to masses where no interference occurs; this aids in the interpretation of the mass spectrum as well as facilitating quantitative analysis.

Chemical reactions which form charged species at a surface can also affect analysis by desorption ionization. The ion at m/z 121$^-$ observed from surfaces coated with benzaldehyde corresponds to the carboxylate anion C$_6$H$_5$COO$^-$ formed by air oxidation. Contaminants at a low level in an organic sample can yield abundant peaks in the spectrum if they are charged species. These complications can sometimes be minimized by deliberately converting the neutral organic analyte to a charged species as well. For instance, aldehydes and ketones can be derivatized with pyrrolidinium perchlorate to form the immonium salts[38] (reaction 4); the neutral organic molecule is then analyzed as the cation

$$(4)$$
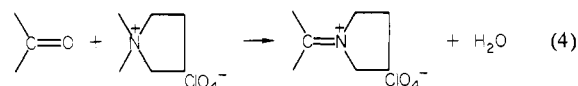
at a mass 54 daltons above that of the neutral organic molecule. These reactions produce the salts in high yield, and benzaldehyde treated with pyrrolidinium perchlorate on ion bombardment produces the expected (M + 54)$^+$ ion at m/z 160 in high abundance.

Figure 6 is the positive ion SIMS spectrum of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxalan-2-ylium dichloroiodate (**1**). These resonance stabilized salts are formed by the reaction of iodine monochloride with the appropriately substituted 1,3-dioxolane (reaction 5).[41,42] As precharged species, these compounds give

$$+\ I^-\ +\ HCI \quad (5)$$

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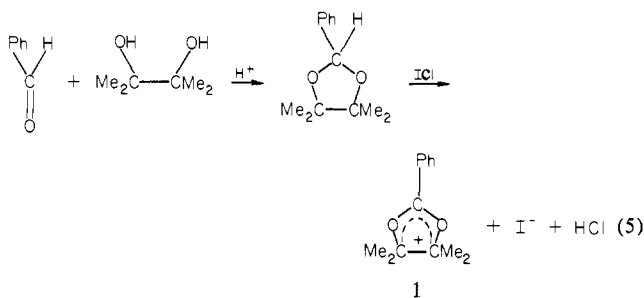
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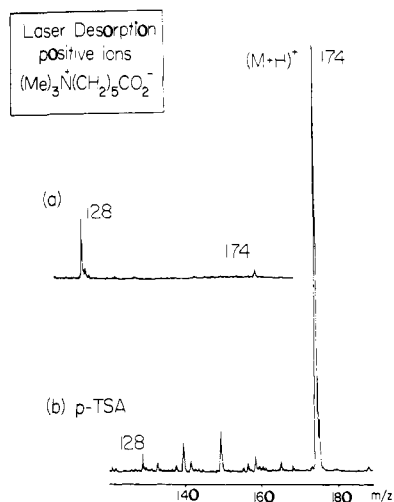(42) Goosen, A.; McCleland, C. W. *J. Chem. Soc., Chem. Commun.* **1979**, 751.

Figure 7. Spectral enhancement by *p*-toluenesulfonic acid for the same ammoniohexanoate shown in Figure 1 observed in laser desorption mass spectrometry. (a) Spectrum obtained from the neutral analyte; (b) spectrum obtained from an acid treated sample.

intact cations with excellent signal-to-noise ratios, and the fragmentations as noted in Figure 6 are reasonable. This straightforward reaction derivatizes the neutral dioxolane (and hence the aldehydes and diols from which they are constituted) to ionic forms which can be analyzed to full advantage by SIMS.

By replacing the ion gun flange on the SIMS with a quartz window, a laser beam can be directed along the same path to perform laser desorption (LD) experiments.[27] Direct comparisons of spectra without complicating instrumental factors can thus be made. The spectra in Figure 7 (7a without acid and 7b after sample treatment with *p*-TSA) show that the derivatization enhancement operates in LD as well. The sample is the same ammoniohexanoate shown in Figure 1, and the SIMS and LD spectra are very nearly identical.

Metals used as cationization reagents in SIMS[32] also form (C + M)$^+$ adducts when both organic molecule (M) and metal (C) are irradiated by a laser beam. We have noted (Ag + M)$^+$ ions for 1,10-phenanthroline supported on silver foil.[27] Here we report that 2-pyridine aldoxime forms an abundant (Ag + M)$^+$ ion in the same manner; both (Cu + M)$^+$ and (Ag + M)$^+$ ions are reported for this compound in SIMS,[43] and metal ion adducts of oximes are well-known.[44,45] Since the spectrum was obtained on a reverse sector MIKES instrument, an MS/MS spectrum of this (Ag + M)$^+$ ion could be obtained and included fragment ions corresponding to water loss, CH_2NO loss, and the silver ion itself. Study of the collision-induced dissociations of these cationized species should provide an idea of the relative strengths of interactions between organic molecules and metallic ions.

Conclusions

In EHD,[46] SIMS,[47] FAB,[48] FD,[49] and API,[50] spectra are obtained from solutions or suspensions and the opportunity for derivatization in solution can be expected to further expand the usefulness of the approach presented here. Another possible area of application is to direct chemical ionization and related in-beam methods.[51] The mechanisms underlying these procedures are not known, but if they resemble those for desorption ionization, then similar enhancements in ion yield can be expected.

In view of the emerging indications of deep-seated similarities in mechanism for the desorption ionization methods,[52] derivatization to form ionic species ("reverse derivatization") would seem to represent a general approach to increase the analytical utility of all these methods. With organic reagents, functional group selectivity can be achieved, while acid/base chemistry seems to be easily applicable. For the majority of analytical applications, nonreversibility of reaction 1 would be desired. For acid/base reactions, however, reversibility of reaction in conjunction with the ability to continuously vary pH over a wide range might allow the analyst to sequentially and selectively desorb species of differing acidities or basicities from complex mixtures.

It is well-known that in atomic SIMS, positive ion yields are enhanced by several orders of magnitude using O$^-$ beams and negative ion yields by using Cs$^+$ beams.[53] Various explanations have been advanced, most recently that ionic surface states are generated.[54] If this hypothesis is substantiated it would provide a unified explanation for the enhancement effects observed in both atomic and molecular systems.

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