Nitrogen Trifluoride: A New Reactant Gas in Chemical Reaction Interface Mass Spectrometry for Detection of Phosphorus, Deuterium, Chlorine, and Sulfur

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A new set of reactions that involve fluorine have been investigated in chemical reaction interface mass spectrometry (CRIMS). The primary goal of this study was to provide a means to selectively detect phosphorus-containing compounds, which fluorine does by generating PF_5. PF_4^+, the main fragment ion of PF_5, provides a sensitive (10 pg/s), selective, and linear ($> 10^3$ dynamic range) channel for phosphorus-containing analytes. This fluorine-rich environment also provides new ways to selectively and simultaneously detect hydrogen isotopes, chlorine, and sulfur. NF_3 as a reactant gas provides the most comprehensive array of elemental and isotopic detection yet available for CRIMS. An application of phosphorus-selective detection was attempted by examination of a plasma sample from a patient who had been treated with cyclophosphamide. The phosphorus-selective channel showed six peaks: one is derivatized phosphate, two are *t*-butyldimethylsilyl (TBDMS) derivatives of cyclophosphamide, another two are TBDMS derivatives of 4-hydroxy-cyclophosphamide, and one is from underivatized cyclophosphamide. The simultaneous detection of chlorine-containing compounds confirmed our results for those peaks related to cyclophosphamide and its metabolite. *(J Am Soc Mass Spectrom 1995, 6, 421–427)*

Chemical reaction interface mass spectrometry (CRIMS) is a technique that combines selective detection of elements and their isotopes and conventional mass spectrometry in a single system. With few modifications to an existing mass spectrometry system, CRIMS has been shown to be capable of selective detection of elements and isotopes including ^2H, ^{13}C, ^{14}C, ^{15}N, S, Cl, Se, and Br [1–13]. It is particularly useful for studying metabolism without the use of radioactive labels, and even without stable isotope labels if a molecule contains an "intrinsic label" such as Cl and S [3, 7, 8, 12, 14].

Phosphorus-containing compounds are very important in biochemistry, medicine, and environmental sciences. A few techniques have been developed to detect these compounds. One example is the nitrogen–phosphorus detector [15] for gas chromatography (GC), which is very sensitive to phosphorus-containing compounds. However, this technique does not provide completely selective detection for phosphorus. The atomic emission detector provides selective detection of phosphorus, with 1.5 pg/s the minimum detectable amount [16]. Because of the potential utility, the lack of availability, and limitations of alternative methods, the development of a strategy to enable the selective detection of P-containing compounds with CRIMS has been a top priority for our laboratory.

Experimental

Apparatus

The GC-CRIMS system used in these experiments was described previously [17]. A Hewlett-Packard 5890II/5971A mass selective detector (MSD) (Sunnyvale, CA) is equipped with a 30-m × 0.25-mm i.d. × 0.1-μm film thickness DB-5 capillary column (J & W Scientific, Folsom, CA). A microwave-powered chemical reaction interface (CRI) is installed in the GC oven between the column and the inlet of the MSD. The helium flow was 0.5 mL/min. A Swagelok (Crawford Fitting Co., Solon, OH) T was used to couple the column, the CRI, and the reactant gas tube. The reactant gas flow is not measured, but it must represent just a small fraction of total gas flow because substantial amounts of the reactant gas quench the helium plasma [17]. The CRI consists of a 1/4-in. o.d. × 1/16-in. i.d. × 5-in. long alumina tube (Omega Engineering, Stamford, CT) and a stainless steel microwave cavity (Vestec, Houston, TX), which is used to transmit microwave power from a 100-W, 2450-MHz generator (Model MPG-4, Opthos, Rockville, MD). A Teknivent Vector 2 data system

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1044-0305/95/$9.50
SSDI 1044-0305(95)00029-D

Received August 17, 1994
Revised January 9, 1995
Accepted January 9, 1995

(Maryland Heights, MO) was used to control the MSD and to process the data. In all experiments, 1 μL of a given solution was injected in splitless mode, the acquisition of data was started 5 min after injection to allow the solvent front to pass, and then the microwave-induced plasma in the CRI was ignited.

Chemicals

NF_3 was obtained from Matheson (East Rutherford, NJ). (Note: Although NF_3 is not spontaneously reactive as is F_2 or HF, it is toxic and requires appropriate care in the laboratory.) The GC carrier gas is ultrapure helium from Air Products and Chemicals (Allentown, PA). Tris-butoxyethyl phosphate (TBOEP), tributyl phosphate (TBP), *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (MSTFA), and nonlabeled amino acids were purchased from Sigma Chemical Co. (St. Louis, MO). L-Phenylalanine-d_8 (D, 98%), L-leucine-d_{10} (D, 98%) and nitrobenzene-d_5 (D, 99%) were from Cambridge Isotope Laboratories (Woburn, MA). Diazepam was obtained from Hoffmann-La Roche Inc. (Nutley, NJ). *p,p'*-DDT [1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane] was from Aldrich Chemical Co. (Milwaukee, WI). All the chemicals were used without further purification. The plasma sample from a patient who received cyclophosphamide, along with pure cyclophosphamide and 4-OH-cyclophosphamide, was provided by Larry Anderson, Clinical Pharmacology Division, Food and Drug Administration, Rockville, MD. Solvents (acetonitrile and toluene) were high-performance liquid chromatography grade from EM Science (Gibbstown, NJ).

Methods

Dependent on the analysis being done, the mass spectrometer could be set in selective ion monitoring (SIM) mode for any or all of the masses indicated below. The following reactions indicate the elements, the products, the fragment ions, and the masses at which the species are detected:

$$C \rightarrow CF_4\ (CF_3^+,\ m/z\ 69)$$

$$H \rightarrow HF\ (^1HF^{+\cdot},\ m/z\ 20;\ ^2HF^{+\cdot},\ m/z\ 21)$$

$$O \rightarrow F_2O\ (F_2O^{+\cdot},\ m/z\ 54)$$

$$+\ \text{other oxygen–fluorine products}$$

$$P \rightarrow PF_5\ (PF_4^+,\ m/z\ 107)$$

$$Cl \rightarrow ClF\ (^{35}ClF^{+\cdot},\ m/z\ 54;\ ^{37}ClF^{+\cdot},\ m/z\ 56)$$

$$S \rightarrow SF_6\ (SF_5^+,\ m/z\ 127)$$

Phosphorus detection. A series of solutions of TBOEP from 1 to 1000 ng/μL was prepared in toluene with TBP as the internal standard (10 ng/μL). The GC column temperature was initially 90 °C for 2 min, then programed to 140 °C at a rate of 40 °C/min, then to 270 °C at 10 °C/min, and held for 5 min. The SIM program used *m/z* 20, 69, and 107.

Deuterium detection. Deuterium-labeled amino acids were used as the samples. A group of solutions in water was prepared with L-phenylalanine-d_8 concentrations from 69 pg/μL to 69 ng/μL and L-leucine-d_{10} and nonlabeled L-phenylalanine at constant concentrations (65 and 63 ng/μL). These solutions were derivatized by the following procedure: 100 μL of solution was dried, and 50 μL of MSTFA and 50 μL of dried acetonitrile were added and heated at 100 °C for 30 min in a sealed reaction vial. The GC column was set at 70 °C for 2 min, programed to 100 °C at a rate of 30 °C/min and held for 1 min, then programed again to 200 °C at 15 °C/min, and held for 5 min. SIM mode used *m/z* 20, 21, and 69.

Sulfur detection. L-Methionine solutions were prepared in water at concentrations from 66 pg/μL to 66 ng/μL with L-cysteine as the standard (24.5 ng/μL). The solutions were derivatized as described in the foregoing text. The GC column was set at 70 °C for 2 min, programed to 130 °C at a rate of 40 °C/min, held for 3 min, programed again to 150 °C at 2.5 °C/min, then to 250 °C at 20 °C/min, and held for 1 min. The MSD was set in SIM mode with *m/z* 69 and 127.

Chlorine detection. A series of diazepam solutions was prepared in toluene from 0.68 to 680 ng/μL with DDT as the internal standard (7.2 ng/μL). The initial GC temperature was set at 70 °C for 2 min, programed to 210 °C at 30 °C/min, then to 250 at 10 °C/min, and held for 5 min. The MSD was set in SIM mode with *m/z* 20, 54, 56, and 69.

A mixture of eight compounds was used to demonstrate the simultaneous and selective detection of all these targeted species: nitrobenzene-d_5, TBP, caffeine, thiopental, methyl palmitate, methyl stearate, TBOEP, and diazepam. The concentrations of these compounds were not precisely measured, but were about 100, 10, 150, 100, 150, 300, 30, and 150 ng/μL, respectively, following their evaporation and reconstitution in toluene. Amino acids were not used because they required derivatization and increased the complexity of the sample. The GC temperature was set at 70 °C for 2 min, programed to 120 °C at 30 °C/min, then to 250 °C at 10 °C/min, and held for 5 min. The mass spectrometer was set in SIM mode with *m/z* 20, 21, 56, 69, 107, and 127.

The plasma sample from the patient who received cyclophosphamide was processed in the Food and Drug Administration laboratories via the following scheme. Reactive metabolites were trapped by collecting blood samples in tubes that contained 2 mL of acetonitrile, 1 mL of methanol, 1 mL of 2-M monobasic sodium

phosphate (pH 4.6), and 250 μL of a methanol solution that contained *O*-pentafluorobenzyl-hydroxylamine HCl (50 mg/mL) and the *O*-pentafluorobenzyloxime derivative of $^2H_4$-aldophosphamide (16 μg/mL). After at least 3 h, the samples were centrifuged and the supernatant was removed and mixed with 1 mL of $CHCl_3$. After vortexing, 1.6 mL of the lower organic layer was removed and evaporated, and the residue was silylated at room temperature for 1 h by addition of 250 μL of acetonitrile and 60 μL of *N*-(*t*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide.

Results and Discussion

Chemistry

Once an analyte from a chromatographic column enters a CRI carried in helium and mixes with the reactant gas, both analyte and reactant gas are decomposed into atoms by a microwave-powered plasma. As atoms leave the reaction chamber, they recombine to form small molecules in accordance with their chemical thermodynamic characteristics. A mass spectrometer in SIM mode serves as the detector to selectively measure the newly formed molecules. The mass spectrometer response provides both qualitative (which elements or isotopes are present) and quantitative (how much of that element or isotope is present) information.

Prior to this research, the CRIMS reactant gases studied could be classified into two categories based on their chemical characteristics: oxidative or reductive. Oxidative reactant gases are O_2, CO_2, and SO_2 and reductive gases are H_2, HCl, NH_3, and N_2. Our original strategy for generation of a volatile, stable CRIMS product that contained phosphorus was based on the observation by Matsumoto et al. [18] that PH_3 could be generated from phosphate in a reductive environment. Efforts to use these gases for the selective detection of phosphorus-containing compounds were not successful.

A new chemical strategy that uses a fluorine-rich environment in the reaction interface was evaluated. Initially, SF_6 was used as the fluorine source. With SF_6 as the reactant gas, phosphorus was converted into PF_5 and could be selectively detected at m/z 107 (PF_4^+), the most abundant peak in the PF_5 mass spectrum. This was the first successful CRIMS experiment to selectively detect phosphorus.

However, SF_6 was not a good reactant gas for several reasons. First, the P-selective detection channel, m/z 107, could be interfered with by $^{34}S^{16}OF_3^+$, a CRIMS product of SF_6 and O_2. In addition, SF_6 is inherently very stable and does not seem to generate a highly reactive fluorinating environment. It did, however, prove the concept that a CRIMS chemistry with fluorine could yield a P-selective species. We wanted to establish this feasibility with an inexpensive reactant gas before proceeding to NF_3, which sells for more than $2000 for a 3-lb tank.

We tried NF_3 and it was a success. The chemistry for NF_3 is similar to that of SF_6 except that NF_3 does not reform itself readily, but yields N_2 and F_2 as products to a major extent. SF_6 preferentially recombined. With abundant fluorine, not only did PF_5 form readily, but other species were noted in accordance with the reactions listed in the Methods section.

Not only does this fluorine-generating scheme provide P-selective detection, it is good for several other elements such as Cl and S as well as the isotopes of hydrogen. ClF is the CRIMS product for chlorine from organic compounds. Both m/z 54 and m/z 56 can be used as the detection channel. However, m/z 54 could be interfered with by SF_4^{++}, which is part of the mass spectrum of SF_6, a CRIMS product when sulfur is present. Another concern was that $F_2O^{+\cdot}$ at m/z 54 could be a CRIMS product of oxygen, although we did not note any peak in the m/z 54 channel in our experiments with oxygen-containing compounds. It would appear that if there are no sulfur-containing compounds present, m/z 54 could be used because it provides a threefold more abundant species than the m/z 56 channel. The selective detection channel for sulfur-containing compounds is m/z 127 (SF_5^+), the base peak in the mass spectrum of SF_6. SF_6 is the primary CRIMS product of sulfur in the fluorinating environment.

Hydrogen fluoride appears as the main CRIMS product of hydrogen atoms from organic compounds. We find that m/z 20 and 21 can be used to selectively measure H and D. Although m/z 20 provides a general detection channel for unlabeled organic compounds, m/z 21 is selective for deuterium-containing compounds. Our previous scheme for selectively monitoring deuterium used H_2 as the reactant gas and monitored HD at m/z 3.022 with a resolving power of 2000 [2, 11]. Its two disadvantages were that it required a high resolution mass spectrometer and we could neither monitor hydrogen nor measure D/H ratios because of the large amount of H_2 that was used as the reactant gas. The procedure described here avoids both of these problems.

CF_3^+ (m/z 69) can be used as a general carbon detection channel. However, the baseline at this mass is high and variable, especially when temperature programs are used. There were many possible carbon sources including GC column coating, bleeding, ferrules, transfer line, and so forth. The recommended measures to reduce this background are to passivate the system by using a higher than normal pressure and temperature of NF_3 and to remove obvious sources of hydrocarbonlike materials and replace them with metal or Teflon®. Further work to accomplish this is planned. Fortunately, HF (m/z 20) could be used as an alternative general detection channel. In this research, we always collected both m/z 20 and 69, and the m/z 20 channel usually provided better chromatograms of or-

ganic compounds. Although we did not demonstrate it, monitoring m/z 70 should provide a channel for ^{13}C detection.

Sensitivity and Dynamic Range

Phosphorus. To determine the sensitivity and dynamic range, a series of TBOEP solutions in toluene were used. The ion at m/z 107 was used as the selective channel. With an integration time of 300 ms, a detection limit of 1 ng of TBOEP was achieved with a signal-to-noise ratio (S/N) greater than 3. With an ~ 8-s peak width at half-height, this equates to 10 pg/s for elemental phosphorus detection. As discussed below, this level of sensitivity is at least an order of magnitude higher than would be expected with our best CRIMS instrumentation. The linear dynamic range is at least 3 orders of magnitude (Figure 1a), and a correlation coefficient (R^2) of 0.997 was obtained. Reproducibility was determined by repeated injection of a sample that contained 100 ng/μL of both TBOEP and TBP. For the area ratio of the two components, a relative standard deviation (RSD) of 3.2% was obtained with $n = 5$.

Deuterium. Phenylalanine-d_8 and leucine-d_{10} were used to determine the sensitivity and linear dynamic range. The results show that the linear dynamic range is more than 2 orders of magnitude with a correlation coefficient of 0.994 (Figure 1b). Reproducibility experi-

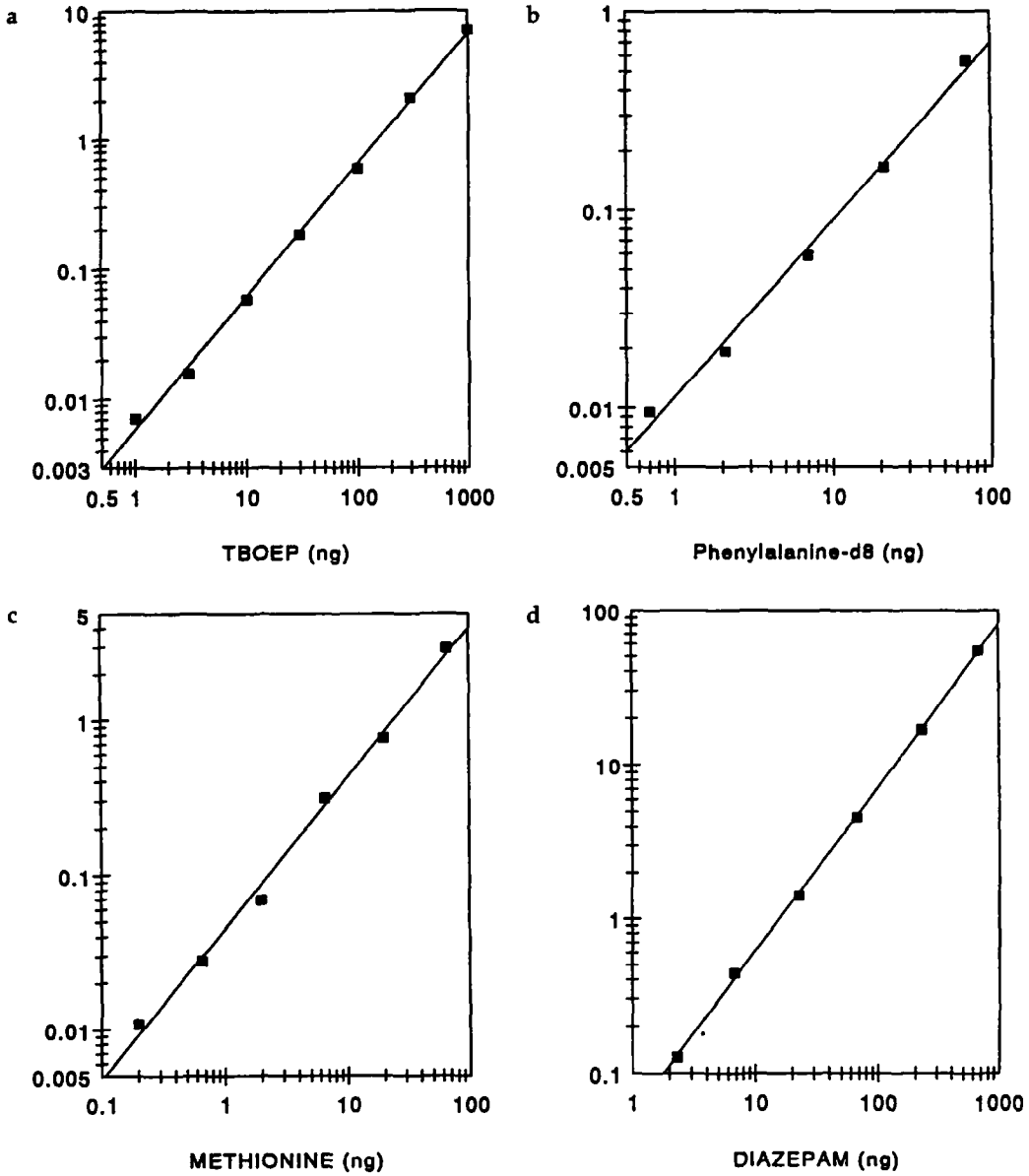

Figure 1. Linearity and dynamic range for P, D, S, and Cl selective detection. (a) Sample = TBOEP, standard = TBP; (b) sample = phenylalanine-d_8, standard = leucine-d_{10}; (c) sample = methionine, standard = cysteine; (d) sample = diazepam, standard = p,p'-DDT.

ments showed an RSD of 2.9% (n = 5) for the area ratio of 60 ng of leucine-d_{10} to phenylalanine-d_8 internal standard. In a separate experiment, the detection limit was found to be 60 pg of phenylalanine-d_8 with an integration time of 300 ms and S/N > 5.

Deuterium enrichment was studied with a group of samples that contained different amounts of L-phenylalanine-d_8 and a constant amount of unlabeled L-phenylalanine as their diTMS (ditrimethylsilyl) derivatives. The D/H ratio for the CRIMS method was obtained from the peak areas in the m/z 21 (D) and m/z 20 (H) chromatograms. We found some nonlinearity when the experimental D/H ratio was plotted against the "theoretical data," especially when the concentration of L-phenylalanine-d_8 was low. To examine this problem, another D/H ratio was obtained in the "normal" gas chromatography–mass spectrometry (GC-MS) mode (with the CRIMS power turned off) by measuring the peak area ratio from the SIM chromatograms of m/z 200 (M-COOTMS for $-d_8$) and m/z 192 (M-COOTMS for $-d_0$), which are the most abundant mass spectrometry peaks of labeled and unlabeled diTMS phenylalanine. The 200/192 ratio then was converted into a D/H ratio by considering the fraction of H atoms in diTMS phenylalanine-d_8. A log-log plot of the D/H ratios of the CRIMS mode against the ratios of the corrected normal GC-MS mode is shown in Figure 2. We found that these two methods—CRIMS and normal GC-MS—agreed closely with each other for the deuterium enrichment experiments. The correlation coefficient is 0.9961 and the slope is 0.94. When regressed against theoretical data, the correlation coefficient was 0.9871 and the slope was 0.81. The nonlinearity mentioned above may be due to errors in the concentrations or purity of the samples, or with other instrumental problems such as ion–molecule reactions [19] or amplifier nonlinearity, but not with the CRIMS analyses.

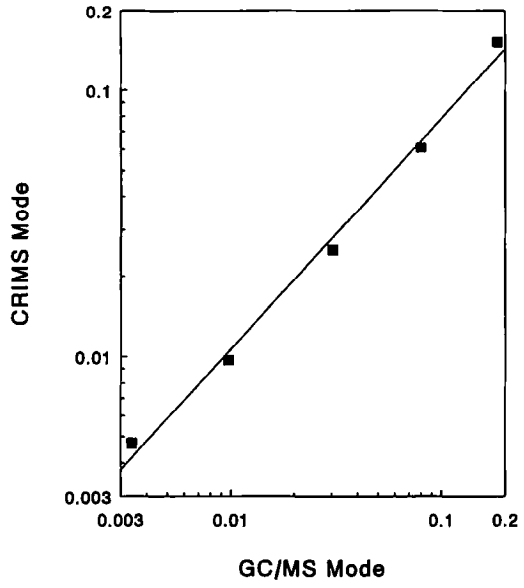

Figure 2. Comparison of the D/H ratio obtained in CRIMS mode and in normal GC/MS mode with diTMS phenylalanine.

Sulfur. A group of solutions of sulfur-containing amino acids was used for the this study. L-Methionine was used as the sample and L-cysteine was used as the internal standard. The detection was linear from 200 pg to 66 ng of methionine. The 66-ng figure is not necessarily the upper limit of the linear dynamic range, although 200 ng of L-methionine produced a deformed peak, which indicated that either the chromatography or the chemistry in the CRI was not right. A log-log plot of these data is shown in Figure 1c with a correlation coefficient of 0.992. A detection limit of 200 pg of L-methionine was obtained with an integration time of 400 ms and signal-to-noise ratio of 3. An RSD of 4.4% (n = 5) was obtained with 20 ng of L-methionine and 24 ng of L-cysteine.

Previously, when the HP 5971A MSD was used with SO_2 as the reactant gas, the detection limit was 1 ng of diazepam [17]. This is comparable with the present work with NF_3 as the reactant gas, which provided a 2-ng limit for the same compound. That report [17] also included a performance comparison of the Extrel C50/400 (Extrel Corp., Pittsburgh, PA) and HP 5971A MSD under several conditions. Although the 2-ng detection limit for Cl does not appear as good as the 50-pg value from a previous study [9] with SO_2 as the reactant gas, that result was achieved on the Extrel instrument with its special 2.1-MHz power supply that maximizes the transmission and resolution at low mass ranges.

Chlorine. Chlorine-containing compounds also can be determined selectively. As was done previously [9], a group of diazepam solutions was prepared in toluene, with p,p'-DDT as the internal standard. The ion at m/z 56, or $^{37}ClF^{+\cdot}$, was used as the selective detection channel. The detection limit is 2 ng of diazepam with a signal-to-noise ratio of 3 and an integration time of 300 ms. A linear dynamic range of 3 orders of magnitude has been achieved with a correlation coefficient of 0.9996 (Figure 1d). A reproducibility test with a sample of 130-ng diazepam and 50-ng DDT showed an RSD of 3.4% (n = 4).

As was true for Cl, the detection limit reported here for sulfur-containing compounds is well above the previously reported result of 30 pg of thiopental [8]. Those experiments used HCl as the reactant gas and Extrel C50/400 with its 2.1-MHz supply as the detector. We generally believe that if the Extrel C50 is equipped with its better rf power supply, it will provide more than tenfold better sensitivity than HP 5971A MSD [14]. If this is true, then NF_3 will provide detection limits below 200 pg for chlorine- and 20 pg for sulfur-containing compounds on the more sensitive

mass spectrometer system. It may be that the NF_3 reactions that yield SF_6 generate a more readily formed and transmitted species than ClS and detection below the 30-pg level can be obtained.

Selectivity

To study the selectivity, a mixture of eight compounds that contained various elements was prepared. The ion at m/z 20 was used to monitor the hydrogen contained in all the organic compounds, and m/z 21, 56, 107, and 127 were used to simultaneously detect deuterium-, chlorine-, phosphorus-, and sulfur-containing compounds, respectively. Figure 3 shows the chromatograms of these channels, all of which appear to be highly selective.

Application to Detection of Phosphorus-Containing Drugs

Cyclophosphamide is an anticancer drug that contains one phosphorus and two chlorine atoms in its structure. With NF_3 as the reactant gas, CRIMS can provide simultaneous detection of P and Cl; thus, it seems to be an ideal choice for the analysis of this drug and its metabolites. A plasma sample from a patient who received cyclophosphamide was analyzed for both phosphorus and chlorine content with CRIMS. The results are shown in Figure 4. General detection (H) is shown in the upper chromatogram, phosphorus-selective detection is in the middle, and chlorine detection is the bottom chromatogram. Although the H channel showed a complex chromatogram, only six peaks were seen in the P-selective channel, and five peaks appeared in the Cl-selective channel. All but the first peak in the phosphorus channel were confirmed as cyclophosphamide related by the response in the chlorine channel.

The first peak in the phosphorus channel was phosphate silylated with three *t*-butyldimethylsilyl (TBDMS) groups, as confirmed by its mass spectrum. A TBDMS-derivatized cyclophosphamide standard solution showed three peaks, which matched the retention times of peaks 2, 3, and 5 in the sample chromatogram. Peak 5 was found to be TBDMS-cyclophosphamide and peak 3 was underivatized cyclophosphamide. Peak 2 showed an area ratio of the Cl to the P channel half the value of other two peaks, which indicated there was a loss of one of the two chlorine atoms in cyclophosphamide. The mass spec-

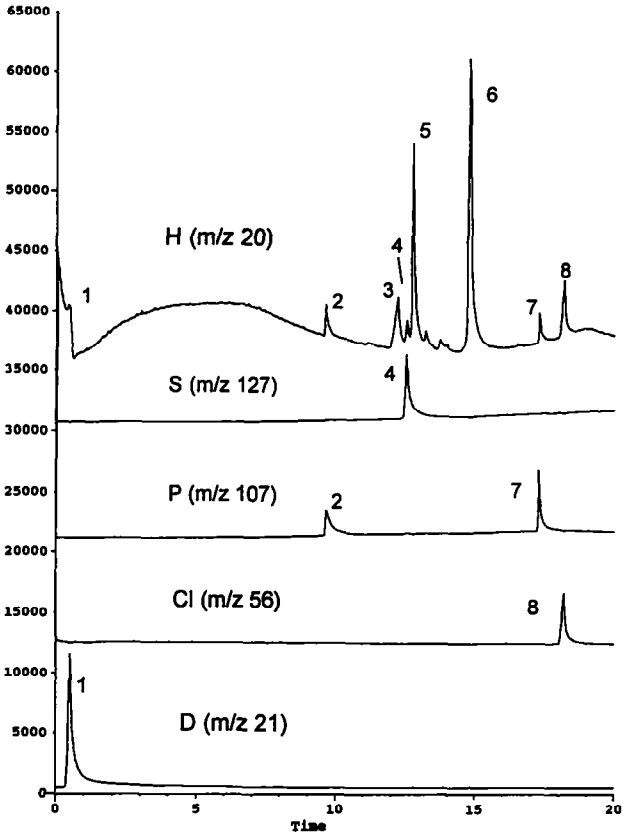

Figure 3. Chromatograms from a test mixture. The chromatograms that show m/z 21, 56, 107, and 127 were magnified 2, 15, 7, and 4 times, respectively, compared to the m/z 20 trace for which the intensity scale is correct. The peak identities are 1 = nitrobenzene-d_5, 2 = TBP, 3 = caffeine, 4 = thiopental, 5 = methyl palmitate, 6 = methyl stearate, 7 = TBOEP, and 8 = diazepam.

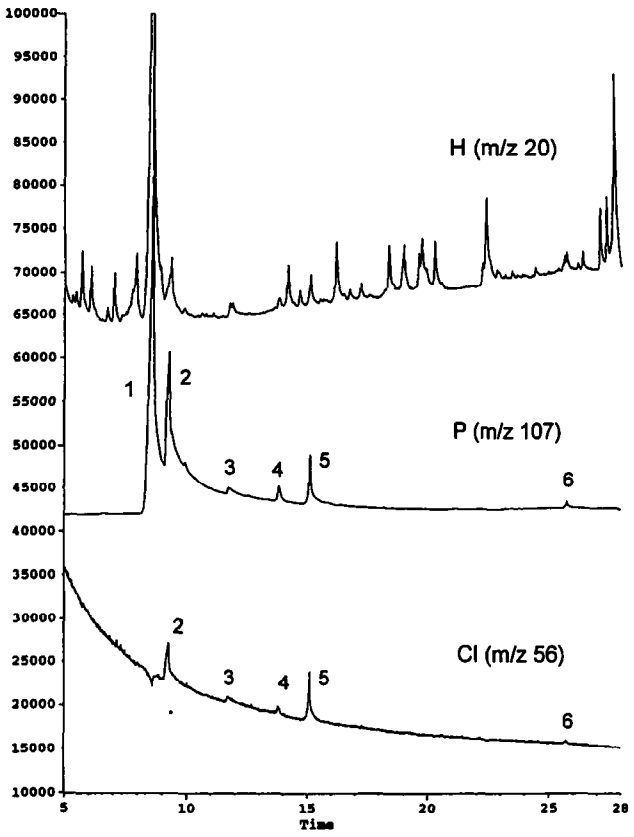

Figure 4. Chromatograms of a plasma sample that contains cyclophosphamide and its metabolites. The m/z 107 and 56 chromatograms are magnified by 2.5 and 25 times compared to the m/z 20 chromatogram for which the intensity axis is correct. The peaks are identified in the text.

trum of this peak suggested that one of the two chloroethyl arms was missing.

A possible explanation is that some cyclophosphamide was decomposed in the GC injector; no further investigation was done to confirm this assumption. Peaks 4 and 6 appeared at the same retention times as the two peaks from the 4-hydroxycyclophosphamide standard. Peak 4 also showed a peak area ratio of Cl to P of only half the other peaks, thereby suggesting a Cl loss in its structure also.

The experimental results indicate that even for a complicated, biologically derived sample, CRIMS with NF_3 provides selective detection for compounds that contain P and Cl. Such drugs fit into our definition of "intrinsically labeled" [12], and therefore can simplify metabolism studies because the special synthesis to incorporate "extrinsic" isotopic labels in the drug would be unnecessary.

System Performance

The most significant drawback of the use of NF_3 as the reactant gas is that the electron multiplier (EM) life was reduced rapidly in the HP 5971A MSD system. The EM had to be changed every two to three months to maintain acceptable sensitivity. The explanation is that the F_2 that is formed in the CRI from NF_3 is very reactive toward the conductive surface of the multipliers. In addition, some etching was found in the fused silica transfer line between the CRIMS tube and the mass spectrometer. When the CRIMS plasma is on, F_2 could continuously attack the EM surface and the life of EM would be shortened. This phenomenon is particularly serious on a system without differential pumping, which has no barrier between the ion source and the analyzer.

We tried different types of electron multipliers: a glass-based EM from Galileo Electro-Optics (Sturbridge, MA), a ceramic-channel EM from K & M Electronics (West Springfield, MA), and a metal EM from ETP Scientific (Auburn, MA). All of these EMs showed short lifetimes, and there was no meaningful variation in the speed of degradation. A separate test that used NF_3 as the reactant gas was conducted on a differentially pumped mass spectrometry system—our DuPont 21-492—with a glass-based Galileo electron multiplier. The instrument was operated in its usual manner and no noticeable change was observed over a time frame in which degradation of sensitivity was substantial in the MSD. Routine CRIMS work has continued on the 21-492 for weeks with NF_3 as the reactant gas, and the sensitivity has still not shown any significant loss. Obviously, differential pumping greatly reduces the deleterious effects of NF_3 CRIMS on electron multipliers.

Conclusions

NF_3 represents a new concept of reactant gases for CRIMS. By providing a fluorinating reaction environment, it permits the selective and simultaneous detection of phosphorus, as well as deuterium, chlorine, and sulfur. The methods are sensitive, linear, and reproducible. As the array of element and isotope selective detection capabilities of CRIMS grows, so should its applications.

Acknowledgments

This research was supported by United States Public Health Service Grant 5-R01-GM36143. We thank Larry Anderson of the Food and Drug Administration for the cyclophosphamide sample and much help in its analysis. This work was presented, in part, at the 42nd Annual Meeting of the American Society for Mass Spectrometry, Chicago, IL, June 1994.

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