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Development of Techniques for Tagging Precursor and Essential Chemicals

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DEVELOPMENT OF TECHNIQUES FOR TAGGING PRECURSOR AND ESSENTIAL CHEMICALS

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ABSTRACT

The ability to identify the manufacturers and distributors of chemicals seized in raids of illicit drug labs would be of great value in controlling the diversion of these chemicals. We developed a tagging scheme based on the addition of sub-ppm concentrations of various combinations of rare-earth elements to the target chemicals and evaluated a number of techniques for detecting the tags. We developed soluble tags for tagging liquids and selected Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) as the preferred detection technique. We developed insoluble tags for tagging solids and developed methods to analyze them and mix them into solid precursors. We have successfully demonstrated the tagging of several solvents and two of the precursor chemicals used in one of the most popular clandestine methamphetamine syntheses (ephedrine reacting with hydriodic acid/red phosphorus). The tagging scheme is capable of yielding tens of thousands of signatures (using holmium as an internal standard and up to 9 rare-earths at up to 3 concentrations yields $3^9 - 1 = 19,682$ signatures) and is applicable to most of the chemicals on the precursor and essential chemicals list. In the concentrations employed, the tags are safe enough to be added to pharmaceuticals and cheap enough to tag tanker loads of chemicals.

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DEVELOPMENT OF TECHNIQUES FOR TAGGING PRECURSOR AND ESSENTIAL CHEMICALS

I. Introduction

Public Law 100-690, which established the Office of National Drug Control Policy (ONDCP) and the Science and Technology Committee (STC), also named a number of National Technology Development Centers (NTDC) to assist in the development of new technologies. Sandia is one of the eight centers named. This chemical tagging project is a small part of Sandia's effort to develop technologies for use in combating drug abuse in this country.

Domestic production of illicit drugs, such as methamphetamine, PCP (phencyclidine), and LSD (d-lysergic acid diethylamide), is a national problem. The Chemical Diversion & Trafficking Act of 1988 attempted to limit access to chemicals that are considered essential to the synthesis of controlled substances by requiring manufacturers, importers, and exporters to maintain records of all transactions involving quantities of these compounds above a threshold level defined by the Drug Enforcement Administration (DEA). Despite an expansion of the list of controlled chemicals and a lowering of the threshold amounts, large quantities of these chemicals are still being diverted to produce illicit drugs. The ability to identify the manufacturers and distributors of precursor and essential chemicals seized in raids of illicit drug labs would be of great value to the DEA in controlling the diversion of these chemicals. We proposed to do this by tagging the chemicals.

Tagging involves purposely adding something to a chemical that will uniquely identify it. There are many ways to do this. For example, some explosives are tagged with small plastic chips that are made by layering plastic of different colors in unique sequences so that the manufacturer and type of explosive can be identified by examining the chips edge-on under a microscope.[1] This technique is useful for tagging solids, but has obvious limitations for tagging liquids because the chips are too large to remain in suspension and have a different density than the liquid. Trace impurities can be added as tags. These tags include chemicals that are inert or those that have similar physical and chemical properties to the substance being tagged. Also, compounds containing trace elements that are absent in the untagged material and detectable at extremely low concentrations are useful tags. Advances in commercially available analytical techniques make it possible to detect many impurities in the sub-part-per-billion range.

Though it has severe limitations, isotopic labeling is also useful in certain situations. Isotopic labeling involves replacing one or more atoms in the target molecule with another isotope of the same atom. For example, carbon-12 could be replaced by carbon-13, hydrogen could be replaced by deuterium, or nitrogen-14 could be replaced by nitrogen-15. Although isotopic tags are very expensive and yield relatively few signatures, an isotopically tagged precursor chemical will usually "carry over" through synthetic procedures into the product drug molecule. Carry-over tagging will be discussed in more detail in a subsequent section.

We focused on developing tagging techniques that have the potential to be applicable to most of the chemicals on the precursor and essential chemicals lists, which include solids and liquids ranging from poisonous industrial chemicals with annual production rates of millions of tons to pharmaceuticals produced in relatively small quantities for human consumption. To demonstrate the utility of the tagging technique, we concentrated on tagging the precursor chemicals for a popular synthesis of methamphetamine.

II. Selection of Target Drug and Drug Synthesis

Methamphetamine hydrochloride (also known as "crank" or "speed") is one of the most frequently abused drugs in the United States.[2] Unlike cocaine or heroin, it is produced in the U.S. and therefore it should be easier to tag the chemicals used in its production. We concluded that methamphetamine was a logical drug to target.

At least ten different methamphetamine syntheses are in use at clandestine drug labs. Some of these are discussed in the open chemical literature while others are described in the underground press. Allen and Cantrell[3] reviewed 95 references concerning the synthesis of amphetamine and methamphetamine in clandestine laboratories. The DEA's efforts to make it more difficult to obtain the chemicals needed for these syntheses have caused changes in the drug business. Chemists were forced to develop more complicated synthetic methods that use chemicals not currently controlled by the DEA. Some clandestine labs have gone into the business of making chemicals which are now on the precursor chemicals list. For example, some years ago the most popular methamphetamine synthesis started with the reaction between phenyl-2-propanone (P2P) and methylamine. This synthesis was so simple and popular that the DEA went beyond making P2P a precursor chemical; they made it a Schedule II Controlled Substance requiring the buyer to be registered with the DEA as a bona fide manufacturer, importer, or researcher. Many of the clandestine drug labs switched to other synthetic methods, but others began making their own P2P.

A synthesis which has became very popular is the reduction of ephedrine with hydriodic acid and red phosphorus. An alternative is the reaction of ephedrine with thionyl chloride to yield chloroephedrine, which is then reduced with hydrogen in the presence of a catalyst to yield methamphetamine. Methamphetamine is also synthesized from the reaction of phenyl-2-propanone (P2P) with methyl amine under reducing conditions. These syntheses are shown in Figure 1.

We chose to focus on ephedrine and hydriodic acid as the chemicals to tag because of the different challenges they present. Ephedrine is a solid organic chemical that is used primarily in pharmaceutical preparations as a bronchodilator. Therefore, toxicity of the material used to do the tagging is a prime concern. All of the approximately 305,000 kilograms of ephedrine used in the U.S. in 1990 was imported.[4] China is the major exporter of natural ephedrine (extracted from the ephedra plant) and Germany is the major exporter of synthetic ephedrine. The threshold quantity for reporting sales of ephedrine, its salts, optical isomers, and salts of optical isomers to the DEA is one kilogram. Ephedrine is usually marketed as its stable hydrochloride salt and is relatively free of contaminants.

Hydriodic acid is an industrial chemical which is also on the precursor chemicals list. It has a threshold quantity of 10 liters for 57% acid. It has legitimate uses as a chemical reagent where it is used as a source of iodide, a reducing agent or an acid. It is also used as a disinfectant and as a trace iodine source for iodine-deficient human diets. Hydriodic acid is an aggressive medium and contains many metallic impurities. These impurities could interfere with some tagging schemes.

Although our efforts for this project were focused on methamphetamine, we wanted to develop a technique with wide applicability to other drugs and to other chemicals on the precursor and essential chemicals lists. These lists influenced our evaluation of potential tagging techniques.

The Chemical Diversion & Trafficking Act of 1988[5] (CDTA) lists the threshold quantities of precursor and essential chemicals for domestic and import/export distribution. These are shown in Table 1.

As laws such as this make it more difficult for illicit drug makers to obtain the listed chemicals, new synthetic and processing methods are devised which use unrestricted chemicals. This eventually results in the addition of new chemicals to the list. The Crime Control Act of 1990 (Pub. L-101-647) amends the list of chemicals which are subject to the CDTA and adds twelve chemicals to the list of precursor chemicals, one of which was previously listed as an essential chemical (hydriodic acid) and another, D-lysergic acid, which is and remains a controlled substance in Schedule III of the Controlled Substances Act. Threshold quantities for hydriodic acid and 3,4-methylenedioxyphenyl-2-propanone have been lowered. In addition, hydrochloric acid and sulfuric have been added to the essential chemicals list for export to designated countries. Table 2 lists the latest additions to the precursor chemicals list. The revised lists can be found in The Code of Federal Regulations.[6]

III. Development of Tagging Scheme

To offer a wide range of options in the utilization of tags, we sought to develop a tagging scheme with the following characteristics:

- **Low-cost tag** - cheap enough to make it feasible to tag shiploads of chemicals.
- **Low-cost analysis** - tags which can be analyzed using sophisticated but commercially available techniques.
- **Many signatures** - selected technique must yield thousands of signatures.
- **Non-toxic** - safe for addition to food and drugs, even though this is not a requirement for most of the chemicals on the precursor and essential chemicals list.
- **Flexible** - useful for many different chemicals, both solids and liquids. Ability to be inserted into the target chemical after it leaves the manufacturer, if necessary.

After considering many tagging options, we concluded that a mixture of rare-earth elements (REE) had the best combination of attributes for this application. They are detectable in small concentrations by a variety of techniques, are harmless at the levels we plan to use, offer the potential for thousands of signatures, and are absent from or are present in very low levels in the chemicals we wish to tag.

The rare earths or lanthanides (atomic numbers 57 through 71) have close chemical similarities, making separation from one another difficult. This is an advantage for tagging because mixtures of lanthanides will not disproportionate, thus making it possible to devise a tagging scheme based on the concentrations of a number of REEs relative to one particular REE (the internal standard).

Our tagging scheme uses holmium as the internal standard and nine other REEs, each at three possible concentrations (one of the concentrations can be zero). This yields $3^9 - 1 = 19{,}682$ possible signatures. The other REEs used in this scheme are lanthanum, cerium, praseodymium, samarium, europium, terbium, dysprosium, thulium, and lutetium. If four different concentrations were used, more than 262,000 signatures would result from the same REEs.

To understand how the scheme works, consider the sample signatures in Table 3. Holmium is the internal standard that is present in every tag. Its concentration is represented by "1", which could be 0.5 ppm or 1 ppm or whatever level is appropriate. The zeroes, ones, or twos under the other nine elements indicate that the element is absent (0), is present at a concentration equal to that of holmium (1), or is present at a concentration equal to twice that of holmium (2). The I.D. (identification #) is the base 10 number equal to the base 3 number generated by the relative concentrations of the nine REEs from Lu through La; e.g. tag #1 contains only Ho and La, with the La concentration equal to the Ho concentration. Tag #5000 (20212012 base 3) contains Tm, Tb, Sm, and La at twice the concentration of Ho and contains Eu and Ce at the same concentration as Ho. Tag #19682 contains all of the nine REEs at twice the concentration of Ho.

With a large number of REEs, only a few concentration levels are required to generate a large number of signatures. Since there are only a few concentration levels, they can be widely spaced; e.g. factors of two in concentration levels. This means that neither the preparation nor the analysis has to be as accurate as when only a few REEs at many, more closely spaced concentration levels are employed.

Tags for Liquids and Solids

The REE-based tagging scheme described above should work for most of the chemicals on the essential and precursor chemicals lists, but the physical and chemical form of the rare-earth elements will necessarily be dependent on the characteristics of the chemical being tagged. We developed soluble tags, which can be used to tag liquids or solids, and insoluble tags, which are used to tag solids. Details on the development of these tags will be included in the experimental section.

Soluble Tags

The easiest way to tag a liquid is to incorporate the REE in a chemical which is soluble in the liquid being tagged. We will call these soluble tags. Mixtures of rare earth nitrates containing REEs in the desired ratios can be easily prepared and are soluble in acids and polar solvents. Less polar solvents may require rare-earth complexes, many of which are commercially available. These will be discussed in the section on experiments.

Insoluble Tags

Insoluble tags have a number of advantages over soluble tags for tagging solid chemicals. The biggest advantage is that each solid particle will contain the tag signature. This makes it more difficult to foil the scheme and allows much smaller tag concentrations to be used. In this section several approaches to the development of insoluble tags are described. Initial efforts focused on ~ 20-25 μm diameter microspheres made of magnesium alumino-silicate glasses doped with about 7 wt % rare earths in various combinations. The microspheres are recovered for analysis by dissolving the solid chemical and filtering the microspheres out of the solution. Because of their characteristic size and shape, the microspheres are readily identifiable under an optical microscope. This makes it much easier and cheaper to identify batches of tagged chemicals than if a complete analysis had to be done to search for REEs. Also, it is possible to tag at well below the FDA (Food & Drug Administration) standards for particulate contamination of pharmaceuticals because a large fraction of the microspheres can be recovered and relatively few of them are needed for analysis.

Technically, REE glass microspheres are an acceptable solution for the tagging of solids, but they are expensive to make. Each tag requires that a new batch of glass containing the REEs in the proper proportions be prepared and spheroidized. Efforts were made to reduce costs by developing new techniques; however, production of a single tag still costs several hundred dollars and yields thousands of times more glass than is needed for the tag. We also investigated diffusing REEs into glass microspheres, but diffusion rates were too low to be practical.

Since the cost of the tag is an important factor, we abandoned glass microspheres and developed a completely different way to make insoluble tags. Zeolites are microporous aluminosilicates which offer an attractive means of encapsulating rare earth cations within a chemically stable host environment. Depending on the rare earth ion and the zeolite framework used, 10-30 wt. % rare earths can be adsorbed easily and inexpensively by suspending the zeolite particles in a solution of the desired ions. This technique permits the simultaneous adsorption of several different rare earths in a single zeolite phase, once the relative selectivities of the ions are learned. The exchanged zeolites are stable through a wide pH range (approximately 4 to 13) and at high temperatures (from 500 to 1000°C).

In addition to using traditional zeolite hosts, a study of rare earth exchange in zinc phosphate zeolite analogues was undertaken in order to take advantage of their tendency to form larger crystallites. These zeolites have a characteristic cubic morphology that makes them as easily distinguishable under a microscope as the glass microspheres.

Mixing Studies for Insoluble Tags

Insoluble tags offer the possibility of using smaller concentrations of tag than the soluble tags, but it is important for the insoluble tags to be uniformly distributed in the solid chemical being tagged (unless it is expected that all of the tagged chemical will be recovered, in which case uniform distribution is unimportant). Otherwise, sampling a small part of the tagged chemical could result in not finding any tag. Under our sponsorship the University of New Mexico/National Science Foundation Center for Micro-Engineered Ceramics developed a process for creating homogeneous mixtures of powders having very different densities, concentrations, and particle sizes.[7] The approach taken was to develop a technique to coat the small inorganic particles (glass microspheres or zeolites) with the organic compound of interest (ephedrine) so that the resulting powder would have roughly the same density and particle size as the organic powder with which these "tagged" particles would subsequently be mixed. The mixing of tagged and untagged powders would then be relatively straightforward using standard blending techniques. It was demonstrated that sub-ppm concentrations of insoluble zeolites could be uniformly incorporated in ephedrine. Details of these mixing studies will be discussed in the experimental section.

Analytical Techniques

The decision to use REEs as tags was based partly on the availability of sensitive techniques for their detection. Among the techniques evaluated were NAA (neutron activation analysis), ICP-MS (Inductively Coupled Plasma-Mass Spectrometry), XRMF (X-ray Microfluorescence spectroscopy), SEM-EDS (scanning electron microscope with an energy dispersive x-ray accessory), and X-PIXE (eXternal Proton Induced X-ray Emission).

NAA is one of the most sensitive ways to detect many of the lanthanides, but the nanogram to picogram sensitivities reported for the lanthanides can usually be realized only in the absence of interfering activities.[8] Although post-irradiation chemical separations can remove some interfering elements, the REEs can interfere with each other, resulting in a loss of sensitivity. In addition, chemical separations greatly increase the cost of an already expensive analysis.

ICP-MS is a relatively new technique compared to NAA and is being used more and more frequently for applications where NAA would formerly have been used.[9],[10],[11],[12],[13] ICP-MS instruments are available from a number of manufacturers and there are many commercial analytical laboratories using the technique. For some of the lanthanides the sensitivity of ICP-MS is equal to or better than NAA.

Some additional techniques were experimentally evaluated for use on insoluble tags. These included XRMF,[14] SEM-EDS, and X-PIXE . All of these techniques use small beam diameters (<50 μm), which makes them ideal for analyzing the kinds of insoluble tags we developed. XRMF and SEM-EDS are commercially available instruments while X-PIXE results were obtained using a research instrument at Sandia/New Mexico. The results of these evaluations will be discussed in the experimental section.

Toxicity of Rare-Earth Compounds

Many of the rare earth compounds are non-toxic and can be detected in extremely low concentrations. Wald reviewed the literature on the toxicity of rare-earth metals[15]. He found that much of the information on the toxicology of the rare-earth metals was gained from evaluation of these materials for medicinal purposes. For example, cerium oxalate was found useful for relieving vomiting during pregnancy[16] and gadolinium -DTPA complexes are used as a contrast agent in magnetic resonance imaging.[17] Haley has done extensive studies of the toxicity of rare earths.[18,19,20,21,22,23,24] Oral animal toxicity measurements showed most rare earth nitrates, chlorides, and oxides to have toxicities of the same order as aspirin[25] and to have one-tenth the toxicity of ephedrine on an equal weight basis[26]. A 1985 study of the safety of rare earths used in agriculture agreed with earlier studies and in addition determined values for Maximum No-effect Dose (200 mg/Kg of body weight) and Acceptable Daily Intake (2 mg/Kg) of rare earth nitrates.[27,28] To put this in perspective: if ephedrine were tagged with a total rare earth concentration of one part per million, a 155 pound man would have to consume 310 pounds of ephedrine daily to receive the Acceptable Daily Intake of rare earths and 15 tons daily to receive the Maximum No-effect Dose. The low oral toxicity of the rare earths was further demonstrated in an evaluation of their use as markers in human nutritional studies.[29]

The addition of small concentrations of tagged zeolite particles or even glass microspheres to chemicals on the precursor and essential chemicals lists does not appear to violate any regulations. The most stringent rules would logically apply to pharmaceuticals, such as ephedrine. The United States Pharmacopoeia[30] lists standards for particulates larger than ten microns in eye ointments and injectibles (particulates less than ten microns are apparently not regulated), but lists no standards for particulate impurities in oral drugs. Nevertheless, the sensitivity of the analysis methods applicable to rare earths in zeolites or glass microspheres coupled with the fact that the particulates can be concentrated by dissolution and filtration of the tagged chemical allows the use of tag concentrations far below the USP standards.

There is evidence in the literature that some pharmaceutical companies have tagged some of their products for the purpose of detecting counterfeit drugs. In a 1967 paper on the use of activation analysis in problems of drug control, Reynolds[31] reports that "pharmaceutical manufacturers have long added small quantities of harmless substances to products for identification purposes." Reynolds says that such tracers are considered by both manufacturer and the FDA (Food and Drug Administration) to be trade secrets. We contacted the FDA to try to find out more about this practice but were refused any information.

IV. Experimental Results

In order to perform these experiments, all of the appropriate permits were obtained from the DEA so that we could work legally with controlled substances. These permits identify which Schedule materials (I, II, III, or IV) can be possessed in a given lab. Most of this work did not require handling controlled substances. Only carry-over experiments that involved the synthesis of controlled substances and the tagging of controlled precursors required permits.

The highest standards of cleanliness and purity were maintained in the lab where tagging was done because traces of pure rare earths can irreversibly tag a large batch of chemicals. The utmost care was taken to insure that no cross contamination occurred. Our laboratory standards may seem inconsistent with the procedures used by illicit drug producers, but rare-earths are not commonly found in an illicit lab and are unlikely to be accidentally introduced in a chemical handling situation by dirt, dust, uncleaned labware, or technical grade solvents.

Soluble Tags

Successful tagging relies on uniform dispersal of the tag throughout the medium. We used two different procedures to disperse the soluble tags: (1) dissolving the tag in the medium or a solution thereof (this was followed by freeze drying when tagging solids such as ephedrine), (2) ball-milling the tag with ephedrine.

We successfully tagged ephedrine, acetone, 2-butanone (MEK), and hydriodic acid. We demonstrated that the tags are reproducible, that the signatures remain viable, and, for the liquids, that the tags are not affected by aging.

Tagging Ephedrine

Impurities in Ephedrine—The first step in determining the feasibility of tagging ephedrine was to measure background concentrations of impurities in representative samples of ephedrine. Results are shown in Figure 2 for samples supplied by the DEA. The labels indicate the origin of the samples. None of the samples contained rare earths above 1 ppb and none of the impurities found presented an interference problem for ICP-MS analysis.

Ball Milling with REE Solutions —Tagging at the sub-ppm level is easily accomplished by the addition of rare-earth stock solutions to the material of interest. These solutions are typically 1000 ppm metal dissolved as the oxide in 2-5% nitric acid. The standard solutions are inexpensive, readily available and have certified, low impurity levels. They can be accurately measured (±1 %) using automated micropipettes. The tiny amount of liquid added is removed by drying under vacuum or in a forced air oven. The added nitric acid is inconsequential as an impurity, but can be neutralized if necessary. We have also used neutral stock solutions of rare-earth nitrates to tag, but these have a limited lifetime and must first be separately measured for exact rare-earth concentrations before they can be used to tag.

Dispersal of the added solutions is accomplished by ball milling the tagged material in a ceramic ball mill for an hour. The material is collected as a fine powder. One potential disadvantage of this method is that the fine powder obtained might be recognized as "processed" by someone receiving the material. The material would still have imperceptibly changed impurity levels, still be useful for subsequent reactions, and still be ≥99.999 % the same as the untagged material.

In our tests, we used ephedrine hydrochloride tagged at the ppm level with rare-earth elements (100 μl of 1000 ppm stock solution tags 100 g of ephedrine to 1 ppm.) The tagging was successful. Though the absolute concentration of the tags varied somewhat, the relative concentration of the tags was always correct, far above background levels, and reproducible among different samples from the same batch.

Solution Processing and Freeze-Drying of Tagged Ephedrine—Alternatively, a solvent can be used to dissolve a material and its tag. Subsequent removal of the solvent from the homogeneous solution yields a homogeneous distribution of the tag. This does not require any consideration of relative solubilities as long as the material is either freeze dried or agitated as the solvent is removed. (Rotary evaporators work well for this.) The tag may precipitate as a different phase than the tagged material but if large crystals are avoided, dispersive forces will distribute the material so that the tag signature is maintained.

Freeze dried solutions have the advantage of uniform dispersal of the tag amid the other crystals but may appear "processed" depending on the usual appearance of the material.

Our experiments with solvent processing of ephedrine tagged with rare-earth nitrates dissolved in acetonitrile, and ephedrine hydrochloride tagged with rare-earth nitrates freeze dried from aqueous solution both showed uniform distribution of the tag.

Reproducibility of REE tags—We routinely used standard methods of duplicate sampling, split sampling, and blank testing to check the reproducibility of both our tagging and the instrumentation that we used. Usually we found that the absolute concentrations of the tags varied, but importantly, the signatures remained readable. Figure 3 (samples **1**, **2**, **3**, and **4**) demonstrates some of the variabilities found in the tagging process. Four analyses are displayed. Samples **1** and **2** are different samples from a larger batch of ephedrine hydrochloride tagged with nine rare earths. The master batch was processed by freeze drying a tagged aqueous solution of the ephedrine hydrochloride (eight rare earths at 100 ppb and holmium at 200 ppb). The material selected for **2** was split into two samples then ashed. The solutions made after ashing were analyzed by ICP-MS. One as **2**, the other was split and analyzed as **3** and **4**. All the samples analyzed showed slightly different tag concentrations. The different concentrations measured in samples **1** and **2** represent the inhomogeneity of the tag throughout the batch combined with the error within the sampling and analysis procedures. The different concentrations measured in samples **3** and **4** represent only the sample-to-sample variation in the ICP-MS analysis. Though the source and magnitude of each error is difficult to quantify, the reproducibility between batches is clearly similar to the reproducibility of the analysis method.

The differences between the measured and targeted tagging levels are evident in the scatter around the 100 ppb mark. These variations are substantial, but the extremely low background levels of rare earths in ephedrine allow unambiguous determination of the tag signature.

Tagging Solvents

Certain tag characteristics are required for tagging solvents. The tag must be soluble at levels well above the final tag concentrations. This allows large containers of solvent to be tagged using small amounts of a concentrated tag solution. This also helps ensure that the tag will not precipitate if drastic temperature changes occur or other impurities are introduced. Tags must be chemically compatible with the solvent, or at least react in a well defined fashion so that tags are unlikely to precipitate. The fact that solvents can easily be pre-concentrated allows dilute tags to be more easily detected.

Our tagging of solvents focused on acetone and 2-butanone (MEK), two solvents commonly used in illicit drug laboratories.

Acetone—Acetone can be tagged with rare earth nitrate hydrates, which are soluble at 10 - 20 % by weight at room temperature. Many of the rare earth nitrate hydrates are extremely hygroscopic, so accurate metal content must be redetermined after handling these materials in room air. Concentrated mixtures of nitrate salts and organic materials are potentially reactive so the tag concentrates should be made just before use, and care should be taken to avoid evaporation of the tag concentrate before dispersal in the material to be tagged.

We tested four brands of high purity acetone for background impurities and found < 0.1 ppb (our detection limit) of all rare earths except lanthanum which was present at 0.1-9.0 ppb. These data are typical of high-purity organics. With this low background of rare earths we can tag high-purity solvents at the ppb level and retrieve the signature using a preconcentration to facilitate the analysis.

As a model tag concentrate we dissolved four rare earth nitrate hydrates to yield an acetone solution containing: Dy, 1.9 %; Eu, 1.4 %; La, 2.2 %; Sm, 1.5 %. The only water present was that from the hydrated salts. The tag concentrate (2.15 µl) was added to 0.5 liter of acetone, the mixture shaken and a sample removed, evaporated and redissolved in 2 % nitric acid for ICP-MS analysis. The concentration of the tag was found to be (calculated to be): Dy, 81ppb (95ppb); Eu, 59ppb (69ppb); La, 94ppb (108ppb); Sm, 58ppb (74ppb).

MEK—MEK was analyzed and tagged in a similar manner to acetone. Background rare earth concentrations from three brands of high-purity MEK were < 1.7 ppb of all rare earths except lanthanum which was present at <7.0 ppb. Concentrating a liter of solvent for ICP-MS analysis yielded typical detection limits of < 1 ppt rare earth in the bulk solvent. The rare earth nitrate hydrates are freely soluble at 0.1 % by weight in MEK.

We modeled the tagging of a 25 metric ton shipment of MEK to check the detectability of a tag added at low concentrations. We also wanted to determine how a tag concentrate would age over extended time periods. We made a tag concentrate: 2 liters of MEK containing about 1 g each of four rare earth nitrate hydrates (Eu, Pr, La, Dy). Upon mixing into a 25 tons shipment of MEK, this would yield ≈ 5 - 10 ppb of each rare earth. The measured background levels of the four elements were: Eu, 0.47 ppb; Pr, 0.01 ppb; La, 0.41 ppb; Dy, 1.67 ppb. The tag concentrate was added to the untagged material to the scale of a 2 liters addition to 25 tons (actual 65 µl added to 1 liter). After mixing, evaporation, and analysis the tags were found at the following levels (predicted from the mass of the salt added to the concentrate): Eu, 4.4 ppb (6.1); Dy, 7.6 ppb (12.6); La, 5.7 ppb (8.1); Pr 8.9 ppb (12.6). Again, though there are some significant variations in the measured as compared to the predicted concentrations, the signature of the tag remains clear and obvious above the background of both the target and other rare earths.

Long-Term Aging of Tagged MEK

We wanted to address the question of longevity of a tag in MEK. A chemical reaction leading to precipitation would lead to an inhomogeneous tag. We tested the tag concentrate as the results would be more obvious in the more concentrated solution. The tag concentrate was left undisturbed for one year in a sealed, dark container. Temperature fluctuations were those of outside weather in Livermore, CA (-5 – 45°C). The bottle was carefully opened and a 10 ml sample removed from the top of the liquid while disturbing the container as little as possible. The container was then shaken vigorously and a second sample removed at once. The concentrations of the tags were measured and are summarized in Figure 4. The tag did not change appreciably in the year since it was added to the MEK. These data support the viability of this tagging scheme for solvents that may be shipped and stored for long periods before the solvent is reanalyzed.

Other Solvents—Many of the solvents used in illicit drug manufacture have very different physical properties from acetone and MEK. Less polar solvents such as toluene and different ethers will not dissolve sufficient quantities of inorganic rare-earth salts for effective tagging. Many conventional salts are soluble at the sub-ppm levels necessary for tagging, but are insufficiently soluble to make a tag concentrate that could be added to larger batches of solvent for bulk tagging.

Fortunately, stable rare earth complexes exist that will dissolve in almost any solvent. Three of these complexing agents are shown in Figure 5. An example of complexes useful in halogenated and aromatic solvents are those of 4,4,4-trifluoro-1-(2-naphthyl)-1,3-butanedione.[32] Thesecomplexes are readily synthesized by literature methods[33] or by the reaction of rare earth carbonates with the diketone in boiling water. For less polar solvents such as hydrocarbons, air-stable complexes of 2,2,6,6-tetramethylheptane-3,5-dione are useful. Many are commercially available; the others are easily synthesized.[34] For example, the ytterbium complex is soluble at >15% by weight in n-hexane, methylcyclohexane and methanol. For highly polar and aqueous solutions rare earth complexes of diethylenetriaminepentaacetic acid would be appropriate. For example, the gadolinium salt of triethylenediaminepentaacetic acid is commercially available from Aldrich Chemical. The other rare earth complexes are easily synthesized by conventional acid-base chemistry. These are just three examples of many rare-earth complexes available to tailor a tagging plan to the particular chemicals of a synthesis. As a target synthesis is identified, the best salts and complexes can be readily identified as effective tags.

Tagging Hydriodic Acid

Hydriodic acid (HI), used in the production of methamphetamine from ephedrine, was also a target material for tagging. Both 47% and 57% aqueous solutions, which are either stabilized (hypophosphorous acid, H_3PO_2) or unstabilized, are the common forms of HI used in illicit drug manufacture. Unstabilized HI oxidizes to elemental iodine upon exposure to air, quickly becoming opaque. Small amounts of iodine do not affect the synthetic utility of the hydriodic acid because the phosphorus added to the reaction reduces any iodine that forms.

Hydriodic acid is a strong, reactive mineral acid and a reducing agent. HI can react with many materials that it might contact yielding potentially high levels of impurities, especially metals. We checked several batches of HI for background impurities and found on average more rare earths in the HI than in the organic materials we checked. A representative 60 element scan of four commercial hydriodic acids is shown in Figure 6. All of the rare earths detected are summarized in Figure 7. The highest rare earth concentrations were found in the stabilized 47% HI from Aldrich Chemical. Those results are summarized in Figure 8. Tagging is feasible with HI by avoiding those rare earths with high background levels or using higher concentrations of tags. We recognize that these four samples do not represent all hydriodic acid; however, any batch of HI to be tagged can be similarly tested so that the proper levels of tag for unambiguous identification can be used.

We tagged HI by direct addition of standardized solutions of rare earth nitrates in nitric acid. We tested our tagging scheme by actually tagging and identifying samples of hydriodic acid. We tagged five samples of Aldrich 47% HI with 200-250 ppb of different rare earths and submitted them to be scrambled by our colleagues. We were able to reidentify all five samples by their tag signatures. This demonstrates the effectiveness of this tagging method. There was, as always, scatter in the data. By normalizing all the concentrations of the tags to the internal standard holmium, the unique signatures remain absolutely clear. The results are summarized in Figure 9. The top graph represents the relative concentrations of the tags as they were added to the original material. The second graph represents the relative concentrations of the tags as they were detected in the scrambled samples. Holmium was added to each sample at 233 ppb and detected in the scrambled samples at 177-374 ppb.

Because we would have no control of the conditions under which a tagged material would be stored, we wanted to see if different storage conditions would affect the viability of the tag signature. We checked the stability of the tag by aging three samples at -30°C, 20°C, and 60°C. The target tag levels were 50 ppb Dy, 500 ppb Pr, and 5000 ppb Ho. One ml of each solution was removed after each of three one week periods, filtered (0.45 µm filter), evaporated, and analyzed for the tag. The results are summarized in Figure 10.

The data for the samples aged two weeks shows unexpectedly low tag levels. Because all the two week data were low, yet the three week data were closer to predictions, we feel that there is some source of error in the sampling or analysis of the two week samples. In any case, though there are significant variations in the measured concentration of the tag over the three week period, the tag remained viable and did not precipitate. The relative concentrations of the three elements remained obvious and the final tag concentrations are essentially the same as the initial concentrations.

Insoluble Tags

This section describes the development of insoluble tags for identification of drug precursors. The insoluble tags considered here are solid particles that are capable of incorporating lanthanide tag ions into their host structures and of being mixed uniformly with the precursor (ephedrine HCl, in this study). There are several advantages to using insoluble tags versus soluble tags to identify precursors or essential chemicals. The tags are unaffected by dilution, and can readily be isolated from the solid or liquid matrix via filtration. Identification of a batch using individual tag particles renders the tags more resistant to tampering, and at the same time allows the use of very small tag concentrations. In principle, a single tag particle of 10 μm^3 volume could be used to identify a 1 kg batch of ephedrine HCl. This would represent a tag concentration of approximately one part in one trillion. In practice, thousands of particles would be added to one kg of chemical. Insoluble tags also offer the possibility of carry-over into the product pharmaceutical if the host particles are not lost or destroyed during synthesis and workup.

Desirable characteristics of insoluble tags include:

- chemical durability, particularly if subjected to a harsh synthetic procedure or used to tag a reactive substrate
- facile isolation and identification
- easy permutation to yield a large number of discrete tags
- mixable with substrate
- low toxicity
- low density and small particle size, if tag is to be suspended in a liquid.

Glass Microspheres

Magnesium alumino-silicate glasses doped with about 7 wt % rare earths in various combinations were synthesized in-house[35] and spheroidized by a commercial producer of glass microspheres[36]. We evaluated microspheres in three size ranges: 10-20 µm, 20-25 µm, and 32-38 µm. Typically an excess of spheres compared to the amount needed to unambiguously identify the tag are easily recovered and identified.

The main issue for effective tagging is uniform distribution of the tag through the matrix. The glass has a material density of about 2.2 g/cm^3, much less than densities of typical organic matrices. We have shown that small batches of solid chemicals can be adequately tagged quickly and easily using the rare earth microspheres, but when complete, uniform distribution is essential we use another method discussed in the zeolite section under "Tagging ephedrine HCl."

In a model experiment, we put 2.3 mg of 20–25 µm microspheres in 10 pounds of granulated sugar (0.5 ppm) contained in its original packaging. We then tumbled the paper bag 25 revolutions. The bag had about 10% headspace so that the materials could mix. Ten percent of the sugar was removed from five different places within the bag and analyzed for dispersed microspheres.

Each sugar sample was dissolved in 1 liter of distilled water, and the solution was filtered through a 0.45 µm Teflon grid filter. Importantly, clean water was run through the filter to remove residual sugar. The filter was carefully removed from its holder, and analyzed by counting the spheres under an optical microscope at 100X. The spheres stood out clearly from all other contamination such as dust or paper fibers. In strong lighting, they were often visible to the naked eye. In the five samples, we counted about 20% of the spheres from 50% of the sugar. The relative distribution of the five samples from top to bottom was: 1: 275: 8: 675: 23. Even in this extremely crude experiment the tag was recoverable. In the fraction with the lowest concentration of tag (the top) there were almost 40 spheres counted. We repeated this experiment with 50 pound barrels of granular and powdered sugar. Again with one minute of agitation the tag was sufficiently dispersed to be isolated in all one pound samples. We feel that this method is fully functional for large samples where reasonable recovery of the product can be expected.

After isolation, the filters with the microspheres are placed on their edges in a test tube, submerged in water and briefly sonicated to remove the microspheres. When the sonication is stopped, the spheres quickly settle to the bottom where they can be removed, dried and collected for analysis. A collection of spheres can be mounted on adhesive tape and analyzed by XRMF.

Zeolites

Zeolites were identified as hosts for lanthanide tags, which can be incorporated into the insoluble zeolite crystals through ion exchange. Zeolites are crystalline, microporous solids that are three-dimensional networks of corner sharing SiO_4 and AlO_4 tetrahedra. These groups form open frameworks that have highly regular pores or channels that are typically between 3 and 13 Å in diameter, and can crystallize in dozens of different phases. The frameworks have a net negative charge, which must be balanced by cations associated with the framework. These cations can often be reversibly exchanged with other ions. The affinity of the cation to the framework frequently depends on the charge of the ion, and divalent and trivalent ions are usually preferentially absorbed with respect to monovalent ions. Zeolites also have a strong affinity for water, and up to 30 weight percent H_2O can be reversibly sorbed into the cages or channels. When heated, zeolite frameworks collapse to condensed phases that are often "stuffed" derivatives of SiO_2 polymorphs.

Zeolites have two properties that identify them as good candidates for tag hosts: they occur as easily identifiable crystals, and they can incorporate rare earth ions from aqueous solution through ion exchange. The zeolite crystals used in these experiments were small enough to be precipitated with the ephedrine HCl to facilitate tagging, but large enough to permit easy recovery and identification. It may also be possible to synthesize zeolite crystals that are sufficiently small and robust to be carried over into the methamphetamine product.

In order to improve the likelihood of successful tagging with zeolites, it is desirable to maximize the amount of lanthanide in the host to increase its detectability during analysis. Also, it is essential to be able to control the ratio of the concentrations of the lanthanide tags with respect to the lanthanide standard (Ho) so that tags containing identical lanthanides in various ratios can be differentiated to a high degree of statistical confidence.

Several investigations must be carried out to develop lanthanide-exchanged zeolites as a tagging system. These are:

a. measuring absorption isotherms to determine the tag:host ratio needed to saturate the host with Ln^{+3} ions.
b. measuring the relative selectivity of the lanthanides chosen as tags with respect to a standard (such as Ho).
c. mixing the tags uniformly with the substrate in very low concentration.
d. developing a convenient method for tag recovery and identification.

In addition, if the tags are to be carried over into the product material, the host phase must:

e. be sufficiently inert to the reaction conditions so that tag release is avoided.
f. crystallize as very fine particles so that they will remain suspended during separation and filtration steps.

Three host phases were used in this study: Zeolite 3A (Linde Type A or LTA), Zeolite 13X (faujasite or FAU), and a microporous cesium zinc phosphate phase (CZP). Zeolites 13X and 3A were commercial NaX ($NaAlSiO_4$) and 3A ($KAlSiO_4$), respectively (Figures 11,12). CZP precipitated from an aqueous solution as oblong pieces 10-15μm across. This phase also crystallized at 25°C, yielding much larger crystallites (Figure 13).

It is known that both LTA and FAU can reversibly exchange lanthanides. CZP tends not exchange ions reversibly because it undergoes a phase change to a condensed structure upon ion exchange. However, it should be noted that reversibility of exchange can be a liability in a tagging application, since it allows the tag to be foiled more easily. An advantage to using CZP as a tag host is its large crystallite size and distinctive cubic morphology, which allows the tag particles to be readily identified using SEM.

Ion Exchange—Complete exchange of trivalent ions into zeolites is very difficult, but it is desirable to incorporate a high concentration of tag lanthanide into the host in order to facilitate tag identification, particularly if several lanthanides are simultaneously present in the same tag host. Therefore, we wish to learn the maximum extent to which Ln^{+3} ions can be exchanged into the hosts under conditions that are convenient to tag synthesis. We thus determined the dependence of the concentration of Ln^{+3} in the exchanged zeolite upon the ratio of the number of equivalents of Ln^{+3} in solution to the number of equivalents of zeolite present. This was done by establishing an equivalent weight of each zeolite, then mixing a standard lanthanide ion with zeolite in equivalent ratios ranging from 1:1 to a 40:1 excess of lanthanide with respect to zeolite.

The zeolite hosts were exchanged by heating the zeolite in an aqueous solution of the lanthanide nitrate or chloride in a polytetrafluoroethylene bottle at 95°C overnight. The hosts were recovered by filtration, then dissolved to allow lanthanide concentrations to be measured using inductively coupled plasma-mass spectrometry (ICP-MS). Initially, the exchanged zeolites were fused with a 10:1 excess (by weight) of lithium metaborate ($LiBO_2$) at 950°C for 15 minutes in a graphite crucible. The resulting melt was poured into a 2% HNO_3 solution. It was eventually found that samples could be dissolved more conveniently and reliably by warming them in a 1.0 N HCl solution for 30 min. Following dilution, samples were analyzed for lanthanide content using ICP-MS.

We found that ICP-MS was suitable for quantifying all major lanthanides in each tag batch, and that trace lanthanides (contaminants in the lanthanide salts used for exchange) could also be identified. In addition to ICP-MS, X-ray fluorescence and scanning electron microscopy (SEM) with energy-dispersive X-ray could also be used to identify major lanthanide constituents, though the results were more qualitative. However, with SEM, we could identify all major lanthanides contained within a single particle.

There was no statistically significant variation of lanthanide concentration for the ranges of lanthanide/zeolite ratios investigated within a given host type. Limits of exchange under the conditions tested are approximately 60 equivalent percent in CZP, 50 equivalent percent in Zeolite 13X, and 60 equivalent percent in Zeolite 3A. (One hundred percent equivalent exchange in CZP, for example, would yield the composition $Ln_{.33}ZnPO_4 \bullet nH_2O$).

Relative Selectivity—In order to produce tags that contain lanthanide ions in predetermined proportions the relative selectivities of the "signal" tags must be measured with respect to the "standard" tag (generally Ho, though initial measurements used Ce as the standard). Initially, equimolar quantities of signal and standard were exchanged with the three tag hosts in a fashion similar to that described above. The ratio of signal to standard in the host was then measured using ICP-MS. This number can then be used to calculate the starting signal/standard ratio needed to synthesize a desired tag, in principle with up to twelve signal lanthanides. This ratio was then tested using the same signal rare earths, but a different standard. The results from this type of test will determine the number of discrete levels of signal tag that can be analytically differentiated.

Relative selectivities of signal lanthanides with respect to a Ce standard are plotted in Figure 14. In general, relative selectivity generally increases with atomic number in Zeolite 3A and in CZP (though more scatter was seen in the CZP data), and decreases with Z in Zeolite 13X. The experiments were repeated with Zeolite 3A, using initial selectivity data to calculate solution phase Ln/Ho ratios that should yield equal concentrations of signal tag and Ho standard in the host. The results are plotted as Ln/Ho vs. atomic number in Figure 15. In general, the observed ratios fell short of unity, indicating that some refinement is needed in either the starting Ln/Ho ratios or the analytical technique.

Acid Resistance—If an insoluble tag is to be carried over through synthesis into the product pharmaceutical, it must be sufficiently robust to endure the conditions of synthesis without becoming lost or releasing tag. In the case of methamphetamine synthesis using the hydriodic acid/red phosphorus reduction, this requires that the tag must at least survive being refluxed in concentrated HI. Under these conditions, all known zeolites would either dissolve or be converted into amorphous silica. In either case, any tag would be lost to the solution. However, heating the tagged zeolites to the point of structural collapse may render them sufficiently inert to survive such conditions.

Differential thermal analysis was used to identify thermal events indicative of structural collapse, allowing an appropriate sintering temperature to be selected. Exothermic events were identified at 670°C in Tb,Ce:CZP, at 1020°C in Tb,Ce:3A, and at 940°C in Tb,Ce:13X. Sintering at 850°C for 30 minutes resulted in no apparent changes in particle size or shape in Ce:CZP, but caused irregular pores to form within the particles, probably due to changes in crystallographic density upon structure collapse (Figure 16). Sintering the 3A at 1050°C for 30 min. caused rounding and necking of the particles (Figure 17), and the 13X particles exposed to these conditions fused together to form large chunks (Figure 18) that were deemed inappropriate for tagging purposes.

Initial checks of acid resistance were performed on sintered Ce:3A and Ce:CZP by soaking them in 47% HI at room temperature for several hours. After filtering, the 3A was recovered, though some weight loss was detected. No CZP could be found, indicating that total dissolution had occurred. Acid resistance of sintered Ce:3A was remeasured by immersing the material in refluxing 47% HI for three hours. The mixture was drowned with water and filtered. The tag experienced a weight loss of approximately 48%. Analysis of the filtrate for Ce indicated that of the Ce originally present in the tag, 12% remained.

Tagging Ephedrine HCl—An experiment was carried out to determine whether zeolite-based tags could be mixed with bulk ephedrine HCl with sufficient homogeneity so that a small sample of tagged ephedrine HCl would contain sufficient tag to permit identification. Tagging was performed by trapping tag crystallites within growing ephedrine HCl crystals, and mixing the tag concentrate into the bulk ephedrine HCl via agitation. The tags were made by exchanging batches of CZP and Zeolite 3A with Gd^{+3}. A batch of condensed Gd:3A was made by sintering the Gd-exchanged 3A at 1100°C for 30 min. The tag concentrates were made by dissolving ephedrine HCl in ethanol to make a nearly saturated solution, suspending the tag crystals in this solution, then precipitating the crystals while stirring the solution using a rotary evaporator. This produced ephedrine HCl crystals containing one part per thousand of tag particles by weight. SEM data revealed that all three tags were successfully coated with ephedrine HCl using this procedure.

A tag concentrate containing Gd:CZP was used to tag bulk ephedrine by adding 0.1 g concentrate to 100 g ephedrine HCl and shaking the container, yielding an overall concentration of 1 ppm. Since the Gd was present in the tag host at a concentration of 9.0 weight percent, this represented a Gd concentration in the bulk ephedrine of 90 ppb. The homogeneity of mixing was measured by sequentially coning and quartering the entire batch in three iterations. Four samples, with an average mass of 0.47 g, were dissolved in 1.0 N HCl and analyzed for Gd using ICP-MS. These results indicated that the concentrations of tag in the four samples has been 6.4, 4.9, 2.3, and 4.4 ppm. This shows that agitation was effective at distributing the tag throughout the ephedrine at detectable concentrations. These concentrations were actually higher than expected, possibly due to inhomogeneous distribution within the tag concentrate.

Other Tag Hosts—In addition to zeolitic hosts, tags were prepared by exchanging amorphous sodium titanate ($NaTi_2O_5H$) with lanthanide salts, and by precipitating lanthanide fluorides from aqueous Ln^{+3} solutions with KF. Both the titanates and fluorides consist of colloidal-sized crystallites, and it was hoped that this property would improve their performance as carry-over tags. Unfortunately these colloids tended to agglomerate, and were easily retained by 1.2 µm filters. These phases do not present morphologies that are nearly as distinctive when viewed using SEM as the zeolites, and thus were considered to be less suitable as precursor tags.

The acid resistance of CeF_3 was measured by stirring this material in hot 47% HI, filtering, and measuring the concentration of Ce in the filtrate. Only 10% of the available Ce was detected in the filtrate, indicating that the acid resistance of this material is excellent.

Comparison of Analysis Techniques

We compared neutron activation analysis (NAA) and ICP-MS for determining trace impurity levels in ephedrine and for measuring the concentrations of soluble rare earths tags in ephedrine. The NAA analyses were done at a commercial facility[37] while the ICP-MS work was initially done in-house and later transferred to a commercial analytical laboratory.[38] Although NAA has greater sensitivity for certain elements, ICP-MS was clearly superior for this application. It was cheaper, had the required sensitivity, was less affected by non-REE impurities, and permitted the use of many REEs. The last attribute is very important because it simplifies analysis and tag preparation.

We determined XRMF (X-ray Microfluorescence spectroscopy) to be the best of the micro-beam X-ray techniques for analysis of insoluble tags. It produced better-resolved spectra than either SEM-EDS or X-PIXE and is a commercially available instrument costing much less than SEM-

EDS. ICP-MS can also be used if you are willing to go to the trouble of using lithium borate fusion to put the "insoluble" zeolites into solution.

Carry-Over Tags

Tagged materials would have added value if their tags would carry over into products synthesized from tagged starting materials. This would allow the history of a material to be followed through one or more chemical modifications. There are a number of strategies for implementing a carry-over tagging scheme such as: impurity tagging, analog tagging, or isotopic labeling, each best suited for a particular situation. Different carry-over tagging methodologies would be preferred depending on the ultimate goal of the program. Rare earth tagging is inexpensive and flexible, but not suited for many reactions (as discussed below). Isotopic labeling offers excellent carry-over, but is expensive and there are only limited numbers of tags with each requiring a separate synthesis. Analog tagging may offer excellent carry-over, but offers a limited number of tags and introduces compounds of potentially unknown toxicity and reactivity. Only carry-over with traces of rare earths will be discussed in this section; other types of carry-over tagging will be covered in other studies.

We explored some reactions that synthesize controlled substances using starting materials that were tagged with traces of rare earths. These experiments suggest that the fate of the tag is extremely dependent on the exact procedures used in the synthesis. Also water soluble rare earth complexes are not the materials of choice for reactions where extractions of organics are made from aqueous solutions. If there is no special affinity between the tag and the materials being tagged, most of the tag may be washed away in the purification procedure. Routine purification procedures can reduce a tag to levels where it is easily confused with background levels of rare earths. Since rare earths may be introduced to a reaction product from any of the starting materials, reagents, solvents or apparatus used in the reaction and purification, a tag signature must remain absolutely certain for carry-over tagging to be viable.

Results from two experiments follow in Table 4. In one experiment (**Reaction 1**) the tag signature was apparently preserved in the synthesis of methamphetamine from ephedrine using hydriodic acid/red phosphorus and also in the subsequent conversion (**Reaction 2**) to the hydrochloride salt with gaseous HCl. In the other experiment, the tag signature was lost after the first reaction.

We tried several carry-over experiments while converting ephedrine to methamphetamine and its hydrochloride. The tags were added to any or all of the starting materials. Reaction 1 was the only example where the tag could be considered to have carried over. All reactions showed a loss of ≥ 90% of the tag. Most of the time this causes the tag to be lost in the background noise of the naturally occurring rare earths.

Similar experiments were performed using tagged phenyl acetone (P2P) in the synthesis of methamphetamine using methyl amine and aluminum amalgam. Again the tag was lost in the reaction. The tag appeared above the detection limits (0.08-0.10 ppb) in the product only when added at > 10 ppm to the P2P starting material. This represents a loss of >99.9% of the tag, and the loss of the signature. Similar negative results were obtained in the synthesis of phenyl acetic acid from tagged phenyl acetonitrile. Clearly this tagging methodology is unsuitable for these reactions.

Recrystallization of Ephedrine from Tagged Solution

We performed experiments to determine if ephedrine hydrochloride would chelate rare earth ions in aqueous solution. We would not expect strong chelation at pH <8, but if even weak chelation occurred, we would have much better chances for successful carry-over tagging in syntheses involving ephedrine. As expected, there was no tendency for the rare earths to precipitate with the ephedrine hydrochloride from aqueous solution. A solution tagged with 20 ppm each of eight rare earth nitrates showed a drop in concentration of approximately 2 orders of magnitude with each crystallization, leaving the tag detectable through two only crystallizations. The balance of the tag was found in the filtrate. These results support the results from the carry-over experiments by demonstrating how quickly standard purification techniques remove the rare earths from these organic materials.

Our carry-over tagging results were disappointing, but considering the value of an effective carry-over tag, it is worthwhile to consider other possible approaches. A carry-over tag could be designed if the synthetic steps it would go through were well defined. Many illicit drugs can be synthesized in a variety of ways so they require a tag that mimics the physical and chemical characteristics of the bulk medium. This is not the case for rare earths tagging organic media. Analog tagging and isotopic labeling would be the most effective as the tag would be most likely to carry-over

V. Summary

We have developed a rare earth tagging technique and demonstrated its feasibility for a number of chemicals having a range of physical and chemical properties, a variety of end uses, and a wide range of production quantities. We are confident that this technique could be applied to most of the chemicals on the precursor and essential chemicals lists. The analytical techniques we selected are sophisticated but commercially available. Tagging procedures have been developed which would allow the tags to be inserted in the target chemical at any time after the final purification step in its production, including clandestine insertion in the field. Procedures have been developed to allow uniform mixing of tagged zeolites with ephedrine, thus enabling identification of a tagged shipment even when only a fraction of the chemical is recovered. Carry-over tagging requires much more work. Experiments thus far indicate that it will be difficult to develop rare earth compounds which will survive the procedures used to make and purify drugs.

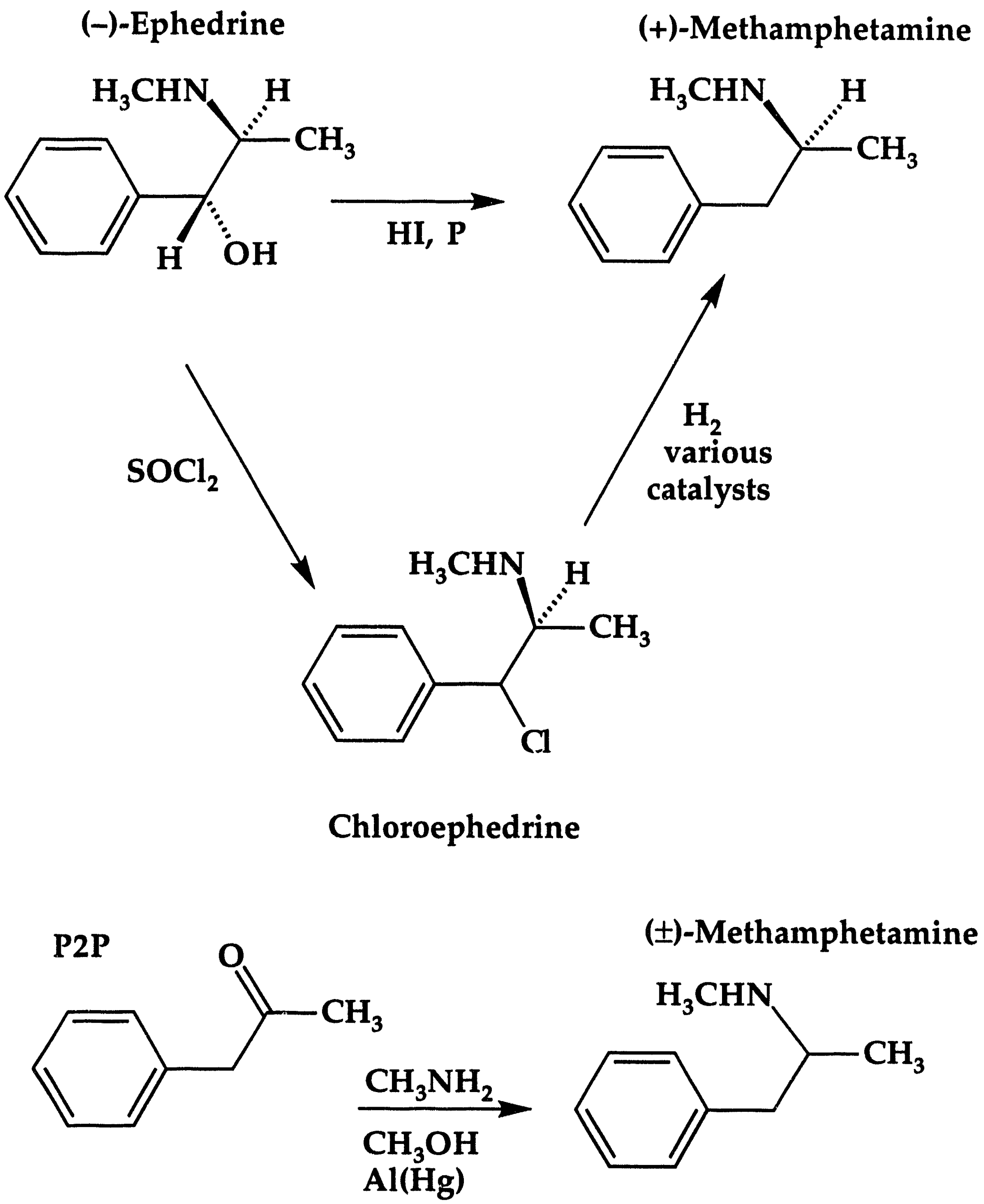


Figure 1. Two syntheses of methamphetamine: 1. The synthesis of (+)- methamphetamine from naturally occurring (–)-ephedrine. 2. Achiral P2P yields racemic methamphetamine

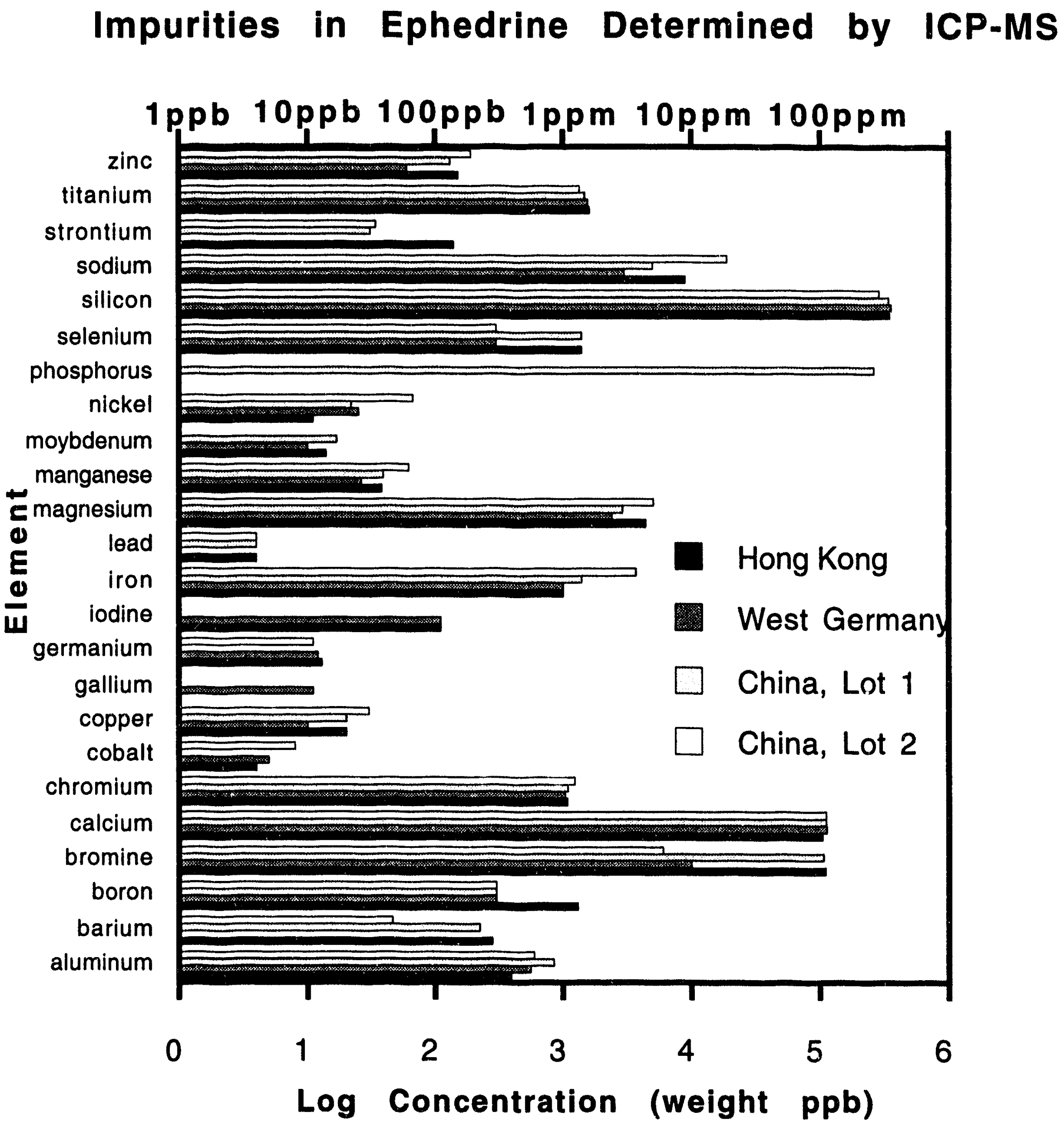


Figure 2. Concentration of impurities found in ephedrine obtained from four different sources. Analysis was done by ICP-MS. Note the absence of rare earth contaminants.

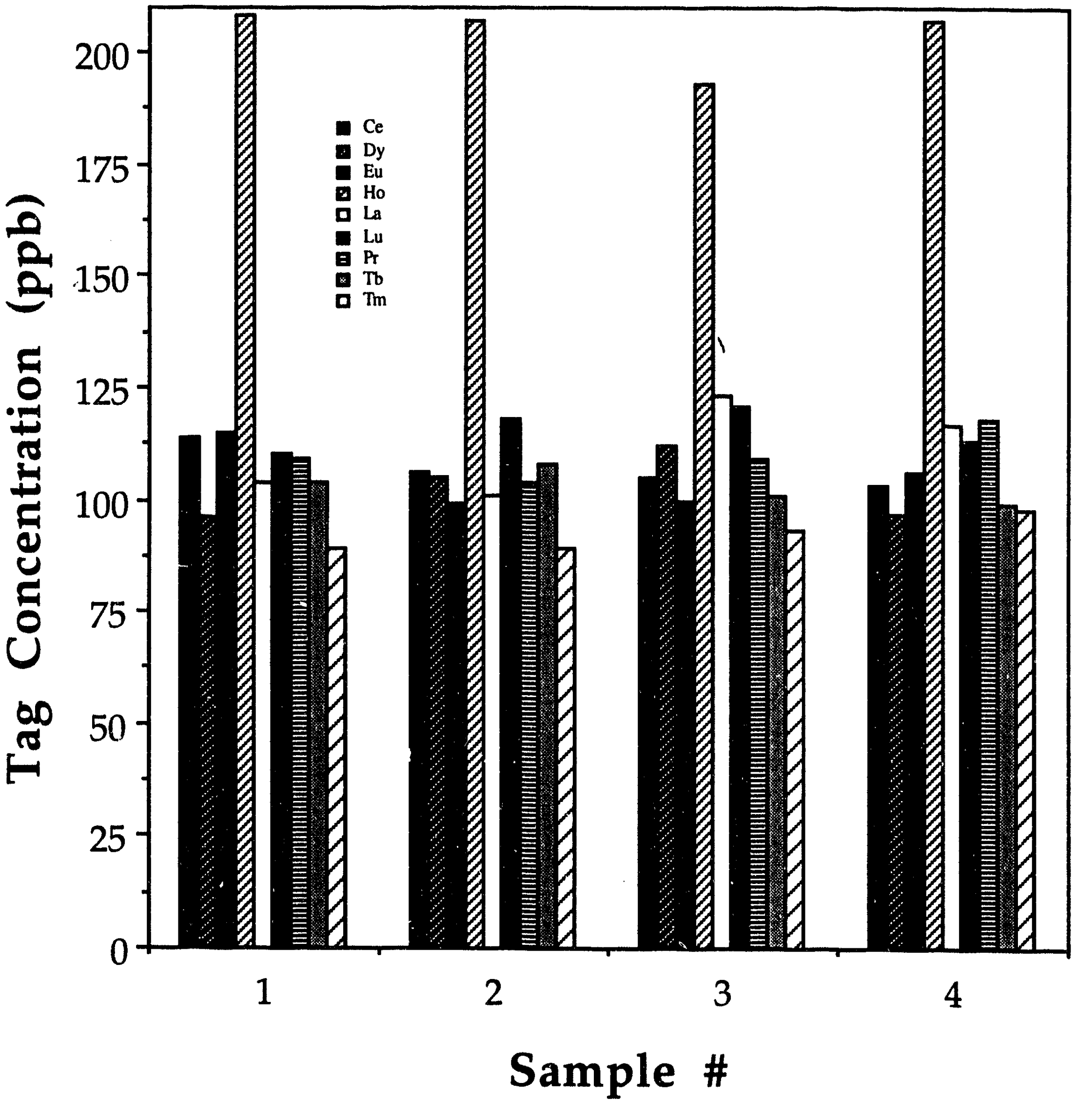


Figure 3. Concentrations of rare earths in tagged ephedrine. Samples 1 and 2 are different samples of a large batch of tagged ephedrine. Samples 2,3 and 4 are different analyses of the same digested sample (sample 2).

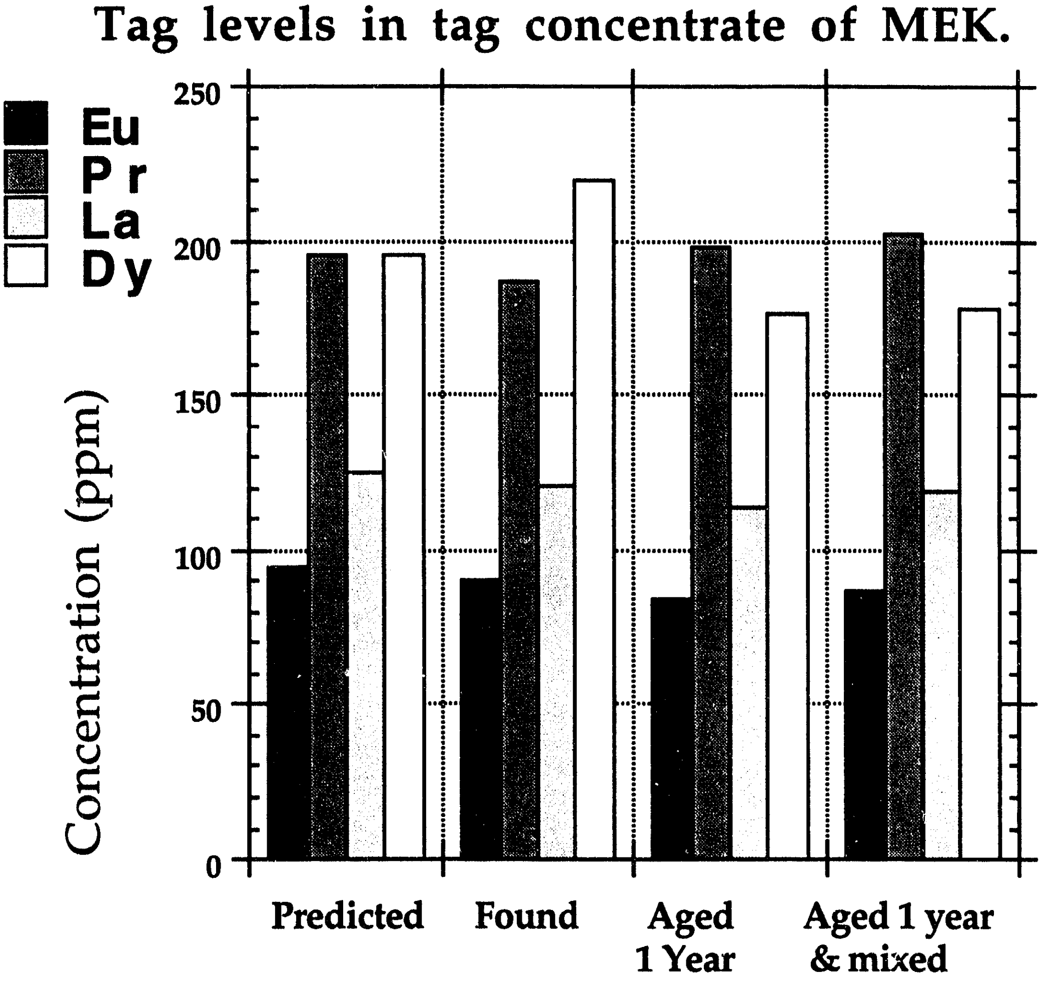
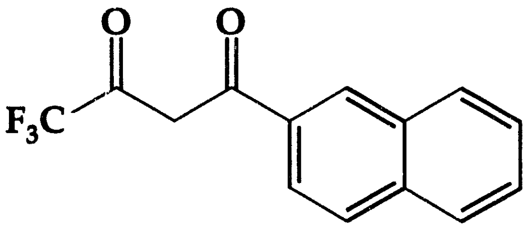
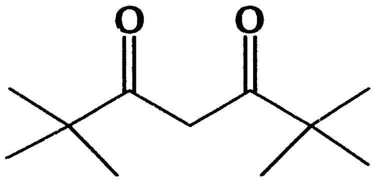


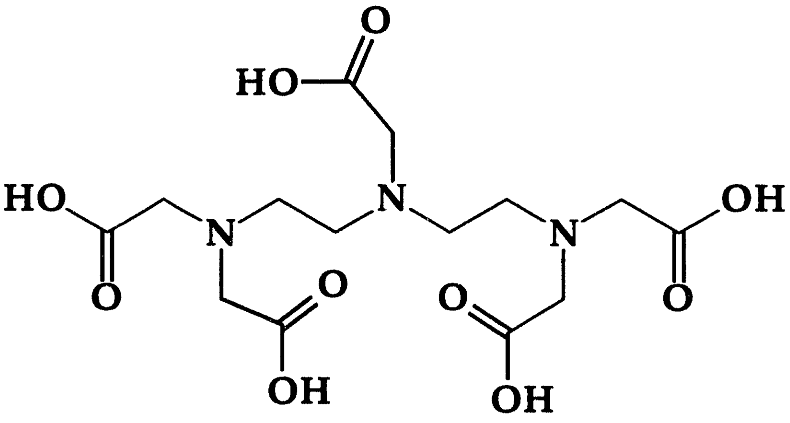
Figure 4. Predicted vs. analyzed concentrations of tags in a sample of MEK both when made and after aging 1 year. The aged MEK was carefully sampled from the top portion of the solvent then thoroughly shaken and resampled.



4,4,4-trifluoro-1-(2-naphthyl)-1,3-butanedione



2,2,6,6-tetramethylheptanedione



diethylenetriaminepentaacetic acid

Figure 5. Complexing agents (upon ionization) for rare earths.

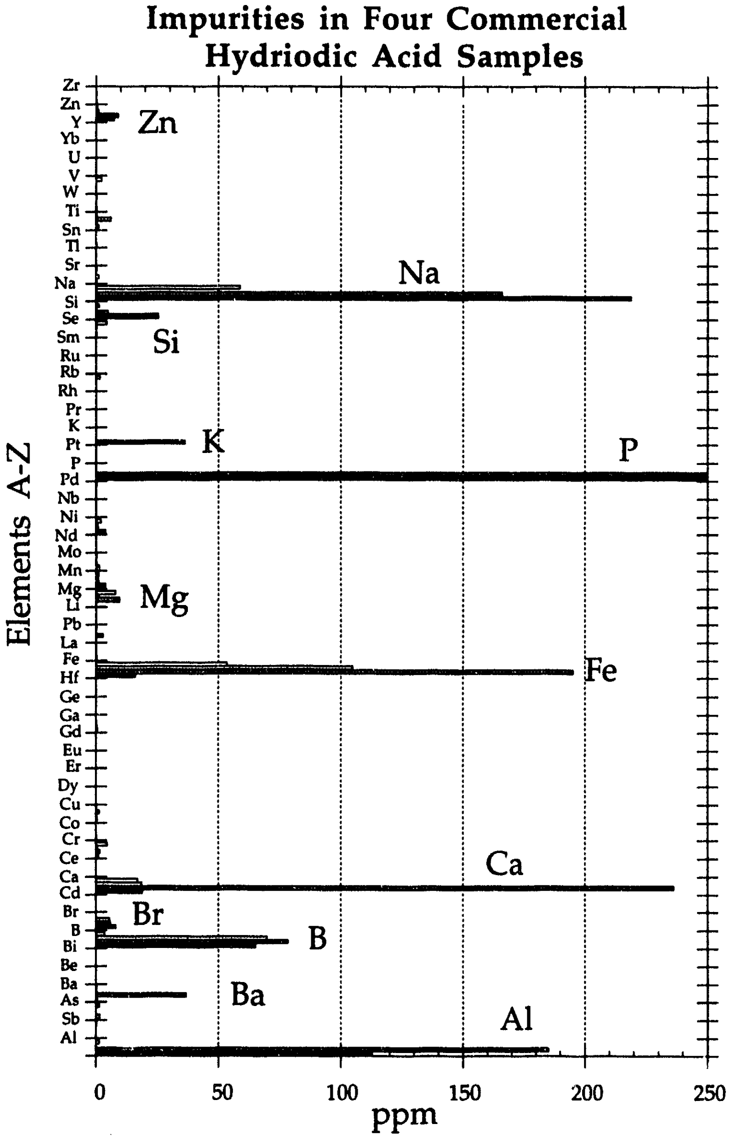


Figure 6. An elemental listing of the many impurities found in four samples of HI. The phosphorus in the two stabilized samples is off scale, it comes from the stabilizer hypophosphorous acid. The values for a given impurity are below the label on the y-axis.

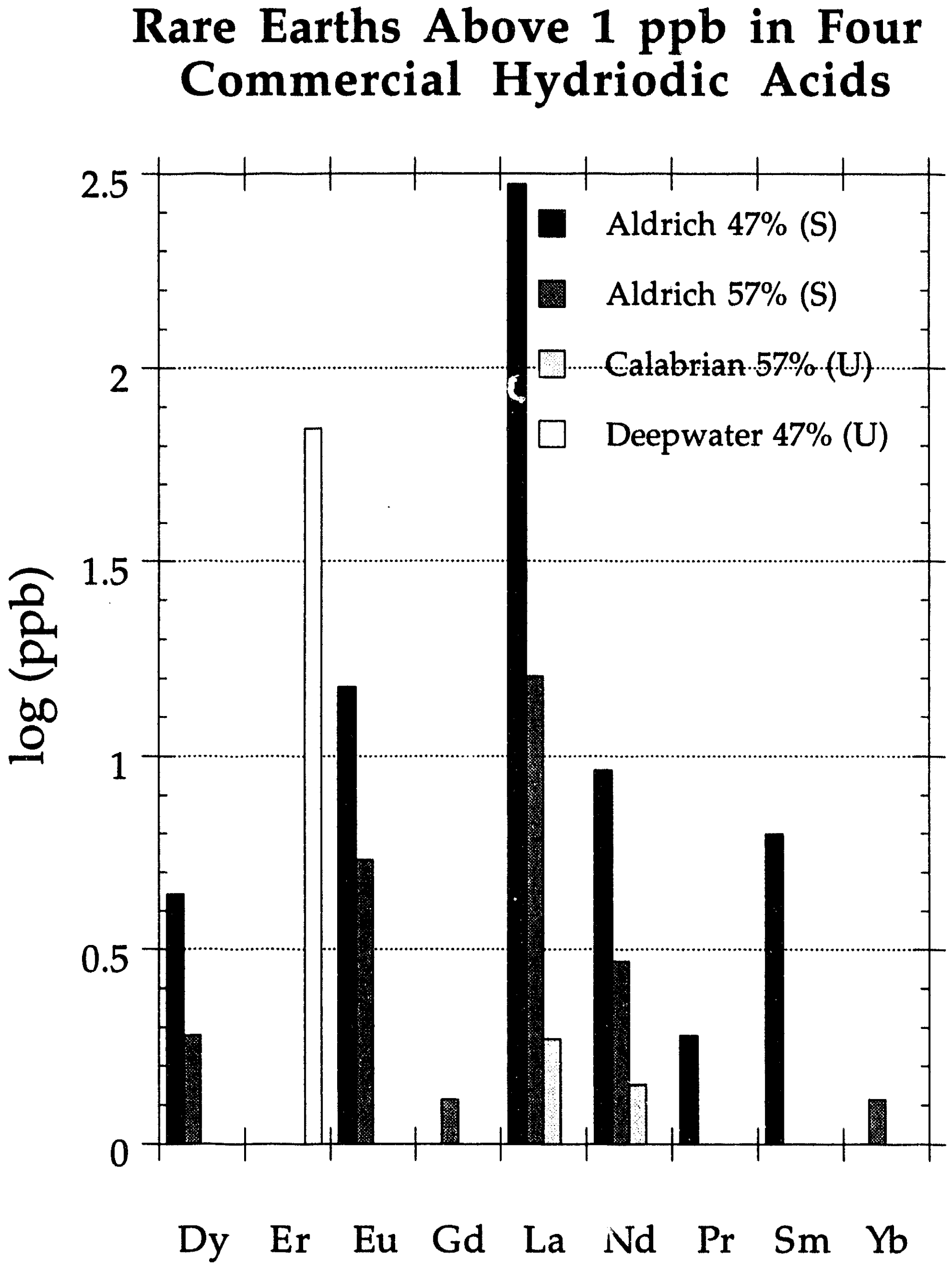


Figure 7. Concentrations of rare earths above 1 ppb in four samples of commercial hydriodic acid. Stabilized (S). Unstabilized (U).

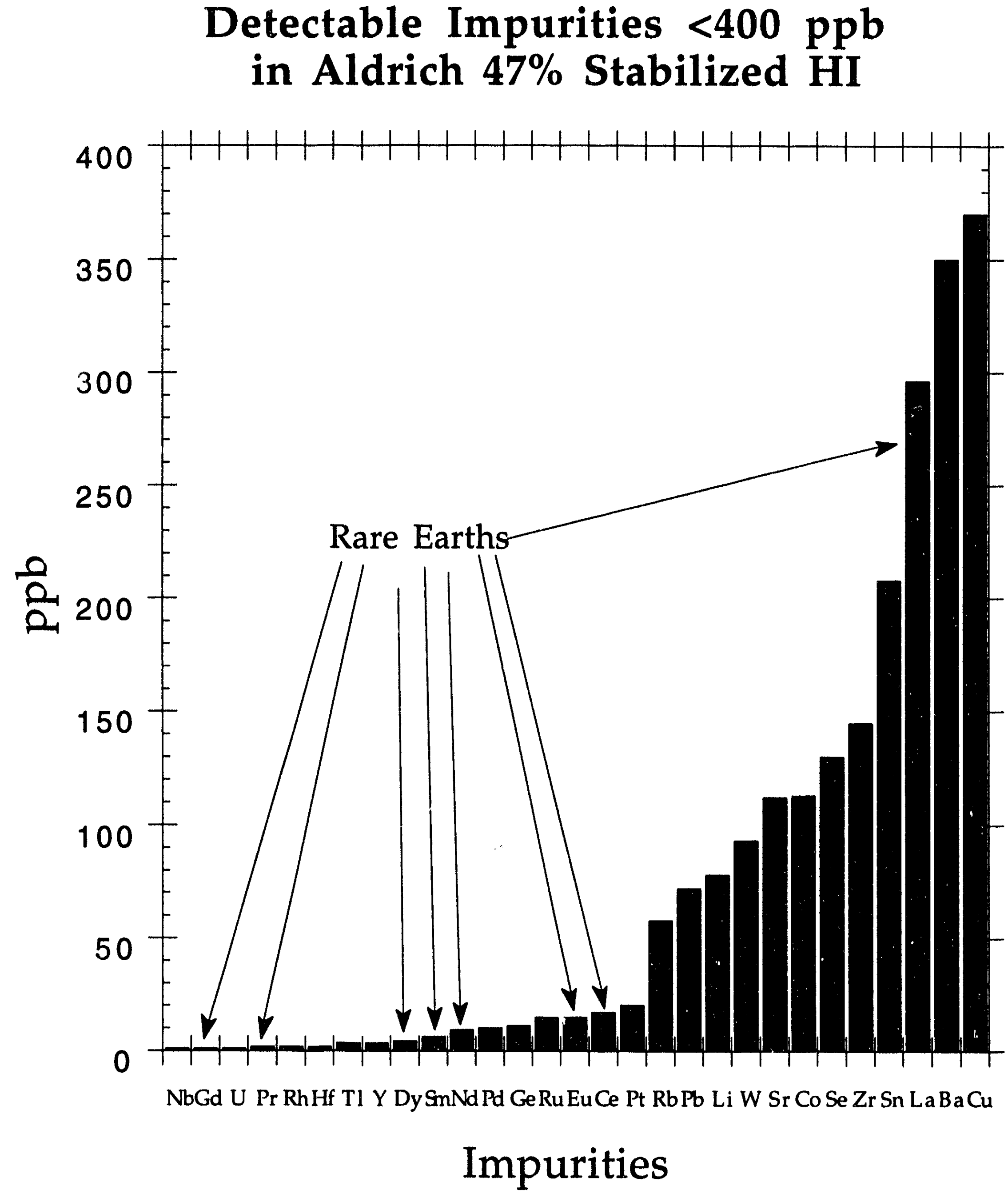
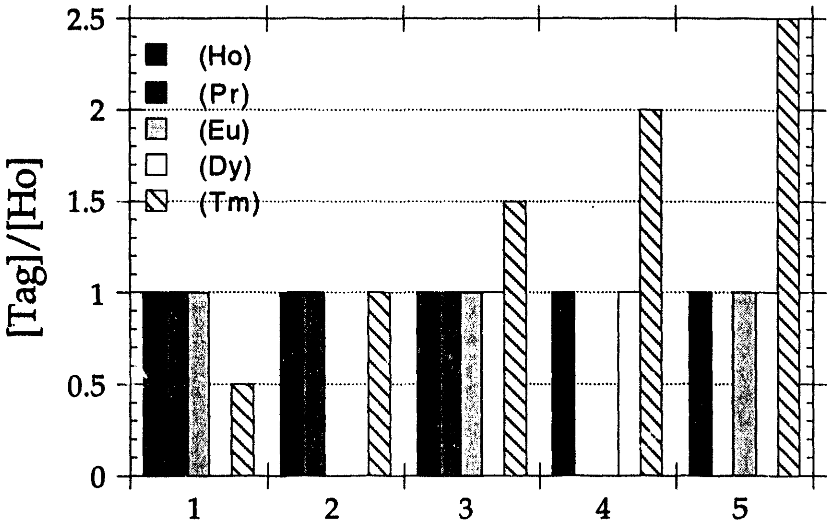
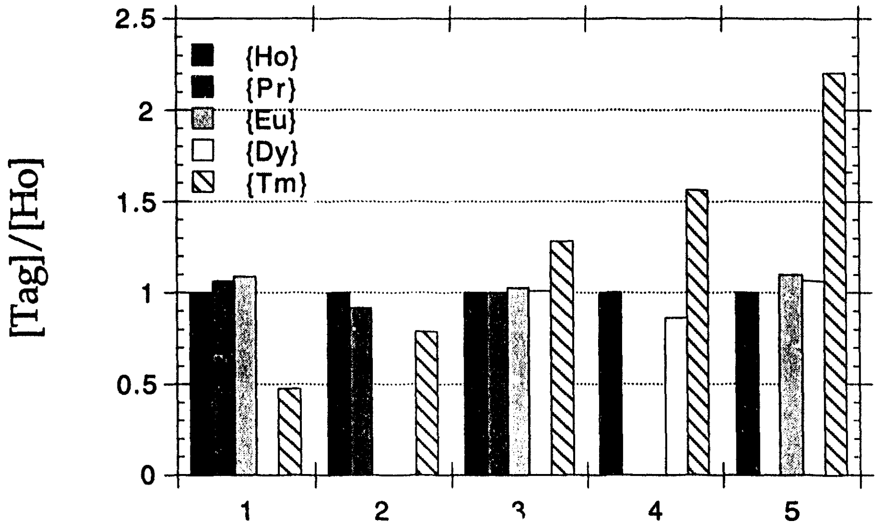


Figure 8. An elemental listing of the impurities detected between 0.5 and 400 ppb in a sample of Aldrich 47% Hydriodic Acid (Stabilized). The rare earth elements are pointed out.



Blind HI Tag Concentrations as Normalized to [Ho] at 233 ppb.



Concentrations of Tags as Normalized to the Analyzed [Ho]. [Ho] = 177–374 ppb

Figure 9. A comparison of the tag concentrations in a set of 5 tagged hydriodic acid samples. All values are normalized to a holmium concentration of 200 ppb. The upper graph represents the concentrations of the tags added to the samples. The lower graph shows the concentrations of the tags found when the scrambled samples were analyzed. The assignment of each tag signature was straightforward.

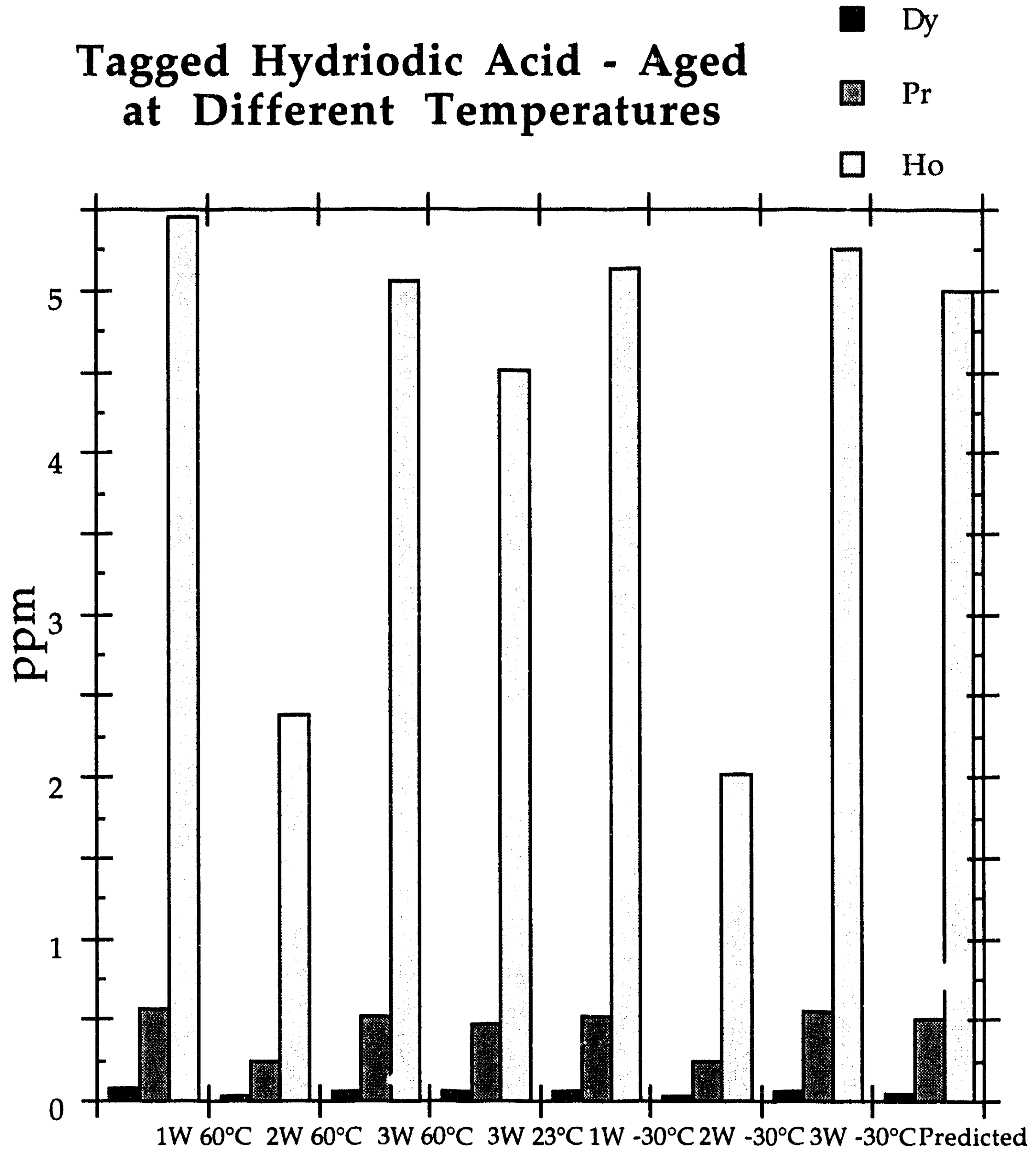
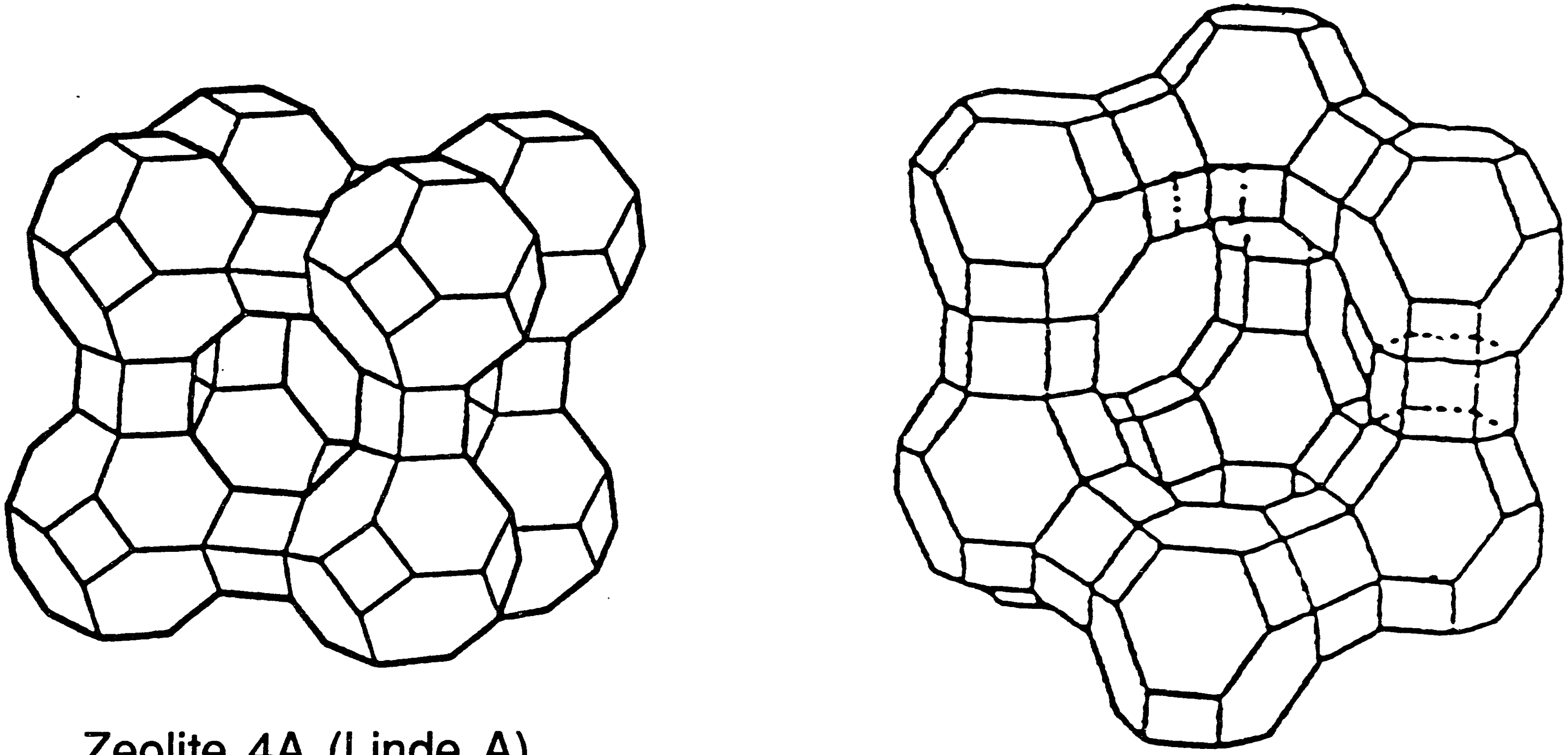


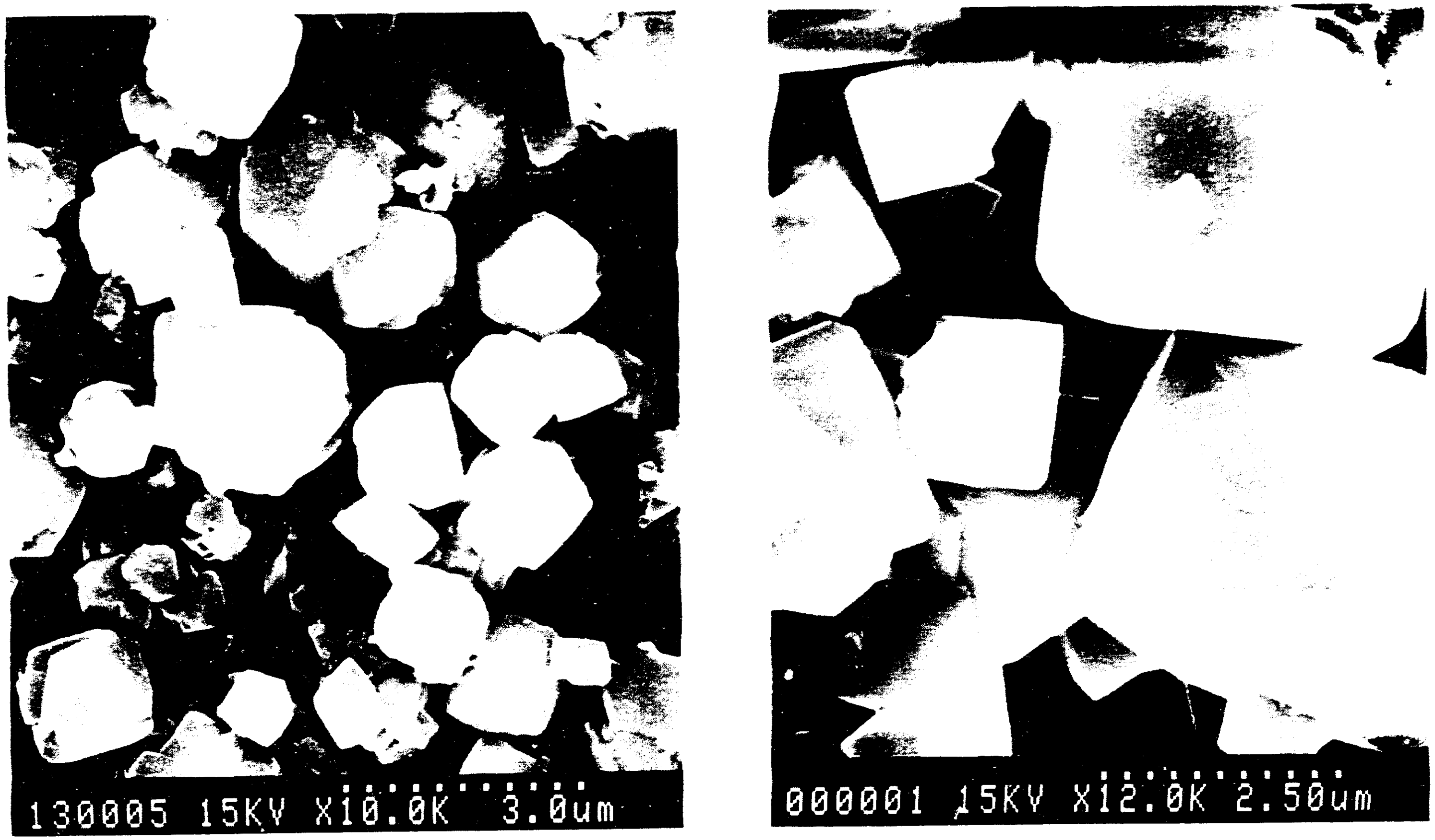
Figure 10. Analyzed tag concentrations in hydriodic acid aged at: –30, 23, and 60°C for 1, 2, and 3 weeks.



Zeolite 4A (Linde A)
$NaAlSiO_4 \cdot nH_2O$
4.1Å pore opening

Zeolite 13X (Faujasite)
$NaAlSiO_4 \cdot nH_2O$
7.4 Å pore opening

Figure 11. Crystal structures of zeolite types LTA (left) and FAU. Each vertex represents an Al or Si atom, and each line corresponds to a Si-O-Al bond. (a) In zeolite 3A, the 4.1 Å pore opening is reduced to 3 Å by an obstructing K$^+$ ion. (b) The pore opening in Zeolite 13X (FAU structure) is 7.4 Å across.



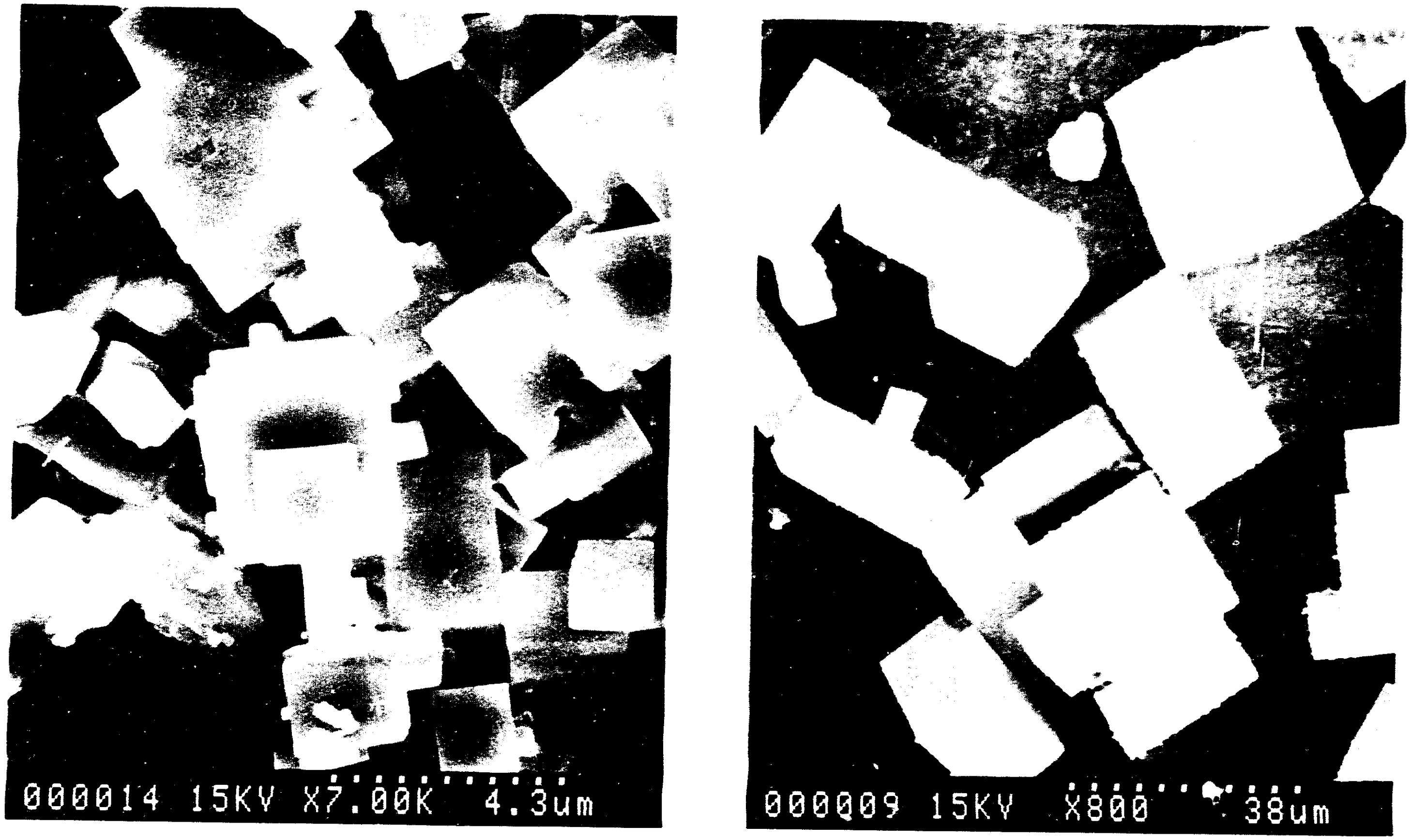
(a)

(b)

Zeolite 13x, FAU structure

Zeolite 3A, LTA structure

Figure 12. SEM micrographs of commercial Zeolites (a) 13X and (b) 3A.



(a)

(b)

CZP, 95° C synthesis

CZP, 25° C synthesis

Figure 13. SEM micrographs of CZP crystals (a) synthesized at 95°C, and (b) much larger crystals synthesized at 25°C.

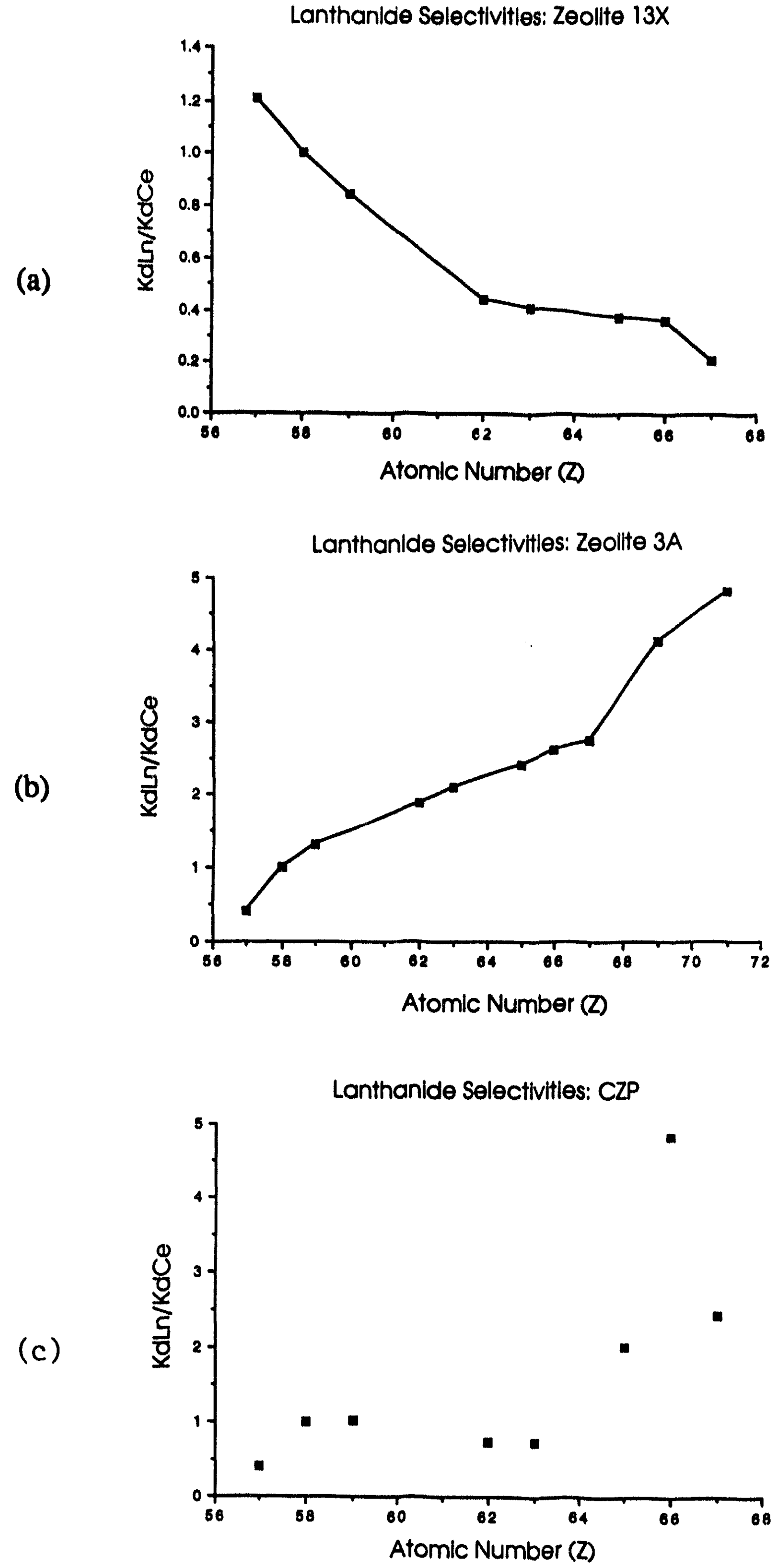


Figure 14. Relative selectivities of tag lanthanides with respect to Ce (measured as $[Ln_{tag}/Ce]_{host}/[Lntag/Ce]_{solution}$) in (a) Zeolite 13X, (b) Zeolite 3A, and (c) CZP.

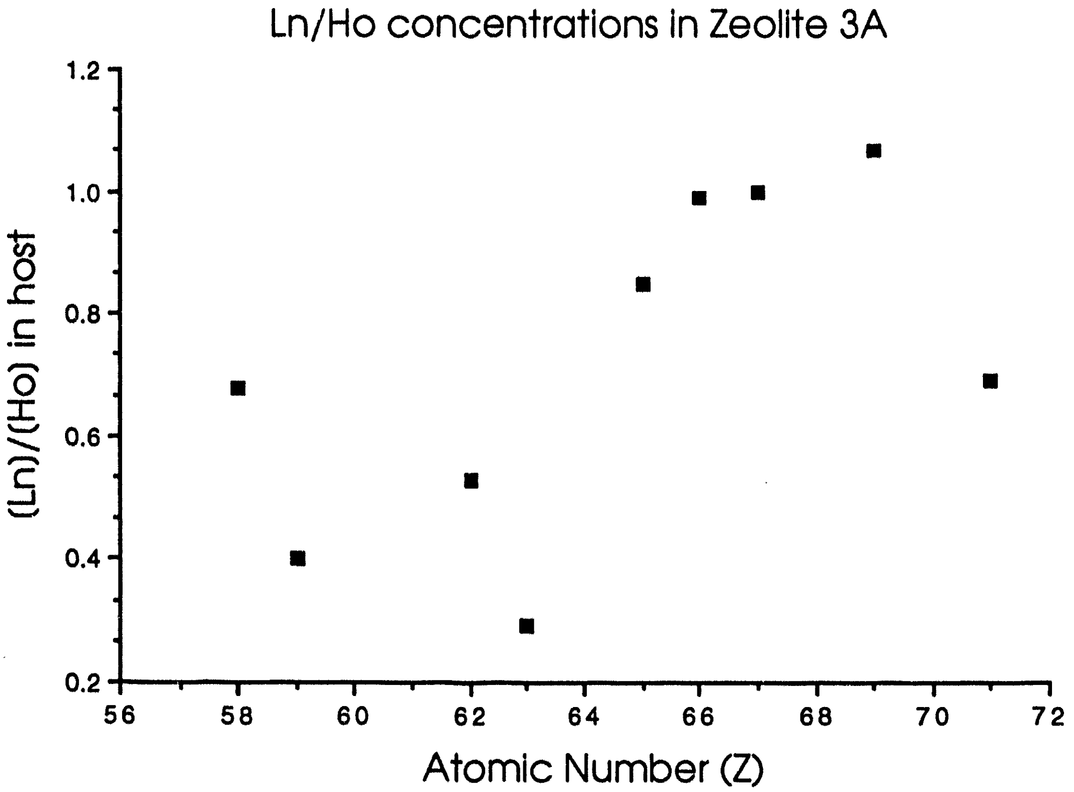
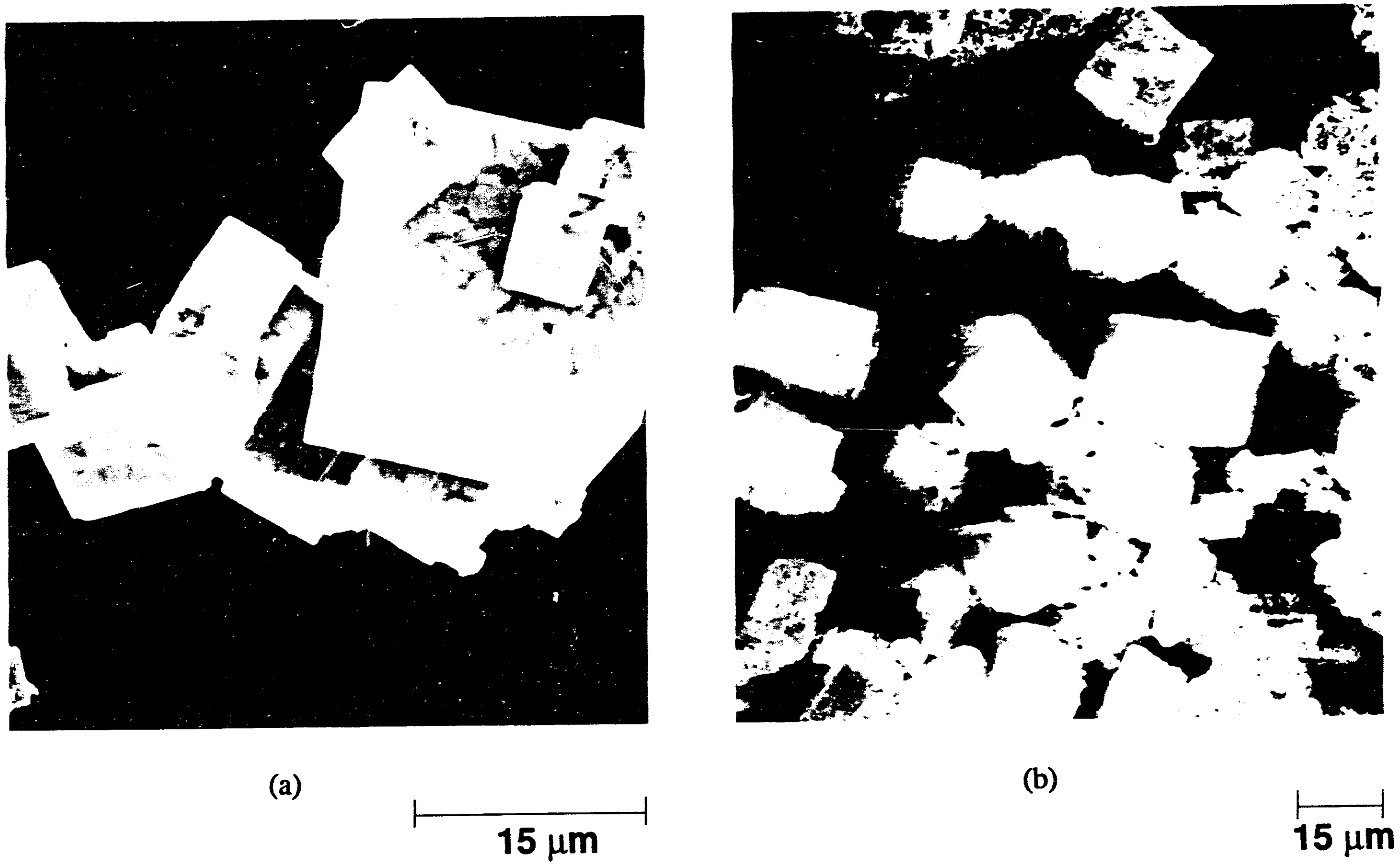


Figure 15. Plot of actual Ln/Ho ratios in Zeolite 3A vs. Z following exchange with solution Ln/Ho ratios normalized using Figure 14 data to yield host Ln/Ho ratios of unity.



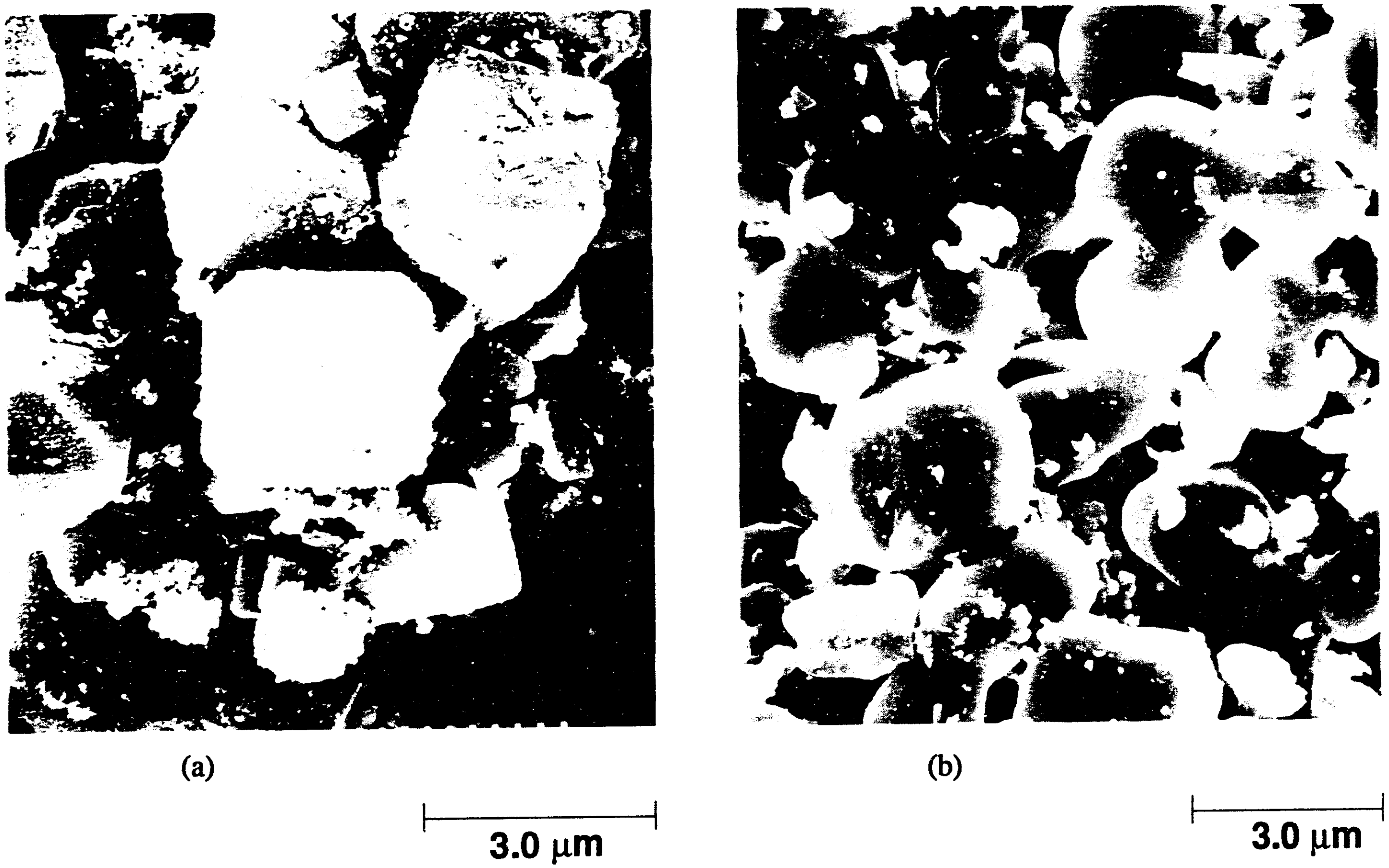
(a)

(b)

Ce - exchanged CZP

Condensed Ce: CZP

Figure 16. SEM micrographs of Ce-exchanged CZP, (a) before and (b) after sintering at 850°C.



Ce - exchanged 3A

Condensed Ce: 3A

Figure 17. SEM micrographs of Ce-exchanged Zeolite 3A, (a) before and (b) after sintering at 1000°C.

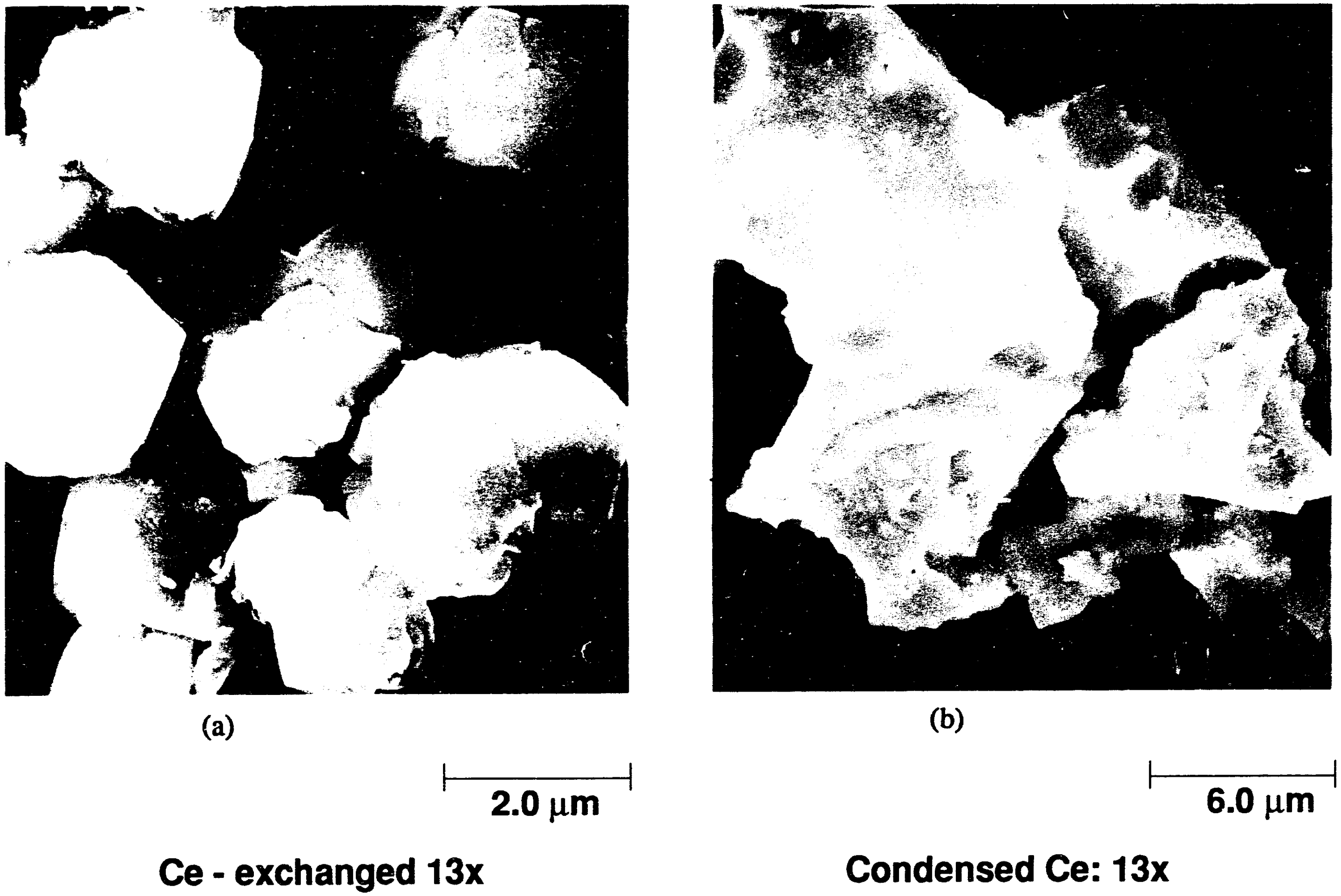


Figure 18. SEM micrographs of Ce-exchanged Zeolite 13X, (a) before and (b) after sintering at 1000°C.

TABLE I. LISTED PRECURSOR AND ESSENTIAL CHEMICALS FROM CDTA OF 1988.

Listed precursor chemicals (domestic, import & export distribution):

1. anthranilic acid (2-aminobenzoic acid) and its salts - Threshold = 30 kilograms
2. benzyl cyanide - Threshold = 1 kilogram
3. ephedrine, its salts, optical isomers, and salts of optical isomers. Threshold = 1 kilogram
4. ergonovine and its salts (solid) - Threshold =10 grams
5. ergotamine and its salts (solid)- Threshold =20 grams
6. N-acetylanthranilic acid and its salts (solid)- Threshold =40 kilograms
7. norpseudoephedrine, its salts, optical isomers, and salts of optical isomers. (solid) - Threshold = 2.5 kilograms
8. phenylacetic acid and its salts (solid) - Threshold = 1 kilogram
9. phenylpropanolamine, its salts, optical isomers, and salts of optical isomers. - Threshold = 2.5 kilograms
10. piperidine and its salts. - Threshold = 500 grams
11. pseudoephedrine, its salts, optical isomers, and salts of optical isomers. (solid) - Threshold = 1 kilogram
12. 3,4-Methylenedioxyphenyl-2-propanone - Threshold = 20 kilograms

Listed essential chemicals (domestic distribution):

1. acetic anhydride - Threshold = 1023 kilograms = 250 gallons
2. acetone - Threshold = 150 kilograms = 50 gallons
3. benzyl chloride (solid) - Threshold = 1 kilogram
4. ethyl ether - Threshold = 136.4 kilograms = 50 gallons
5. hydriodic acid - Threshold = 5.7 kilograms = 10 liters (57%)
6. potassium permanganate (solid) - Threshold = 55 kilograms
7. 2-butanone (or methyl ethyl ketone or MEK) - Threshold = 145 kilograms = 50 gallons
8. toluene - Threshold = 159 kilograms = 50 gallons

Listed essential chemicals (import & export distribution):

1. acetic anhydride - Threshold = 1023 kilograms = 250 gallons
2. acetone - Threshold = 1500 kilograms = 500 gallons
3. benzyl chloride (solid) - Threshold = 4 kilogram
4. ethyl ether - Threshold = 1364 kilograms = 50 gallons
5. hydriodic acid - Threshold = 5.7 kilograms = 10 liters (57%)
6. potassium permanganate (solid) - Threshold = 500 kilograms
7. 2-butanone (or methyl ethyl ketone or MEK) - Threshold = 1455 kilograms = 500 gallons
8. toluene - Threshold = 1591 kilograms = 500 gallons

TABLE II. NEW PRECURSOR CHEMICALS

methylamine

ethylamine

D-lysergic acid

propionic anhydride

isosafrole

safrole

piperonal

N-methylephedrine

N-ethylephedrine

N-methylpseudoephedrine

N-ethylpseudoephedrine

hydriodic acid

TABLE III. ILLUSTRATION OF TAG NUMBERING PROTOCOL

Ho	I.D.	Lu	Tm	Dy	Tb	Eu	Sm	Pr	Ce	La
1	1	0	0	0	0	0	0	0	0	1
1	2	0	0	0	0	0	0	0	0	2
1	3	0	0	0	0	0	0	0	1	0
1	4	0	0	0	0	0	0	0	1	1
1	5	0	0	0	0	0	0	0	1	2
1	6	0	0	0	0	0	0	0	2	0
1	5000	0	2	0	2	1	2	0	1	2
1	19680	2	2	2	2	2	2	2	2	0
1	19681	2	2	2	2	2	2	2	2	1
1	19682	2	2	2	2	2	2	2	2	2

TABLE IV. RESULTS OF TWO CARRY-OVER EXPERIMENTS

The tags were added at 200 ppb to the ephedrine.
All carryover experiments showed ≥ 90% loss of the tag.
("ND" = not detected, typical detection limits are 0.1 ppb;
"–" = not added to the ephedrine, or analyzed for in this reaction)

Relative tag concentrations for each element as normalized to [Eu]. All tag concentrations were <12 ppb in the product	Eu	Pr	Dy	Ho	La	Tb
Reaction 1						
Metamphetamine from HI/P + ephedrine. Observed values.	1.00	1.13	0.99	ND	–	–
Metamphetamine from HI/P + ephedrine. Predicted values	1	1	1	0	–	–
Methamphetamine•HCl from methamphetamine + $HCl_{(g)}$. Observed values.	1.00	1.15	2.34	ND	–	–
Methamphetamine•HCl from methamphetamine + $HCl_{(g)}$. Predicted values.	1	1	1	0	–	–
Reaction 2						
Metamphetamine from HI/P + ephedrine. Observed values.	1.00	0.20	0.92	–	1.21	0.07
Metamphetamine from HI/P + ephedrine. Predicted values	1	1	0	–	1	1

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