increased charge–charge repulsion between the deprotonated sulfhydryl and carboxylic acid groups in the cis conformation of the A^{2-} form. Space-filling molecular models show the separation of these two groups to be larger in the trans conformation.

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Acid-Catalyzed Reactions of 2,2,2-Trifluorodiazoethane for Analysis of Functional Groups by ^{19}F Nuclear Magnetic Resonance Spectrometry

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The acid-catalyzed reactions of trifluorodiazoethane with alcohols, phenols, thiols, and carboxylic acids are reported. The yield data for these trifluoroethyl derivatives suggest a simple, and in many cases, quantitative method for introduction of a fluorine tagging group. The ^{19}F chemical shifts indicate that most functional groups (e.g., phenols, alcohols, etc.) have fairly well resolved chemical shift regions. In addition, paramagnetic shift reagents have been utilized to selectively differentiate carboxylic acids from other active hydrogen functional groups.

Presently there are several methods available utilizing nuclear magnetic resonance for identification and quantitation of various functional groups. Most NMR analytical techniques involve characterization of functional groups using either ^{1}H (*1–8*) or ^{19}F (*9–22*) NMR. Unfortunately the ^{19}F NMR tagging reagents presently available have several limitations which have restricted their widespread applicability. For example, one basic limitation of the trifluoroacetate (*9–14*, *22*) and hexafluoroacetone (*15–20*) derivatives is their chemical lability. A second disadvantage of these reagents is the poor yields obtained in many cases.

With this in mind, an oxytrifluoroethylation method using fluorinated diazoalkanes has been investigated. The general reaction for this reagent is analogous to the well-known acid-catalyzed reactions of diazoalkanes, for example, diazomethane (*23*). The general reaction for the 2,2,2-trifluorodiazoethane reagent is illustrated in eq 1.

$$CF_3C(H){=}N{=}N + HXR \xrightarrow{HBF_4} CF_3CH_2XR + N_2\uparrow \quad (1)$$

$$\text{where } X = O \text{ and } S$$

The 2,2,2-trifluorodiazoethane provides modest to high yields with carboxylic acids, alcohols, phenols and thiols to provide the corresponding trifluoroethyl esters or trifluoroethyl ethers. One of the major advantages of this reagent is the inherent chemical stability of the ether and ester derivative in comparison with other fluorine tagging reagents. For example, trifluoroacetate derivatives are very susceptible to hydrolysis (*24*). A second advantage of this reagent is the ease of derivative preparation and absence of major byproducts except for innocuous nitrogen and reaction with water (see Results and Discussion section). A possible disadvantage is the necessity of an acid catalyst (fluoroboric acid) which normally excludes derivative preparation of amines by formation of an acid–base salt between the fluoroboric acid and any amines present in the sample. Solvents which can be utilized with this reagent include diethyl ether, carbon tetrachloride, and chloroform. However, certain solvents (e.g., tetrahydrofuran) react with the reagent in the presence of the acid catalyst.

In this paper we report conditions for derivative preparations, yield, and ^{19}F NMR chemical shifts for these trifluoroethyl derivatives. In addition, the potential utility of enhanced ^{19}F NMR spectral resolution of certain derivatives (e.g., trifluoroethyl esters of carboxylic acids) is explored via the use of paramagnetic shift reagents.

EXPERIMENTAL SECTION

Varian EM-390 and Jeolco PS-100 nuclear magnetic resonance spectrometers were used to obtain ^{19}F spectra at 84.7 MHz and 94.1 MHz, respectively. The ^{19}F NMR spectra were taken using 1,2-difluorotetrachloroethane as the reference and integration standard. A stock solution containing a known weight of 1,2-difluorotetrachloroethane was made in $CDCl_3$ and $^1/_2$ mL of this

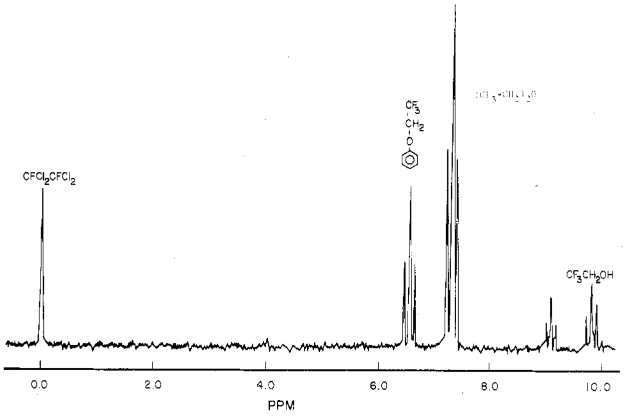

Figure 1. ^{19}F NMR spectrum of trifluorodiazoethane derivative of benzyl alcohol.

was added to each test tube. The yield data were based on comparing the integral of 1,2-difluorotetrachloroethane with that of the trifluorodiazoethane derivative. We estimate a relative error in this procedure of ±5% for all yield data reported.

General Reaction Conditions for Preparation of Derivatives. One to two milliliters of 2,2,2-trifluorodiazoethane in $CDCl_3$ was added to a known weight of model compound (0.20–0.40 mmol) in a small test tube. The catalyst, 50% aqueous tetrafluoroboric acid (20 μL), was then added. The solution was continuously swirled during the reaction which began immediately after addition of the catalyst. The reaction was exothermic. More 2,2,2-trifluorodiazoethane solution was added during the reaction as the yellow color faded. Addition was stopped when the yellow color persisted. This was usually achieved after another milliliter of the 2,2,2-trifluorodiazoethane solution was added.

Synthesis of 2,2,2-Trifluorodiazoethane. 2,2,2-Trifluorodiazoethane was made by mixing 1.0:1.1 molar ratios of trifluoroethylamine hydrochloride (Aldrich Chemical Co.) and sodium nitrite in water. 2,2,2-Trifluorodiazoethane evolved as a yellow gas and was bubbled into $CDCl_3$. The following conditions were used for the generation of 2,2,2-trifluorodiazoethane which was used in this model study. In a typical preparation, 2,2,2-trifluoroethylamine hydrochloride (3.0 g) was dissolved in 10 mL of water at 0 °C and sodium nitrite (1.7 g) in 10 mL of water was added. The generation procedure was similar to that of Dyatkin and Mochalina (*25*) except that trifluorodiazoethane was collected in $CDCl_3$ instead of as a neat liquid. ^{19}F NMR spectra of 2,2,2-trifluorodiazoethane in $CDCl_3$ show a doublet at 13.15 ppm downfield from 1,2-difluorotetrachloroethane. No other fluorine peaks were observed.

The paramagnetic shift reagents, for example, $Eu(fod)_3$, tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium, were obtained from Aldrich Chemical Co. and were used without further purification. However, the derivative sample in $CDCl_3$ prepared by the methods described above were successively washed with dilute sodium bicarbonate and water and finally dried with anhydrous sodium sulfate. To the $CDCl_3$ solutions of the derivatives, the paramagnetic shift reagents were added directly. The wash procedure described above also effectively removed the trifluoroethanol.

RESULTS AND DISCUSSION

Catalyst Study for 2,2,2-Trifluorodiazoethane Reactions. A 50% aqueous solution of tetrafluoroboric acid was found to be the best catalyst in terms of quantitative yields and impurities for the reaction of 2,2,2-trifluorodiazoethane with alcohols, carboxylic acids, and phenols. A typical ^{19}F spectrum is presented in Figure 1 for the model benzyl alcohol. Three impurity peaks, all triplets, were observed in the ^{19}F spectrum in Figure 1. One large peak at −7.40 ppm more shielded than 1,2-difluorotetrachloroethane was found to be due to hexafluorodiethyl ether by spiking a sample with hexafluorodiethyl ether, prepared independently. A smaller triplet observed at approximately −10.0 ppm was found to be trifluoroethanol by spiking a sample with trifluoroethanol.

$$CF_3C(H){=}N{=}N + H_2O \xrightarrow{HBF_4} CF_3CH_2OH + N_2\uparrow \quad (2)$$

$$CF_3C(H){=}N{=}N + CF_3CH_2OH \xrightarrow{HBF_4} CF_3CH_2OCH_2CF_3 + N_2\uparrow \quad (3)$$

These two peaks are easily explained by the reaction of water with 2,2,2-trifluorodiazoethane. The water present is mostly due to that present in the catalyst. The third impurity peak was a triplet at approximately −9.0 ppm. This has not been positively identified but is believed to be a complex of the tetrafluoroboric acid either with trifluoroethanol or with hexafluorodiethyl ether. No water peak was observed in the proton NMR spectra of the samples after the reaction so it seems complexation of tetrafluoroboric acid with either of these compounds is likely. These impurity peaks (except for hexafluorodiethyl ether) were easily removed when necessary by the sodium bicarbonate and water wash procedure described in the Experimental Section.

In one run, differing amounts of catalyst were added to 0.10 mmol of 2-naphthol in a trifluorodiazoethane and $CDCl_3$ solution. With 5.0 μL of aqueous tetrafluoroboric acid, the yield was only 56% whereas when 20 μL of catalyst was added the yield was 92%. Addition of 50 μL resulted in a yield of 89% for the 2-naphthol derivative. From these data and similar studies, 20 μL of aqueous tetrafluoroboric acid was chosen as the amount of catalyst to be added for 0.2–0.4 mmol of substrate.

Preliminary experiments attempting to use other proton and Lewis acid catalysts did not improve product yields. In exploration of the use of other acid catalysts, side reactions commonly occurred. The low nucleophility of the tetrafluoroborate anion was found to be an important factor in the choice of tetrafluoroboric acid as the catalyst. However, several catalysts could possibly be appropriate for some reactions when water products are undesirable. Nevertheless, extensive work into improving the use of these catalysts was not done and therefore improvements on experimental conditions could be possible.

Reaction of 2,2,2-Trifluorodiazoethane with Alcohols. The reactions of alcohols with trifluorodiazoethane would be expected to yield an ether product as described by reaction 4. All derivative ^{19}F NMR peaks observed were triplets as

$$CF_3CHN_2 + ROH \xrightarrow{HBF_4} CF_3CH_2OR + N_2\uparrow \quad (4)$$

would be expected (Figure 1). Table I lists several alcohols employed in this study and corresponding ^{19}F chemical shifts and product yield as determined by NMR integration. In general, yields of primary alcohols were greater than 90%. However, yields for secondary and tertiary alcohols were somewhat lower.

Several trends were observed in the ^{19}F chemical shifts of the ether products. The chemical shift for saturated alkyl substituents on the carbon α to the hydroxyl group are progressively shielded as illustrated by the chemical shifts of *n*-butyl alcohol (−7.00 ppm), *sec*-butyl alcohol (−7.36 ppm), and *tert*-butyl alcohol (−7.46 ppm). However, substitution of alkyl groups at the β or γ positions apparently yield only relatively minor perturbations of the ^{19}F chemical shielding for the trifluoroethyl group. For example, the ^{19}F chemical shift for the *n*-butyl alcohol and neopentyl alcohol trifluoroethyl ether derivatives are −7.00 and −6.97 ppm, respectively. Successive substitution of phenyl groups at the carbon α to oxygen exerts a progressive deshielding influence on the ^{19}F chemical shifts as reflected by the values for benzyl (−6.65 ppm), benzhydrol (−6.51 ppm), and triphenyl alcohol (−6.10 ppm) derivatives. The influence of phenyl substituents at the β and γ positions is a relatively small deshielding influence. A similar deshielding influence is exhibited by unsaturated

Table I. Chemical Shifts and Yields for the Products of the Reaction of 2,2,2-Trifluorodiazoethane with Alcohols

compound	δ F[a]	yield,[b] %
n-butyl alcohol	−7.00	97
sec-butyl alcohol[c]	−7.36	87
tert-butyl alcohol[c]	−7.43	81
tert-amyl alcohol[c]	−7.39	56
neopentyl alcohol	−6.97	100
benzyl alcohol	−6.65	95
benzhydrol	−6.51	68
triphenylmethanol	−6.10	20
m-nitrobenzyl alcohol	−6.54	95
p-nitrobenzyl alcohol	−6.66	87
3-phenyl-1-propanol	−6.90	90
phenethyl alcohol	−6.92	100
allyl alcohol	−6.87	90
diethylene glycol[d]	−7.10	100
ethylene glycol[d]	−7.08	100
2-octanol	−7.32	100
cholesterol[c]	−7.36	100

[a] All values are reported relative to the internal reference 1,2-difluorotetrachlorethane. Increasing negative values denote increasing shielding relative to the reference. [b] The ^{19}F NMR yield data are based on integration of the internal reference (1,2-difluorotetrachloroethane) peak for a known molar concentration of reference relative to the integral for the trifluoroethyl ether derivative. We estimate an error of ±5% in this procedure. [c] Yield data estimated because of partial overlap with hexafluoroethyl ether (−7.40 ppm) impurity. [d] Yield data presented are based on the bis(trifluoroethyl) derivative.

Table II. Chemical Shifts and Yields for the Products of the Reaction of 2,2,2-Trifluorodiazoethane with Phenols

phenol	δ F[a]	yield,[b] %
1-naphthol	−6.51	47
2-naphthol	−6.53	89
phenol	−6.73	86
m-cresol	−6.79	89
p-cresol	−6.79	94
hydroquinone[c]	−6.81/−6.87	82
p-chlorophenol	−6.68	84
pyrocatechol[c]	−6.84/−7.04	53
resorcinol[c]	−6.72/−6.74	59
o-cresol	−6.94	53

[a] All values are reported relative to the internal reference 1,2-difluorotetrachlorethane. Increasing negative values denote increasing shielding relative to the reference. [b] The ^{19}F NMR yield data are based on integration of the internal reference (1,2-difluorotetrachloroethane) peak for a known molar concentration of reference relative to the integral for the trifluoroethyl ether derivative. We estimate an error of ±5% in this procedure. [c] Yield data presented are based on the bis(trifluoroethyl) derivative.

Table III. Chemical Shifts and Yields for the Products of the Reaction of 2,2,2-Trifluorodiazoethane with Carboxylic Acids

carboxylic acid	δ F[a]	yield,[b] %
hexanoic acid	−6.64	100
octanoic acid	−6.64	100
decanoic acid	−6.64	95
lauric acid	−6.64	100
hydrocinnamic acid	−6.54	99
phenylacetic acid	−6.56	95
diphenylacetic acid	−6.36	100
triphenylacetic acid	−5.98	99
1-naphthylacetic acid	−6.52	100
2-naphthylacetic acid	−6.50	100
benzoic acid	−6.43	100
o-bromobenzoic acid	−6.14	100
m-bromobenzoic acid	−6.38	99
p-bromobenzoic acid	−6.41	100
o-chlorobenzoic acid	−6.22	100
m-chlorobenzoic acid	−6.39	100
p-chlorobenzoic acid	−6.43	93
homophthalic acid[c]	−6.33/−6.54	89
1-naphthoic acid	−6.20	100
2-naphthoic acid	−6.33	96
(2-naphthoxy)acetic acid	−6.48	72
trans-cinnamic acid	−6.46	95
anthacene-9-carboxylic acid	−5.78	100

[a] All values are reported relative to the internal reference 1,2-difluorotetrachlorethane. Increasing negative values denote increasing shielding relative to the reference. [b] The ^{19}F NMR yield data are based on integration of the internal reference (1,2-difluorotetrachloroethane) peak for a known molar concentration of reference relative to the integral for the trifluoroethyl ether derivative. We estimate an error of ±5% in this procedure. [c] Yield data presented are based on the bis(trifluoroethyl) derivative.

alcohols (e.g., allyl alcohol derivatives). These trends are consistent with previously published results for trifluoroacetate derivatives of alcohols (*22*).

Reactions of 2,2,2-Trifluorodiazoethane with Phenols. As with alcohols, the reaction of phenols with trifluorodiazoethane yields ethers as products in a similar manner. As seen from Table II, for para-substituted phenols only a narrow ^{19}F chemical shift range of less than 0.20 ppm (−6.68 to −6.87) was observed. For the only meta-substituted phenol which was examined, resorcinol, both the mono- and disubstituted products had about the same chemical shift (−6.72 and −6.74 ppm). The large 1- and 2-naphthol ether systems had ^{19}F chemical shifts further downfield at −6.51 and −6.53 ppm, respectively.

For an ortho-substituted phenol such as pyrocatechol, the monosubstituted product was more shielded by only 0.1 ppm from phenol whereas the bulkier disubstituted product had a ^{19}F chemical shift of 0.31 ppm upfield from phenol. The magnitudes of these shifts are similar with those found by Ho (*18*) and by Leader (*20*) for ortho-substituted phenol adducts formed by hexafluoroacetone. That is, bulkier ortho groups generally exhibit a large change in chemical shift. However, for most ortho-substituted groups they found ^{19}F deshielding as opposed to a shielding influence. The difference found here may be due to a different geometric orientation of the CF_3 groups with respect to the ring.

On the basis of the limited data of substituted phenols in Table II, yields of the derivative products were generally greater than 80%. Phenols which have electron-withdrawing substituents appear to exhibit lower yields. When an ortho-substituent was present, the yield dropped to 53% for pyrocatechol based on the disubstituted product and to 37% for 2,6-dimethylphenol.

Reactions of 2,2,2-Trifluorodiazoethane with Carboxylic Acids. The reaction for carboxylic acids with trifluorodiazoethane gives an ester product as shown in eq 5.

$$RC({=}O)OH + CF_3CHN_2 \xrightarrow{HBF_4} RC({=}O)OCH_2CF_3 + N_2\uparrow \quad (5)$$

Unlike the previous two fluorinating reagents used for ^{19}F NMR analytical purposes, trifluoroacetic anhydride and hexafluoroacetone, trifluorodiazoethane readily reacts with carboxylic acids (Table III). For a wide range of carboxylic acid derivatives it was found that the reaction gave very high yields, even for acids where the carbon is substituted by bulky groups such as in triphenylacetic acid.

The ^{19}F chemical shifts for the trifluoroethyl ester derivatives of aliphatic carboxylic acids are not sensitive to subtle changes such as reflected by variable alkyl chain length. For example, the ^{19}F chemical shifts for the trifluoroethyl esters

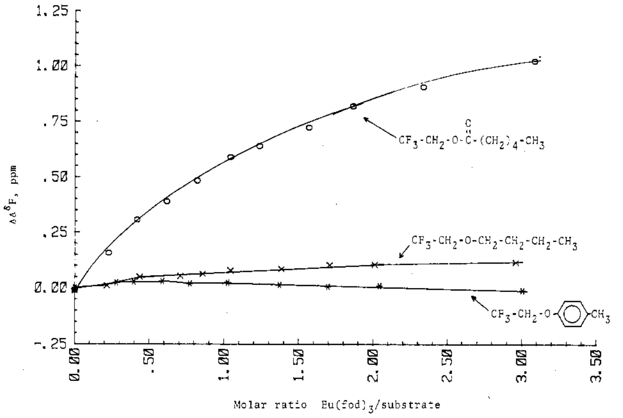

Figure 2. Plots of $\Delta\Delta^{\delta}F$ vs. Eu(fod)$_3$/substrate molar ratio for trifluoroethyl derivatives of *p*-cresol, *n*-butyl alcohol, and hexanoic acid.

of hexanoic, octanoic, decanoic, and lauric acid are all at −6.64 ppm. A general feature of all aromatic carboxylic trifluoroethyl ester derivatives is substantial deshielding relative to aliphatic carboxylic acids. The aromatic carboxylic esters of phenylacetic, diphenylacetic, and triphenylacetic acids are progressively deshielded (−6.56, −6.36, and −5.98 ppm, respectively) for increasing phenyl substitution at the α carbon. In similar fashion larger condensed aromatic carboxylic ester derivatives (e.g., benzoic, 1- and 2-naphthoic, and anthracene-9-carboxylic) are also progressively deshielded with increasing ring size. In fact, the trifluoroethyl anthracene-9-carboxylic ester is the most deshielded example found in the present study.

It is interesting to note that the para-substituted benzoate ester derivatives have ^{19}F chemical shifts very close to the trifluoroethyl benzoate, whereas, the *ortho*-substituted benzoic esters (e.g., trifluoroethyl *o*-bromobenzoate and *o*-chlorobenzoate) exhibit significant deshielding. The deshielding influence of ortho-substituents for the aromatic carboxylic esters is in sharp contrast to the ortho effects previously discussed for ortho-substituted phenol esters (vida supra).

NMR Shift Reagents and Trifluoroethyl Derivatives. As indicated by the data in Tables I–III, considerable overlap of the ^{19}F NMR spectral regions occurs for each class (i.e., alcohols, phenols, and carboxylic acids) of the trifluoroethyl derivatives. In order to help alleviate this problem, Sievers explored the possible advantages of added paramagnetic shift reagents (*26*). Although several lanthanide shift reagents were examined including Eu(thd)$_3$, Dy(thd)$_3$, Pr(fod)$_3$, Yb(thd)$_3$, and Eu(fod)$_3$, the latter was found to be generally the most effective for the present study. The derivatized samples in chloroform-*d* were treated with dilute base, washed, and dried as described in the Experimental Section. An appropriate weighed amount of Eu(fod)$_3$ was added to each sample of interest. The strong electron-withdrawing trifluoroethyl group would be expected to decrease the nucleophilicity of all the ether and ester derivatives, thereby, forming weaker acid–base complexes with the Lewis acid, Eu(fod)$_3$. Specifically, the Eu(fod)$_3$ was found to only complex effectively with those trifluoroethyl derivatives which contain carbonyl groups (e.g., trifluoroethyl esters). The trifluoroethyl ethers (alcohol and phenol derivatives) in the presence of Eu(fod)$_3$ exhibited only very small induced ^{19}F chemical shifts (typically less than 0.1 ppm) for molar ratios of Eu(fod)$_3$ to substrate as high as unity. This is illustrated in Figure 2 for the three representative model trifluoroethyl substrates of *p*-cresol, *n*-butyl alcohol, and hexanoic acid. As indicated in Figure 2, the molar ratio of Eu(fod)$_3$ to substrate was varied for each separate sample covering the range of 0 to over 3. The only trifluoroethyl derivative to exhibit a significant induced ^{19}F shift in the presence of Eu(fod)$_3$ was the trifluoroethyl hexanoate. As a further illustration of this point, a model mixture containing the aforementioned models was prepared and ^{19}F spectra were obtained in the absence and presence of Eu(fod)$_3$, Figure 3. The identity of each peak was confirmed in all cases by spiking with an authentic substrate sample. Similar results were obtained for other trifluoroethyl derivatives and mixtures.

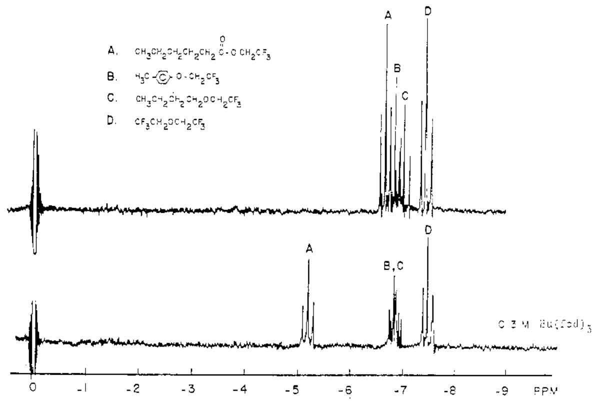

Figure 3. ^{19}F NMR spectra of trifluoroethyl derivatives in the presence of Eu(fod)$_3$.

Other Reactions of 2,2,2-Trifluorodiazoethane. Two thiols, thiophenol and hexanethiol, reacted with 2,2,2-trifluorodiazoethane in the presence of catalyst to give a product at −0.95 ppm and −0.77 ppm downfield from 1,2-difluorotetrachloroethane in 62% and 70% yields, respectively. The derivative peaks are considerably downfield from any products containing an oxygen atom, that is, alcohol, phenols, and acids.

Amines such as *n*-butylamine, diethylamine, triethylamine, and aniline did not react but instead neutralized the tetrafluoroboric acid catalyst and even prevented the reaction of trifluorodiazoethane with water to any appreciable extent.

The reaction of 2,2,2-trifluorodiazoethane with ketones and aldehydes in the presence of water generally provided trifluoroethyl ketals or acetals. For example, benzophenone reacted to give one triplet at −6.82 ppm in 189% yield based on a monoderivative. The supporting spectral and physical data clearly support formation of benzophenone bis(trifluoroethyl) ketal. The reactions of trifluorodiazoethane with ketones and aldehydes have been submitted for publication (*27*).

CONCLUSION

The results of the present study indicate that the acid-catalyzed reactions of 2,2,2-trifluorodiazoethane provide a convenient and simple method of ^{19}F tagging active hydrogen compounds in high yields. The stability of the trifluoroethyl ester and ether derivatives is in sharp contrast to other fluorine tagging reagents. This advantage could also be beneficial to other analytical approaches requiring stable samples with higher volatility (e.g., GC-MS). The ^{19}F chemical shift regions for each class (i.e., alcohols, phenols, etc.) was not as clearly separated as might have been anticipated. However, the results obtained suggest that carboxylic acid derivatives can be readily spectrally resolved in complex mixtures containing alcohols, phenols, and thiols by the addition of the Eu(fod)$_3$ reagents as outlined above. Furthermore, the trifluoroethyl functional group could be important in establishing specific site(s) of complexation with the Eu(fod)$_3$ or other Lewis acids. The results in this study suggest that the carbonyl oxygen is the preferential site of complexation in trifluoroethyl ether and ester derivatives.

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Measurement of Aerosol Transport Efficiency in Atomic Spectrometry

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The measurement of transport efficiency (ϵ_n) by direct aerosol collection is found to be capable of superior accuracy and precision to indirect methods. A comparison of different direct methods, using cascade impactor, filter, and silica gel trap collection with indirect methods, using analyte waste collection, is made. Cascade impactor collection is preferred for an atomic absorption nebulizer/spray chamber system, whereas either cascade impactor or filter collection procedures give comparable data for an inductively coupled plasma/spray chamber combination. Indirect methods are shown to have poor precision and lead frequently to high ϵ_n values. The transport efficiency for a typical atomic absorption nebulizer/spray chamber/burner head combination is found to be 6.6 ± 0.3% and for a typical inductively coupled plasma nebulizer/spray chamber/torch combination to be 1.1 ± 0.1%.

The introduction of liquid samples into a flame or plasma as a finely dispersed aerosol is the most common procedure for sample introduction in atomic spectrometry. The relative performance of various nebulizer/spray chamber configurations is generally assessed through comparison of the efficiency of nebulization, ϵ_n, defined (*1*) as the ratio of the amount of analyte entering the flame (or plasma) to the amount of analyte aspirated. Since the geometry and dimensions of the spray chamber, as well as devices such as mixer paddles and impact beads all influence the transport process significantly (*2*), the following discussion more appropriately describes ϵ_n as the *transport efficiency*. A number of studies have been published in which values of ϵ_n were determined either for fundamental purposes (*3–9*) or for the comparison of various nebulizer/spray chamber systems (*10–12*).

Methods which have been used to determine ϵ_n may be divided conveniently into two basic categories, depending on whether the aerosol itself is collected (e.g., *direct* methods) or whether the liquid going to waste from the system is measured (e.g., *indirect* methods). With indirect methods, the fraction of analyte passing to the flame (or plasma) is calculated by taking the difference between the amount of analyte aspirated and that passing to waste. Of the two approaches, indirect methods have been used most widely as they are simple (in principle) to perform and require no specialized aerosol collection equipment. Alkemade (*3*) and Willis (*4*) have given the most complete details of procedures for indirect methods, and Alkemade in particular has emphasized (*3*) the need to determine analyte mass passing to waste, rather than simply solvent volume passing to waste, in order to avoid solvent evaporation errors.

Even with such precautions, the calculation of ϵ_n by indirect procedures is prone to significant error, because of the sensitivity of the measurement to even very small recovery losses. These losses may occur in the spray chamber, on mixing paddles, or in the burner head or plasma torch. For this reason, values of ϵ_n reported in the literature are generally used to indicate internally consistent experimental trends and are rarely transferable between laboratories. The lack of accurate, comparable ϵ_n values makes evaluation of new aerosol generation and transport systems difficult, in addition to placing a considerable restriction on fundamental calculations requiring such data.

In order to minimize errors which can arise from sample recovery loss, one may employ direct aerosol measurement procedures. In these, the aerosol is measured as it leaves the spray chamber or burner head, and calculated ϵ_n values therefore refer directly to the analyte mass reaching the flame or plasma. With direct methods, efficient aerosol collection is crucial to the accuracy of the results.

Relatively complex procedures for trapping aqueous aerosols, such as electrostatic precipitation (*13*), cocondensation with water vapor (*14*), and collection of aerosol containing ^{60}Co radioisotope on a filter, followed by radiocounting (*15*), have been described. However, a simpler direct procedure for estimating the transport efficiency of desolvated aerosols was used by Olson, Haas, and Fassel (*10*). These workers collected dry aerosol particles on a 0.4-μm pore size membrane filter and calculated the transport efficiency from the ratio of the