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NEW METHODS FOR PREPARING N, N-DIALKYLTRIFLUOROACETAMIDES

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ABSTRACT

The customary preparative methods for N,N-dialkyltrifluoroacetamides involve the acylation of an amine by trifluoroacetic acid or its derivatives. In this paper the synthesis of N,N-dialkyltrifluoroacetamides by reacting trifluoroacetic anhydride or acid with disubstituted formamides and acetamides is discussed. These reactions are interpreted with the aid of gas chromatographic analysis. Different reaction mechanisms are proposed for the reactions of formamides and acetamides with trifluoroacetic anhydride or acid. The use of the proposed reaction mechanisms for the synthesis of other fluorinated compounds is discussed.

INTRODUCTION

The intractable nature of high temperature polymers has made it very difficult to process them into useful articles. There are a number of approaches for improving the processing characteristics of high temperature polymers. Prior investigators have attempted to improve the processability of high temperature polymers by modifying their chemical structure (ref. 1). An alternative route to overcome the processing difficulties is to develop a new solvent which is more volatile and has a stronger solvent power than those conventionally used for high temperature polymers.

Fluorinated solvents are generally more volatile than their corresponding hydrogen-containing analogs. In addition, the introduction of fluorine into the structures of aliphatic alcohols, ketones, and acids had been found to significantly increase their solvent power for certain polymeric materials (ref. 2).

This report describes the synthesis of fluorinated amides and imides. During the course of these studies a new method for the synthesis of N,N-dialkyltrifluoroacetamides was developed. Trifluoroacetic anhydride or acid was reacted with disubstituted formamides and acetamides. The reactions were studied using the technique of gas chromatography and mechanistic interpretations were developed.

EXPERIMENTAL

Chemicals

All chemicals except trifluoroacetic acid and anhydride were used as received. Trifluoroacetic acid and trifluoroacetic anhydride (over phosphorus pentoxide) were distilled with a spinning band distillation apparatus and checked by gas chromatography before use.

Instruments

Spinning band distillation apparatus. – The apparatus was composed of a nichrome heating glass column of 10-millimeter bore and 36 inches height, an automatic reflux control device, and a direct bearing driven stainless steel spiral screen band having 300 teeth per inch. The apparatus may be operated for distillation at atmospheric or reduced pressure.

Analytical gas-liquid chromatograph. - The chromatograph was equipped with a thermal conductivity detector with the bridge current fixed at 100 milliamperes, a 10 millivolts chart recorder having the chart driving speed fixed at 2 minutes per inch, and an electronic digital integrator for automatically counting the retention time of the peak in seconds and calculating the relative peak areas. All analyses were performed using a 6 feet long and 1/4 inch diameter copper tubing column packed with 15% Dow Corning 200 silicone oil on 60/80 mesh chromosorb W at the oven temperature and helium flow rate designated on the figures. Authentic retention time of the components involved in the reactions was obtained separately under corresponding chromatographic conditions.

General Procedure for the Syntheses of

N,N-dialkyltrifluoroacetamides

In a 200 or 500-milliter 3-neck round bottom flask fitted with a magnetic stirrer, a gas inlet, a thermometer, a graduated pressure equalizing separatory funnel, and a condenser cooled with a coolant at a temperature of about -20° C, 0.1 to 0.5 mole of trifluoroacetic anhydride or acid was introduced and covered with a blanket of dry nitrogen gas. From the funnel, an equal mole amount of N,N-dialkyl formamide or acetamide was slowly added with stirring and occasional cooling to control any exothermic reactions. When all the amide had been added, and the exotherm had subsided, the reaction mixture was heated to and held at reflux until gas chromatographic analysis showed that the trifluoroacetic anhydride or acid peaks had nearly disappeared or an equilibrium

had been reached. The reaction mixture was fractionated with a spinning band distillation apparatus at atmospheric pressure. N,N-dimethyltrifluoroacetamide was collected at 130-134° C and N,N-diethyltrifluoroacetamide at 157-160° C. Percentages of yield based on N,N-dialkylformamide or acetamide for all the reactions except that involving trifluoroacetic acid and N,N-dimethylformamide (less than 10%) ranged within 70-90%. No special effort was made to obtain optimum reaction conditions for maximum yields. Infrared spectrophotometry was also used to identify the products.

Gas-Liquid Chromatographic Studies for the Equilibria

of Mixed Anhydride and Anhydride-Acid Systems

Involving Acetyltrifluoroacetate

In a 100-milliliter 3-neck round bottom flask with the same setup as for the syntheses of N,N-dialkyltrifluoroacetamides, 0.05 mole of trifluoroacetic anhydride or acid was introduced and covered with a blanket of dry nitrogen gas. An equal mole amount of acetic anhydride or acid was added slowly from the funnel so that the reaction mixture was kept below room temperature by occasional cooling with cold water. After the reactants had been added and the exotherm was over, the solution was brought to room temperature and a sample was taken for gas chromatrographic analysis. The reaction mixture was then transferred to a glass bottle, and stored at room temperature. Gas chromatographic analysis was performed repeatedly after appropriate intervals of time until the reaction mixture reached an equilibrium condition.

Competitive Hydrolysis of N,N-dimethylacetamide and
N,N-dimethyltrifluoroacetamide

A homogeneous solution was obtained at room temperature by mixing 0.0224 mole (1.943 grams) of N,N-dimethylacetamide, 0.0158 mole (2.237 grams) of N,N-dimethyltrifluoroacetamide, and 0.0158 mole (0.3 milliliter) of water with acetone (1:1 by volume). A sample of the mixture was taken for gas chromotographic analysis at 120° C and at a helium flow rate of 240 milliliters per minute. About 90% of the mixture was refluxed at 112-140° C for 22 hours, while the remaining 10% was kept at room temperature for 50 days prior to further gas chromatographic analysis.

Preparation of N-methyl Trifluoroacetamide

In a 200-milliliter 3-neck round bottom flask with the same setup as for the syntheses of N,N-dialkyltrifluoroacetamides, 0.5 mole each of N-methyl acetamide (36.5 grams) and trifluoroacetic anhydride (70 milliliters) were refluxed at 120-142° C for 35 hours. The reaction mixture was then distilled at atmospheric pressure with a spinning band distillation apparatus. The fraction that distilled over at 157-160° C was collected. Yield 39 grams (61% based on N-methyl acetamide). Melting point 48.5° C. Infrared carbonyl assignment 1720 cm^{-1}.

## Preparation of N-methylbis(trifluoroacetyl)imide

In a 200-milliliter flask, 0.25 mole each of N-methyl trifluoroacetamide (31.8 grams) and trifluoroacetic anhydride (35 milliliters) were refluxed at 48-65° C for 100 hours. The reaction mixture was distilled with a spinning band distillation apparatus. Ten grams of the fraction

boiling at 118-120° C were collected (18% yield based on N-methyltrifluoroacetamide used, or 61% yield based on unreacted N-methyltrifluoroacetamide recovered). Infrared carbonyl assignment 1750 cm^{-1}.
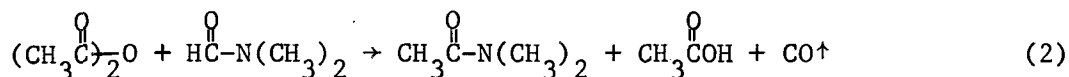
RESULTS AND DISCUSSION
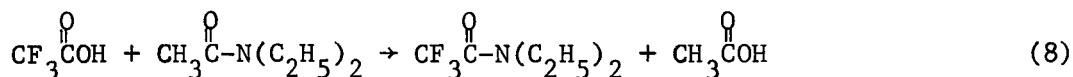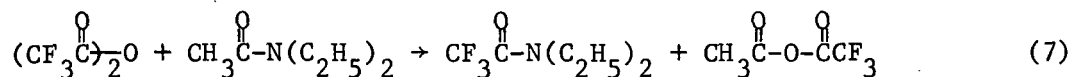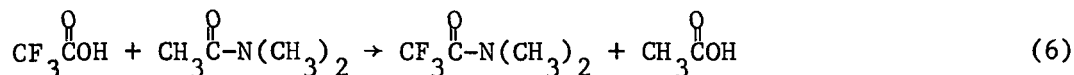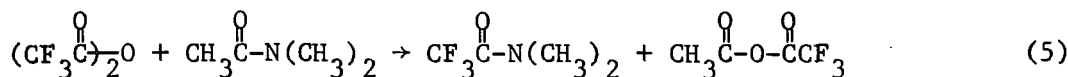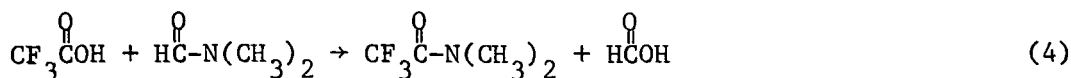
Syntheses of N,N-dialkyltrifluoroacetamides

The initial objective of this work was to use N,N-dimethyltrifluoroacetamide as the starting material for preparing partially fluorinated N,N-dimethyltrifluoroacetamides by controlled electrochemical fluorination. N,N-dimethyltrifluoroacetamide is not commercially available. The best method reported in the literature (ref. 3) for the synthesis of it is by reacting ethyltrifluoroacetate with dimethylamine as shown in the equation (1).

$$CF_3\overset{O}{\underset{}{C}}-OC_2H_5 + H-N(CH_3)_2 \rightarrow CF_3\overset{O}{\underset{}{C}}-N(CH_3)_2 + C_2H_5OH \qquad (1)$$
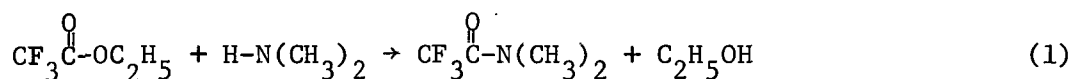
Coppinger had prepared N,N-dimethylacetamide by reacting acetic anhydride with N,N-dimethylformamide (ref. 4) according to the equation (2):

$$(CH_3\overset{O}{\underset{}{C}})_2O + H\overset{O}{\underset{}{C}}-N(CH_3)_2 \rightarrow CH_3\overset{O}{\underset{}{C}}-N(CH_3)_2 + CH_3\overset{O}{\underset{}{C}}OH + CO\uparrow \qquad (2)$$

It was obvious to us that there should be no difficulty to prepare N,N-dimethyltrifluoroacetamide by modifying Coppinger's procedure by the replacement of acetic anhydride with trifluoroacetic anhydride. We tried trifluoroacetic acid as well as anhydride (see eqs. (3) and (4)). We also used N,N-dimethylacetamide and N,N-diethylacetamide in addition to N,N-dimethylformamide (see eqs. (5), (6), (7), and (8)).

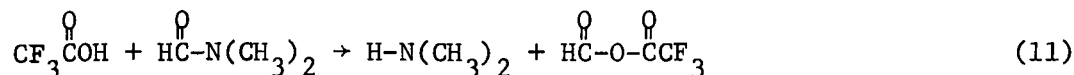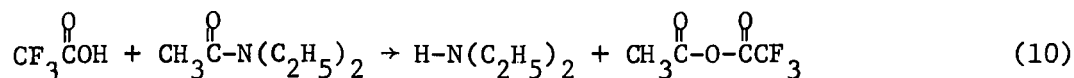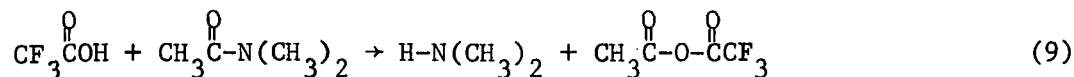$$(CF_3\overset{O}{\overset{\|}{C}})_2O + H\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 + CF_3\overset{O}{\overset{\|}{C}}OH + CO \uparrow \qquad (3)$$

$$CF_3\overset{O}{\overset{\|}{C}}OH + H\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 + H\overset{O}{\overset{\|}{C}}OH \qquad (4)$$

$$(CF_3\overset{O}{\overset{\|}{C}})_2O + CH_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 + CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 \qquad (5)$$

$$CF_3\overset{O}{\overset{\|}{C}}OH + CH_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 + CH_3\overset{O}{\overset{\|}{C}}OH \qquad (6)$$

$$(CF_3\overset{O}{\overset{\|}{C}})_2O + CH_3\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2 + CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 \qquad (7)$$

$$CF_3\overset{O}{\overset{\|}{C}}OH + CH_3\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2 + CH_3\overset{O}{\overset{\|}{C}}OH \qquad (8)$$
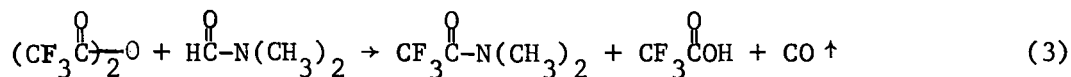
All these postulated reactions were found workable to various degrees. N,N-dialkyltrifluoacetamides were obtained in good yields (70-90%) except reaction (4) utilizing trifluoroacetic acid and N,N-dimethylformamide which resulted in yields less than 10%.

The formation of N,N-dialkyltrifluoroacetamides by reacting trifluoroacetic anhydride with N,N-disubstituted amides was expected. The experimental result that N,N-dialkyltrifluoroacetamides were also formed from trifluoroacetic acid and the amides was rather surprising, as they were expected to produce dialkylamines as follows:

$$CF_3\overset{O}{\overset{\|}{C}}OH + CH_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow H-N(CH_3)_2 + CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 \qquad (9)$$

$$CF_3\overset{O}{\overset{\|}{C}}OH + CH_3\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2 \rightarrow H-N(C_2H_5)_2 + CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 \qquad (10)$$

$$CF_3\overset{O}{\overset{\|}{C}}OH + H\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow H-N(CH_3)_2 + H\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 \qquad (11)$$
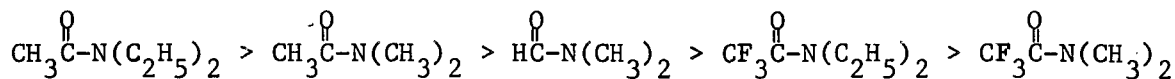
The unexpected experimental result of the formation of N,N-dialkyltrifluoroacetamides by reacting trifluoroacetic acid with amides specifically with N,N-dialkylacetamides stimulated us to study the reaction mechanisms involved in these reactions.

Mechanistic Interpretation of Reactions Involving Trifluoroacetic Anhydride and N,N-disubstituted Amides

Figures 1, 2, and 3 are the chromatograms for the reactions given by equations (3), (5), and (7) which were conducted at various time and temperature conditions. It can be seen in figures 1 to 3 that each of the reactions conducted at room temperature formed a complex. The chromatograms for the reactions that had been carried out at reflux temperatures indicate various levels of stability for the complexes depending on the nature of the amides and the composition of the complexes. For example, after 35 hours at 60° C the complex formed between trifluoroacetic anhydride and N,N-dimethylformamide at room temperature had disappeared (fig. 1(b)). The stability of these complexes is apparently related to the basicity of the amides according to the following order:

$$CH_3\overset{O}{\overset{\|}{C}}\text{-}N(C_2H_5)_2 > CH_3\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2 > H\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2 > CF_3\overset{O}{\overset{\|}{C}}\text{-}N(C_2H_5)_2 > CF_3\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2$$
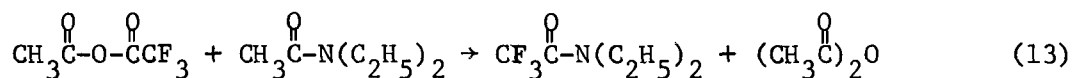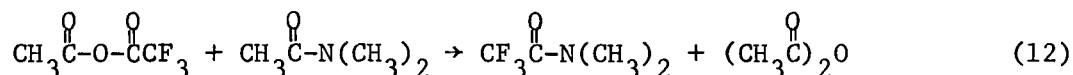
During the reaction of trifluoroacetic anhydride with N,N-dimethylformamide, formyltrifluoroacetate might have formed which was unstable and decomposed into trifluoroacetic acid and carbon monoxide (fig. 1).

For the reaction of trifluoroacetic anhydride with N,N-dimethyl- or N,N-diethylacetamide (figs. 2 and 3), acetyltrifluoroacetate was expected

to be one of the products. However, a peak could not be assigned to it.
Instead, we found peaks with retention times corresponding to those of
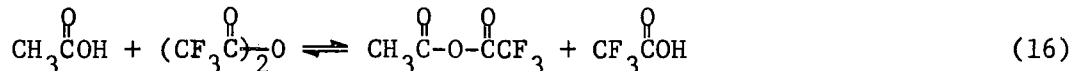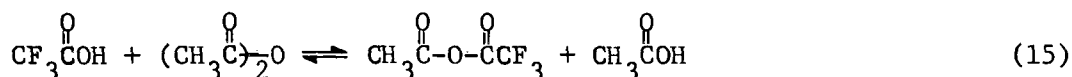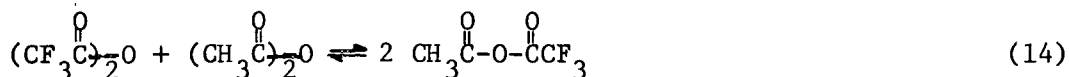acetic anhydride, trifluoroacetic acid and/or acetic acid.

The appearance of the peak of acetic anhydride and the disappear-
ance of the peak of acetyltrifluoroacetate in figures 2(a), 2(b), 3(a),
and 3(b) may be reasonably explained as follows. The acetyltrifluoro-
acetate formed in situ was assumed much more reactive than trifluoro-
acetic anhydride. As soon as it was produced from the reaction of tri-
fluoroacetic anhydride with N,N-dimethyl- or N,N-diethylacetamide, the
acetyltrifluoroacetate reacted immediately with the disubstituted acet-
amides to form the corresponding trifluoroacetamides and acetic anhy-
dride as postulated in equations (12) and (13).

$$CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 + CH_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 + (CH_3\overset{O}{\overset{\|}{C}})_2O \qquad (12)$$

$$CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 + CH_3\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2 + (CH_3\overset{O}{\overset{\|}{C}})_2O \qquad (13)$$

The formation of trifluoroacetic acid and acetic acid during the reflux-
ing of trifluoroacetic anhydride with N,N-dimethyl- or N,N-diethylacetamide
apparently resulted from side reactions. The drastic reaction conditions
could have generated trifluoroacetoxy free radicals ($CF_3\overset{O}{\overset{\|}{C}}-O\cdot$) from tri-
fluoroacetic anhydride and/or acetoxy free radicals ($CH_3\overset{O}{\overset{\|}{C}}-O\cdot$) from acetic
anhydride. These free radicals then abstracted hydrogen from the acetyl
group of the acetamides forming trifluoroacetic acid and/or acetic acid
(figs. 2(b) and 3(b)).

The actual reactions of course were expected to be more complicated
than what we had just described. The acetic anhydride formed would be

expected to react with trifluoroacetic anhydride to produce acetyltri-

fluoroacetate, and the trifluoroacetic acid or acetic acid formed would

also possibly react with acetic anhydride or trifluoroacetic anhydride

as shown in the following equilibria equations reported by Bourne,

Randles, Stacey, Tatlow, and Tedder (refs. 5 and 6).

$$(CF_3\overset{O}{\overset{\|}{C}})_2O + (CH_3\overset{O}{\overset{\|}{C}})_2O \rightleftharpoons 2\ CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 \tag{14}$$

$$CF_3\overset{O}{\overset{\|}{C}}OH + (CH_3\overset{O}{\overset{\|}{C}})_2O \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 + CH_3\overset{O}{\overset{\|}{C}}OH \tag{15}$$

$$CH_3\overset{O}{\overset{\|}{C}}OH + (CF_3\overset{O}{\overset{\|}{C}})_2O \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 + CF_3\overset{O}{\overset{\|}{C}}OH \tag{16}$$

To support our own results as well as to further substantiate the

findings of the British chemists, we took the opportunity to conduct the

reactions given in equations (14), (15), and (16) at room temperature

and followed their course with gas chromatographic analysis. These

chromatograms are shown in figures 4, 5, and 6. Our results are in good

agreement with the results that the British investigators had obtained

using infrared spectroscopy, cryoscopy, and conductivity measurements

(ref. 5). The acetyltrifluoroacetate was present in equilibrium at room

temperature to the extent of over 90% for reaction (14), at about 65% for

reaction (15), and at approximately 25% for reaction (16) all in relative
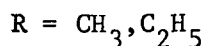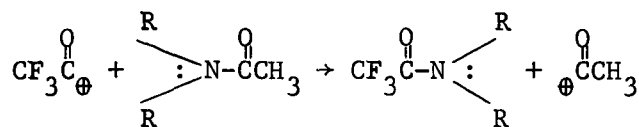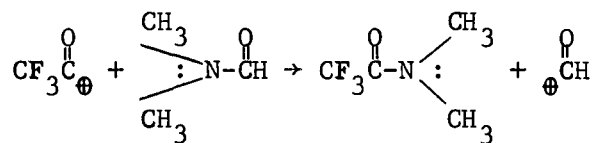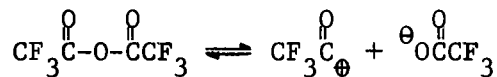
peak areas.

The chromatograms presented in figures 1, 2, and 3 also show that

N,N-dialkyltrifluoroacetamides were formed at room temperature as well as

at reflux temperatures. As expected their rate of formation was directly

proportional to the reaction temperature. The reaction rate of

trifluoroacetic anhydride with the disubstituted amides at room temper-

ature was approximately in the following order as given by the relative

peak-area-percentages of N,N-dialkyltrifluoroacetamides:

$$\text{Rate}_{DEAC}(20\%\text{--}5 \text{ min.}) \simeq \text{Rate}_{DMAC}(19\%\text{--}5 \text{ min.}) \gg \text{Rate}_{DMF}(7\%\text{--}22 \text{ hrs.})$$
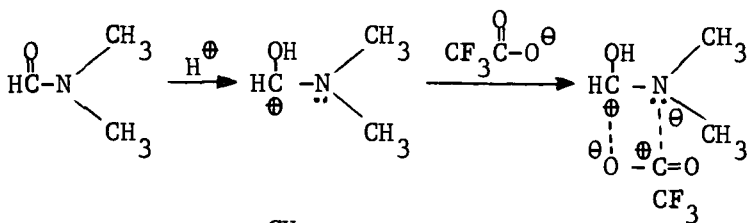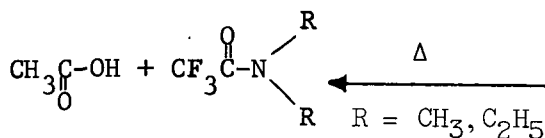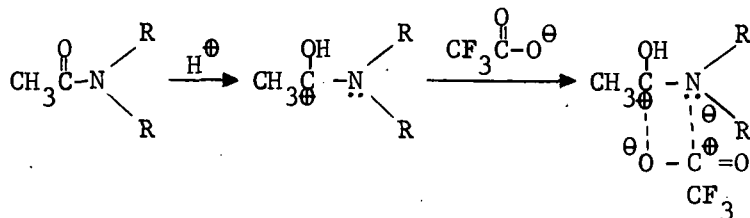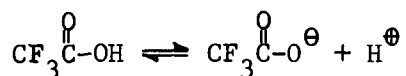
These results indicate that the N-atom of the amide is the reaction

center and that the C-N bond between the carbonyl C-atom and the amide

N-atom ruptures during the reaction. The methyl group bonded to the

carbonyl carbon of either N,N-dimethyl or N-N-diethylacetamide had little

steric influence for the access of the electrophilic reagent, $CF_3\overset{O}{\overset{\|}{C}}\oplus$,

toward the N-atom of the amide. At the same time the electron donating

property of the methyl group weakened the C-N bond of concern and facil-

itated easier substitution of the acetyl cation, $CH_3\overset{O}{\overset{\|}{C}}\oplus$, than the formyl

cation, $H\overset{O}{\overset{\|}{C}}\oplus$.

In these reactions, the amides are taken to be the substrate, and

trifluoroacetic anhydride the reagent. Therefore, the following elec-

trophilic substitution toward N-atom mechanism is proposed to be

operative:

$$CF_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3 \rightleftharpoons CF_3\overset{O}{\overset{\|}{C}}_\oplus + {}^\ominus O\overset{O}{\overset{\|}{C}}CF_3$$

$$CF_3\overset{O}{\overset{\|}{C}}_\oplus + \underset{CH_3}{\overset{CH_3}{>}}\!\!:\!\!N-\overset{O}{\overset{\|}{C}}H \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N\underset{CH_3}{\overset{CH_3}{<}}\!\!: + {}_\oplus\overset{O}{\overset{\|}{C}}H$$

$$CF_3\overset{O}{\overset{\|}{C}}_\oplus + \underset{R}{\overset{R}{>}}\!\!:\!\!N-\overset{O}{\overset{\|}{C}}CH_3 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N\underset{R}{\overset{R}{<}}\!\!: + {}_\oplus\overset{O}{\overset{\|}{C}}CH_3$$

$$R = CH_3, C_2H_5$$

Mechanistic Interpretation of Reactions Involving Trifluoroacetic

Acid and N,N-disubstituted Amides

The chromatograms shown in figures 7, 8, and 9 indicate that trifluoroacetic acid formed stable high boiling complexes with N,N-dimethylacetamide, N,N-diethylacetamide, or N,N-dimethylformamide (ref. 7), and that heating was necessary for the formation of N,N-dialkyltrifluoroacetamides in all three cases. The following "Oxy-protonated 4-center nucleophilic substitution toward C-atom" mechanism is proposed for the reactions involving trifluoroacetic acid and N,N-disubstituted amides:

$$CF_3\overset{O}{\underset{\|}{C}}-OH \;\rightleftharpoons\; CF_3\overset{O}{\underset{\|}{C}}-O^{\ominus} + H^{\oplus}$$

$$CH_3\overset{O}{\underset{\|}{C}}-N\overset{R}{\underset{R}{<}} \;\xrightarrow{H^{\oplus}}\; CH_3\overset{OH}{\underset{\oplus}{C}}-\overset{..}{N}\overset{R}{\underset{R}{<}} \;\xrightarrow{CF_3\overset{O}{\underset{\|}{C}}-O^{\ominus}}\; CH_3\underset{\overset{\ominus}{O}\,-\,\overset{\oplus}{C}=O}{\overset{OH}{\underset{CF_3}{\underset{\|}{C}}}}\overset{R}{\underset{\ominus\,\,R}{-N}}$$

$$CH_3\overset{O}{\underset{\|}{C}}-OH + CF_3\overset{O}{\underset{\|}{C}}-N\overset{R}{\underset{R}{<}} \;\xleftarrow{\;\Delta\;}\;\quad R = CH_3, C_2H_5$$

$$H\overset{O}{\underset{\|}{C}}-N\overset{CH_3}{\underset{CH_3}{<}} \;\xrightarrow{H^{\oplus}}\; H\overset{OH}{\underset{\oplus}{C}}-\overset{..}{N}\overset{CH_3}{\underset{CH_3}{<}} \;\xrightarrow{CF_3\overset{O}{\underset{\|}{C}}-O^{\ominus}}\; H\underset{\overset{\ominus}{O}\,-\,\overset{\oplus}{C}=O}{\overset{OH}{\underset{CF_3}{\underset{\oplus}{C}}}}\overset{CH_3}{\underset{\ominus\,\,CH_3}{-N}}$$

$$H\overset{O}{\underset{\|}{C}}-OH + CF_3\overset{O}{\underset{\|}{C}}-N\overset{CH_3}{\underset{CH_3}{<}} \;\xleftarrow{\;\Delta\;}$$
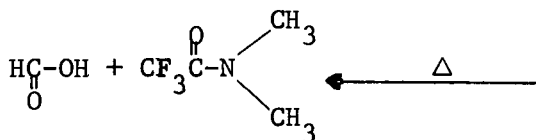
The proton is thought to initiate the reaction. The reagent actually attacking the reaction site of the amides was the nucleophilic trifluoroacetate anion ($CF_3\overset{\overset{O}{\|}}{C}$-O $\ominus$).

For the reaction of trifluoroacetic acid with N,N-dimethylformamide (fig. 9(b)), the other products expected were carbon monoxide and water resulting from the decomposition of formic acid at the reaction conditions. No water peak, however, was found and the peak having a retention time of 23 seconds was found not to be carbon monoxide but dimethylamine. The formation of dimethylamine might have resulted from a reaction according to equation (11), or by hydrolysis of the fluorinated amides formed, e.g., N,N-dimethyltrifluoroacetamide is even more susceptible to hydrolysis than N,N-dimethylformamide (ref. 2).

$$CF_3\overset{\overset{O}{\|}}{C}\text{-N(CH}_3)_2 + H_2O \rightarrow HN(CH_3)_2 + CF_3\overset{\overset{O}{\|}}{C}OH \tag{17}$$
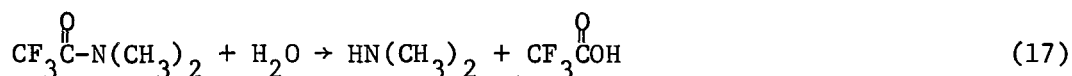
It has been reported that trifluoroacetic acid forms a constant boiling mixture with water. The mixture contains 79.4% trifluoroacetic acid and has a boiling point of 105.5° C (ref. 8). We found that trifluoroacetic acid mixed with up to 14% by weight of water could not be separated from each other under the gas chromatographic conditions employed. This also suggests that the trifluoroacetic acid which forms the adduct with water would not be available as a source of protons for protonation of the carbonyl oxygen of N,N-dimethylformamide. This perhaps is why the reaction of trifluoroacetic acid with N,N-dimethylformamide resulted in a very low yield.

For the reaction of trifluoroacetic acid with N,N-dimethylacetamide, as expected acetic acid was the sole byproduct (fig. 7(b)). For the

reaction of trifluoroacetic acid with N,N-diethylacetamide (fig. 8(b)), no peak of acetic acid was found, instead peaks corresponding to acetic anhydride and diethylamine in relatively small peak-area-percentages were found. The formation of diethylamine may be attributed to reaction (10). And the occurrance of acetic anhydride might be due to a combination of reactions (10) and (13) or (10) and (14). However, the reasons for the absence of an acetic acid peak in figure 8(b) are not apparent. The fact that the acetic acid peak was also absent in figure 3(b) led us to suspect that acetic acid might form complexes with N,N-diethyltrifluoroacetamide. This was found to be true. When N,N-diethyltrifluoroacetamide was mixed with 5-20% by weight of acetic acid, the gas chromotographic results showed that most part of the acetic acid complexed with N,N-diethyltrifluoroacetamide and the rest had longer retention times than its authentic retention time and close to those of trifluoroacetic acid or acetic anhydride peaks.
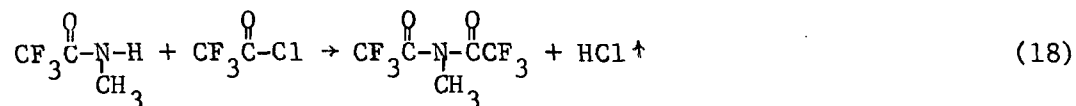
Competitive Hydrolysis of N,N-dimethylacetamide and

N,N-dimethyltrifluoroacetamide

It was mentioned previously that fluorinated amides are more susceptible to hydrolysis. Since the C-N bond between the carbonyl C-atom and the N-atom of trifluoroacetamides is supposed to be shorter (stronger) than that of acetamides, and the three fluorine atoms on trifluoroacetyl group would prevent access of water molecules toward the reaction site, we might have predicted that the reverse would be true. We conducted an experiment of competitive hydrolysis by mixing N,N-dimethylacetamide, N,N-dimethyltrifluoroacetamide, and water in 1.4:1.0:1.0 molar ratio
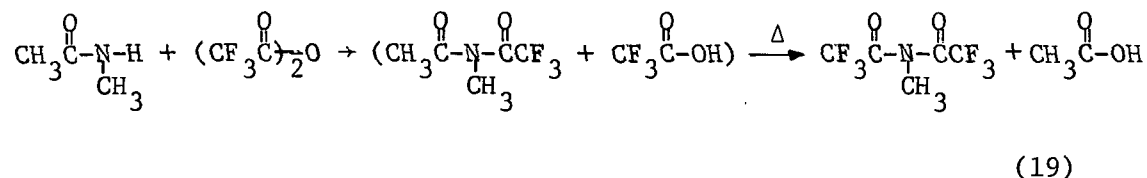
with acetone to form a homogeneous solution. After storing the mixture

at room temperature for 50 days, gas chromatographic analysis did not

show any significant change in peak area ratio. When the mixture was re-

fluxed at 112-140° C for 22 hours, dimethylamine was formed and the peak

area ratio of N,N-dimethylacetamide to N,N-dimethyltrifluoroacetamide

increased from 44.7/46.8 (or 0.95) to 73.5/21.6 (or 3.4) as shown in fig-

ure 10. Our experiment further proved that N,N-dimethyltrifluoroacetamide

is more susceptible to hydrolysis than N,N-dimethylacetamide. One explan-

ation might be that whereas N,N-dimethyltrifluoroacetamide may be more

thermodynamically stable to hydrolysis than N,N-dimethylacetamide, kinet-

ically it is not.

Synthesis of N-methyl-bis(trifluoroacetyl)imide

On the basis of the rule of thumb that "like dissolves like", it was

thought possible that imides might be useful solvents for polyimides. How-

ever, most imides including fluorinated ones are solids. N-methyl-bis

(trifluoroacetyl)imide is a liquid and has a boiling point of 118° C.

Young, Durrell and Dresdner prepared it by reacting N-

methyltrifluoroacetamide with trifluoroacetyl chloride (ref. 9).

$$CF_3\overset{O}{\overset{\|}{C}}-\underset{\underset{CH_3}{|}}{N}-H + CF_3\overset{O}{\overset{\|}{C}}-Cl \rightarrow CF_3\overset{O}{\overset{\|}{C}}-\underset{\underset{CH_3}{|}}{N}-\overset{O}{\overset{\|}{C}}CF_3 + HCl\uparrow \qquad (18)$$
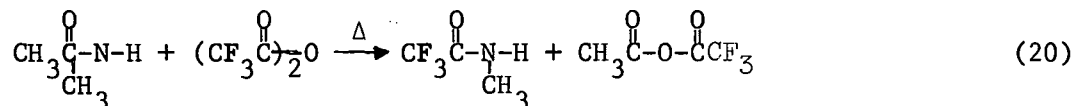
We thought that it might be synthesized more conveniently by heating

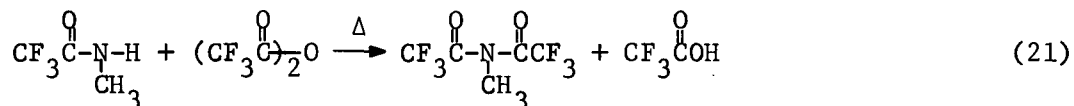N-methylacetamide with trifluoroacetic anhydride according to equation (19):

$$CH_3\overset{O}{\overset{\|}{C}}-\underset{\underset{CH_3}{|}}{N}-H + (CF_3\overset{O}{\overset{\|}{C}})_2O \rightarrow (CH_3\overset{O}{\overset{\|}{C}}-\underset{\underset{CH_3}{|}}{N}-\overset{O}{\overset{\|}{C}}CF_3 + CF_3\overset{O}{\overset{\|}{C}}-OH) \overset{\Delta}{\longrightarrow} CF_3\overset{O}{\overset{\|}{C}}-\underset{\underset{CH_3}{|}}{N}-\overset{O}{\overset{\|}{C}}CF_3 + CH_3\overset{O}{\overset{\|}{C}}-OH$$

$$(19)$$

Because the trifluoroacetyl ion had displaced the acetyl ion rather than

the proton, the product that was obtained was N-methyltrifluoroacetamide.

$$CH_3\overset{O}{\underset{\underset{CH_3}{|}}{C}}-N-H \ + \ (CF_3\overset{O}{C})_2O \ \overset{\Delta}{\longrightarrow} \ CF_3\overset{O}{\underset{\underset{CH_3}{|}}{C}}-N-H \ + \ CH_3\overset{O}{C}-O-\overset{O}{C}CF_3 \qquad (20)$$

This indicates that the "electrophilic substitution toward N-atom" mech-

anism proposed for the reaction of trifluoroacetic anhydride with

N,N-disubstituted amides is applicable for N-monosubstituted amides as

well. However, N-methylbis(trifluoroacetyl)imide was prepared by pro-

longed refluxing of N-methyltrifluoroacetamide with trifluoroacetic

anhydride.

$$CF_3\overset{O}{\underset{\underset{CH_3}{|}}{C}}-N-H \ + \ (CF_3\overset{O}{C})_2O \ \overset{\Delta}{\longrightarrow} \ CF_3\overset{O}{\underset{\underset{CH_3}{|}}{C}}-N-\overset{O}{C}CF_3 \ + \ CF_3\overset{O}{C}OH \qquad (21)$$

CONCLUDING REMARKS

N,N-dialkyltrifluoroacetamides were prepared in good yields by

reacting trifluoroacetic anhydride or acid with appropriate dialkyl-

acetamides. Reaction of trifluoroacetic anhydride or acid with

N,N-dimethylformamide resulted in the synthesis of N,N-

dimethyltrifluoroacetamide. However, the yield of the N,N-

dimethyltrifluoroacetamide that was obtained using trifluoroacetic

acid was very low.

An electrophilic substitution toward the nitrogen atom of the amides

appears to be operative for the reactions of trifluoroacetic anhydride

with either of the disubstituted amides. An oxygen protonated 4-center

nucleophilic substitution toward carbonyl carbon atom of the amides was

postulated for the reactions using trifluoroacetic acid.

The new method for substitution with trifluoroacetyl groups utilizing the reaction of trifluoroacetic anhydride or acid with substituted amides may be useful for synthesizing polypeptides of unique structure or property.
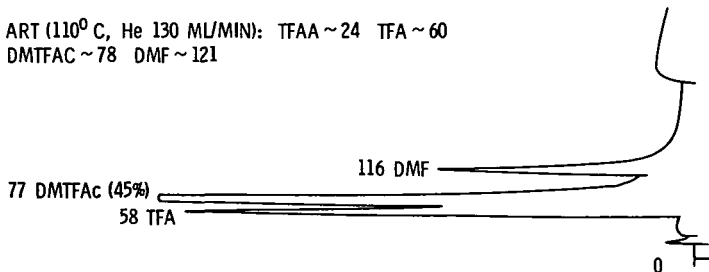
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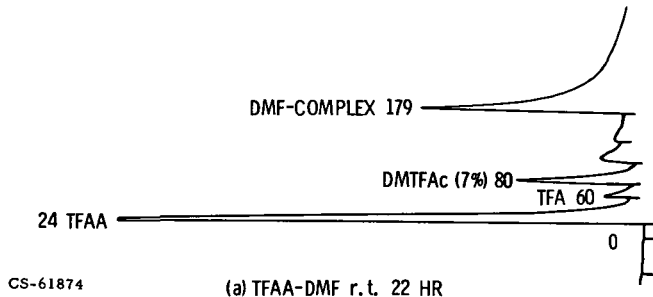
APPENDIX – SYMBOLS

Symbols used in the figures:

TFAA	trifluoroacetic anhydride
TFA	trifluoroacetic acid
Ac_2O	acetic anhydride
AcOH	acetic acid
DMA	dimethylamine
DEA	diethylamine
ATFA	acetyltrifluoroacetate
R	CH_3, C_2H_5
DMF	N,N-dimethylformamide
DMAc	N,N-dimethylacetamide
DEAc	N,N-diethylacetamide
DMTFAc	N,N-dimethyltrifluoroacetamide
DETFAc	N,N-diethyltrifluoroacetamide
ART	authentic retention time
r.t.	room temperature

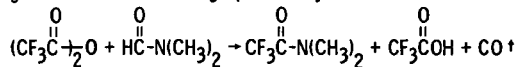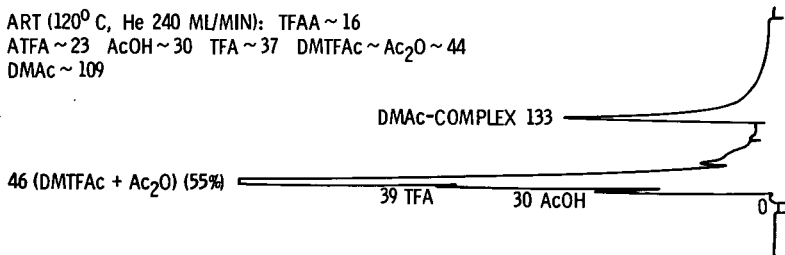ART (110° C, He 130 ML/MIN): TFAA ~ 24 TFA ~ 60
DMTFAC ~ 78 DMF ~ 121

116 DMF

77 DMTFAc (45%)

58 TFA

0

(b) TFAA-DMF 60° C 35 HR

DMF-COMPLEX 179

DMTFAc (7%) 80

TFA 60

24 TFAA

0

CS-61874   (a) TFAA-DMF r.t. 22 HR

Figure 1. - Gas chromatographic analysis of

$$(CF_3\overset{O}{\overset{\|}{C}}{\displaystyle\frac{}{2}}O + H\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 + CF_3\overset{O}{\overset{\|}{C}}OH + CO\uparrow$$

ART (120° C, He 240 ML/MIN): TFAA ~ 16
ATFA ~ 23 AcOH ~ 30 TFA ~ 37 DMTFAc ~ Ac$_2$O ~ 44
DMAc ~ 109

DMAc-COMPLEX 133

46 (DMTFAc + Ac$_2$O) (55%)

39 TFA   30 AcOH

0

(b) TFAA-DMAc 85-140° C 15 HR

DMAc-COMPLEX 129

44 (DMTFAc + Ac$_2$O) (38%)

16 TFAA

0
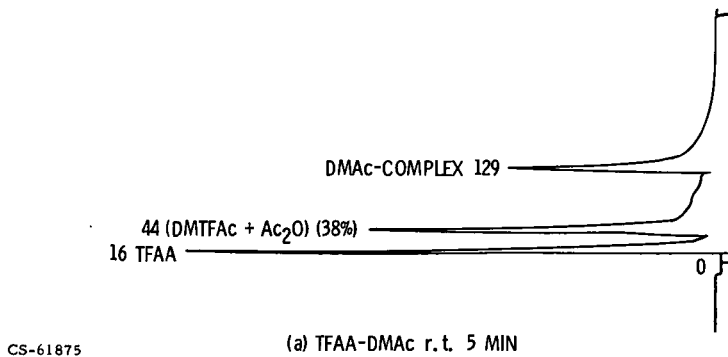
CS-61875   (a) TFAA-DMAc r.t. 5 MIN

Figure 2. - Gas chromatographic analysis of

$$(CF_3\overset{O}{\overset{\|}{C}}{\displaystyle\frac{}{2}}O + CH_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 + CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_3$$
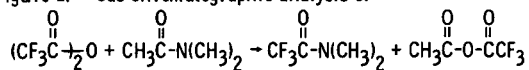
ART (150° C, He 85 ML/MIN): TFAA ~ 28 ATFA ~ 36
AcOH ~ 41 TFA ~ 46 Ac₂O ~ 54 DETFAc ~ 81 DEAc ~ 160

DEAc-COMPLEX 211

81 DETFAc (61%)

Ac₂O 56

TFA 46

0

(b) TFAA-DEAc 140°-153° C 17 HR

DEAc-COMPLEX 183

85 DETFAc (20%)

Ac₂O 54

28 TFAA

0

CS-61876   (a) TFAA-DEAc r.t. 5 MIN
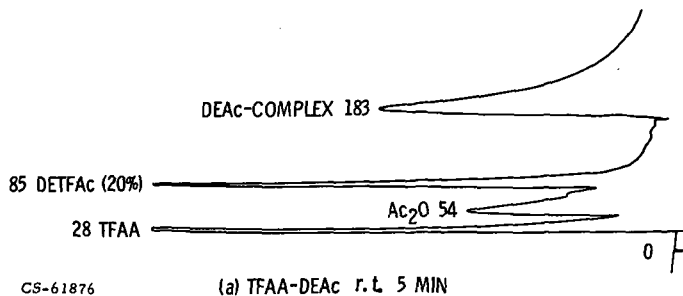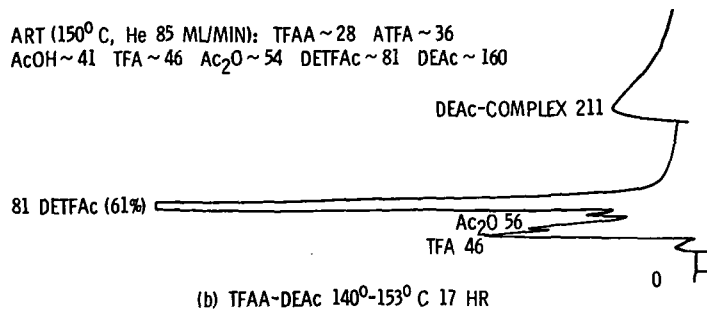
Figure 3. - Gas chromatographic analysis of

$$(CF_3\overset{O}{\overset{\|}{C}}{\rightarrow}_2 O + CH_3\overset{O}{\overset{\|}{C}}{-}N\overset{C_2H_5}{\diagdown_{C_2H_5}} \rightarrow CF_3\overset{O}{\overset{\|}{C}}{-}N\overset{C_2H_5}{\diagdown_{C_2H_5}} + CH_3\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}CF_3$$
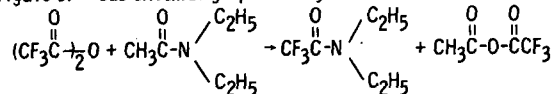
ART (90° C, He 70 ML/MIN): TFAA ~ 37 Ac₂O ~ 159

Ac₂O 159

69 ATFA (91%)

TFAA 40

0

(c) TFAA-Ac₂O r.t. 42 DAYS

Ac₂O 162

69 ATFA (91%)

TFAA 40

0

(b) TFAA-Ac₂O r.t. 2 HR

Ac₂O 160

69 ATFA (49%)

TFAA 38

0

CS-61882   (a) TFAA-Ac₂O r.t. 1 HR
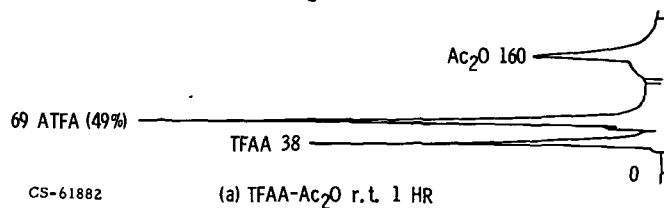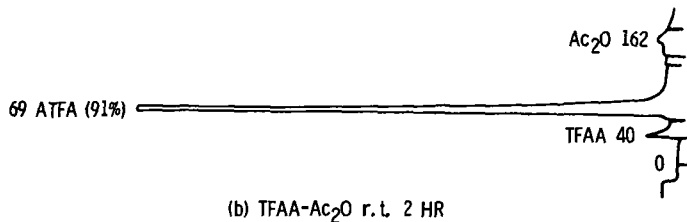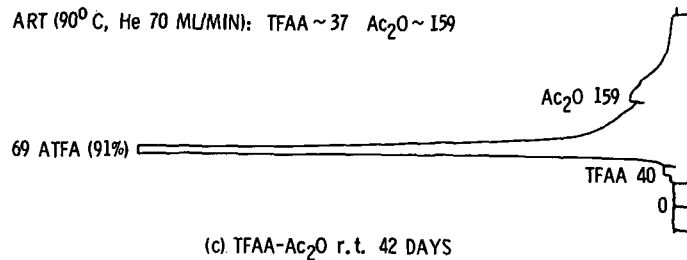
Figure 4. - Gas chromatographic analysis of

$$(CF_3\overset{O}{\overset{\|}{C}}{\rightarrow}_2 O + (CH_3\overset{O}{\overset{\|}{C}}{\rightarrow}_2 O \rightleftharpoons 2CH_3\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}CF_3$$
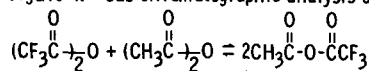
ART (90° C, He 70 ML/MIN): TFAA ~ 37
ATFA ~ 69   AcOH ~ 99   TFA ~ 136   Ac$_2$O ~ 159

149

70 ATFA (65%)

TFAA 40

0

(c) TFAA-AcOH r.t. 42 DAYS

146

70 ATFA (54%)

TFAA 39

0

(b) TFAA-AcOH r.t. 4 HR

TFA 134
AcOH 116

69 ATFA (46%)

TFAA 40

0

CS-61681   (a) TFAA-AcOH r.t. 1/2 HR
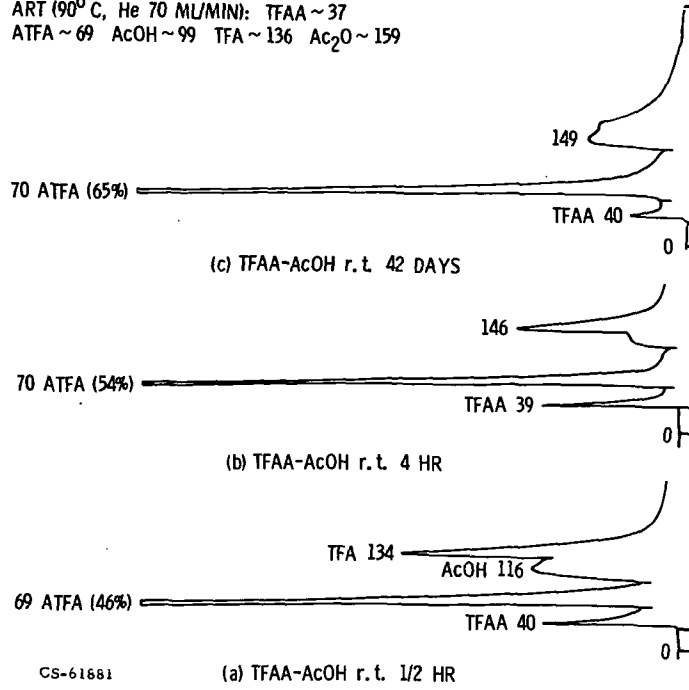
Figure 5. - Gas chromatographic analysis of

$$(CF_3\overset{O}{\overset{\|}{C}}\cdot)_2O + CH_3\overset{O}{\overset{\|}{C}}OH \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}CF_3 + CF_3\overset{O}{\overset{\|}{C}}OH$$
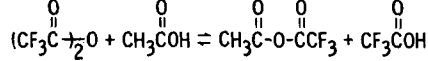
ART (90° C, He 70 ML/MIN): ATFA ~ 69
AcOH ~ 99   TFA ~ 136   Ac$_2$O ~ 159

163 Ac$_2$O
TFA 127
AcOH 100

69 ATFA (25%)

0

(c) TFA-Ac$_2$O r.t. 42 DAYS

165 Ac$_2$O
TFA 140

AcOH 100

70 ATFA (22%)

0

(b) TFA-Ac$_2$O r.t. 24 HR

163 Ac$_2$O
TFA 136

AcOH 99

ATFA (21%)

CS-61883   (a) TFA-Ac$_2$O r.t. 3 HR

0
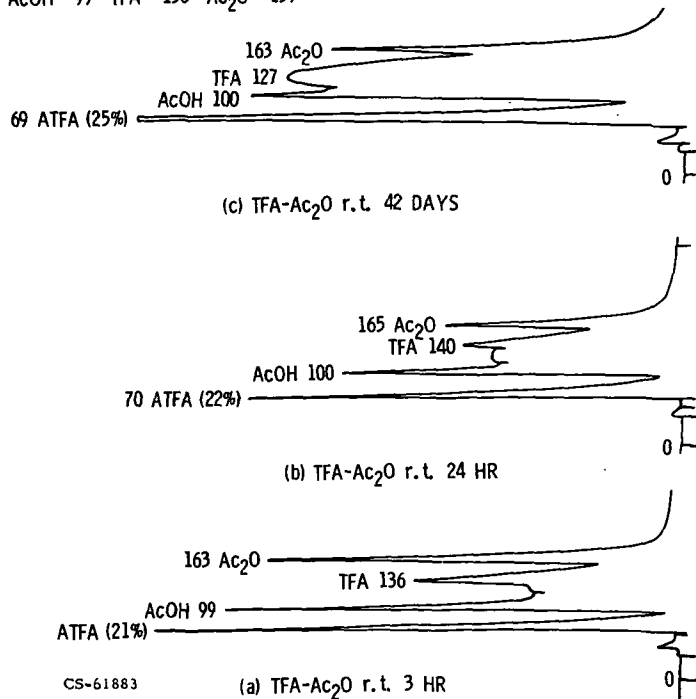
Figure 6. - Gas chromatographic analysis of

$$CF_3\overset{O}{\overset{\|}{C}}OH + (CH_3\overset{O}{\overset{\|}{C}}\cdot)_2O \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}CF_3 + CH_3\overset{O}{\overset{\|}{C}}OH$$
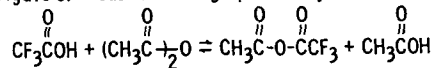
ART (120° C, He 240 ML/MIN): AcOH ~ 30
TFA ~ 37   DMTFAc ~ 44   DMAc ~ 109

DMAc-COMPLEX 130

42 DMTFAc (50%)

AcOH 30

0
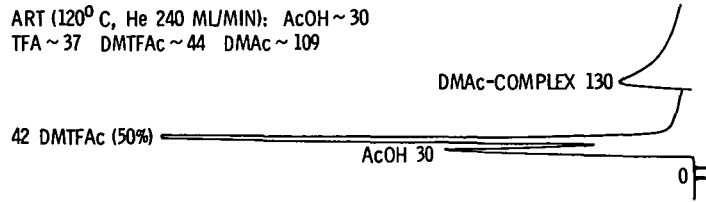
(b) TFA-DMAc 180°-153° C 36 HR

129 DMAc-COMPLEX

49

0
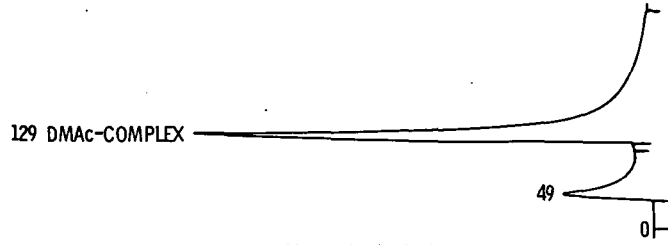
CS-61878   (a) TFA-DMAc r. t. 6 DAYS

Figure 7. - Gas chromatographic analysis of

$$CF_3\overset{O}{\overset{\|}{C}}OH + CH_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 + CH_3\overset{O}{\overset{\|}{C}}OH$$
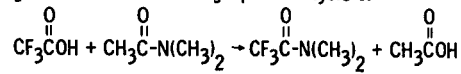
ART (150° C, He 85 ML/MIN): AcOH ~ 41   TFA ~ 46
Ac₂O ~ 54   DETFAc ~ 81   DEAc ~ 160

DEAc-COMPLEX 169

78 DETFAc (56%)

Ac₂O 52

DEA 26

0
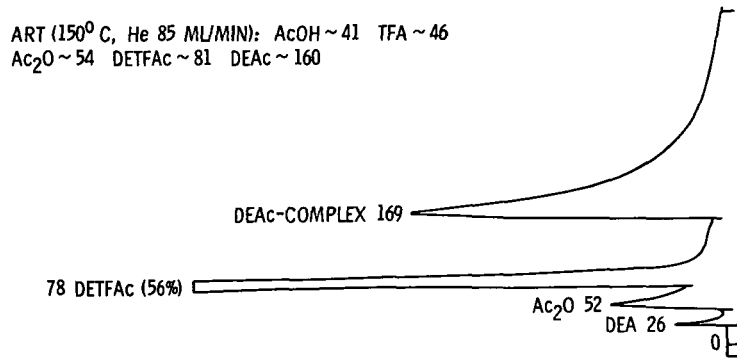
(b) TFA-DEAc 188°-170° C 24 HR

172 DEAc-COMPLEX

56
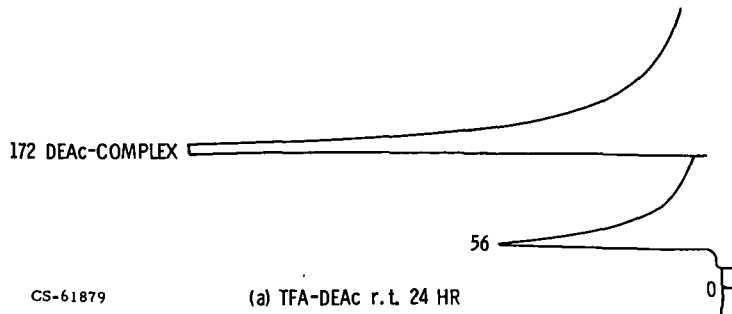
CS-61879   (a) TFA-DEAc r. t. 24 HR

0

Figure 8. - Gas chromatographic analysis of

$$CF_3\overset{O}{\overset{\|}{C}}OH + CH_3\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2 + CH_3\overset{O}{\overset{\|}{C}}OH$$

ART (110° C, He 130 ML/MIN): TFA ~ 60
DMTFAc ~ 78   DMF ~ 121

DMF-COMPLEX 132

DMTFAc (6%) 76

DMA 23

0

(b) TFA-DMF 185°-110° C 72 HR

DMF-COMPLEX 233

0

CS-61880   (a) TFA-DMF r.t. 48 HR
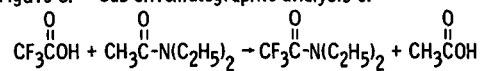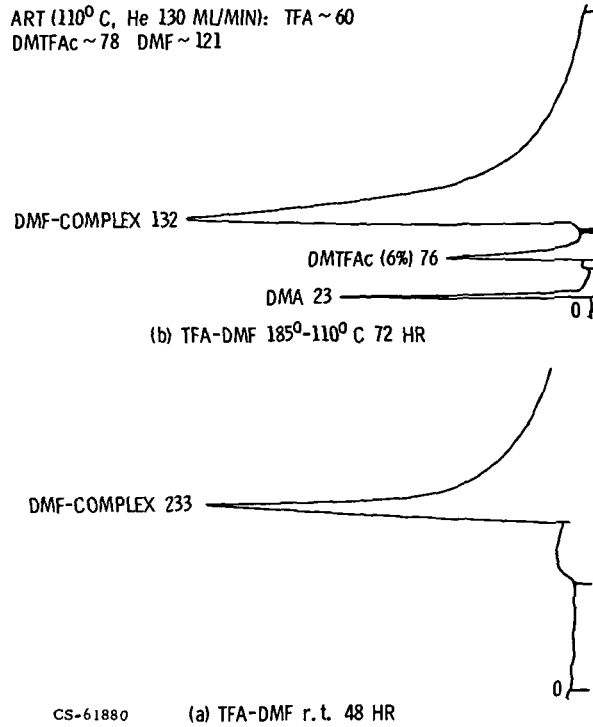
Figure 9. - Gas chromatographic analysis of

$$CF_3\overset{O}{\overset{\|}{C}}OH + H\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 + H_2O + CO \uparrow$$

ART (120° C, He 240 ML/MIN): H$_2$O-ACETONE ~ 26
AcOH ~ 30   TFA ~ 37   DMTFAc ~ 44   DMAc ~ 109

108 DMAc (73.5%)

50 DMTFAc (21.6%)

H$_2$O-ACTONE 26
DMA 17

0

(b) DMAc-DMTFAc-H$_2$O-ACETONE 112°-140° C 22 HR

105 DMAc (44.7%)

50 DMTFAc (46.8%)
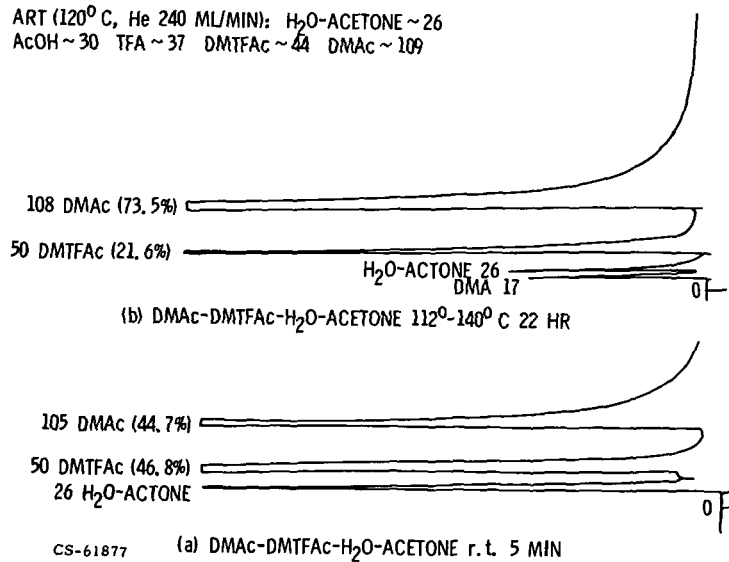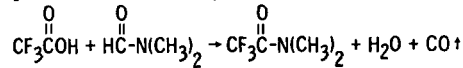26 H$_2$O-ACTONE

0

CS-61877   (a) DMAc-DMTFAc-H$_2$O-ACETONE r.t. 5 MIN

Figure 10. - Gas chromatographic analysis of

$$\left.\begin{array}{l} CH_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \\ CF_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \end{array}\right\} + H_2O \rightarrow H-N(CH_3)_2 + \left\{\begin{array}{l} CH_3\overset{O}{\overset{\|}{C}}OH \\ CF_3\overset{O}{\overset{\|}{C}}OH \end{array}\right.$$