NASA TECHNICAL NOTE

NASA TN D-6836

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NASA TN D-6836

NEW METHODS FOR PREPARING N,N-DIALKYLTRIFLUOROACETAMIDES

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NATIONAL AERONAUTICS AND SPACE ADMINISTRATION • WASHINGTON, D. C. • JUNE 1972

1. Report No. NASA TN D-6836	2. Government Accession No.	3. Recipient's Catalog No.
4. Title and Subtitle NEW METHODS FOR PREPARING N, N-DIALKYLTRIFLUOROACETAMIDES		5. Report Date June 1972
		6. Performing Organization Code
7. Author(s) Li-Chen Hsu		8. Performing Organization Report No. E-6777
		10. Work Unit No. 134-03
9. Performing Organization Name and Address Lewis Research Center National Aeronautics and Space Administration Cleveland, Ohio 44135		11. Contract or Grant No.
		13. Type of Report and Period Covered Technical Note
12. Sponsoring Agency Name and Address National Aeronautics and Space Administration Washington, D.C. 20546		14. Sponsoring Agency Code
15. Supplementary Notes		

16. Abstract

The customary preparative methods for N, N-dialkyltrifluoroacetamides involve the acylation of an amine by trifluoroacetic acid or its derivatives. In this report 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.

17. Key Words (Suggested by Author(s)) Fluorinated amides Gas chromatography Reaction mechanism	18. Distribution Statement Unclassified - unlimited

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price*
Unclassified	Unclassified	21	$3.00

*For sale by the National Technical Information Service, Springfield, Virginia 22151

NEW METHODS FOR PREPARING N, N-DIALKYLTRIFLUOROACETAMIDES

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SUMMARY

N, N-Dialkyltrifluoroacetamides were prepared by reacting trifluoroacetic anhydride with appropriate N, N-dialkylacetamides or formamides at room temperature as well as at reflux conditions. Their reactions were followed with gas chromatographic analysis. The results from these studies indicated that the nitrogen (N) atom of the amide is the reaction center and that the carbon-nitrogen (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 the N, N-dialkylacetamides had little steric influence on the access of the electrophilic trifluoroacetyl ion to the N atom of the amides. At the same time the electron donating property of the methyl group weakened the C-N bond of concern and facilitated substitution of the acetyl ion rather than the formyl ion. An "electrophilic substitution toward the N atom" mechanism was proposed for the reactions of trifluoroacetic anhydride with either of the disubstituted amides.

N, N-Dialkyltrifluoroacetamides were also obtained by refluxing trifluoroacetic acid with appropriate N, N-dialkylacetamides or formamides. The results from the gas chromatographic analyses indicated that an "oxygen protonated four-center nucleophilic substitution toward the C atom" mechanism appeared to be operative for the reactions of trifluoroacetic acid with the disubstituted amides. Trifluoroacetic acid dissociates into protons and trifluoroacetate anions. The proton is thought to initiate the reaction. The reagent actually attacking the carbonyl C atom of the amides is thought to be the nucleophilic trifluoroacetate anion, which consequently forms the high-boiling four-center complex. The stable four-center complex upon prolonged heating then breaks down into the corresponding dialkyltrifluoroacetamide and acetic or formic acid.

In this work, the equilibria of mixed anhydride and anhydride-acid systems involving acetyltrifluoroacetate were also studied with the aid of gas chromatographic analysis. The results are in good agreement with the results that previous investigators had obtained by using infrared spectroscopy, cryoscopy, and conductivity measurements

The gas chromatographic analysis method was also used to study the competitive hydrolysis of N, N-dimethylacetamide and N, N-dimethyltrifluoroacetamide. The results provided further substantiation that fluorinated amides are more susceptible to hydrolysis.

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 overcoming 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 increase significantly their solvent power for certain polymeric materials (refs. 2 and 3).

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 by using the technique of gas chromatography, and mechanistic interpretations were developed.

EXPERIMENTAL APPARATUS AND PROCEDURE

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 91-centimeter height, an automatic reflux control device, and a direct-bearing-driven stainless-steel spiral screen band having 118 teeth per centimeter. 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-millivolt chart recorder having the chart driving speed fixed at 47 seconds per centimeter, 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 by using a 1.83-meter-long, 6.35-millimeter-diameter copper tubing column packed with 15 percent Dow Corning 200 silicone oil on 60/80 mesh Chromosorb W at the oven temperature and helium flow rate designated in 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

Trifluoroacetic anhydride or acid (0.1 to 0.5 mole) was introduced into a 200- or 500-cubic-centimeter three-neck round-bottom flask fitted with a magnetic stirrer, a gas inlet, a thermometer, a graduated pressure equalizing separatory funnel, and a condenser with a coolant at about -20° C. The anhydride or acid was covered with a blanket of dry nitrogen gas. From the funnel, an equal molar 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 the reflux temperature 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° to 134° C and N, N-diethyltrifluoroacetamide at 157° to 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 percent) ranged from 70 to 90 percent. 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

Trifluoroacetic anhydride or acid (0.05 mole) was introduced into a 100-cubic-centimeter three-neck round-bottom flask with the same setup as for the syntheses of N, N-dialkyltrifluoroacetamides and was covered with a blanket of dry nitrogen gas. An equal molar 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 chromatographic 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 g) of N, N-dimethylacetamide, 0.0158 mole (2.237 g) of N, N-dimethyltrifluoroacetamide, and 0.0158 mole (0.3 cm^3) of water with acetone (1:1 by volume). A sample of the mixture was taken for gas chromatographic analysis at 120° C and at a helium flow rate of 240 cubic centimeters per minute. About 90 percent of the mixture was refluxed at 112° to 140° C for 22 hours, while the remaining 10 percent was kept at room temperature for 50 days prior to further gas chromatographic analysis.

Preparation of N-methyl Trifluoroacetamide

A mixture of 0.5 mole each of N-methyl acetamide (36.5 g) and trifluoroacetic anhydride (70 cm^3) was refluxed at 120° to 142° C for 35 hours in a 200-cubic-centimeter three-neck round-bottom flask with the same setup as for the syntheses of N, N-dialkyltrifluoroacetamides. The reaction mixture was then distilled at atmospheric pressure with a spinning-band distillation apparatus. The fraction that distilled over at 157° to 160° C was collected, and the yield was 39 grams (61 percent based on N-methyl acetamide). The melting point was 48.5° C, and infrared carbonyl assignment was 1720 $centimeter^{-1}$.

Preparation of N-methylbis(trifluoroacetyl)imide

In a 200-cubic-centimeter flask, 0.25 mole each of N-methyl trifluoroacetamide (31.8 g) and trifluoroacetic anhydride (35 cm^3) were refluxed at 48° to 65° C for 100 hours. The reaction mixture was distilled with a spinning-band distillation apparatus. Ten grams of the fraction boiling at 118° to 120° C were collected (18 percent yield based on N-methyltrifluoroacetamide used, or 61 percent yield based on unreacted N-methyltrifluoroacetamide recovered). Infrared carbonyl assignment was 1750 $centimeter^{-1}$.

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. 4) for the synthesis of it is by reacting ethyltrifluoroacetate with dimethylamine as shown in equation (1):

$$CF_3\overset{O}{\overset{\|}{C}}\text{-}OC_2H_5 + H\text{-}N(CH_3)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2 + C_2H_5OH \qquad (1)$$

Coppinger had prepared N, N-dimethylacetamide by reacting acetic anhydride with N, N-dimethylformamide (ref. 5) according to equation (2):

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

It was obvious that there should be no difficulty in preparing N, N-dimethyltrifluoroacetamide by modifying Coppinger's procedure by the replacement of acetic anhydride with trifluoroacetic anhydride. Trifluoroacetic acid, as well as anhydride, was tried:

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

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

Also used were N, N-dimethylacetamide and N, N-diethylacetamide in addition to N, N-dimethylformamide:

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

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

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

$$CF_3\overset{O}{\overset{\|}{C}}OH + CH_3\overset{O}{\overset{\|}{C}}\text{-}N(C_2H_5)_2 \rightarrow CF_3\overset{O}{\overset{\|}{C}}\text{-}N(C_2H_5)_2 + CH_3\overset{O}{\overset{\|}{C}}OH \tag{8}$$

All these postulated reactions were found workable to various degrees. N, N-dialkyltrifluoroacetamides were obtained in good yields (70 to 90 percent) except from reaction (4), utilizing trifluoroacetic acid and N, N-dimethylformamide, which resulted in yields of less than 10 percent.

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:

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

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

$$CF_3\overset{O}{\overset{\|}{C}}OH + H\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2 \rightarrow H\text{-}N(CH_3)_2 + H\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}CF_3 \tag{11}$$

The unexpected experimental result of the formation of N, N-dialkyltrifluoroacetamides by reacting trifluoroacetic acid with amides, specifically with N, N-dialkylacetamides, prompted a study of the reaction mechanisms involved in these reactions.

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

Figures 1 to 3 are the chromatograms for the reactions given by equations (3), (5), and (7), which were conducted at various time and temperature conditions. (Abbreviations used in the figures are defined in the appendix.) 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 were 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 which was unstable might have formed and decomposed into trifluoroacetic acid and carbon monoxide (fig. 1).

The reaction of trifluoroacetic anhydride with N, N-dimethyl- or N, N-diethylacetamide (figs. 2 and 3) was expected to yield acetyltrifluoroacetate as one of the products. However, a peak could not be assigned to it. Instead, peaks were found 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 disappearance of the peak of acetyltrifluoroacetate in figures 2 and 3 may be reasonably explained as follows. The acetyltrifluoroacetate formed in situ was assumed much more reactive than trifluoroacetic anhydride. As soon as it was produced from the reaction of trifluoroacetic anhydride with N, N-dimethyl- or N, N-diethylacetamide, the acetyltrifluoroacetate reacted with the disubstituted acetamides to form the corresponding trifluoroacetamides and acetic anhydride as postulated in equations (12) and (13):

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

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

The formation of trifluoroacetic acid and acetic acid during the refluxing 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 ($CF_3\overset{O}{\overset{\|}{C}}\text{-}O\cdot$) from trifluoroacetic anhydride and/or acetoxy free radicals ($CH_3\overset{O}{\overset{\|}{C}}\text{-}O\cdot$) from acetic anhydride. These free radicals then abstracted hydrogen from the acetyl group of the acetamides and formed trifluoroacetic acid and/or acetic acid (figs. 2(b) and 3(b)).

The actual reactions, of course, were expected to be more complicated than those just described. The acetic anhydride formed would be expected to react with trifluoroacetic anhydride to produce acetyltrifluoroacetate, 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. 6 and 7):

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

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

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

To support Lewis Research Center results as well as to further substantiate the findings of the British chemists, the reactions given in equations (14), (15), and (16) were run at room temperature and their course was followed with gas chromatographic analysis. These chromatograms are shown in figures 4 to 6. The results are in good agreement with the results that the British investigators had obtained by using infrared spectroscopy, cryoscopy, and conductivity measurements (ref. 6). The acetyltrifluoroacetate was present in equilibrium at room temperature to the extent of over 90 percent for reaction (14), about 65 percent for reaction (15), and approximately 25 percent for reaction (16), all in relative peak areas.

The chromatograms presented in figures 1 to 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 temperature was approximately in the following order, as given by the relative peak-area percentages of N, N-dialkyltrifluoroacetamides:

$$\text{Rate}_{DEAC}(20\%\text{-}5\ \text{min}) \simeq \text{Rate}_{DMAC}(19\%\text{-}5\ \text{min}) \gg \text{Rate}_{DMF}(7\%\text{-}22\ \text{hr})$$

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, $CF_3\overset{O}{\overset{\|}{C}}\oplus$, to 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 facilitated substitution of the acetyl cation, $CH_3\overset{O}{\overset{\|}{C}}{}^{\oplus}$, rather 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 "electrophilic substitution toward the N atom" mechanism is proposed to be operative:

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

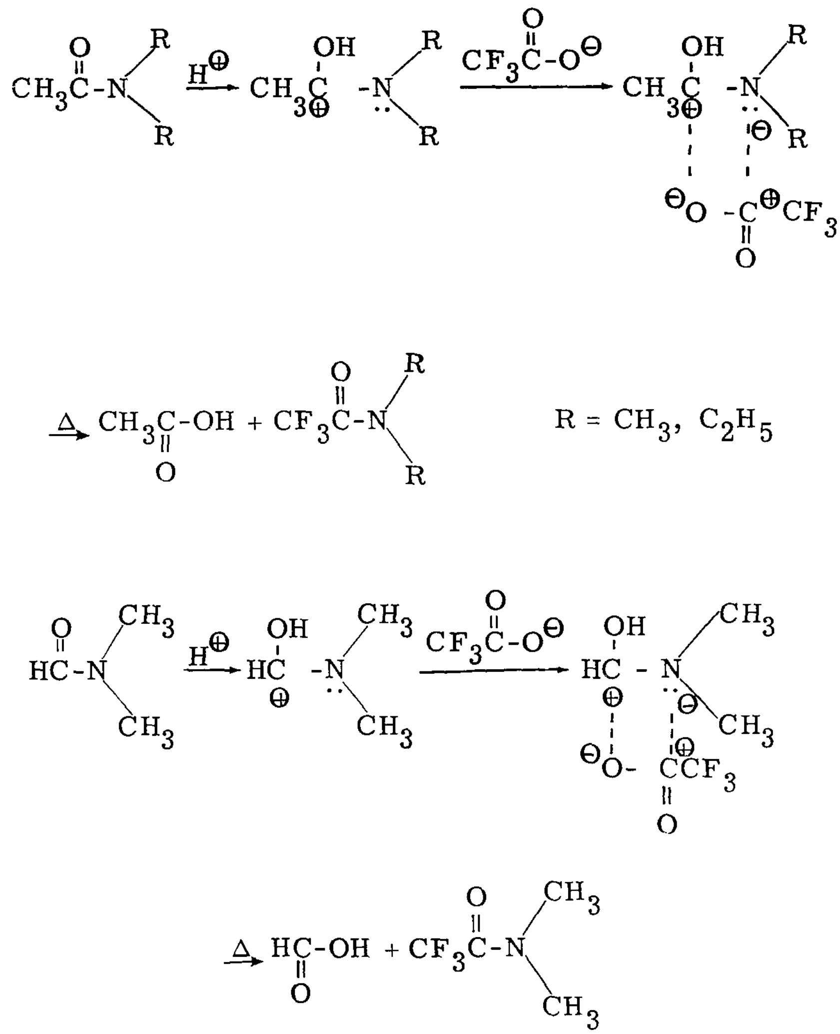
$$CF_3\overset{O}{\overset{\|}{C}}{}_{\oplus} + \,:\!\underset{CH_3}{\overset{CH_3}{\diagdown\!\!\!\diagup}}\text{N-}\overset{O}{\overset{\|}{C}}H \rightarrow CF_3\overset{O}{\overset{\|}{C}}\text{-N}\underset{CH_3}{\overset{CH_3}{\diagup\!\!\!\diagdown}}\!: + {}_{\oplus}\overset{O}{\overset{\|}{C}}H$$

$$CF_3\overset{O}{\overset{\|}{C}}{}_{\oplus} + \,:\!\underset{R}{\overset{R}{\diagdown\!\!\!\diagup}}\text{N-}\overset{O}{\overset{\|}{C}}CH_3 \rightarrow CF_3\overset{O}{\overset{\|}{C}}\text{-N}\underset{R}{\overset{R}{\diagup\!\!\!\diagdown}}\!: + {}_{\oplus}\overset{O}{\overset{\|}{C}}CH_3 \qquad R = CH_3, C_2H_5$$

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

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

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



Trifluoroacetic acid dissociates into trifluoroacetate anions and protons. The proton is thought to initiate the reaction. The reagent actually attacking the carbonyl C atom of the amides is thought to be the nucleophilic trifluoroacetate anion, which consequently forms the high-boiling four-center complex. To force this stable complex through its transition state, heating apparently is needed. Because the C-N bond between the carbonyl C atom of the trifluoroacetyl group and the N atom is stronger than that between the carbonyl C atom of the acetyl group and the same N atom, the four-center complex upon prolonged heating then breaks down into the corresponding dialkytrifluoroacetamide and acetic or formic acid instead of reforming the initial reactants. It appears that this is a one-way reaction. Indeed, no N, N-dimethyl or N, N-diethylacetamide was formed when corresponding dialkyltrifluoroacetamide was refluxed with acetic acid over night.

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 not 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; for example, N, N-dimethyltrifluoroacetamide is even more susceptible to hydrolysis than N, N-dimethylformamide (refs. 2 and 3):

$$CF_3\overset{\overset{O}{\|}}{C}\text{-}N(CH_3)_2 + H_2O \rightarrow HN(CH_3)_2 + CF_3\overset{\overset{O}{\|}}{C}OH \tag{17}$$

It has been reported that trifluoroacetic acid forms a constant-boiling mixture with water. The mixture contains 79. 4 percent trifluoroacetic acid and has a boiling point of 105. 5^{O} C (ref. 9). It was found that trifluoroacetic acid mixed with up to 14 percent by weight of water could not be separated from the water under the gas chromatographic conditions employed. The DMF complex with a retention time of 132 seconds (fig. 9(b)) was found to be formed from N, N-dimethylformamide, trifluoroacetic acid, and water; while the one with a longer retention time of 233 seconds (fig. 9(a)) was formed by N, N-dimethylformamide and trifluoroacetic acid. 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, and this is perhaps the reason 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 occurrence 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) indicated that acetic acid might form complexes with N, N-diethyltrifluoroacetamide. This was found to be true. When N, N-diethyltrifluoroacetamide was mixed with 5 to 20 percent by weight of acetic acid, the gas chromatographic results showed that most of the acetic acid complexed with N, N-diethyltrifluoroacetamide and the rest had retention times longer 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 the trifluoroacetyl group would prevent access of water molecules to the reaction site, the reverse might have been predicted. An experiment involving competitive hydrolysis was conducted by mixing N, N-dimethylacetamide, N, N-dimethyltrifluoroacetamide, and water in a 1. 4:1. 0:1. 0 molar ratio with acetone to form a homogeneous solution. After the mixture was stored at room temperature for 50 days, gas chromatographic analysis did not show any significant change in peak area ratio. When the mixture was refluxed at 112° to 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 figure 10. The experiment further proved that N, N-dimethyltrifluoroacetamide is more susceptible to hydrolysis than N, N-dimethylacetamide. One explanation might be that, whereas N, N-dimethyltrifluoroacetamide may be more thermodynamically resistant to hydrolysis than N, N-dimethylacetamide, kinetically it is not.

Synthesis of N-methyl-bis(trifluoroacetyl)imide

On the basis of the rule that "like dissolves like," it was thought possible that imides might be useful solvents for polyimides. However, 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. 10):

$$CF_3\overset{\overset{O}{\|}}{C}\text{-}\underset{CH_3}{N}\text{-}H + CF_3\overset{\overset{O}{\|}}{C}\text{-}Cl \rightarrow CF_3\overset{\overset{O}{\|}}{C}\text{-}\underset{CH_3}{N}\text{-}\overset{\overset{O}{\|}}{C}CF_3 + HCl\uparrow \qquad (18)$$

An attempt was made to synthesize N-methyl-bis(trifluoroacetyl)imide more conveniently by heating N-methylacetamide with trifluoroacetic anhydride according to the equation

$$CH_3\overset{\overset{O}{\|}}{C}\text{-}\underset{CH_3}{N}\text{-}H + (CF_3\overset{\overset{O}{\|}}{C})_2O \rightarrow (CH_3\overset{\overset{O}{\|}}{C}\text{-}\underset{CH_3}{N}\text{-}\overset{\overset{O}{\|}}{C}CF_3 + CF_3\overset{\overset{O}{\|}}{C}\text{-}OH) \xrightarrow{\Delta} CF_3\overset{\overset{O}{\|}}{C}\text{-}\underset{CH_3}{N}\text{-}\overset{\overset{O}{\|}}{C}CF_3 + CH_3\overset{\overset{O}{\|}}{C}\text{-}OH \qquad (19)$$

Because the trifluoroacetyl ion had displaced the acetyl ion rather than the proton, the product that was obtained was N-methyltrifluoroacetamide:

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

This indicates that the electrophilic substitution toward the N atom mechanism 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 prolonged refluxing of N-methyltrifluoroacetamide with trifluoroacetic anhydride.

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

CONCLUDING REMARKS

N, N-dialkyltrifluoroacetamides were prepared in good yields by reacting trifluoroacetic anhydride or acid with appropriate dialkylacetamides. 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 by 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 four-center nucleophilic substitution toward the 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.

Lewis Research Center,
National Aeronautics and Space Administration,
Cleveland, Ohio, April 7, 1972,
134-03.

APPENDIX - ABBREVIATIONS USED IN THE FIGURES

Ac_2O	acetic anhydride
AcOH	acetic acid
ATFA	acetyltrifluoroacetate
DEA	diethylamine
DEAc	N, N-diethylacetamide
DETFAc	N, N-diethyltrifluoroacetamide
DMA	dimethylamine
DMAc	N, N-dimethylacetamide
DMF	N, N-dimethylformamide
DMTFAc	N, N-dimethyltrifluoroacetamide
R	CH_3, C_2H_5
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

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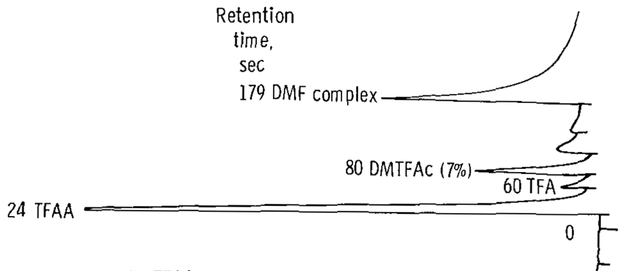
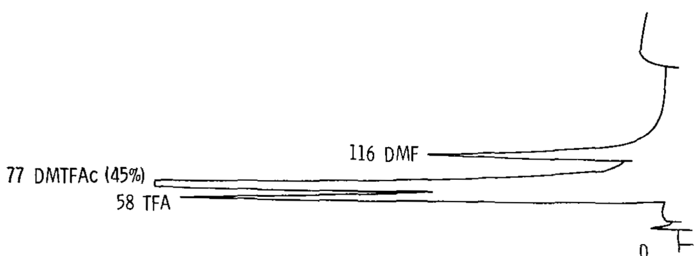


(a) TFAA-DMF at room temperature for 22 hours.

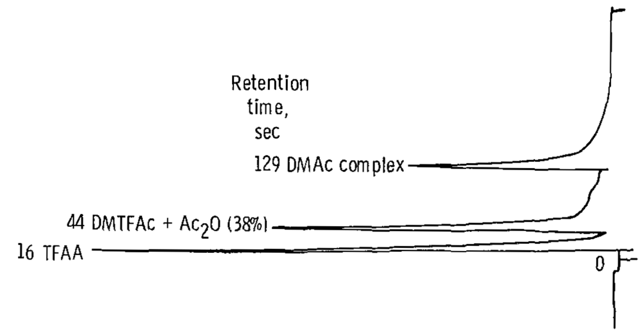


(b) TFAA-DMF at 60° C for 35 hours.

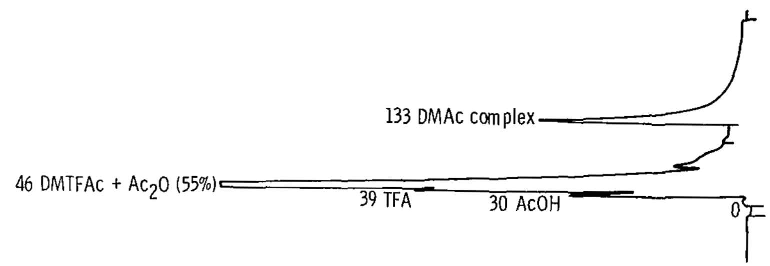
Figure 1. - Gas chromatographic analysis of

$$(CF_3\overset{O}{\overset{\|}{C}}\!\text{-})_2O + H\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2 \longrightarrow CF_3\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2 + CF_3\overset{O}{\overset{\|}{C}}OH + CO\uparrow$$

Oven temperature, 110° C; helium flow rate, 130 cubic centimeters per minute; approximate authentic retention times, in seconds: TFAA, 24; TFA, 60; DMTFAc, 78; DMF, 121.



(a) TFAA-DMAc at room temperature for 5 minutes.

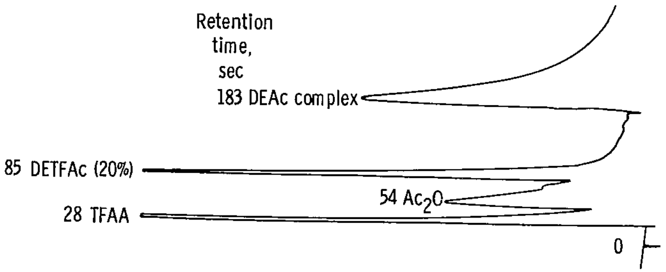


(b) TFAA-DMAc at 85° to 140° C for 15 hours.

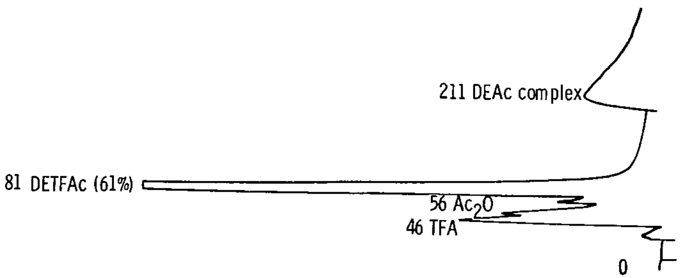
Figure 2. - Gas chromatographic analysis of

$$(CF_3\overset{O}{\overset{\|}{C}}\!\text{-})_2O + CH_3\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2 \longrightarrow CF_3\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2 + CH_3\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}CF_3.$$

Oven temperature, 120° C; helium flow rate, 240 cubic centimeters per minute; approximate authentic retention times, in seconds: TFAA, 16; ATFA, 23; AcOH, 30; TFA, 37; DMTFAc and Ac_2O, 44; DMAc, 109.



(a) TFAA-DEAc at room temperature for 5 minutes.

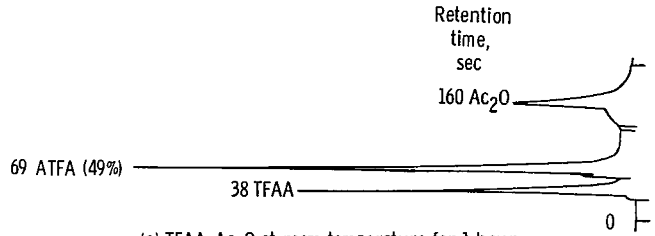


(b) TFAA-DEAc at 140° to 153° C for 17 hours.

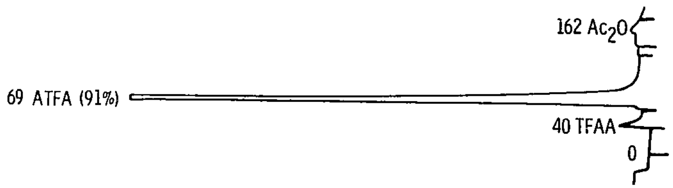
Figure 3. - Gas chromatographic analysis of

$$(CF_3\overset{O}{\overset{\|}{C}}\!-\!)_2O + CH_3\overset{O}{\overset{\|}{C}}\!-\!N(C_2H_5)_2 \longrightarrow CF_3\overset{O}{\overset{\|}{C}}\!-\!N(C_2H_5)_2 + CH_3\overset{O}{\overset{\|}{C}}\!-\!O\!-\!\overset{O}{\overset{\|}{C}}CF_3.$$

Oven temperature, 150° C; helium flow rate, 85 cubic centimeters per minute; approximate authentic retention times, in seconds: TFAA, 28; ATFA, 36; AcOH, 41; TFA, 46; Ac_2O, 54; DETFAc, 81; DEAc, 160.



(a) TFAA-Ac_2O at room temperature for 1 hour.



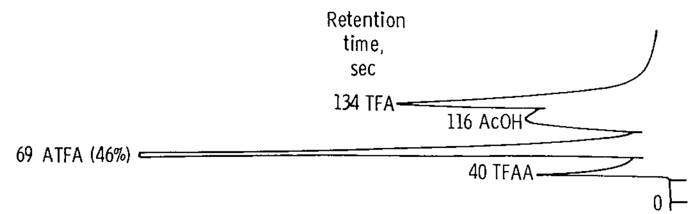
(b) TFAA-Ac_2O at room temperature for 2 hours.

(c) TFAA-Ac_2O at room temperature for 42 days.

Figure 4. - Gas chromatographic analysis of

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

Oven temperature, 90° C; helium flow rate, 70 cubic centimeters per minute; approximate authentic retention times, in seconds: TFAA, 37; Ac_2O, 159.



(a) TFAA-AcOH at room temperature for 1/2 hour.

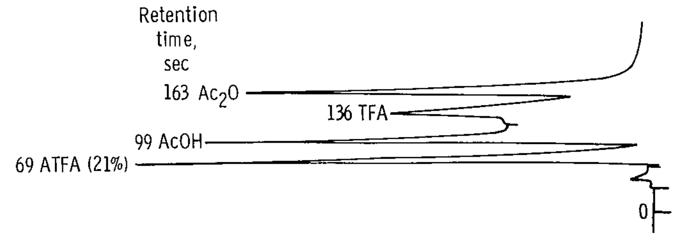
(b) TFAA-AcOH at room temperature for 4 hours.

(c) TFAA-AcOH at room temperature for 42 days.

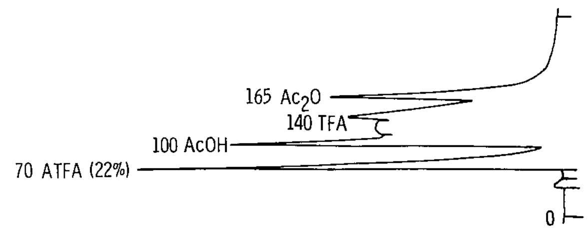
Figure 5. - Gas chromatographic analysis of

$$(CF_3\overset{O}{\overset{\|}{C}}\!\!-\!)_2O + CH_3\overset{O}{\overset{\|}{C}}OH \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}CF_3 + CF_3\overset{O}{\overset{\|}{C}}OH.$$

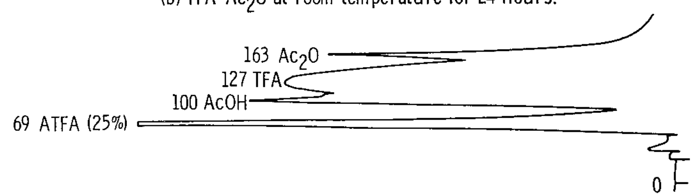
Oven temperature, 90° C; helium flow rate, 70 cubic centimeters per minute; approximate authentic retention times, in seconds: TFAA, 37; ATFA, 69; AcOH, 99; TFA, 136; Ac_2O, 159.



(a) TFA-Ac_2O at room temperature for 3 hours.



(b) TFA-Ac_2O at room temperature for 24 hours.

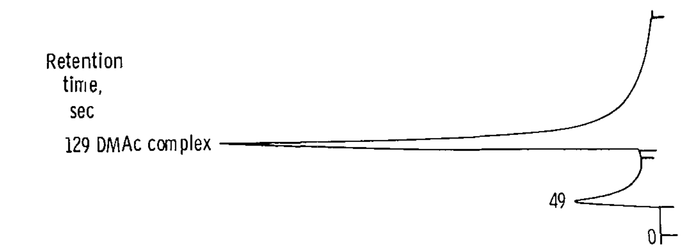


(c) TFA-Ac_2O at room temperature for 42 days.

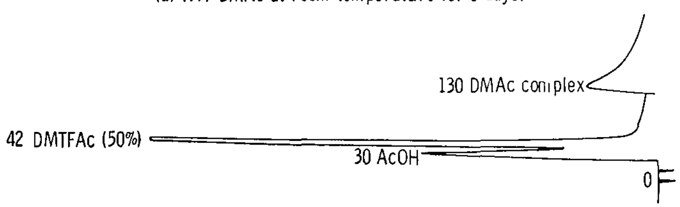
Figure 6. - Gas chromatographic analysis of

$$CF_3\overset{O}{\overset{\|}{C}}OH + (CH_3\overset{O}{\overset{\|}{C}}\!\!-\!)_2O \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}CF_3 + CH_3\overset{O}{\overset{\|}{C}}OH.$$

Oven temperature, 90° C; helium flow rate, 70 cubic centimeters per minute; approximate authentic retention times, in seconds: ATFA, 69; AcOH, 99; TFA, 136; Ac_2O, 159.



(a) TFA-DMAc at room temperature for 6 days.

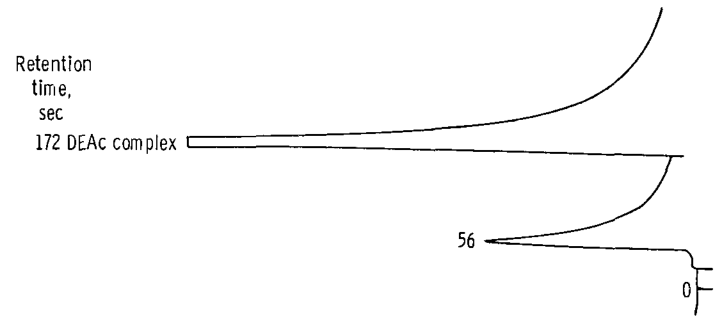


(b) TFA-DMAc at 180° to 153° C for 36 hours.

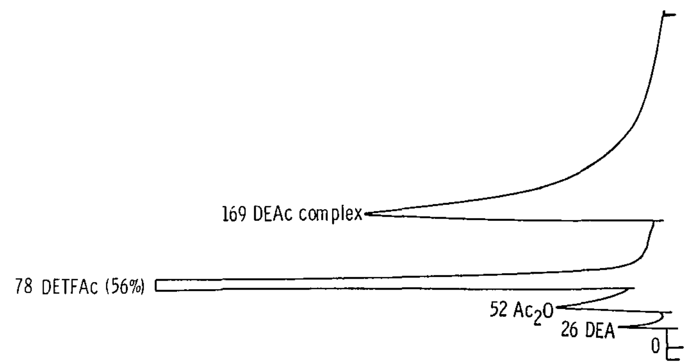
Figure 7. - Gas chromatographic analysis of

$$CF_3\overset{O}{\overset{\|}{C}}OH + CH_3\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2 \longrightarrow CF_3\overset{O}{\overset{\|}{C}}\text{-}N(CH_3)_2 + CH_3\overset{O}{\overset{\|}{C}}OH.$$

Oven temperature, 120° C; helium flow rate, 240 cubic centimeters per minute; approximate authentic retention times, in seconds: AcOH, 30; TFA, 37; DMTFAc, 44; DMAc, 109.



(a) TFA-DEAc at room temperature for 24 hours.

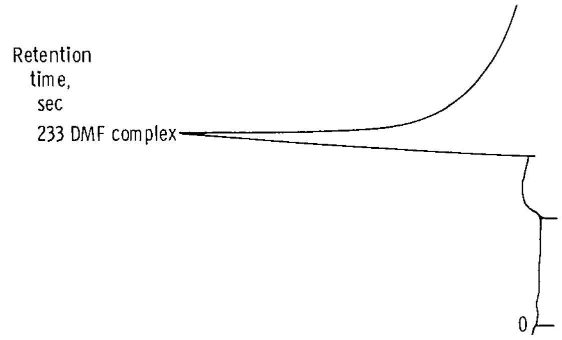


(b) TFA-DEAc at 188° to 170° C for 24 hours.

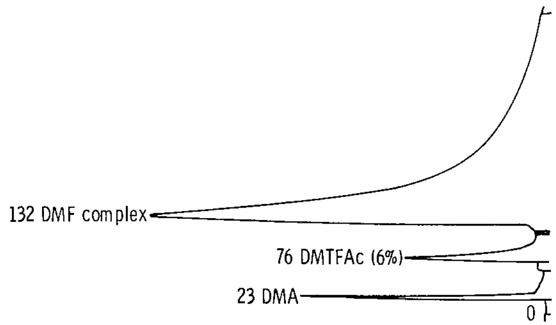
Figure 8. - Gas chromatographic analysis of

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

Oven temperature, 150° C; helium flow rate, 85 cubic centimeters per minute; approximate authentic retention times, in seconds: AcOH, 41; TFA, 46; Ac_2O, 54; DETFA, 81; DEAc, 160.



(a) TFA-DMF at room temperature for 48 hours.

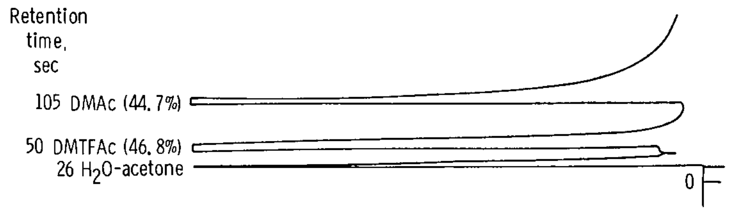


(b) TFA-DMF at 185^{0} to 110^{0} C for 72 hours.

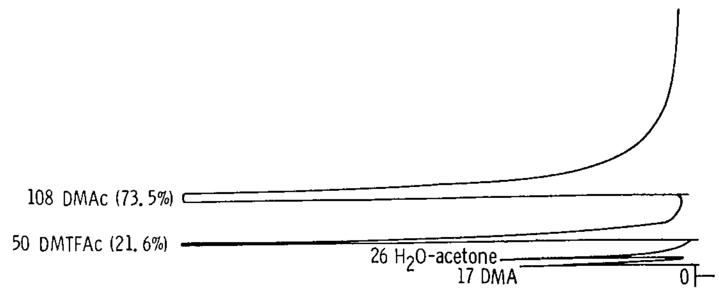
Figure 9. - Gas chromatographic analysis of

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

Oven temperature, 110^{0} C; helium flow rate, 130 cubic centimeters per minute; approximate authentic retention times, in seconds: TFA, 60; DMTFAc, 78; DMF, 121.



(a) DMAc-DMTFAc-H_2O-acetone at room temperature for 5 minutes.



(b) DMAc-DMTFAc-H_2O-acetone at 112^{0} to 140^{0} C for 22 hours.

Figure 10. - Gas chromatographic analysis of

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

Oven temperature, 120^{0} C; helium flow rate, 240 cubic centimeters per minute; approximate authentic retention times, in seconds: H_2O-acetone, 26; AcOH, 30; TFA, 37; DMTFAc, 44; DMAc, 109.

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