μL (0.03 mmol) of tetramethylpiperidine in 2 mL of ether (ice bath) was added 0.97 mL (1.55 mmol) of *n*-butyllithium in hexane. After 1 h 0.22 mL (1.7 mmol) of Me_3SiCl was added, with stirring continued for 0.5 h with the ice bath removed. Then 86 μL (0.62 mmol) of 1-bromonaphthalene was added, followed by 1.55 mmol of LTMP in 2 mL of ether. The mixture was stirred for 5 h and then worked up in the usual manner to obtain a dark oil. A portion was set aside for protiodesilylation as described below, while the major amount was chromatographed on 20 g of activity III alumina (7% ether/hexanes) to give 95 mg (75%) of product as an oil: ^1H NMR 0.56 (br s, 9 H, overlapping trimethylsilyl groups), 1.50–1.59 (3 H, overlapping triplets), 4.10–4.32 (m, 2 H), 7.25–7.80 (m), 8.0 (d, J = 8.5 Hz), 8.16 (d, J = 8.5 Hz), 8.38 (d, J = 8.5 Hz); the ratio of the three doublets in the aromatic region was 41/26/33 before chromatography and 41/26/32 after, indicating that no fractionation had taken place; MS calcd for $C_{27}H_{26}O_2Si$ 410.1702, found, 410.1747.

The portion of crude product mentioned above was taken up in 5 mL of THF and treated with 0.11 mmol of TBAF at ambient temperature (under N_2) for 10 min. After the normal isolation procedure, the crude product was examined by NMR; the spectrum contained no absorptions at 0.56 ppm (indicating complete reaction) and exhibited two singlets at 6.6 and 7.0 ppm, in a ratio of 74/26; MS calcd for $C_{24}H_{18}O_2$ 338.1307, found 338.1311. Attempted isolation/purification of these products caused decomposition, probably to quinones. The major cycloadduct **24** had NMR features identical with those of the minor product of eq 9, and its protiodesilylation product[9] was also correlated in this manner.

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Fluorination of Alkanes by Chlorine Trifluoride. Hydride Abstraction Mechanism

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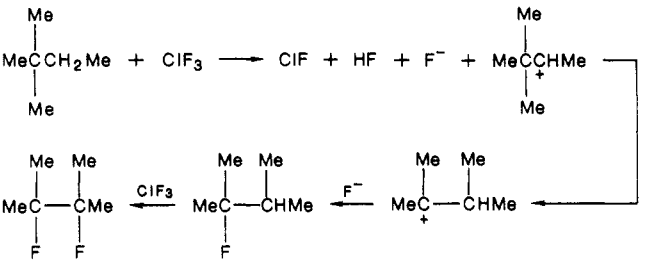
Addition of chlorine trifluoride to a solution of alkane in Freon or liquid carbon dioxide at −75 °C gives good yields of monofluoroalkane along with difluoro- and trifluoroalkanes in amounts dependent on reactant proportions. The inorganic products are HF and ClF. The reaction is highly selective for 3° over 2° positions. Methane and hexamethylethane are unreactive. Neohexane fluorinates with rearrangement, but 2-fluoro-3,3-dimethylbutane exposed to the postreaction medium does not rearrange. A hydride abstraction mechanism is inferred.

A recent paper from this laboratory describes the chemistry and thermochemistry of explosions produced by rapid mixing of liquid chlorine trifluoride with liquid hydrocarbons and halocarbons.[1] A thought-provoking aspect of these reactions is that gaseous mixtures of ClF_3 with methane or propane at room temperature with partial pressures near 1 atm each do not react over a period of hours[1,2] whereas liquid mixtures explode violently with an induction period of less than 1 ms at all temperatures down to the melting point of ClF_3, −76 °C. This behavior suggests an ionic rather than a free-radical mechanism. In an effort to learn more about the initial stages of the reaction, we added ClF_3 at −75 °C to dilute solutions of hydrocarbons in inert solvents such as 1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114) and dichlorodifluoromethane (Freon 112) in open vessels, and liquid carbon dioxide in a pressure vessel. To our surprise, we found that under certain conditions alkanes and cycloalkanes are smoothly fluorinated with excellent yield according to eq 1. The fluoroalkane products have been

$$RH + ClF_3 \rightarrow RF + HF + ClF \quad (1)$$

identified and quantified by GC/MS, and the formation of ClF was shown by trapping with cyclohexene and ethylene to give *trans*-1-chloro-2-fluorocyclohexane and 1-chloro-2-fluoroethane.

Scheme I



The products shown in eq 1 will react further if allowed to warm to room temperature, but reaction can be arrested at this stage by scavenging the ClF with ethylene or any higher olefin or a suitable reducing agent such as hydrogen sulfide. If ClF is allowed to react further, it gives products containing both chlorine and fluorine. Incorporation of chlorine also results from too-rapid addition of ClF_3. This may occur by a cage process of the type proposed by Skell and Baxter[3] for multiple substitution in free-radical chlorination. Another possibility is that it results from HF-catalyzed elimination of HF in localized regions of high temperature followed by addition of ClF.

Mechanism

With the original intention of evaluating the selectivity ratio for replacement of hydrogen on methyl and methy-

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(2) Baddiel, C. B.; Cullis, C. F. *Symp. (Int.) Combust., [Proc.], 8th* **1960**.
(3) Skell, P. S.; Baxter, H. N. III *J. Am. Chem. Soc.* **1985**, *107*, 2823.

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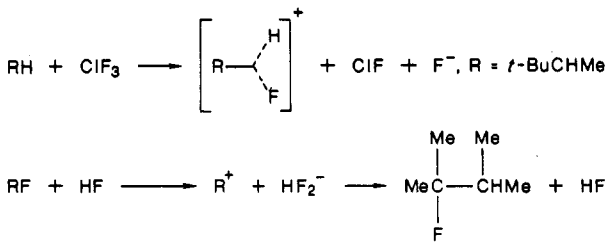
Scheme II



lene groups, we fluorinated 2,2-dimethylbutane. None of the three expected isomeric monofluorides was found. The chief product was 2,3-difluoro-2,3-dimethylbutane, which, we surmise, was formed by the route shown in Scheme I. As will be shown later, the 3°/2° selectivity ratio is large so that 2-fluoro-2,3-dimethylbutane reacts faster than neohexane. Another possibility is that 3-fluoro-2,2-dimethylbutane was formed as an intermediate and subsequently isomerized by the anhydrous HF. The primary step could be a front-sided electrophilic substitution with a transition state of the type proposed by Olah and coworkers as shown in Scheme II.[4]

Since HF plays a key role in Scheme II, we attempted to reduce its chemical activity by adding a variety of reagents to the reaction mixture. The only one that did not consume ClF_3 was finely divided amorphous silica (Cabosil), and it did not divert the reaction to form unrearranged fluoride. As a further test of Scheme II, we set out to prepare 3-fluoro-2,2-dimethylbutane and subject it to the same conditions as in the usual fluorination procedure to see whether it rearranges or survives. The substance was prepared by reaction of pinacolin alcohol with Olah's reagent,[5] which is claimed not to cause rearrangement of neopentyl alcohol. We did observe rearrangement, however, and after trying several variations obtained a mixture containing 8% 3-fluoro-2,2-dimethylbutane and 92% 2-fluoro-2,3-dimethylbutane. This mixture was added to a fluorination of heptane by the usual procedure. The molar ratio of 2° hydrogen in heptane to that in the 3-fluoro-2,2-dimethylbutane was large, so we did not expect to lose much of the latter by fluorination. It was, however, exposed to anhydrous HF in the same medium (Freon 112) at the same temperature (dry ice bath) for the same time as in the fluorination of neohexane. The ion chromatogram of the reaction mixture showed no significant reduction in the amount of 3-fluoro-2,2-dimethylbutane, and we conclude that it is not an intermediate in the formation of 2,3-difluoro-2,3-dimethylbutane. Scheme II is therefore invalidated, and the most probable mechanism is the hydride abstraction shown in Scheme I. The extreme difference in reactivity of methyl, methylene, and methine groups also points to the intermediacy of carbocations.

Selectivity

Several experiments provide information on the selectivity ratio of methylene and methine groups. All are partly clouded by the possibility of hydride shifts in the carbocation intermediates. Fluorination of methylcyclohexane gave 47% 1-fluoro-1-methylcyclohexane, 18% 1-methylcyclohexene, 4% 1-methoxy-1-methylcyclohexane (methanol was added during workup to deactivate HF), 13% other monofluorides, and 16% unreacted starting material. Assuming that the alkene and ether were derived from 1-fluoro-1-methylcyclohexane, the selectivity ratio, 3°/2°, is 50.

Isopentane was fluorinated and gave a mixture containing 2-methyl-1-butene, 2-methyl-2-butene, 2-fluoro-2-methylbutane, 3,3-difluoro-2-methylbutane, 2,3,3-trifluoro-2-methylbutane, 1,2-difluoro-2-methylbutane, and 2-methyl-2-butanol. The latter probably formed from 2-fluoro-2-methylbutane by exposure to atmospheric moisture. We were surprised to find no 3-fluoro-2-methylbutane. The ratio of the sum of products derived from reaction at the 2-position to those of the 3-position was 10, and the selectivity ratio is therefore 20.

Fluorination of adamantane gave three substances, which we have tentatively identified as 1-fluoro-, 1,3-difluoro-, and 1,3,5-trifluoroadamantane on the basis of GC/MS retention times and parent peaks, which were intense. Most alkyl fluorides give very weak parent peaks, and the strongest peak is often found at MW − 20 due to elimination of HF. Bridgehead fluorines on adamantane should be resistant to this elimination. No monofluoride other than 1-fluoroadamantane was found, and the selectivity ratio is apparently too large to be evaluated.

The 2°/1° selectivity ratio must be even larger than the 3°/2° ratio since we have not been able to achieve any controlled substitution reaction between ClF_3 and methane or hexamethylethane. The usual procedure at −75 °C gives only unreacted starting material. A reaction mixture containing hexamethylethane in a 10-mL stainless steel pressure vessel was warmed to −30 °C for 1 h, but analysis showed only starting material and no fluorinated derivatives. Mixtures of methane (1 mmol) and ClF_3 (2 mmol) in the pressure vessel with and without Freon solvent were warmed to −30 °C for several hours. A gaseous aliquot showed only unreacted methane and ClF_3 by FTIR. The presence of fluoromethane could easily have been detected but was not. Both methane and hexamethylethane are capable of explosive reactions with ClF_3 in the absence of solvent, but these are probably runaway free-radical reactions. Fluorination of propane gas by ClF_3 without solvent at −30 °C gave 42% propane, 48% 2-fluoropropane, 7% 2,2-difluoropropane, 2% 1,1-difluoropropane, and 1% 1-fluoropropane. The formation of 1,1-difluoropropane can be explained by resonance stabilization of the ion: $CH_3CH_2CH{=}F^+$. At first it was thought that direct substitution had occurred at the 1-position, but in the light of the findings above, it seems more plausible that 2-propyl cation rearranges by hydride shift and combines with F^- to give 1-fluoropropane (cf. Scheme I). The fluoropropane mixture did not change its composition after standing for 70 h at 25 °C in contact with HF, so we conclude that 1-fluoropropane does not arise by isomerization of 2-fluoropropane. At equilibrium, the propyl chlorides and bromides contain 12% and 11%, respectively, of the 1-isomers.[7]

Reaction Rate

The most slowly reacting compound in this study, apart from methane and hexamethylethane, should be cyclohexane or cyclopentane. A fluorination of cyclohexane by the usual procedure was quenched as rapidly as possible after addition of ClF_3 was completed, and analysis indicated more than 90% reaction. Assuming that the rate law is second-order, the rate constant would be not less

(4) Olah, G. A.; Halpern, Y.; Shen, J.; Mo, Y. K. *J. Am. Chem. Soc.* **1971**, *93*, 1251. Olah, G. A.; Olah, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 1256. Olah, G. A.; Lin, H. C. *J. Am. Chem. Soc.* **1971**, *93*, 1259.
(5) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872.
(6) Pryor, W. A. *Introduction to Free Radical Chemistry*; Prentice-Hall: Englewood Cliffs, 1966; p 53.
(7) Schmerling, L., U.S. Patent 3644517; Chem. Abstr. **1972**, *76*, 99083.

than 1 M^{-1} s^{-1}. Another limit can be estimated from the time to explosion of mixtures without solvent,[1] which is ca. 10^{-4} s. Assuming that the reaction goes out of control after a 30 °C rise of temperature (ca. 1% reaction) and that $M = 5$, the minimum rate constant would be 20 M^{-1} s^{-1}. Application of ARRT theory with an assumed activation entropy of −15 eu and $T = 198$ K gives a maximum activation energy of 7500 cal. In this light it seems incomprehensible that methane and hexamethylethane would fail to react in dilute solution and would only react with explosion otherwise. Numerous attempts to induce their fluorination in solution gave negative results.

Yield and Product Distribution

When 1 mol of substituting reagent is reacted with 1 mol of any alkane having two or more equivalent hydrogen atoms, it is inevitable that the product will be a mixture of molecules containing zero, one, two, or more substituents. This is a serious limitation on the synthetic utility of any such reaction, since the formation of di- and polysubstituted products can only be suppressed by using low conversions and separating monosubstituted product from a large amount of unreacted starting material.

Cyclohexane and cyclopentane were selected as substrates for a detailed study of the randomness of fluorination of equivalent positions by chlorine trifluoride because they contain only equivalent secondary hydrogen atoms. After substitution of one fluorine atom, the remaining hydrogens are distinguishable, but there is little reason to expect variation of reactivity except perhaps at the 1-position. A statistical treatment of the distribution of m atoms of fluorine among 12 indistinguishable positions in cyclohexane gives the following formula for the mole fraction, x_n of molecules, containing n atoms of fluorine:

$$x_n = \left(\frac{12 - m}{12}\right)^{12-n}\left(\frac{m}{12}\right)^{n}\left(\frac{12!}{(12 - n)!n!}\right) \qquad (2)$$

An expression for cyclopentane is obtained by replacing the number 12 by 10. Although our method of analysis separates the difluorocycloalkanes and gives their individual mass spectra, we are not able to assign structures because the differences from one isomer to another appear only in the proportions of ion fragments. We therefore sum the integrals of the difluorides for the purpose of testing eq 2. The percentage distribution for $m = 1$ (equimolar mixture of ClF_3 and cycloalkane) is shown in Table I. The theoretical percentages are enclosed in parentheses. The agreement is satisfactory in view of the expected 10% relative error in the ion chromatographic analyses. Cyclohexane also gave 5% chlorocyclohexane and a number of unidentifiable small peaks. Cyclopentane gave no other significant peaks. Since evaporation of the product at low temperature leaves no residue, the percentages may be interpreted as percentage yields.

Action of ClF_3 on Compounds Other Than Alkanes

Previous studies of reactions of ClF_3 with various organic compounds are summarized in a review.[8] The results have not seemed to be very useful. Since the temperatures were not usually very low, it seemed worthwhile to reinvestigate by using dilute solutions in Freon at −75 °C. Unfortunately, this procedure is also mainly destructive to substances other than alkanes. We find that aromatic substrates are fluorinated and chlorinated, but chlorination predominates. Tarry degradation products are obtained even from such compounds as nitrobenzene and pyridine, which are ordinarily not very sensitive to acidic oxidizing agents. Fluorination of toluene was attempted by adding ClF_3 to a cold solution of toluene and also by adding toluene to a cold solution of ClF_3. The reaction mixtures gave 2- and 4-chlorotoluene but no benzyl chloride. Nitrobenzene gave 3-chloronitrobenzene. Similar results were obtained by using liquid CO_2 at −60 °C. The evidence points to electrophilic aromatic substitution. The failure to obtain benzyl chloride indicates the absence of a chain radical mechanism. We surmise that ClF_3 is initially degraded to ClF by a reaction leading to HF and polymeric products. The ClF then chlorinates the surviving aromatic nuclei.

A solution of acetone in Freon 112 at −75 °C was reacted with ClF_3 for 10 min, and excess toluene was added. The reaction mixture contained chloroacetone, fluorotoluene, and chlorotoluene. No other derivatives of acetone could be isolated and identified. Application of the same procedure to methanol instead of acetone gave mono- and difluorotoluene, chlorofluorotoluene, chlorotoluene, and dichlorotoluene. These results show that some very reactive electrophile, probably ClF, remains after the initial reaction of acetone or methanol with ClF_3.

Comparison of Other Reagents to ClF_3

Chlorine trifluoride could be the reagent of choice for preparing some fluoroalkanes. Its extreme regioselectivity would be useful in certain cases. It is commercially available, and the reaction can be done with very simple apparatus. Other reagents that have been advocated for low-level fluorination of alkanes are dilute molecular fluorine,[9,10] trifluoromethyl hypofluorite,[10] and xenon difluoride.[11] Because of differences in reactivity, mechanism, and selectivity, one might prefer one or another of these reagents. A brief comparison is offered.

Direct fluorination by F_2 is usually assumed to be a free-radical process, but the evidence is scanty. It may be that in many cases fluorine reacts with solvent or substrate to produce an electrophile in which fluorine is bonded to an electronegative atom. Fluorination of adamantane is reported to give an 84% yield of 1-fluoroadamantane.[10] The regioselectivity in this reaction would appear to be greater than expected for a free-radical mechanism. Fluorine at −78 °C converts hexamethylethane to a mixture of polyfluorides including the perfluoro derivative.[12] This contrasts with the low reactivity of ClF_3 toward methyl groups and may indicate a difference of mechanism.

In the absence of inhibitors, trifluoromethyl hypofluorite shows little regioselectivity and is thought to react via free radicals.[10] Norbornane, for example, reacts at both secondary and tertiary positions. In the presence of inhibitors, it becomes less reactive and more regioselective, which has been ascribed to a polar mechanism similar to that of Scheme II.

Xenon difluoride is said to react only by the free-radical mechanism.[11] Adamantane is converted to 1-fluoroadamantane in 35% yield,[13] and hexamethylbenzene gives

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(9) Badachape, R. B.; Hauge, R. H.; Lagow, R. J.; Margrave, J. L. *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley-Interscience: New York, 1980; Vol. 10, p 840.

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(12) Maraschin, H. J.; Lagow, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 8601.

Table I. Reaction Mixture Composition

	$n = 0$	$n = 1$	$n = 2$	$n > 2$
$C_6H_{12-n}F_n$	28 (35)	41 (38)	18 (19)	0 (8)
$C_5H_{10-n}F_n$	41 (35)	49 (39)	10 (19)	0 (7)

pentamethylbenzyl fluoride.[14]

Experimental Section

General Fluorination Procedure. Freon 112 is passed through a glass delivery tube into a test tube immersed in a cold bath at −75 °C until ca. 10 mL has condensed. A 2-mmol portion of alkane is added, and a bent glass rod agitator is placed inside. A stainless steel reservoir of 100-mL capacity that is fitted with a stainless steel pressure transducer is charged with ClF_3 to ca. 400 torr gauge pressure at room temperature. The transfer of ClF_3 from a commercial cylinder (Air Products) is managed by stainless steel needle valves and $^1/_8$-in. stainless steel (SS) tubing. All operations involving ClF_3 are done inside a fume hood. The outlet valve of the reservoir is opened very slightly to allow the gas to flow into the air space at the top of the test tube while the contents are agitated by hand. The delivery tube should not be cooled or the ClF_3 may be condensed and delivered discontinuously. Slow delivery is essential to avoid multiple substitution and incorporation of chlorine. After 2 mmol (320 torr) of ClF_3 has been delivered in the course of 2 min, the reaction vessel and cooling bath are set aside and the stirrer is removed. The solution has a pale yellow color, which is apparently due to chlorine. Unreacted halogen, chiefly ClF, is consumed by adding 2 mmol (60 mL) of gaseous H_2S or C_2H_4 from a glass syringe fitted with $^1/_8$-in. SS tubing. A 2-mmol portion of cyclohexene in solution may be used instead. The product is usually extended by adding 0.5–1.0 mL of inert solvent (CH_2Cl_2, pentane, heptane, etc.) before allowing the Freon and HF to boil off at atmospheric pressure. The residue is decanted from sulfur whenever H_2S is used for quenching, washed with water, and dried with $MgSO_4$. Exposure of the reaction mixture to bases during workup should be avoided since many alkyl fluorides are easily dehydrofluorinated.

Fluorination in liquid CO_2 is managed by use of two 10-mL SS cylinders. One cylinder is charged with 2 mmol of ClF_3 and CO_2 gas at 60 atm, and the other is similarly charged with 2 mmol of hydrocarbon and CO_2 gas. The first is cooled with liquid N_2 to freeze CO_2 and ClF_3, and the contents of the second are mixed with it by means of a connecting tube and valve. The tube containing the reaction mixture is disconnected and warmed with constant agitation to −60 °C to induce liquefaction and reaction. After a few minutes, the CO_2 is allowed to escape at its own vaporization temperature, and HF and ClF codistill with it.

Analysis. Both qualitative and quantitative analyses were obtained by use of a Hewlett-Packard 5890 capillary GC coupled to a 5970 selective mass detector. In a few cases, the structural assignments were confirmed by a Perkin-Elmer 1750 FTIR fitted with the 1700 GC/IR accessory. Compounds boiling higher than the dichloride of the starting hydrocarbon were rarely found in significant quantity, and evaporation of the reaction mixtures left negligible residues. The mass spectra of perhaps half of the fluorinated products could be directly compared with recorded mass spectra in the EPA/NIH Mass Spectral Data Base, which is available from the National Technical Information Service. Almost all of the compounds gave parent peaks of significant intensity. In some cases, notably the difluorocyclohexanes, we were unable to assign complete structures to the several isomeric components. The only fluorinated propane whose mass spectrum was not on record was 1,1-difluoropropane, which gave mass fragments 29 (C_2H_5), 51 (CHF_2), and 80 (parent) in order of decreasing intensity. 2-Fluoro-2,3-dimethylbutane gave 43 ($C-H_3CHCH_3$), 61 (CH_3CFCH_3), 71 (parent − HF − CH_3), 89 (parent − CH_3), and 104 (parent). 2,3-Difluoro-2,3-dimethylbutane gave 61 (CH_3CFCH_3), 87 (parent − HF − CH_3), 107 (parent − CH_3), and 122 (parent). 3-Fluoro-2,2-dimethylbutane gave 57 (*t*-Bu), 41 (C_3H_5), 47 (CH_3CHF), 69 (parent − HF − CH_3), and 89 (parent − CH_3). Several isomers of difluorocyclohexane gave 59, 85, 80, 41, 46, and 72 in comparable abundances along with the weaker peaks, 120 (parent) and 100 (parent − HF). 1-Fluoroadamantane gave 154 (intense parent) and 97. 1,3-Difluoroadamantane gave 172 (intense parent) and 115. 1,3,5-Trifluoroadamantane gave 190 (intense parent), 115, and 133. Peaks obtained from 2-fluoro-2-methylbutane were 61 (CH_3CFCH_3), 75 (parent − CH_3), and 55 (parent − HF − CH_3). 3,3-Difluoro-2-methylbutane gave 65 (CH_3CF_2), 43 (CH_3CHCH_3), 93 (parent − CH_3), and 73 (parent − HF − CH_3). 1,2-Difluoro-2-methylbutane gave 79 (CH_3CFCH_2F), 59 (79 − HF), and 108 (parent).

Table II. Summary of Alkane Fluorinations (1:1 Molar Ratio)

substrate	product	% yield
methane	no reaction	
propane	propane	42
	$CH_3CH_2CH_2F$	1
	CH_3CHFCH_3	48
	$CH_3CH_2CHF_2$	7
2-methylbutane	2-methylbutane	28
	2-methyl-1-butene	8
	2-methyl-2-butene	24
	$(CH_3)_2CFCH_2CH_3$	33
	$(CH_3)_2CHCF_2CH_3$	5
	$(CH_3)_2CFCF_2CH_3$	2
2,2-dimethylbutane	2,2-dimethylbutane	5
	$(CH_3)_2CFCH(CH_3)_2$	69
	$(CH_3)_2CFCF(CH_3)_2$	26
2,3-dimethylbutane	2,3-dimethylbutane	25
	$(CH_3)_2CFCH(CH_3)_2$	55
	$(CH_3)_2CFCF(CH_3)_2$	20
2,2,3,3-tetramethylbutane	no reaction	
cyclopentane	cyclopentane	41
	C_5H_9F	49
	$C_5H_8F_2$	10
cyclohexane	cyclohexane	28
	$C_6H_{11}F$	41
	$C_6H_{11}Cl$	5
	$C_6H_{10}F_2$	18
methylcyclohexane	methylcyclohexane	16
	1-fluoro derivative	47
	1-methylcyclohexene	18
	all others	17
adamantane	adamantane	39
	1-fluoro derivative	22
	1,3-difluoro derivative	30
	all others	9

Quantitation. Many of the fluorination products would be accessible as authentic samples only with great difficulty. We therefore integrated the total ion chromatograms of known mixtures of fluorides and their parent hydrocarbons, using as many fluorides as we could readily obtain without regard to their relation to reaction products. The series included 1-fluoropentane, fluorocyclohexane, 1-fluorohexane, perfluorohexane, 1-fluorononane, fluorobenzene, and fluoroacetonitrile. Surprisingly and fortunately, the response factors of the hydrocarbons and their fluorides were nearly equal in all cases. The greatest difference was found in the case of hexane/1-fluorohexane, for which the ratio of response factors was 0.7. The response factors of hexane and perfluorohexane were nearly equal. We therefore assumed equal response factors for analysis of total ion chromatograms of reaction mixtures.

Preparation of 3-Fluoro-2,2-dimethylbutane. A solution of 1.0 g of pinacolin alcohol in 5 mL of heptane was stirred with 15 mL of Olah's pyridine/HF reagent[5] at room temperature for 4 h. Water was added, and the heptane layer was removed for further washing and then dried with $MgSO_4$. Analysis by GC/MS showed a 12:1 ratio of 2-fluoro-2,3-dimethylbutane to 3-fluoro-2,2-dimethylbutane. This mixture was subjected to the general fluorination procedure in Freon 112 without further treatment.

Summary of Fluorination Reactions. Most of the experiments were done on a small scale, using 2 mmol of substrate. In one experiment, we used 1.0 mL of cyclohexane without incident, and the product was distilled but not fractionated, owing to the requirement of a very efficient column. The product composition was similar to that of the small-scale run, and we can see no serious

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(14) Zupan, M. *Chimia* **1976**, *30*, 305.

impediment to preparatory applications of the general fluorination procedure. High-boiling residues were not encountered, and the ion chromatograms showed only negligible peaks beyond those of the highest boiling components reported. The percentage yields listed in Table II are therefore based on composition rather than quantity of analysand injected.

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Reaction of Thiamin Analogues with Sulfite Ion: An Example of Zero-Order Kinetics

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Although the cleavage of thiamin (vitamin B_1, 1) and *N*-methyl vitamin B_1 (**1a**) with sulfite ion is known to be first order in sulfite ion, two molecules of this nucleophile are involved in the complex process. By contrast, the *N*-methyl analogue **1e** having 3-cyanopyridine as a leaving group does not show any kinetic dependence on the sulfite ion concentration. A proton NMR investigation of the reaction mixture clearly shows the formation of a sulfite adduct, reducing the concentration of the quaternized leaving group dramatically. Coupling constants are observed for the first time in a sulfite adduct of a nitrogen heterocycle. The equilibrium constant was estimated from kinetic data to be 5×10^6 M^{-1}, the highest ever reported. The analogue having nicotinamide as a leaving group has an equilibrium constant of only 62 M^{-1}. A model pyrimidine having a cyano group in position 5 and a 4-nitrobenzyl group in position 1 clearly adds sulfite mainly at position 6 to form adduct **4a**, revealing the likely site of attack of this nucleophile during substitution.

Vitamin B_1 (thiamin, 1)[1,2] and 1'-methylthiaminium ion[3] **1a** and its pyridinium analogue[4] **1b** are cleaved by sulfite ion in a multistep mechanism[5] to give the sulfonic acids **1c** and **1d**, the free thiazole and pyridine, respectively (Chart I). It is well-established that *two* molecules of sulfite are involved, the first in or before the rate-determining step, the second, that in the final product, reacting after the rate-limiting step.[2,6] A probable position of catalytic attack of the first sulfite ion is C-6 in the pyrimidine part of the vitamin.[2,7] The usual kinetic data show a first-order dependence on both the substrate and sulfite ion concentrations. However, two different approaches employing either very low sulfite concentrations[8] or a common ion effect[9] established the true second-order dependence of sulfite ion.

We now show that under certain conditions the usual first-order kinetic dependence in sulfite ion can change to zero order. Moreover, with a model compound it is possible to make an authentic sulfite ion adduct and thereby provide evidence for the position of addition of sulfite ion to the pyrimidine part of the vitamin.

Results and Discussion

The rates of cleavage of substituted pyridinium analogues of *N*-methylthiamin (e.g., **1b**, **1f**) with sulfite ion have been measured.[4] Reactivity increases about 700 times when the 3,4-dimethylpyridine (pK_a = 6.5) leaving group is changed to 3-carbamoylpyridine (pK_a = 3.4). A Brønsted plot is linear with slope −0.86.[4] Therefore, it was anticipated that **1e**, with 3-cyanopyridine (pK_a = 1.4) as a leaving group, would be the most reactive pyridine-containing substrate toward sulfite ion studied to date. However, kinetic measurements of the second-order rate constant reveal (Table I) that there is no dependence of the very small pseudo-first-order rate constant on the sulfite concentration. The UV spectrum of **1e** immediately after the addition of sulfite showed a new absorption maximum at 327 nm, which disappeared slowly to give finally the spectra of 3-cyanopyridine and **1d**. An ^1H NMR experiment revealed the nature of the retardation: **1e** formed sulfite adduct **2** with the pyridine part of the molecule, changing it to a poor leaving group (Chart I). Chemical shifts are reported in Table II.

Table I. Observed First-Order Rate Constant (s^{-1}) for the Cleavage of 1e with Aqueous Sulfite Ion at 25 °C and Ionic Strength 1.0 (KCl)

pH	$10^4[SO_3^{2-}]$,[a] M	$10^4 k_{obs}$, s^{-1}
5.98	1.96	0.910
6.20	7.80	0.950
6.40	19.30	0.925

[a] Free base concentration calculated by using pK_a = 6.59.

The literature shows that there are many sulfite adducts at heterocycles bearing a quaternary center, but these have been characterized usually by UV spectra only.[10-12] Johnson and Woo Smith observed an NMR spectrum of a sulfite adduct of NAD, but they just got very broad signals.[13] Because of the lack of coupling constants, an assignment of their signals is difficult. Better comparison is possible with the data of Damji and Fyfe.[14] They published NMR data of the methoxide adduct **2b** with chemical shifts very similar to those of the sulfite adduct

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