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EFFECTS OF REACTION CONDITIONS ON RATES OF INCORPORATION OF NO-CARRIER ADDED F-18 FLUORIDE INTO SEVERAL ORGANIC COMPOUNDS

ML Korguth, TR DeGrado, JE Holden
Dept. of Medical Physics, University of Wisconsin, Madison, WI 53706
SJ Gatley[+]Franklin McLean Institute,University of Chicago, Chicago, IL 60637

SUMMARY

Apparent rate constants (fractional incorporation per minute per mole of organic reactant) were determined for reaction of no-carrier added F-18 fluoride with several aliphatic and aromatic substrates in acetonitrile or DMSO. No large differences were seen between tetraethylammonium and potassium Kryptofix-2,2,2 as supporting cation. Three hexose derivatives with triflate or cyclic sulfate leaving groups all gave apparent rate constants (obtained by dividing fractional incorporation by time in minutes and by molar concentration of reactant) near 0.4 at 23° and 5 at 55°. An aliphatic iodide reacted ten times more slowly. Aromatic substrates tested showed a wide range of rate constants from >50 at 23° (isotope exchange in 2,4-dinitrofluorobenzene) to 0.6 at 134° (p-nitroacetophenone).

Keywords: Fluorine-18, kinetics, positron tomography.

[+] Author to whom correspondence should be addressed.

INTRODUCTION

Fluorine-18 compounds have found extensive application with positron tomography studies (1,2) because of the C-F bond stability, the convenient half-life of the isotope and the biochemical properties of many carbon-fluoride compounds. In the last few years, nucleophilic substitution with no-carrier added fluoride has developed as a main avenue to ^{18}F radiotracers. A supporting salt-consisting of a large, easily dehydrated cation, such as tetraethylammonium (TEA^+) (3), and a basic, poorly nucleophilic anion, such as hydroxide (4) - which is soluble in polar aprotic solvents is necessary in order for reactions to proceed.

In published procedures for ^{18}F labeled compounds, various groups have used different solvents, reaction temperatures and cations. Furthermore, other experimental variables, such as

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traces of metal ions from accelerator targets, have been uncontrolled (5). Thus it is frequently difficult to compare the experimental results which are generally reported as radiochemical yields. The present study represents a systematic investigation of the rates of synthesis of some classes ^{18}F compounds of interest in PET studies with a highly reactive and reproducible source of ^{18}F purified via fluorotrimethylsilane (6,7). Preliminary experiments demonstrated that initial rates of incorporation of ^{18}F linearly increased with time and with concentration of organic reactants. Therefore, relative rates were calculated in the form of first-order apparent rate-constants to allow convenient comparison of different reactions (8). The nucleophilic attack of ^{18}F-fluoride on organic precursors has been measured in aprotic media at several temperatures. Both TEA^+ and K^+/Kryptofix-222 (9) have been used as the cationic species. The classes of compounds examined include sugar and fatty acid derivatives, and aromatics. Those in the latter group are of interest especially for the synthesis of neurotransmitter analogs and receptor-binding compounds. One reason for conducting these experiments was to facilitate the comparison of different drying procedures and reaction conditions, and of different preparations of ^{18}F (e.g. from the $^{18}O(p,n)^{18}F$ reaction with various target- and foil-materials). Although radiochemical yields are of ultimate practical interest, measurement of initial rates of reactions under defined conditions can indicate whether poor yields are due to an intrinsically poor starting material, or to a factor such as part of the initial ^{18}F being in an unreactive form. The effects on relative rates of water and some other compounds which inhibit incorporation of ^{18}F were also examined over a range of concentrations.

MATERIALS AND METHODS

Materials. The following compounds were synthesized according to the published procedures: 1-beta-O-methyl-2, 3-sulfato-4, 6-benzylidene-D-mannose, (Cyclic sulfate 1) (10); 1,2-5, 6-diisopropylidene-3-0-trifluoromethanesulfonyl-D-allose (Triflate 2) (11); 1, 3, 4, 6-tetra-0-acetyl-2-0-trifluoromethanesulfonyl-D-mannose (Triflate 3) (9); 16-iodo-hexadecanoic acid methyl ester (Iodide 4) (12). Methyl 16-bromohexadecanoate was prepared analogously to compound 4. Spiroperidol was obtained from Dr. O.T. DeJesus and all other compounds were purchased from the Sigma or Aldrich Chemical Companies. Acetonitrile was freshly distilled from calcium hydride.

Preparation of F-18 Reagent. Fluorine-18 was produced in a nuclear reactor from $LiOH.H_20$ (13) and purified via trimethylsilane distillation as previously described (6). Either TEA.OH or

Kryptofix-222 plus equimolar KOH were placed as aqueous solutions in the cold trap during the distillation. The same fraction of ^{18}F was trapped with either cation. The $TEA^+(^{18}F)$ and K^+/Kryptofix (^{18}F) solutions were repeatedly evaporated to dryness with acetonitrile as previously described. Carrier-added TEA^+ fluoride was prepared by carefully neutralizing the hydroxide with aqueous HF and removing water as above.

Kinetic Measurements. Reactions were carried out in conical Silli-Vials (Pierce) that were either kept at room temperature (23°) or maintained at 55° or 134° in a heating block. Vials, pipette tips, and other materials were kept dry in a dessicator over P_2O_5 before use. All test compounds, including water, used in the inhibition experiments were made up in acetonitrile. The standard reaction mixture in experiments with sugar derivatives, and dinitrobenzenes contained 25mM organic compound and 25 mM TEA.OH (^{18}F) or K^+/Kryptofix (^{18}F) in a total volume of 0.4 ml acetonitrile. The incubation time was 2 min., and the reaction was stopped with 50 µl (11% final concentration) water.

In experiments with iodide 4, the reactant concentration was 42mM and the volume was 0.6 ml. After a 7 minute incubation period, 70 µl of water (10%) was added to the acetonitrile to stop the reaction. Other compounds were reacted at 40 mM with equimolar cation and were heated in 0.5 ml DMSO at 134°. Any deviations from these standard conditions are indicated for the individual experiments. Analyses of the reaction mixtures were carried out immediately.

TLC and Assay of Radioactivity. TLC was done on strips of Polygram Sil G/UV 254 (Macherey-Nagel). Three to four µl of the reaction mixture were spotted with a 5-µl micropipette (Accupette Pipets, Dade Diagnostics Inc., Aguda, P.R.). During preliminary time-course experiments, in which water had not been added to the acetonitrile to stop the reaction, it was found that a significant amount of unreacted ^{18}F remained absorbed on the walls of the micropipette (5). This artifact was eliminated if the micropipettes were prewashed with water (three rinses), or if 10% water was present at the time of sampling. Thus the prewashing step was adopted as standard procedure for time course experiments and the water addition was retained for all others. The strips were run in one or two of the following solvents: A) 25% methanol - 75% dichloromethane, B) 15% methanol - 85% dichloromethane, C) 1% methanol - 99% dichloromethane, D) 30% ether - 70% hexane, E) 100% dichloromethane. The radioactive spots were localized by autoradiography on XRP-1 (Kodak) film. The unreacted fluoride remained at the origin in all systems while the ^{18}F-labeled organic compound migrated away from the origin. The radioactive portions of the TLC strips were cut out, placed in glass tubes and counted in a Searle Gamma Counter.

Calculations. The data were calculated as the fraction of ^{18}F incorporated in each organic compound. In order to compare the different experiments in which the effect of inhibitors was examined, the results were normalized as follows. The amount of ^{18}F incorporated in the absence of an inhibitor was set at 100. The amount of incorporation obtained in the presence of an inhibitor was expressed as a percent of this value. Apparent rate constants were calculated according to the following expression: $k = X/M.t$, where X is the fractional incorporation of ^{18}F, M is the molarity of the reactant, and t is the time in minutes.

Isotope exchange in nitrofluorobenzenes. Exchange was initiated by addition of 10mM fluoro-compound to a solution of 10mM carrier-added ^{18}F-TEA^+ fluoride in acetonitrile at room temperature. After 1 minute 50µl samples were taken. The vial was then sealed and warmed to 120°, and a further sample taken after 5 minutes. All samples were immediately added to test-tubes containing 5ml water plus 5ml ether. The tubes were vortexed, the phases separated and radioactivity in the ether layer assayed. The ^{18}F used in this experiment was not purified via fluorotrimethylsilane.

RESULTS

Rate Constants. Relative rates for the reaction of the three hexose derivatives (1, 2 and 3) with ^{18}F were measured at 23° and 55° (Table I). Very similar rates were found for these compounds at both temperatures. The k values, expressed as the fractional incorporation per M per min., were 0.2-0.6 at 23° and 3.9-8.3 at 55° with TEA^+. Thus the rate at 55° was approximately 10-fold higher than that at 23°. The values obtained with K^+/Kryptofix were 2.6-5.8 at 55°. Considering the variation among different batches of ^{18}F, they were not significantly different from those obtained with TEA^+. In another series of experiments (not shown in Table 1) using 20mM carrier added TEA^+ fluoride, apparent rate-constants of 2.45 ± 1.50 (5) and 2.90 ± 1.85 (7) $min^{-1}M^{-1}$ were measured for 1 and 2 respectively at 23°. (Number of batches of ^{18}F shown in parenthesis.)

The omega-halogenated fatty acid methyl ester, (4) reacted with ^{18}F at 55° at least 10 times more slowly than the sugar compounds. The mean value was 0.3 with TEA^+ and 0.1 with K^+/Kryptofix. Since the SD was 0.1 in both cases, the k values were not significantly different. In one experiment the reactions of 4 and its bromo analog were measured with the same batch of TEA.OH(^{18}F). The apparent rate constants obtained were 0.5 and 0.3, respectively, indicating that, as expected, the iodo-compound reacts faster than the bromo-compound.

TABLE I

APPARENT RATE CONSTANTS FOR NO-CARRIER-ADDED ^{18}F REACTIONS*

CATION	TEA^+		K^+/ Kryptofix	
Temp.	23°	55°	23°	55°
Cyclic Sulfate 1	0.4 ± 0.2 (3)	8.1 ± 3.3 (4)	---	2.6 ± 1.6 (3)
Triflate 2	0.6 ± 0.3 (2)	3.9 ± 2.1 (2)	---	2.7 ± 1.2 (4)
Triflate 3	0.2	8.3 ± 4.0 (3)	---	5.8 ± 1.9 (2)
Iodide 4	---	0.3 ± 0.1 (6)	---	0.1 ± 0.09(4)
Fluorodinitrobenzene	>60	---	>50	---
Chlorodinitrobenzene	0.9 ± 0.5 (4)	>10	0.4 ± 0.2 (3)	5.0 ± 3.5 (3)

	134°	134°
p-NO_2-Benzonitrile	1.2 ± 0.3 (4)	1.8 ± 0.7 (5)
p-NO_2-Acetophenone	0.4	0.8
p-NO_2-Piperonal	0.2	0.4
p-NO_2-Benzofluoride**	8.0 ± 2.7 (2)	5.3 ± 0.01 (2)

* Values are expressed as the fraction of ^{18}F incorporated per M organic compound per min; mean ± standard deviation with the number of experiments in parentheses.

** Based on 2 and 3 min. time points. Initial rates may be higher.

Of the aromatic compounds tested, 2,4-dinitrofluorobenzene was the most reactive. F-exchange occured rapidly at 23°, and the apparent rate constants with either cation were estimated to be >50 on the basis of fractional incorporation after one minute. The C1-^{18}F exchange with chlorodinitrobenzene proceeded less readily; the k value was <1 at 23°, and 5-10 at 55°, similarly to 1, 2 and 3. There was no difference between TEA^+ and K^+/Kryptofix supported reactions. The mononitrobenzene substitutions reactions were slower. There was no measurable ^{18}F

incorporation at 55°, therefore the reactions were carred out in DMSO at 134°. Three compounds, p-nitro cyanobenzene, p-nitro acetophenone, and 6-nitro piperonal, in which ^{18}F displaces the nitro-leaving group, were investigated. The cyano-compound was the most reactive of the three above compounds, but less reactive than p-nitro-fluorobenzene, which undergoes a fluoride exchange. In the latter case the extent of reaction reached a maximum within the first few minutes and declined thereafter.

Inhibition by Water. The effect of water was studied on the reaction of TEA.OH (^{18}F) with cyclic sulfate 1, iodide 4 and chlorodinitrobenzene. The amount of water was varied while the concentration of the organic reactant and TEA.OH remained constant. The actual percent of ^{18}F incorporation without water was as follows: cyclic sulfate, 35%; ClDNB, 4%; iodide 4, 5-12%. In order to compare the data for all compounds, the percent of incorporation was normalized as described in Materials and Methods and plotted against the molar ratio of water to organic compound. The effect of water is very similar in all three cases (Fig. 1). No inhibition was apparent until the amount of water reaches one half the concentration of the organic compound and TEA^+. Half maximum inhibition was achieved at a molar ratio of 2.

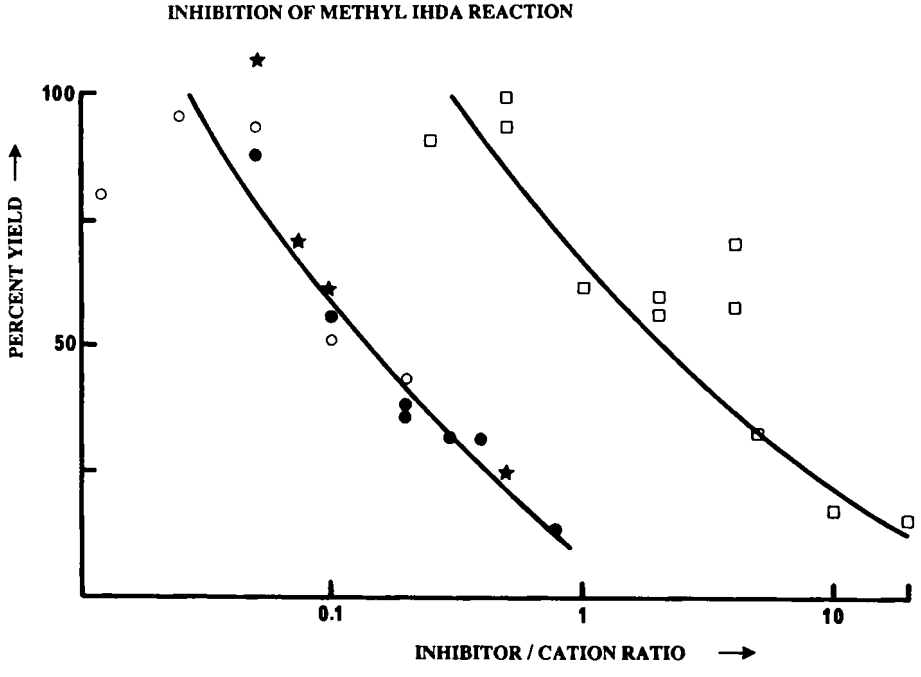

Fig. 1. Inhibition of incorporation of F-18 into methyl 16-fluoro-hexadecanoate. Closed circles, cyclic sulfate; open circles, spiroperidol; stars, chloro-dinitrobenzene; squares, water.

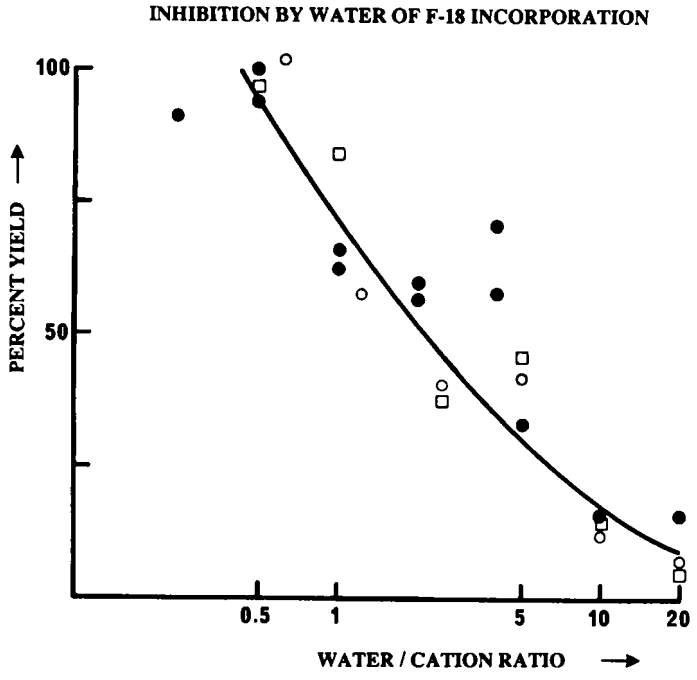

Fig. 2. Inhibition of F-18 incorporation by water. Closed circles, methyl 16-iodohexadecanoate; open circles, cyclic sulfate; squares, chlorodinitro benzene.

Inhibitors of the Reaction of F-18 with cyclic sulfate 1 and with iodide 4. The reaction of 42 mM iodide 4 with 42 mM TEA.OH(^{18}F) was examined in the presence of increasing concentrations of three other compounds that might compete for ^{18}F, cyclic sulfate 1, spiroperidol and chlorodinitrobenzene (Fig. 2). Spiroperidol is a dopamine agonist and is of interest in PET studies of brain. It proved to be a potent inhibitor even though a ^{18}F-spiroperidol product was not visualized on autoradiographs of TLC's. The inhibition curves were the same in all three cases: half maximal inhibition was achieved at 4.2 mM concentration which is 0.1 of that of iodide 4 and TEA.OH. Water required still higher levels (50 mM; see Fig. 1) and is included for comparison. Similar experiments with 25 mM cyclic sulfate 1, 25 mM TEA.OH and varying amounts of spiroperidol and chlorodinitrobenzene were reported previously (8). One half maximal inhibition occured when the spiroperidol concentration was 2.5 mM or one-tenth the concentration of the reactants. Chlorodinitrobenzene was less active as an inhibitor, because the same effect was achieved at 10mM or 0.4 the concentration of cyclic sulfate and TEA^+.

The Effect of Varying Amounts of TEA.OH. The effect of different concentrations of TEA.OH was studied on the reaction of no-carrier-added ^{18}F with compounds 1 and 4. The higher

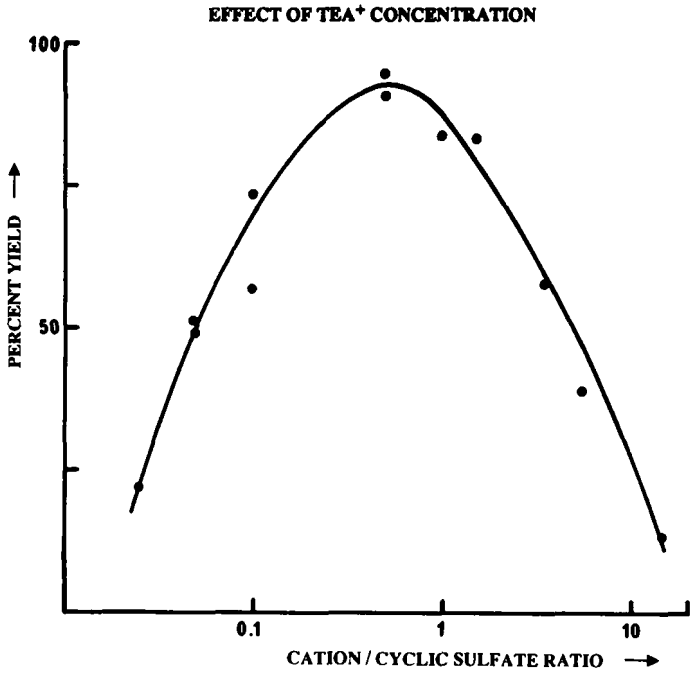

Fig. 3. Effect of concentration of tetraethylammonium on the rate of reaction of cyclic sulfate with F-18. Normalized initial rates are plotted against log ratio cation/cyclic sulfate.

concentrations of TEA^+ required for some experiments were achieved by adding unlabelled TEA.OH. The aqueous solution of the base was evaporated to dryness under vacuum, acetonitrile was added three times and dried down each time. Labelled and unlabelled TEA.OH were pipetted into the reaction vessel before the organic compound was added. The data were normalized by setting at 100 the amount of ^{18}F incorporation obtained at equimolar amounts of total TEA.OH and organic reactant.

The highest incorporation of ^{18}F occurred when the TEA.OH concentration was equal to or somewhat lower than that of the organic compound (e.g. Fig. 3). When the molar ratio of TEA^+ fell below 0.1 or exceeded 2.0, a significant reduction of ^{18}F incorporation occurred.

Isotope exchange in nitrofluorobenzenes. In this semi-quantitative experiment equimolar fluoride and fluorobenzenes were incubated together. Maximum extent of isotope incorporation is thus 50%. The 23^o time points indicate the large increase in reacitivity caused by two activating nitro groups. The 120^o data illustrate the expected difference in yield between meta and ortho or para substitution. Solutions of TEA^+ fluoride plus the 2-nitro, 4-nitro or 2,4-dinitro compounds were intensely colored. The 2,4-dinitrofluorobenzene equilibrated within one minute at room

temperature, but yields decreased with time at elevated temperatures, evidently because of decomposition of the organic compound. HPLC analyses (C_{18} column with 50% aqueous acetonitrile) revealed no labeled peaks other than fluoride and the added fluoronitro compounds (data not shown).

DISCUSSION

Relative rates of substitution reactions

The utilization of ^{18}F fluorotrimethylsilane as an intermediate in the preparation of nucleophilic ^{18}F fluorinating agents has enhanced the reproducibility of reaction kinetics. Although there remains some variability in reactivity from batch to batch of ^{18}F as seen by the standard deviations in Table 1, the data are consistent enough to allow some general statements.

No essential differences were seen between TEA^+ and K^+/Kryptofix as supporting cations. Although the aminopolyether gave slightly lower rates for aliphatic substitution reactions, and higher rates with the aromatic substrates, these differences were not statistically significant.

Three rather reactive hexose derivatives, one cyclic sulphate and two triflates, gave initial rates which were identical within experimental error. This confirms our earlier report that compounds 1 and 2 showed identical time-courses with the same batch of TEA.F (7).

The aliphatic substitution in iodide 4 was an order of magnitude slower than for the hexose derivatives. Again, there was no significant difference between K^+/Kryptofix and TEA^+ supported ^{18}F. Near quantitative yields of the fatty acid derivatives can be obtained with either K^+/Kryptofix or TEA^+ with suitable temperatures and reaction times (12, 14). Two recent notes (15,16) have described the use of KF or CsF dried onto a CaF_2 support as a source of fluoride for nucleophilic substitution reactions. The time-course for substitution in benzyl bromide with this material (16) in acetonitrile at 80°, suggests similar reactivity to that seen with TEA^+ fluoride.

A wider range of substrate reactivities for attack at carbon were found in our survey of aromatic compounds. All the compounds studied react by the addition-elimination mechanism, and their relative rates are easily interpreted by the ease of stabilization of the anionic intermediates by electron-withdrawing groups. The nitro group behaves both as an excellent leaving group for fluoride and as an activating group when in the ortho- or para- position. The presence of two activating nitro groups in 2,4-dinitrofluorobenzene gives a very great rate enhancement over the situation with 4-nitrofluorobenzene; isotope exchange with the dinitro compound is too fast to measure accurately at room temperature. Assuming that $Q_{10} = 2$ the enhancement is at least

10,000-fold. Reactivities of all compounds tested thus varied over about six orders of magnitude. Both fluoride-for-fluoride and fluoride-for-chloride exchanges were favored over fluoride-for-nitro exchange, when both nitro and halogen were present in the same molecule. The hetero-halide exchange, however, is much slower than isotope exchange; chlorodinitrobenzene reacts about as rapidly as the aliphatic triflates and cyclic sulfate.

Synthesis of ^{18}F p-fluorophenylcyanide in 50-70% yield from the nitrocompound has been reported (17, 18); it was used as an intermediate in the preparation of several butyrophenone neuroleptics (19). Incorporation was considerably slower with 4-nitroacetophenone, and slower still with the more complex substrate 6-nitropiperonal.

Cacace et al. (20) have published kinetic data for isotope exchange of ^{18}F with hexafluorobenzene and several other aromatic compounds, including p-nitrofluorobenzene. They used carrier-added KF (1.3mM) in DMSO at 40-70° with water (about 5mM) added to give more reproducible reaction rates. Extrapolation of their calculated Arrhenius parameters for p-nitrofluorobenzene to 134° yields a k-value of 58, compared with our values of 5-8 (Table 1) for no-carrier added ^{18}F. Rate-constants for aromatic substrates may be decreased under our conditions by fluoride acting as a leaving group for attack by hydroxide, or by the resulting phenolates.

Mechanistic implications

It is well-known that water decreases the reactivity of fluoride, and that aqueous fluoride is an extremely poor nucleophile at carbon. It is also known that TEA^+ fluoride or hydroxide cannot be dried below the level of one or two water molecules per F or OH (21). In the solid salts the residual water is organized by strong hydrogen bonding into negatively charged clusters containing two anions (22,3). The state of no carrier added ^{18}F in a polar aprotic solvent with hydroxide as bulk anion is unknown but in view of the extremely low concentration of fluoride it seems unlikely that clusters containing two or more F atoms would be present. However, the rather similar rates of reaction of compound I and II in the presence and absence of carrier fluoride suggests that the states may be similar. The nearly identical k-values for compounds 1, 2 and 3 suggest that these aliphatic substrates must share a common slow step at or before nucleophilic attack. One possibility, that we have advanced before, is that bulk ^{18}F is in equilibrium with a more reactive species, such that overall reaction is limited by disequilibrium to the reactive form. The much faster rates of isotope exchange with fluorodinitrobenzene, and of substitution of chloride in chlorotrimethylsilane (7), would require direct reaction with bulk ^{18}F. An alternative hypothesis,

of reaction limited by dissolution from ^{18}F absorbed on vessel walls or incorporated into microaggregates, would not easily account for the fluorodinitrobenzene and chlorotrimethylsilane data.

Compounds 1 and 4 and chlorodinitrobenzene exhibited very similar inhibition curves for water (Fig. 1). This suggests that ^{18}F species in the same hydration state are involved in substitution reactions with the three molecules.

Hajami et al (24) suggest from kinetic and spectroscopic studies with substituted benzyl halides that formation of hydrogen-bonded/electrostatic complexes can precede substitution by halide ions. Effects increased in the order I^-, Br^-, Cl^-. Their reaction mixtures were similar to ours, containing TEA^+ salts in polar aprotic solvents. Detailed kinetic studies with TEA^+ fluoride were precluded by rapidity of the reactions (25). The profound inhibition of iodide displacement (Fig.2) before ^{18}F has been incorporated into competing substrates, could thus be interpreted as more rapid formation of a pre-reaction complex with the cyclic sulfate or chlorodinitrobenzene.

Tetraethylammonium in high concentrations was somewhat less inhibitory than water, although one mole of TEA^+ contains about two moles of water. No carrier added ^{18}F fluoride ions (<1nmol in our experiments) would have a large hydration sphere in the absence of other species able to tie up water if even a trace of adventitious water were present. Hydroxide may be able to dehydrate fluoride. Gas phase studies of addition of successive water molecules to fluoride (26) show that the two anions have similar hydration energies for each value of n with that of fluoride being stronger for n=1(about 450 kcal/mol), but that of hydroxide being stronger for n>2. Further, hydroxide but not fluoride can desolvate other anions under phase-transfer catalysis conditions, confirming that hydroxide has the larger overall hydration energy (27). Thus the optimum TEA^+ concentration may represent a compromise between hydroxide pulling water off fluoride, on the one hand, and unavoidable addition of water, on the other. The supporting salt may also function in part by competitively inhibiting interactions of fluoride with vessel walls.

Unlike TEA^+ fluoride, K^+/Kryptofix fluoride should be able to be rendered totally anhydrous since base catalysed decomposition cannot occur. However, the very similar initial reaction rates obtained by us suggest that the ^{18}F is in the same state with both cations. This could be because our drying conditions (0.1-1mm Hg; 70°; 10 minutes) are insufficiently rigorous either to remove all the water from the K^+/Kryptofix reagent, or to break down the onium salt. Sharma and Fry reported about 50% decomposition of TEA^+ fluoride in 3 hours at 77° (20). As a result of this, fluoride is converted to the bifluoride ion. In our no-carrier added ^{18}F preparation, however,

TABLE 2

FRACTIONAL INCORPORATION OF LABEL FROM CARRIER-ADDED TEA$^+$ FLUORIDE INTO NITRO-SUBSTITUTED FLUOROBENZENES

	23°	120°
Position of Nitro-Substituent	1 min.	5 min.
none	.004	.066
o-	.012	.48
m-	.015	.033
p-	.011	.48
o-, p- di-	.43	.32
*o-, p- di-	.67	.44

* A 2-fold excess of 2,4-dinitro-fluorobenzene was used in this experiment.

HF formed by beta-elimination should react with hydroxide, to regenerate fluoride, both because hydroxide is a stronger base than fluoride, and because the concentration of fluoride is very much lower.

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