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Chemistry of Fluorine-18 Radiopharmaceuticals

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Introduction

The chemistry of ^{18}F has the reputation of being difficult and this is to a large extent supported by a survey of the literature, where there are many reports of reactions involving ^{18}F where the yields are low and the reactions erratic. However, in the nine years since the last review of the chemistry of ^{18}F in this journal[1] considerable progress has been made in understanding and controlling these difficulties. It would be an exaggeration to claim that all the problems are solved but there are now a number of ^{18}F containing radiopharmaceuticals produced on a daily basis in a reproducible fashion at different centres around the world.

The chemistry of ^{18}F can conveniently be divided into electrophilic and nucleophilic reactions with minor contributions from hot atom reactions. There are no clearly demonstrated examples of fluorine radicals being involved in ^{18}F radiopharmacetical chemistry.

The reactions can be further divided on the basis of specific activity into carrier added and no carrier added reactions. The specific activity of useful ^{18}F radiopharmaceuticals is always high, in the mCi's per micromole range, but there are occasions when it must be much higher. When the product is toxic or when the biological process being examined is easily saturated, such as with receptor binding ligands and some enzyme inhibitors the specific activity must be in the Ci per micromole range. There has been considerable progress in raising the specific activity of ^{18}F compounds and in understanding the sources of ^{19}F which contaminate ^{18}F preparations and cause the compounds to be no carrier added and not carrier free.[2,3]

The methods used for producing ^{18}F are reviewed elsewhere in this issue and will not be discussed in any detail here. However, in many cases the reactions used to synthesize a particular product will be dictated by the methods used to make the ^{18}F and in these cases the methods will be briefly discussed.

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Hot Atom and "In Target" Reactions

Reactions involving fluorine radicals or hot atoms are normally only successful on simple compounds. In compounds containing carbon–hydrogen bonds the hydrogen abstraction reaction to form HF is normally favored over the formation of carbon–fluorine bonds and even when C–F bonds are formed the selectivity is low.[4] However, there is a report of the successful synthesis of monofluoroacetic acid by the use of $^{19}F(\gamma, n)^{18}F$ on mixtures of acetic acid and potassium fluoride.[5]

There has been a number of publications involving both thermal and nonthermal ^{18}F atoms produced by the $^{19}F(n, 2n)^{18}F$ reaction. These are devoted to exploring the mechanisms of the reactions and are not intended or suitable for preparative purposes. These papers have been recently reviewed.[4,6]

Some successful reactions have been performed in target, where reagents are added to the target gas and the target is conditioned, normally by the formation of an adhesive layer of metal fluoride on the target walls. Thus, bombardment of neon containing small quantities of fluorochlorocarbons has given reasonable yields of products containing one more fluorine than the starting material, i.e. an F and Cl exchange reaction.[7,8] The reaction also worked with CF_4 and SF_4; that is, an F for F exchange. Bombardment of neon containing F_2, hydrogen, nitric oxide or Cl_2 gave $[^{18}F]F_2$, $[^{18}F]HF$, $[^{18}F]NOF$ and $[^{18}F]ClF$ respectively.[9] Interestingly, bombardment of neon containing COF_2 and F_2 in an attempted in target synthesis of $[^{18}F]CF_3OF$ gave $[^{18}F]CF_4$ as the only volatile product. However, bombardment of a neon target containing anhydrous CsF which was then treated with COF_2 and F_2 gave $[^{18}F]CF_3OF$ in respectable yields.[10] Nickel fluoride failed to catalyze this reaction.

Reagents

A number of fluorinating agents have been prepared directly from the target product. Thus ^{18}F diethylaminosulfur trifluoride (DAST) has been pre-

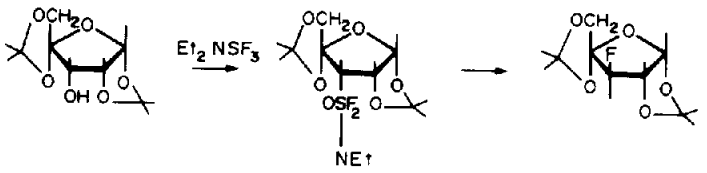

Fig. 1

pared by direct exchange with the product from a recirculating neon/hydrogen target and the labeled DAST then used to prepare methyl fluoride, ethyl fluoride and fluoroethanol from the appropriate alcohols.[11] Although the chemical yields of these reactions are good, only one third of the available ^{18}F is incorporated into the final product and so the radiochemical yield is not that encouraging. With 1,2,5,6-di-O-isopropylidene allofuranose and DAST an intermediate is formed at room temperature and this reacts with fluoride at higher temperatures to give the protected 3-deoxy-3-fluoroglucose derivative as shown in Fig. 1. Addition of [^{18}F]fluoride salts to the preformed intermediate gave the ^{18}F derivative in higher yields than those obtained by forming the labeled DAST before the reaction.[12]

Xenon difluoride has been prepared containing ^{18}F by fluoride exchange between XeF_2 and [^{18}F]fluoride[13] and by reaction of [^{18}F]F_2 with xenon.[14]

Fluorine-18 perchlorylfluoride has been prepared from potassium chlorate and [^{18}F]F_2 and used successfully for the preparation of fluoroaromatics by reaction with lithiated precursors.[15] The yields of the fluoro-aromatics varied between 3 and 30% of the ^{18}F produced.

Acetyl hypofluorite, a useful electrophillic fluorinating agent has been prepared by the reaction of [^{18}F]F_2 with acetate salts, either in solution[16] or by the reaction of the gas with solid salts.[17] The reaction is clean and yield is generally close to the theoretical.

All of the above reagents are carrier added, in that reagents containing stable fluorine had to be added in order to extract the ^{18}F from the target or to make the reaction go. They are also relatively inefficient in that the reagents carry more than one fluorine atom but only one fluorine atom ends up in the product. Thus a proportion of the ^{18}F is not available for incorporation in the final product.

There are two very recent reports on the preparation of simple no carrier added fluorinated compounds that are suitable for addition to more complex molecules to make ^{18}F labelled radiopharmaceuticals. These are bromofluoromethane[18] prepared by nucleophillic displacement with [^{18}F]potassium fluoride/Kryptofix complex on dibromomethane and [^{18}F]1-bromo-2-fluoralkanes[19] prepared by the reaction of N-bromosuccinimide and a [^{18}F]fluoride salt in the presence of the appropriate alkene as shown in Fig. 2.

Both reactions are performed with no carrier added fluoride salts and so the specific activities are high. The reactions are simple, clean and give high yields based upon ^{18}F. The details are sparse as yet but both reactions appear very promising.

Electrophillic Reactions

There is an ongoing discussion as to whether any reactions involving fluorine can be described as electrophillic.[20,21] There is agreement that the species $F^{\oplus}$ can never exist in solution but the degree of polarization involved in fluorinating agents as to whether the fluorine atom carries a partial positive charge is not resolved. However, the reactions give products which are most easily described as being due to electrophillic fluorine and we will describe it as such.

Fluorine gas is the original electrophillic fluorinating agent and is the progenitor of the other available reagents. Fluorine has the justified reputation as a violently reactive gas that is indiscriminantly reactive with organic molecules leading to mixtures of products. However, the use of fluorine diluted with an inert gas gives a more controllable reagent that can react selectively with organic compounds. Typical bombardments for producing [^{18}F]fluorine gas result in F_2 at concentrations of 0.1–2% in neon. Under these conditions F_2 is a relatively controllable reagent. It should be noted that there are some discrepancies in the literature on the yields and selectivities of [^{18}F]fluorine. Different accelerator characteristics dictate the variations in concentrations of the fluorine in the target gas from 0.1 to 2% and one possible explanation for the discrepancies is the different fluorine concentrations used.

Fluorine-18 fluorine has been successfully added across double bonds. Reaction with triacetoxy glucal gave 2-deoxy-2-fluoroglucose[22] and uracil and uridine[23-25] gave the 5-fluoro uracil and uridine. Antipyrine[26] gave 4-fluoroantipyrine in a similar reaction. The reaction typically gives *cis*-addition across the double bond but is not particularly selective as to which face of the molecule it adds across.

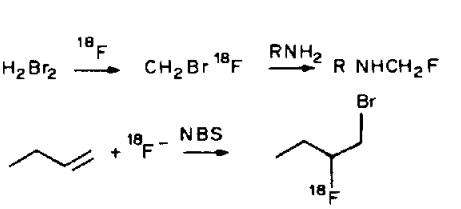

Fig. 2

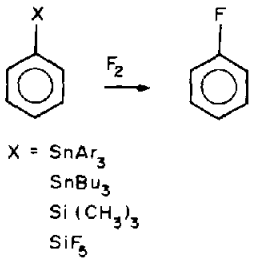

Fig. 3

Thus with triacetoxy glucal both gluco- and manno-2-deoxy-2-fluoropyranosyl fluorides are produced by addition from both the α and β faces of the molecule.[27]

The reaction is successful, in that it gives mainly or only products that are the result of simple addition across the double bond, in cases where one end of the double bond is substituted with electron donating groups that can stabilize the intermediate cation produced. In the absence of such stabilization more complex product mixtures can be expected.[28]

Fluorine has also been used for the preparation of aryl fluorides. Reaction of L-dopa with $[^{18}F]F_2$ in anhydrous HF at $-78°C$ gives a mixture of 2, 3 and 6 fluoro-dopa.[29] The overall fluorination yield is quite respectable ($\sim 25\%$) but the separation of the isomers is difficult and time consuming. The final yield of the required 6-fluoro-dopa is on the order of $2 \sim 3\%$ of the available ^{18}F.

Fluorine has also been used with aryl organometalic compounds with some success. Tetraphenyl tin and phenyl tri-n-butyl tin both react with fluorine to give fluorobenzene in 4–15% yield.[30,31] Substituted aryl fluorides have also been prepared from the appropriate aryl tri-n-butyl tin compounds.[32,33] Very high yields are reported for these reactions.

In a similar fashion aryl–silicon bonds have been cleaved with fluorine to give aryl fluorides. Substrates for the reaction are either aryl pentafluorosilicate salts[34] or aryl trimethylsilanes.[35] Reported yields are of the order of 20% of the total ^{18}F available. A synthesis of $[^{18}F]$6-fluoro-L-dopa by reaction of a protected trimethyl silane with F_2 has been reported, which appears to offer some advantages over the direct reaction with F_2.[36]

Acetyl hypofluorite was introduced as a less vigorous electrophillic alternative to F_2.[16] The initial application was to the preparation of 2-deoxy-2-fluoro-glucose via addition to triacetyl-glucal. The reagent adds the elements of CH_3CO_2F across the double bond. In the initial report the reagent was reported to be more stereoselective than fluorine, adding exclusively to the α-face of the molecule. However, further work showed that the reagent could best be described as having different stereoselectivity from fluorine[37] and that the selectivity of both reagents is a function of the solvent used[38,39] and the substrate.[40–42] Acetyl hypofluorite has been used for direct fluorination of aromatic systems in the synthesis of $[^{18}F]$fluoroantipyrine[44] 6-fluoro-dopa[45] and dimethoxy N,N-dimethyl amphetamine derivatives.[46] Both yields and selectivities appear to be higher than with fluorine in these reactions, but not dramatically so.

Acetyl hypofluorite has also been reacted with aryl mercurials[47] trimethyl silanes and pentafluorosilicates[48,49] to give the required aryl fluorides. Again, the reagent appears to offer some advantages over fluorine in these reactions but the improvements are not dramatic. A vinyl tri-n-butyl tin derivative has also been fluorinated with $[^{18}F]$acetyl hypofluorinate to give the vinyl fluoride in modest yield.[50] Fluorine-18 perfluoroacetyl hypofluorite has also been prepared[51] but it is not clear whether there are any advantages with this reagent over acetylhypofluorite.

N-fluoro alkyl sulphonamides have been prepared by the reaction of the alkyl sulphonamide with fluorine. The N-fluorosulphonamides will then react with aryl lithiums and aryl Grignards to give the appropriate aryl fluorides.[52,53]

Nucleophilic Fluorination Methods

Introduction

As a general synthetic approach, nucleophilic fluorination differs from electrophilic fluorination not only in the obvious mechanistic sense, but also in its range of diversity. While many electrophilic reagents have been developed and used with varying success on a variety of substrate classes, there is only one nucleophilic fluorinating reagent: fluoride ion. The diversity of the applications of this reaction arises from the wide range of leaving groups, substrates, and reaction conditions which can be used. Much of the work which will be discussed deals with optimization of reaction yields by manipulation of conditions and leaving groups.

Nucleophilic fluorination offers the only currently available method for no-carrier-added reactions with ^{18}F. For applications which require very high specific activity a nucleophilic approach is therefore required. It should be pointed out, however, that carrier fluoride can be, and quite often is, added to nucleophilic fluorinations. This is rarely required by the chemistry of the reaction, but has often been done to improve the recovery of fluoride from the isotope production system.

A great deal of work has gone into the investigation of systems for fluoride production, recovery, and preparation for nucleophilic reaction.[54–60] This subject has been treated in depth elsewhere in this volume. Briefly, in order to perform nucleophilic substitution effectively reactive fluoride ion is required. The solubility of the fluoride in the solvent is also a major concern. Impurities which, in excessive quantities can render fluoride non-reactive are[54,63] water, certain metal ions, certain competitive anions,

and any species (i.e. silanes) which preferentially react with fluoride to form unreactive compounds. Water, once thought to be the primary difficulty in nucleophilic fluorination, can apparently be present in relatively large amounts (0.5 mmol) without severe adverse effects.[63] Therefore a combination of poor solubility and interfering ions is likely to be the cause of poor results in many instances. Reactive fluoride is reliably obtained by production from gaseous reagents such as molecular fluorine (carrier-added), and by trapping of gaseous HF. Fluoride produced in other forms can be prepared by distillation from acid solution if precautions are taken to exclude distillation of undesired anions, by distillation of fluorotrimethylsilane, or by other treatment to remove ionic impurities. Fluoride produced in a water target is directly usable if precautions are taken to exclude interfering metal ions. The water is removed by distillation from added base (potassium carbonate or tetraalkylammonium hydroxide) and the fluoride salt is dried by azeotropic distillation with acetonitrile or microwave heating. The solvent is an important parameter and dipolar aprotic solvents are generally chosen. Insofar as direct comparisons have been made dimethyl sulfoxide appears to give the most rapid reactions at the lowest temperatures. However, DMSO is an oxidising agent in its own right and its high boiling point (192°C) can make complete removal of the solvent difficult.

Acetonitrile generally works in a similar fashion to DMSO and its lower boiling point facilitates its complete removal from the final product. Thus in most cases acetonitrile is the solvent of choice for the reactions. Any of these methods are capable of providing a reactive [^{18}F]fluoride preparation for further synthetic use.

With a reactive preparation of fluoride ion available one can choose a variety of methods for its introduction into an organic compound. The methods can conveniently be divided into two major classes: aliphatic and aromatic fluorinations.

Aliphatic nucleophilic substitutions

Aliphatic nucleophilic fluorination generally follows the trends that one would expect of any nucleophilic substitution reaction. Elimination reactions need to be considered as a source of side reactions, and at high specific activity the byproducts which form from substitution by nucleophiles other than fluorine may also become important. At high specific activity one can also usually expect a large proportion of unchanged starting material to remain after labeling is complete.

Halogen as the leaving group. In the nucleophilic substitution literature halogens are encountered quite often as leaving groups. Among the halogens, leaving group reactivity decreases up the periodic table from iodine to fluorine. However, fluorine-for-fluorine substitution reactions are facilitated by the cancellation of solvation effects, making this a viable labeling approach for low specific activity work. Curiously, fluoride exchange labeling is not well represented in the literature of aliphatic labeling, although it is used for labeling aromatic compounds.

While the reactivity of the halogens as leaving groups does vary, the differences between halogens is small when compared to differences caused by other parameters of the reaction and differences between the halogens and other leaving groups.

Studies of fluorination in the gas phase at 200°C by reaction of fluoride on silver wool using a large array of halogenated alkanes as substrates have been performed.[64] Yields varied from 0.2% for primary chloride to 60% for a secondary iodide. An earlier related technique[65] was used to label aliphatic esters. Fluorine was absorbed on an anion exchange resin packed into a gas chromatograph. Alpha-bromo esters were then passed over the column, allowing substitution to take place in the gas phase. The low molecular weight substrates were labeled in good yield. Higher molecular weight esters were not labeled as efficiently, perhaps due to degradation at the higher temperatures required. It must be noted that a gas-phase reaction is not normally the method of choice, and that higher yields are usually obtainable in solution. One very successful example of halogen substitution labeling involves the formation of a fluorine–silicon bond by reaction of trimethyl silyl chloride with [^{18}F]fluorine.[58,59] Trimethylfluorosilane is a useful intermediate for purification of fluoride by distillation since it is easily cleaved by base to regenerate fluoride. Yields approach 100%, probably due more to the properties of silicon than to any advantage of chloride.

A variety of aliphatic compounds have been labeled by halogen exchange. Yields varying in excess of 75% have been reported[61] for fluoromethane, fluoroethane, and fluoropropane using the corresponding alkyl iodides as substrates. Similarly, 90% incorporation into fluoromethane[62] and 60% incorporation into fluoropropane[66] were reported from substitution on the corresponding iodides. In both cases the fluoride was produced from molecular fluorine passed into a solution of tetraethylammonium hydroxide with or without silver(I) oxide, which gives a very clean, reactive fluoride. In other applications chemical yields of fluorination of alkyl positions based on fluoride have ranged from 10 to 70% using iodide and bromide as the leaving groups.[54,57,67–69]

The most common conditions for these reactions is brief refluxing in acetonitrile solution with a base present. The base may be either a tetraalkyl ammonium hydroxide or potassium hydroxide or carbonate. If potassium salts are used then a crown ether is often used to facilitate solubility. There have been conflicting reports on the efficacy of crown ether for this purpose but the majority of the evidence is in favor of its use when potassium is the cation. At present there is no basis for preferring either

potassium/crown ether or tetraalkyl ammonium as the cation from the point of view of reaction efficiency. A thorough examination of the effect of solvent[63] found that acetonitrile was the preferred solvent. Other dipolar, aprotic solvents were also effective, and the optimum choice probably also depends on the nature of the substrates. It is apparent that both the solubility of the substrates and of the fluoride are major concerns.

Other halogen exchange reactions which have been reported are low yield exchange for aliphatic bromine in labeling fatty acids in an acetamide melt,[70] exchange with glucosyl bromide in 15% yield using silver fluoride,[71] and exchange on bromine or iodine[72-74] in positions alpha to a carbonyl, also in fairly low, but acceptable, yields. Overall, a few of the halogen exchange reactions have been very successful, while most are useful for synthesis but leave room for improvement.

Sulfonate as the leaving group. While a wide variety of sulfonate leaving groups are available and described in the current chemical literature, only the best known among them have been applied in labeling with ^{18}F. The groups in current use are *p*-toluenesulfonyl (tosyl), methanesulfonyl (mesyl), trifluoromethanesulfonyl (triflyl) and 1,2-cyclic sulfate or sulfite.

The tosyl group is not as well represented in the literature as the mesyl or triflyl groups. This may be due to its lower reactivity, and the associated possibility of lower labeling yields, when compared to the other sulfonates. In some instances the tosyl group has been used as a first attempt only to be discarded in favor of a more efficient method. It does have the advantages that it is more reactive than the halogens as a leaving group and it absorbs u.v. light which makes the purification and identification of the desired intermediates more straightforward. The tosyl group has been used as the leaving group in labeling 6-deoxy-6-fluoro-[α]-D-galactopyranose[75] with added carrier in low yield, and for labeling 2-fluoro-2-deoxy-D-glucose[76] in good yield.

The mesyl group is intermediate in reactivity between the tosyl and triflyl groups and has found some application. It is useful when more reactivity is desired than is available from the tosyl group but when the triflyl compound may be subject to troublesome elimination reactions. It has been used in steroid and fatty acid labeling.[60,74,77-79] Incorporation yields were generally low (10–25%), however this may be due to factors other than the leaving group.

The triflyl group is the most reactive of the leaving groups in use for ^{18}F labeling. It is approximately 40,000 times more reactive than the tosyl. Its major application to date in ^{18}F labeling has been the synthesis of 3-fluoro-3-deoxyglucose[80-83] in up to 80% yield. The related 2-fluoro-2-deoxyglucose has also been labeled from the triflate in good yield.[84,85] In these instances the ring structure combined with the adjacent functional groups serves to inhibit elimination reactions, and there are no other functional groups in the substrate which might inhibit the fluoride substitution. In other, less optimal, situations the triflyl group has also been useful, although lower yields have been obtained. An opiate, 3-acetylcyclofoxy,[86] a series of estrogenic compounds,[87] and an amino acid, 4-fluoroproline,[88] have all been successfully labeled. In a series of hexesterol derivatives the triflyl group was sufficiently reactive for intramolecular electrophillic cyclization reactions to compete with the fluorination reactions.[87]

The first application of a cyclic leaving group to ^{18}F labeling was for the production of fluoroethanol by displacement of glycol sulfite.[89] The high yield, clean reaction and lack of problems due to elimination were encouraging for further applications. Unfortunately, no other cyclic sulfites have yet been found to be useful for fluoride substitution. A further development, the use of the related cyclic sulfate for the synthesis of 2-fluoro-2-deoxyglucose,[90] has proved to provide very high labeling yields and has gained widespread use due to the importance of the final product. The approach has also been applied to the synthesis of labeled 16-[α]-fluoroestradiol with similar results.[91]

The effects of reaction conditions on the progress of various sulfonate substitutions have been investigated. The most important parameters seem to be the structure of the substrate and the leaving group. Once these are determined, solvent is important. The most effective solvents are undoubtedly dipolar aprotic.[78,81] Acetonitrile has consistently proven to be among the most effective solvents and has come to be the preferred solvent. Acetone is somewhat less effective. Dimethylformamide, dimethylacetamide and dimethylsulfoxide are also effective, except when they contribute to the decomposition of the substrate. In one report[78] chloroform was reported to be more effective than acetonitrile while using potassium fluoride in the presence of a crown ether, 18-crown-6.

Other leaving groups. The most successful use of a leaving group which does not fit into the above categories was not for synthesis of a labeled compound, but for the purification of fluoride.[92] In this application the fluoride was allowed to react with bis-trimethyl siloxane. The resulting fluorotrimethyl silane evaporated and was trapped and the fluoride regenerated in high yield during a 2 h transport to the laboratory. An aziridine ring was also used as a leaving group in the preparation of labeled nitrosoureas[93] in low yield. Epoxide ring opening has also been used for introduction of fluorine into a uracil derivative[94] and a cell sensitizer, 1-(2-nitro-1-imidazolyl)-3-fluoro-2-propanol,[95] both in low yield.

Aromatic nucleophilic substitution

In most cases nucleophilic substitution occurs so

slowly at an aromatic position regardless of the leaving group or the reaction conditions that the reaction is not practical for synthetic use even without the time constraints imposed by a short-lived isotope. The reaction is feasible however, when there is sufficient activation of the aromatic ring by electron-withdrawing groups in the *ortho* and *para* positions. In the absence of electron withdrawing groups fluoride ion can be reacted with a reactive intermediate such as that formed by the decomposition of a diazonium salt or a benzyne. These reactions are generally less satisfactory than a simple nucleophilic substitution reaction but they are feasable.

The only method that was known for the introduction of [^{18}F]fluoride into aromatic rings until the late 1970's was the Balz–Schiemann decomposition of an aromatic diazonium fluoborate. Although it is not a nucleophilic substitution in the usual sense, it is treated here as the forerunner of the current methods. The reaction suffers from typically low yields and necessarily results in a low specific activity product. This reaction has fallen into disuse with the discovery of more productive approaches. Within the scope of this review only two papers have appeared, in 1978 and 1979, which used this reaction. These were the labeling of 4'-fluoroantipyrine[96] and 4-fluoroestradiol[97] in approximately 2% yield. The preparation typically requires 2–3 h.

The first improvement in nucleophilic aromatic fluorination was the application of the Wallach triazene decomposition reaction. The reaction is essentially a diazonium salt reaction with the advantage that the triazene is a stable compound which can be isolated and purified. It is then heated in an anhydrous acidic medium to decompose the compound and complete the reaction. The exact mechanism is not known, but the result of the decomposition is either an aromatic cation or the very powerful leaving group, the N_2 cation. In either case the intermediate is extremely reactive and scavenges all anions in the solution, including fluoride. The reaction produces a vast array of products, both labeled and unlabeled, but has the advantage of high specific activity. The yields with some substrates are quite respectable, however with most complex substrates the incorporation yields are very low. The reaction was first used with ^{18}F in 1979,[98] and has predominantly been used to label the butyrophenone neuroleptics, haloperidol and spiperone.[96–101]

A related, if somewhat more limited, method is the decomposition of a stabilized diazonium salt in which the anion for the salt is a carboxyl group at a position *ortho* to the diazonium ion.[102] 2-Fluorobenzoic acid was labeled in 32% yield using various sources of fluoride.[102] The method is interesting for the novel approach to stabilizing the diazo precursor, but it is not likely to offer significant improvement in yields or versatility over the triazine method. For fluoride incorporation, the diazonium approach has largely been abandoned in favor of more conventional nucleophilic substitution.

There has recently appeared a variety of papers which employ substitution of fluoride for other anionic leaving groups at aromatic positions. As mentioned above, the successful application of this approach requires that the aromatic ring be activated by electron withdrawing substitutents. An extreme case of ring activation which deserves consideration as a completely different chemical situation from the other reactions in this category is the 2-position of a pyridine ring. Halogens in this position are extremely susceptible to substitution. Two examples of the use of this fact have been published. They are the labeling of 2-fluoronicotinic acid and 2- and 6-fluoronicotine.[103,104] The no-carrier-added reactions were quite efficient compared to previous methods. In light of further information concerning aromatic substitution it is somewhat surprising that the yields were only in the range of 10–40%.

While exchange of radioisotopes for their stable counterparts in a molecule is not a new concept in general or in the particular case of ^{18}F, the change to nucleophilic aromatic fluorination began with two papers on F-for-F exchange on small model compounds.[105,106] The yields obtained varied from below 50 to 90%. The cation which was used with the fluoride was rubidium. In the chemical literature the leaving group ability increases down the periodic table from fluorine to iodine, and the nitro group is also encountered frequently as a strong leaving group. All of these have been used for labeling purposes as well. In the case of exchange with ^{18}F, fluoride is a better leaving group than would otherwise be predicted probably due to the effects of solvation of the fluoride. Exchange of ^{18}F for fluoride does have the drawback that a large quantity of carrier product is inevitably introduced.

Similar success was obtained by performing essentially the same reaction as is used for labeling by isotopic exchange, but using an aromatic nitro compound as the substrate. The yields obtained with activated nitroaromatic compounds ranged from 15 to 80%.[107,108] The exchange was performed in hot DMSO (150°C) in 20 min. Other studies, again using simple model compounds, compared the nitro group and halogens as leaving groups.[109,110] The results of the studies done to date confirm that the aromatic substrate must be activated by electron-withdrawing groups. Lack of activation (halobenzenes, nitrobenzene) results in yields near 20%. Yields of 80% are obtainable in simple substrates activated by a nitro, cyano or carbonyl group. The reaction conditions (DMSO at temperatures from 130 to 180°C for 10–20 min) demand that the substrate be very stable. When this is not the case extremely low product yields are obtained. The reaction is stable to small amounts of water, similarly to aliphatic substitutions. Potassium fluoride seems to be the most efficient form of fluoride, although rubidium and cesium fluorides

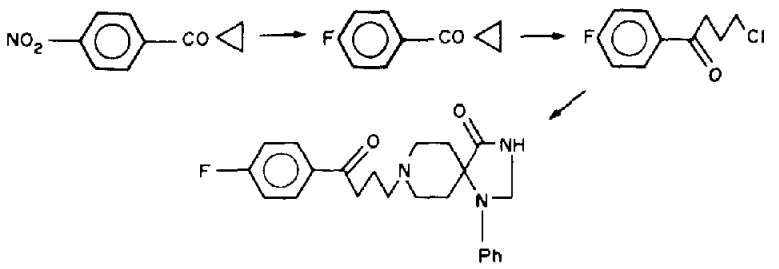

Fig. 4

are also useful. Tetraalkylammonium salts are not stable under the reaction conditions.

Aromatic nucleophilic substitution has been used for the synthesis of the various neuroleptic butyrophenones in low yield.[111-113] The cause of the low yield is primarily the sensitivity of the substrates to the reaction conditions. Very low yields (2%) are obtained from the direct reaction,[113] leading to the strategy of labeling a synthetic precursor in high yield (80%) which is then incorporated synthetically into the final target molecule.[111,112] Unfortunately, the synthesis of these compounds is not a high yield process and the final yields are 6–15%. The reaction has not yet been applied to other products of interest, but one might expect it to be very useful under favorable circumstances.

Another class of leaving group that has shown some promise for aromatic substitution, but has not yet been extensively investigated is the aryltrimethylammonium group. The purine ring has been labeled at position 6 by displacement of the trimethylammonium group in 15–35% yield.[114,115] The conditions were DMF at less than 100°C. Higher yields have since been obtained with this and related leaving groups,[116] but in DMSO at higher temperatures. This is a topic of active research, and significant advances in labeling with ^{18}F by nucleophilic aromatic substitution can be expected in the future.

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