# LABELED ARYL FLUORIDES FROM THE NUCLEOPHILIC DISPLACEMENT OF ACTIVATED NITRO GROUPS BY $^{18}F\text{-}F^-$

Marina Attinà*, Fulvio Cacace*, Alfred P. Wolf+
* Istituto di Chimica Farmaceutica, University of Rome, 00100 Rome, Italy
+ Department of Chemistry, Brookhaven National Laboratory, Upton, N.Y. 11973;

## SUMMARY

Nucleophilic displacement of activated nitro groups by $^{18}F$-fluoride ion is an efficient route to fluorine-18 labeled aromatics, which can be obtained in the no-carrier-added state if required.

The basic features of the fluorodenitration process are comparatively evaluated, and the influence of the experimental variables on its course are discussed. Examples concerning the preparation of typical $^{18}F$-labeled aromatic molecules are reported.

## INTRODUCTION

The growing need for high specific-activity $^{18}F$-labeled radiopharmaceuticals, often required in the no-carrier-added (NCA) state, has spurred interest in nucleophilic substitution by $^{18}F^-$ as a route to $^{18}F$-fluorinated aromatics. In fact, in contrast with other fluorinating reagents, such as $^{18}F\text{-}F_2$, acyl hypofluorites, etc., inorganic $^{18}F$-fluorides can be obtained in high yields by convenient procedures not requiring addition of carriers.

As a first example of the application of nucleophilic aromatic substitution by $^{18}F\text{-}F^-$ we have previously investigated the isotopic exchange of activated aryl fluorides, e.g. fluoronitrobenzenes and fluorobenzonitriles, with $Rb^{18}F$ in dimethylsulfoxide (1). As expected, on the grounds of the leaving ability of fluorine, the exchange proved to represent a rapid and efficient route to $^{18}F$-fluorinated aromatics. However, despite the considerable increase in the specific activity of the products allowed by experimental refinements (2), the inability of isotopic exchange reactions to yield NCA or carrier-free (CF) products is an inherent limitation that can be overcome only by using leaving

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groups other than fluorine itself. Based on the long established (3) leaving ability order in bimolecular aromatic substitutions, the nitro group appeared to be the most promising candidate.

Indeed, numerous examples of nucleophilic substitution by reagents such as $CH_3O^-$, $C_6H_5O^-$, $RS^-$, $CN^-$, etc. of nitro groups activated by substituents such as the nitro, or the cyano group, have been reported (3-9). Examples of fluorodenitration, however to polyhalonitrobenzenes, have been reported as well (10).

The present study is devoted to a comparative evaluation of nucleophilic displacement of activated nitro groups by $^{18}F\text{-}F^-$ as a useful labeling route to NCA or CF $^{18}F$-fluorinated aromatics.

## EXPERIMENTAL

Materials. Rubidium carbonate and chloride were obtained from Alfa Products Division, Ventron, Inc. Dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were Gold Label reagents from Aldrich Chemical Co., with a stated water content below 0.05%. These reagents were further dried over 4A molecular sieves. The organic substrates, all purchased from Aldrich, except 4,4'-dinitrostilbene from Pfalz and Bauer, Inc., were purified by crystallization and/or sublimation and thoroughly dried before use. Methyl 4-nitrobenzoate, 3,5-dinitrobenzoate, 4-nitrobenzenesulfonate, and dimethyl 3-nitrophthalate were prepared according to established procedures from the corresponding acids. 2-Chloro-6-fluorobenzonitrile, required as a chromatographic standard, was prepared by allowing 2-chloro-6-nitro-benzonitrile (Aldrich Chemical Co.) to react with an excess of dry, pulverized RbF in dry DMSO at 140° for one hour. The reaction mixture was then cooled, poured in water and extracted with ether and the 2-chloro-6-fluorobenzonitrile formed isolated by preparative glc, using a 3 m silicone fluid XF-1112 column, operated at 190° with a He flow rate of 100 ml/min. The product obtained, m.p. 60-2°, had properties identical to those reported for 2-chloro-6-fluorobenzonitrile prepared via different routes (11,12).

Preparation of the $^{18}F$-RbF Reagent. NCA $Rb^{18}F$ as tracer was prepared by dissolving 5 mg/ml $Rb_2CO_3$ into triply distilled water previously bombarded with $^3He$ particles from the BNL 60" cyclotron, $^{16}O(^3He,p)^{18}F$.

Preparation of Fluorine-18. Three nuclear reactions were used depending on the level of tracer and precursor required. The $^{20}Ne(d,\alpha)^{18}F$ was used to prepare $^{18}F$-$F_2$. The $^{16}O(^3He,p)^{18}F$ reaction was used to prepare trace levels of $^{18}F$-$F^-$. High levels of $^{18}F$-$F^-$ (> 100 mCi) were produced using the $^{18}O(p,n)^{18}F$ reaction and a 20% enriched $^{18}O$-$H_2O$ target. Conventional methods were used to prepare the radionuclide (20). The aqueous solution was evaporated at 180° under reduced pressure and the residue subjected to azeotropic distillation, following addition of dry benzene. The $^{18}F$-$F^-$ activity can be extracted with dry DMSO or DMF under continuous agitation at 150-160°. It should be noted however, that only a fraction (5 to 10%) of the $^{18}F$-$F^-$ activity is extracted using this procedure. The preparative reactions are best carried out in the same vessel used for the evaporation of the $^{18}F$-RbF solution, a procedure that was found to ensure a much better radiochemical yield. As an example, the following activity balance was obtained in a typical preparation of $^{18}F$-p-fluoronitrobenzene from p-dinitrobenzene at 85° (all activities corrected for decay):

| | |
|---|---|
| $^{18}F$-$F^-$ activity in the solid deposit of $Rb_2CO_3$ | : 35 mCi |
| Activity of $^{18}F$-p-fluorobenzene formed | : 23.4 mCi |
| Water-soluble activity of unreacted $^{18}F$-$F^-$ | : 11.5 mCi |
| Residual activity on the walls | : 0.04 mCi |

Whenever dilution of the radioactive fluoride with inactive carrier is not detrimental, the reagent can be conveniently prepared from $^{18}F$-$F_2$. To this end, Ne gas containing 0.1 vol % $F_2$, bombarded with deuterons from the BNL 60" cyclotron $^{20}Ne(d,\alpha)^{18}F$, was bubbled through an aqueous solution containing 5 mg/ml $Rb_2CO_3$, subsequently worked out as previously described. Alternatively, anhydrous $^{18}F$-$F_2$ was allowed to bleed through a 10-mm long, 1-mm i.d. teflon tubing packed with finely ground RbCl crystals. The $^{18}F$-RbF formed was then extracted with dry DMSO. Such a procedure, while dispensing with the water-removal step, leads however, to only partial recovery of the $^{18}F$-$F_2$

activity, ranging from 10 to 60%, depending on the flow rate of the $^{18}F-F_2/Ne$ mixture through the capillary tubing and the packing density of the RbCl crystals.

Reaction Conditions and Analytical Procedures. A measured aliquot of a $^{18}F-RbF$ solution, prepared as outlined in the previous paragraph, was added to the aromatic substrate dissolved in the same solvent at a typical concentration of $3 \cdot 10^{-2}$ M.

The reactions were carried out in teflon-stoppered glass vessels maintained at the desired temperature in a thermostatic oven. After the appropriate reaction time, the vessels were allowed to cool, water added, and their contents extracted with ether, benzene or carbon disulphide. The activity of the aqueous and organic layers was then measured in a scintillation counter, Picker Nuclear Inc., in order to estimate the fraction of the $^{18}F-F^-$ activity incorporated into the organic products. The latter were analyzed by radio glc and hplc. The combination of a Hewlett-Packard Model 7620A gas chromatograph with a high-temperature flow proportional counter (13) was used for radio glc, carried out with the following 6-mm o.d. stainless steel columns:

(i) a 3 m long column, packed with Carbowax K 20M, 20% w/w on AW Chromosorb W.

(ii) a 1.8 m long column, packed with DC 710 silicone fluid, 20% w/w on AW, DMCS-treated Chromosorb W.

(iii) a 3 m long column, packed with XF-1112 silicone oil, 20% w/w on S support from Perkin-Elmer Co.

Radio hplc was carried out using a Series 3 chromatograph from Perkin-Elmer Co., equipped with a 254-nm UV detector and coupled to a LB 503 flow scintillation counter from Berthold Laboratories. A 4.5 x 100 mm 1-μ RP-18 silica column from Perkin-Elmer Co. was used in all separations, with water/methanol mixtures as the mobile phase. Hplc was used as a preparative technique, as well, collecting all radioactive peaks from a given reaction into separate vials, and measuring their activity in the scintillation counter. Any radioactive compound that failed to

emerge from the column could be detected, and its activity measured, by disconnecting the column from the chromatograph and counting the column in toto in the Picker instrument. This procedure provided a detailed balance of all the activity contained in the organic extract from the reaction, thus providing a reliable measure of the radiochemical yields. In several instances, thin-layer radio chromatography was also carried out to confirm the radio glc and hplc results.

The identity of the $^{18}F$-labeled products was established by comparing their retention parameters, both in hplc and glc, with those of authentic standards. In several cases, however, the latter were not available, and consequently the assignment of the products had to be based on a comparative chromatographic study, involving suitable analogs. Two criteria were used, namely that the $^{18}F$-activity assigned to a product must appear in a single elution peak from all glc and hplc columns used, and that the retention time on all columns had to be close to those of the strictly related compounds available for comparison. As an example, the activity peak traced to 4-fluoro-4'-nitrostilbene had a retention volume similar to, and bracketed by, those of the available 4,4'-dinitro- and 4,4'-difluorostilbene.

While the identification obtained in such a way must be regarded as tentative, the very nature of the reaction studied, leading to a clean F- for- $NO_2$ substitution in the numerous cases where products could be positively identified, makes the suggested assignments likely.

## RESULTS AND DISCUSSION

The radiochemical yields of the $^{18}F$-labeled products from various substrates studied are given in Table 1. The reactions leading to the results listed were carried out at 150°, i.e. at a temperature where no appreciable decomposition of DMSO occurs.

It should be noted that the reaction is exceedingly sensitive to traces of water, and therefore the use of properly dried reagents, vessels and solvents is

Table 1. $^{18}F$-Labeled Products from the Displacement of Aromatic Nitro Groups in DMSO at 150° [a]

| Substrate | Product | Radiochemical Yield (%)[b] |
|---|---|---|
| o-Nitrobenzonitrile | [$^{18}F$] o-Fluorobenzonitrile[c] | 86% |
| p-Dinitrobenzene | [$^{18}F$] p-Fluoronitrobenzene[c] | 83% |
| p-Nitrobenzonitrile | [$^{18}F$] p-Fluorobenzonitrile[c] | 81% |
| Methyl p-nitrobenzenesulfonate | [$^{18}F$] Methyl p-fluorobenzenesulfonate[d] | 60% |
| 2-Chloro-6-Nitrobenzonitrile | [$^{18}F$] 2-Chloro-6-fluorobenzonitrile[c] | 55% |
| | [$^{18}F$] 6-Fluoro-2-nitrobenzonitrile[d] | 17% |
| 2,4,7-Trinitrofluorenone | [$^{18}F$] Fluorodinitrofluorenone(s)[d] | 62% |
| o-Dinitrobenzene | [$^{18}F$] o-Fluoronitrobenzene[c] | 58% |
| Pentachloronitrobenzene | [$^{18}F$] Pentachlorofluorobenzene[c] | 11% |
| | [$^{18}F$] Isomeric $^{18}F$ Tetrachlorofluoro-nitrobenzenes[d] | 29% |
| Methyl 3,5-dinitrobenzoate | [$^{18}F$] Methyl 3-Fluoro-5-nitrobenzoate[c] | 34% |
| | [$^{18}F$] Unknown[d] | 10% |
| Methyl p-nitrobenzoate | [$^{18}F$] Methyl p-fluorobenzoate[c] | 34% |
| 3,4-Dinitrotoluene | [$^{18}F$] Fluoronitrotoluene(s)[d] | 32% |
| Dimethyl 3-nitrophthalate | [$^{18}F$] Dimethyl 3-fluorophthalate[d] | 25% |
| m-Dinitrobenzene | [$^{18}F$] m-Fluoronitrobenzene | 17.4% |
| p-Nitrobenzophenone | [$^{18}F$] p-Fluorobenzophenone[d] | 16% |
| 4,4'-Dinitrostilbene | [$^{18}F$] 4-Fluoro-4'-nitrostilbene[d] | 14% |

(a) Reaction time 20 minutes, typical substrate concentration 5 mg/ml.

(b) Percentage of the initial activity isolated in the product, corrected for decay. Standard deviation of yields ± 10%.

(c) Identified by comparison of their retention volumes on glc and hplc columns with those of authentic samples.

(d) Tentative assignment, see text.

of paramount importance. DMSO, being highly hygroscopic, must be carefully dried and handled to prevent contamination by moisture. On the other hand, the yields are insensitive to the extent of dilution of the radioactive reagent. No significant differences are detected between reactions involving NCA $^{18}F\text{-}F^-$ and those where $^{18}F\text{-}F^-$ had been diluted with inactive fluoride, at typical concentrations of $2 \cdot 10^{-3}$ M.

Comparative experiments have confirmed that DMSO is the most convenient solvent, consistent with its recognized utility in nucleophilic aromatic substitution (14), and with the results obtained in the isotopic exchange of $^{18}F\text{-}F^-$ with aryl fluorides (1). As an example, reaction of p-dinitrobenzene and, methyl 3,5-dinitrobenzoate with $^{18}F\text{-}F^-$ in DMF at 150°C gave 26% $^{18}F$-p-fluoronitrobenzene and 7% $^{18}F$-methyl 3-fluoro-5-nitrobenzoate respectively, well below the yields obtained in DMSO under identical conditions. Rubidium fluoride was used in all experiments, since preliminary tests study indicated that other fluoride salts, such as KF and CsF, gave lower yields and/or were too highly hygroscopic.

The effect of reaction temperature on the yields of selected substrates is illustrated in Table 2.

The most interesting feature of fluorodenitration is that, in contrast with other nucleophilic fluorination reactions, it remains sufficiently fast for practical radiopharmaceutical labeling even at relatively mild temperatures. Indeed, running the reaction below 150° is not only feasible, but even desirable for a highly activated substrates such as p-dinitrobenzene. The effect of the reaction time on the yields at different temperatures is illustrated in Table 3. The data show that useful $^{18}F$ activities can be incorporated into labeled aryl fluorides in conveniently short reaction times.

The effect of the substrate concentration on the yields has been briefly evaluated in one case, i.e. fluorodenitration of p-dinitrobenzene. The yields increase with the concentration of the substrate, yet the reaction rate does not appear to increase in proportion. As an example, the yield from a $3 \cdot 10^{-3}$M solution of p-dinitrobenzene is 36% after 30 minutes at 80° and 49% at 90°.

Table 2. Effect of the Reaction Temperature on the Radiochemical Yield of $^{18}F$ Product[a]

| Substrate | Temperature (°) | Radiochemical Yield[b] (%) |
|---|---|---|
| p-Dinitrobenzene | 70° | 36 |
| | 80° | 50 |
| | 90° | 62 |
| | 110° | 87 |
| o-Nitrobenzonitrile | 70° | 11 |
| | 90° | 15 |
| | 110° | 41 |
| | 150° | 85 |

(a) Reaction time 30 minutes, substrate concentration 5 mg/ml.

(b) Standard deviation ca. 10%.

Table 3. Radiochemical Yields of $^{18}F$-p-Fluoronitrobenzene From p-Dinitrobenzene as a Function of the Reaction Time[a]

| Temperature (°) | Reaction Time (Minutes) | Yield[b] (%) |
|---|---|---|
| 80° | 5 | 12 |
| | 10 | 19 |
| | 20 | 44 |
| | 30 | 50 |
| 90° | 5 | 16 |
| | 10 | 45 |
| | 20 | 57 |
| | 30 | 62 |
| 110° | 5 | 64 |
| | 10 | 77 |
| | 15 | 80 |
| | 22 | 81 |
| | 30 | 87 |

(a) Substrate concentration $2.98 \cdot 10^{-2}$ M.

(b) Standard deviation ± 10%.

Under the same conditions, the yields from a $3 \cdot 10^{-2}$M solution are respectively 50% and 62%.

It should be emphasized that no kinetically significant conclusion can be drawn from the present data, owing to the preparative nature of the investigation and to the limited range of temperatures, concentrations and reaction times studied.

Competition Experiments. As shown in the previous paragraph, fluorodenitration causes a clean displacement of the nitro group by $^{18}F\text{-}F^-$ without appreciable isomerization.

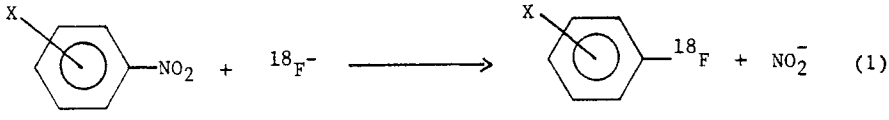
This feature allowed the carrying out of competition experiments designed to obtain a quantitative estimate of the activating power of the various substituent groups, and to measure the nucleofugality of $NO_2$ relative to other leaving groups, in particular fluorine, whose displacement had been previously investigated (1,15).

As to the first question, the results summarized in Table 4 show that the activating effect of the substituent groups X in the fluorodenitration of $C_6H_4(NO_2)X$ in DMSO at 150° increases in the order:

$$m\text{-}NO_2 \ll p\text{-}CN \simeq o\text{-}NO_2 < o\text{-}CN < p\text{-}NO_2$$

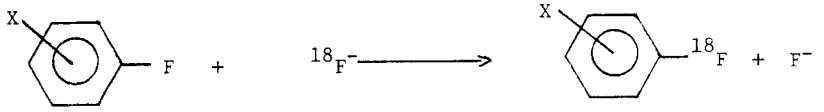
The data available suggest that such an order is but little affected by temperature changes in the range from 56° to 150°.

As expected, m-dinitrobenzene reactivity is quite low when compared to those of its ortho and para isomers. A quantitative measurement, allowed by the sensitive radio chromatographic techniques employed, has shown that starting from an equimolecular mixture of meta- and para-dinitrobenzene, the ratio of the yields of $^{18}F$-meta- and para-fluoronitrobenzene is ca. 1:1700 at 150°C. The other problem addressed, i.e., the leaving ability at $NO_2$ relative to other groups, was investigated by comparing the rate of the fluorodenitration process



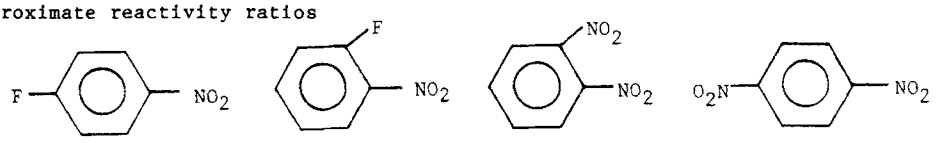

(1)

with that of the isotopic exchange reaction




(2)

in competition experiments. The results are given in the first 3 entries of Table 4. The data from crossed runs, carried out at 150°, yield the following approximate reactivity ratios




1.0 1.4 1.8 10

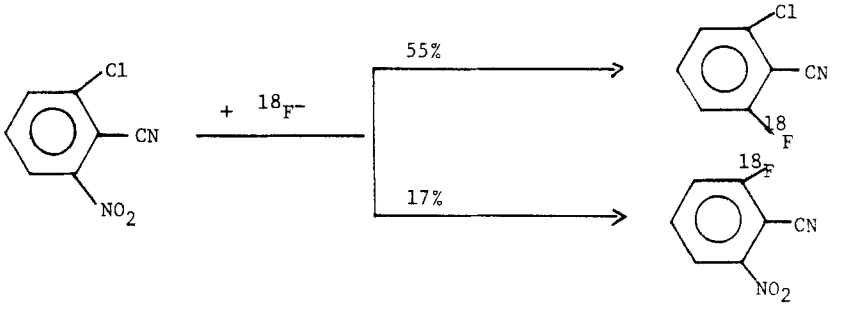
At lower temperatures, competition between processes (1) and (2) appears to shift slightly in favour of the latter, yet fluorodinitration remains faster at all temperatures.

The results show that $NO_2$ is a better leaving group than fluorine itself in nucleophilic aromatic substitution by $^{18}F$-$F^-$ in DMSO.

This conclusion does not fit into the general trend prevailing in related reactions, nevertheless a number of exceptions (16) have been noted. Indeed, examples have been reported (17) showing that the leaving ability of $NO_2$ exceeds that of F, or, for that matter, of all other groups, in certain aromatic nucleophilic displacement reactions.

As expected, the nucleofugality of $NO_2$ is higher than that of Cl, as shown by the competition of p-chloronitrobenzene with p-dinitrobenzene, and from the distribution of labeled products where intramolecular competition is possible.

Thus, chloronitrobenzonitrile undergoes predominant fluorodenitration




(3)

(4)

Table 4. Competition of Substituted Nitrobenzenes for $^{18}F\text{-}F^-$ in DMSO

| Competing Substrates[a] | Temperature (°) | Relative Yields of Labeled Products[b] |
|---|---|---|
| o-Fluoronitrobenzene<br>p-Fluoronitrobenzene | 150° | $\frac{[^{18}F]\ \text{p-Fluoronitrobenzene}}{[^{18}F]\ \text{o-Fluoronitrobenzene}} = 0.70$ |
| o-Fluoronitrobenzene<br>p-Dinitrobenzene | 150°<br>110°<br>80° | $\frac{[^{18}F]\ \text{p-Fluoronitrobenzene}}{[^{18}F]\ \text{o-Fluoronitrobenzene}} = 7.0;\ 6.3;\ 2.8$ |
| p-Fluoronitrobenzene<br>o-Dinitrobenzene | 150°<br>110° | $\frac{[^{18}F]\ \text{p-Fluoronitrobenzene}}{[^{18}F]\ \text{o-Fluoronitrobenzene}} = 0.50;\ 0.56$ |
| p-Chloronitrobenzene<br>o-Dinitrobenzene | 150° | $\frac{[^{18}F]\ \text{p-Fluoronitrobenzene}}{[^{18}F]\ \text{o-Fluoronitrobenzene}} < 0.01$ |
| o-Dinitrobenzene<br>p-Dinitrobenzene | 150°<br>110°<br>80°<br>56° | $\frac{[^{18}F]\ \text{p-Fluoronitrobenzene}}{[^{18}F]\ \text{o-Fluoronitrobenzene}} = 5.4;\ 4.5;\ 4.4;\ 4.6$ |
| p-Dinitrobenzene<br>m-Dinitrobenzene | 150° | $\frac{[^{18}F]\ \text{m-Fluoronitrobenzene}}{[^{18}F]\ \text{p-Fluoronitrobenzene}} < 0.01$ |
| p-Dinitrobenzene<br>p-Nitrobenzonitrile | 152° | $\frac{[^{18}F]\ \text{p-Fluoronitrobenzene}}{[^{18}F]\ \text{p-Fluorobenzonitrile}} = 6.2$ |
| o-Nitrobenzonitrile<br>p-Nitrobenzonitrile | 150° | $\frac{[^{18}F]\ \text{o-fluorobenzonitrile}}{[^{18}F]\ \text{p-Fluorobenzonitrile}} = 2.6$ |

(a) All reactions carried out with equimolecular amounts of competing reagents. Reaction time 30 minutes.

(b) Standard deviation of the ratios ± 20%.

The distribution of products from pentachloronitrobenzene supports the above conclusions, once the statistical factor and the higher activating power of $NO_2$ have been taken into account, consistent with previous results concerning other nucleophiles (18).

## CONCLUSION

The nucleophilic displacement of activated nitro groups by $^{18}F^-$ represents an efficient and general route to $^{18}F$-labeled aromatics. In comparison with conventional nucleophilic displacement of other groups, such as Cl, Br and I, fluorodenitration is much faster, which allows it to be carried out at considerably lower temperatures, a most significant factor when complex, thermolabile substrates are involved, obvious applications being the preparation of $^{18}F$-spiroperidol from its inactive nitro analog, or of synthetically useful labeled intermediates (19). In fact, the versatile reactivity pattern of any activating nitro groups present in the substrate makes $^{18}F$-fluorodenitration of polynitrobenzenes a synthetic route of considerable scope. A pertinent example is afforded by p-dinitrobenzene, the most active of the substrates tested, whose reaction with $^{18}F^-$ gives high yields of $^{18}F$-p-fluoronitrobenzene. The latter can be rapidly reduced to aniline and to p-fluorobenzenediazonium salts in excellent yields allowing the replacement of nitro group with $NH_2$, CN, H, OH, OMe, halogens, etc. Further obvious synthetic pathways are open by readily available $^{18}F$-aromatics containing such activating groups as CN, COR, COOR, OH, OR, etc.

Fluorodinitration is <u>even faster</u> than isotope exchange of activated fluorobenzenes with $^{18}F$-$F^-$ and presents, in addition, the advantage of yielding NCA products. Detailed experiments are in progress to determine the dilution of the $^{18}F$ ligand, if any.

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16. A general prediction of the order of leaving ability in nucleophilic aromatic substitution is impossible, owing to the variety of energy profiles and the corresponding kinetic laws, cf. de Boer, Th.J. and Dirkx, I.P., in "The Chemistry of the Nitro and the Nitroso Groups", Fener, H. (Ed.), Interscience Publisher 1969, Part 1, p. 542 and citations therein.

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