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NUCLEOPHILIC AROMATIC SUBSTITUTION OF ACTIVATED CATIONIC GROUPS BY ^{18}F-LABELED FLUORIDE. A USEFUL ROUTE TO NO-CARRIER-ADDED (NCA) ^{18}F-LABELED ARYL FLUORIDES

G. ANGELINI*, M. SPERANZA*, A. P. WOLF** and C.-Y. SHIUE

Chemistry Department, Brookhaven National Laboratory, Upton, NY 11973 (U.S.A.)

SUMMARY

A method is described for the rapid preparation of no-carrier-added (NCA) ^{18}F-labeled aryl fluorides by treatment of the corresponding aryltrimethylammonium perchlorates with ^{18}F-labeled fluoride in DMSO. The basic features of the ^{18}F-for-$^{+}$NMe$_3$ displacement process are evaluated as a function of the experimental variables and compared with related substitution routes to NCA ^{18}F-labeled aryl fluorides. The relative nucleofugicity of the ammonium group in the nucleophilic substitution reactions surpasses that of the best neutral leaving groups, including NO_2 and F itself. In contrast, radiofluoride incorporation into aromatic rings *via* other cationic substrates, such as aryldimethylsulfonium perchlorates, is prevented by the fast methyl group transfer from the starting compound to the nucleophiles present. The use of the ammonium function as a leaving group in nucleophilic substitutions by $^{18}F^-$ may give access to the rapid preparation of novel NCA ^{18}F-radiopharmaceuticals by facilitating the synthesis and the purification of their labeled precursors.

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*Permanent Address: Istituto di Chimica Nucleare del C.N.R., C.P. 10, 00016 Monterotondo Stazione, Rome (Italy).

**Author to whom inquiries should be addressed.

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INTRODUCTION

Since a number of ^{18}F-labeled radiopharmaceuticals have been used in in vivo metabolic studies via positron emission tomography (PET) [1], and ^{18}F-labeled aryl fluorides are common structural components of these radiopharmaceuticals, considerable research effort has been directed towards the rapid preparation of these ^{18}F-labeled aryl fluorides [2]. To date, the preparation of ^{18}F-labeled aryl fluorides has relied mainly on two types of reactions: the nucleophilic and electrophilic substitution reactions. While electrophilic fluorination reactions with $[^{18}F]F_2$ give ^{18}F-labeled products with low specific activity, the nucleophilic substitution reactions with ^{18}F-fluoride have the potential of giving products with high specific activity or no-carrier-added (NCA) with near 100% incorporation. Therefore, many successful synthetic routes to NCA ^{18}F-labeled compounds can involve the nucleophilic substitution of NCA $^{18}F^-$ on aliphatic or aromatic precursors containing suitable leaving groups [2].

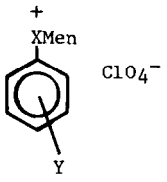
Until recently, preparation of aryl $[^{18}F]$fluorides by $^{18}F^-$ substitution has relied principally on the Balz-Schiemann reaction [3], which is characterized by low radiochemical yields and low specific activity, and on the decomposition of aryl triazenes in the presence of $H^{18}F$ or $Cs^{18}F$ which gives NCA radiotracers in low yields [4].

More recently, isotopic exchange of $^{18}F^-$ with activated aryl fluorides has been shown to give high yields of aryl $[^{18}F]$fluorides with low specific activity [5]. The drawback of low specific activity has been overcome by using leaving groups such as a nitro group, thereby providing access to NCA aryl $[^{18}F]$fluorides [6]. Although the nitro group displacement has shown considerable promise, its use requires moderately high temperatures (130-160°C), a limitation in applications where the substrate is thermally labile under the reaction conditions. In order to expand the scope of this reaction, we have investigated the reactivity of other nucleofugic groups with a view of identifying those which undergo the displacement reaction under milder conditions and yield reaction mixtures which are more amenable to rapid purification.

Based on the long established leaving group ability order in nucleophilic aromatic substitution [7], cationic groups, such as $^+SMe_2$ or $^+NMe_3$, appear to be the best leaving groups (along with N_2^+) toward nucleophilic substitution. Several examples of rapid and efficient nucleophilic substitution of cationic moieties by a variety of nucleophiles,

including F^-, have been reported, although the evidence is restricted to strongly activated heteroaromatic substrates [8]. Accordingly, ^{18}F-labeled purine has been successfully prepared from the corresponding trimethylammonium salt [9].

The present study is aimed at investigating the kinetic features of cationic group displacement by fluoride in activated benzene systems 1-7. Comparative analysis of the effect of the substituent on the nucleofugic properties of the cationic group may enable evaluation of this particular nucleophilic aromatic substitution as a useful route to NCA ^{18}F-labeled aryl fluorides.



	X	n	Y
1	S	2	p-NO_2
2	S	2	p-CHO
3	N	3	p-NO_2
4	N	3	p-CN
5	N	3	p-$COCH_3$
6	N	3	p-CHO
7	N	3	m-NO_2

EXPERIMENTAL

Materials

'Anhydrous' CsF and Cs_2CO_3 were obtained from Alfa Products Division of Ventron, Inc. and further dehydrated at 150°C under vacuum for 24 hrs. All other inorganic compounds and most organic standards and solvents were research grade chemicals from Aldrich Chemical Co. Dimethylsulfoxide (DMSO) was a Gold Label reagent from Aldrich Chemical Co., with a stated water content below 0.05%. It was further dried for one month over 4Å Molecular Sieve (Fisher Scientific Co.) which had been activated under vacuum at 350°C. Research grade N,N-dimethylanilines and p-N,N-dimethylthioanisoles were purchased from Pfaltz and Bauer, Inc. N,N-Dimethyl-m-nitroaniline and p-nitrothiophenol were obtained from Aldrich Chemical Co.

Substituted phenyldimethylsulfonium (1 and 2) and phenyltrimethylammonium perchlorates (3-7) were prepared according to established procedures from the corresponding aniline or thioanisole, methyl iodide, and silver perchlorate [10], and recrystallized from acetonitrile. The perchlorates were thoroughly dried under vacuum at 120°C for 1 week.

Labeled reagent

NCA $Cs^{18}F$ was prepared by adding 0.5 mg of Cs_2CO_3 to 1 ml of aqueous $H^{18}F$ solution prepared from the $^{18}O(p,n)^{18}F$ nuclear reaction [11,12]. The aqueous solution was placed in a platinum crucible, evaporated to dryness at 150°C under a slow stream of nitrogen and then co-evaporated to dryness with acetonitrile. For kinetic measurements, the $^{18}F^-$ activity was solubilized with dry DMSO under continuous agitation at 150-160°C. It should be noted, however, that only a fraction (50-80%) of the ^{18}F activity is solubilized using this procedure. The preparative reactions are best carried out in the same platinum crucible used for the evaporation of the $Cs^{18}F$ solution, a procedure that was found to ensure a better radiochemical yield.

Reaction conditions and analytical procedures

A measured aliquot of a $Cs^{18}F$-DMSO solution, prepared as outlined in the previous paragraph, was added to the aromatic substrate(s) dissolved in the appropriate solvent at concentrations ranging from 10^{-6} to 10^{-3} mol l^{-1}.

The reactions were carried out in teflon-stoppered glass vessels maintained at the desired temperature in a thermostated silicone oil bath. After thorough mixing, aliquots of the reaction solution were withdrawn at different time intervals, quenched by cooling at -78°C, and used for product analysis and kinetic measurements. In some experiments, the appropriate reaction mixture was allowed to cool, water was added, and their contents extracted with ether, benzene, or carbon disulphide and dried (Na_2SO_4). The activities of the aqueous and organic layers were then measured in a scintillation counter (Picker Nuclear Inc.) to determine the fraction of the $^{18}F^-$ activity incorporated into the organic products.

The ^{18}F-labeled products were analyzed by radio glc (Varian Aerograph Model 920 gas chromatograph, equipped with a hot-wire detector and connected to a heated flow proportional counter) [13] and by radio hplc (Perkin Elmer Series 3B liquid chromatograph, equipped with a UV detector and connected to a Berthold Radioactivity Monitor, Model LB 503 flow scintillation counter).

The identities of the labeled products were established by comparison of their retention times with those of authentic, unlabeled samples on at least two glc columns and with at least two different solvent systems using hplc. The glc analyses were carried out with the following stainless steel columns: (i) 20% Carbowax 20 M on AW Chromosorb W (3.6 m x 6 mm); (ii) 20% DC 710 silicone fluid on AW, DMCS-treated Chromosorb W (1.8 m x 6 mm); (iii) 20% XF-1112 silicone oil on S support (3.6 m x 6 mm). The hplc analyses were performed on a 4.5 x 100 mm C-18 column from IBM Co., using two different solvent systems (MeOH-H_2O, 40:60 and MeOH-0.01M $(NH_4)_2HPO_4$, 70:30). Static activity analyses were also carried out using a Picker NaI well counter.

RESULTS

Preliminary experiments with stable fluoride

Exploratory experiments were carried out to determine the most suitable experimental conditions for nucleophilic fluorination. Thus, onium salts 1-7 were subjected to prolonged heating (up to 4 hrs) at 150°C in a variety of dipolar aprotic solvents (dimethylsulfoxide, dimethylformamide, hexamethylphosphotriamide, etc.) in order to check their tendency to undergo isomerization [14] or decomposition under such conditions. The effect of prolonged heating on the selected substrates was followed by conventional ^{1}H-NMR analyses. Extensive conversion (> 50%) of the sulfonium salts 1 and 2 to their corresponding thioanisole precursors were observed after 20 minutes in all solvent systems studied. The addition of a large excess of fluoride, or a decrease of the reaction temperature below 80°C, does not significantly change the result, thus further demonstrating the tendency of sulfonium salts 1 and 2 to transfer rapidly one of their methyl groups to even weak nucleophiles, such as the solvent molecules present [15]. Demethylation of 1 and 2 can be completely suppressed when the solvent used is dry acetonitrile and the reaction temperature is below 60°C. Under such conditions, however, the addition of unlabeled CsF promotes demethylation of the substrate, without any appreciable ring substitution by fluoride.

Both Hofmann-Martius methyl transfer [14] and nucleophilic substitution are, instead, observed when ammonium salts 3-7 are heated in the presence of an excess of CsF in all selected aprotic solvents. In general, the relative extent of ring substitution increases in dry DMSO or CH_3CN at the lowest reaction temperatures, and appears to depend upon the nature and the position

of the activating group in the aromatic ring. Thus, in DMSO at 80°C for 20 min, the relative extent of F-for-$^{+}NMe_3$ displacement decreases in the order: p-NO_2 (71%) > p-CN (24%) > p-CH_3CO (15%) > p-CHO ($\lesssim$ 5%) $\simeq$ m-NO_2 ($\lesssim$ 5%). This was expected in view of the significant electron-withdrawing effects of the substituent group upon the ortho-para ring carbons, as compared to the limited (if any) influence upon the methyl carbons. The Hofmann-Martius reaction in ammonium salts 3-7 can be efficiently suppressed by lowering the reaction temperature. In particular, if 3 is allowed to react with CsF in dry DMSO at 40°C for 3 hrs., exclusive formation of p-fluoronitrobenzene is observed without any appreciable demethylation of compound 3.

The Hofmann-Martius reaction in compounds 3-7 appears to be promoted by the presence and the concentration of fluoride ions. In fact, when compounds 3-7 were dissolved in DMSO and subjected to prolonged heating (up to 4 hrs at 150°C) in the absence of fluoride, no appreciable demethylation was observed.

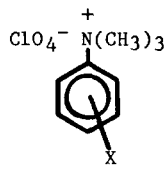
It is concluded that the most favorable conditions for nucleophilic aromatic substitution of compounds 3-7 by fluoride involve use of DMSO as the solvent, and reaction temperatures not exceeding 150°C, together with the minimum concentrations allowable for the nucleophile (i.e., $^{18}F^-$ in the NCA state).

Radiofluorination

The actual radiofluorination experiments were carried out under the conditions which had been optimized in the unlabeled fluorinations using NCA $^{18}F^-$ as nucleophile. The radiochemical yields of the aryl [^{18}F]fluorides obtained by nucleophilic radiofluorination of ammonium salts 3, 4, 5 and 7 with $^{18}F^-$ at temperatures up to 140°C are reported in Table 1. The yields appear rather insensitive to limited dilution of the radioactive reagent with non-radioactive reagent. No significant differences are detected between reactions involving NCA $^{18}F^-$ (Table 1) and those where $^{18}F^-$ had been diluted with inactive fluoride at concentrations below 10^{-3} mol l^{-1}. In contrast to compounds 3, 4, 5 and 7, no ^{18}F incorporation is observed under the same conditions when the sulfonium ions 1 and 2 or the ammonium salt 6 are used as substrates. In these cases, most of the activity remains in $^{18}F^-$ form, whereas a number of ^{18}F-labeled organic products are formed in low yields (overall yield < 15%). A similar result is observed, when the concentration of substrates 3, 4, 5 and 7 is lowered to levels (10^{-5}-10^{-6} mol l^{-1})

TABLE 1

Radiochemical yield of F-18 aryl fluorides from the displacement of a trimethylammonium group by ^{18}F-fluoride[a]

Substrate X	Temp (°C)	Product	Yield (%)[b]
			
p-NO_2	40	4-[^{18}F]$C_6H_4NO_2$	10
	60		18
	70		30
	80		71
	120		91
	140		86
p-CN	80	4-[^{18}F]C_6H_4CN	24
	120		91
	140		76
p-$COCH_3$	80	4-[^{18}F]$C_6H_4COCH_3$	15
	140		35
m-NO_2	80	3-[^{18}F]$C_6H_4NO_2$	5
	140		51

[a] Reactions were run in DMSO. Reaction time: 20 min. Substrate concentration: 10^{-4} mol ℓ^{-1}.

[b] Percentage of activity isolated in the product, corrected for decay.

comparable to those of the impurities invariably present in the solvent used. In this case, however, the overall yield of the numerous organic products formed (including a minor amount of the radiofluorinated derivative) often exceeds the activity level of the inorganic $^{18}F^-$.

The addition of limited amounts of water to DMSO does not seem to appreciably affect the radiochemical yield of the substituted derivative, as well as the relative distribution of the labeled products as illustrated in Table 2.

TABLE 2

Effect of water concentration on the radiochemical yield of p-[^{18}F]fluoro nitrobenzene from the displacement of p-nitrophenyltrimethylammonium perchlorate by ^{18}F-fluoride[a]

[H_2O] (mol %)	Yield (%)[b]
< 10^{-4}[c]	91
0.1	79
1.0	97
5.0	94

[a] Solvent: DMSO. Reaction temperature: 120°C. Reaction time: 20 min. Substrate concentration: 10^{-4} mol ℓ^{-1}.

[b] See footnote (b) of Table 1.

[c] "Dry" DMSO.

TABLE 3

The influence of Cs_2CO_3 concentration on yield of p-fluorobenzonitrile from p-cyanophenyltrimethylammonium perchlorate[a]

[Substrate]/[Cs_2CO_3]	Radiochemical Yield (%)[b]
3.3	64
1.3	62
0.6	43
0.13	24

[a] All reactions were carried out at 140° with substrate concentration of 3.5×10^{-3} M. Reaction time: 20 min.

[b] See footnote (b) of Table 1.

The yields of ^{18}F-labeled aryl fluorides also depend on the molar ratio of substrate with cesium carbonate as shown in Table 3. This is probably due to reaction of the substrate with cesium carbonate to form the free base.

Competitive Experiments

As shown in the previous paragraph, ^{18}F-for-$^{+}NMe_3$ displacement in reaction mixtures containing NCA $^{18}F^-$ and sufficient concentrations (> 10^{-4} mol l^{-1}) of 3, 4, 5 and 7 is the only significant process leading to incorporation of radiofluorine into organic products. Displacement without appreciable competition from secondary processes, allowed us to carry out the competition experiments to obtain a quantitative estimate of the activating power of the various substituent groups, and compare the nucleofugicity of the trimethylammonium group with respect to other leaving groups, such as NO_2 and F, whose displacement by $^{18}F^-$ had been previously investigated [5,6]. Competition experiments were carried out in the temperature range from 80 to 140°C, using 10^{-3} mol l^{-1} of the competing substrates dissolved in dry DMSO. The results are summarized in Tables 4 and 5. The relevant calculated rate constants are reported in Figure 1 as a function of the reaction temperature. A least squares treatment of the data of Figure 1 gave the approximate Arrhenius parameters listed in Table 6, which contain, for comparison purposes, the pertinent data for o-fluoronitrobenzene, p-dinitrobenzene, and p-nitrobenzonitrile measured under similar conditions [5,6].

DISCUSSION

Tables 1 and 2 show that the reaction of $Cs^{18}F$ either in the NCA state or slightly diluted with inactive fluoride (typically, 10^{-3} mol l^{-1}) in DMSO at moderate temperatures with activated aryltrimethylammonium perchlorates gives the corresponding aryl [^{18}F]fluorides in high yield. These features confirm ^{18}F-for-$^{+}NMe_3$ displacement as an efficient labeling procedure, suitable for the direct preparation of NCA ^{18}F-labeled radiopharmaceuticals [9], and extend its applicability to the rapid synthesis of even poorly activated ^{18}F-labeled aromatic intermediates. The viability of ^{18}F-for-$^{+}NMe_3$ nucleophilic displacement as an efficient route to NCA aryl [^{18}F]fluorides is demonstrated by the competition reactions data which is shown in Tables 4 and 5. As expected, the activating effect of the substituent group X in the ^{18}F-for-$^{+}NMe_3$ displacement in the selected ammonium perchlorates

TABLE 4

Relative reactivity of some activated nitrobenzene and phenyltrimethylammonium perchlorates with NCA ^{18}F-fluoride in dry DMSO[a]

Substrate		Relative Rate Constants[b]			
		140°	120°	100°	80°
X	Y				
NO_2	$\overset{+}{N}(CH_3)_3ClO_4^-$	60	400	2900	30000
NO_2	NO_2	11	40	160	420
CN	$\overset{+}{N}(CH_3)_3ClO_4^-$	8	16	70	100
$COCH_3$	$\overset{+}{N}(CH_3)_3ClO_4^-$	4	8	14	33
CN	NO_2	1	1	1	1

[a] All competition experiments were carried out with equimolar amounts of competing reactants: 10^{-3} mol/ℓ. Reaction time: 20 min.

[b] *p*-Nitrobenzonitrile was used as the reference substrate at all temperatures. Standard deviation of the ratio: ± 20%.

follows the same order observed in the related fluorodenitration reactions carried out on substituted nitrobenzenes in DMSO at 150°C [6], namely:

m-NO_2 < *p*-CH_3CO < *p*-CN < *p*-NO_2

Table 4 also shows that such an order is not affected by temperature changes in the range from 80° to 140°C. It should be noted that no ^{18}F incorporation is observed in 6 under the same conditions, although the reaction center is activated by a CHO group at the *para* position. This is probably due to effective interaction between the proton of the CHO moiety and the $^{18}F^-$ base.

TABLE 5

Relative yields of F-18 aryl fluorides from NO_2 vs $(CH_3)_3N^+$ as leaving groups at 80° and 140°[a]

Substrate		Temperature (°C)	Product	Yield (%)[b]
				
X	Y			
CN	NO_2	80 140	4-[^{18}F]C_6H_4CN	7 40
CN	$\overset{+}{N}(CH_3)_3ClO_4^-$	80 140	4-[^{18}F]C_6H_4CN	24 61
NO_2	NO_2	80 140	4-[^{18}F]$C_6H_4NO_2$	50 62
NO_2	$\overset{+}{N}(CH_3)_3ClO_4^-$	80 140	4-[^{18}F]$C_6H_4NO_2$	55 78

[a] Typical substrate concentrations: 3.6×10^{-3} M. [Substrate]/[Cs_2CO_3] ~ 2. Reaction time: 20 min.

[b] Percentage of activity isolated in the product, corrected for decay.

The leaving ability of $-^+NMe_3$ relative to other groups emerges directly from comparison of the rates of the ^{18}F-for-$^+NMe_3$ processes and the relevant fluorodenitration substitutions in competition experiments. The pertinent data of Table 4 derived from crossed competition reactions corroborates the hypothesis that cationic groups, such as $-^+NMe_3$, are much better leaving groups than the best neutral ones, including NO_2 and F itself, in nucleophilic aromatic substitution by $^{18}F^-$ in DMSO. This conclusion fits into the general order defined for related nucleophiles (e.g., MeO^-) [7], and is in agreement with its theoretical justification. A further analogy is, in fact, observed as to the Arrhenius parameters measured in the nucleophilic substitution by $^{18}F^-$/DMSO and by MeO^-/MeOH (Table 6).

TABLE 6

Arrhenius parameters for nucleophilic substitution of some substituted nitrobenzenes and phenyltrimethylammonium perchlorates by NCA ^{18}F-fluoride in dry DMSO

Substrate	Arrhenius Equation[a]	Correlation Coefficient	ΔH^* (kcal mol^{-1})	ΔS^* (e.u.)
o-$O_2NC_6H_4F$	log k = 10.79-19.4x	0.973	19	-11
p-$C_6H_4(NO_2)_2$	log k = 12.87-22.29x	0.997	22	- 2
p-$NCC_6H_4NO_2$	log k = 18.05-33.77x	0.994	33	+22
p-$O_2NC_6H_4\overset{+}{N}Me_3ClO_4^-$ (3)	log k = 7.90-10.98x	0.992	10	-25
p-$NCC_6H_4\overset{+}{N}Me_3ClO_4$ (4)	log k = 15.73-27.39x	0.994	27	+11
p-$CH_3COC_6H_4\overset{+}{N}Me_3ClO_4$ (5)	log k = 17.14-30.63x	0.999	30	+17

[a] $x = \frac{1000}{2.303RT}$; R in cal mol^{-1} degree^{-1}.

The most interesting feature of the ^{18}F-for-$^+$NMe$_3$ substitution reaction is that the radiochemical yield of the labeled products is reasonably high even at relatively mild temperatures. This is important in applications where the substrate is thermally labile. Furthermore, this reaction does not require dry solvents or the presence of powerful activating groups in the ionic substrate. Therefore, it may in principle allow rapid one-step preparation of NCA ^{18}F-labeled radiopharmaceuticals provided that the starting aryltrimethylammonium salts are soluble in DMSO, stable at moderate temperatures, and activated by electron-withdrawing group (e.g., an acyl moiety at the para position). In general, the presence of other potential leaving groups (e.g., NO_2 in 3 or 7) in the aromatic ring of the aryltrimethylammonium salt does not appreciably interfere with the relatively fast ^{18}F-for-$^+$NMe$_3$ displacement process and therefore leads to the exclusive formation of the corresponding labeled product. Finally, another potential advantage of the ^{18}F-for-$^+$NMe$_3$ route over the more conventional nucleophilic substitutions to produce aryl [^{18}F]fluorides arises from the different physical properties of the starting ammonium salt and of the ^{18}F-labeled product. The unique feature of the cationic group displacement by $^{18}F^-$, namely the conversion of an ionic precursor (the aryltrimethylammonium salt) which is normally insoluble in most organic media, into a neutral NCA aryl[^{18}F]fluoride, which is readily soluble in most organic solvents, allows

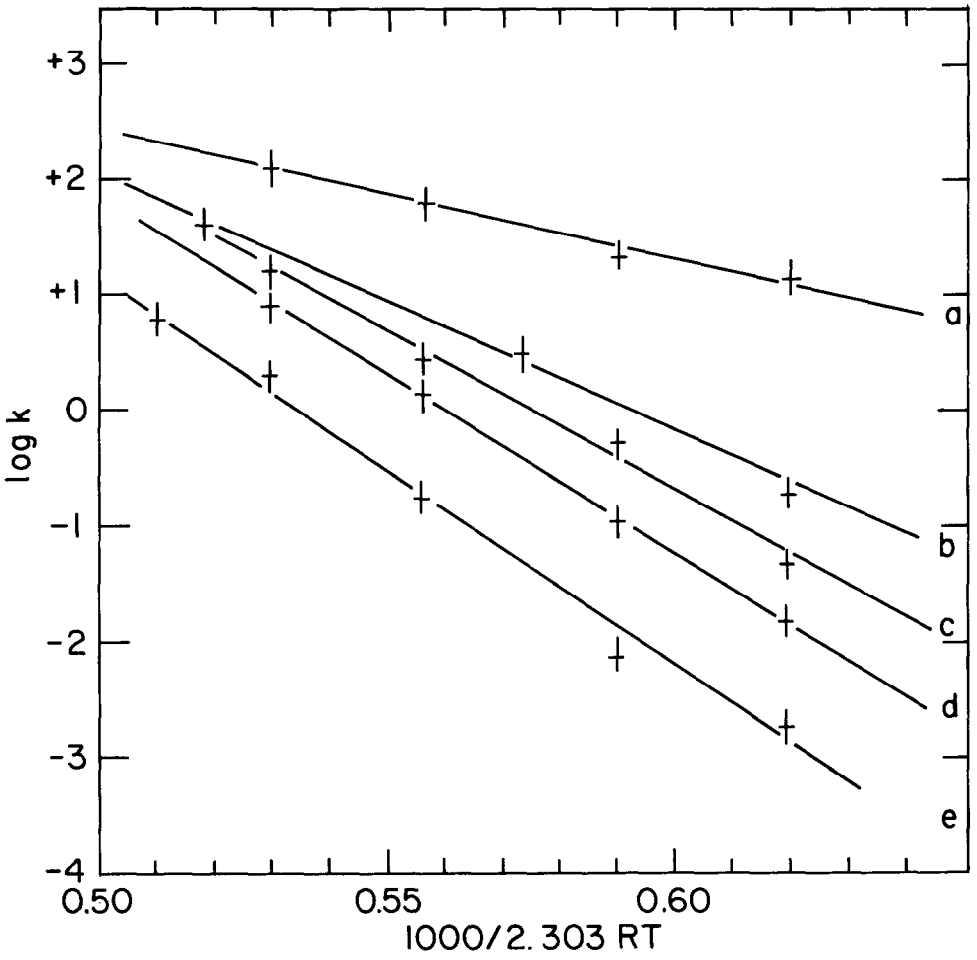


Fig. 1. Arrhenius plots for the nucleophilic substitution of $p\text{-}C_6H_4\overset{+}{Y}NMe_3ClO_4^-$ and $p\text{-}C_6H_4XNO_2$ by NCA ^{18}F-fluoride in dry DMSO: (a) Y = NO_2; (b) X = NO_2; (c) Y = CN; (d) Y = $COCH_3$; (e) X = CN.

rapid and complete removal of any residual starting compound from the ^{18}F-labeled product. The presence of residual inactive impurities from the starting material is often as detrimental as isotopic dilution in the synthesis of short-lived radioactive compounds for demanding biomedical applications, including receptor studies, and their removal often requires elaborate and time-consuming separation and purification procedures.

CONCLUSION

The methodology of rapid synthesis of ^{18}F-labeled compounds via nucleophilic substitution of activated ammonium groups by $^{18}F^-$ has been extended to simple aromatic molecules and has been shown to be an efficient and general route to NCA ^{18}F-labeled aryl fluorides. In comparison with related nucleophilic displacements involving neutral leaving groups, such as NO_2 or F, the rate of the ^{18}F-for-$^{+}NMe_3$ displacement in activated aryltrimethylammonium perchlorates is higher, thus allowing a significant decrease of reaction temperature and reaction time (20 min or less). A pertinent example is afforded by p-nitrophenyltrimethylammonium perchlorate, the most active substrate studied whose reaction with NCA $^{18}F^-$ gave 71% (at 80°C) and 10% (at 40°C) of p-[^{18}F]fluoronitrobenzene after 20 min. These aspects, together with the possibility of fast purification of the ^{18}F-labeled products, make ^{18}F-for-$^{+}NMe_3$ displacement the reaction of choice for the rapid synthesis of NCA ^{18}F-radiopharmaceuticals from thermolabile precursors. In contrast, no F-for-$^{+}SMe_2$ displacement can be observed in highly activated aryldimethylsulfonium perchlorates, when treated with inorganic fluoride under the same conditions.

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