

Fast and High-Yield Microreactor Syntheses of *ortho*-Substituted [^{18}F]Fluoroarenes from Reactions of [^{18}F]Fluoride Ion with Diaryliodonium Salts

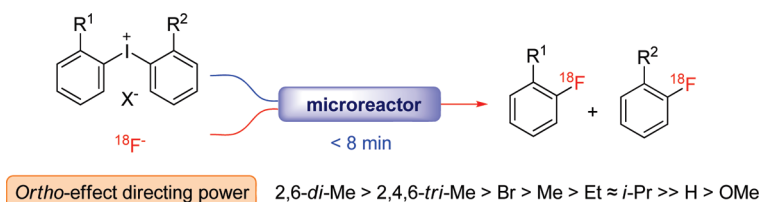
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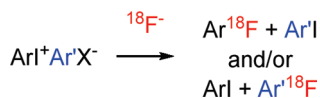
A microreactor was applied to produce *ortho*-substituted [^{18}F]fluoroarenes from the reactions of cyclotron-produced [^{18}F]fluoride ion ($t_{1/2} = 109.7$ min) with diaryliodonium salts. The microreactor provided a very convenient means for running sequential reactions rapidly with small amounts of reagents under well-controlled conditions, thereby allowing reaction kinetics to be followed and Arrhenius activation energies (E_a) to be measured. Prepared symmetrical iodonium chlorides ($\text{Ar}_2\text{I}^+\text{Cl}^-$) rapidly (< 4 min) gave moderate ($\text{Ar} = 2\text{-MeOC}_6\text{H}_4$, 51%) to high ($\text{Ar} = \text{Ph}$ or $2\text{-MeC}_6\text{H}_4$, 85%) decay-corrected radiochemical yields (RCYs) of a single radioactive product (Ar^{18}F). Reaction velocity with respect to Ar group was $2\text{-MeOC}_6\text{H}_4 < \text{Ph} < 2\text{-MeC}_6\text{H}_4$. Activation energies were in the range 18–28 kcal/mol. Prepared unsymmetrical salts (e.g., $2\text{-RC}_6\text{H}_4\text{I}^+2\text{-R}'\text{C}_6\text{H}_4\text{X}^-$; $\text{X} = \text{Cl}$ or OTs) also rapidly gave two products ($2\text{-RC}_6\text{H}_4^{18}\text{F}$ and $2\text{-R}'\text{C}_6\text{H}_4^{18}\text{F}$) in generally high total RCYs (79–93%). Selectivity for product [^{18}F]fluoroarene was controlled by the nature of the *ortho* substituents. The power of *ortho* substituents to impart an *ortho*-effect was in the following order: 2,6-di-Me > 2,4,6-tri-Me > Br > Me > Et \approx *i*-Pr \gg H > OMe. For (2-methylphenyl)(phenyl)iodonium chloride, the time-course of reaction product selectivity was constant and consistent with the operation of the Curtin–Hammett principle. These results will aid in the design of diaryliodonium salt precursors to ^{18}F -labeled tracers for molecular imaging.

1. Introduction

Fluorine-18 is a short-lived ($t_{1/2} = 109.7$ min) positron emitter that finds increasing application for labeling tracers for molecular imaging in animal and human subjects with positron emission tomography (PET).¹ For many of these applications, the fluorine-18 must be at high specific radioactivity, meaning that dilution of the radiotracer with non-radioactive tracer must be low, i.e., the ratio of ^{18}F to ^{19}F

compound must be high. In practice, this ratio is of the order of $1(^{18}\text{F}):200(^{19}\text{F})$, and corresponds to specific radioactivities of the order of 8 Ci/ μmol . In PET imaging studies, this level of specific radioactivity is usually adequate for avoiding toxic or pharmacological effects and also for establishing true tracer conditions in which a biochemical target (e.g., a neurotransmitter receptor) or pathway to be imaged does not become saturated and obscured with the co-administered nonradioactive tracer. For fluorine-18 to be at high specific radioactivity, it must usually be produced as the single-atom species, [^{18}F]fluoride ion. This is usually achieved by the

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SCHEME 1. Reactions of Diaryliodonium Salts with [¹⁸F]Fluoride Ion


¹⁸O(p,n)¹⁸F reaction on ¹⁸O-enriched water, using a moderate-energy proton beam from a compact cyclotron.² This is a highly productive nuclear reaction, capable of generating multi-Curie levels of fluorine-18.

A major challenge in PET radiotracer development is to find efficient methods for rapidly incorporating cyclotron-produced [¹⁸F]fluoride ion into organic molecules. This may be achieved at aliphatic sites and in electron-deficient arenes by nucleophilic substitution reactions.¹ A greater challenge is the incorporation of [¹⁸F]fluoride ion into electron-rich arenes, for which classical aromatic nucleophilic substitution is generally a disfavored process, giving low or negligible yields. The reactions of diaryliodonium salts with [¹⁸F]fluoride ion³ (Scheme 1) do not share this limitation and may be applied to labeling both electron-rich and electron-deficient arenes with fluorine-18. These reactions have therefore gained considerable interest.^{4–6} Notwithstanding, these reactions exhibit unusual features, and their detailed mechanisms are not yet well understood. As part of our ongoing investigations into the scope and nature of these reactions for PET radiotracer development, we wished to explore the influence of substituents, particularly *ortho* substituents, on reaction rates, energetics and product selectivity under varied but well-controlled conditions. Here, we show first the utility of a microreactor apparatus for this radiochemical purpose and second further insights into the mechanism and outcomes of the radiofluorination reaction. These findings will assist in future PET radiotracer design and production.

2. Results and Discussion

2.1. Chemistry. Two main methods were used to prepare substituted diaryliodonium tosylates, namely, reaction of Koser's reagent ([hydroxy(tosyloxy)]iodobenzene; PhI(OH)OTs) or an *ortho*-substituted derivative (RC₆H₄I(OH)OTs) with an arylboronic acid⁷ or tri(alkyl)stannylarene⁸

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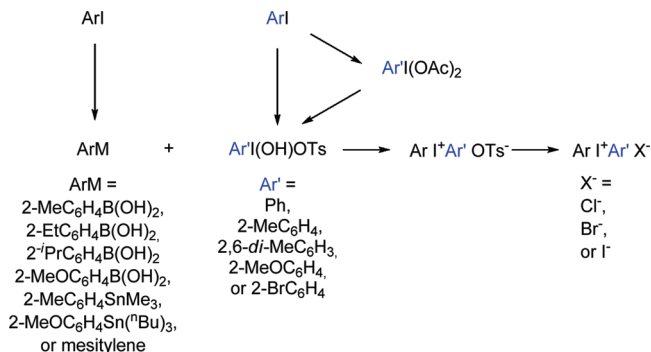
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SCHEME 2. Routes Used for the Syntheses of Diaryliodonium Salts in This Study


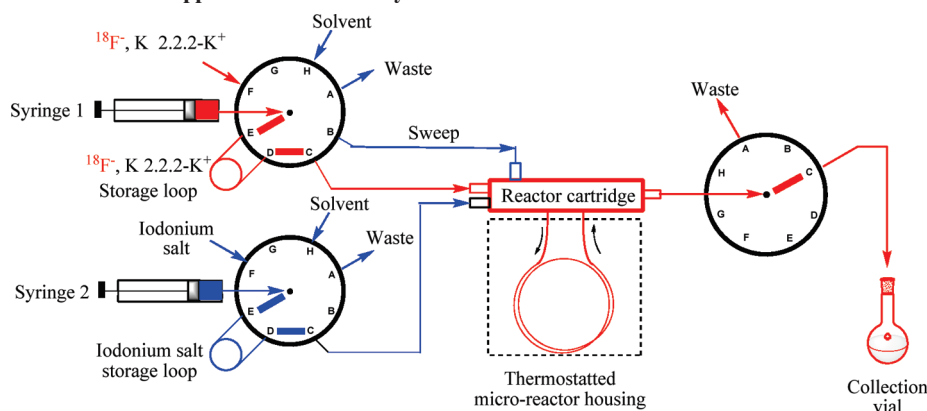
(Scheme 2). The derivatives of Koser's reagent were prepared by treating the appropriate iodoarene diacetate with *p*-tosic acid.⁹ The reactions of Koser's reagent and derivatives with (tri(alkyl)stannyl)arenes exhibited excellent regioselectivity and gave moderate (38%) to high yields (90%). Reactions with arylboronic acids were regioselective for acids bearing an *o*-methyl substituent but not for arylboronic acids bearing an *o*-methoxy substituent. Yields were low (20%) to moderate (49%). Direct reactions with mesitylene were effective for making (mesityl)aryliodonium salts, since with the methyl substitution pattern, only one positional isomer is possible. Diaryliodonium tosylates were readily converted into their corresponding halides in moderate (27%) to high yields (88%) by metathesis reactions. In each case, metathesis was readily confirmed by the absence of signals for tosylate in the ¹H NMR spectrum.

2.2. Radiofluorination Reactions within a Microreactor. The potential advantages of microreactor technology for PET radiochemistry are increasingly recognized.^{10,11} In this study, all radiofluorination reactions were performed in a commercially available microreactor apparatus (Nanotek; Advion). The use of this apparatus offers several advantages over traditional methods of studying radiofluorination reactions, which are usually performed singly with substantial amounts of nonradioactive precursor (e.g., milligram quantities of precursor for labeling).^{1,6} As we have recently shown,¹¹ by use of the microreactor apparatus, a series of reactions can be performed rapidly with very low fixed quantities of reagents, under precisely controlled conditions of temperature, time, and reaction stoichiometry. The whole microreactor is heated to a controlled temperature, which can be well above the boiling point of most organic solvents due to the elevated pressure of the system. Because of the small internal volume of the microreactor (15.7 μ L for 2-m

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SCHEME 3. Setup of Microfluidic Apparatus for the Study of Radiofluorination Reactions



length; 31.4 μL for 4-m length), entering reactant solutions rapidly mix under laminar flow and reach the set reactor temperature. Reaction time simply equates to the residence time of reactants within the reactor, which is determined by the flow rates of the reactants. These flow rates were precisely determined with mechanically driven syringes. Reaction stoichiometry was controlled by setting the concentration of reactants in the loaded solutions and also their flow rates into the reactor.

In this study we performed reactions with [^{18}F]fluoride ion in either a no-carrier-added state (NCA) (i.e., at high specific radioactivity) or a carrier-added (CA) state (at low specific activity). [^{18}F]Fluoride ion was dried in the presence of the cryptand (Kryptofix 2.2.2; K 2.2.2), plus base (K_2CO_3) to maintain a NCA state or in the presence of a known amount of potassium fluoride–K 2.2.2 to produce CA reagent. The generated [^{18}F]fluoride ion complex was then dissolved in the solvent for reaction. A solution of the diaryliodonium salt was prepared in the same solvent. These reagent solutions were loaded into their respective storage loops in the microreactor apparatus and fed into the reactor at set flow rates (Scheme 3).

Reactions were quenched by diluting the output of the reactor in water–acetonitrile (1:1 v/v) at room temperature. Recovery of radioactivity from the reactor was $83 \pm 19\%$, (mean \pm SD, $n = 13$) and $79 \pm 16\%$ (mean \pm SD, $n = 20$) for CA and NCA reactions, respectively. There was no discernible dependence of these values on the nature of the iodonium salt used in the reaction. Control experiments showed that all of the retained radioactivity was polar in reverse phase HPLC analysis, consistent with identity as [^{18}F]fluoride ion. Quenched reaction mixtures were analyzed by reverse phase radio-HPLC. All reactions gave a simple radioactive product distribution. Thus, chromatograms showed only unchanged [^{18}F]fluoride ion (at or near the solvent front), followed either by one peak for a single [^{18}F]fluoroarene (from a symmetrical diaryliodonium salt) or two peaks for two [^{18}F]fluoroarenes (from an unsymmetrical salt). Recovery of radioactive injectate was checked by collection of all radioactive eluate fractions and separate measurement in a dose calibrator. Decay-corrected radiochemical yields (RCYs) were calculated from the radiochromatograms.

Initially, we tested the feasibility of using the microreactor apparatus for radiofluorination of a diaryliodonium salt, the reaction of [^{18}F]fluoride ion with diphenyliodonium chloride. Reactions were performed with NCA [^{18}F]fluoride ion in DMF or CA [^{18}F]fluoride ion in DMF–0.25% water at set

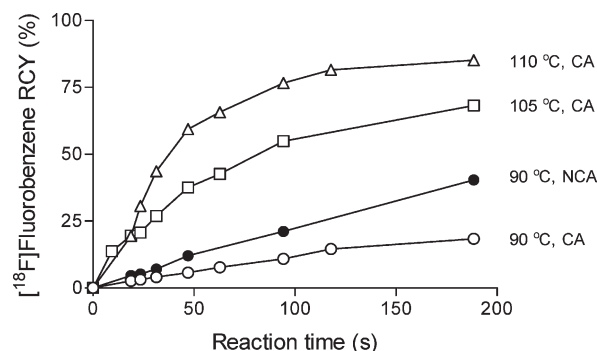


FIGURE 1. Time-course of [^{18}F]fluorobenzene RCY from reactions of [^{18}F]fluoride ion with diphenyliodonium chloride (5 mM) in DMF–0.25% water in the presence of 0.5 mM KF–K 2.2.2 at 90, 105, and 110 °C (CA) or in DMF in the presence of K_2CO_3 –K 2.2.2 at 90 °C (NCA).

temperatures (Figure 1). At 90 °C NCA [^{18}F]fluoride ion gave a RCY higher than that of CA [^{18}F]fluoride ion. CA reactions performed at higher temperatures gave higher RCYs. Remarkably, an 85% RCY of [^{18}F]fluorobenzene was produced from [^{18}F]fluoride ion in < 3.2 min at 110 °C. Clearly the presence of a low concentration of water was well tolerated in these CA reactions.

2.3. Investigation of the *ortho*-Effect. An intriguing feature of the reaction of diaryliodonium salts with nucleophiles is the influence of *ortho* substituents, which have been reported to direct an incoming nucleophile to attack the same ring as the substituent.¹² Here we wished to study this effect more closely for the reactions of [^{18}F]fluoride ion with *ortho*-substituted diaryliodonium salts. We therefore extended the application of the microreactor to the study of the NCA radiofluorination of four (2-methylphenyl)(phenyl)iodonium salts in different solvents. Each reaction was studied at various temperatures up to 200 °C for reaction times up to 4 min. The highest observed RCYs of [^{18}F]fluoroarenes are listed in Table 1 with the corresponding reaction conditions. Each salt gave a higher RCY in DMF than in acetonitrile containing a low proportion (1.5%) of water, or for one salt, the tosylate, in anhydrous acetonitrile. The

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TABLE 1. NCA Radiofluorination of (2-Methylphenyl)(phenyl)iodonium Salts in Different Solvents

entry	anion	solvent	temp (°C)	time (s)	RCY of [¹⁸ F]fluoroarenes ^a (%)			selectivity for main product
					total	[¹⁸ F]2-F-toluene	[¹⁸ F]F-benzene	
1	Cl ⁻	MeCN–1.5% H ₂ O	150	47	46	32	14	2.29
2		DMF	150	157	77	53	24	2.21
3	Br ⁻	MeCN–1.5% H ₂ O	150	94	26	18	8	2.25
4		DMF	130	94	99	67	32	2.09
5	I ⁻	MeCN–1.5% H ₂ O	160	75	12	8	4	2.00
6		DMF	130	126	48	33	15	2.54
7	OTs ⁻	MeCN	140	188	12	9	3	3.00
8		MeCN–1.5% H ₂ O	150	94	50	34	16	2.13
9		DMF	130	126	98	66	32	2.06

^aHighest observed RCYs (the temperature and times are the conditions giving these yields).

TABLE 2. Radiochemical Yields of [¹⁸F]Fluoroarenes from the Radiofluorination of *ortho*-Substituted Diaryliodonium Salts

entry ^a	diaryliodonium salt (ArI ⁺ Ar'X ⁻)		temp (°C)	time (s)	RCY of [¹⁸ F]fluoroarene (%)			selectivity for main product	G _{Ts2} – G _{Ts1} (kcal/mol)
	Ar	Ar'			total	Ar ¹⁸ F	Ar' ¹⁸ F		
1	Ph	Ph	110	188	85	85			
2	2-MeC ₆ H ₄	2-MeC ₆ H ₄	140	188	83	83			
3	2-MeC ₆ H ₄	Ph	110	188	82	57	25	2.28	0.63
4	Ph	2-MeOC ₆ H ₄	140	188	66	60	6.5	9.22	1.8
5	2-MeC ₆ H ₄	2-MeOC ₆ H ₄	140	188	79	75	4	18.8	2.4
6	2-MeOC ₆ H ₄	2-MeOC ₆ H ₄	140	188	51	51			
7	2-BrC ₆ H ₄	2-MeC ₆ H ₄	170	236	86	48	38	1.26	0.20
8	2-MeC ₆ H ₄	2-EtC ₆ H ₄	170	236	95	52	43	1.21	0.17
9	2-MeC ₆ H ₄	2- ⁱ PrC ₆ H ₄	170	236	88	48	40	1.20	0.16
10	2,6-di-MeC ₆ H ₃	2-MeC ₆ H ₄	170	236	74	62	11	5.56	1.5
11	2,4,6-tri-MeC ₆ H ₂	2-MeC ₆ H ₄	130	236	92	59	33	1.78	0.46
12	2,4,6-tri-MeC ₆ H ₂	Ph	150	236	82	63	19	3.24	0.99
13	2,6-di-MeC ₆ H ₃	2,4,6-tri-MeC ₆ H ₂	190	236	82	61	21	3.00	1.0
14	2-BrC ₆ H ₄	Ph	190	236	93	68	25	2.72	0.92

^aEntries 1–6 were performed with CA [¹⁸F]fluoride ion and chloride salts in DMF–0.25% water. Entries 7–11 and 14 were performed with NCA [¹⁸F]fluoride ion and chlorides in DMF. Entries 12 and 13 were performed with NCA [¹⁸F]fluoride ion and tosylates in DMF.

bromide and tosylate of (2-methylphenyl)(phenyl)iodonium gave almost quantitative incorporation of [¹⁸F]fluoride ion into [¹⁸F]fluoroarenes in DMF, whereas incorporations were significantly lower for the iodide and chloride. Ermert et al.¹³ have previously observed the similar reactivity of diaryliodonium tosylate and bromides with [¹⁸F]fluoride ion. In all of our reactions, [¹⁸F]2-fluorotoluene was the major radioactive product and [¹⁸F]fluorobenzene the minor radioactive product. The selectivity for producing [¹⁸F]2-fluorotoluene was quite similar across reactions, ranging from 2.00 to 3.00, thereby verifying that a methyl substituent confers an *ortho*-effect in these reactions.

In order to further understand the *ortho*-effect, studies were extended to a larger range of diaryliodonium salts bearing a range of *ortho* substituents. The radiofluorination of each salt was studied under either CA or NCA conditions in dry DMF or wet DMF over various temperatures and times. Maximal observed RCYs, and the corresponding reaction conditions, are recorded in Table 2. The total RCYs of [¹⁸F]fluoroarenes were impressively high, ranging from 51% to 95%. Yields were lower for salts bearing an *o*-methoxy group, with the symmetrical di-*o*-methoxy substituted salt giving lowest yield. For unsymmetrical salts, product selectivities ranged from 1.20 to 18.8 (Table 2). Surprisingly, an *o*-methoxy group failed to confer an *ortho*-

effect, since 2-[¹⁸F]fluoroanisole was always the least preferred product (Table 2, entries 4 and 5). From all the product selectivity values listed in Table 2, it may be deduced that the power of *ortho* substituents to impart an *ortho*-effect was in the following order: 2,6-di-Me > 2,4,6-tri-Me > Br > Me > Et ≈ ⁱPr > H > OMe. The selectivity values will be useful in the rational design of diaryliodonium salt precursors to ¹⁸F-labeled tracers.

The *ortho*-effect has frequently been ascribed to the steric influence of the *o*-substituent on the conformation of the iodonium salt, leading to a preference for the *ortho*-substituted aryl ring to rest in the equatorial plane of a trigonal bipyramidal structure with therefore easy access for attack by an apically associated nucleophile. Previous studies on the *ortho*-effect have only investigated *o*-alkyl substituents.¹² Our results with *o*-methoxy substituted diaryliodonium salts show that the *ortho*-effect is not purely related to substituent bulk. Rather than substituent bulk, selectivity may be enhanced by the presence of one or more *ortho* hydrophobic groups (e.g., methyl), which create a lipophilic microenvironment in which the incoming [¹⁸F]fluoride ion can act as a powerful nucleophile, by first loosely binding to the hypervalent iodine atom and then attacking the locally lipophilic *ortho*-substituted ring. Opposing (as for OMe) or reinforcing (as for Br) electronic influences also appear to be important in determining product selectivity.

The reliability of the radiofluorination reactions of diphenyliodonium salts have been claimed to be enhanced by

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addition of a free-radical scavenger, such as TEMPO.¹⁴ In this study, we found that radiofluorination reactions were consistent and reliable in the absence of a free-radical scavenger. In fact, in a pilot experiment, we found that TEMPO had no beneficial effect. In general, iodonium salts are well-known to show photosensitivity¹⁵ and indeed much research has been directed to their use as photoinitiators.¹⁶ The microreactor device used in this study stores and uses the iodonium salt reagent in the dark, and this may have contributed to the reliability of the reactions by avoiding radical generation. The tolerance of these reactions for a low concentration of water is also striking and is in accord with a previous claim.¹⁷ This tolerance indicates the generally high reactivity of the iodonium salts for reaction with fluoride ion that is in a moderately hydrated and therefore moderately nucleophilic state.

2.4. Kinetics and Energetics of Radiofluorination Reactions.

Examples of the determination of the Arrhenius activation energies (E_a) for reactions of [¹⁸F]fluoride ion are rare, being confined to isotopic exchange with polyfluoroarenes.¹⁸ The absence of such data may partly derive from the practical limitations of working with a short-lived radionuclide from a cyclotron source. The microreactor apparatus afforded an opportunity to overcome some of these limitations, since well-controlled reaction conditions could be established for rapid sequential reactions from the same “stocks” of radioactive and nonradioactive reagents. In order to gain kinetic data and derive E_a values, we decided to perform reactions with CA [¹⁸F]fluoride ion (0.5 mM) with a 10-fold molar excess of diaryliodonium salt (5 mM) in the presence of $K^+ - K$ 2.2.2. Fluoride ion nucleophilicity is well known to depend on the state of ion hydration.^{1,19} Therefore, we decided to include a small concentration of water (0.25% v/v) in the reaction medium (DMF) to control the hydration of the [¹⁸F]fluoride ion at a fixed carrier concentration and hence its nucleophilicity. Six diaryliodonium chlorides were studied in this manner. Reactions were performed at various set temperatures for several reaction times up to 188 s.

Figure 2 shows an example of acquired kinetic data, that from the reaction of CA [¹⁸F]fluoride ion with bis(*o*-methylphenyl)iodonium chloride. The kinetic data were used to estimate initial reaction velocities, which were then used in Arrhenius plots to estimate activation energies (e.g., Figure 3). The E_a values for the reactions of several diaryliodonium chlorides with CA [¹⁸F]fluoride ion in DMF–0.25% water were estimated to be in the range 18–28 kcal/mol. Activation energies appeared to increase as first one substituent, either an *o*-methyl or *o*-methoxy group, and then a second was introduced into the opposite ring of the diaryliodonium salt (Table 3). The symmetrical *o*-methoxy substituted salt was estimated to

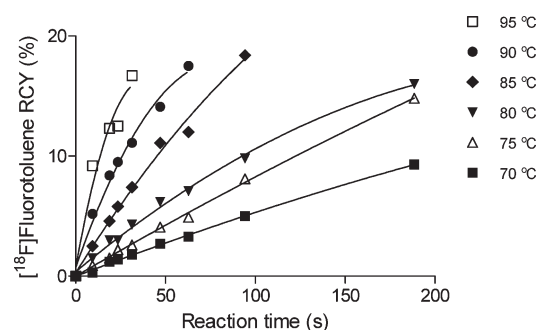


FIGURE 2. Kinetics of the radiofluorination of bis(*o*-methylphenyl)iodonium chloride in DMF–0.25% H₂O to give [¹⁸F]2-fluorotoluene at different temperatures.

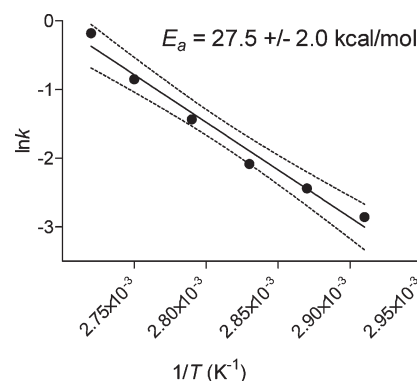


FIGURE 3. Arrhenius plot for the reaction of [¹⁸F]fluoride ion with bis(*o*-methylphenyl)iodonium chloride (data derived from that in Figure 2). The solid line is the best fit determined by linear regression and the dotted lines are the 90% confidence limits (see Experimental Section).

TABLE 3. Arrhenius Activation Energies (E_a) for the Reactions of Diaryliodonium Chlorides with CA [¹⁸F]Fluoride Ion in DMF–0.25% H₂O (in the Presence of $K^+ - K$ 2.2.2)

diaryliodonium chloride		E_a (kcal/mol)	
R	R'	R	R'
H	H	20.9 ± 1.6	20.9 ± 1.6
H	2-MeO	22.5 ± 2.9	n.d.
H	2-Me	23.5 ± 1.6	18.3 ± 0.9
2-Me	2-MeO	25.1 ± 2.6	n.d.
2-Me	2-Me	27.5 ± 2.0	27.5 ± 2.0
2-MeO	2-MeO	28.0 ± 1.6	28.0 ± 1.6

have the highest E_a value. Estimates of E_a values for other reactions of diaryliodonium salts with nucleophiles have been reported and fall in the range 19–37 kcal/mol. For example, the decomposition of various substituted diphenyliodonium halides (halide = Cl^- , Br^- , or I^-) in DMF occurred with E_a values in the range 25.5–36.7 kcal/mol.²⁰ Reactions of diphenyliodonium salts with phenoxide ions in dioxane–water (1:1 v/v) to give diphenyl ethers have an E_a value of 25.9 kcal/mol.²¹

2.5. Selectivities of Reactions; Compliance with the Curtin–Hammett Principle and Mechanistic Considerations.

During

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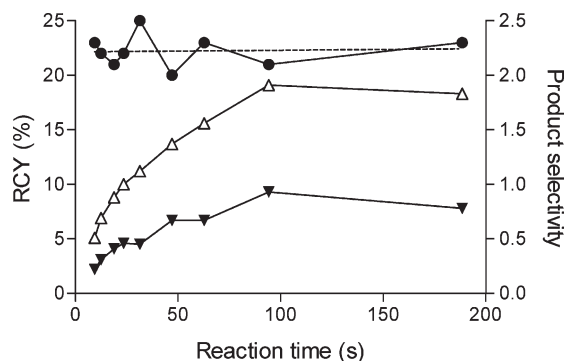
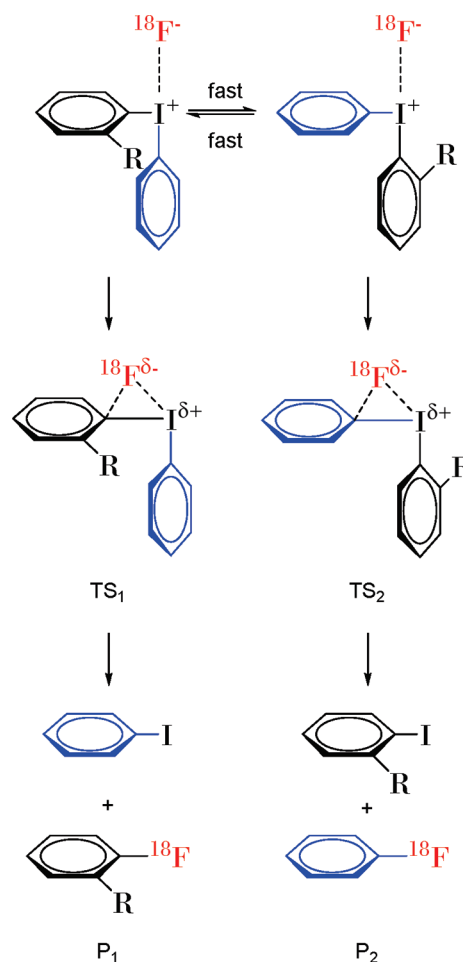


FIGURE 4. Time-course of the decay-corrected radiochemical yield (RCY) of [¹⁸F]2-fluorotoluene (Δ) and [¹⁸F]fluorobenzene (▼) and of the product selectivity (●), from the reaction of CA [¹⁸F]fluoride ion with (2-methylphenyl)(phenyl)iodonium chloride at 110 °C in DMF–0.25% H₂O, in the presence of K⁺–K 2.2.2. Reagents and K⁺–K 2.2.2 were each initially at 2.5 mM. The dashed line is the line of linear regression for the product selectivity data.

the accumulation of the data summarized in Table 2, we were impressed that product selectivities appeared constant for any particular diaryliodonium salt precursor (small variations occurred more with solvent than with anion; see examples reported in Table 1). This suggested that reactions might be taking place in accord with the Curtin–Hammett principle.²² This principle states that the relative amounts of products formed from two critical conformations of substrate are completely independent of the relative populations of the conformations and depend only upon the difference in the free energy of the transition states, provided that the rates of reaction are much slower than the rates of conformational interconversion. The appearance of products in a constant ratio during the reaction course under set conditions constitutes a test of whether a process that involves one substrate to give two products complies with the Curtin–Hammett principle.²³ Thus, we set up an experiment with CA [¹⁸F]fluoride ion and (2-methylphenyl)(phenyl)iodonium chloride as reactants in equimolar proportions in DMF at 110 °C and measured the RCYs of the two products with time (Figure 4). The ratio of products (2.21) was found to be constant over the measured time course (up to 30% total substrate conversion) in accord with the Curtin–Hammett principle. The product selectivity was also measured at other temperatures and was essentially invariant. Scrutiny of other data accumulated in this study revealed very little variation in product selectivity over the time course of reactions.

Monomeric iodonium cations are expected to be highly fluxional and able to interconvert through conformations in which the ligands rapidly interchange equatorial and axial positions relative to the anion, which is secondarily bonded to the pivotal hypervalent iodine atom.²⁴ It may be envisaged that when the anion is an incoming nucleophile it will be able to attack only the carbon atom in the equatorial ring from an apical position. Thus, we propose that the radiofluorination of an unsymmetrical diaryliodonium salt involves attack of [¹⁸F]fluoride ion onto either of two rapidly interconverting conformers, yielding two transition states that each give a

SCHEME 4. Suggested Outline Mechanism for the Radiofluorination of an Unsymmetrical Diaryliodonium Salt, through Transition States TS₁ and TS₂ To Give Products P₁ and P₂, Respectively



single radiofluorinated product (Scheme 4). Assuming all of the radiofluorination reactions follow the Curtin–Hammett principle, the ratio of radiofluorinated products then depends solely on the difference in the free energies of the two transition states. This difference can be calculated from the product selectivity value (P_1/P_2) according to the equation $P_1/P_2 = e^{-(G_{TS1} - G_{TS2})/RT}$, where G_{TS1} and G_{TS2} are the free energies of the transition states 1 and 2, respectively. The values for $G_{TS2} - G_{TS1}$ for the reactions studied here range from 0.16 to 2.4 kcal/mol (Table 2) and are therefore relatively small compared to the activation energies for the same reactions (Table 3).

3. Summary

This study demonstrates that microreactor technology can be excellent for the rigorous and efficient study of radiofluorination reactions under well-controlled conditions using small amounts of material. Furthermore, the reactions of CA and NCA [¹⁸F]fluoride ion with readily synthesized *ortho*-substituted diaryliodonium salts can produce [¹⁸F]fluoroarenes rapidly and in very high RCYs, even for salts bearing electron-donating alkyl or methoxy groups. The powers of individual *ortho* substituents to impart the *ortho*-effect were ranked and showed that this effect is not due solely to substituent bulk. The activation energies determined for some of these reactions are within the range

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estimated for similar reactions of diaryliodonium salts. Finally, we found evidence that the reactions of [^{18}F]fluoride ion with unsymmetrical diaryliodonium salts comply with the Curtin–Hammett principle. These results will aid in our design of diaryliodonium salts as substrates for producing previously inaccessible ^{18}F -labeled tracers for molecular imaging.

4. Experimental Section

Materials, general methods, and details of diaryliodonium salts syntheses are documented in Supporting Information.

4.1. Production of [^{18}F]Fluoride Ion Reagents.

4.1.1. No-Carrier-Added. Cyclotron-produced no-carrier-added [^{18}F]fluoride ion (10–200 mCi) in [^{18}O]water (95 atom %, 225–350 μL) was first adsorbed onto a small anion resin (i.e., MP-1 or QMA) cartridge within the CE module of a NanoTek apparatus (Advion; Louisville, TN) and then released with a solution of K_2CO_3 (0.8 mg; 5 μmol) plus K 2.2.2 (4.5 mg; 11 μmol) in MeCN– H_2O (9:1 v/v; 150 μL) into a 5-mL V-vial. The solution was dried by two cycles of azeotropic evaporation with acetonitrile (0.45 mL) at 100 $^\circ\text{C}$.

4.1.2. Carrier-added. Cyclotron-produced no-carrier-added [^{18}F]fluoride ion (120–200 mCi) in [^{18}O]water (225–350 μL) was dried²⁵ by four cycles of azeotropic evaporation with acetonitrile (0.65 mL for each addition) at 90 W \times 2 min in a microwave cavity (type-521; Resonance Instruments Inc., Skokie, IL) housed within a modified Synthia²⁶ module. KF (1 mM) and K 2.2.2 (1 mM) in 0.5% $\text{H}_2\text{O}/\text{DMF}$ (v/v; 400 μL) were added to the prepared dry $^{18}\text{F}^-$ –K 2.2.2– K^+ complex and mixed in a 5-mL V-vial. The solution was then loaded into the storage loop (255 μL) of the microfluidic apparatus.

4.2. Configuration and Operation of the Microreactor Apparatus. The setup of the LF module used in this work is depicted in Scheme 3. The microreactor is composed of coiled silica glass tubing (e.g., length, 4 m; internal diameter, 100 μm ; internal volume, 31.4 μL), housed in a brass ring filled with high-temperature resistant poly(silicone). The reactor could be heated and thermostatted to a set temperature. The reactor may be fed with reagents from storage loops at set flow rates, by the action of mechanically driven syringes. The reactor may operate up to pressures of 300 psi, which is monitored.

The apparatus was cleaned by flushing tubes and reactors with acetonitrile at the beginning of each experimental session and again at the end. Reagent solutions were loaded into their respective storage loops from different source vials. To perform one reaction, 10–20 μL of solution from each loop were infused (via valve connection from the respective syringe pump \rightarrow E \rightarrow D \rightarrow C) into the microreactor at a set flow rate and temperature. A bolus of acetonitrile was then infused from syringe pump 1 (via valve connection from syringe pump 1 \rightarrow B) to sweep all reaction mixture out of the microreactor and into the collection vial via the distribution valve. The volume of the sweeping solvent just exceeded the aggregate internal volume of the microreactor and subsequent transfer tubing. Once the source vials were in place, all operations were programmed to run in sequence automatically and remotely.

4.3. Radiofluorination Reactions. Dry $^{18}\text{F}^-$ –K 2.2.2– K^+ complex (100–150 mCi) was dissolved in reaction solvent (typically, DMF–0.5% H_2O , DMF, or MeCN; 255 μL). A solution of diaryliodonium salt (10 mM) was prepared in matching solvent. Each of the two solutions (255 μL) was loaded into a separate storage loop of the microfluidic apparatus. For reac-

tions, each solution (10–15 μL) was infused simultaneously into either the 2-m- or 4-m-length coiled silica glass tube microreactor of the apparatus at a set flow rate in the range 4–100 $\mu\text{L}/\text{min}$ and preset temperature. The microreactor output was quenched with MeCN– H_2O (1:1 v/v; 1 mL). The radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), was added to some reactions.¹⁴ Amounts of precursor, temperature and flow rates were varied. Decay-corrected radiochemical yields (RCYs) of [^{18}F]fluoroarenes were measured by reverse phase radio-HPLC on a Luna C18 column (250 mm \times 4.6 mm i.d., 10 μm ; Phenomenex, Torrance, CA) eluted at 1.75 mL/min with a gradient of MeCN– H_2O (60:40 v/v) with the percentage of MeCN increased linearly from 60% to 90% over 7 min.

4.4. Kinetics and Energetics of Radiofluorination Reactions. Reactions were run between a large molar excess of diaryliodonium salt, relative to fluoride ion, in DMF containing 0.5% water, in the presence of carrier potassium fluoride and K 2.2.2. Reaction times were controlled by the rates at which [^{18}F]fluoride–KF–K 2.2.2 solution and the diaryliodonium chloride solution were passed through the microreactor. Reactor outputs were quenched by dilution with acetonitrile–water (1:1 v/v) at room temperature. Reactions were run at a minimum of six different temperatures each separated by at least 5 $^\circ\text{C}$ for several reaction times ranging up to 188 s. RCYs were determined by radio-HPLC analysis of reaction products, by comparing the integral of the radiochromatogram for each labeled product with that of unchanged [^{18}F]fluoride ion. Full recovery of radioactivity from the HPLC system was verified by measurement of all eluted radioactivity in a dose calibrator. With the program Prism 3.0, RCYs below 20% were plotted against time (including zero RCY at zero time), and each curve was fitted to a first-order polynomial. The initial apparent velocities of reaction (V_0^{app} , expressed as % RCY/min) were calculated as the initial slopes of the fitted curves (i.e., as the coefficient of the second term in the equation of the polynomial fit). In V_0^{app} was plotted against the inverse of the reaction temperature ($1/T$, K^{-1}), and the data fitted to a linear curve with Prism 3.0, which also provided curves for 90% confidence limits. Arrhenius activation energies (E_a) were calculated from the fitted slopes, which equal $-E_a/RT$ (R = gas constant).

4.5. Test of Curtin–Hammett Principle. Reactions between CA [^{18}F]fluoride ion (2.5 mM) and (2-methylphenyl)(phenyl)iodonium chloride (2.5 mM) in DMF–0.25% water, in the presence of K^+ –K 2.2.2 (2.5 mM) were performed in the microfluidic apparatus at 110 $^\circ\text{C}$ for various times up to 188 s. The radiochemical yields of the two radioactive products, [^{18}F]2-fluorotoluene and [^{18}F]fluorobenzene, were measured, and the product selectivity for major product, as the ratio of these two products, was calculated for each reaction time.

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Note Added after ASAP Publication. The version published ASAP April 2, 2010 contained errors in the reported data due to an error in the computation of microreactor residence times. Tables 1 and 2, Figures 1–4, and text were corrected in the version reposted April 22, 2010.

Supporting Information Available: Full experimental and characterization data for the new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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