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Mechanistic study of nucleophilic fluorination for the synthesis of fluorine-18 labeled fluoroform with high molar activity from *N*-difluoromethyltriazolium triflate†

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The synthesis of fluorine-18 labeled fluoroform with high molar activity has grown in importance for the development of fluorine-18 labeled aryl-CF_3 radiopharmaceuticals that are useful as diagnostic radiotracers for the powerful technique of positron emission tomography (PET). We designed a strategy of synthesizing fluorine-18 labeled fluoroform from *N*1-difluoromethyl-*N*3-methyltriazolium triflate (**1**) *via* S_N2 fluorination without stable fluorine isotope scrambling. Fluoroform was generated at rt in 10 min by fluorination of the triazolium precursor with TBAF (6 equiv.). We propose three routes (a), (b), and (c) for this fluorination. Quantum chemical calculations have been carried out to elucidate the mechanism of experimentally observed nucleophilic attack of fluoride at difluoromethyl group *via* route (a), not *N*3-methyl *via* route (b). ^{1}H and ^{19}F NMR studies using deuterium source have been performed to examine the competition between S_N2 fluorination (route (a)) and the formation of difluorocarbene (route (c)). The observed superiority of S_N2 pathway to formation of difluorocarbene in the reaction of the precursor using CsF in ($CD_3CN/(CD_3)_3COD$ (17.8 : 1)) gives the possibility of preparing the fluorine-18 labeled fluoroform in high molar activity.

Introduction

Aryl-CF_3 is a moiety widely found in the structure of drugs.[1] Among the fluorine containing drugs approved by the Food and Drug Administration during 1950–2014, twenty-one percent contained aryl-CF_3 and 1% contained alkyl-CF_3.[2] As the positron emission tomography (PET) gains more and more importance as a powerful technique for probing the distribution of injected radiopharmaceuticals labeled with positron emitter radionuclides in the human body,[3] the synthesis of radiopharmaceuticals becomes a critical task to apply this robust method to a variety of medical problems. Since fluorine-18 has relatively low energy (638 keV) and the approximately 110 min of half-life, the radioisotope fluorine-18 is considered to be the best positron emitter.[4] Synthesis of [^{18}F]aryl-CF_3 radiopharmaceuticals[5,6] makes it possible to easily measure the biodistribution of drugs with PET, consequently shortening the drug development period. It is especially important that introduction of fluorine-18 into drugs should proceed under mild conditions, *i.e.*, at

low temperatures, and be carried out fast due to the short half-life of fluorine-18 radionuclide.[7]

A recent method to prepare aryl-CF_3 is to use trifluoromethyl anion generated from fluoroform for trifluoromethylation reaction.[8] The aryl-[^{18}F]CF_3 is prepared through the formation of [^{18}F]$CuCF_3$ intermediate from [^{18}F]fluoroform. Among the [^{18}F]fluoroform synthesis methods, that using difluoroiodo-methane or difluoromethylsulfonium salt as a difluorocarbene precursor has been studied (Scheme 1).[9,10] However, due to the isotopic dilution phenomenon,[10] the difluorocarbene pathway gave a low molar activity (A_m) of [^{18}F]fluoroform (A_m = 1–32 GBq μmol^{-1}).[9] A method of synthesizing [^{18}F]fluoroform with improved A_m has been recently reported, which was achieved by limiting the difluorocarbene formation using [^{18}F]fluoro-methane and CoF_3 (A_m = maximum 163 GBq μmol^{-1} and average of 38 ± 35 GBq μmol^{-1} (n = 20)).[11] In addition, a study of producing [^{18}F]fluoroform with increased A_m has been reported, based on the strategy using [^{18}F]triflyl fluoride under less basic condition to reduce the decomposition of difluoro-oiodomethane (A_m = 97 ± 20 GBq μmol^{-1} (n = 3)).[12]

In 2013, we reported that the triazolium group of 1,2,3-triazolium triflate functioned as a very good nucleofuge for displacement by the fluoride ion.[13] The experimental conditions of this method were so mild that it could be used for the preparation of PET radiopharmaceuticals bearing *O*-[^{18}F]

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† Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H and ^{19}F NMR studies, and computational details. See DOI: 10.1039/d0ra09827b

previous work

synthesis of ^{18}F-fluoroform using difluorocarbene precursor
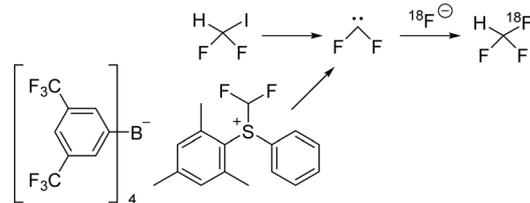
this work

synthesis of fluoroform using triazolium precursor for S_N2 fluorination
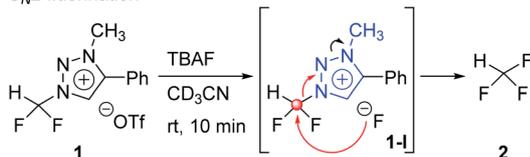
Scheme 1 Previous work and this work.

fluoromethyl groups. As mentioned earlier, the synthesis of [18F]fluoroform with high molar activity is very critical. We have designed a strategy of synthesizing [18F]fluoroform from N-difluoromethyltriazolium triflate **1**, utilizing the fact that 1,2,3-triazolium group may act as an excellent leaving group in fluorination reactions (Scheme 1). If this reaction proceeds *via* S_N2 mechanism without stable fluorine isotope scrambling, the synthesis of [18F]fluoroform with high A_m would be possible. Here, we consider two plausible mechanisms for the synthesis of fluoroform from triazolium precursor **1** – either *via* S_N2 fluorination or *via* the formation of difluorocarbene. We investigated: (1) the stability of triazolium precursor **1** with respect to temperature and solvents, (2) optimal fluorination conditions, (3) the nucleophilic selectivity toward $N1$-difluoromethyl and $N3$-methyl groups of triazolium precursor, (4) the effect of hydrogen bonding with C5-hydrogen and fluoride in the fluorination of triazolium precursor, (5) the mechanism (pre-reaction complex, transition state, post-reaction complex) of the reactions along with the energetics of triazolium precursor by quantum chemical calculations, and (6) the confirmation of the S_N2 reaction mechanism by NMR study of fluorination.

Results and discussion

Stability of triazolium precursor 1

To confirm the stability of triazolium precursor **1**, experiments were performed by changing solvents and temperature (Table 1). Decomposition of precursor **1** was not observed when **1** was heated at 80 °C for 60 h in acetonitrile. Precursor **1** was very stable in acetonitrile at high temperature (entry 1). DMF (bp = 153 °C) was used to confirm the stability of **1** at higher temperature in the following attempts: when **1** was heated at 110 °C for 36 h in DMF, demethylation occurred, resulting in **3** (entry 3). Following the reaction at 110 °C, the temperature was

Table 1 Investigation of stability of precursor **1**[a]

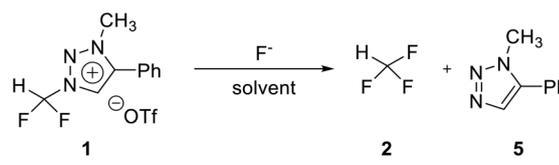| Entry	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)	
				1	**3**
1	CD$_3$CN	80	60	100	0
2	DMF-d_7	110	1	100	0
3	DMF-d_7	110	36	94	6
4	DMF-d_7	110 to 150	48	81	19
5	DMF-d_7	110 to 150	72	68	32

[a] All reactions were carried out on a 0.084 mmol reaction scale of triazolium precursor **1** in 0.75 mL of solvent in a sealed NMR tube. [b] ^{1}H NMR yields.

raised to 150 °C. Then the demethylation occurred in a total yield of 32% when **1** was heated for additional 36 h (entry 5). The precursor **1** decomposed very slowly in DMF at high temperature. Compound **3** was confirmed by observing the signals of the CF$_2$H and C5 proton in ^{1}H NMR (see ESI†).

Optimization of fluorination from triazolium precursor 1

Difluoroiodomethane is a gas, whereas triazolium precursor **1** is a bench-stable solid. Thus, triazolium precursor **1** is more convenient to weigh and to quantify the experimental observations. We searched efficiently the optimal condition of the synthesis of fluoroform. The reaction conditions of fluorination were investigated by using CsF or TBAF (Table 2). When CsF (2 equiv.) was used, the reaction proceeded 70% after 1 h and it was complete after 8 h (entries 1 and 4). When CsF was increased to 6 equiv., the reaction proceeded 77% after 1 h and it was complete after 5 h (entries 5 and 6). When TBAF (6 equiv.) was used instead of CsF, fluoroform **2** was generated faster. After 10 min at 80 °C, the reaction was complete (entry 7). The ^{1}H NMR signal of $N3$-methyl group of **1** decreased and the signal of methyl group of **5** as a leaving group increased (see ESI†). A quartet from fluoroform **2** was observed in ^{1}H NMR. Fluorination using TBAF was faster, indicating that reactivity of F$^-$ in TBAF was higher than that in CsF. When reaction temperature was lowered to rt, the reaction proceeded 86% after 10 min (entry 8). The reaction rate decreased when TBAF was reduced to 2 equiv. (entries 9 and 10). When DMF-d_7 was used as solvent, the reaction was complete in 10 min at 80 °C (entry 11).

Table 2 Optimization of reaction conditions using precursor 1^a

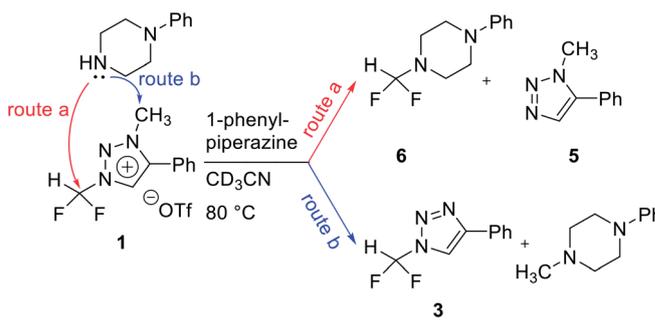| Entry	F⁻ source (equiv.)	Solvent	Temp. (°C)	Time	Yield 5^b (%)
1	CsF (2.0)	CD$_3$CN	80	1 h	70
2	CsF (2.0)	CD$_3$CN	80	2 h	81
3	CsF (2.0)	CD$_3$CN	80	4 h	93
4	CsF (2.0)	CD$_3$CN	80	8 h	100
5	CsF (6.0)	CD$_3$CN	80	1 h	77
6	CsF (6.0)	CD$_3$CN	80	5 h	100
7	TBAF (6.0)	CD$_3$CN	80	10 min	100
8	TBAF (6.0)	CD$_3$CN	rt	10 min	86
9	TBAF (2.0)	CD$_3$CN	rt	10 min	51
10	TBAF (2.0)	CD$_3$CN	rt	1 h	64
11	TBAF (2.0)	DMF-d_7	80	10 min	100

^{a} All reactions were carried out on a 0.084 mmol reaction scale of triazolium precursor **1** in 0.75 mL of solvent in a sealed NMR tube. ^{b} ^{1}H NMR yields.

Table 3 Reactions of triazolium precursor **1** with 1-phenylpiperazine^a

		Yield^b (%)		
Entry	Time (h)	**1**	**3**	**5**
1	5.5	68	25	7
2	10	60	32	8
3	24	43	47	10
4	48	28	59	13

^{a} All reactions were carried out on a 0.084 mmol reaction scale of triazolium precursor **1** in 0.75 mL of CD$_3$CN in a sealed NMR tube. 1-Phenylpiperazine (3 equiv.) was used as a nucleophile. ^{b} ^{1}H NMR yields.

Nucleophilic selectivity toward triazolium precursor 1

We propose three competing routes (a), (b), and (c). Route (a) is the desired route, in which the fluoride attacks the carbon of N1-difluoromethyl *via* S$_N$2 pathway, producing fluoroform. In route (b), which is a side route, F⁻ attacks the carbon of N3-methyl. The last route (c) is an undesired route, in which the nucleophile F⁻ attacks the hydrogen atom of N1-difluoromethyl, consequently giving fluoroform *via* the formation of difluorocarbene.

Triazolium precursor **1** was also allowed to react with 1-phenylpiperazine to study the nucleophilic selectivity toward **1** (Table 3). If the nucleophile 1-phenylpiperazine attacks the difluoromethyl group, **6** and methyltriazole **5** will be formed through route (a). On the other hand, if the nucleophile 1-phenylpiperazine attacks N3-methyl, difluoromethyltriazole **3** will be formed through route (b). When precursor **1** reacted with 1-phenylpiperazine as a nucleophile at 80 °C, demethylation of N3-methyl group occurred predominantly than route (a).

When F⁻ was used as a nucleophile (Table 2), only route (a) proceeded, producing fluoroform (**2**). On the other hand, when 1-phenylpiperazine (3 equiv.) was used as a nucleophile, route (b) was followed, giving **3** as the main product (Table 3). There are two reasons why demethylation of N3-methyl group occurred. First, the difluoromethyl group has a steric hindrance compared to methyl group. The difluoromethyl group is difficult to react with 1-phenylpiperazine *via* S$_N$2 due to the steric hindrance of fluorine, which is slightly larger in volume than hydrogen. However, as N3-methyl has only hydrogen atoms having smaller volume than a fluorine, S$_N$2 reaction can occur well. Fluoride produced fluoroform well because the fluoride received less steric hindrance toward difluoromethyl group than 1-phenylpiperazine did. Since fluoride is a nucleophile of

smaller size than 1-phenylpiperazine, it attacks the difluoromethyl group, producing fluoroform. On the contrary, 1-phenylpiperazine attacked N3-methyl with less steric hindrance, and demethylation occurred. Second, there is a difference in the efficiency of exchange of the nucleophile with triflate anion. It may be speculated that fluoride was able to selectively produce fluoroform because of the increased access to difluoromethyl, after the fluoride anion exchanged with triflate anion of triazolium precursor. In the case of 1-phenylpiperazine, it is also presumed that demethylation occurred in relatively accessible N3-methyl, since there was no anion exchange between the triflate anion and the nucleophile.

Reactions of benzotriazolium precursor 7

To confirm the effects of hydrogen bonding of C5 proton of triazolium precursor **1** with fluoride anion, the reaction of benzotriazolium precursor **7** with no C5 proton of triazolium precursor **1** was investigated (Table 4). When CsF reacted with benzotriazolium precursor **7** at 80 °C for 24 h, 47% of starting material **7** remained, confirming that the reactivity of **7** was lower than that of triazolium precursor **1** (entry 1).

The positive charge of the benzotriazolium leaving group seems to be delocalized, because it can be distributed over both triazole and benzene rings. Thus, the benzotriazolium leaving group is difficult to fall off than triazolium. In addition, fluoroform (**2**) and methylbenzotriazole **8** were generated by fluorination reaction *via* route (a) as shown in Table 4. Difluoromethylbenzotriazole **9** was generated by demethylation through route (b). Unlike triazolium precursor **1**, demethylation occurred in the reaction with CsF, because fluoride is less likely to produce fluoroform due to the lack of hydrogen bond involving C5 proton of triazolium salt **1**. It is known that in

Table 4 Nucleophilic reactions of benzotriazolium precursor **7**[a]
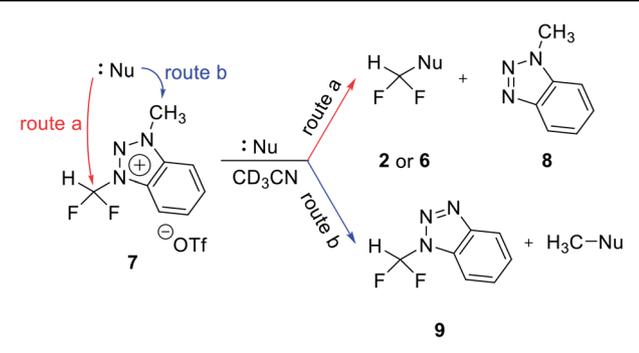
Entry	Nucleophile (equiv.)	Temp. (°C)	Time	7	9	8
				Yield[b] (%)		
1	CsF (2.0)	80	24 h	47	27	26
2	TBAF (2.0)	rt	10 min	46	1	53
3	TBAF (2.0)	rt	3.5 h	28	2	70
4	TBAF (2.0)	rt	27.5 h	0	3	97
5	1-Phenylpiperazine (3.0)	80	5.5 h	78	19	3
6	1-Phenylpiperazine (3.0)	80	10 h	65	31	4
7	1-Phenylpiperazine (3.0)	80	24 h	45	51	4
8	1-Phenylpiperazine (3.0)	80	48 h	27	68	5

[a] All reactions were carried out on a 0.090 mmol reaction scale of benzotriazolium precursor **7** in 0.75 mL of CD_3CN in a sealed NMR tube. [b] ^1H NMR yields.

nucleophilic fluorination, *tert*-alcohols exhibit the effects of weakening the ionic bond of CsF by the formation of hydrogen bonding with fluoride of CsF, thus making fluoride a good nucleophile by solvating it.[14] The pK_a of C5 proton of *N*3-alkylated 1,2,3-triazolium salt is about 24,[15] lower in acidity to *tert*-alcohol ($pK_a = 19$). Therefore, the C5 proton of triazolium precursor **1** seems to increase the nucleophilicity of fluoride through hydrogen bonding.

When TBAF reacted with **7** at rt, the formation of fluoroform proceeded in 53% of yield *via* route (a) after 10 min, and demethylation occurred only 1% (entry 2). We suggest that the observed low demethylation indicates that the fluoride of TBAF is more nucleophilic than CsF, so the fluoroform production reaction occurs quickly and predominantly. In reactions of **7** with 1-phenylpiperazine, demethylation *via* route (b) occurred more readily than fluoroform formation (route (a)) (entries 5–8), similar to the case of triazolium precursor **1**.

Quantum chemical analysis of reaction mechanism

We carried out Natural Atomic Orbital (NAO)[16] analysis, finding that the carbon atom of CF_2H has partial positive charge ($\sim+0.79$) because of the strong electron-withdrawing inductive effects of two Fs, whereas the electric charge of the methyl C atom is negative (~-0.37) because of electron-donating property of the methyl group (Fig. 1). This may well explain the fact that fluoride reacts selectively to CF_2H of triazolium precursor **1** when CsF or TBAF is used as a nucleophile. However, it seems to be difficult to explain why the S_N2 reaction also occurred toward
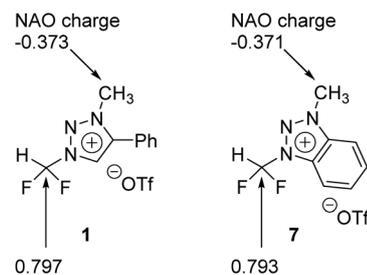

Fig. 1 Natural atomic orbital analysis of precursors **1** and **7**.

the methyl side when 1-phenylpiperazine was used as a nucleophile.

To elucidate the mechanism of these experimentally observed reactions using triazolium precursor **1**, we carried out systematic quantum chemical calculations using the M06-2X[17] method with 6-311+G** basis set for H, C, N, O, S atoms, as implemented in Gaussian 09.[18] The LANL2DZ pseudo-potential[19] and its corresponding basis set is used for Cs atom. We found that all reactions proceeded by S_N2 mechanism *via* single transition state, as it was the case for nucleophilic fluorination using CsF in various solvent/promoters. Fig. 2 depicts the pre-reaction complexes of fluorination using CsF at $-CF_2H$ and at $-CH_3$ side. In $(CsF-1)_{Pre}$, in which the nucleophile F^- attacks the $-CF_2H$ side, F^- forms strong hydrogen bond with H of the $-CF_2H$ group with a distance of 1.727 Å. Cs^+ lies close to F and two O atoms of $-OTf$ above the triazolium ring. In $(CsF-2)_{Pre}$, F^- approaches the carbon center at $-CH_3$. The local environment of Cs^+ with respect to F and two O atoms is similar to $(CsF-1)_{Pre}$, with the distances of 2.978, 3.232, 3.345 Å, respectively. The distance between F^- and methyl H is 2.057 Å, which is somewhat larger than that between F^- and H of CF_2H of $(CsF-1)_{Pre}$ because of the less polarized $-CH_3$ in the absence of the inductive effects of the F atoms. Consequently, F^- interacts slightly more strongly with the Cs atom ($R_{Cs\cdots F} = 2.978$ Å) as compared with $(CsF-1)_{Pre}$ ($R_{Cs\cdots F} = 2.998$ Å).

Our calculations show that the Gibbs free energy of the pre-reaction complex for fluorination at $-CF_2H$ is much lower (by 4.0 kcal mol^{-1}) than that for the reaction at $-CH_3$ side, indicating that the former complex is much more stable. This seems to be the result of much stronger electrostatic attraction between the nucleophile and the partially positive charged
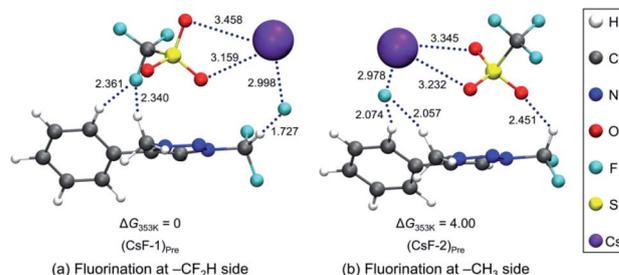
Fig. 2 Pre-reaction complexes of reactions using CsF (a) at $-CF_2H$ and (b) $-CH_3$ side.

(+0.797) C center in –CF$_2$H than that in –CH$_3$ whose carbon center is partially *negative* (−0.373). The relative thermodynamic stability of (CsF-1)$_{Pre}$ with respect to (CsF-2)$_{Pre}$ (ΔG = 4.0 kcal mol^{-1}) indicates that the population of pre-reaction (CsF-1)$_{Pre}$ at thermal equilibrium (that is, according to the Boltzmann distribution $P_1/P_2 = \exp(-(G_1 - G_2)/RT)$) would be much larger (by a factor of ~250 : 1, suggesting that the relative population of (CsF-2)$_{Pre}$ is essentially vanishing), well accounting for the experimentally observed exclusive formation of compound **5** (100% in 8 h, Table 2, entry 4) resulting from the reaction at –CF$_2$H side.

Pre-reaction complexes and transition states for the [triazolium][piperazine] system are shown in Fig. 3 along with the energetics of reaction. In (PZ-1)$_{Pre}$, the pre-reaction complex for reaction at –CF$_2$H site, due to the inductive effect of 'CF$_2$', the highly polarized C–H forms hydrogen bond with lone pair electrons of N4 nitrogen of 1-phenylpiperazine and with an O atom of –OTf. In (PZ-2)$_{Pre}$, the nucleophile (1-phenylpiperazine) reacts at the –CH$_3$ group. The piperazine moiety is on the opposite side of –OTf of the phenyl ring of triazolium molecule. The distance between N4 and H of CH$_3$ group is 2.414 Å which value is larger than that of (PZ-1)$_{Pre}$ ($R_{N\cdots H}$ = 2.373 Å). In both structures the –OTf group lies above the triazolium, forming hydrogen bond with the –CF$_2$H group. The Gibbs free energies at 353 K for these two structures are very similar.

Fig. 3 also presents the transition states. In (PZ-1)$_{TS}$, The N4 lone pair electrons point toward C of –CF$_2$H group due to the hydrogen bond. The distance $R_{H\cdots O}$ between –OTf and C–H of the –CF$_2$H group decreases from 2.310 Å in the pre-reaction complex (PZ-1)$_{Pre}$ to 1.996 Å, indicating that the hydrogen bond is strengthened in the transition state. The O atoms of –OTf are near the phenyl hydrogens of the triazolium molecule and of piperazine moiety. In (PZ-2)$_{TS}$, however, the –OTf group is above the triazolium ring and far away from the piperazine moiety. The N4 of 1-phenylpiperazine in (PZ-1)$_{TS}$ is slightly closer to the C of CF$_2$H group with the distance of 2.036 Å in comparison with the corresponding distance (2.042 Å) in (PZ-2)$_{TS}$.

The activation barrier of reaction at –CF$_2$H and –CH$_3$ side is 27.2 and 24.7 kcal mol^{-1}, respectively (Fig. 3c). Lower (by

2.5 kcal mol^{-1}) activation barrier at –CH$_3$ than at –CF$_2$H side indicates that the rate of the former reaction (at –CH$_3$) is larger than that at –CF$_2$H side, in excellent agreement with the experimental observations of much larger yield (59%) of reaction using 1-phenylpiperazine at –CH$_3$ compared with that (13%) at –CF$_2$H side after 48 h at 80 °C (Table 3, entry 4). This observation is especially conspicuous, because the Natural Atomic Orbital (NAO)[16] charge of the C atom on which the nucleophile (1-phenylpiperazine) carries out the nucleophilic attack is −0.373 (+0.797) for reactions at –CH$_3$ (–CF$_2$H) group in the pre-reaction complex (PZ-1)$_{Pre}$ ((PZ-2)$_{Pre}$). Common sense would predict that 1-phenylpiperazine would prefer –CF$_2$H to –CH$_3$ side, whose carbon atom even exhibits a partial *negative* charge. The origin of this stark contrast of reaction yields using 1-phenylpiperazine compared with those using CsF, in which no reaction at –CH$_3$ side is observed, is highly intriguing, and necessitates a systematic mechanistic elucidation.

Because the two pre-reaction complexes are essentially degenerate, this difference in activation barriers at –CF$_2$H and –CH$_3$ side seems to originate from the structures of the transition states. Most notable difference in (PZ-1)$_{TS}$ and (PZ-2)$_{TS}$ shown in Fig. 3 is the location of the –OTf group with respect to the 1-phenylpiperazine and triazolium moieties: in (PZ-1)$_{TS}$ the –OTf group lies between these two latter functional groups, and the electronegative O atom in –OTf exerts attractive force on the piperazine unit, pulling N4 toward –CF$_2$H. In (PZ-2)$_{TS}$, no such effects of –OTf exists, because it lies above triazolium far from the piperazine molecule in (PZ-2)$_{TS}$. This difference can be seen from the distance R_{N-C} in (PZ-1)$_{TS}$ (2.036 Å) and in (PZ-2)$_{TS}$ (2.042 Å). As compared with (PZ-2)$_{TS}$, the better proximity of N4 to the carbon center in –CF$_2$H in the transition state (PZ-1)$_{TS}$ against the electrostatic repulsion by the electronegative F atoms in –CF$_2$H renders the activation barrier for reaction at the –CF$_2$H side larger than that at –CH$_3$ side.

Competition between S$_N$2 and difluorocarbene pathways

The mechanism of fluorination of **1** was as proposed in Scheme 2. Triflate ion was substituted with F$^-$ in TBAF. Because of high nucleophilicity of F$^-$ substituted on the triazolium ring, fluorination could proceed *via* S$_N$2 pathway. We expect that S$_N$2 fluorination will generate [^{18}F]fluoroform with higher A_m.

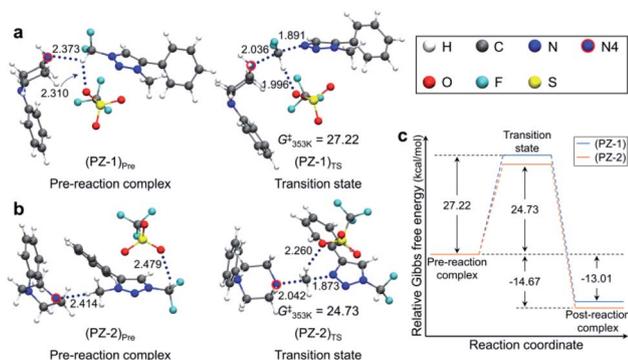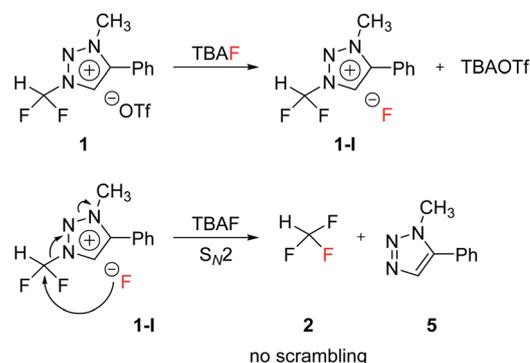**Fig. 3** Pre-reaction complexes and transition states of reactions using 1-phenylpiperazine (a) at –CF$_2$H and (b) –CH$_3$ side and (c) energetics of reaction.

Scheme 2 Proposed mechanism.

When triazolium precursor **1** reacted with CsF or TBAF, fluoroform (**2**) was formed. There are two possible pathways to form fluoroform: (1) fluoride attacks the carbon of difluoromethyl *via* S_N2, and/or (2) fluoride deprotonates proton of difluoromethyl, leading to formation of difluorocarbene. To examine the competition between two pathways, ^{1}H and ^{19}F NMR studies using either CD_3OD, CD_3CN/CD_3OD or $CD_3CN/(CD_3)_3COD$ were performed (Table 5), because nucleophilic fluorination goes well in non-polar protic solvent (*tert*-alcohol) rather than polar protic solvent (methanol).[14] If reaction proceeds *via* S_N2 fashion (route (a)), the proton of difluoromethyl will not be attacked and thus CF_3H will be formed. In contrast, if difluorocarbene is produced *via* route (c), **14** will react with deuterium source and thus CF_3D will be generated. Also, if **14** reacts with H_2O in the reaction mixture, CF_3H will be formed. Thus, the total yield of fluoroform (**2**) is the sum of the yield of **2** *via* route (a) only and the yield of **2** from **14**. Thus, we modified the calculated values (Table 6) from Table 5 using the ratio of exchangeable deuterium source and H_2O (see ESI, Table S1†). As shown in Table 6, we indicated the yield of **2** *via* S_N2 (route (a)) only, and the yield of **11** from **14** if reaction mixture contains only exchangeable deuterium source and no H_2O.
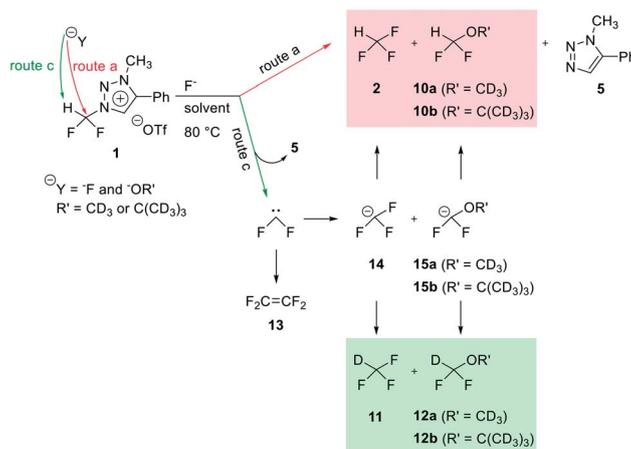
When **1** reacted with TBAF in CD_3OD, **2** and **10a** were observed in ^{1}H NMR (see ESI†). When S_N2 reaction occurred between **1** and CD_3O^-, **10a** would be formed. We observed that in ^{19}F NMR experiments, not only **2** and **10a** *via* route (a), but also **11** and **12a** *via* route (c) were obtained. **11** was formed in larger quantity than **2**, and more of **12a** was formed than **10a** (Table 6, entry 1). When solvent was changed from CD_3OD to CD_3CN/CD_3OD (6.5 : 1), the S_N2 reaction rates significantly increased, the reaction being complete after 20 min at 80 °C, as **2** and **10a** were detected by ^{1}H NMR. Thus it seems that increasing the amount of acetonitrile leads to faster S_N2 reaction. To reduce the amount of moisture in the reaction mixture, we carried out the reaction using CsF as the source of F^- under the Ar atmosphere. It was found that the reaction was complete after 5 h in CD_3CN/CD_3OD (6.5 : 1) (entry 3).

Compared to the reaction of entry 2, production of **2** was slower probably because the nucleophilicity of F^- in CsF was lower than that in TBAF. To further increase the rates of S_N2 reactions, we changed the ratio of CD_3CN/CD_3OD to 17.8 : 1 (entry 4). Compared to the reaction of entry 3, the formation of **2** *via* only route (a) increased to 32.5% and the yield of **10a** increased to 11.4%. As **2 : 11** was 1 : 1.22, the yields of the two products were similar.

We have reported in our previous work[14] that the rates of fluorination increased as the steric hindrance of alcoholic solvent increased. Thus we changed the deuterium source from CD_3OD to $(CD_3)_3COD$. When $CD_3CN/(CD_3)_3COD$ (6.5 : 1) was used, compared to the reaction of entry 3, the yield of **2** *via* only route (a) increased from 6.6% to 22.9%, and **2 : 11** was formed in a ratio of 1 : 3.25 (entry 5). When $CD_3CN/(CD_3)_3COD$ (17.8 : 1)

Table 5 Experimental evidence^{a,b}

Entry	F^-	Solvent	Time	Yield^c (%)				
				2	**11**	**10a**	**12a**	**13**
1	TBAF	CD_3OD	17 h	10	22	10	41	17
2	TBAF	CD_3CN/CD_3OD (6.5 : 1)	20 min	36	23	21	15	5
3	CsF	CD_3CN/CD_3OD (6.5 : 1)	5 h	7.8	51.5	4.2	34.9	1.6
4	CsF	CD_3CN/CD_3OD (17.8 : 1)	5 h	34	38	12	15	1
5	CsF	$CD_3CN/(CD_3)_3COD$ (6.5 : 1)	5 h	31.5	65.9	—	—	0
6	CsF	$CD_3CN/(CD_3)_3COD$ (17.8 : 1)	5 h	65	35	—	—	0

^{a} All reactions were carried out on a 0.084 mmol reaction scale of triazolium precursor **1** in 0.75 mL of solvent in a sealed NMR tube. TBAF·$3H_2O$ or CsF (6 equiv.) was used as F^- source. ^{b} Traces of **10b** and **12b** were detected by ^{19}F NMR. ^{c} ^{19}F NMR yield.

Table 6 Modified data from Table 5[a,b]

Entry	F⁻	Solvent	Time	Yield[c] (%)				
				2	**11**	**10a**	**12a**	**13**
1	TBAF	CD_3OD	17 h	4.9	27.1	0.4	50.6	17
2	TBAF	CD_3CN/CD_3OD (6.5 : 1)	20 min	21.5	37.5	11.6	24.4	5
3	CsF	CD_3CN/CD_3OD (6.5 : 1)	5 h	6.6	52.7	3.4	35.7	1.6
4	CsF	CD_3CN/CD_3OD (17.8 : 1)	5 h	32.5	39.5	11.4	15.6	1
5	CsF	$CD_3CN/(CD_3)_3COD$ (6.5 : 1)	5 h	22.9	74.5	—	—	0
6	CsF	$CD_3CN/(CD_3)_3COD$ (17.8 : 1)	5 h	58.3	41.7	—	—	0

[a] All reactions were carried out on a 0.084 mmol reaction scale of triazolium precursor **1** in 0.75 mL of solvent in a sealed NMR tube. TBAF·3H$_2$O or CsF (6 equiv.) was used as F⁻ source. [b] Traces of **10b** and **12b** were detected by ^{19}F NMR. [c] Modified values from Table 5, except for **13**: yields of **2** and **10a** via route (a) only; yields of **11** and **12a** from **14** and **15a** respectively if reaction mixture contains only deuterium source and no H$_2$O.

was used, compared to the reaction of entry 4, the yield of **2** increased from 32.5% to 58.3% (entry 6). We found that **2** via only route (a) was formed predominantly than **11**, as **2** : **11** was formed in the ratio of 1.40 : 1.

Thus, in $CD_3CN/(CD_3)_3COD$ (17.8 : 1) as solvent, S$_N$2 pathway (route (a)) was superior to route (c). A small amount of *t*-butanol-d_{10} was used because the degree of route (c) (formation of difluorocarbene) could not be measured without it.

Conclusions

In summary, the fluorination reactions have been developed for the triazolium precursor to generate [^{18}F]fluoroform presumably having high molar activity via S$_N$2 pathway. The precursor was very stable in acetonitrile and decomposed very slowly in DMF. Fluoroform was formed rapidly at rt in 10 min by fluorination of the precursor with TBAF (6 equiv.). Fluoride attacked the electropositive carbon of difluoromethyl group, whereas 1-phenylpiperazine attacked *N*3-methyl group that was less sterically hindered. We also observed the nucleophilic selectivity toward the precursor. When benzotriazolium precursor and CsF were used, we confirmed that C5 proton acting as a hydrogen bond donor affected the selective generation of fluoroform. Moreover, NMR studies were in favor of S$_N$2 pathway that was superior to formation of difluorocarbene in the reaction of the triazolium precursor using CsF and $CD_3CN/(CD_3)_3COD$ (17.8 : 1). Fluorination of the precursor via S$_N$2 will be possible to generate [^{18}F]fluoroform with improved molar activity. Based on these very positive preliminary results, our investigations for the synthesis of [^{18}F]fluoroform with high A_m are ongoing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 (a) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (b) W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Aceña, K. Izawa, H. Liu and V. A. Soloshonok, *J. Fluorine Chem.*, 2014, **167**, 37–54; (c) C. Alonso, E. Martínez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847–1935.

2 A. Harsanyi and G. Sandford, *Org. Process Res. Dev.*, 2014, **18**, 981–992.

3 (a) R. Littich and P. J. H. Scott, *Angew. Chem., Int. Ed.*, 2012, **51**, 1106–1109; (b) D. Le Bars, *J. Fluorine Chem.*, 2006, **127**, 1488–1493; (c) O. Jacobson, D. O. Kiesewetter and X. Chen, *Bioconjugate Chem.*, 2015, **26**, 1–18.

4 P. J. Riss, V. Ferrari, L. Brichard, P. Burke, R. Smith and F. I. Aigbirhio, *Org. Biomol. Chem.*, 2012, **10**, 6980–6986.

5 M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur and J. Passchier, *Nat. Chem.*, 2013, **5**, 941–944.

6 S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719–766.

7 A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford and P. J. H. Scott, *Chem. Sci.*, 2014, **5**, 4545–4553.

8 A. Lishchynskyi, M. A. Novikov, E. Martin, E. C. Escudero-Adán, P. Novák and V. V. Grushin, *J. Org. Chem.*, 2013, **78**, 11126–11146.

9 D. van der Born, C. Sewing, J. D. M. Herscheid, A. D. Windhorst, R. V. A. Orru and D. J. Vugts, *Angew. Chem., Int. Ed.*, 2014, **53**, 11046–11050.

10 P. Ivashkin, G. Lemonnier, J. Cousin, V. Grégoire, D. Labar, P. Jubault and X. Pannecoucke, *Chem.–Eur. J.*, 2014, **20**, 9514–9518.

11 B. Y. Yang, S. Telu, M. B. Haskali, C. L. Morse and V. W. Pike, *Sci. Rep.*, 2019, **9**, 14835.

12 A. Pees, A. D. Windhorst, M. J. W. D. Vosjan, V. Tadino and D. J. Vugts, *Eur. J. Org. Chem.*, 2020, **2020**, 1177–1185.

13 C. Park, B. S. Lee and D. Y. Chi, *Org. Lett.*, 2013, **15**, 4346–4349.

14 (a) D. W. Kim, D.-S. Ahn, Y.-H. Oh, S. Lee, H. S. Kil, S. J. Oh, S. J. Lee, J. S. Kim, J. S. Ryu, D. H. Moon and D. Y. Chi, *J. Am. Chem. Soc.*, 2006, **128**, 16394–16397; (b) D. W. Kim, H.-J. Jeong, S. T. Lim, M.-H. Sohn, J. A. Katzenellenbogen and D. Y. Chi, *J. Org. Chem.*, 2008, **73**, 957–962; (c) J.-W. Lee, M. T. Oliveira, H. B. Jang, S. Lee, D. Y. Chi, D. W. Kim and C. E. Song, *Chem. Soc. Rev.*, 2016, **45**, 4638–4650.

15 B. Schulze and U. S. Schubert, *Chem. Soc. Rev.*, 2014, **43**, 2522–2571.

16 E. D. Glendening, C. R. Landis and F. Weinhold, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2012, **2**, 1–42.

17 (a) Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215–241; (b) A. D. McLean and G. S. Chandler, *J. Chem. Phys.*, 1980, **72**, 5639–5648; (c) R. Krishnan, J. S. Binkley, R. Seeger and J. A. Pople, *J. Chem. Phys.*, 1980, **72**, 650–654.

18 M. J. Frisch, *et al.*, *Gaussian 09 Revision A.01*, Gaussian Inc., Wallingford, CT, 2009.

19 P. J. Hay and W. R. Wadt, *J. Chem. Phys.*, 1985, **82**, 299–310.