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Facile calculation of specific rate constants and activation energies of ^{18}F-fluorination reaction using combined processes of coat-capture–elution and microfluidics

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ABSTRACT

Calculation of a specific rate constant (k) and activation energy (E_a) of ^{18}F-labeling reaction is important to obtain objective data. However, it has never been tried, because short time heating required for the calculation of the parameters was difficult. In the present study, we could calculate the parameters using combination of coat-capture–elution method (Aerts et al.) and microfluidic processes. The E_a values obtained for Ts-naphthol in acetone, MeCN and *t*-BuOH were 5.83, 8.98, and 13.54 kcal/mol, respectively, and for Ms-naphthol in the same solvents were 5.81, 8.16, and 19.34 kcal/mol, respectively. Calculation of these parameters might be useful for setting up [^{18}F]fluorination procedure and for developing new precursors.

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1. Introduction

Positron emission tomography (PET) is an influential modality for molecular imaging,[1] and ^{18}F-labeled agents, such as [^{18}F]FDG are the most important and widely used probes for PET. And thus the development of ^{18}F-labeling methods has been always hot issue for PET, and as the demand for PET increase, it requires more effective synthesis methods for radio tracers.[2]

Most ^{18}F-labeling reactions are nucleophilic substitution using [^{18}F]fluoride produced by bombardment of [^{18}O]water with accelerated proton.[3,4] Generally, [^{18}F]fluoride is captured on an anion exchange resin and then eluted with base solution such as K_2CO_3/Kryptofix 2.2.2 (K222) or tetrabutylammonium bicarbonate (TBAB) (Fig. 1a). The base solution should contain significant amount of water to elute ionic bonded [^{18}F]fluoride from the anion resin. And thus obtained [^{18}F]fluoride is highly solvated with water, which prevents nucleophilic substitution reaction. So, the water should be removed to activate [^{18}F]fluoride, and azeotropic evaporation by heating under reduced pressure with inert gas flow is the most common procedure, which requires time and significant size reaction vessel. Therefore the evaporation step is the most challenging process for automation and microfluidics system for ^{18}F-labeling.

Several trials have been reported to exclude the evaporation step. For example, a special quaternary ammonium solid-phase resin was developed.[5] In this report, ^{18}F is captured on the resin, water is removed by washing with organic solvent, and then ^{18}F-labeling is performed on the solid phase system with continuous flow of precursor solution in organic solvent. However, this method was suffered with low and fluctuating labeling yields, because the reaction on a solid phase is significantly slower than the solution-phase reaction. Another trial was using ionic liquid without evaporation step,[6] however, this method has problems due to high viscosity of ionic liquid and residual ionic liquid in the final product. An electrochemical cell method can exclude evaporation step, however, it requires specially designed electrochemical cell.[7] A labeling method by formation of [^{18}F]aluminum fluoride chelate[8,9] do not need evaporation step, because this reaction occurs in aqueous solution. However, its application field is limited for some special

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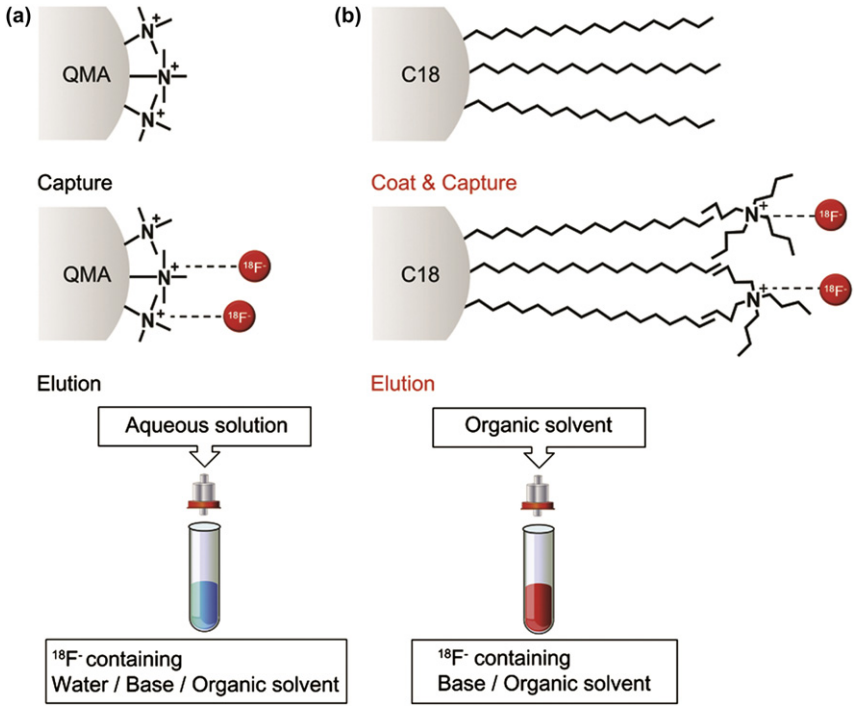


Fig. 1. Comparison of (a) conventional and (b) CCE process (Aerts et al.).[13] [^{18}F]Fluoride produced by a cyclotron is transported as an aqueous solution in ^{18}O-water. (a) In conventional process, [^{18}F]fluoride in water is captured by a cation exchange resin and then eluted with a base solution in water and organic solvent mixture. The final solution contains [^{18}F]fluoride, base, organic solvent, and water, and water should be removed for the next labeling reaction. (b) In CCE process, [^{18}F]fluoride is captured by a reverse phase cartridge pre-coated with TBA and then eluted with an organic solvent together with TBA. The final solution contains [^{18}F]fluoride, base, and organic solvent, and is ready for the next labeling reaction.

molecules, because they label synthons for labeling of ligands but not ligands themselves, that are similar with silicon-based building block[10] or hydrazone formation method.[11] Recently, a method of using special base solutions in MeCN showed very efficient elution of the captured [^{18}F]fluoride from the resin and high radiolabeling yield, and thus is regarded as an important progress in ^{18}F-labeling.[12]

Another important method was developed by Aerts et al.,[13] which could be represented as a Coat-Capture–Elution (CCE) process (Fig. 1b). This method has combined solid-phase and solution-phase system. Solid-phase coat and capture step provides a simplicity and a solution-phase reaction provides high reaction yield compare to a solid-phase reaction. The coating step can be eliminated by using a pre-coated resin during labeling process. Pre-coating of reverse phase cartridge can be done by passing aqueous base solution and subsequent washing with water. [^{18}F] Fluoride is captured on the pre-coated cartridge and then eluted with organic solvent together with base, which can act as a base catalyst. The advantages expected from the CCE process are: (1) the design of automatic synthesis module can be simplified due to the exclusion of evaporation step, (2) the labeling reaction occurs in a solution phase, which gives higher reaction yield than a solid-phase reaction (both of two reacting molecules move in solution-phase, however, only one reacting molecule can move in solid-phase), (3) the eluate solution can compose complete elements for labeling such as [^{18}F]fluoride, base catalyst, precursor, and organic solvent, by eluting the cartridge using an organic solvent containing precursor and thus enable to design a simplified automatic synthesis module, (4) the eluate directly can be input to a microfluidic system through a single entrance, which also enables to design a simpler microfluidic system, and (5) straightforward calculation of specific rate constants (k) and activation energies (E_a) is made possible because of the short time reaction in microfluidic system.

In the present study, we tried to calculate k's and E_a's of ^{18}F-labeling reactions by combination of CCE process and microfluidic system. Generally, ^{18}F-labeling study is just checking the labeling efficiencies with changing parameters, such as, temperature, solvent, base, time, precursors, and so on, and the derived data are somewhat subjective. We might have more accurate and objective data by calculating k's and E_a's, which would provide important information for development of new ^{18}F-labeling methods.

Microfluidic system is called as microfabricated or lab-on-a-chip system, which is a technology of using microscale fluids and channels.[14] Microfluidic system is developing its field to expand covering control, detection, and reaction. Application of microfluidics provides several advantages for automated PET radiopharmaceutical synthesis system, such as low cost, short time processing, small footprints for analysis, and compact size.[14–18] The small size synthesis chip can be put in a small shielding, and thus small hot cell space might be enough for installation of synthesis module, which might facilitate good manufacturing practice (GMP) establishment in small organizations. All synthesis steps such as radiolabeling, purification, and analysis, are processed rapidly, and thus resulted in enhanced radiochemical yield by reducing decayed radioactivity during synthesis procedure. Some PET agents are already synthesized using microfludic systems.[15,16,19]

2. Results and discussion

2.1. [^{18}F]Fluorination using CCE process

We pre-coated reverse phase cartridges (C18, tC18, C8, and phenyl) with either TBAB or K222. Aqueous no-carrier-added [^{18}F] fluoride solution was produced from a cyclotron, and its 1 mL aliquot was passed through a pre-coated cartridge and purged with nitrogen gas (2.84 psi) for 5 min. The [^{18}F]fluoride-captured pre-coated cartridge was eluted using 1 mL of organic solvents, such as

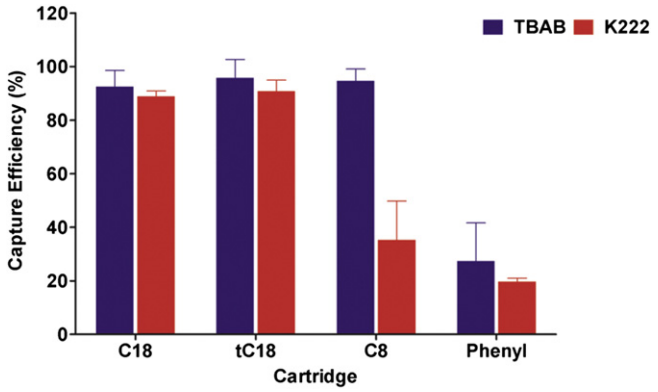


Fig. 2. Capture efficiencies of ^{18}F activity using two different base solutions from pre-coated reverse phase cartridges, such as C18, tC18, C8 (n=27), and phenyl (n=9).

acetone, methylethylketone (MEK), diethylketone (DEK), cyclohexanone (CHX), *t*-BuOH, *tert*-amylalcohol (*t*-AmOH), MeCN, dimethylformamide (DMF), and dimethylsulfoxide (DMSO).

Generally the cartridges, especially C8, coated with TBAB captured [^{18}F]fluoride significantly more efficiently than the cartridges coated with K222 (Fig. 2). Trifunctional tC18 cartridge[20] showed slightly higher capture efficiency than the original C18 cartridge. Phenyl cartridge showed the lowest capture efficiency, and the difference between two base solutions were not significant (P=0.60) (Fig. 2).

Captured [^{18}F]fluoride was eluted with various organic solvents. The adequate solvents for elution were dependent to cartridges and bases (Fig. 3). Acetone showed the highest elution efficiencies for C18 and tC18 cartridges coated either with TBAB or with K222. However, other ketone-containing solvents MEK and DEK were not efficient for elution in any case. The lower polarities of MEK and DEK might be less effective to dissolve the polar TBAB or K222 and might be less effective for elution consequently. A protic solvent *t*-BuOH was the most efficient for elution from TBAB coated C8 cartridge, but, was not efficient for K222 coated C8 cartridge interestingly. Both of *t*-BuOH and MeCN were efficient for either TBAB or K222 coated tC18 cartridges, however, both of the solvents were not efficient for K222 coated cartridges (Fig. 3). However, it was difficult to predict theoretically the best solvent for eluting the coated cartridges.

Microfluidic [^{18}F]fluorination after CCE process is shown diagrammatically (Fig. 4). Two precursors, Ts-naphthol (**1**) and Ms-naphthol (**3**), were synthesized and used for evaluation of ^{18}F-labeling efficiency (Scheme 1). The captured [^{18}F]fluoride and pre-coated TBAB on a C18 cartridge were eluted by 1 mL of organic solvents (acetone, MeCN, or *t*-BuOH) containing 5 mg of each precursor using a syringe pump. Among the three solvents, acetone was used because of its efficient recovery of [^{18}F]fluoride using CCE process, MeCN was used because it is the most frequently used solvent for ^{18}F-labeling, and *t*-BuOH was used because of the reported increased labeling yield of protic solvents.[21–23] The resulting eluate was directly input into a pre-heated microfluidic loop (765 μm inner diameter×0.5 m length) made of polyetheretherketone polymer-sheathed fused silica (PEEKsil). The labeled product was collected in a glass vial and fluorination efficiency was checked by TLC. The reaction time in the loop was controlled by a flow rate from 0.25 to 4 min (Supplementary data Table S1).

Generally, the labeling efficiencies of both **1** and **3** increased as the reaction time and temperature increased (Fig. 5). Both precursors showed low labeling efficiencies (<10%) at 90 °C in all three solvents. In acetone, **1** showed maximum labeling efficiency of

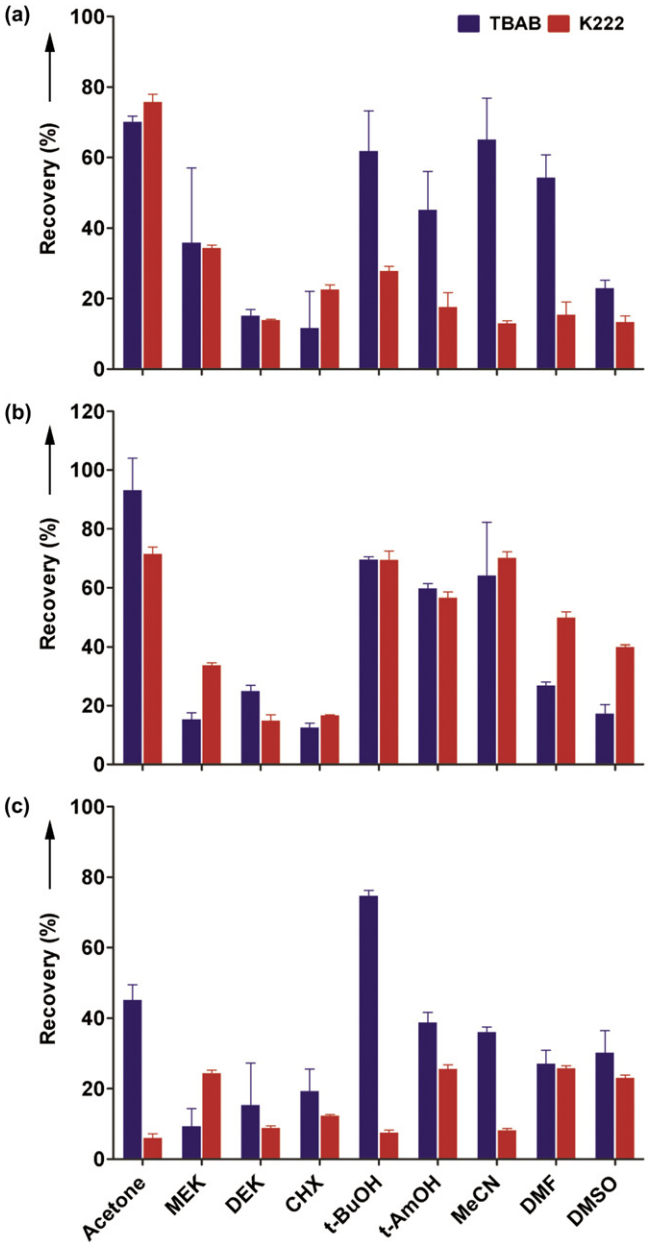


Fig. 3. Capture and elution recoveries of ^{18}F from reverse phase cartridges (a) C18, (b) tC18, and (c) C8 pre-coated with bases (TBAB or K222) using nine different organic solvents. (n=3). Recovery=Capture efficiency×Elution efficiency×100%. Capture efficiency=Radioactivity captured on cartridge/(Radioactivity captured on cartridge+Uncaptured radioactivity). Elution efficiency=Eluted radioactivity/(Eluted radioactivity+Radioactivity remaining on cartridge). All checked radioactivities (MBq) were decay-corrected.

about 80% at 2 min reaction time and decreased after that both at 140 °C (Fig. 5a). In MeCN and *t*-BuOH, labeling efficiency of **1** increased for 2 min and then the increase rate was slowed down (Fig. 5c and e). In case of **3**, the labeling efficiency reached plateau at 1 min reaction time at 140 °C in all three solvents, however, continuously increasing labeling efficiency was observed at 120 °C in all three solvents (Fig. 5b, d, and f). **3** showed about 80% of maximum labeling efficiencies at 1 min reaction time both in acetone and MeCN at 140 °C (Fig. 5b and d), however, only about 55% of maximum efficiency was found in *t*-BuOH (Fig. 5f). At 120 °C, **3** showed increasing labeling efficiencies as the reaction time increase, however, reached plateau about 70% in MeCN at 4 min (Fig. 5d).

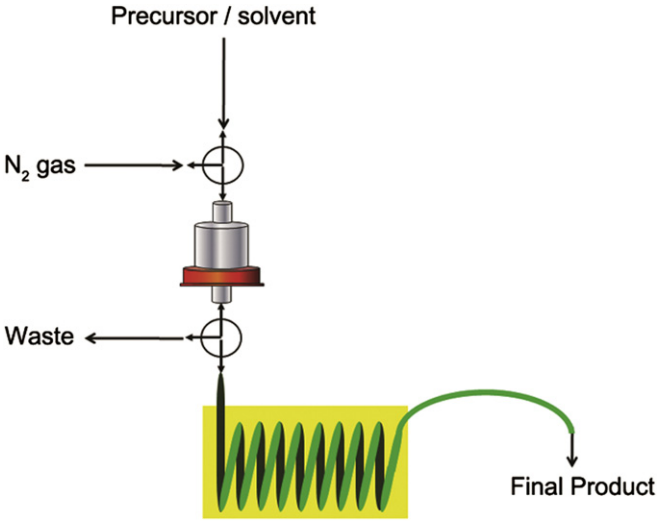


Fig. 4. A diagram of microfluidic ^{18}F-labeling combined with CCE process. [^{18}F]Fluoride in 1 mL of ^{18}O-water is captured by a C18 cartridge pre-coated with TBA and purged with 2.84 psi nitrogen gas for 5 min. And then [^{18}F]fluoride and TBA together are eluted with 1 mL of organic solvent containing 5 mg precursor, and the eluted mixture is entered into a pre-heated loop directly. The labeled final product is collected in a glass vial.

$$r = k \times [^{18}F] \times [P] \quad (1)$$

$$-\ln(1-F) = \frac{[^{18}F]+[P]}{[^{18}F]\times[P]} \times r \times t \quad (2)$$

$\ln(1-F) = -k \times a \times t$

$-2.303 \log(1-F) = p \times t$

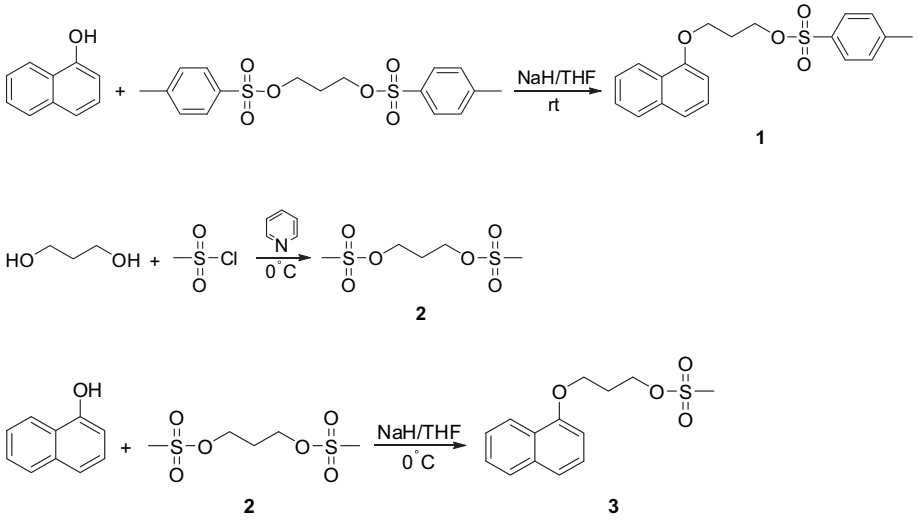
$k = 2.303 \times p/a$

$a = [^{18}F^-] + [P] \fallingdotseq [P]$

$p = -E_a/2.303 \times R$

r=Radiolabeling rate (mol L^{-1} min^{-1}); [^{18}F]=Concentration of ^{18}F$^-$ (mol L^{-1}); [P]=Concentration of precursor (mol L^{-1}); t=Time (min); F=Radiochemical yield at time t; k=Specific rate constant (L mol^{-1} min^{-1}).

Activation energies (E_a) for fluorination of **1** and **3** could be derived using k values and Arrhenius equation [Eq. 3]. E_a is the minimum required energy for reactants to be transformed into products, and is an important value, because it can represent reaction rate and be used for supporting experimental results. The log k values were plotted as a function of time (Fig. 7), and then activation energy of each compound in each solvent was obtained from the slope ($-E_a$) of each line (Table 2). The order of E_a values of ^{18}F-labeling reaction were t-BuOH, MeCN, and acetone representing the reverse order of reaction rate.



Scheme 1. Synthesis of precursors.

2.2. Calculation of k and E_a

It is well-known that the radioisotope labeling reactions are pseudo-first order reaction due to the low concentration of radioisotope compared to precursor, and thus the reaction rate is dependent only on the concentration of [^{18}F]fluoride because the concentration change of precursor is negligible [Eq. 1].[24,25] In this model, labeling efficiency graphs could be converted to line graphs of reaction time versus log(1−F) [Eq. 2] (Fig. 6), of which slopes represent specific rate constants ($-k$) of compounds at specific temperatures (Table 1). The reaction rates were influenced by temperature as well as reaction solvent. In all given conditions, k value increased as the temperature increased. When acetone or MeCN were used as solvents, **3** was better precursor than **1**, however, **1** was better for t-BuOH. The highest k value was found with **3** at 140 °C in acetone, which is the proposed condition for labeling naphthol with ^{18}F from the results of this experiment.

$$k = A \times e^{\frac{-E_a}{R-T}} \quad (3)$$

$\ln k = -E_a/R \times T + \text{constant}$

A=Frequency factor or the reaction, constant; E_a=Activation energy (kcal mol^{-1}); R=Gas constant (8.31447 J K^{-1} mol^{-1}); T=Absolute temperature.

Above calculations were possible because the measurement of labeling efficiencies in short time, such as 0.25, 0.5, and 1 min was possible by application of microfluidic system. In addition, the simple CCE process can be performed without any special control device for microfluidic lab-on-a-chip.

Calculation of the activation energies would give new insights for ^{18}F-labeling chemistry and provide objective data for the reactions. Then the obtained parameters might be used for evaluation of the reactions and be helpful for set up of labeling procedure and for developing new precursors.

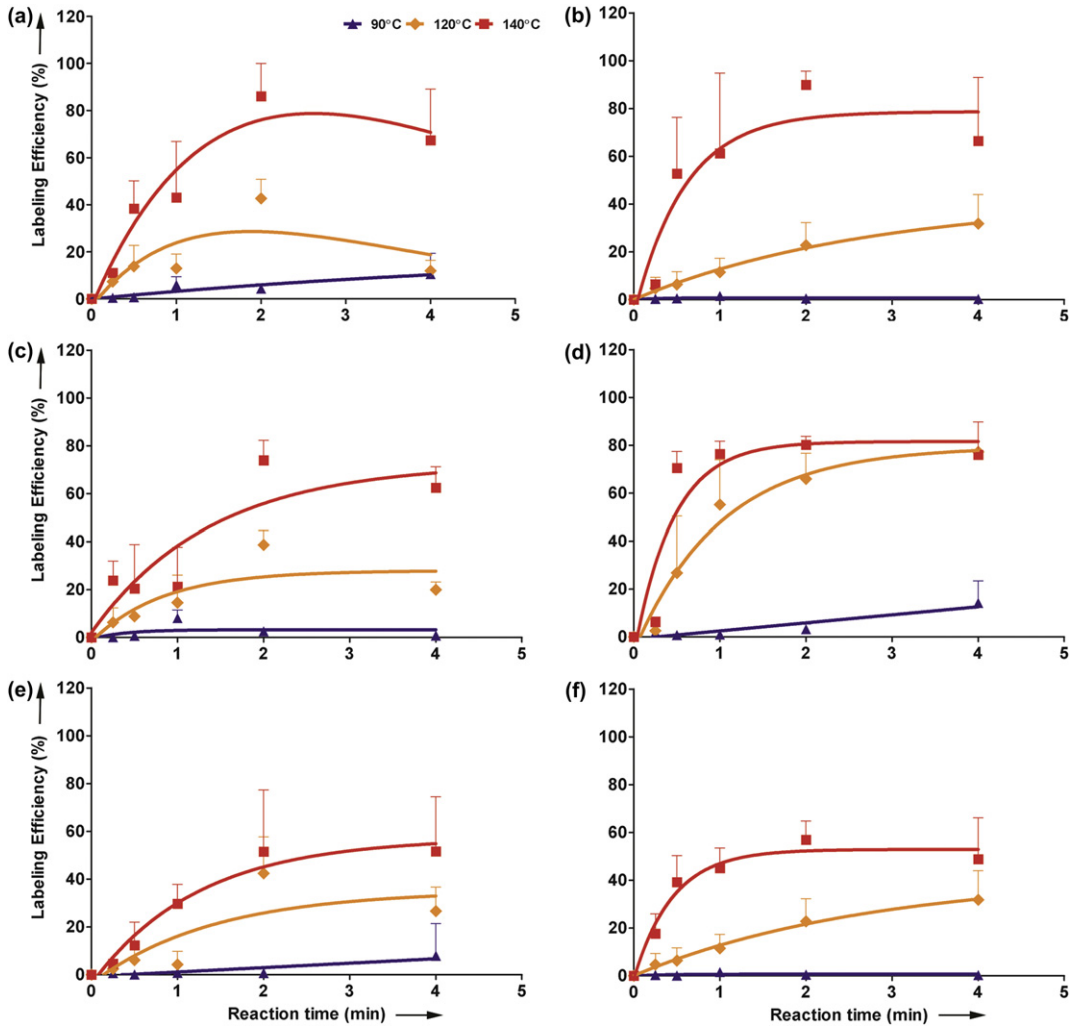


Fig. 5. Labeling efficiencies of **1** and **3** in various solvents at 90, 120, and 140 °C. (a) **1** in acetone, (b) **3** in acetone, (c) **1** in MeCN, (d) **3** in MeCN, (e) **1** in *t*-BuOH, and (f) **3** in *t*-BuOH.

3. Conclusion

In this study, [^{18}F]fluorination of two precursors by nucleophilic substitution reaction was performed successfully using CCE process with microfluidics system. Capturing and elution of [^{18}F]fluoride on base-coated reverse phase cartridges showed high efficiencies, and successive labeling reaction was straightforward and efficient. We could calculate specific rate constants and activation energies and found that acetone was the first proposed solvent in this reaction. This simple and efficient procedure to calculate activation energy might give a great impact for development of ^{18}F-labeling instruments and study of ^{18}F-labeling kinetics.

4. Experimental

4.1. General

[^{18}F]Fluoride was produced by the ^{18}O(p, n)^{18}F reaction using ^{18}*O*-enriched (95%) water and a 13-MeV proton beam generated by a TR-13 cyclotron (Ebco Technologies, Vancouver, Canada). The produced [^{18}F]fluoride was used after more than 1 h storage. Electrospray ionization mass spectra (ESI-MS) were acquired on a Waters 3100 Liquid chromatography-mass spectroscopy (LC–MS) (Waters Corporation, MA, USA) ESI ion trap spectrometer for positive and negative ions detection. The samples were diluted 1 to 100 with methanol and injected directly into the source. Chemical shifts (δ) were reported in parts per million downfield from tetramethylsilane. Fast atomic bombardment (FAB^+) ionization mass spectra were acquired on JEOL, JMS-600 W Azilent 6890 series spectrometer (JEOL Ltd, Tokyo, Japan) for positive mode. JMS-LA400 with LFG model has used for 400 MHz NMR to obtain ^{13}C NMR data (JEOL Ltd, Tokyo, Japan). Infrared spectra were obtained from KBr pellets on an FT-IR spectrophotometer Nicolet 6700 (Thermo Fisher Scientific, MA, USA). Radio-thin layer chromatography (TLC) was counted using a Bio-Scan AR-2000 System imaging scanner (Bioscan, Inc, WA, USA). 11Plus syringe pump was purchased from Harvard Apparatus (Harvard Apparatus, MA, USA). C18, tC18 and C8 SepPak solid-phase cartridges were purchased from Waters (Waters Corporation, MA, USA). Phenyl cartridge, Discovery® DSC-Ph SPE Tube was purchased from Supelco (Supelco, Inc, PA, USA). Thin-layer chromatography (TLC silica gel 60 F_{254} Aluminum sheets) was purchased from Merck (Merck KGaA, Darmstadt, Germany). Commercial chemicals were from Sigma–Aldrich (Sigma–Aldrich®, MO, USA) and TCI (Tokyo Chemical Industry Co., Ltc, Tokyo, Japan). Microscale spiral tube was used Tubing, Spiral-link (Upchurch Scientific, WA, USA).

4.2. Synthesis of precursors

*4.2.1. 3-(Naphthalene-1-yloxy)propyl 4-methylbenzenesulfonate (Ts-naphthol) (**1**).* To a solution of 1-naphthol (100 mg, 0.69 mmol) in 4 mL of THF, sodium hydride (68 mg, 1.38 mmol) was added and stirred for 15 min. 1,3-Bis(Tsoxy)propane (530 mg, 1.38 mmol) was added to the reaction mixture and stirred for 2 h at room

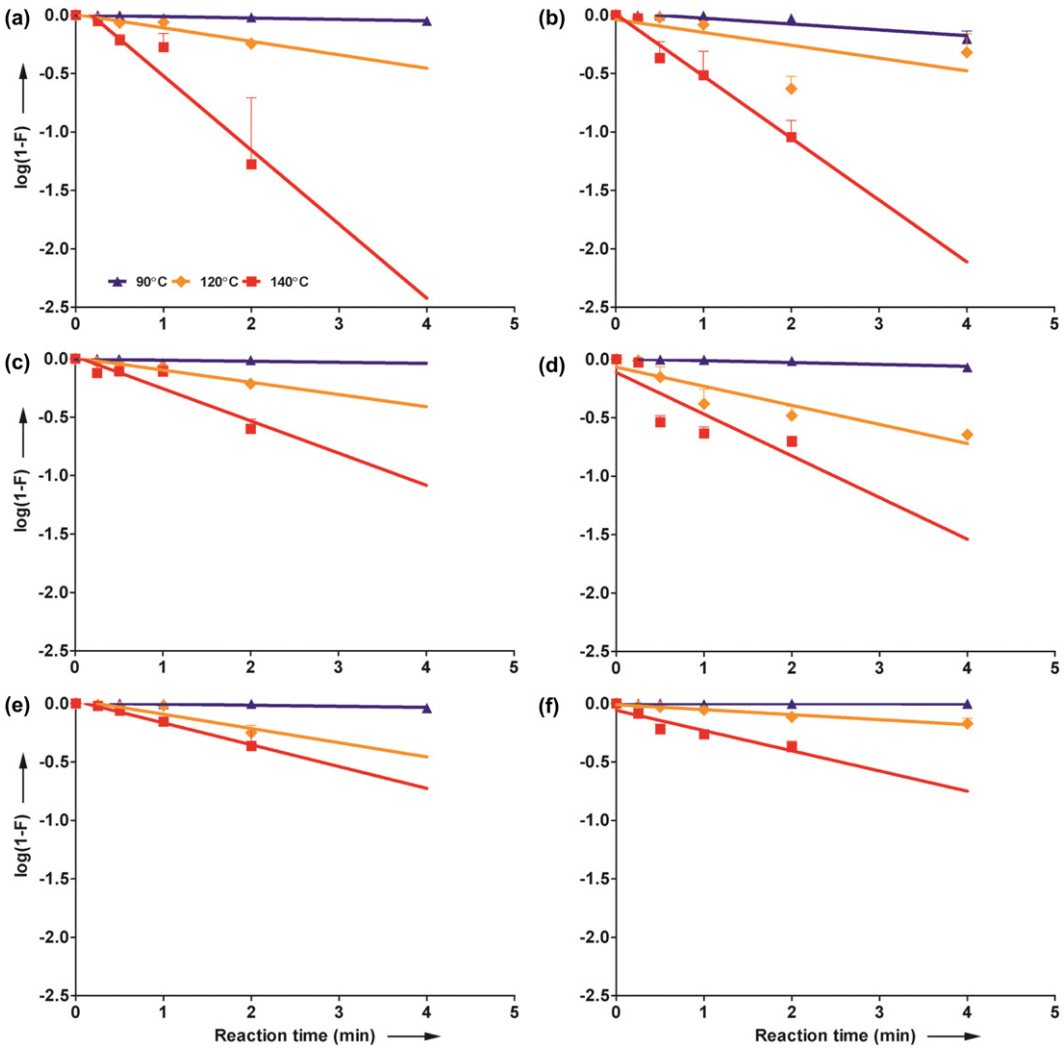


Fig. 6. Reaction time versus log(1−F) graph. (a) **1** in acetone, (b) **3** in acetone (c) **1** in MeCN, (d) **3** in MeCN, (e) **1** in *t*-BuOH, and (f) **3** in *t*-BuOH.

Table 1
Specific rate constants calculated for ^{18}F-labeling of **1** and **3** at 90, 120, and 140 °C in acetone, MeCN, and *t*-BuOH

Compound	**1**			**3**		
Temperature (°C)	140	120	90	140	120	90
Acetone	1.443	0.296	0.135	2.649	0.548	0.249
MeCN	1.378	0.522	0.045	1.781	0.816	0.081
t-BuOH	0.932	0.608	0.006	0.864	0.214	0.001

Values represent specific rate constants *k* (L/mol min).

temperature. The reaction mixture was extracted with EtOAc (50 mL), the organic layer was washed with brine (2×200 mL), dried over anhydrous sodium sulfate (~3 g) for 10 min, and concentrated using a rotary vacuum evaporator at 50 °C. The resulting oil was purified using a silica gel (~40 g) column chromatography (25:75 EtOAc/*n*-hexane; R_f=0.4). Pure product was obtained as a bright yellow powder after drying using a rotary vacuum evaporator at 45 °C. Yield=0.16 g, ^{1}H NMR [300 MHz, $CDCl_3$]: δ 7.93–7.96 (m, 1H), 7.66–7.68 (m, 1H), 7.50–7.51 (m, 1H),7.41–7.43 (m, 1H), 7.36–7,40 (m, 1H), 7.31–7.33 (m, 2H), 7.26–7.30 (m, 1H), 6.95–6.98 (m, 1H), 6.65–6.68 (m, 1H), 4.35 (t, 2H), 4.09 (t, 2H), 2.62 (s, 3H), 2.25 (Quintet, 2H). ^{13}C NMR [400 MHz, $CDCl_3$]: δ 21.34, 28.78, 62.80, 66.95, 104.35, 120.36, 121.71, 125.03, 125.75, 126.35, 127.65, 129.62, 144.70, 153.99. IR (KBr, cm^{-1}): 2978, 1364, 1188, 1173. MS (ESI+) *m*/*z* calculated for $C_{20}H_{20}O_4SNa$: $[M+Na]^+$ 379.0980, found 379.1039. Mp=51 °C.

*4.2.2. 1,3-Bis(mesylsoxy)propane (**2**).* Methanesulfonyl chloride (1 mL, 38.76 mmol) was added to ice-cooled pyridine solution of 1,3-propandiol (1 mL, 13.84 mmol) and stirred for 1 h at 0 °C for 1 h. The reaction mixture was extracted with EtOAc (50 mL), the organic layer was washed with brine (2×200 mL), dried over anhydrous sodium sulfate (~3 g) for 10 min, and concentrated using a rotary vacuum evaporator at 50 °C. The resulting oil was purified using a silica gel (~15 g) column chromatography (25:75 EtOAc/*n*-hexane; R_f=0.2). Pure product was obtained as a colorless oil after drying using a rotary vacuum evaporator at 45 °C. Yield=1.56 g, ^{1}H NMR [300 MHz, $CDCl_3$]: δ 1.77–1.85 (m, 2H), 2.90 (s, 6H), (t, 4H). ^{13}C NMR [400 MHz, $CDCl_3$]: δ 28.28, 36.59, 65.49. IR (KBr, cm^{-1}): 3053, 1354, 1174. MS (ESI) *m*/*z* calculated for $C_5H_{12}O_6S_2$: $[M+H]^+$ 233.0154, found 232.9997. MS (ESI^+) *m*/*z* calculated for $C_5H_{12}O_6S_2Na$: $[M+Na]^+$ 254.9973, found 254.9247.

*4.2.3. 3-(Naphthalene-1-yloxy)propyl methanesulfonate (Ms-naphthol) (**3**).* To a solution of 1-naphthol (1.10 g, 7.63 mmol) in 4 mL of THF, sodium hydride (500 mg, 20.83 mmol) was added and stirred for 30 min. Compound **2** (1.61 g, 6.94 mmol) was added to the reaction mixture and stirred for 2 h at 0 °C. The reaction mixture was extracted with EtOAc (100 mL), the organic layer was washed with

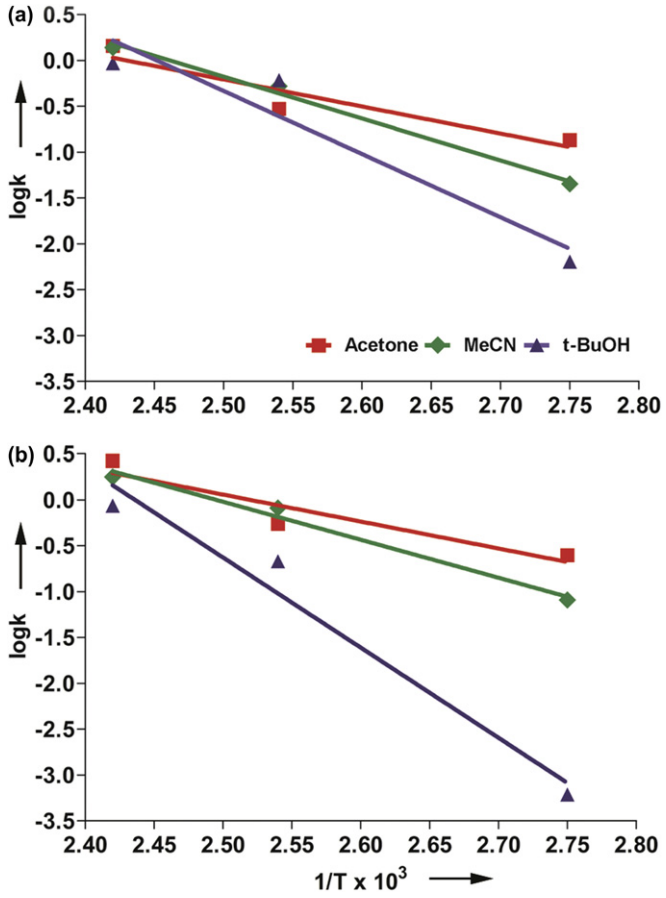


Fig. 7. Activation energy (E_a) graph of (a) **1** and (b) **3**.

Table 2
Activation energies calculated for ^{18}F-Labeling of **1** and **3** in acetone, MeCN, and *t*-BuOH

Solvent	Precursor	
	1	**3**
Acetone	5.83	5.81
MeCN	8.98	8.16
t-BuOH	13.54	19.34

Values represent activation energies E_a (kcal/mol).

brine (2×400 mL), dried over anhydrous sodium sulfate (~5 g) for 15 min, and concentrated using a rotary vacuum evaporator at 50 °C. The resulting oil was purified using a silica gel (~60 g) column chromatography (25:75 EtOAc/*n*-hexane; R_f=0.5). Pure product was obtained as a brown oil after drying using a rotary vacuum evaporator at 45 °C. Yield=0.30 g, ^{1}H NMR [300 MHz, $CDCl_3$]: δ 7.83 (m, 1H), 7.80 (m, 1H), 7.61–7.63 (m, 1H), 7.52 (m, 1H), 7.50–7.51 (m, 1H), 7.44–7.47 (m, 1H), 4.38 (t, 2H), 3.65 (t, 2H), 3.21 (s, 3H), 2.18 (Quintet, 2H). ^{13}C NMR [400 MHz, $CDCl_3$]: δ 29.03, 37.05, 65.32, 66.27, 104.59, 121.70, 125.11, 125.24, 125.74, 126.28, 127.39, 134.34, 154.39. IR (KBr, cm^{-1}): 1359, 1190, 1171. MS (ESI$^+$) *m*/*z* calculated for $C_{14}H_{16}O_4SNa$: $[M+Na]^+$ 303.0667, found 303.0591.

4.3. Pre-coating of solid-phase cartridges for CCE process

Tetrabutylammonium bicarbonate (TBAB) solution was prepared by purging CO_2 gas into 40% tetrabutylammonium hydroxide for 6 h, and then 40% TBAB 0.87 mL, deionized water 2.5 mL, and MeCN 17.4 mL were mixed. K_2CO_3/kryptofix 2.2.2 (K222) solution was prepared by dissolving 181 mg of kryptofix 2.2.2 and 29 mg of K_2CO_3 in 10 mL deionized water. A C18 SepPak cartridge was prewashed with ethanol (3 mL) and deionized water (5 mL) sequentially. The pre-conditioned cartridge was coated with 1 mL of each prepared TBAB or K222 solution by passing through the cartridge. After coating, cartridge was washed with deionized water (5 mL) to remove the remaining solution. And captured 1 mL of [^{18}F]fluoride, which was produced from cyclotron. [^{18}F]Fluoride captured cartridge was purged with nitrogen gas for 5 min (2.84 psi).

4.4. Determination of labeling efficiency

Labeling efficiency (%) was checked by TLC silica aluminum sheet and radioactivity was scanner by using a radioTLC scanner. The eluant was 95% (v/v) MeCN in water. R_f value of [^{18}F]fluoride was 0.1 and that of [^{18}F]naphthol was 1.0.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.01.088. These data include MOL files and InChIKeys of the most important compounds described in this article.

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