Available online at www.sciencedirect.com
ScienceDirect
Journal of Fluorine Chemistry 128 (2007) 806–812
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Competitive demethylation and substitution in *N*,*N*,*N*-trimethylanilinium fluorides

Haoran Sun, Stephen G. DiMagno *

Department of Chemistry and Nebraska Center for Materials and Nanoscience, University of Nebraska, Lincoln, NE 68588-0304, USA

Received 1 February 2007; received in revised form 7 March 2007; accepted 8 March 2007
Available online 12 March 2007

Abstract

Fluorination of aromatic compounds by nucleophilic displacement of trimethylanilinium salts by fluoride is a commonly used reaction for radiotracer synthesis. Though the liberated trimethylamine is thought to be an excellent leaving group for this type of S_NAr reaction, scattered reports show that amine demethylation (reverse Menschutkin reaction) sometimes dominates over substitution, particularly when relatively electron rich fluoroarenes are the desired targets. Here we provide systematic experimental and theoretical studies of trimethylanilinium demethylation and substitution. Results from these studies highlight the limits of this leaving group in fluoroarene synthesis and have important ramifications for the design of nucleophilic fluorinating agents featuring ammonium cations.

Keywords: Tetrabutylammonium fluoride; Amine deprotection; Demethylation; Nucleophilic substitution; S_N2; S_NAr; Arene fluorination; PET; Leaving groups; Reverse Menschutkin

1. Introduction

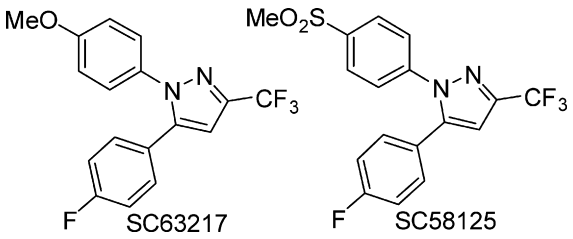
Nucleophilic aromatic substitution (S_NAr) is a particularly useful transformation for preparing fluorinated radiotracers for positron emission tomography (PET) [1–5]. Advantages of using nucleophilic reactions for the introduction of [^{18}F] fluoride include the high chemical yields, excellent regioselectivity, and the high radiochemical purity associated with radiotracers prepared by this technique. Nucleophilic reactions are also the only means by which radiofluorination can be performed under no-carrier-added (n.c.a.) conditions. Important experimental parameters for optimizing nucleophilic aromatic fluorination are reaction time, temperature, solvent, fluoride counterion, substrate substituents, and leaving group. Typical requirements for radiofluorination are relatively short reaction times (<30 min), elevated temperatures, and polar aprotic solvents (acetonitrile, DMF, DMSO). The fluoride source commonly employed is Kryptofix [2.2.2] [^{18}F] KF, in which a cryptand complexes the potassium ion to provide a relatively nucleophilic fluoride ion. A commonly encountered problem with nucleophilic aromatic fluorination is the necessity for electron-withdrawing groups *ortho* or *para* to the desired site of fluorination. In practice, this requirement often necessitates multistep syntheses in which the activating substituent is subject to functional group transformations after the fluorine is introduced into the molecule. This limitation is among the principal unsolved problems in [^{18}F] radiotracer synthesis.

The nature of the leaving group has a profound influence on the success of S_NAr fluorination reactions. Typical leaving groups for S_NAr reactions are the halides, NO_2^-, $N(CH_3)_3$, ArI, and N_2. Here we will focus on substitution reactions of trimethylanilinium triflates. Because these substrates are readily synthesized and are highly reactive toward substitution, they have become workhorses for nucleophilic aromatic radiofluorination.

Early work on the radiofluorination of aryltrimethylammonium salts [6–9] demonstrated that the neutral trimethylamine leaving group was more active than halides and comparable in reactivity to the nitro group [10]. For certain substrates, for example in the radiofluorination of COX-1 and COX-2 inhibitors SC63217 and SC58125, the trimethylammonium salts seem to be clearly superior to the nitrated derivatives [11]. In other cases, particularly when the aromatic ring is relatively electron rich, the nitro group offers clear advantages.

* Corresponding author. Tel.: +1 402 472 9895; fax: +1 402 472 9402.
E-mail address: sdimagno1@unl.edu (S.G. DiMagno).

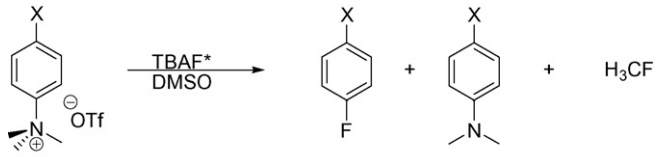
0022-1139/$ – see front matter
doi:10.1016/j.jfluchem.2007.03.009



An activated aromatic ring (i.e. a ring bearing at least one electron-withdrawing group) is required to effect substitution of the trimethylammonium group with fluoride. *N*,*N*,*N*-Trimethyl-4-nitroanilinium triflates undergo relatively rapid substitution with Kryptofix [^{18}F] KF. In DMSO, substitution is complete within 10 min at slightly elevated temperature (55–100 °C) [10,12]; harsher conditions are required if electron-donating groups are present on the nitroarene [13]. Anhydrous acetonitrile has also been used as a solvent for fluorodeamination of *N*,*N*,*N*-trimethyl-2-chloro-4-nitroanilinium triflate; in this case the reaction takes place at room temperature [14]. Trimethylanilinium salts bearing cyano substituents are also rapidly fluorinated, providing a straightforward, high yield entry into [^{18}F] *N*-(4-fluorobenzyl)-2-bromoacetamide for radiolabeling oligonucleotides [15–23]. If electron-withdrawing groups less potent than cyano are present on the trimethylanilinium ring, radiofluorination yields begin to decline. Corrected radiofluorination yields for *para*-trimethylammonium aryl aldehydes [24–27], ketones [28–32], and esters [33–36] range from excellent (80%) for aryl aldehydes to fair (50%) for aryl esters. For relatively unactivated rings, fluorodeamination is difficult; Ermert and coworkers [37] studied substitution in 4-bromo-*N*,*N*,*N*-trimethylanilinium triflates and found that only 8–12% yields of the desired 4-fluorobromobenzenes were obtained under optimized conditions.

The low yields obtained for S_NAr fluorination of relatively unactivated trimethylanilinium triflates stems, in part, from formation of methyl fluoride from a competing S_N2 (reverse Menschutkin [38]) reaction. Formation of [^{18}F] methyl fluoride has been observed in some cases where it is suspected to be the main deleterious side reaction [11,28]. The reverse Menschutkin reaction was also exploited for the preparation of labeled methyl fluoride; 2-acetyl-*N*,*N*,*N*-trimethylanilinium triflate readily undergoes microwave-induced [^{18}F] fluorodemethylation [39]. These literature data suggest that the demethylation/substitution partition ratios are closely correlated to the nature of the aryl ring substituents; though no truly quantitative study examining this partition ratio has yet been published.

Here we report quantitative experimental and theoretical studies to investigate the impact of substrate substituents upon the competing S_NAr and S_N2 pathways for the reaction of *N*,*N*,*N*-trimethylanilinium triflates with fluoride ion. We are aided in these efforts by our recent synthesis of anhydrous tetrabutylammonium fluoride (TBAF*) [40], a convenient source of highly nucleophilic fluoride ion [41] that may be used for radiotracer synthesis [42].



Scheme 1.

2. Results and discussion

Differentially substituted substrates were selected to provide a broad range of electron-withdrawing ability. The trimethylanilinium triflates were prepared either by exhaustive alkylation of the corresponding commercially available anilines with methyl iodide followed by ion-exchange (for the electron rich anilines), or by direct alkylation with methyl triflate according to literature methods [20]. Yields for these alkylation reactions generally exceeded 80%. TBAF*, synthesized and isolated according to previously reported procedures [40], was combined with these substrates in d_6-DMSO in temperature controlled, sealed NMR tubes. The final concentration of the substrate was 0.4 M; all reactions were performed on a 0.2 mmol scale. The reactions investigated are shown in Scheme 1.

2.1. Ion exchange experiments

Upon mixing of TBAF* (1.4 equiv.) with the trimethylanilinium triflates, two of the salts (X = CF_3, CN) formed precipitates at room temperature, suggesting an instantaneous ion exchange reaction. (The CF_3-substituted derivative proved so insoluble that further studies on the reactions of this compound were abandoned.) Changes in the ^{19}F and ^{1}H NMR spectra observed upon mixing of the TBAF* with the substrates also gave evidence for ion exchange: the signals for the fluoride anion shifted upfield and broadened significantly in the ^{19}F NMR spectra, and the aromatic regions of the ^{1}H NMR spectra showed significantly larger separations in the chemical shifts of the *ortho* and *meta* proton signals (Fig. 1).

The attribution of these spectral changes to ion exchange was supported strongly by ^{1}H–^{19}F heteronuclear Overhauser effect spectroscopy (HOESY) experiments performed in our laboratory. Pregosin and coworkers exploited HOESY experiments to gain insight into the nature of ion pairing [43] for ammonium salts. Where tight ion pairing between an organic cation and a fluorinated anion occurs, ^{1}H–^{19}F HOESY data can also indicate the site(s) of the ion pairing interaction(s). Our ^{1}H–^{19}F HOESY data (Fig. 2) demonstrate the usefulness of this technique for ammonium fluoride salts. These spectra indicate that TBAF* is tightly ion paired in DMSO solution, and that the principal interaction of fluoride is with the α-CH_2 group of the TBA cation. When 4-methyl-*N*,*N*,*N*-trimethylanilinium triflate is added to this solution, ion exchange occurs and the fluoride is bound exclusively (within the experimental detection limits, >100:1) to the anilinium cation. Moreover, the significant cross peak attributable to the *ortho*-hydrogen atom on the anilinium ring suggest an ion pair structure in which the fluoride is

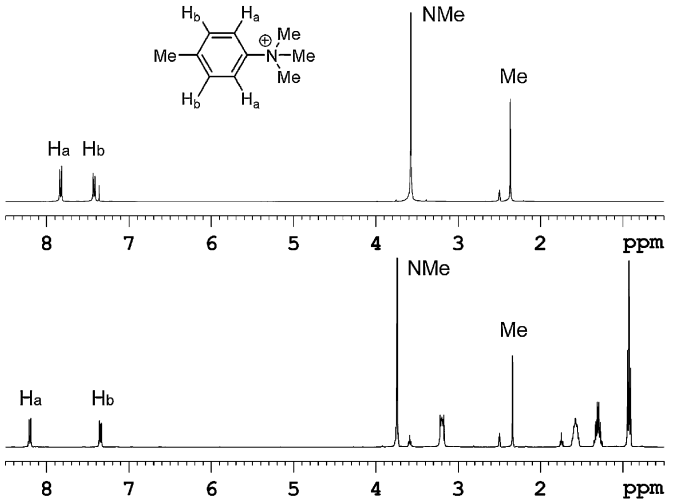


Fig. 1. ^{1}H NMR spectra showing the spectral shifts of 4-methyl-*N*,*N*,*N*-trimethylanilinium triflate in d_6-DMSO upon addition of TBAF*.

strongly hydrogen bonded to this position. (The integrated cross peak volumes at 3.8 and 8.2 ppm are almost equal.) The experiments that confirm fluoride ion transfer from the relatively weakly coordinating tetrabutylammonium cation to the relatively strongly ion pairing trimethylanilinium cation are quite important in the context of S_NAr reactions of trimethylanilinium salts, since they indicate that *nothing is to be gained from the synthesis of cations more weakly coordinating than TBA for this type of fluorination reaction*. Similarly, the preparation of trimethylanilinium salts featuring more weakly coordinating anions (PF_6^-, tetraarylborates) is also shown to be unwarranted, since *the synthetic studies reported here are conducted at the reactivity limit for displacement of trimethylamine in DMSO*.

2.2. Fluorination reactions

The results of fluorination reactions for the series of *para*-substituted *N*,*N*,*N*-trimethylanilinium salts are reported in

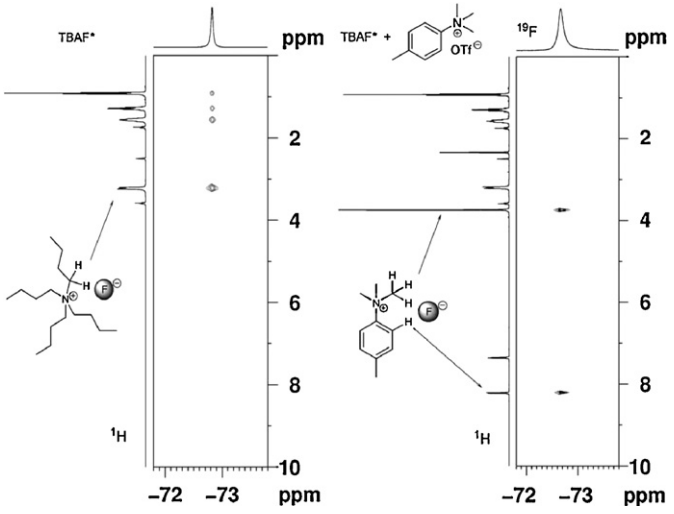


Fig. 2. ^{1}H–^{19}F HOESY spectra of TBAF* (left) and a mixture of TBAF* and 4-methyl-*N*,*N*,*N*-trimethylanilinium triflate (right) in d_6-DMSO solution.

Table 1
Hammett σ_p^- constants and observed aryl/alkyl fluorination ratios observed in DMSO at 100 °C

Substituent	σ_p^-	Reaction time (min)	Prod. ratio
NO_2	1.27	1[a]	>99:1
CHO[b]	1.03	1	>99:1
CN	1.00	1	99:1
COPh	0.84	1	99:1
CO_2Me	0.64	2	96:4
Br	0.25	10	2:98
H	0.0	10	<1:99
Me	−0.17	10	<1:99
OMe	−0.26	30	<1:99

[a] Reaction is complete within 10 min at room temperature.
[b] Some decomposition noted at elevated temperature.

Table 1 along with the σ_p^- values [44] for these substituents. (Since both the demethylation and substitution reactions proceed through transition states in which increasing electron density is directly conjugated with the aromatic ring, the σ_p^- parameter set most accurately reflects the electronic effects for the selected substituents.) All reactions were conducted at 100 °C in d_6-DMSO in sealed NMR tubes in order to capture any volatiles produced during the reaction. ^{1}H, ^{13}C, and ^{19}F NMR spectral data were used to identify and quantify the principal products of the fluorination reactions. In every case examined, the reaction ran to completion and only two fluorinated products were observed by NMR spectroscopy: fluoroarene and/or methyl fluoride. Inspection of Table 1 indicates that there is a sharp demarcation between reactions that yield almost exclusively the fluoroarene products of S_NAr reactions (X = NO_2, CHO, CN, COPh, CO_2Me) and those that produce methyl fluoride as the principal product (X = Br, H, CH_3, OCH_3). Interestingly, even the reaction featuring a relatively electron rich arene ring (X = OMe) was still completed relatively rapidly at elevated temperature. The electron poor systems (X = NO_2, CHO, CN, COPh, CO_2Me) are also substituted relatively rapidly at room temperature under these anhydrous conditions, and the product ratios obtained are virtually identical to those obtained at 100 °C. The quantitative yields of the two products indicate that caution should be exercised in radiochemical preparations employing relatively electron rich trimethylanilinium salts, as ^{18}F-labeled methyl fluoride is sure to be produced in good yields in these reactions. Taken together, the ion pairing and reaction data suggest that these fluorination reactions proceed through the collapse of ion pair intermediates, and that the product ratios obtained in DMSO result only from the difference in activation barriers for the S_NAr and S_N2 pathways. To test this hypothesis, we examined the ion pairing, kinetics, and thermodynamics of tetraalkylammonium dealkylation using computational methods.

2.3. Theoretical modeling of tetramethylammonium fluoride

Though Collie first reported [45,46] the preparation of methyl fluoride by the decomposition of the "dry" salt of

tetramethylammonium fluoride (TMAF) at 180 °C, we are unaware of any theoretical treatment of this simple reaction. Two recent theoretical studies of TMAF have focused on the nature and strength of the ion pairing interaction in the gas phase and solid state. Harmon argued that IR spectra and *ab initio* molecular orbital calculations suggest that TMAF contains the strongest C–H···F^- hydrogen bond yet observed [47]. Davies, George and Howard examined the gas phase structure of the TMAF ion pair and found the most stable ion pairing arrangement to possess C_{3v} symmetry, with one hydrogen from each of three methyl groups forming close contacts to the fluoride ion [48]. In contrast, in a classical S_N2 attack trajectory the incoming fluoride ion interacts solely with the hydrogen atoms of a single methyl group. We investigated the gas phase and solution phase energetics of ion pairing and fluorodemethylation at the MP2(6-311G+(d, p)) level. Basis set superposition error (BSSE) corrections were made for the gas phase calculations. Energies for reactions modeled in THF and DMSO solution (PCM solvation treatment) were not corrected for BSSE. The calculated structures and their free energies at room temperature (ZPE and thermal corrections employed) are summarized in Fig. 3.

Inspection of Fig. 3 shows that the separation of the transition state and the lowest energy ion pair structure ($\Delta\Delta G^\circ = \Delta G^\circ_{TS} - \Delta G^\circ_{ion\ pair}$) varies only modestly with solvent, ($\Delta\Delta G^\circ_{gas}$ = 25.7 kcal/mol, $\Delta\Delta G^\circ_{THF}$ = 42.1 kcal/mol, $\Delta\Delta G^\circ_{DMSO}$ = 32.6 kcal/mol) with the largest barrier occurring for THF. This result is easily explained. In THF, the carbon atom in the transition state is nearly coplanar with its three attached hydrogen atoms, while the gas phase calculation (early TS) and DMSO calculation (late TS) show somewhat pyramidal carbon atoms at the transition state.

The calculations showing ready access to the transition state for S_N2 reactions of TMAF in DMSO prompted us to investigate decomposition of TMAF in solution. When $TMAPF_6$ and TBAF were mixed in d_6-DMSO and heated to 100 °C for 20 min, methyl fluoride and trimethylamine were indeed formed in a reaction similar to that observed for the electron rich trimethylanilinium triflates. Evidently, pyrolysis of the dry salt is unnecessary for a relatively rapid reverse Menschutkin reaction. Unfortunately, demethylation of TMAF was not as clean as the reactions with the trimethylanilinium salts, as some decomposition of the tetrabutylammonium cation was observed. Nevertheless, this study indicates that the methyl groups on TMA cation and related ammonium cations are quite labile in the presence of anhydrous fluoride.

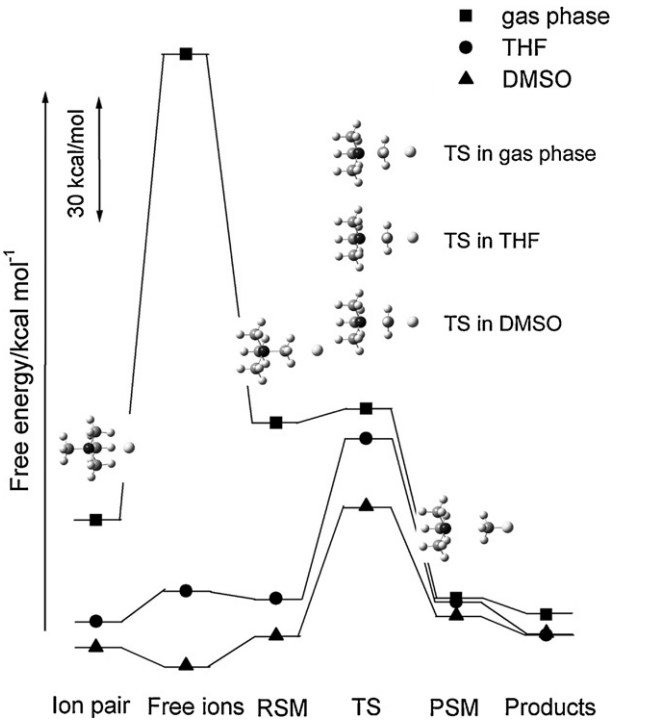
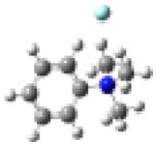
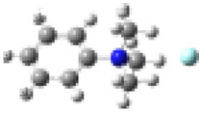


Fig. 3. Results of MP2(6-311G+(d, p)) calculations for the TMAF ion pair and for the reverse Menschutkin reaction (TMAF → trimethylamine + CH_3F) in the gas phase, and in solution (THF, DMSO). Free energies are given for the following calculated structures (from left to right) (1) C_3v ion pair, (2) dissociated TMA and fluoride ion, (3) the reaction side minima (RSM), (4) transition state (TS), (5) product side minima (PSM), and (6) dissociated products. The TS structures are labeled; the remaining, unlabeled structures are true minima derived from gas phase calculations.

2.4. Theoretical modeling of trimethylanilinium fluorides

Table 2 compares the two calculated (B3LYP/6-311G++(d, p)) lowest energy optimized ion pair structures for trimethylanilinium fluoride. In agreement with the ^1H–^{19}F HOESY experiments, the structure with the fluoride ion located in the

Table 2
DFT (B3LYP/6-311G++(d, p)) calculated ion pair structures and free energies and enthalpies at room temperature

Ion pair structure										
	$d_{F\text{-}Hph}$	$d_{F\text{-}HMe}$	μ (Debye)	ΔG°	ΔH°	$d_{F\text{-}HMe}$[a]	$d_{F\text{-}HMe}$[b]	μ (Debye)	ΔG°	ΔH°
gas	1.764	1.804	9.563	−105.3	−113.8	1.815	1.843	10.374	−105.5	−113.6
THF	1.939	2.036	13.845	−6.4	−13.9	2.021	2.061	14.405	−7.3	−14.5
DMSO	1.979	2.125	15.071	3.7	−3.3	2.080	2.129	15.372	2.9	−4.0

[a] Hydrogen bond length for the in-plane methyl proton and fluoride.
[b] Hydrogen bond length for the out-of-plane protons and fluoride; ΔG° and ΔH° are in kcal/mol and are referenced to the free ion values; distance in Å; the PCM solvation model is used to for THF and DMSO.

plane of the aromatic ring (Table 2, left) is calculated to be of similar energy to that of the end-on fluoride structure reminiscent of the C_3v structure of TMAF (Table 2, right). The exceptionally short *ortho*-aryl C–H···F^- hydrogen bond indicates that this is a remarkably strong interaction; the predicted short interaction distance may also account for the disproportionately large HOESY cross peak observed in the 2D spectrum (*vide supra*).

Previous computational work from our laboratory indicated that the activation barrier for fluorodenitration reactions was strongly dependent upon the substituent σ-value [41]. This strong substituent effect arises because the rate-determining step in nucleophilic aromatic substitution is formation of a Meisenheimer intermediate. The transition state for the formation of the Meisenheimer intermediate exhibits extensive negative charge injection into the aromatic ring. Thus, S_NAr reactions of trimethylanilinium triflates are expected to (and do) show large substituent effects similar to nitroarenes. Here we report thermodynamic studies for the competing S_NAr and reverse Menschutkin reactions, which, in conjunction with experimental studies, indicate that solution phase trimethylanilinium fluoride decomposition is indeed under kinetic control.

Fig. 4 summarizes the results of B3LYP/6-311G++(d, p) calculations for the reaction of fluoride ion with substituted trimethylanilinium salts in the gas phase and in DMSO and THF solutions. The linear free energy plots show that the thermodynamically most stable product is not obtained in DMSO. The slopes of the plots for methyl transfer are so much steeper (gas phase: $\rho = -12.7$, THF: $\rho = -9.2$, DMSO: $\rho = -8.9$) than they are for fluorination (gas phase: $\rho = -8.4$, THF: $\rho = -3.9$, DMSO: $\rho = -3.1$) that the demethylation product is predicted to be thermodynamically favored for electron deficient ring systems under all conditions. Similarly, and also contrary to experiment, the fluorination product is predicted to be thermodynamically favored for electron rich rings. The reason for this seeming discrepancy between theory and experiment is, of course, that the product formation is under kinetic control. Furthermore, since development of ring electron density at the transition state is expected to be larger for formation of the Meisenheimer intermediate than for demethylation, the rate for S_NAr substitution is expected to be much more strongly affected by the substituents. This classical kinetic argument is borne out by experiment.

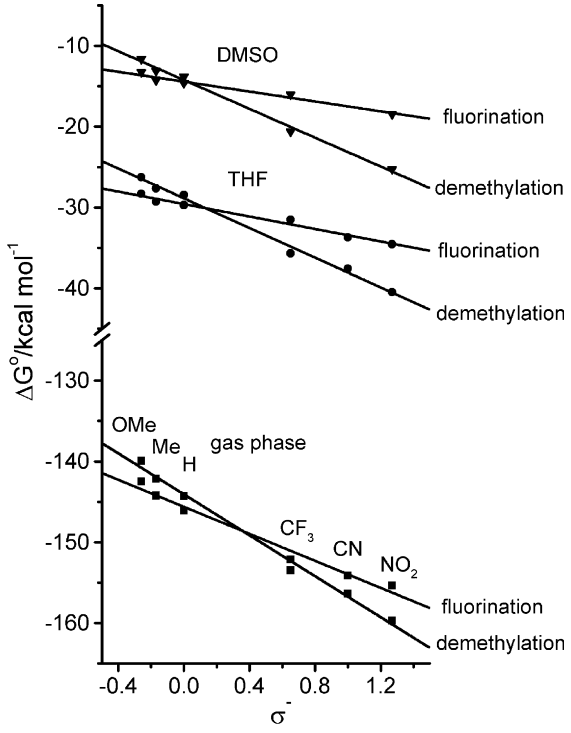


Fig. 4. Calculated free energy changes for both demethylation and fluorination of trimethylanilinium salts in the gas phase and in solution (THF, DMSO). (B3LYP/6-311G++(d, p) with PCM solvation model).

3. Conclusions

Several important conclusions can be drawn from this work. (1) The tetrabutylammonium cation is significantly more weakly ion paired to fluoride than trimethylanilinium cations are. (2) Trimethylanilinium fluorides are tightly ion paired in DMSO solution, thus these ion pair reactions represent the reactivity limit for this type of substitution reaction. (3) Under anhydrous conditions in DMSO, decomposition of these salts is rapid at 100 °C, regardless of the nature of the substituents on the ring. (4) Except for the case of extremely electron poor aromatic substrates (*para*-nitro), methyl fluoride is always generated in nucleophilic aromatic fluorination reactions of trimethylanilinium salts. Precautions to guard against exposure to this gaseous byproduct should be implemented if radiotracer syntheses are conducted using trimethylanilinium precursors. (5) The aryl/alkyl substitution ratio is correlated to the σ_p^- value of the substituent. (6) Theoretical studies are consistent with the notion that fluorodeamination is under kinetic control; the stability of the Meisenheimer intermediate, not the overall driving force for the reaction, determines the rate and extent of arene fluorination. Taken together, these studies imply that fluorodeamination of trimethylanilinium triflates may be intrinsically limited only by competitive demethylation, and suggest that relatively electron rich anilinium salts featuring more robust substituent groups could be fluorinated more effectively than trimethylanilinium triflates.

4. Experimental

4.1. General experimental procedures

All reagents were handled under N_2. Hexafluorobenzene (C_6F_6) (99%, SynQuest) was passed through a column of activated (130 °C for 5 h) silica gel and distilled from CaH_2. Acetonitrile (HPLC grade, Aldrich) was distilled from P_2O_5 and redistilled under reduced pressure from CaH_2. THF (anhydrous, Aldrich) was vacuum transferred from $LiAlH_4$. DMSO was distilled under N_2 from CaH_2. Purified solvents were stored under N_2 in Schlenk-style, Teflon-capped storage flasks. Tetra-*n*-butylammonium cyanide (TBACN) (97%) was

obtained from Fluka Chemical Co. and dried under vacuum at 40 °C overnight prior to use. TBAF* was prepared from TBACN as was described previously [40]. Tetramethylammonium hexafluorophosphate ($TMAPF_6$) was obtained from Fluka and dried under vacuum. All other reagents were of analytical grade, from Aldrich Chemical Company. ^1H, ^{13}C and ^{19}F NMR spectra were collected and analyzed in the Instrumentation Center at the University of Nebraska-Lincoln. 400 MHz (QNP probe) and 600 MHz (HF probe) NMR spectrometers were used in this study.

4.2. Computational studies

All calculations were performed on a 128 node computer (Prairie Fire) at the University of Nebraska-Lincoln computing facility. The Gaussian-view 03W interface and Gaussian-03 programs were used for the calculations.

4.3. Syntheses of trimethylanilinium triflate salts [20]

To a solution of *para*-substituted dimethylaniline (4.0 mmol) dissolved in dry benzene (10 mL) was added methyl triflate (0.63 mL) at room temperature. The reaction mixture was stirred at room temperature to 40 °C for 30 min to 8 h. At the conclusion of the reaction the trimethylanilinium triflate salt precipitated from solution. The precipitate was isolated by filtration, washed with dry benzene (5× 5 mL), and residual solvent was removed in vacuo. Excellent yields (>80% isolated) were obtained for all of the methylation reactions. These previously reported compounds were characterized by ^1H, ^{19}F, and ^{13}C NMR spectroscopy.

4.4. Reaction of TBAF* with trimethylanilinium triflate salts

To a solution of the appropriate trimethylanilinium triflate salt (0.2 mmol in 0.3 mL of d_6-DMSO) was added a solution of TBAF* (0.26 mmol) in 0.2 mL d_6-DMSO. The resulting solution was mixed well and transferred into an NMR tube equipped with a Teflon screw cap closure. The NMR tube was placed into a preheated (100 °C) oil bath for the time indicated in Table 1. The mixture was cooled by immersing the tube in a cold water bath before the solution was assayed by ^1H, ^{19}F, and ^{13}C NMR spectroscopy. The identities of all products were confirmed by comparison of the spectra to those of authentic samples.

Acknowledgments

We thank the Nebraska Research Initiative for financial support. This research was performed in facilities renovated with funds from the National Institutes of Health (RR16544-01).

References

[1] M.R. Kilbourn, Fluorine-18 Labeling of Radiopharmaceuticals, National Academy Press, 1990.
[2] Y.-S. Ding, J.S. Fowler, Drug Dev. Res. 59 (2003) 227–239.
[3] J.S. Fowler, N.D. Volkow, G.-J. Wang, Y.-S. Ding, S.L. Dewey, J. Nucl. Med. 40 (1999) 1154–1163.
[4] M.-C. Lasne, C. Perrio, J. Rouden, L. Barre, D. Roeda, F. Dolle, C. Crouzel, Top. Curr. Chem. 222 (2002) 201–258.
[5] R. Weissleder, Science 312 (2006) 1168–1171.
[6] T. Irie, K. Fukushi, T. Ido, Int. J. Appl. Rad. Isotopes 33 (1982) 445–448.
[7] T. Irie, K. Fukushi, O. Inoue, T. Yamasaki, T. Ido, T. Nozaki, Int. J. Appl. Rad. Isotopes 33 (1982) 633–636.
[8] G. Angelini, M. Speranza, A.P. Wolf, C.Y. Shiue, J. Fluorine Chem. 27 (1985) 177–191.
[9] C.Y. Shiue, J.S. Fowler, A.P. Wolf, D.W. McPherson, C.D. Arnett, L. Zecca, J. Nucl. Med. 27 (1986) 226–234.
[10] M.S. Haka, M.R. Kilbourn, G.L. Watkins, S.A. Toorongian, J. Labell. Compd. Radiopharm. 27 (1989) 823–833.
[11] T.J. McCarthy, A.U. Sheriff, M.J. Graneto, J.J. Talley, M.J. Welch, J. Nucl. Med. 43 (2002) 117–124.
[12] S. Oya, S.R. Choi, H. Coenen, H.F. Kung, J. Med. Chem. 45 (2002) 4716–4723.
[13] A.A. Wilson, R.F. Dannals, H.T. Ravert, M.S. Sonders, E. Weber, H.N. Wagner Jr., J. Med. Chem. 34 (1991) 1867–1870.
[14] Y. Seimbille, M.E. Phelps, J. Czernin, D.H.S. Silverman, J. Labell. Compd. Radiopharm. 48 (2005) 829–843.
[15] G. Getvoldsen, A. Fredriksson, N. Elander, S. Stone-Elander, J. Labell. Compd. Radiopharm. 47 (2004) 139–145.
[16] B. Kuhnast, S. Klussmann, F. Hinnen, R. Boisgard, B. Rousseau, J.P. Fuerste, B. Tavitian, F. Dolle, J. Labell. Compd. Radiopharm. 46 (2003) 1205–1219.
[17] B. Kuhnast, F. Hinnen, R. Boisgard, B. Tavitian, F. Dolle, J. Labell. Compd. Radiopharm. 46 (2003) 1093–1103.
[18] E.F.J. de Vries, J. Vroegh, P.H. Elsinga, W. Vaalburg, Appl. Radiat. Isotopes 58 (2003) 469–476.
[19] B. Kuhnast, F. Dolle, B. Tavitian, J. Labell. Compd. Radiopharm. 45 (2002) 1–11.
[20] B. Kuehnast, F. Dolle, S. Terrazzino, B. Rousseau, C. Loc'h, F. Vaufrey, F. Hinnen, I. Doignon, F. Pillon, C. David, C. Crouzel, B. Tavitian, Bioconj. Chem. 11 (2000) 627–636.
[21] B. Kuhnast, F. Dolle, F. Vaufrey, F. Hinnen, C. Crouzel, B. Tavitian, J. Labell. Compd. Radiopharm. 43 (2000) 837–848.
[22] T. Haradahira, Y. Hasegawa, K. Furuta, M. Suzuki, Y. Watanabe, K. Suzuki, Appl. Radiat. Isotopes 49 (1998) 1551–1556.
[23] F. Dolle, F. Hinnen, F. Vaufrey, B. Tavitian, C. Crouzel, J. Labell. Compd. Radiopharm. 39 (1997) 319–329.
[24] T. Toyokuni, J.C. Walsh, A. Dominguez, M.E. Phelps, J.R. Barrio, S.S. Gambhir, N. Satyamurthy, Bioconjug. Chem. 14 (2003) 1253–1259.
[25] T. Poethko, M. Schottelius, G. Thumshirn, U. Hersel, M. Herz, G. Henriksen, H. Kessler, M. Schwaiger, H.-J. Wester, J. Nucl. Med. 45 (2004) 892–902.
[26] H.T. Ravert, I. Madar, R.F. Dannals, J. Labell. Compd. Radiopharm. 47 (2004) 469–476.
[27] R.R. Kavali, B.C. Lee, B.S. Moon, S.D. Yang, K.S. Chun, C.W. Choi, C.-H. Lee, D.Y. Chi, J. Labell. Compd. Radiopharm. 48 (2005) 749–758.
[28] E.D. Hostetler, S.D. Jonson, M.J. Welch, J.A. Katzenellenbogen, J. Org. Chem. 64 (1999) 178–185.
[29] J. Ermert, K. Hamacher, H.H. Coenen, J. Labell. Compd. Radiopharm. 43 (2000) 1345–1363.
[30] Z. Li, Y.-S. Ding, A. Gifford, J.S. Fowler, J.S. Gatley, Bioconjug. Chem. 14 (2003) 287–294.
[31] W.R. Banks, R.D. Borchert, D.R. Hwang, Appl. Radiat. Isotopes 45 (1994) 75–81.
[32] W.R. Banks, D.R. Hwang, Appl. Radiat. Isotopes 45 (1994) 599–608.
[33] L. Lang, E. Jagoda, B. Schmall, B.-K. Vuong, H.R. Adams, D.L. Nelson, R.E. Carson, W.C. Eckelman, J. Med. Chem. 42 (1999) 1576–1586.
[34] A.R. Jalilian, S.A. Tabatabai, A. Shafiee, H. Afarideh, R. Najafi, M. Bineshmarvasti, J. Labell. Compd. Radiopharm. 43 (2000) 545–555.
[35] K.J. Guenther, S. Yoganathan, R. Garofalo, T. Kawabata, T. Strack, R. Labiris, M. Dolovich, R. Chirakal, J.F. Valliant, J. Med. Chem. 49 (2006) 1466–1474.

[36] Y. Seimbille, J. Czernin, M.E. Phelps, D.H.S. Silverman, J. Labell. Compd. Radiopharm. 48 (2005) 819–827.
[37] J. Ermert, C. Hocke, T. Ludwig, R. Gail, H.H. Coenen, J. Labell. Compd. Radiopharm. 47 (2004) 429–441.
[38] J.-L.M. Abboud, R. Notario, J. Bertran, M. Sola, Prog. Phys. Org. Chem. 10 (1993) 1–183.
[39] W.R. Banks, M.R. Satter, D.R. Hwang, Appl. Radiat. Isotopes 45 (1994) 69–74.
[40] H. Sun, S.G. DiMagno, J. Am. Chem. Soc. 127 (2005) 2050–2051;
The asterisk is used here to denote the anhydrous reagent and to distinguish it from the commercially available hydrated salt.
[41] H. Sun, S.G. DiMagno, Angew. Chem. Int. 45 (2006) 2720–2725.
[42] H. Sun, S.G. DiMagno, Chem. Commun. (2007) 528–529.
[43] I. Fernandez, E. Martinez-Viviente, P.S. Pregosin, Inorg. Chem. 44 (2005) 5509–5513.
[44] C. Hansch, A. Leo, R.W. Taft 91 (1991) 165–195.
[45] N. Collie, J. Chem. Soc. 55 (1889) 110–113.
[46] A.T. Lawson, N. Collie, J. Chem. Soc. 53 (1888) 624–636.
[47] K.M. Harmon, S.L. Madeira, J. Mol. Struct. 560 (2001) 179–188.
[48] A.S. Davies, W.O. George, S.T. Howard, Phys. Chem. Chem. Phys. 5 (2003) 4533–4540.