Solvent Dependent Leaving Group Fluorine Kinetic Isotope Effect in a Nucleophilic Aromatic Substitution Reaction

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Abstract: Fluorine kinetic isotope effects (F KIEs) have been determined using the accelerator-produced short-lived radionuclide ^{18}F in combination with natural ^{19}F. The solvent dependence of the leaving group F KIE was investigated for the nucleophilic aromatic substitution reaction (S_NAr) of 2,4-dinitrofluorobenzene with piperidine at 22 °C. The F KIE was determined to be 1.0262 ± 0.0007 in tetrahydrofuran (THF) and 0.9982 ± 0.0004 in acetonitrile. The significant F KIE in THF suggests that, in this solvent, departure of the leaving group is the rate-limiting step. On the other hand, the almost vanishing KIE in acetonitrile is consistent with addition of the nucleophile to the aromatic substrate being the rate-limiting step. A full account of the previously communicated (Matsson *et al. J. Am. Chem. Soc.* **1993**, *115*, 5288−5289) experimental method for determination of fluorine KIEs is also given.

Introduction

Displacement reactions on activated aromatic molecules have been the subject of considerable mechanistic interest over the years. A great deal of attention has been directed to nitro aromatics with halogen or other leaving groups.[1] The influence of nucleophile, solvent, leaving group, and the presence of base catalysis on kinetic parameters are some of the system variations that have been employed in these mechanistic investigations.

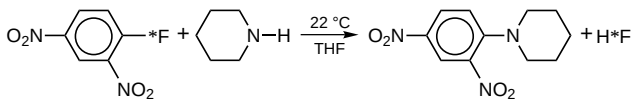
For several reasons the nucleophilic substitution of 2,4-dinitrofluorobenzene (DNFB) with secondary amines appeared to be a good candidate as a model system for the demonstration of a fluorine KIE. We recently reported[2] the first example of a $^{18}F/^{19}F$ leaving group KIE for such a reaction.

The generally accepted mechanism for nucleophilic aromatic substitution (the S_NAr mechanism) is an addition−elimination and involves the formation of a Meisenheimer type of intermediate.[3] Whether the rate-limiting step of this mechanism is the formation of the intermediate or expulsion of the leaving group has been found to depend on the character of the nucleophile and the leaving group as well as on the solvent. The existence of a significant leaving group F KIE for the reaction of DNFB with piperidine in tetrahydrofuran (THF) at 22 °C (Scheme 1), observed by us earlier, unequivocally demonstrates that C−F bond cleavage is rate limiting in that system. Therefore we thought it would be of interest to know if the rate-limiting step is affected by change of solvent, as reported by Nudelman *et al.*,[4] and if this could be confirmed by determining the leaving group F KIE.

Results

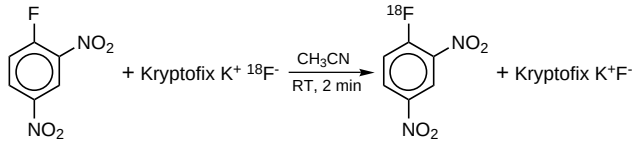
The ^{18}F labeled DNFB was prepared in an exchange reaction between unlabeled DNFB and [^{18}F]fluoride (Scheme 2).[5] The optimal yield was obtained after 2 min at room temperature; prolonged reaction times or heating resulted in a lower yield of DN^{18}FB.

Scheme 1



* = 18 or 19

Scheme 2



The kinetic method is based on HPLC fractionation of reactants and products and is similar to the method for determination of KIEs using short-lived ^{11}C in combination with ^{14}C which was developed earlier in our laboratory.[6] Measurement of the ^{18}F radioactivity was performed by liquid scintillation counting. Accurate measurements of ^{19}F, regarded as equivalent to the total DNFB,[7] were done by careful analysis using the integrated signal from the UV detector. The KIEs were calculated from the isotopic fractions of reaction determined for a series of samples where the extents of reaction were predetermined by adding different amounts of piperidine to an excess of DNFB.

The radiochromatograms showed only the reactant peak (retention time, r.t., 2.45 min). In the UV chromatogram, toluene (internal standard; r.t. 4.48 min) and the product *N*-(2,4-dinitrophenyl)piperidine (r.t. 5.78 min) were observed in addition to the DNFB peak (see Figure 1).

The KIEs obtained from the kinetic experiments in THF and acetonitrile were 1.0262 ± 0.0007 and 0.9982 ± 0.0004, respectively. The results from the different experiments performed in THF and acetonitrile are shown in Table 1.

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(3) See *e.g.* ref 1, Chapter 1.

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(5) A study of ^{18}F incorporation in DNFB has been reported earlier: Korguth, M. L.; DeGrado, T. R.; Holden, J. E.; Gatley, S. J. *J. Lab. Comp. Radiopharm.* **1988**, *25*, 369.

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(7) The relative amount of labeled DNFB is approximately 0.01% in the reaction solution.

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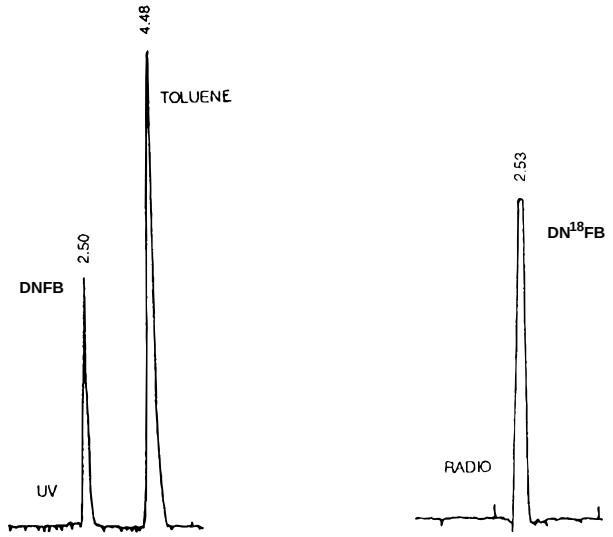

Figure 1. Radiochromatogram (right) and UV chromatogram for the HPLC analysis of the reaction solution. Toluene is the internal standard. The product peak was eluted.

Table 1. The $^{18}F/^{19}F$ KIEs Determined for the Reaction of Labeled DNFB[a] with Piperidine in THF and Acetonitrile at 22 °C

expt no.	point KIE ± std dev	no. of points	solvent	KIEs obtained in expt #2
1	1.0274 ± 0.0053	5	THF	1.0257 (2.91)[b]
2	1.0251 ± 0.0074	4	THF	1.0158 (2.47)[b]
3	1.0260 ± 0.0064	2	THF	1.0250 (1.65)[b]
4	0.9978 ± 0.0061	5	acetonitrile	1.0339 (0.859)[b]
5	0.9985 ± 0.0071	2	acetonitrile	

[a] The concentration of DNFB was *ca.* 3.3 10^{-3} M. The last column shows the individual KIEs obtained in experiment #2. [b] Starting concentration of piperidine (mM).

Discussion

In mechanistic investigations fluoride is commonly employed as a leaving group in elimination and substitution reactions.

The determination and interpretation of kinetic isotope effects provide one of the most important tools in physical organic and bioorganic chemistry. It therefore seemed worthwhile to try to include fluorine among the heavy atoms used for kinetic isotope effect measurements. Since natural fluorine consists of 100% of the isotope ^{19}F and since no long-lived radioisotopes are available, the only way to accomplish determination of F KIEs is to use a short lived radionuclide. Among these the accelerator-produced ^{18}F has a convenient half-life of 110 min and is routinely produced in many laboratories; the isotope ^{18}F is used in the labeling of radiopharmaceuticals and other compounds used for biomedical research and clinical diagnosis utilizing the PET-imaging technique.[8] Nucleophilic as well as electrophilic labeling reagents are available and quite a number of compounds have been labeled with ^{18}F; these include carbohydrates, alkyl halides, fatty acids, and steroids.[9]

Leaving group KIEs are fairly easy to interpret and have been utilized for a long time in mechanistic investigations of nucleophilic aliphatic substitution[10] and elimination reactions.[11]

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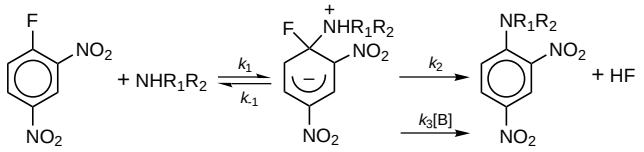
Scheme 3



A leaving group KIE is expected to monotonously increase with increasing degree of bond breaking between the isotopic leaving group atom and the α-carbon in the transition state of the rate-limiting step. Thus sulfur, oxygen, and chlorine leaving group KIEs have been reported.[10] Nucleophilic reactions on activated aromatic substrates are particularly attractive as model systems for fluorine kinetic isotope effects since the reaction is quick enough to work with short-lived isotopes. Fluorine has also been employed as the leaving group in many other mechanistic studies of this reaction type. Nucleophilic aromatic displacement on activated substrates has recently been reviewed in a very useful monograph by Terrier.[1]

The current mechanistic view of the S_NAr reaction for neutral nucleophiles such as primary or secondary amines is an addition−elimination type of mechanism (see Scheme 3) in which the nucleophile is first added to the aromatic substrate forming a zwitterionic intermediate.[3] Decomposition of the intermediate may be base catalyzed as indicated in Scheme 3 (k_3[B]). Either the nucleophile or some added base acts as the catalyst. The observation of base catalysis has been used as a mechanistic criterion of whether the formation or the decomposition of the intermediate is rate limiting. The rate expression for this mechanism, assuming steady state conditions for the intermediate, is given by eq 1.

$$d[Ar]/dt = k_A[Ar][Nuc];$$
$$k_A = (k_1k_2 + k_1k_3[B])/(k_{-1} + k_2 + k_3[B]) \quad (1)$$

Variations in the relative rates for the different elementary steps yield situations where formation or breakdown of the intermediate is rate limiting. Three different cases have been experimentally demonstrated:

(i) $k_2 + k_3[B] \gg k_{-1}$. Base catalysis is not observed. This occurs when the first elementary reaction step *i.e.*, formation of the intermediate, is rate limiting. The rate expression simplifies to

$$k_A = k_1 \quad (2)$$

(ii) $k_2 + k_3[B] \ll k_{-1}$. The intermediate is formed in a preequilibrium and decomposition of the intermediate is rate limiting. Base catalysis is observed and the rate constant depends linearly on the concentration of base (eq 3).

$$k_A = k_1/k_{-1}(k_2 + k_3[B]) = k' + k''[B] \quad (3)$$

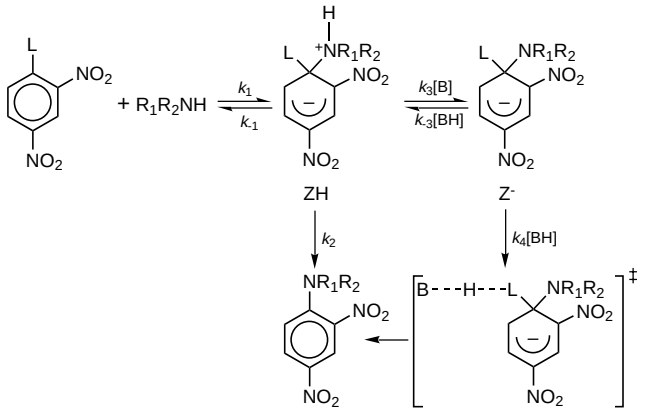
(iii) $k_2 + k_3[B] \approx k_{-1}$. Base catalysis is observed but in this case k_A depends on [B] in a curvlinear fashion.

The base catalysis in reactions where decomposition of the intermediate is rate limiting or partially rate limiting may operate *via* two different mechanisms: The specific base−general acid (SB-GA) mechanism or the rate-limiting proton transfer mechanism (RLPT).[3] In both cases the base deprotonates the initially formed zwitterionic intermediate ZH (Scheme 4) yielding the anionic intermediate Z^-.

In the SB-GA mechanism a rapid base catalyzed proton abstraction from ZH takes place, followed by rate limiting general acid catalyzed expulsion of the leaving group from the anionic intermediate Z^-.[12] Evidence for this mechanism have been obtained in dipolar aprotic media.[13] The situation in media

(12) Reference 1, Chapter 1.6.1, and references therein.

Scheme 4



of low permittivity[14] is sometimes complicated by existence of dimers of the nucleophile[15] and by formation of complexes between the substrate and the nucleophile or base catalyst.[14,16]

In the RLPT mechanism,[17] base promoted deprotonation of the zwitterionic intermediate ZH is rate limiting. This mechanism is operative mainly in protic media.

The expression for the observed rate constant for the SB-GA mechanism in Scheme 4, based on the steady state assumption for the intermediates, is given by eq 4,

$$k_A = (k_1k_2 + k_1k_4K_3[B])/(k_{-1} + k_2 + k_4K_3[B]) \qquad (4)$$

where K_3 is the equilibrium constant for deprotonation of ZH to Z^- and k_4 is the rate constant for the general acid catalyzed expulsion of the leaving group from Z^-. Again, as for the simplified mechanism in Scheme 3, there are two limiting cases: (i) fully rate limiting formation of the zwitterionic intermediate, *i.e.* rate-limiting addition of the nucleophile to the substrate, and (ii) rate-limiting departure of the leaving group in a catalyzed step. The kinetic isotope effect for case (i) is given by eq 5,

$$KIE_{obs} = k_1/k_1^* \qquad (5)$$

where the asterisk indicates the heavy isotope. For the present case with isotopic fluorine as a leaving group a secondary KIE may be observed for k_1. The hybridization for the carbon bound to fluorine changes from sp^2 to sp^3 when going from the reactant to the transition state. This is associated with a small increase of the force field for the isotopic atom since one normal mode out-of-plane bending vibration is transformed to a valence angle bending vibration possessing a somewhat higher frequency. Thus, the leaving group fluorine isotope effect for the addition step is expected to be very small and inverse.

For case (ii) the expression for the KIE is more complex and made up of three different contributions (eq 6), assuming that the uncatalyzed path k_2 is negligible as compared to the catalyzed decomposition k_4.

$$KIE_{obs} = (K_1/K_1^*)(k_4/k_4^*)(K_3/K_3^*) \qquad (6)$$

The first factor (K_1/K_1^*) in eq 6 is the equilibrium isotope effect (EIE) for the addition step. This EIE should be small and inverse according to the argument concerning the KIE for this step discussed above for case (i). In fact the maximal secondary KIE for the addition step should be equal to this EIE *i.e.,* the limiting value obtained for a TS with a structure identical to the intermediate ZH. The third factor in eq 6 is the EIE for the proton transfer reaction $ZH + B \rightleftarrows Z^- + BH^+$. This factor is expected to be very close to unity, since the force field for the isotopic heavy atom is hardly changed at all in the proton transfer process. Thus the main contributor to the leaving group fluorine KIE for case (ii) is the second factor in eq 6. This factor corresponds to the KIE for the general acid assisted departure of the fluorine from the anionic intermediate Z^-. A maximum value for this KIE was earlier estimated to be approximately 3% using a simple diatomic C−F model.[2]

Our observation of a significant leaving group fluorine KIE (2.6%) for the reaction run in THF thus clearly demonstrates that departure of the leaving group is rate limiting in this solvent, *i.e.,* case (ii) of the SB-GA mechanism above holds. This is consistent with Nudelmans finding[4] that the reaction is subject to base catalysis in THF. The close to maximal value for the fluorine KIE determined suggests that breaking of the carbon−fluorine bond is well advanced in the rate limiting TS. In fact, the KIE should be even somewhat larger than the observed value since it is multiplied by the slightly inverse EIE for the addition step (eq 6).

In acetonitrile no significant fluorine KIE is observed, although the small inverse value determined might be attributed to the very small secondary effect expected for rate limiting formation of the intermediate ZH (case (i)). Again, the leaving group KIE is consistent with the conclusions based on variation of the concentration of base: the first reaction step is rate limiting since no base catalysis was found for the reaction run in acetonitrile.[4,18] This change of rate limiting step between the solvents THF and acetonitrile has been attributed to their different hydrogen bond donating (HBD) abilities.[4] Solvent HBD acidity may be estimated using the α-parameters by Kamlet and Taft.[19] Acetonitrile has a finite albeit small α-value (0.270), whereas THF has an α-value of zero. Accordingly, acetonitrile being a better HBD solvent would act as a general acid to assist departure of the fluoride resulting in a diminished need for catalysis by the conjugate acid of the base. The F KIE would, however, be smaller in acetonitrile even if expulsion of fluoride was rate limiting or partially rate limiting in this solvent since the interaction between the departing fluoride and a solvent molecule tends to decrease the isotope effect. The importance of solvation effects on chlorine KIEs has been experimentally demonstrated by Cromartie and Swain.[20]

Except for a few studies of deuterium KIEs,[21,22] the literature is lacking in reports of isotope effects for S_NAr reactions. In a study by Hart and Bourns[23] the ^{18}O leaving group KIE for the nucleophilic aromatic substitution reaction of 1-phenoxy-2,4-dinitrobenzene with piperidine in aqueous dioxane was determined. In that investigation k_{16}/k_{18} was found to decrease with increasing concentration of hydroxide ion added; this was interpreted as evidence for a change from rate-limiting decomposition of the intermediate to a rate-limiting addition step.

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(22) Hawthorne, M. F. *J. Am. Chem. Soc.* **1954**, *76*, 6358−6360.

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Conclusions

A method has been developed which permits the determination of fluorine KIEs accurate enough to be mechanistically significant. This should be of general use in the study of incoming and leaving group KIEs in organic and bio-organic reaction systems.

For the S_NAr reaction of DNFB with piperidine a significant F KIE is observed when the solvent is THF. When acetonitrile is used as the solvent no such F KIE is observed. These observations are consistent with a switch in rate-limiting step from the addition step (in acetonitrile) to the elimination step (in THF).

Experimental Section

General. The ^{18}F was obtained as **[**^{18}F**]**fluoride (specific activity approximately 180 GBq/μmol) in 30−90% ^{18}O-enriched water in a $^{18}O(p,n)^{18}F$ nuclear reaction[24] using the Scanditronix MC-17 cyclotron at the Uppsala University PET Centre. A proportional regulating thermostat (HETO) with a regulating accuracy of ±0.005 °C was used. The temperature of the water in the thermostat never deviated more than ±0.02 °C from the reported value during a kinetic run. The glassware used was washed in chromic acid and then with water and ethanol, dried at 150 °C, and kept over silica gel in a desiccator under nitrogen atmosphere. The syringes were washed with 2.0 M hydrochloric acid, 2.0 M sodium hydroxide, distilled water, ethanol, and finally dry ether. The syringes were kept over silica gel in a desiccator under a nitrogen atmosphere until used.

The HPLC analyses were performed on a Hewlett Packard 1084 HPLC with a β^+-flow detector in series with the UV detector of the instrument. The HPLC was equipped with a fraction collector (Hewlett Packard 79825 A). The fraction collector was slightly modified by removing the Teflon insert. The HPLC analyses were performed on a column, 200 × 4.6 mm, packed with Nucleosil RP C-18, 5 μm. The mobile phase was 0.05 M ammonium formate, pH 3.5, and methanol gradient flow 2.00 mL/min (0−4 min, 60% MeOH; 4−5 min, 60−80% MeOH; 5−7 min, 80% MeOH; 7−8 min, 80−60% MeOH). The wavelength used was 254 nm using 430 nm as a reference. A UV calibration curve was obtained by plotting the integrated UV area versus different concentrations of DNFB. Usually 10 samples were used to construct the calibration curve.

The radioactive counting was performed using a liquid scintillation counter LKB 1214 with the energy window set to 1−2000 keV. The counting time was 1−2 min depending on the amount of radioactivity present. The radioactive HPLC fractions (usually 4 mL) were collected in scintillation bottles containing 15 mL of scintillation liquid (Zinsser Quickzint 1). Analytical GC was run on a Varian 3400 gas chromatograph, equipped with a flame-ionization detector and a Varian 4270 integrator, using a DB5−30W capillary column. ^1H NMR spectra were obtained with a Varian Unity 400 spectrometer. The evaporations were performed using a Büchi Rotavapor M connected to an Edwards High Vacuum Pump.

Materials. 2,4-Dinitrofluorobenzene (from Aldrich) was used as bought without further purification and was stored over silica gel in a desiccator under a nitrogen atmosphere. The purity (99%) was determined prior to use by ^1H NMR and HPLC. Tetrahydrofuran (THF) and acetonitrile, predried with molecular sieves, were freshly distilled from calcium hydride and kept over 3 Å molecular sieves under a nitrogen atmosphere. Piperidine predried with molecular sieves was freshly distilled from calcium hydride in a Fischer Spaltrhor distillation apparatus and kept under a nitrogen atmosphere. The purity (>99%) was determined using ^1H NMR and GC.

2,4-Dinitro[^{18}F]fluorobenzene. To an aqueous solution (0.5−1 mL) of [^{18}F]fluoride (usually 0.5−1.9 GBq) was added Kryptofix[2.2.2] (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane, 6.2 mg, 0.0166 mmol), potassium carbonate (2.3 mg, 0.0166 mmol), and 1 mL of acetonitrile. The water was removed azeotropically by evaporation of the solvent *in vacuo*. The procedure of addition and distillation of acetonitrile was repeated three times after which a final 1 mL of acetonitrile was added. To this solution was added 1 mL of a 0.1 M solution of DNFB in acetonitrile. After 2 min of reaction at room temperature the solution was introduced onto a silica column (3 mL, neutral, washed with 15 mL of acetonitrile) and the product was eluted with acetonitrile. After evaporation of the solvent *in vacuo*, a 5-mL solution of THF or acetonitrile containing toluene as an internal standard was added yielding a final concentration of DNFB of approximately 0.02 M. The concentration of DNFB was determined by HPLC (UV) using the calibration curve.

Kinetic Procedure. Five vials containing 1.00-mL solutions of different concentrations of piperidine in THF or acetonitrile were prepared. The vials were capped and thermostated at 22.00 °C after which the reaction was started by addition of 0.200 mL of the DNFB solution *via* a thermostated syringe. The DNFB was in excess in all vials. The amounts of piperidine were chosen to yield extents of reaction ranging from 0% up to 70%. The concentration of the piperidine was usually between 8.3×10^{-4} and 2.5×10^{-3} M in the reaction samples. After complete reaction, each sample was diluted with acetonitrile (the amount determined by weight) so that a linear UV response was obtained. The radioactive fluoride formed in the reaction was removed by passing the reaction solution through a silica column or by direct injection on the HPLC column. Since no difference could be detected, the simpler method of direct injection was followed. The analysis of the eluent did not reveal any significant amount of radioactive fluorine passing through the column. Careful analysis of the background radioactivity was performed during the entire experiment to ensure that no radioactive fluorine was leaking out of the column. Each sample was analyzed five times by HPLC and the DNFB fraction was collected in scintillation bottles containing 15 mL of scintillation liquid. The ^{18}F radioactivity of the fraction bottles was immediately measured by liquid scintillation counting and the fractions of least radioactivity being measured first. The ^{18}F-CPM (counts per minute) were corrected for background and half-life. The half-life corrections were made according to eq 7:

$$\mathrm{CPM}_{\mathrm{corr}} = Z/\{0.5^{(t/t_{1/2})}\} \tag{7}$$

where $\mathrm{CPM}_{\mathrm{corr}}$ and Z are the uncorrected and the decay-corrected ^{18}F CPM values, respectively, t is the elapsed time in seconds, and $t_{1/2}$ is the ^{18}F half-life. Each sample was counted five times and the mean value from these measurements was used in the calculations. The dead-time in liquid scintillation counting is dependent on the total amount of radioactivity present in the samples. Dead-time corrections made by the instrument were checked and found to be accurate up to 15% but no data with dead-times over 6% were used. At a dead-time of 5% the CPM values were approximately between 70000 and 150000 CPM. The KIE was calculated as the mean value of the KIE at each point according to eq 8 which is valid when the reaction is of first order in the labeled reactant.[25]

$$k_{18}/k_{19} = \ln(1 - f_{18})/\ln(1 - f_{19}) \tag{8}$$

The fraction of reaction for DN^{18}FB, f_{18}, was calculated as the ratio $\{1 - C(x)\}/\{1 - C(0)\}$ for each sample, where $C(x)$ is the corrected CPM value for unreacted DN^{18}FB at x% reaction and $C(0)$ is the corrected CPM value at 0% reaction (no piperidine added). The fraction of reaction of DN^{19}FB, regarded as equivalent to the total fraction of reaction,[7] was determined by dividing the ratio of the reactant and internal standard UV areas for each sample with that obtained for 0% reaction. The quench error was low in these experiments since the composition of the mobile phase was identical for all the fraction bottles.

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(24) ^{13}N was formed as a side product in the nuclear reaction $^{16}O(p,\alpha)^{13}N$. This radionuclide has a half-life of 10 min.

(25) Reference 11, Chapter 4.2.1