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Review Article

Isotope effects for fluorine-18 and carbon-11 in the study of reaction mechanisms†

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Abstract: The use of kinetic isotope effects (KIEs) for the short-lived radionuclides ^{11}C and ^{18}F in the study of reaction mechanisms is described using some examples. Leaving group fluorine KIEs (k^{18}/k^{19}) have been utilized to determine the rate-limiting step for nucleophilic aromatic substitution reactions (S_NAr). The fluorine KIE was also used to probe the effect of changing solvent and nucleophile steric hindrance on rate-limiting step. The mechanism for a base promoted elimination reaction was determined to be stepwise (E1cB) by a multiple KIE study including the leaving group fluorine KIE. The transition state structures for aliphatic nucleophilic substitution reactions (S_N2) have been investigated by multiple KIE studies for cases where the substrate substitution, leaving group or solvent has been varied. Carbon KIEs for labelled α-carbon atom in the substrate are large, $k^{11}/k^{14} = 1.189–1.220$. For labelled nucleophile cyanide ion, $k^{11}/k^{14} = 0.99951–1.0119$. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: short-lived radionuclide; kinetic isotope effect; reaction mechanism; S_N2; S_NAr

Introduction

The isotopes of the elements are utilized in different ways in the investigation of reaction mechanisms: (i) as *tracers* and (ii) by determining *kinetic isotope effects* (KIEs), i.e. effects on the reaction rate caused by isotopic substitution.

The study of KIEs may provide answers to some of the fundamental mechanistic questions:[1–3]

(i) Which atoms undergo rate-limiting bonding change (forming or breaking of bonds)?
(ii) What is the structure of the activated complex? Is the TS constant or does it vary when the system is perturbed by substitution, change of solvent, etc.? Is the TS reactant like or product like, or is it 'symmetric'? Do bonding changes take place in a synchronous or asynchronous fashion?

An unusual experimental method that has some advantages (and certainly also drawbacks) is the use of accelerator-produced short-lived radionuclides in the study of isotope effects on reaction rate.

Short-lived radionuclides today are largely used in biomedical research and clinical diagnosis in connection with positron emission tomography (PET).[4] The nuclides that have been utilized in isotope effect studies are ^{11}C ($t_{1/2} = 20.4$ min) and ^{18}F ($t_{1/2} = 110$ min) which both decay almost exclusively by positron emission (98.1% β^+ and 97% β^+, respectively) thus producing γ-photons by annihilation.

Fluorine kinetic isotope effects

Fluoride is commonly employed as a leaving group in the study of elimination and substitution reactions.

Since natural fluorine consists of 100% of the isotope ^{19}F, the determination of KIEs has for a long time been replaced by determination of element effects, i.e. substituting for another halogenide as the leaving group. However, the determination of F KIEs can be accomplished by using the accelerator-produced radionuclide ^{18}F which has a convenient half-life of 110 min and is routinely produced in many laboratories. The isotope ^{18}F is used in the labelling of radiopharmaceuticals and other compounds used for biomedical research and diagnosis utilizing the PET-imaging technique.[5] Nucleophilic as well as electrophilic

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labelling reagents are available and a number of compounds have been labelled with ^{18}F; these include, e.g. carbohydrates, alkyl halides, fatty acids and steroids.[6]

The maximal $^{18}F/^{19}F$ KIE for breaking of a carbon–fluorine bond has been estimated at ca. 3% based on the ratio of reduced masses for isotopic diatomic oscillators (^{12}C–^{18}F and ^{12}C–^{19}F, respectively) and a C–F stretching frequency of 1250 cm^{-1}.[7]

Carbon kinetic isotope effects

Traditionally carbon KIEs have been determined by mass spectrometry using ^{13}C or by radioactivity measurements using ^{14}C. The advantage of using the short-lived carbon isotope ^{11}C in combination with the long-lived radioisotope ^{14}C is that the observed isotope effect is then maximized. Heavy element isotope effects like those for carbon are small so it is very valuable to increase the mass ratio in order to determine the KIEs with highest possible precision. This is particularly important when studying the often small changes of the KIEs caused by system variations such as the presence of substituents with different electronic properties in a reacting substrate molecule, different steric requirements or choosing solvents of different polarities. Some drawbacks with this approach are that a special equipment is needed for the production and handling of radionuclides, the necessity of radiation protection and the requirements set by the short half-life on synthesis and kinetics, i.e. choice of system.

Labelling synthesis with short-lived radionuclides

Traditional organic chemistry methods can be adapted to the synthesis of compounds radiolabelled with short-lived nuclides. However, modifications of the original synthetic method are usually needed and sometimes new synthetic strategies must be developed. Preferably, the synthetic route is chosen so that only a few rapid steps remain when the radionuclide has been incorporated. Synthesis of tracer compounds labelled with short-lived radionuclides involves production of the radionuclide and the labelling precursor, synthesis of the tracer molecule, purification and analysis.

When synthesizing compounds labelled with short-lived radionuclides, a very important parameter is time. While the buildup of the product is governed by kinetics of the chemical transformation, there is always a competing decay of the radionuclide.[8]

The most commonly used starting material in ^{11}C synthesis is [^{11}C]carbon dioxide.[9] It is produced by bombardment of nitrogen gas with high-energy protons, the $^{14}N(p,\alpha)^{11}C$ nuclear reaction. Trace amounts of oxygen gas in the target gas combine with the high-energy ^{11}C atoms to produce $[^{11}C]O_2$ as a primary precursor.[9] Since the number of chemical transformations that can be achieved by $[^{11}C]O_2$ is limited, the primary precursor is generally converted to a more reactive secondary precursor which can be further used to label a molecule of interest. A more recent and very promising development is the use of [^{11}C]O as a primary precursor.[10]

Introduction of ^{18}F into a molecule can be performed by electrophilic or nucleophilic addition of the radionuclide.[5a,6] Common methods for ^{18}F preparation are the $^{20}Ne(d,\alpha)^{18}F$ and $^{18}O(p,n)^{18}F$ nuclear reactions. Both the methods can give either $[^{18}F]F_2$ or $[^{18}F]F^-$.

Electrophilic fluorination with $[^{18}F]F_2$ provides a facile means of introducing ^{18}F into alkenes or aromatic rings. Due to its rather unspecific reactivity, the use of electrophilic fluorine is limited. Improvements have been achieved by deactivating the fluorine by dilution with an inert gas or formation of new fluorinating agents such as $[^{18}F]CH_3COOF$.[5a,6]

Nucleophilic fluorination with $[^{18}F]^-$ is usually accomplished either via nucleophilic displacement of halide or sulphonate leaving groups in aliphatic systems or nucleophilic aromatic substitution of a nitro or trialkylammonium group in activated aromatic systems. Reagents such as quaternary ammonium salts or a potassium cation complexed by the kryptand Kryptofix 2.2.2 are commonly used to increase reactivity and solubility of the fluoride nucleophile.[5a,6]

Kinetic methods

The methodology for determining KIEs using short-lived radionuclides is based on separation of reactants and products by liquid chromatography followed by radioactivity measurements using liquid scintillation. The method for determination of carbon KIEs has certain advantages in addition to the already mentioned fact that the largest practical mass ratio of carbon isotopes is used: (i) The HPLC technique is usually easily applied to different chemical systems; (ii) no workup or degradation of the samples is required; (iii) the analyses are insensitive to unlabelled impurities as long as these do not cause any quenching of scintillation; (iv) both isotopic species can be quantitatively determined with high precision using the same instrument; (v) the large difference in half-life for the two carbon isotopes used simplifies the measurement. Experiments with ^{11}C and ^{18}F implore rapid execution and the experiments have to be carefully prepared before starting of the synthesis.

The determination of a $^{11}C/^{14}C$ KIE typically involves the following steps:[11] The kinetic reaction is started by

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mixing the ^{11}C-labelled substrate, which has been prepared immediately prior to the kinetic experiment, and the previously synthesized ^{14}C-substrate with any other necessary reactants. At suitable time intervals, samples are withdrawn and analysed by HPLC. The fractions containing the labelled reactant and product are collected in scintillation liquid. The HPLC instrument is equipped with a radioactivity detector as a complement to the UV detector. The total radioactivity (^{11}C +^{14} C) of each fraction is immediately measured by liquid scintillation counting, usually for 1–2 min. After decay of the ^{11}C, typically the next day, the ^{14}C-radioactivities of the samples are measured for a period long enough to keep the statistical error at a tolerable level. The ^{11}C-radioactivity is obtained as the difference between the total and ^{14}C-radioactivity and is then corrected for radioactive decay. Having these data at hand, the KIE for each sample is calculated as

$$\mathrm{KIE} = \ln(1 - f_{11})/\ln(1 - f_{14}) \quad (1)$$

where f_{11} and f_{14} are the fractions of reaction for the isotopic reactions, calculated from the radioactivities for reactant and product fractions. As an alternative, one may follow the formalism traditionally used for competitive kinetics when determining heavy atom KIEs.

Depending on whether the reactant or the product is monitored, the KIE can be calculated according to the following expressions:

$$\mathrm{KIE} = \ln(1 - f)/\ln[(1 - f)(R_s/R_0)] \quad (2)$$

$$\mathrm{KIE} = \ln(1 - f)/\ln[1 - f\,R_p/R_0] \quad (3)$$

The fraction of reaction, f, is a measure of the extent of conversion of the reaction with the light isotopologue. R_s and R_p are the isotopic ratios at a fraction of reaction, f, for the reactant and the product, respectively. The isotopic ratio at 0% conversion is denoted by R_0. In order to ensure minimal contribution to KIE from the error arising from the determination of f, the reaction should be stopped at an early stage, i.e. $f < 15\%$, if the isotopic ratios of the product are used. For the same reason, a conversion of about 50% is desirable when the isotopic ratios of the reactant are utilized. In practice, this may be in conflict with the investigated system, causing the fraction of reaction in the experiment to deviate substantially from the ideal situation. In fact, it is advisable to have a spread of fractions of reaction in an experimental series in order to ensure that the observed KIE is independent on f. Figure 1 depicts the overall kinetic procedure for the case of a ^{11}C/^{14}C KIE determination with labelled cyanide.

For the fluorine KIEs, the protocol is basically the same,[7,12] except that, of course, ^{19}F is not radioactive.

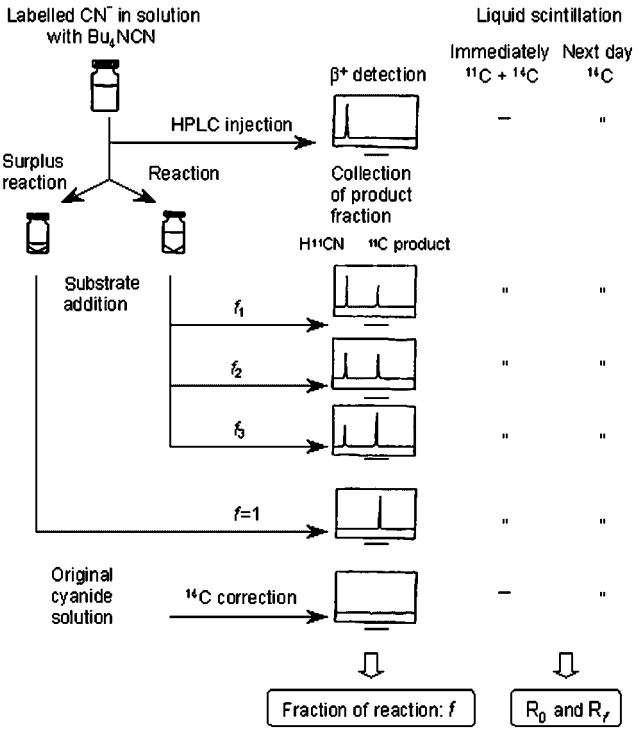

Figure 1 The overall kinetic procedure for the case of a ^{11}C/^{14}C KIE determination with labelled cyanide.

The unlabelled substrate may under fortunate conditions be quantitatively detected by means of the HPLC UV detector provided that careful use of internal standard and repeated injections are performed.

Remote labelling might be a way to increase precision in certain cases. By labelling the ^{19}F-substrate with ^{14}C in a position remote from the reacting centre it is possible to determine both ^{18}F and ^{19}F-labelled molecules by liquid scintillation counting. This strategy was used in a study of a HF elimination reaction.[13,14]

Determination of rate-limiting steps for nucleophilic aromatic substitution using leaving group F KIEs

Displacement reactions on activated aromatic molecules have been the subject of considerable mechanistic interest over the years.[15] The generally accepted mechanism for nucleophilic aromatic substitution of activated substrates, the S_NAr mechanism, is an addition elimination.[15] Whether the rate-limiting step 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. Decomposition of the intermediate may be base catalysed as indicated in Scheme 1 (k_3[B]). The observation of base catalysis has been used

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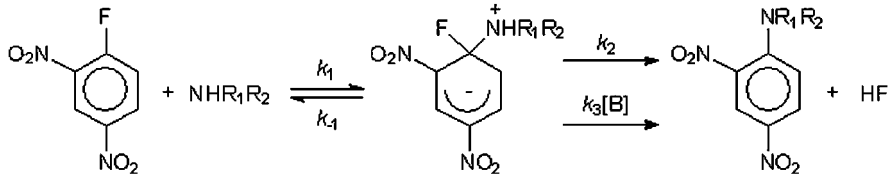
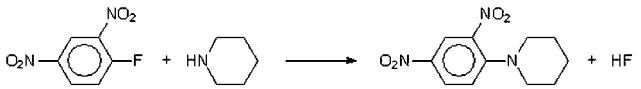


Scheme 1

as a mechanistic criterion of whether the formation or the decomposition of the intermediate is rate limiting.

The nucleophilic substitution of 2,4-dinitrofluorobenzene (DNFB) with a secondary amine was used as a model system for the first demonstration of a fluorine KIE. The observation of a significant leaving group F KIE of 1.0262 ± 0.0007 for the reaction of DNFB with piperidine in tetrahydrofuran (THF) at 30°C (Scheme 2) demonstrates that the C–F bond cleavage is a rate-



Scheme 2

limiting step in that system.[7] The value is close to what is expected from an estimate of the maximal $^{18}F/^{19}F$ KIE for complete loss of zero-point energy.[7]

Probing the effect of solvent

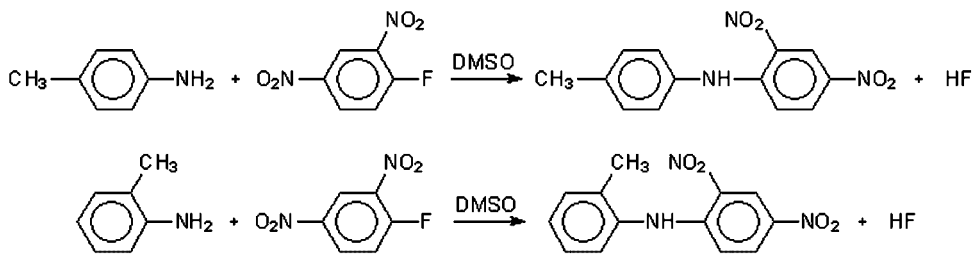
The leaving group F KIE probe offers an opportunity to learn whether the rate-limiting step is affected by a change of solvent. On the basis of an investigation of base catalysis, Nudelman has earlier concluded that a shift from rate-limiting elimination to rate-limiting addition takes place when the solvent is changed to one with slightly hydrogen-bond-accepting properties, e.g. acetonitrile, from the one lacking such properties, e.g. THF.[16] The resulting leaving group KIE when changing the solvent is therefore interesting; it also gives further evidence that the observed KIE is real and not an artefact.

The isotopic rate constant ratio obtained from the kinetic experiments in acetonitrile was 0.9982 ± 0.0004.[12] Thus, 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 involving sp^2 to sp^3 rehybridization.

Probing the effect of nucleophile steric hindrance

For reaction of methylanilines with DNFB, it has been reported that the rate was reduced by a factor of 198 when the position of the methyl substituent was changed from *para* to *ortho* in the nucleophile (Scheme 3).[17] Onyido and Hirst from studies of base catalysis in this system concluded that a change in the rate-limiting step was induced by a steric effect of the *o*-methyl group.[17] A change in the rate-limiting step induced by changing the steric properties of the nucleophile should be confirmed by determination of the F KIEs.

The KIE determined in DMSO at 30°C was 1.0005 ± 0.0030 for *p*-methylaniline and 1.0119 ± 0.0037 for *o*-methylaniline.[18] The significant F KIE observed for the reaction between DNFB and the sterically more hindered nucleophile *o*-methylaniline show that an expulsion of the nucleofuge is at least partially rate limiting. The virtually unity value of the F KIE for the reaction of *p*-methylaniline is consistent with rate-limiting addition of the nucleophile.



Scheme 3

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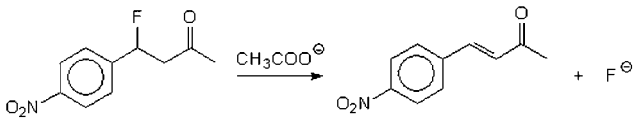


Scheme 4

Concerted or stepwise? Using F KIEs and double labelling for a base promoted elimination reaction

A fundamental mechanistic problem is whether several bonding changes take place in a concerted fashion in one elementary step or stepwise through two or more transition states.

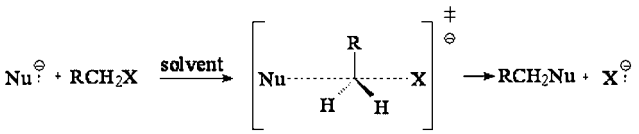
The elimination of hydrogen fluoride from the fluoroketone shown in Scheme 4 is base promoted and as demonstrated by Schultz and coworkers also antibody catalysed.[19]

The observation of a significant primary deuterium KIE rules out the stepwise E1 mechanism with rate-limiting carbocation formation.[13,19] The mechanism is thus either concerted (E2) or stepwise (E1cB). A significant but rather small F KIE of 1.0047 ± 0.0012, which is consistent with the E2 or E1cB mechanisms, was observed using acetate base (75% methanol (aq); 38°C)[13]. However, by determining the F KIE for a substrate where deuterium has been substituted for leaving protium in the 3-position, it was possible to show that the mechanism was stepwise, see Scheme 5. The deuterium substitution selectively slows down the reversal to reactant (k_{-1}) thus making fluoride detachment less rate limiting. The observed value of 1.0009 ± 0.0010 for the F KIE for the deuterated substrate therefore provides very strong evidence in favour of the stepwise mechanism.[14] For a concerted proton abstraction and elimination of fluoride, the F KIE would not be expected to be affected by deuterium substitution.

Probing transition state structure for nucleophilic aliphatic substitution reactions using $^{11}C/^{14}C$ carbon KIEs

Proof of concept

The first $^{11}C/^{14}C$ KIE reported was the primary carbon isotope effect for the bimolecular nucleophilic aliphatic reaction (S_N2) of *N,N*-dimethyl-*p*-toluidine with methyl iodide (Scheme 6).[11,20]



Scheme 6

At 30°C the $^{11}C/^{14}C$ KIE was found to be 1.202 ± 0.008.[11] In another study, hydroxide ion was used as nucleophile. In 50% dioxane/water at 25°C, the $^{11}C/^{14}C$ KIE was determined to be 1.192 ± 0.001.[21] As exemplified by these two S_N2 reactions of methyl iodide, where different nucleophiles have been used, the primary carbon KIE is large and can be determined with reasonable accuracy, which demonstrates that the method undoubtedly can be used as a tool for obtaining mechanistic information.

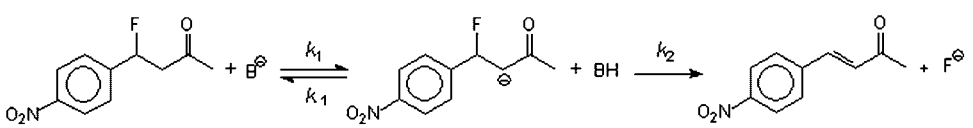
Probing TS structure: labelled α-carbon

In Table 1, the α-carbon $^{11}C/^{14}C$ KIEs determined for some S_N2 reactions with methyl- and ethyl-substrates and various nitrogen and oxygen nucleophiles are collected. These studies addressed various aspects such as the relative carbon KIEs for different isotope ratios, the effect of solvent polarity, the effect of nucleophile steric demand or evaluation of different methods commonly used for quantum chemical calculation of transition structures and the corresponding KIEs.

The observed primary $^{11}C/^{14}C$ KIEs are large for all cases studied, close to maximal as estimated on the basis of loss of zero-point energy in going from initial to transition state. As for the case of deuterium KIEs on hydron transfer, maximal primary carbon KIEs are expected for symmetric transition states where donor and acceptor are bound with equal strength to the isotopic atom in transfer.[22] However, a recent theoretical investigation of α-carbon KIEs for a large number of nucleophiles reacting with methyl chloride indicates that near maximal KIEs are found for a wide range of transition structures.[23]

Probing TS structure: labelled nucleophile

Isotope effects arising from labelling of the incoming group (nucleophile) of a substitution reaction are interesting since they provide knowledge concerning



Scheme 5

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Table 1 The α-carbon kinetic isotope effects for some S_N2 reactions

Substrate	Nucleophile	Solvent	Temperature (°C)	k^{11}/k^{14}
Methyl iodide	Hydroxide ion	Dioxane/water 50%	25	1.192 ± 0.001[21]
Methyl iodide	*N*,*N*-dimethyl-*p*-toluidine	Methanol	30	1.202 ± 0.008[11]
Methyl iodide	Quinuclidine	1,2-DME	15	1.220 ± 0.005[24]
Methyl iodide	Triethylamine	1,2-DME	15	1.221 ± 0.006[24]
Methyl iodide	2,6-Dimethyl-pyridine	Acetonitrile	30	1.220 ± 0.009[24]
Methyl iodide	2,4-Dimethyl-pyridine	Acetonitrile	30	1.189 ± 0.012[24]
Ethyl chloride	Cyanide ion	DMSO	30	1.208 ± 0.019[25]
Ethyl chloride	Cyanide ion	THF	30	1.212 ± 0.021[26]

Table 2 The nucleophile carbon kinetic isotope effects for the S_N2 reactions between labelled cyanide ion and a series of *p*-substituted benzyl chlorides in aq. DMSO and THF, respectively

p-Substituent	k^{11}/k^{14} (20% aq. DMSO; 30°C)[24]	k^{11}/k^{14} (THF; 20°C)[28]
CH_3	1.0104 ± 0.001	0.99951 ± 0.0013
H	1.0105 ± 0.002	1.00467 ± 0.0009
Cl	1.0070 ± 0.001	1.00158 ± 0.0025

Table 3 The nucleophile carbon kinetic isotope effects for the S_N2 reactions between a series of *m*-chlorobenzyl *p*-substituted benzenesulfonates and labelled cyanide ion in 0.5% aqueous acetonitrile at 0°C[29]

p-Substituent	k^{11}/k^{14}
CH_3	1.0119 ± 0.0010
H	1.0111 ± 0.0020
Cl	1.0096 ± 0.0005

Table 4 The nucleophile carbon kinetic isotope effects for the S_N2 reactions between a series of ethyl substrates and labelled cyanide ion in anhydrous DMSO at 20°C[30]

Leaving group	k^{11}/k^{14}
I	1.0066 ± 0.0008
Br	1.0028 ± 0.0015
OTs	1.0015 ± 0.0011

the amount of bond forming in the transition state. Nucleophile KIEs have been reported for oxygen and nitrogen. However, such KIEs are very small. Therefore, this is an ideal case to utilize the fact that the carbon KIE is maximized with regard to isotopic mass ratio.

The bonding to the labelled carbon atom of the nucleophile will be greater in the TS than in the reactants because the nucleophile–α-carbon bond is forming in the S_N2 TS. As a result the primary incoming group KIE will decrease and eventually become inverse with increasing bond formation.

The $^{11}C/^{14}C$ KIE found in the benzyl chloride–cyanide ion S_N2 reaction were found to be large enough (1.0105 ± 0.002, see Table 2)[27] to suggest that these isotope effects could be used to learn how system variation affects the amount of bond formation to the nucleophile in the transition state. The nucleophile $^{11}C/^{14}C$ KIEs for a number of S_N2 reaction systems where substrate, leaving group or solvent has been varied are collected in Tables 2–4. For instance, the nucleophile KIE decreases from 1.0105 to 1.0070 when changing the substrate from benzyl chloride to *p*-chloro-benzyl chloride in the polar solvent 20% aqueous DMSO. This change represents a somewhat, but not much, more advanced bond forming between the nucleophile carbon and the α-carbon in the S_N2 transition state for the more electron withdrawing substituent.[27] In the much less polar solvent THF, the same trend is observed but the nucleophile KIEs are somewhat smaller, suggesting more transition state bond formation in this less solvating medium.[28] Tables 3 and 4 show the nucleophile KIEs observed when the leaving group was varied in benzyl and ethyl systems, respectively. For *m*-chlorobenzyl *p*-substituted benzenesulphonates a better leaving group leads to a transition state with slightly more bond formation, see Table 3.[29] For the ethyl systems, however, the data suggests a transition state with slightly increasing bond formation when the substrate has a poorer leaving group.[30] For a thorough discussion of these data, including theoretical calculations of the KIEs, we refer to the original publications.

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REFERENCES

1. Melander L, Saunders WH Jr. *Reaction Rates of Isotopic Molecules*. Wiley: New York, 1980.
2. Kaye JA (ed.). *Isotope Effects in Gas-phase Chemistry*, ACS Symposium Series, vol. 502. American Chemical Society: Washington, DC, 1992.
3. Cook PF (ed.). *Enzyme Mechanism from Isotope Effects*. CRC Press: Boca Raton, FL, 1991.
4. (a) Greitz T, Ingvar DH, Widén L (eds). *The Metabolism of the Human Brain Studied with Positron Emission Tomography*. Raven Press: New York, 1985; (b) Phelps M, Mazziotta I, Schelbert H (eds). *Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart*. Raven Press: New York, 1986; (c) Brennan MB. C&EN, 1996; 26–33.
5. (a) Ferrieri RA. Production and application of synthetic precursors labelled with carbon-11 and fluorine-18. In *Handbook of Radiopharmaceuticals*. Welch MJ, Redvanly CS (eds). Wiley: 2003; 229–282; (b) Fowler JS, Wolf AP. *Acc Chem Res* 1997; **30**: 181–188; (c) Feliu AL. *J Chem Ed* 1990; **67**: 364–367.
6. (a) Kilbourn MR. *Fluorine-18 Labeling of Radiopharmaceuticals*, Nuclear Science Series NAS-NS-3203, National Academy Press: Washington, DC, 1990; (b) Snyder SE, Kilbourn MR. Chemistry of fluorine-18 radiopharmaceuticals. In *Handbook of Radiopharmaceuticals*, Welch MJ, Redvanly CS (eds). Wiley: 2003; 195–228.
7. Matsson O, Persson J, Axelsson BS, Långström B. *J Am Chem Soc* 1993; **115**: 5288–5289.
8. Långström B, Bergson G. *Radiochem Radioanal Lett* 1980; **43**: 47–54.
9. Antoni G, Kihlberg T, Långström B. Aspects of ^{11}C-labelled compounds. In *Handbook of Radiopharmaceuticals*, Welch MJ, Redvanly CS (eds). Wiley: New York, 2003; 141–194.
10. Eriksson J, Antoni G, Långström B. *J Lab Comp Radiopharm* 2004; **47**: 723–731.
11. Axelsson BS, Matsson O, Långström B. *J Phys Org Chem* 1991; **4**: 77–86.
12. Persson J, Axelsson S, Matsson O. *J Am Chem Soc* 1996; **118**: 20–23.
13. Ryberg P, Matsson O. *J Am Chem Soc* 2001; **123**: 2712–2718.
14. Ryberg P, Matsson O. *J Org Chem* 2002; **67**: 811–814.
15. Terrier F. *Nucleophilic Aromatic Displacement. The Influence of the Nitro Group*. VCH Publishers: Weinheim, 1991.
16. Nudelman NS, Mancini PME, Martinez RD, Vottero LR. *J Chem Soc Perkin Trans* 1987; **2**: 951–954.
17. Onyido I, Hirst J. *J Phys Org Chem* 1991; **4**: 367–371.
18. Persson J, Matsson O. *J Org Chem* 1998; **63**: 9348–9350.
19. (a) Shokat K, Uno T, Schultz PG. *J Am Chem Soc* 1994; **116**: 2261–2270; (b) Romesberg FE, Flanagan ME, Uno T, Schultz PG. *J Am Chem Soc* 1998; **120**: 5160–5167.
20. Axelsson BS, Långström B, Matsson O. *J Am Chem Soc* 1987; **109**: 7233–7235.
21. Axelsson BS, Matsson O, Långström B. *J Am Chem Soc* 1990; **112**: 6661–6668.
22. (a) Yamataka H, Ando T. *J Am Chem Soc* 1979; **101**: 266–267; (b) Yamataka H, Ando T. *Tetrahedron Lett* 1975; **16**: 1059–1062.
23. Matsson O, Dybala-Defratyka A, Rostkowski M, Paneth P, Westaway KC. *J Org Chem* 2005; **70**(10): 4022–4027.
24. Persson J, Berg U, Matsson O. *J Org Chem* 1995; **60**: 5037–5040.
25. Fang Y, Gao Y, Ryberg P, Eriksson J, Kolodziejska-Huben M, Dybala-Defraktyka A, Madhavan S, Danielsson R, Paneth P, Matsson O, Westaway KC. *Chem Eur J* 2003; **9**: 2696–2709.
26. Fang Y-R, MacMillar S, Eriksson J, Kolodziejska-Huben M, Dybala-Defratyka A, Paneth P, Matsson O, Westaway KC. *J Org Chem* 2006; **71**(13): 4742–4747.
27. Matsson O, Persson J, Axelsson BS, Långström B, Fang Y, Westaway KC. *J Am Chem Soc* 1996; **118**: 6350–6354.
28. Westaway KC, Fang Y-R, MacMillar S, Matsson O, Islam SM, Poirier RA. *J Phys Chem A* 2007, in press, DOI: 10.1021/jp073646n, WEB release 31-jul-2007.
29. Westaway KC, Fang Y, Persson J, Matsson O. *J Am Chem Soc* 1998; **120**: 3340–3344.
30. MacMillar S, Matsson O. The nucleophile carbon ^{11}C/^{14}C kinetic isotope effects for the reactions between cyanide ions and ethyl substrates in DMSO. *Technical Note*. Isotopes as mechanism spies. *Thesis*, 2007. ISBN 978-91-554-6776-8.