Elucidation of reaction mechanisms using kinetic isotope effects of short-lived radionuclides

Olle Matsson

Abstract The use of the short-lived radionuclides ^{11}C and ^{18}F for the elucidation of organic reaction mechanisms is described. Examples of the different mechanistic problems that are discussed include concerted *vs.* stepwise base catalysed elimination (E2 or E1cB) and finding the rate limiting step for nucleophilic aromatic substitution (S_NAr). The use of radionuclides to learn details about transition state structure for concerted nucleophilic aliphatic substitution (S_N2) is also described.

Key words carbon-11 • fluorine-18 • kinetic isotope effect • reaction mechanism • short-lived radionuclide

Kinetic isotope effects

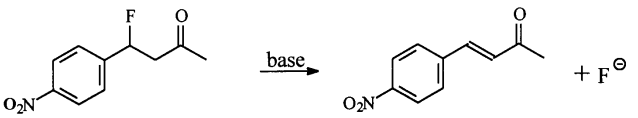
Kinetic isotope effects (KIEs) [9] are the effects on chemical reaction rates caused by isotopic substitution in the reacting system. KIEs report on bonding changes to the isotopic atom(s) when going from reactant state to transition state (TS). KIE studies are therefore of great use in solving mechanistic problems such as:

(i) concerted or stepwise reaction?
(ii) which is the rate limiting step of the reaction?
(iii) what are the structural features of the activated complex in the TS?

Short-lived radionuclides

Accelerator-produced short-lived radionuclides are used in labelling a variety of organic compounds that are used in PET-investigations in biomedical research and clinical diagnosis. Commonly used isotopes are ^{11}C (half-life 20.4 min) and ^{18}F (half-life 110 min) [2, 3].

Since KIEs for carbon are very small it is advantageous to use ^{11}C in combination with ^{14}C in order to maximize the KIE by the increased mass ratio [1]. Furthermore, KIEs for the element fluorine may be determined by using ^{18}F in combination with ^{19}F [8]. This is actually the only possible way to determine fluorine KIEs since ^{19}F is the only isotope that occurs naturally.



Scheme 1. The base catalyzed elimination reaction of HF from a fluorobutanone.

O. Matsson
Uppsala University, Institute of Chemistry,
P.O. Box 531, SE-751 21 Uppsala, Sweden,
Tel.: +46 18/ 471 3797, Fax: +46 18/ 512 524,
e-mail: olle.matsson@kemi.uu.se

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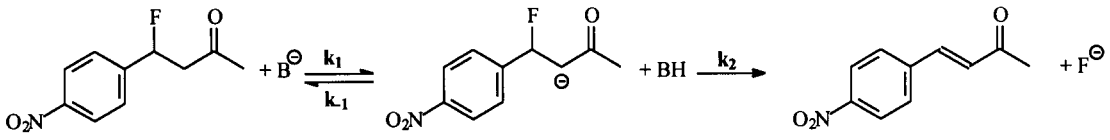


Scheme 2. The stepwise E1cB$_{ip}$ mechanism for base catalyzed elimination reaction of HF from a fluorobutanone.

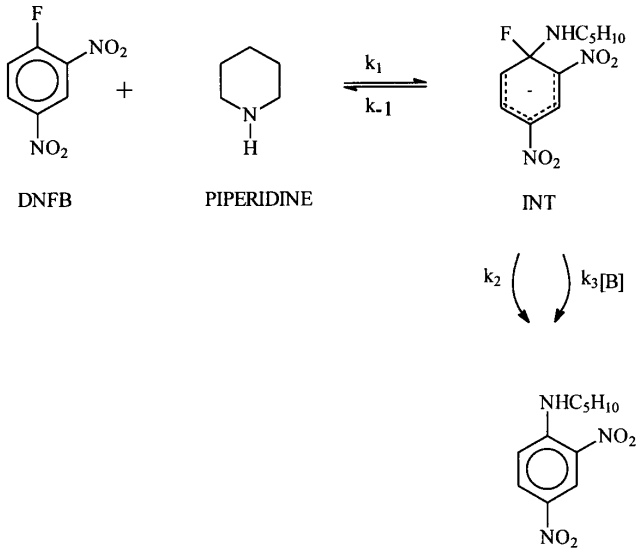
One drawback of these short-lived isotopes in KIE studies is the experimental inconvenience caused by the short half--life. As Joliot and Curie [5] noted in the publication of the first case of artificial radioactivity that: "Of course, the chemical reactions must be completed in a few minutes, before the activity has disappeared". Another crucial consideration is radiation protection since these isotopes decay by positron emission yielding high energy gamma radiation by annihilation.

Mechanistic applications [6]*

Concerted or stepwise reaction

Elimination of hydrogen fluoride from the fluoroketone shown in Scheme 1 is catalyzed by an antibody and by bases such as acetate ion [11].

The observation of a significant primary deuterium KIE rules out the stepwise E1 mechanistic alternative [11, 12]. The mechanism is thus either concerted (E2) or stepwise (E1cB). Using the leaving group KIE as a mechanistic probe helps to discriminate between these alternatives. A significant but rather small F KIE of 1.0047±0.0012, which is consistent with the E2 as well as the E1cB$_{ip}$ mechanisms, was observed [12]. However, by using a double isotopic fractionation methodology to determine 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 2. The deuterium substitution selectively slows down the reversal to reactant (k_{-1}) thus making fluoride detachment less rate limiting.



Scheme 3. Simplified mechanism for the S_NAr reaction of dinitrofluorobenzene with piperidine.

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.

Rate limiting step of a reaction

Nucleophilic aromatic substitution on activated substrates proceeds by a stepwise addition-elimination mechanism (Scheme 3). Depending on the reaction conditions (nucleophile, substrate structure, solvent) the addition of the nucleophile or the detachment of the leaving group may be rate limiting [13]. As a model system the reaction of 2,4-dinitrofluorobenzene with piperidine in tetrahydrofuran at 30°C was employed. The observation of a significant F KIE, k_{18}/k_{19} = 1.0262±0.0007, for isotopically labelled leaving group demonstrates that the elimination step is rate limiting in this case [8]. This value is close to the estimated maximum for complete cleavage of a C-F bond. By changing the solvent to acetonitrile, it was possible to induce a switch to rate limiting nucleophile addition, as demonstrated by the vanishing F KIE (k_{18}/k_{19} = 0.9982±0.0004) [10].

Structure of the transition state

Isotope effects arising from labelling the incoming group of a nucleophilic substitution reaction are interesting since they would provide information concerning the amount of bond formation of the new bond in the TS. These effects are very small due to the balance between an inverse zero point energy contribution from the bond forming process and a normal imaginary frequency ratio. This is therefore an ideal case to utilize the fact that the carbon KIEs are maximized by using $^{11}C/^{14}C$. The S_N2 reactions between a series of *p*-substituted benzyl chlorides and carbon labelled cyanide ion, were chosen as model system in this study [7]. Table 1 shows the results including the literature data for the chlorine leaving group KIEs [4].

Taking the possible range for the carbon incoming group and chlorine leaving group KIEs into consideration, these results show that the amount of bond formation in the transition state is almost constant for the three substrates (the change is 2.4% of the maximum). The amount of bond breaking, however, varies considerably (17%) from the methyl- to the chloro-substituted substrate [7].

Table 1. Incoming group carbon [7] and leaving group chlorine [4] KIEs for the S_N2 reaction of *para*-substituted benzyl chlorides with cyanide ion in 20% aqueous dimethyl sulphoxide at 30.00°C.

para-substituent	k_{11}/k_{14}	k_{35}/k_{37}
CH_3	1.0104	1.0079
H	1.0105	1.0072
Cl	1.0070	1.0060

Conclusion

The short-lived radionuclides ^{11}C and ^{18}F may be utilized to determine kinetic isotope effects with high enough accuracy for various types of mechanistic assignments.

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* The labelling syntheses for the specific examples discussed are described in the original papers cited.

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