Use of Fluorine Kinetic Isotope Effects in the Study of Steric Effects in Nucleophilic Aromatic Substitution Reactions

Jonas Persson and Olle Matsson*

Department of Organic Chemistry, Institute of Chemistry, Uppsala University
P.O. Box 531, S-751 21 Uppsala, Sweden

Received July 6, 1998

Leaving group fluorine kinetic isotope effects (F KIEs) have been determined in order to probe the influence of steric effects on the mechanism of the nucleophilic aromatic substitution (S_NAr) reaction of 2,4-dinitrofluorobenzene (DNFB) with 2- and 4-methylaniline, respectively. The $^{18}F/^{19}F$ KIE using isotopically labeled substrate was determined to be 1.0005 ± 0.0030 for 4-methylaniline and 1.0119 ± 0.0037 for 2-methylaniline in DMSO at 30 °C. The large F KIE for 2-methylaniline suggests rate-limiting leaving group departure for this sterically more hindered nucleophile, whereas the insignificant F KIE for the less sterically hindered 4-methylaniline indicates rate-limiting addition of the nucleophile.

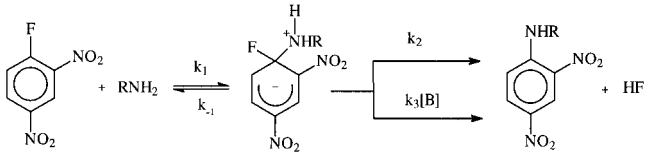
The mechanism of S_NAr reactions has been a subject of discussion over the years.[1] The influence of solvent, nucleophile, and leaving group are some of the factors that have been studied in the mechanistic investigations. The generally accepted mechanism for nucleophilic aromatic substitution reactions of substrates activated by electron-withdrawing groups is an addition-elimination mechanism first proposed by Bunnett and Zahler.[2] This mechanism involves the formation of a Meisenheimer type intermediate (Scheme 1).

The presence or absence of base catalysis, exerted by the nucleophile itself or by an externally added base, has played an important role in deciding whether formation or decomposition of the intermediate complex is rate limiting.[1a] Most data available concerns electronic effects, whereas, the influence of steric effects on the mechanism are less well investigated.

However, Onyido and Hirst have employed 2-methylaniline and 4-methylaniline as nucleophiles in the reaction with 2,4-dinitrofluorobenzene (DNFB) in DMSO (Scheme 2). From studies of base catalysis they concluded that a change in the rate-limiting step was induced by the steric effect of the *o*-methyl group.[3] The rate of reaction was reduced by a factor of 198 when the position of the methyl substituent was changed from *para* to *ortho* in the nucleophile.[3]

Recently we introduced fluorine kinetic isotope effects (KIEs) as a new mechanistic tool utilizing the accelerator-produced short-lived radionuclide ^{18}F in combination with the naturally occurring isotope ^{19}F.[4] Furthermore, a solvent-induced shift in the rate-limiting step for the reaction of DNFB with piperidine in THF or acetonitrile has been detected by the leaving group F KIE probe.[5] We therefore thought it would be of interest to see if the reported[3] change in the rate-limiting step induced by changing the steric properties of the nucleophile (see Scheme 2) could be confirmed by determination of the F KIEs.

Scheme 1



Results

The synthesis of the DN[^{18}F]B has been reported earlier.[4,5] The previously described kinetic method for determination of $^{18}F/^{19}F$ KIEs which is based on HPLC fractionation and liquid scintillation counting was followed with some exceptions.

The average value of the KIE obtained from three kinetic experiments performed in DMSO at 30 °C was 1.0005 ± 0.0030 for 4-methylaniline and 1.0119 ± 0.0037 for 2-methylaniline. The results from the individual experiments performed are shown in Table 1.

Discussion

The significant F KIE (1.0119) observed for the reaction between DNFB and the sterically more hindered nucleophile 2-methylaniline shows that expulsion of the nucleofuge is at least partially rate-limiting. This is in accordance with the conclusion based on the observation of a small but distinct curvlinear dependence of reaction rate on base concentration observed by Onyido and Hirst for 2-methylaniline.[3] A larger value of the F KIE (1.0262) for the reaction of DNFB with piperidine in THF was reported earlier.[4] This value is close to the maximal value of 1.032 estimated for total loss of C−F stretching

* To whom correspondence should be addressed. e-mail: ollem@kemi.uu.se; Fax: +46 18 512524, phone: +46 18 471 3797.

(1) For reviews see: (a) Bernasconi, C. F. *MTP International Reviews of Science, Series 1*; pp 33−63; Butterworths: London, 1973, Vol. 3. (b) Terrier, F. *Nucleophilic Aromatic Displacement. The Influence of the Nitro Group*; VCH Publishers: Weiheim, 1991. (c) Vlasov, V. M. *J. Fluor. Chem.* **1993**, *61*, 193−216.
(2) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 275.
(3) Onyido, I.; Hirst, J. *J. Phys. Org. Chem.* **1991**, *4*, 367−371.
(4) Matsson, O.; Persson, J.; Axelsson, B. S.; Långström, B. *J. Am. Chem. Soc.* **1993**, *115*, 5288−5289.
(5) Persson, J.; Axelsson, S.; Matsson, O. *J. Am. Chem. Soc.* **1996**, *118*, 20−23.

10.1021/jo981301i CCC: $15.00
Published on Web 11/13/1998

Scheme 2

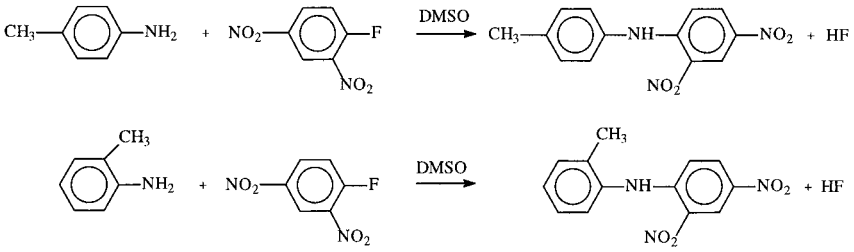


Table 1. Leaving Group F KIEs for the Reaction of DNFB (4×10^{-3} M) with 2-Methylaniline and 4-Methylaniline, Respectively, in DMSO at 30 °C. The Concentration of Aniline was ca. 5×10^{-3} M

KIE ± std dev for 4-methylaniline	KIE ± std dev for 2-methylaniline
1.0021 ± 0.0041(4)[a]	1.0105 ± 0.0053(4)[a]
0.9983 ± 0.0061(5)[a]	1.0110 ± 0.0059(5)[a]
1.0011 ± 0.0056(3)[a]	1.0141 ± 0.0078(5)[a]

[a] The number of kinetic points in each experiment.

vibrational zero point energy in the TS.[4] The smaller value for the 2-methylaniline in DMSO as compared to piperidine in THF is understandable in terms of the steady-state rate expression (eq 1) for the mechanism in

$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]} \quad (1)$$

Scheme 1. For a fully rate-limiting decomposition of the intermediate under conditions where a linear dependence of reaction rate on base concentration is observed ($k_{-1} \gg k_2 + k_3[B]$; observed for piperidine in THF at moderate base concentration[6]) the observed KIE $(k^{18}/k^{19})_{obs}$ is identical to the primary KIE for the expulsion step times the equilibrium isotope effect for formation of the intermediate. For 2-methylaniline, however, which exhibits a curvlinear dependence of rate on base concentration, no simplification of the rate expression is possible ($k_{-1} \cong k_2 + k_3[B]$), and the observed rate constant is given by eq 1. The concentration of base used in this investigation is low (ca. 5×10^{-3} M) and corresponds to the nearly linear part of the k_A vs [B] plot (see Figure 1 in ref 3). Thus decomposition of the intermediate is expected to be rate limiting. Assuming a negligible secondary isotope effect on k_1, and a normal (>1) KIE on the decomposition of the intermediate ($k_2 + k_3[B]$), the complex kinetic situation implies that the observed F KIE will be attenuated as compared to the actual KIE on the decomposition step. Therefore, a smaller observed F KIE is expected for 2-methylaniline than for piperidine. The magnitude of the primary F KIE for the decomposition of the intermediate will, of course, also be affected by the position of the TS along the reaction coordinate; an earlier TS yielding a smaller KIE.

The F KIE for the reaction of 4-methylaniline is virtually nil and is thus consistent with rate-limiting addition of the nucleophile to the substrate ($k_{-1} \ll k_2 + k_3[B]$; $k_A = k_1$). In this case the observed F KIE is equal to the KIE for the addition step, which is a secondary one and therefore expected to be very small for such a heavy element as fluorine. Again, the earlier conclusion based on the absence of any detectable base catalysis is confirmed by the observed leaving group F KIE.

What is the cause of this change to partially rate-limiting leaving group expulsion for the sterically more hindered 2-methylaniline? Steric effects may in principle be reflected in all elementary reaction rate constants in Scheme 1. Bernasconi and de Rossi[7] have discussed the importance of steric effects in determining the different behavior of primary and secondary amines as nucleophiles in S_NAr reactions. For the present reaction system, some suggestions were given by Onyido and Hirst.[3] Steric compression in the intermediate may, for bulky nucleophiles, be relieved by reversion to reactants. Such a release of steric strain enhances k_{-1}[8] which tends to make the addition step less rate limiting (eq 1). The TS for formation of the intermediate is the same as for its reversal to reactants and, according to the Hammond postulate, it is structurally close to the intermediate. Therefore a reduction of the rate constant for the addition of the nucleophile to the aromatic substrate, k_1, is expected for formation of a more sterically compressed intermediate. Steric factors may in principle also affect the rate for decomposition of the intermediate to products, although it is difficult to estimate the relative effect of the *ortho* substituent on the free energy of the intermediate and the TS for its expulsion of the fluoride. Thus it seems that the main effect of moving the methyl substituent from the *para* to the *ortho* position is an increased rate constant for reversal of the intermediate to starting materials. The significant F KIE observed for 2-methylaniline as compared to 4-methylaniline clearly demonstrates a change to rate-limiting nucleofuge detachment for the sterically more hindered nucleophile.

Experimental Section

The HPLC analyses were performed on a Beckman HPLC with a β^+-flow detector in series with the UV-detector of the instrument. The HPLC was equipped with an injector/fraction collector (Gilson). The HPLC analyses were performed on a column, 200 × 4.6 mm, packed with Nucleosil RP C-18, 5 μm. The mobile phase was water and acetonitrile 47:53 (v:v), isocratic flow 2.00 mL/min. The wavelength used was 254 nm using 430 nm as a reference.

The radioactive HPLC fractions (usually 4 mL) were collected in scintillation bottles containing 15 mL of scintillation liquid (Zinsser Quickzint 1). The radioactive counting was performed using a liquid scintillation counter Beckman LL 6000L. The counting time was usually 1 min.

DMSO (Aldrich Sure-Seal) was used as bought without further purification. The anilines were purified by repeated distillation. The distilled 4-methylaniline was recrystallized from absolute ethanol. The purity (>98%) was determined

(6) Nudelman, N.; Mancini, P. M. E.; Martinez, R. D.; Vottero, L. R. *J. Chem. Soc., Perkin Trans. 2* **1987**, 951−954.

(7) Bernasconi, C. F.; de Rossi, R. H. *J. Org. Chem.* **1976**, *41*, 44−49.

(8) Bunnett, J. F.; Garst, R. H. *J. Am. Chem. Soc.* **1965**, *87*, 3875−3878.

using ^{1}H NMR (Varian Unity 400) and GC (Varian 3400 gas chromatograph). A solution of the desired aniline, 6×10^{-3} M, was prepared and thermostated. When the synthesis of DN[^{18}F]B was complete, 0.200 mL of the DNFB solution, containing the DN[^{18}F]B, was transferred via a syringe to the reaction vial containing 1 mL of the aniline solution. The reaction clock was started, and the solution was distributed to 3−6 reaction vials using a thermostated syringe. The vials were capped and placed in the thermostat. The amount of the reaction solution distributed to the different vials was determined by weight. The quenching of a reaction point was performed by addition of acid to the reaction vial followed by immediate freezing in liquid nitrogen. After quenching, each sample was injected five times on the HPLC and the DNFB fraction was collected in scintillation bottles containing 14 mL of scintillation liquid. The calculation of the KIE for each reaction point was performed as described earlier[4,5] using the HPLC UV-detector and liquid scintillation data.

Acknowledgment. We thank Professor Bengt Långström and the staff at Uppsala University PET-center for providing the radioactive fluorine and for putting the excellent facilities at our disposal. We thank Dr. Svante Axelsson for assistance and Dr. Anita Hussénius for valuable comments on the manuscript. Olle Matsson is indebted to Professor François Terrier, Université de Versailles, for his hospitality when this manuscript was written. The project is supported by the Swedish Natural Science Research Council.

JO981301I