The Mechanism of Base-Promoted HF Elimination from 4-Fluoro-4-(4′-nitrophenyl)butan-2-one: A Multiple Isotope Effect Study Including the Leaving Group $^{18}F/^{19}F$ KIE

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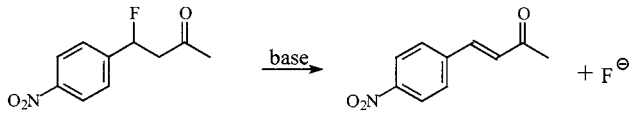
Abstract: Leaving-group fluorine as well as the primary and secondary deuterium kinetic isotope effects (KIEs) have been determined for the base-promoted elimination of hydrogen fluoride from 4-fluoro-4-(4′-nitrophenyl)-butan-2-one in aqueous solution. The elimination was studied for formate, acetate, and imidazole as the catalyzing base. The fluorine KIEs were determined using the accelerator-produced short-lived radionuclide ^{18}F in combination with natural ^{19}F. The ^{19}F substrate was labeled with ^{14}C in a remote position to enable radioactivity measurement of both isotopic substrates. The elimination reaction exhibits large primary deuterium KIEs: 3.2, 3.7, and 7.5 for formate, acetate, and imidazole, respectively, thus excluding the E1 mechanism. The corresponding C_4-secondary deuterium KIEs are 1.038, 1.050 and 1.014 and the leaving group fluorine KIEs are 1.0037, 1.0047 and 1.0013, respectively. The size of the fluorine KIEs corresponds to 5−15% of the estimated maximum of 1.03 for complete C−F bond breakage. No H/D exchange is observed during the reaction. The size and trends of the KIEs for the different bases are consistent with an E1cB-like E2 or an $E1cB_{ip}$ mechanism.

Introduction

Previously Schultz et al. have shown that the catalytic antibody 43D4-3D12 promotes elimination from 4-fluoro-4-(4′-nitrophenyl)butan-2-one[1] and have reported significant primary deuterium KIEs (PD KIEs) for both the antibody- and acetate-promoted reactions.[1b] These results rule out an E1 mechanism in which the rate-limiting detachment of the leaving group precedes a fast proton-transfer step, but are consistent with a rate-limiting bond breakage of the proton being transferred in either a concerted E2 or a stepwise E1cB mechanism (Scheme 1).

Leaving-group kinetic isotope effects (LG KIEs) can be used to determine whether the bond breakage of the leaving group is rate-limiting and may also be used to distinguish between stepwise and concerted elimination mechanisms.[2] Fluorine has commonly been employed as a leaving group in mechanistic studies of elimination and substitution reactions.[3] However, since nature provides 100% of ^{19}F, experimental F KIEs had not been available until a few years ago when Matsson et al. reported the first fluorine KIEs[4] which were determined for studies of nucleophilic aromatic substitution reactions, where steric effects[5] or change in solvent[6] were demonstrated to cause a switch in the rate-limiting step. The F KIEs were determined by using a combination of the accelerator-produced short-lived tracer nuclide ^{18}F with the naturally abundant ^{19}F. Theoretical F KIEs on model E2 and E1cB elimination reactions have recently been reported by Saunders, Jr.[7] Therefore, it was of interest to use our recently developed method for the determination of leaving-group $^{18}F/^{19}F$ KIEs for an elimination reaction. The base-promoted HF elimination from 4-fluoro-4-(4′-nitrophenyl)butan-2-one appeared to be a suitable candidate for such a study. When combined with the PD KIEs, the LG KIEs for a series of bases with different basicity could provide enough information to distinguish between the mechanistic alternatives. In addition, the secondary α-deuterium KIEs (C_4-SKIEs) for the same reactions have also been determined, since they are expected to exhibit a similar trend as the LG F KIEs.

Scheme 1



Results

Synthesis. The ^{18}F-labeled 4-fluoro-4-(4′-nitrophenyl)butan-2-one was synthesized according to Scheme 2.

Prior to each kinetic experiment compound **3** was radiofluorinated via nucleophilic substitution to give compound **4** which was then deprotected to give the ^{18}F substrate **5**.

The ^{19}F substrate with a remote ^{14}C label was synthesized from [^{14}C]methyliodide according to Scheme 3. The [^{14}C]-methyliodide was converted to [^{14}C]methyllithium by treatment with *n*-butyllithium in hexane.[8] The [^{14}C]methyllithium was treated with lithium(2-thienyl)cyanocuprate to give [^{14}C]meth-

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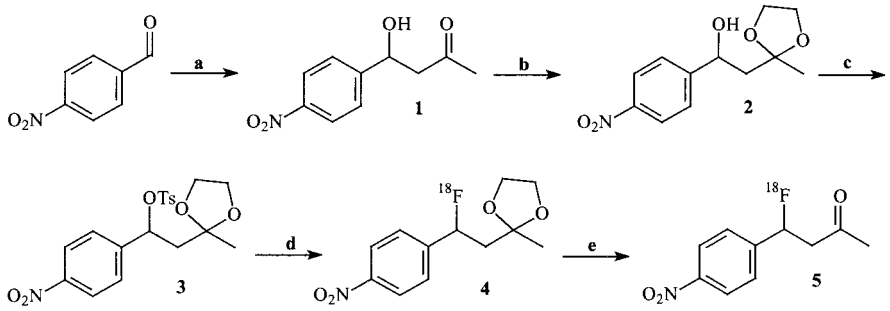
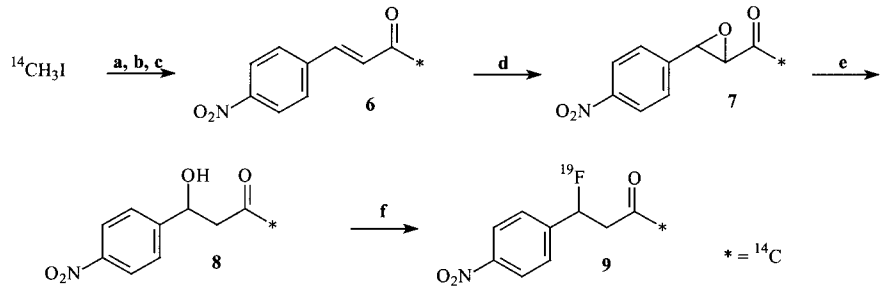
Scheme 2[a]



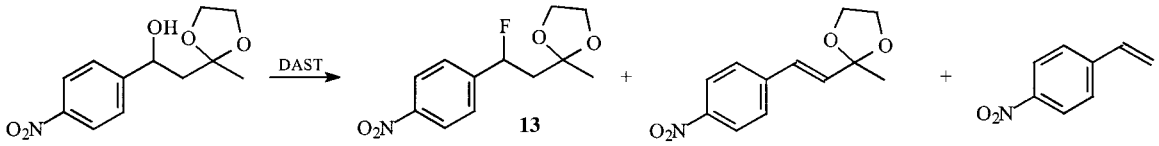
[a] a) acetone, NaOH(aq); b) ethyleneglycol, PPTs, benzene (Dean−Stark); c) *p*-TsCl, pyridine; d) Kryptofix(2.2.2)$K^{+18}F^-$, MeCN; e) *p*-TsOH, acetone/H_2O.

Scheme 3[a]

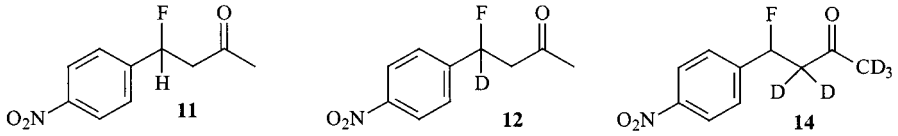


[a] a) *n*-BuLi(hexane); b) (2-Th)CuCNLi(Et_2O); c) 4-nitrocinnamoyl chloride (THF); d) H_2O_2, NaOH, MeOH; e) $(PhSe)_2$, NAC, NaOH, MeOH; f) DAST, CH_2Cl_2.

Scheme 4



Scheme 5



yldilithio(2-thienyl)cyanocuprate[9] which upon reaction with 4-nitrocinnamoyl chloride gave the α, *β*- unsaturated ketone **6**.

The deuterated substrate **12** was synthesized from 4-nitro-(α-^{2}H)benzaldehyde **10** via the same route as that for compounds **11** and **14**, described below (see Schemes 4 and 5). The 4-nitro-(α-^{2}H)benzaldehyde was obtained by reduction of 4-nitrobenzoyl chloride with lithium tri-*tert*-butoxyaluminodeuteride.[10]

The 4-fluoro-4-(4′-nitrophenyl)-butan-2-one **11** and 4-fluoro-4-(4′-nitrophenyl)−(1,1,1,3,3-$^2H_5$)butan-2-one **14** were synthesized as described by Schultz et al.[1b] Compound **13** which was needed as a reference for HPLC was obtained by treatment of the hydroxyacetal **2** with DAST, according to Scheme 4. An interesting observation is that 4-nitrostyrene was formed as the major product.

Kinetic Isotope Effects. The kinetic isotope effects observed in the base-promoted HF elimination experiments are shown in Table 1. A *t*-test on the F KIEs and S D KIEs shows that both acetate and formate differ from imidazole at the 95% level of confidence. The values for acetate and formate are, however, not significantly different according to the *t*-test.

Table 1. Rate Constants, Primary Deuterium KIEs, C_4-secondary Deuterium KIEs, and Leaving-Group Fluorine KIEs for Formate-, Acetate-, and Imidazole-Promoted Dehydrofluorination of the Fluorobutanone in 75% Aqueous Methanol[a]

pK_a	base	k $min^{-1}M^{-1}$	primary k^H/k^D	secondary k^H/k^D	leaving group k^{18}/k^{19}
3.7	formate	0.0073	3.2 ± 0.1	1.038 ± 0.013	1.0037 ± 0.0020
4.7	acetate	0.028	3.7 ± 0.1	1.050 ± 0.014	1.0047 ± 0.0012
6.95	imidazol	0.55	7.45 ± 0.1	1.014 ± 0.017	1.0013 ± 0.0012

[a] The KIES are average values from several separate kinetic experiments as described under Experimental Section. The experimental uncertainty was calculated as the standard deviation of the mean.

All experiments were run at 38 °C under pseudo-first-order conditions using a 75% aqueous methanol kinetic buffer. The sodium formate and sodium acetate concentrations were 1 M. The pH was adjusted with HCl to 5.2 and 6.0, respectively. The imidazole solution was 120 mM in imidazole and 0.94 M in NaCl; the pH was adjusted to 7.0 by addition of HCl. In all cases the substrate concentration was 5 mM or less.

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The possibility of H/D-exchange was investigated for the acetate-promoted elimination reaction. No isotopic exchange was observed. In all cases the (*E*)-alkene was the only product formed in the elimination reaction.

Kinetic Methods. The kinetic method for F KIE determination is a one-pot technique based on HPLC separation of reactants and products in a series of samples representing different extents of reaction followed by liquid scintillation counting of the collected radioactive fractions.

The method used for F KIE determination was similar to the methods for determination of KIEs using short-lived ^{11}C in combination with ^{14}C and short-lived ^{18}F in combination with natural ^{19}F which were developed earlier in our laboratory.[4,6,11] In this study the method has been modified by introducing a remote ^{14}C label in the naturally abundant ^{19}F substrate. This modification was done because of difficulties in obtaining high enough precision in preliminary experiments using the previous method with integration of the UV-detector signals. We also wanted to evaluate the potential of the remote labeling technique[12] since this might be expected to possess several advantages, that is (i) both substrates can be measured quantitatively using the same instrument and (ii) in the HPLC fractionation, it is of little importance that the reactant and product fractions are free from impurities, as long as they are radiochemically pure. Measurement of the ^{18}F and ^{14}C radioactivity were performed by liquid scintillation counting. The F KIEs were calculated from the $^{18}F/^{19}F(^{14}C)$ isotopic ratios at 0% and 80−95% reaction. For each base studied at least three separate kinetic experiments were performed and 2−4 point KIEs were determined for each experiment. Then the average value was calculated, and the uncertainty was calculated as the standard deviation of the mean.

Values for the primary and secondary deuterium KIEs were calculated from the ratio of the rate constants for the light and heavy reactants. The data used for constructing the rate curves were obtained by integration of the UV peak at 270 nm for the reactant in samples taken at different extents of reaction. The radiochromatograms showed only the reactant peak (retention time $t_R = 8.1$ min). In the UV chromatogram only the internal standard (phenol, $t_R = 3.6$ min) and the product ($t_R = 10.5$ min) were observed in addition to the reactant peak.

Discussion

The determination and interpretation of kinetic isotope effects provides one of the most powerful tools in physical organic and bioorganic chemistry.[13] The observation of a KIE demonstrates the rate-limiting change of bonding to the isotopic atom. Traditionally deuterium kinetic isotope effects have been the most frequently studied due to their importance, large magnitude and relative ease of determination. However, the development of very accurate methods based on mass spectrometry,[14] NMR,[15] polarimetry,[16] or radioactivity measurements[14b,16a] has enabled chemists to determine mechanistically significant heavy-atom KIEs with high precision. The most frequently utilized elements have been carbon, nitrogen, oxygen, sulfur, and chlorine. Recently Matsson et al. added fluorine to the list of elements for which KIEs can be determined.[4] The fluoride ion is a commonly employed leaving group in mechanistic investigations of elimination and substitution reactions.[3] Leaving-group KIEs are fairly easy to interpret, particularly for one-atom groups, and have been utilized for a long time in mechanistic investigations.

A leaving-group KIE is expected to monotonically increase with the increasing degree of bond breakage between the isotopic leaving-group atom and the α-carbon in the transition state of the rate-limiting step.[17,18] Several investigators have utilized leaving-group KIEs in mechanistic studies of elimination reactions, including KIEs of nitrogen for the bimolecular elimination of arylethylammonium ions,[19] of sulfur for elimination of 2-phenylethyldimethylsulfonium ion,[20] of chlorine for dehydrochlorination reactions,[21] and that of oxygen for the enzymatic fumarase and crotonase reactions.[22]

As suggested by Thibblin and Ahlberg[23] and demonstrated by Saunders in computational studies,[7] a secondary leaving-group fluorine KIE may appear on the deprotonation step in an E1cB elimination reaction due to negative ion hyperconjugation. Calculations by Saunders suggest that the TS of the E2 reaction of hydroxide ion with ethyl fluoride was very similar to that of the proton-transfer step of the E1cB reaction of 1,1,1-trifluoroethane.[7] Fluorine isotope effects ($^{18}F/^{19}F$) as large as 1.0058 (corresponding to 18% of the estimated maximal F KIE for complete breakage of a C−F bond[4]) were calculated for the E1cB proton-transfer TS.

The size of primary deuterium KIEs for proton-transfer processes, such as elimination reactions, are generally considered as a measure of the symmetry of the transition state for the transfer. On the basis of the transition state theory, the Melander−Westheimer postulate predicts that the maximal primary KIE occurs for the most symmetrical activated complex, that is where the proton is bound with equal strength to both the donor and acceptor.[24] This usually occurs when the donor and acceptor are of equal pK_a strength.[25] Several examples of

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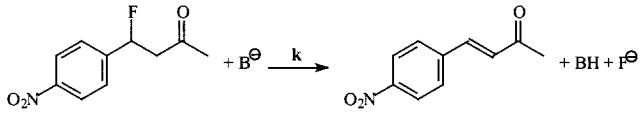
Scheme 6



the use of primary deuterium KIEs in the investigation of the mechanisms of elimination reactions have been reported.[26]

Secondary deuterium KIEs are usually used to monitor rehybridization in the TS.[27] On the basis of theoretical calculations it has been suggested that the secondary KIEs for the α-position are more reliable than that for the β-position as a measure of rehybridization in elimination reactions.[18b]

Base-promoted β-eliminations may follow either the E2 (Scheme 6) or the E1cB (Scheme 7) pathway. The actual pathway chosen will be dependent on the stability of the carbanion intermediate. It has been proposed by Dewar,[28] that since generally two-bond activations cost more energy than one-bond activation, an E1cB mechanism would be energetically more favorable than an E2. If, however, the putative carbanion is too unstable to have any significant lifetime, the reaction would then be forced to go via the E2 mechanism. Since both mechanisms may have similar kinetic characteristics, it can prove to be difficult to distinguish between either of them. Solvent H/D exchange is indicative for an E1cB mechanism where the carbanion is reprotonated by the solvent.

For the present reaction system no H/D exchange was observed when acetate was used as the base. The elimination reaction exhibits deuterium KIEs that are large enough to be safely classified as primary (3.2−7.45) and increases with base strength. Since the substrate is doubly deuterated in the 3-position, the deuterium not being transferred may introduce a secondary KIE affecting the size of the observed primary KIE. Experimentally determined secondary KIEs for the corresponding position have been reported for the dehydrobromination and dehydrotosylation of cyclohexyl derivatives.[29] These studies suggest that the size of such a KIE may be in the range of 1.15−1.25. Somewhat larger values have been obtained in theoretical calculations.[18b] Due to the relatively small size of the C_3-SKIE as compared to that of the primary KIE, the trend in the observed values (Table 1) may be assumed to reflect the variation of the primary KIE. The absolute magnitude is, however, slightly too large. The three deuteriums on the terminal methyl group are remote from the reaction center and are not expected to introduce any significant KIE.

The C_4-SKIEs and leaving-group F KIEs observed are very small and decrease with increasing pK_a-value when going from acetate or formate to imidazole. However, the differences in these KIEs between the acetate- and formate-promoted reactions are within experimental error. The combination of large PD KIEs and small LG F KIEs and SD KIEs together with the absence of any detectable H/D-exchange fits with either the E1cB-like E2 or the $E1cB_{ip}$.

The E2 Mechanistic Alternative. According to the variable TS structure model the effect of a stronger base on a symmetric E2 TS would be an unchanged degree of C−H bond breakage and a decrease in C−F bond breaking. This would be observed as an unchanged primary deuterium KIE. The effect of less bond breakage to the leaving group would result in a smaller LG F KIE. For the E1cB-like E2 mechanism the change to a stronger base would be accompanied by a decrease in C−H bond breakage and also a decrease in C−F bond breakage. This should be observed as an increase in PD KIE, provided that the conjugate acid of the catalyzing base is stronger than the donor. The size of the LG KIE would decrease just as for the case of a symmetric E2 TS. The degree of rehybridization at the α-carbon may be considered to correlate with the degree of bond breaking to the leaving group resulting in a corresponding decrease of the secondary deuterium KIE. However, on the basis of experimental as well as computational studies Bernasconi and other workers have demonstrated cases of nonperfect synchronization between proton-transfer and rehybridization.[30] If such a time-lag is allowed in the present reaction system, then a smaller than expected secondary deuterium KIE would be observed.

The observed primary deuterium, secondary deuterium ,and leaving group F KIEs conform with the trends predicted by the variable TS structure model for the E1cB-like E2-mechanism. Both the C_4-SKIEs and the leaving-group KIEs decrease significantly, that is from 1.050 to 1.014 and from 1.0047 to 1.0013, respectively, when changing from acetate to imidazole as the catalyzing base. The primary deuterium KIE at the same time changes in the direction expected for the E1cB-like TS from 3.7 to 7.45. Thus, these observations are consistent with the predictions based on the variable TS structure model for an E1cB-like E2 mechanism.

The E1cB Mechanistic Alternative. For the E1cB case the interpretation of the KIEs is more complicated due to the kinetic complexity. The relationship between the mechanistic KIEs and the size of the observed leaving-group KIEs for an E1cB reaction are given by eq 1. The same holds for the C_4-SKIEs of the k_2 step. For the observed primary deuterium KIE the situation is more complex and will be discussed separately in detail below.

$$\mathrm{KIE_{OBS}} = \frac{k_2^{\mathrm{L}}}{k_2^{\mathrm{H}}} \times \frac{k_2^{\mathrm{H}} + k_{-1}[\mathrm{BH}]}{k_2^{\mathrm{L}} + k_{-1}[\mathrm{BH}]} \qquad (1)$$

(L = isotopically lighter species, H = isotopically heavier species).

From eq 1 it is clear that the size of the observed LG KIEs are dependent on the ratio between the rate of reprotonation of

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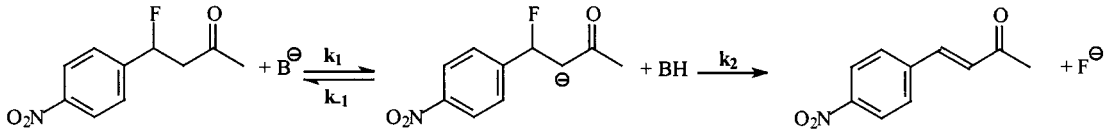
Scheme 7



the carbanion and the rate of elimination of the leaving group. Two extreme situations may be identified.

(a) When reprotonation of the carbanion is fast compared to elimination of the LG.

(b) When reprotonation of the carbanion is slow compared to elimination.

In case (a) where reprotonation is fast compared to elimination, and reprotonation occurs from the solvent, the size of the observed primary deuterium KIE will be affected by H/D-exchange, that is the deuterated reactant will rapidly be converted to the ^{1}H analogue. Consequently, a very small primary deuterium KIE which varies with the extent of reaction will be observed. The magnitude of the observed leaving group and secondary deuterium KIEs would, on the other hand, be close to the intrinsic KIEs on the elimination step (k_2) as predicted from eq 1. This type of mechanism is usually classified as a reversible E1cB (E1cB$_{rev}$).

In case (b) exchange of ^{2}H for ^{1}H with solvent is slow compared to elimination. Thus, the observed primary deuterium KIE will be close to the intrinsic value. According to eq 1 the leaving-group KIE and C_4-SKIEs are predicted to be negligible. This mechanism is denoted irreversible E1cB (E1cB$_{irr}$).

A third situation occurs when the carbanion remains intimately associated with the newly protonated base, either as an ion pair if the protonated base is positively charged or as a hydrogen-bonded pair if the protonated base is neutral. This mechanism is denoted as the ion pair E1cB (E1cB$_{ip}$). If internal return is allowed (rehydronation occurs with the previously removed Hydron), then eq 2, where [IP − H] and [IP − D] denotes the steady-state concentrations of the protic and deuterated hydrogen-bonded complexes, is valid. Assuming that there is a KIE on the reprotonation step, this would lead to a situation where the size of the primary deuterium KIE is dependent on the ratio between k_{-1}[IP − H] and k_2.

Our observation of the large primary deuterium KIEs together with the absence of H/D-exchange is consistent with either an E1cB$_{irr}$ or an E1cB$_{ip}$ mechanism but not with an E1cB$_{rev}$ mechanism.

$$\mathrm{KIE_{OBS}} = \frac{k_1^{\mathrm{H}}}{k_1^{\mathrm{D}}} \times \frac{k_2 + k_{-1}^{\mathrm{D}}[\mathrm{IP-D}]}{k_2 + k_{-1}^{\mathrm{H}}[\mathrm{IP-H}]} \qquad (2)$$

The small leaving-group and secondary deuterium KIEs may be explained by an E1cB$_{irr}$ or an E1cB$_{ip}$ mechanism. Since the intermediate from which the elimination occurs is identical for the different bases, it is reasonable to assume that the intrinsic leaving- group and secondary deuterium KIEs on the k_2 step are independent of base strength. Then, the variation in leaving-group and secondary deuterium KIEs when the catalyzing base is changed would be a consequence of different rates of reprotonation. This observation is only consistent with the E1cB$_{ip}$ mechanism, primarily because the very observation of a primary leaving-group KIE for any E1cB mechanism except for the E1cB$_{ip}$ requires reprotonation of the carbanion by solvent. This would be accompanied by H/D-exchange. Moreover, the rate of reprotonation of the carbanion in an E1cB$_{irr}$ mechanism would be independent of the base, and consequently the leaving-group and secondary deuterium KIEs should not vary with base strength.

Assuming an E1cB$_{ip}$ mechanism, it is not surprising that the smallest leaving-group and secondary deuterium KIEs are observed for the strongest base imidazole. One may guess that the stability of the hydrogen-bonded carbanion-protonated base complex increases with base strength. It would also be reasonable to assume that the rate of reprotonation is dependent on the stability of this complex, that is the more stable complex gives the slower reprotonation. Slower reprotonation would be observed as smaller leaving-group and secondary deuterium KIEs (eq 1). When changing from acetate (pK_a = 4.7) to imidazole (pK_a = 6.95) as catalyzing base, the leaving,group and secondary deuterium KIEs decrease from 1.0047 to 1.0013 and from 1.050 to 1.014, respectively. When changing from formate to acetate, the trend is reversed but is much less pronounced.

The variation in size of the primary D KIEs is more likely a result of changes both in the intrinsic KIEs and the rates of reprotonation. The effect of a stronger base on the deprotonation step should result in a more symmetrical TS. This would be observed as a larger KIE for the proton transfer, provided that the conjugate acid of the catalyzing base is stronger than that of the proton donor. The large PD KIE of 7.45 for imidazole is probably close to the intrinsic value, whereas for the acetate, which is a weaker base, a smaller intrinsic value is assumed. The observed PD KIE ($k^{\mathrm{H}}/k^{\mathrm{D}}$ = 3.7) would then be smaller than the intrinsic KIE due to internal return. The same arguments should also account for formate.

On the basis of these arguments one may conclude that an E1cB-like E2 or an E1cB$_{ip}$ mechanism are the only alternatives which are fully consistent with the observations reported herein.

Experimental Section

General. The ^{18}F-fluoride was prepared by use of the Scanditronix MC-17 cyclotron at the Uppsala University PET Centre. The ^{18}O(p,n)^{18}F reaction was performed in a high-pressure silver target containing ^{18}O-enriched water bombarded with 17 MeV protons.

HPLC was performed with a Beckman 126 gradient pump and a Beckman 166 variable wavelength or a Beckman 168 diode array UV-detector in series with a β^+ flow detector.

For analytical HPLC a Phenomenex spherisorb 5 ODS(2) 250 × 4.6 mm ID C_{18} column was used. For semipreparative HPLC a Phenomenex spherisorb 10 ODS(2) 250 × 10 mm ID C_{18} column was used. Datacollection and HPLC control were performed with the use of a Beckman System Gold chromatography software package.

Sample injection and fraction collection were performed by a Gilson 231 XL sampling injector in combination with a Gilson 401C dilutor.

Liquid scintillation counting was performed with a Beckman LS 6000 LL liquid scintillation counter in wide open mode, using Zinsser Quicksafe A as scintillation cocktail in Zinsser 20 mL poly vials.

^{1}H- and ^{13}C NMR spectra were recorded on a Varian Unity 400 MHz spectrometer at 400 and 100.6 MHz, respectively, with (^{2}H)-chloroform as internal standard.

Kinetic Procedure. The kinetic experiments were run under pseudo-first-order conditions. Analytical HPLC system was as descibed under General**.** Solvent system was methanol/50 mM ammonium formate pH 3.5, 0−9 min 55% methanol, 9−10 min 55−95% methanol, 14−15 min 95−55% methanol 1 mL/min. In this system the reactant eluted at

t_R = 8.1 min, and the product eluted at t_R = 10.5 min, and they were baseline separated for 1.4 min.

The ^{18}F substrate in 0.5 mL of 50% aqueous methanol and the ^{14}C-labeled ^{19}F substrate 35 KBq in 50 μL of acetonitrile were mixed in a 2 mL septum-covered HPLC vial, and four 10 μL aliquots were injected to the HPLC. For each injection three fractions were collected into 20 mL liquid scintillation vials containing 14 mL of liquid scintillation cocktail. Fraction 1 (t_R = 6−7 min) was collected just before the reactant fraction, fraction 2 (t_R = 7.7−8.7 min) was the reactant fraction, and fraction 3 (t_R = 9.5−11.2 min) was the product fraction. Then the base was added to the substrate mixture, and the reaction was allowed to proceed to 80−95% conversion at 38 °C. Then 700 μL out of the total 1000 μL of kinetic solution was withdrawn and passed through a 100 mg C-18 SPE column. The column was washed with 1 mL of H_2O and then eluted with 1 mL of acetonitrile.The eluate was concentrated in vacuo and redissolved in 0.4 mL 50% aqueous methanol. From this eluate three 100 μL aliquots were injected to the HPLC, and fractions were collected as above. The remaining 300 μL of the kinetic solution was allowed reach complete reaction, and then methanol 100 μL was added, and three 100 μL aliquots were injected on the HPLC. The reactant and product fractions were collected as above.

As a consequence of the ^{18}F-fluoride temporarily binding to the HPLC column a ^{18}F background radioactivity appeared, which had to be corrected for. Thus, samples from fraction 1 were collected. It was also observed that the reactant fraction contained a small, although often negligible, ^{14}C background which also had to be corrected for. These corrections were performed according to the procedure described below.

When all of the fractions had been collected, the ^{18}F background radioactivity, $^{18}F_{bg}$, and the total reactant radioactivity, $(^{18}F + {}^{14}C)_{react}$, were determined by measuring the radioactivity in all fraction 1 samples and fraction 2 samples simultaneously. Thus, by measuring the samples from each injection pairwise with a counting time of 2 min/vial, no decay correction was needed for further calculations.

To obtain a high precision value for the total reactant radioactivity, $(^{18}F + {}^{14}C)^*_{react}$, needed for KIE calculations, the fraction 2 samples were remeasured with a counting time of 20−40 min/vial.

When all ^{18}F had decayed (48 h), the ^{14}C radioactivity in the fraction 2 and fraction 3 samples were measured again to give the reactant ^{14}C radioactivity, $^{14}C_{react}$, and the product ^{14}C radioactivity, $^{14}C_{prod}$. The counting was continued until a precision of 2σ = 0.1−0.2% was obtained.

The ^{14}C radioactivity in the reactant and product fractions for the samples taken at complete reaction were also measured to give the ^{14}C background radioactivity in the reactant fraction at complete reaction, $^{14}C_{react,\ \infty}$, and the product ^{14}C radioactivity at complete reaction, $^{14}C_{prod,\ \infty}$.

The data were also corrected for instrumental background before any further calculations were made.

The relative ^{18}F background,$^{18}F_{rel,\ bg}$, was obtained from the $^{18}F_{bg}$ and the $(^{18}F + {}^{14}C)_{react}$ according to eq 3. The reactant ^{18}F radioactivity, $^{18}F_{react}$, was obtained according to eq 4. The $^{18}F_{react}$ was then corrected for decay according to eq 5, where t is the elapsed time from the start of the radioactivity measurements in minutes and $k = \ln 2/t_{1/2}$. This gave the true reactant ^{18}F radioactivity, $^{18}F_{react,\ true}$, used for KIE calculation. The $^{14}C_{react}$ was corrected for ^{14}C background and instrumental background, eq 6, to give the true reactant ^{14}C radioactivity, $^{14}C_{react,\ true}$, used for the KIE calculations.

$$^{18}F_{rel,bg} = {}^{18}F_{bg}/[(^{18}F + {}^{14}C)_{react} - {}^{14}C_{react}] \quad (3)$$

$$^{18}F_{react} = [(^{18}F + {}^{14}C)^*_{react} - {}^{14}C_{react}] \times (1 - {}^{18}F_{rel,bg}) \quad (4)$$

$$^{18}F_{react,true} = {}^{18}F_{react} \times e^{kt} \quad (5)$$

$$^{14}C_{react,true} = {}^{14}C_{react} \times [1 - {}^{14}C_{react,\infty}/(^{14}C_{react,\infty} + {}^{14}C_{prod,\infty})] \quad (6)$$

The point F KIE for each individual sample was calculated according to eq 7[31] where 1 − f was calculated according to eq 8, R_0 is the initial ratio between the ^{18}F and $^{19}F(^{14}C)$ reactants and R is the corresponding ratio at (1 − f).

$$\mathrm{KIE} = \frac{\ln(1 - f)}{\ln((1 - f)R/R_0)} \quad (7)$$

$$1 - f = \frac{^{14}C_{react}}{^{14}C_{react} + {}^{14}C_{prod}} \quad (8)$$

H/D Exchange Experiment. In the H/D exchange experiment 4-fluoro-4-(4′-nitrophenyl)-butan-2-one (300 mg) was dissolved in 0.5 M sodium acetate in D_2O/MeOD/THF 1:1:2 (40 mL). The mixture was stirred at rt for 110 min (corresponding to 60% reaction), then saturated aqueous NaCl (50 mL) was added, and the mixture was extracted with Et_2O. The Et_2O phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in chloroform, and unreacted 4-fluoro-4-(4′-nitrophenyl)-butan-2-one was analyzed by ^2H NMR spectroscopy. No ^2H incorporation could be detected.

Synthesis. 4-(4′-Nitrophenyl)-[1-^{14}C]but-3-ene-2-one (6). The ^{14}C-labeled methyl iodide 37 MBq (2.04 Gbq/mmol) was vacuum transferred to dry hexane 1 mL at −100 °C. To 0.5 mL of this solution (18.5 MBq) was added normal methyl iodide (20 μL, 0.4 mmol). *n*-BuLi 1.6 M in hexane (0.44 mL, 0.7 mmol) was added to a 3 mL oven dried tube covered with a rubber septum and flushed with N_2. The methyl iodide solution was added to the BuLi at rt, and the tube was agitated for 10 min while a white precipitate of MeLi(s) was formed. The tube was centrifuged for 5 min at 3000 rpm, giving a pellet of MeLi at the bottom of the tube. The supernatant containing excess BuLi and butyl iodide was removed via a syringe, and *n*-BuLi (0.16 M, 1.3 mL in diethyl ether) was added, giving a clear solution. This solution was added to (2-Th)CuCNLi (0.25 M, 2.5 mL, 0.65 mmol)in dry THF (2.5 mL) at −78 °C. The mixture was stirred for 10 min and then added to *p*-nitrocinnamoyl chloride (158 mg, 0.75 mmol) in THF (3 mL) at −78 °C. After 20 min the reaction was quenched with methanol 1 mL and poured into saturated NaCl(aq) (20 mL). The mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were concentrated in vacuo, and the product was purified by prep. TLC using diethyl ether/hexane 1:1 as eluent. R_f = 0.26. **6 (**15 MBq, 81%) was obtained with >99% radiochemical purity according to radio TLC. The product was identified by HPLC.

3,4-Epoxy-4-(4′-nitrophenyl)-[1-^{14}C]butan-2-one (7). 6 (15 Mbq) was dissolved in methanol (6 mL). Aqueous 27% H_2O_2 (0.1 mL) and NaOH(aq) (6 M) 4 drops were added, and the mixture was stirred at rt for 10 min and then poured into saturated NaCl(aq) (15 mL). Extraction with CH_2Cl_2 (3 × 10 mL) and concentration in vacuo gave **7** 11 MBq (73%) as a yellow oil. The product was analyzed by radio TLC and HPLC, showing both high radiochemical and UV purity.

4-Hydroxy-4-(4′-nitrophenyl)-[1-^{14}C]butan-2-one (8). 7 (11 Mbq) dissolved in methanol 3 mL was added to a solution of *N*-acetylcysteine (100 mg, 0.61 mmol), $(PhSe)_2$ (3 mg, 0.0096 mmol, and NaOH(aq) (0.1 mL 6 M, 0.6 mmol) in methanol 4 mL.[32] The mixture was stirred under N_2 at rt for 13 h and then poured into saturated NaCl(aq) (20 mL); extraction with diethyl ether (3 × 10 mL) and concentration in vacuo gave **8** as yellow crystals. The product was purified by preparative TLC using diethyl ether/hexane 3:1 as eluent; R_f = 0.57. Only the middle part of the fraction containing **8** was recovered, yielding 9 MBq (82%) of pure product according to HPLC.

4-Fluoro-4-(4′-nitrophenyl)-[1-^{14}C]butan-2-one (9). 8 (2.1MBq) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C under N_2. Diethylaminosulfur trifluoride (DAST) (10 μL) was added, and the mixture was stirred at −78 °C for 20 min and then heated to rt. Water (1 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). The product was purified by semipreparative HPLC on a Phenomenex C-18 column using 50 mM ammonium formate pH 3.5/acetonitrile as eluent system (4 mL/min.). The gradient was 0−2 min 10% acetonitrile, 2−21 min 10−65% acetonitrile. A fraction between t_R 17.3−19.5 was collected. The collected fraction was poured into saturated aqueous NaCl (20 mL) and extracted with (3 × 5 mL) CH_2Cl_2. Drying over $MgSO_4$ and removal of solvent in vacuo yielded 1.53

(31) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: New York, 1980; p 95.

(32) Engman, L.; Stern, D. *J. Org. Chem.* **1994**, *59*, 5179−5183.

MBq (73%) of radiochemically pure **9**. The product was dissolved in acetonitrile (3 mL) containing 5% of methanol and stored at −15 °C.

4-Hydroxy-4-(4′-nitrophenyl)-butan-2-one ethylene acetal (2). 4-Hydroxy-4-(4′-nitrophenyl)-butan-2-one (2.15 g, 10 mmol), 1,2-ethanediol (3 g, 48 mmol), and pyridinium *p*-toluenesulfonate (0,5 g, 2 mmol) were weighed into a round-bottomed flask equipped with a Dean−Stark water separator. Benzene (75 mL) was added, and the mixture was refluxed until no more water separated (2 h). The benzene was removed in vacuo, and diethyl ether (100 mL) was added to the brownish residue. This ether solution was washed with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL) and then dried over $MgSO_4$. Removal of the ether in vacuo yielded a brown oil that crystallizes to yellow needles. The product was purified by chromatography on silica using diethyl ether/pentane/triethylamine 100:50:1 as eluent. **2** (1.53 g, 60%) was obtained. ^{1}H NMR δ 1.41 (s, 3H), 2.03 (m, 2H), 4.06 (m, 4H), 4.28 (s, 1H), 5.11 (m, 1H), 7.55−8.19 (m, 4H). ^{13}C NMR δ 151.7, 147.1, 126.5, 123.6, 109.9, 64.9, 64.4, 47.2, 24.2. Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91%; H, 5.97%; N, 5.53%. Found: C, 56.84%; H, 5.94%; N, 5.58%.

4-(4′-Nitrophenyl)-4-*p*-toluenesulfoxybutan-2-one ethylene acetal (3). **2** (800 mg, 3.2 mmol), *p*-toluenesulfonyl chloride (900 mg, 4.7 mmol), *N*,*N*-(dimethylamino)pyridine (390 mg, 3.2 mmol), and triethylamine (0.45 g, 4.4 mmol) were stirred in dichloromethane (10 mL) for 30 h. The mixture was diluted with diethyl ether (60 mL) and filtered. The etheral extract was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and then dried over $MgSO_4$. The product was purified by chromatography on silica using diethyl ether/pentane/triethylamine 80:20:2 as eluent. Yield: 400 mg (28%).

^{1}H NMR δ 1.25 (s, 3H), 2.12 (dd, 1H, J = 5.58, 15.0), 2.34 (s, 3H), 2.45 (dd, 1H, J = 7.02, 15.0), 3.85 (m, 4H), 5.78 (dd, 1H, J = 5.53, 7.01), 7.11−7.6 (m, 4H), 7.32−8.06 (m, 4H). ^{13}C NMR δ 148.0, 146.4, 145.0, 134.4, 129.7, 128.0, 127.9, 123.7, 107.9, 79.4, 64.7, 45.8, 24.7, 21.7. Anal. Calcd for $C_{19}H_{21}NO_7S$: C, 56.01%; H, 5.19%; N, 3.44%. Found: C, 55.88%; H, 5.20%; N, 3.42%.

[4-^{18}F]Fluoro-4-(4′-Nitrophenyl)-butan-2-one (5). The aqueous $[^{18}F]F^-$ solution 1−2 GBq (0.5−1 mL) was added to K_2CO_3 (1.5−2 mg) and Kryptofix(2.2.2) 3−4 mg in a 3 mL septum covered vial. The water was removed by repeated azeotropic evaporation with acetonitrile under a flow of nitrogen at 100 °C. When the vial was completely dry, the nitrogen flow was stopped, and **3** (3 mg) dissolved in acetonitrile (0.2 mL) was added. The resulting violet solution was kept at 80−90 °C for 30 min and then cooled to 70 °C. Then *p*-TsOH in H_2O/acetone 1:5 (20 mg/ml, 0.5 mL) was added, and the mixture was kept at 70 °C for 10 min. The mixture was cooled to rt, H_2O (0.5 mL) was added, and the solution was injected to a semipreparative Phenomenex C-18 HPLC column. Eluent system: acetonitrile, 50 Mm ammonium formate pH 3.5, 4 mL/min. Gradient: 0−2 min 10% acetonitrile, 2−21 min 10−65% acetonitrile. The fraction between t_R 17.6−19.2 was collected. The collected fraction was diluted with H_2O (10 mL) and passed through a Supelco Supelclean ENVI-18 SPE column. The column was washed with H_2O (3 mL) and then eluted with acetonitrile (2 mL). The acetonitrile was removed in vacuo, and the residue was dissolved in H_2O (0.5 mL). Typically 150−250 MBq of radiochemically pure **5** was obtained, corresponding to 30−50% decay corrected radiochemical yield.

4-Nitro-(α-^{2}H)benzaldehyde (10). $LiAlD_4$ (0.6 g) was suspended in diglyme (7 mL), and *tert*-butyl alcohol (5 mL) was added. The mixture was stirred for 30 min and then slowly cannulated (20 min) to 4-nitrobenzoyl chloride (2 g) in diglyme (10 mL) at −78 °C. The mixture was stirred for an additional 30 min, and then H_2O (2 mL) was added. The mixture was filtered through a plug of silica using Et_2O/pentane 1:1 as eluent. The eluate was cooled to 0 °C, and water was added. The product was filtered off and dried in a vacuum desiccator and used without further purification.

4-Hydroxy-4-(4′-nitrophenyl)−(4-^{2}H)butan-2-one. 4-Nitro-(α-^{2}H)-benzaldehyde (1 g, 6.5 mmol) was dissolved in acetone 20 mL at 0 °C and 1% aqueous NaOH (0.5 mL) was added. After 10 min the mixture was neutralized with aqueous HCl and concentrated in vacuo. The brown residue was dissolved in ether (30 mL) and washed with H_2O (30 mL). Drying over $MgSO_4$, concentration in vacuo and flash chromatography on silica gave 0.8 g (57%) of product. ^{1}H NMR δ 2.11 (s, 3H), 2.76 (m, 2H,), 4.02 (s, 1H), 7.45−8.05 (m, 4H). ^{13}C NMR δ 208.3, 150.4, 146.5, 126.2, 123.3, 68.0 (t, J(C^{2}H) = 30.7), 65.5, 51.3. Isotopic purity > 98%.

4-Fluoro-4-(4′-nitrophenyl)-(4-^{2}H)butan-2-one (12). 4-(4′-Nitrophenyl)-4-hydroxy-(4-^{2}H)butan-2-one (0.2 g, 0.93 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C. Then DAST (0.15 mL, 1 mmol) was added, and the mixture was stirred for 20 min, poured into H_2O (30 mL), and extracted with CH_2Cl_2 (20 mL). After this solution was dried over $MgSO_4$, a small amount of silica was added to the solution. The CH_2Cl_2 was evaporated off, and the silica was applied to a column prepacked with silica. The product was eluted with Et_2O/pentane 1:1. Yield: 0.18 g (90%). ^{1}H NMR δ 2.21 (s, 3H), 2.87 (dd, 1H, J = 16.8, 29.2), 3.22 (dd, 1H, J = 16.8, 16.8), 7.5−8.25 (m, 4H) ^{13}C NMR δ 203.7 (s), 147.8 (s), 146.2 (d, J(CF) = 20), 126.3 (d, J(CF) = 6.9), 124.1 (d, J(CF) = 30.4), 88.7 (dt, J(CF) = 170, J(C^{2}H) = 30.9), 50.3 (d, J(CF) = 25), 30.9(s)

4-Fluoro-4-(4′-nitrophenyl)-butan-2-one ethylene Acetal (13). **2** (202 mg, 0.8 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C. DAST (154 μL, 0.8 mmol) was added; the mixture was stirred for 15 min and then poured into H_2O (30 mL) and extracted with CH_2Cl_2 (30 mL). The CH_2Cl_2 phase was dried over $MgSO_4$ and then concentrated in vacuo. Purification by chromatography on silica using Et_2O/pentane/Et_3N 50:50:1 gave 86 mg (43%) of pure product. ^{1}H NMR δ 1.43 (s, 3H), 2.08 (ddd, 1H, J = 2.84, 15.22, 34.73), 2.38 (ddd, 1H, J = 8.77, 15.14, 18.75), 3.89−4.03 (m, 4H), 5.78 (ddd, 1H, J = 2.90, 8.71, 48.12), 7.49−8.25 (m, 4H). ^{13}C NMR δ 148.0 (d, J(CF) = 20), 126.3 (d, J(CF) = 7.6), 124.0 (s), 108.4 (s), 90.2 (d J(CF) = 172.2), 64.9 (d, J(CF) = 4.6), 46.7 (d, J(CF) = 22.8), 22.9 (d, J(CF) = 3.1). Anal. Calcd for $C_{12}H_{14}NO_4F$: C, 56.47%; H, 5.53%; N, 5.49%. Found: C, 56.64%; H, 5.53%; N, 5.55%.

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