The Mechanism of Base-Promoted HF Elimination from 4-Fluoro-4-(4-nitrophenyl)butan-2-one Is E1cB. Evidence from Double Isotopic Fractionation Experiments

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Leaving-group fluorine and secondary deuterium multiple kinetic isotope effects (KIEs) have been determined for the base-promoted HF elimination from the 4-fluoro-4-(4′-nitrophenyl)-(1,1,1,3,3-$^2H_5$)butan-2-one. The fluorine KIE was determined by using the accelerator-produced short-lived radionuclide ^{18}F in combination with the naturally abundant ^{19}F. The ^{19}F substrate was labeled with ^{14}C in a remote position to enable radioactivity measurements of both substrates. The size of the determined fluorine KIE is 1.0009 ± 0.0010 when acetate is used as base. The secondary deuterium KIEs are 1.009 ± 0.017, 1.000 ± 0.018, and 1.010 ± 0.023 for formate, acetate, and imidazole, respectively. The magnitudes of these KIEs are sigificantly smaller compared to the corresponding KIEs that we recently reported for the protic substrate. This new data clearly demonstrates that the elimination proceeds via an E1cB mechanism.

Introduction

Schultz et al. have shown that the catalytic antibody 43D4−3D12 promotes elimination from 4-fluoro-4-(4′-nitrophenyl)butan-2-one[1] (Scheme 1) and have reported significant primary deuterium KIEs (PD KIEs) for both the antibody and acetate-promoted reactions.[1b]

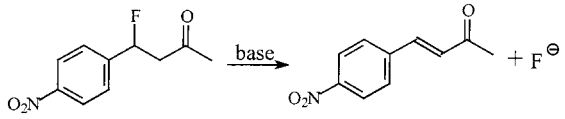
These results rule out an E1 mechanism in which the rate-limiting detachment of the leaving group precedes a fast proton-transfer step but are consistent with a rate-limiting bond breakage of the proton being transferred in either a concerted E2 or a stepwise E1cB mechanism.

We have recently demonstrated that the base-promoted HF elimination from 4-fluoro-4-(4′-nitrophenyl)butan-2-one in aqueous solution proceeds via either an ion-pair E1cB (or an E1cB mechanism where the carbanion and the protonated base remain as a hydrogen-bonded pair;[2] Scheme 2) or an E1cB-like E2 mechanism (Scheme 3).[3]

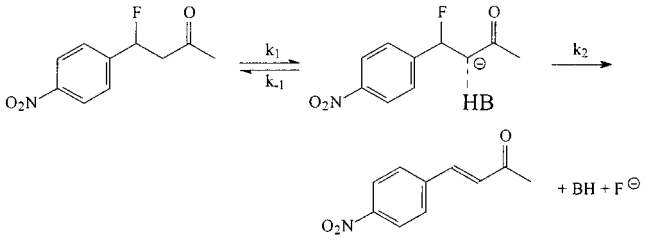
This conclusion was based on the primary and secondary deuterium KIEs and the leaving group F KIEs, which were determined for a set of bases with varying pK_a strengths.

The elimination reaction exhibited large primary deuterium KIEs of 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 were 1.038, 1.050, and 1.014, and the leaving group fluorine KIEs were 1.0037, 1.0047, and 1.0013, respectively. The observation that there was no H/D exchange with the solvent during the reaction was also consistent with this conclusion.

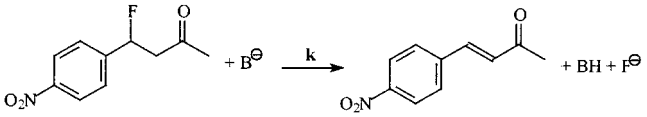
Scheme 1



Scheme 2



Scheme 3



To distinguish between the two remaining mechanistic alternatives, we decided to determine the secondary deuterium (k_H^D/k_D^D) and leaving group fluorine (k_{18}^D/k_{19}^D) multiple kinetic isotope effects for the substrates deuterated in the primary (C_3) position. Compounds **5** and **6** were thus used to determine the secondary D KIE and compounds **4** and **3** were used for the F KIE (see Chart 1).

The double-isotopic fractionation method[4] consists of using deuterium substitution to selectively slow down the

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(1) (a) Uno, T.; Schultz, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 6573−6574. (b) Shokat, K. M.; Uno, T.; Schultz, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 2261−2270. (c) Romesberg, F. E.; Flanagan, M. E.; Uno, T.; Schultz, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 5160−5167.

(2) The ion-pair E1cB terminology will be used in the discussion to cover both these possibilities. As one reviewer has pointed out, ion pairing is not likely in purely aqueous solution. However, since the reaction is studied in 25% aqueous methanol the possibility of ion pairing cannot be entirely neglected.

(3) Ryberg, P.; Matsson, O. *J. Am. Chem. Soc.* **2001**, *123*, 2712−2718.

(4) Cleland, W. W. In *Enzyme Mechanism from Isotope Effects*; Cook, P. F., Ed.; CRC Press: Boca Raton, 1991; Chapter 9.

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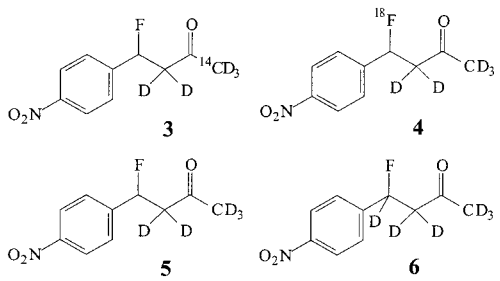
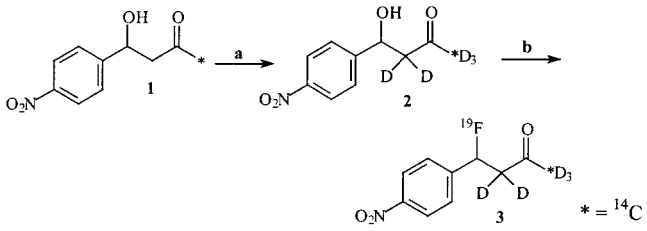
Chart 1



Scheme 4[a]



[a] Key: (a) CD_3OD, NaOD; (b) DAST, CH_2Cl_2 −78 °C.

rate of one step in a reaction and observing the changes in a second kinetic isotope effect. When the two isotope effects are on the same step, the second isotope effect is either enhanced because this step has become slower and thus more rate limiting or alternatively shows no change if the step was originally rate limiting. When deuteration and the second isotope effect affect different steps in the mechanism, deuteration slows down a step other than that which is isotope sensitive and thus decreases the observed size of the second isotope effect.

The F KIE[5] was determined according to our recently reported method where a ^{14}C label was introduced in the naturally abundant ^{19}F substrate to enable radioactivity measurement of both substrates.[3]

Results

Synthesis. The deuterated ^{19}F substrate with a ^{14}C label was obtained (Scheme 4) via the hydroxy ketone **1**, which was synthesized according to a previously reported procedure.[3] The deuterated hydroxy ketone **2** was obtained via an exchange reaction between hydroxy ketone **1** and alkaline deuterated methanol. Under the conditions described in the Experimental Section, the exchange reaction was completed within 2 min. If the mixture was left longer, the hydroxy ketone underwent base-promoted elimination. The deuterated hydroxy ketone was then fluorinated with DAST to give substrate **3**. The deuterated ^{18}F substrate **4** was synthesized according to an previously reported procedure[3] with the exception that all reagents and solvents were deuterated.

Substrates **5** and **6** were synthesized from isotopically normal[1b] and deuterated[3] 4-nitrobenzaldehyde and acetone-d_6, respectively.

Kinetic Methods. The kinetic method for F KIE determination is a competitive 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 F KIE was determined according to our recently reported remote label procedure where a ^{14}C label was introduced in the naturally abundant ^{19}F substrate.[3] The F KIEs were calculated from the reactant $^{18}F/^{19}F[^{14}C]$ isotopic ratios at 0% and 80−95% reaction. 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 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 the HPLC chromatograms for a series of 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.

Since both the KIEs and any possible change in the size of these KIEs are very small, the outcome of this experiment was highly dependent on the deuterium content in the substrates. Therefore, it was important that the deuterium content in the two isotopic substrates was identical.

By our experience, it is difficult to synthesize the deuterium-labeled substrates with more than 98% isotopic purity, and the results tend to vary from time to time. Since a difference in deuterium content of as little as 0.5% would introduce an error equal to the size of the KIE, the substrates could not be used as initially obtained.

To carry out the study, we had to develop a method to increase and level out the deuterium content in the substrates. The method chosen was based on kinetic isotopic fractionation. If the incompletely deuterated substrates were allowed to react with a base that introduces a large *primary* deuterium KIE, the deuterium content in the unreacted substrate would rapidly approach 100% according to eq 1, where the protium content in percent is expressed as a function of the fractional conversion of the deuterated substrate. X is the percentage of protium at the fractional conversion F_D for the deuterated substrate and X_0 is the protium content in the initial mixture.

$$X = X_0(1 - F_D)^{KIE-1} \quad (1)$$

If the initial content of deuterated substrate is much larger than the content of protic substrate then the approximation that $F_D = F_D + F_H$ is valid and F_D can easily be determined.

In the present case, imidazole (PD KIE = 7.4) was used as a base. Under these conditions, a substrate initially containing 95% deuterium would after 50% conversion contain 99.94% deuterium and a substrate initially containing 98% deuterium would after 50% conversion contain 99.98% deuterium. The deviation of 0.04% in isotopic purity would be negligible.

This methodology was applied in the present study. The necessity of the procedure was demonstrated by comparing F KIEs from experiments where deuterated

(5) (a) Matsson, O.; Persson, J.; Axelsson, S.; Långström, B. *J. Am. Chem. Soc.* **1993**, *115*, 5288−5289. (b) Persson, J.; Axelsson, S.; Matsson, O. *J. Am. Chem. Soc.* **1996**, *118*, 20−23. (c) Persson, J.; Matsson, O. *J. Org. Chem.* **1998**, *63*, 9348−9350.

Table 1. C_4-Secondary Deuterium (k_H^D/k_D^D and k_H^H/k_D^H) and Leaving Group Fluorine (k_{18}^D/k_{19}^D and k_{18}^H/k_{19}^H) KIEs for Formate-, Acetate-, and Imidazole-Promoted Dehydrofluorination of the Deuterated and Undeuterated Fluorobutanone, Respectively[a]

base	k_H^D/k_D^D	k_H^H/k_D^H	k_{18}^D/k_{19}^D	k_{18}^H/k_{19}^H [d]
formate	1.009 ± 0.017[b]	1.038 ± 0.013		1.0037 ± 0.0020
acetate	1.000 ± 0.018[b]	1.050 ± 0.014	1.0009 ± 0.0010[c]	1.0047 ± 0.0012
imidazole	1.010 ± 0.023[b]	1.014 ± 0.017		1.0013 ± 0.0012

[a] The superscript D or H refers to the isotope in the 3-position of the substrate. [b] The error limit is given as the standard deviation of the mean from 5 separate determination of the KIE. [c] The error limit is given as the standard deviation of the mean from 10 point-KIEs in three separate experiments. [d] Values from ref 3.

substrates were used directly with F KIEs from experiments where the substrates were reacted to 50% with imidazole prior to KIE determination. When untreated substrates were used, irreproducible and erroneous results were obtained.

Kinetic Isotope Effects. The kinetic isotope effects observed in the base-promoted HF elimination reaction are shown in Table 1.

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

Discussion

The double-isotopic fractionation method[6] has been utilized by several workers to distinguish between stepwise and concerted mechanisms, primarily in enzyme-catalyzed reaction systems. In the present study, we have used the method to distinguish between the concerted E1cB-like E2 and the stepwise ion-pair E1cB mechanisms. These two alternatives can be difficult to distinguish from each other since their kinetic characteristics are similar. However, the study of primary deuterium and leaving group KIEs for a set of bases with varying pK_a strengths may in some cases provide enough information. We have previously studied the dehydrofluorination according to this strategy, but the results were insufficient for a complete mechanistic assignment.[3]

The applicability of the double isotopic fractionation methodology to the present case is illustrated by eqs 2 and 3, where the relationships between the mechanistic KIEs and the size of the observed secondary deuterium and leaving group KIEs for an E2 (eq 2, Scheme 3) and an E1cB (eq 3, Scheme 2) mechanism are given (* denotes the heavier isotopic species).

$$\mathrm{KIE}_{obs} = k/k^* \tag{2}$$

$$\mathrm{KIE}_{obs} = \frac{k_2}{k_2^*} \times \frac{k_2^* + k_{-1}}{k_2 + k_{-1}} \tag{3}$$

For the E2 case, the observed rate constant for the elimination equals the mechanistic rate constant, and consequently as demonstrated by eq 2, the size of the observed KIE equals the size of the mechanistic KIE. This implies that for an E2 mechanism deuteration does not affect the size of the observed secondary deuterium or leaving group KIE.

However, for the E1cB case where the observed rate constant for the elimination contain contributions from the rate constants from all the mechanistic steps, the size of the observed KIE for an isotope effect on the k_2 step is governed by the ratio between k_{-1} and k_2, i.e., the rate of elimination versus the rate of reprotonation.

In the case where the rate of reprotonation is fast compared to the rate of elimination, i.e., $k_{-1} \gg k_2$, the size of the observed KIE will be identical to the mechanistic KIE, i.e. ,$\mathrm{KIE}_{obs} = k_2/k_2^*$. If instead, however, the rate of reprotonation is slow compared to the rate of elimination, i.e., $k_{-1} \ll k_2$, the size of the observed KIE will approach unity, i.e., $\mathrm{KIE}_{obs} = 1$. By assuming that deuteration introduces a normal KIE on the k_{-1} step, which is then slowed, it is clear from eq 3 that the observed KIE for an isotope effect on the k_2 step will be smaller for the deuterated substrate in comparison to the protic substrate.

When acetate was used as the base, the leaving group F KIE for the deuterated substrate decreased to 1.0009 (Table 1). This was roughly 20% of the size of our earlier reported leaving group F KIE of 1.0047 for the protic substrate.[3] Due to practical reasons, it was only possible to perform this experiment with acetate as the promoting base.

The secondary deuterium KIEs for the deuterated substrate are 1.009, 1.000, and 1.010 for formate, acetate, and imidazole, respectively. These values are also, except for imidazole, significantly smaller than the corresponding values for the protic substrate, which are 1.038, 1.050, and 1.014, respectively.[3] A *t*-test confirms that both the LG F KIE and the secondary D KIEs are significantly smaller for the deuterated than for the protic substrates.

These results provide very strong evidence that the mechanism for the base-promoted HF-elimination from 4-fluoro-4-(4-nitrophenyl)butan-2-one is $E1cB_{ip}$ in aqueous solution.

Any other E1cB mechanism except for the ion pair/hydrogen bonded pair E1cB can be excluded since they proceed via solvent H/D-exchange.

Experimental Section

General Methods. [^{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 126 variable-wavelength UV detector 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 i.d. C_{18} column was used. For semipreparative

(6) Hermes, J. D.; Roeske, C. A.; O'Leary, M. H.; Cleland, W. W. *Biochemistry* **1982**, *21*, 5106−5114.

HPLC, a Phenomenex spherisorb 10 ODS(2) 250 × 10 mm i.d. C_{18} column was used. Data collection 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 chloroform-d_1 as internal standard.

Kinetic Procedure. The kinetic experiments were run under pseudo-first-order conditions. HPLC system 4.6 × 250 mm Phenomenex C-18 column, solvent system methanol/50mM ammoniumformate 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 method for determining the F KIEs was identical to the one used for determination of the F KIEs on protic substrate.[3]

Leveling of the Deuterium Content in the ^{18}F and ^{19}F Substrates. The deuterated ^{18}F and ^{19}F[^{14}C] substrates were dissolved in 0.4 mL of CD_3OD, and 0.4 mL 1 M imidazole in (D_2O) pH 6.9 was added. The mixture was kept at 38 °C until 50% conversion (30−40 min). Then the mixture was injected on the HPLC (10 × 250 mm C-18 4 mL/min, 55% methanol/45% 50mM ammonium formate pH 3.5), and the fraction containing unreacted starting material was collected. The collected fraction (4 mL) was diluted with 6 mL of H_2O and passed through a 500 mg C-18 SPE column. The column was washed with 2 mL of H_2O and then eluted with 2 mL of acetonitrile. The eluate was concentrated in vacuo and redissolved in 0.5 mL 50% aquous methanol.

4-Hydroxy-4-(4′-nitrophenyl)-[1-^{14}C]-(1,1,1,3,3-$^2H_5$)butan-2-one (2). Hydroxy ketone **1** (9 MBq) was dissolved in CD_3OD (10 mL), and 4% NaOD (D_2O) (5 drops) was added. The mixture was stirred for 5 min, and then 2% DCl (D_2O) (10 drops) was added. The mixture was poured into D_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extracts were dried over $MgSO_4$ and concentrated in vacuo. A 6 MBq sample of **2** was obtained. Analysis by ^{1}H NMR showed that the deuterium content was at least 95%.

4-Fluoro-4-(4′-nitrophenyl)-[1-^{14}C]-(1,1,1,3,3-$^2H_5$)butan-2-one (3). The deuterated hydroxy ketone **2** (6 MBq) was dissolved in dry CH_2Cl_2 (3 mL) and cooled to −78 °C under N_2. DAST (20 μL) was added, and the mixture was stirred for 20 min and then heated to rt. The mixture was poured into D_2O (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 extracts were dried over $MgSO_4$ and concentrated in vacuo. The product was identified by HPLC. A 4 MBq sample of **3** was obtained.

4-Hydroxy-4-(4′-nitrophenyl)-(1,1,1,3,3,4-$^2H_6$)butan-2-one. 4-Nitro-(α-^{2}H)benzaldehyde (1 g, 6.6 mmol) was dissolved in acetone-d_6 (20 mL) at 0 °C, and NaOD 1% in D_2O (0.5 mL, 0.1 mmol) 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 Et_2O/pentane 2:1 gave 0.8 g (3.7 mmol, 56%) of the title compound. The deuterium content in the 1-, 3-, and 4-positions was analyzed by ^{1}H NMR and found to be >98%.

4-Fluoro-4-(4′-nitrophenyl)-(1,1,1,3,3,4-$^2H_6$)butan-2-one. 4-Hydroxy-4-(4′-nitrophenyl)-(1,1,1,3,3,4-$^2H_6$)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, 1.13 mmol) was added, and the mixture was stirred for 20 min and then poured into H_2O (30 mL) and extracted with CH_2Cl_2 (20 mL). After the mixture 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, and 150 mg 75% of product was obtained.

4-Hydroxy-4-(4′-nitrophenyl)-(1,1,1,3,3-$^2H_5$)butan-2-one Ethylene Acetal (6). 1,2-Ethanediol (5.4 g, 87 mmol), D_2O (2 mL), and pyridinium *p*-toluenesulfonate (0.5 g) 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. Another 2 mL of D_2O was added, and the procedure was repeated. In total, seven 2 mL portions of D_2O were added. Then 4-hydroxy-4-(4′-nitrophenyl)-(1,1,1,3,3-$^2H_5$)butan-2-one (2.4 g, 11.2 mmol) 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 ethereal solution was washed with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL) and dried over $MgSO_4$. Removal of the ether in vacuo yielded a brown oil. The product was purified by chromatography on silica using diethyl ether/pentane/triethylamine 100:50:1 as eluent. A 1.53 g (53%) portion of **6** was obtained. ^{1}H NMR: 3.95−4.12 (m, 4H), 4.27 (s, 1H), 5.09 (s, 1H), 7.5−8.2 (m, 4H). ^{13}C: 64.3, 64.8, 69.5, 123.6, 126.4, 147.5, 151.8.

4-Toluenesulfoxy-4-(4′-nitrophenyl)-(1,1,1,3,3-$^2H_5$)butan-2-one Ethylene Acetal (7). 4-Hydroxy-4-(4′-nitrophenyl)-(1,1,1,3,3-$^2H_5$)butan-2-one ethyl acetal (800 mg, 3.1 mmol), *p*-toluenesulfonyl chloride (900 mg, 4.7 mmol), *N*,*N*-(dimethylamino)pyridine (390 mg, 3.2 mmol), and triethylamine (0.55 mL, 3.2 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 dried over $MgSO_4$. The product was purified by chromatography on silica using diethyl ether/pentane/triethylamine 80:20:2 as eluent. Yield: 0.4 g, 32%. ^{1}H NMR δ: 2.35 (s, 3H), 3.8−3.92 (m, 4H), 5.75 (s, 1H), 7.1−7.5 (m, 4H), 7.3−8.06 (m, 4H). ^{13}C: 21.5, 64.4, 79.1, 123.5, 127.6, 127.7, 129.4, 133.9, 144.8, 146.1, 147.5.

4-[^{18}F]Fluoro-4-(4′-nitrophenyl)-(1,1,1,3,3-$^2H_5$)butan-2-one. 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 compound **7** (3 mg) dissolved in deuterated 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*-TsOD in D_2O/acetone-d_6 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, 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 55% aqueous methanol (0.5 mL). Typically, 150−250 MBq of radiochemically pure **8** was obtained corresponding to 30−50% decay corrected radiochemical yield.

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