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CARBON-14 KINETIC ISOTOPE EFFECTS AND MECHANISM IN THE SOLVOLYSIS OF 1,1,1-TRIFLUORO-2-PHENYL-2-PROPYL-3-^{14}C p-TOLUENESULFONATE[1]

Zili Guo and Arthur Fry*

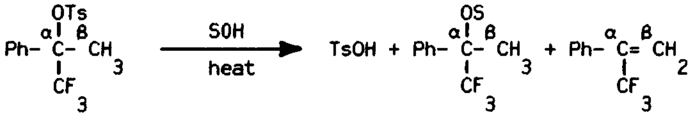
Department of Chemistry and Biochemistry, University of Arkansas,
Fayetteville, AR 72701, U.S.A.

Abstract: In the solvolysis of 1,1,1-trifouoro-2-phenyl-2-propyl-3-^{14}C p-toluenesulfonate there is only a small $^{\beta}$C isotope effect, $k/^{\beta}k$ = 1.008 ± 0.002. The result is as expected for a branching $S_N1/E1$ reaction (mostly S_N1). This is the first example of such a measurement.

For many years our research group has been investigating the mechanisms of substitution[2] and elimination[3,4] reactions using the successive labeling isotope effect technique[5]. In particular, we have sought a convenient "calibration example" for the E1 mechanism. Qualitatively, isotope effects are to be expected when and only when[2-5] there are bonding changes at the labeled position in the rate-determining (sometimes subsequent product-determing) step of the reaction. For elimination reactions of alpha and beta carbon-14 labeled substrates, then, the expectation is for isotope effects for alpha- but not for beta-labeled compounds for the irreversible E1 mechanism; for both alpha- and beta-labeled compounds for the E2 mechanism; and for beta- but not alpha-labeled compounds for the irreversible E1cb mechanism. Extension of the argument to reversible versions of the E1 and E1cb mechanisms is straightforward.

Until the present work, all the elimination reaction systems studied showed sizeable carbon-14 isotope effects at both the alpha and beta carbons[3,4,6-8] leading to the conclusion that all these systems react by the E2 mechanism, with varying amounts of E1 and (mostly) E1cb character in the activated complex. Our research on base-promoted dehydrohalogenation in the beta-carbon-14 labeled substituted 1-phenylethyl system[8] is the only reported heavy atom isotope effect study in a system even approaching the E1 side of the mechanistic spectrum. In that case the values of $^{12}k/^{14}k$ were 1.038, 1.059, and 1.070 for the p-methyl-, unsubstituted, and p-chloro-1-phenylethyl-2-^{14}C chlorides. Clearly there are bonding changes at the beta carbon in those reactions, so those compounds cannot be reacting by the E1 mechanism.

We have been led to a carbon-14 isotope effect study of beta- (and maybe later alpha-) labeled 1,1,1-trifluoro-2-phenyl-2-propyl tosylate by the reports[9,10] that this and related compounds solvolyze in a variety of solvents by the $S_N1/E1$ mechanism, and that substantial amounts, up to 35 %, of elimination product are obtained:



$$\mathrm{Ph{-}\overset{OTs}{\underset{CF_3}{\overset{\alpha}{C}}}{-}\overset{\beta}{CH_3}} \xrightarrow[\text{heat}]{\text{SOH}} \mathrm{TsOH + Ph{-}\overset{OS}{\underset{CF_3}{\overset{\alpha}{C}}}{-}\overset{\beta}{CH_3} + Ph{-}\underset{CF_3}{\overset{\alpha}{C}}{=}\overset{\beta}{CH_2}}$$

This is a tertiary benzylic system. But this and closely related compounds are strongly deactivated[9-11] by the CF_3 group, $k_H/k_{CF_3} = 2 \times 10^5$, so they react at convenient rates. The rate variations with solvent and the salt effects follow those of 2-adamantyl tosylate; rho (using sigma$^+$) = - 6.7 to - 11.9 (largest negative rho values known); k_{CH_3}/k_{CD_3} = 1.3 for more ionizing solvents; 1.6 for less ionizing solvents--normal for 2° β-deuterium isotope effects for an $S_N1/E1$ reaction, but far too low for E2 1° β-deuterium isotope effects. The conclusion that these compounds react by the $S_N1/E1$ mechanism seems well founded.[9,10]

For a pure S_N1 mechanism, we would expect the beta carbon isotope effect to be unity, or at least very small (probably inverse), as would be expected for a secondary carbon isotope effect. On the other hand, if there is a substantial component of an E2 or E1-like E2 mechanism, or if there is substantial E1 branching from an intermediate carbenium ion, there should be a substantial beta carbon isotope effect. **We now report that there is only a very small $^{\beta}$C isotope effect, $k/^{\beta}k$ = 1.008 ± 0.002, in this solvolysis reaction.** In spite of many literature statements about "expectations" and "assumptions" that there should be no $^{\beta}$C isotope effects in solvolysis (S_N1) reactions, **there are no prior reports of such an experimental study.**

1,1,1-Trifluoro-2-phenyl-2-propyl-3-^{14}C p-toluenesulfonate was synthesized from the alcohol by treatment with butyl lithium followed by tosyl chloride.[10] The labeled alcohol was prepared by a Grignard reaction using trifluoroacetophenone and commercially available carbon-14 labeled methyl iodide. The trifluoroacetophenone was prepared by the reaction between phenylmagnesium bromide and trifluoroacetic acid.[12] The solvolysis reaction was carried out in glacial acetic acid in a constant temperature bath set at 75 °C. In preliminary experiments the first order rate constant was found to be 3.33×10^{-5} sec^{-1}, compared to the literature value[10] of 3.83×10^{-5} sec^{-1}. These kinetic data were used to set the reaction times for the isotope effect experiments. The recovered tosylate and product ester were separated and purified by repeated recrystallation and column chromatography; the ester was converted to the tosylate for radioassay. Despite considerable effort we were unable to recover useful amounts of the alkene product. It's presence in amounts of 10-20 % was demonstrated by spectral analyses. We were disappointed that we did not find the reported[9] 35 % of alkene product. The exact fractions of reaction, f, were established by titration.

Radioactivities of the reactant tosylate, **R_o**, the recovered tosylate reactant, **R_r**, and the product ester (as the tosylate), **R_p**, were measured by liquid scintillation counting[8], and the kinetic isotope effects, $k/^{\beta}k$, were calculated by the Tong and Yankwich equations[13]. Since the observed isotope effects are so very small, the results are given in full detail in **Table 1** below in order to present the case most convincingly.

Table 1. Fractions of Reaction, Molar Activities,[a] and Carbon-14 Kinetic Isotope Effects, for the Solvolysis of 1,1,1-Trifluoro-2-phenyl-2-propyl-3-^{14}C p-Toluenesulfonate in Glacial Acetic Acid at 75 °C.

Fraction of Reaction	R_r	R_p	$k/^{\beta}k$ obtained from:[b]			
f	mCi/mole	mCi/mole	R_o, R_r, R_p	R_o, R_r, f	R_o, R_p, f	R_r, R_p, f
0.209	0.3770	0.3731	1.0097	1.0056	1.0102	1.0093
0.412	0.3783	0.3734	1.0105	1.0091	1.0109	1.0102
0.686	0.3788	0.3748	1.0072	1.0054	1.0086	1.0064
0.809	0.3812	0.3759	1.0056	1.0075	1.0039	1.0068

[a] R_o = 0.3765; [b] Overall mean: $k/^{\beta}k$ = 1.008 ± 0.0024 (standard deviation).

There are no significant trends outside the experimental error in the data in the table as the fraction of reaction or as the equation used for calculation changes. This gives us high confidence in the chemical and radiochemical purities of the reactants and products and demonstrates that our reaction and workup procedures are adequate.[8] Furthermore, the activities of the reactants and the products at 100 % reaction agreed closely as they should.

The overall $^{\beta}C$ carbon-14 isotope effect for formation of the substitution product in this solvolysis reaction is seen to be 1.008 ± 0.002. Could our small isotope effect be a secondary carbon isotope effect in the $S_N1/E1$ mechanism? We think not; hyperconjugation should strengthen the $^{\alpha}C-^{\beta}C$ bond, which should lead to an inverse isotope effect. The isotope effect expected for reaction by a substitution mechanism uncomplicated by elimination is 1.000. Reaction by the E2 mechanism should give an isotope effect of about 1.05. If, as proposed,[9,10] this reaction goes through a carbenium ion intermediate, with $S_N1/E1$ substitution/elimination branching in the subsequent product-determining step, reaction by the substitution branch should proceed without an isotope effect, while the elimination branch should proceed (should probably proceed--no one has made such a measurement) with a normal isotope effect of about 1.05 (as in the E2 mechanism). This elimination reaction isotope effect would result in an increase in the radioactivity of the carbenium ion, which would be reflected in an increase in R_p for the substitution product, showing a "false isotope effect" for the substitution process. Exactly the same argument applies to a competition between substitution and E2 elimination. Simple sample calculations show that the apparent isotope effect for the substitution product would be 1.010 ± 0.003 (compare to the experimental value of 1.008 ± 0.002), on the assumption of the S_N1/E1 mechanism and an 85 % substitution/15 % elimination product branching, with no isotope effect in the substitution branch and with an isotope effect of 1.05 in the elimination branch. For instance, for f = 0.412 and R_r = 0.3783 (Table 1), the value of R_p corresponding to the isotope effect for 100 % elimination (using 1.05) is 0.3553. Fifteen % of the difference between this number and R_o, substracted from R_o, gives 0.3732 for the calculated substitution product R_p, which gives a calculated isotope effect of 1.0106 ± 0.0011 (compare to the second data line in Table 1). These calculations, and these results, by themselves, do not distinguish between a substitution/E2 elimination competition and the second (product-determining) substitution/elimination competition step for the S_N1/E1 mechanism for a reversibly formed carbenium ion, but, overall, the S_N1/E1 mechanism implication is strong. These results do, however, argue against pure rate-determining carbenium ion formation, since then R_r should always equal R_o, and that is clearly not the case (Table 1)!

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