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# Tunneling in Elimination Reactions. Structural Effects on the Secondary $\beta$-Tritium Isotope Effect

**Sue Lin and William H. Saunders, Jr.***

*Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627*

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**Abstract:** Secondary tritium isotope effects have been determined for the elimination reactions of (2-(*p*-(trifluoromethyl)-phenyl)ethyl-*2-t*)- and *-2-d-2-t*)trimethylammonium bromide (**1**) ($EtO^-/EtOH$), (1-phenylethyl-*2-t*)- and *-2-d₂-2-t*)-trimethylammonium bromide (**2**) (*t*-$BuO^-$/*t*-BuOH), and (1-phenyl-2-(*p*-chlorophenyl)ethyl-*2-t*)- and *-2-d-2-t*)-trimethylammonium bromide (**3**) ($EtO^-/EtOH$). $k_H{}^H/k_H{}^T$ values at 50 °C were in the range 1.22–1.27 (errors ±0.01 or less), with **1** giving the greatest effect. These values are all large enough to suggest significant contributions from tunneling. Studies of the temperature dependences give $A_{aH}/A_{aT}$ values well below unity (0.60–0.90), and the secondary isotope effect is depressed when deuterium rather than protium is the transferred atom, results which also implicate tunneling. It appears that a carbanion-like E2 transition state is especially conducive to tunneling.

## Introduction

We reported some time ago that secondary $\beta$-tritium isotope effects in elimination reactions were larger than could be accounted for by zero-point energy effects alone.[1] Model calculations of isotope effects suggested that tunneling was responsible for this phenomenon.[2] These calculations predicted that the temperature dependences of these secondary isotope effects should be abnormally steep in the presence of tunneling, just as is the case for primary effects, and that the secondary tritium isotope effect should be diminished when the transferred atom is deuterium instead of protium. These predictions were subsequently confirmed experimentally for eliminations from a number of 2-arylethyl deriviatives.[3] The present investigation was undertaken to see if there was a systematic effect of varying the alkyl group when the leaving group, the base, and the solvent were kept constant.

The substrates chosen were **1–3**, where L denotes the H (or D) which remains behind in the elimination reactions and T denotes tracer labeling with tritium. The syntheses of the labeled materials are described in the Experimental Section. It was expected that these substrates would react via a spectrum of transition-state structures: very E1cB-like for **1**, central or E1-like for **2**, and intermediate for **3**. The original intention was to employ $EtO^-/EtOH$ as the base/solvent system for all three, but the reaction of **2** under these conditions proved to be too slow to be practical. The reaction with *t*-$BuO^-$/*t*-BuOH was satisfactory. While this change could shift the transition-state structure away from E1-like, it was hoped that the shift would not be too great.

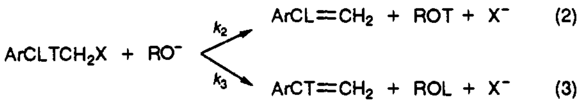
$p\text{-}CF_3PhCLTCH_2NMe_3{}^+Br^-$ **1**

$PhCH(NMe_3{}^+Br^-)CL_2T$ **2**

$p\text{-}ClPhCLTCH(NMe_3{}^+Br^-)Ph$ **3**

The secondary isotope effects were determined as before by comparing the activity of the product olefin at the beginning of the reaction with the activity of the quaternary ammonium salt.[1,3] The method is illustrated for **1** in eqs 1–4. When L = H, $k_1/k_3 = k_H{}^H/k_H{}^T$, where the subscript represents the transferred atom and the superscript the atom that remains behind, while when L = D, $k_1/k_3 = k_D{}^D/k_D{}^T$. Because **2** has three instead of two reactive hydrogens, eq 5 is appropriate for calculating the isotope effects in its reactions. In eqs 4 and 5 $R_0$ is the activity of the reactant, and $R^0{}_s$, the initial activity of the olefinic product.

$$ArCL_2CH_2X + RO^- \xrightarrow{2k_1} ArCL{=}CH_2 + ROL + X^- \quad (1)$$



$$ArCLTCH_2X + RO^- \xrightarrow{k_2} ArCL{=}CH_2 + ROT + X^- \quad (2)$$

$$ArCLTCH_2X + RO^- \xrightarrow{k_3} ArCT{=}CH_2 + ROL + X^- \quad (3)$$

$$k_1/k_3 = 0.5R_0/R^0{}_s \quad (4)$$

$$k_1/k_3 = 2R_0/3R^0{}_s \quad (5)$$

## Results and Discussion

The secondary tritium isotope effects at various temperatures are listed in Table 1. We have previously shown that the maximum secondary isotope effect to be expected in the absence of tunneling can be estimated from the fractionation factors of Hartshorn and Shiner.[1,4,5] The result is the equilibrium isotope effect, $K_H{}^H/K_H{}^T$, for complete $sp^3$ to $sp^2$ rehybridization at the isotopically substituted position. Its value was 1.17 at 50 °C. All of the isotope effects in Table 1 are well above this figure, particularly when one considers that rehybridization is unlikely to be complete in the transition structure for the elimination reaction.

The range of the effects is not large, but the precision of the results is sufficient to make it clear that the effects for **1** are consistently larger than those for **2** and **3**. While **3** seems to give a slightly larger effect than **2** at most temperatures, the values are close enough that one cannot say with confidence that the difference is real.

The Arrhenius parameters present a clearer picture. There is no doubt that the $A_{aH}/A_{aT}$ value for **1** is decisively below those for the other two substrates. Indeed, it is the lowest value we have observed for any system studied so far.[3] There also seems to be a reasonably clear distinction between **2** and **3**, with the latter giving the smaller value. Although the value for **2** is not very far below unity, the magnitude of the isotope effect strongly

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[1] Subramanian, Rm.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 7887–7890.

[2] Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 164–169.

[3] Amin, M.; Price, R. C.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 4467–4471.

[4] Hartshorn, S. R.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 9002–9012.

[5] Buddenbaum, W. E.; Shiner, V. J., Jr. In *Isotope Effects on Enzyme-Catalyzed Reactions*; Cleland, W. W., O'Leary, M. H., Northrup, D. B., Eds.; University Park Press: Baltimore, MD, 1977, p 11.

0002-7863/94/1516-6107$04.50/0

**Table 1.** Temperature Dependence of Secondary Tritium Isotope Effects in E2 Reactions of $RNMe_3^+Br^-$

| R | base/solvent | $t$, °C[a] | $k_H^H/k_H^T$ [b] |
|---|---|---|---|
| $p$-$CF_3PhCHTCH_2$ | $EtO^-/EtOH$ | 29.60 | 1.332 ± 0.009 |
| | | 40.00 | 1.293 ± 0.008 |
| | | 50.20 | 1.266 ± 0.013 |
| | | 60.00 | 1.245 ± 0.006 |
| | | 69.80 | 1.209 ± 0.003 |
| $PhCHCH_2T$ | $t$-$BuO^-/t$-$BuOH$ | 35.50 | 1.252 ± 0.004 |
| | | 44.95 | 1.238 ± 0.004 |
| | | 54.50 | 1.224 ± 0.005 |
| | | 54.80 | 1.223 ± 0.004 |
| | | 65.05 | 1.217 ± 0.004 |
| | | 74.00 | 1.206 ± 0.006 |
| $p$-$ClPhCHTCHPh$ | $EtO^-/EtOH$ | 29.90 | 1.271 ± 0.006 |
| | | 40.35 | 1.258 ± 0.003 |
| | | 50.00 | 1.238 ± 0.004 |
| | | 60.40 | 1.228 ± 0.003 |
| | | 70.20 | 1.206 ± 0.008 |

[a] ±0.05 °C in most cases, ±0.10 °C in worst cases. [b] Rate of proton removal from unlabeled substrate divided by rate of proton removal from labeled substrate. Error limits reflect combined standard deviations of the mean of $R_0$ and $R^0_s$ (eqs 4 and 5).

**Table 2.** Arrhenius Parameters of Secondary Isotope Effects in E2 Reactions of $RNMe_3^+Br^-$

| R | base/solvent | $E_{aT} - E_{aH}$, kcal mol$^{-1}$ | $A_{aH}/A_{aT}$ |
|---|---|---|---|
| $p$-$CF_3PhCH_2CH_2$ | $EtO^-/EtOH$ | 0.478 ± 0.028 | 0.602 ± 0.026 |
| $PhCHCH_3$ | $t$-$BuO^-/t$-$BuOH$ | 0.203 ± 0.015 | 0.898 ± 0.020 |
| $p$-$ClPhCH_2CHPh$ | $EtO^-/EtOH$ | 0.264 ± 0.021 | 0.821 ± 0.027 |

[a] From linear least-squares fits to the Arrhenius equation of the data from Table 1. Error limits are standard deviations.

**Table 3.** Secondary H/T and D/T Isotope Effects in E2 Reactions of $RNMe_3^+Br^-$ at 50 °C

| R | base/solvent | L | $k_L^L/k_L^T$ | $R$[a] |
|---|---|---|---|---|
| $p$-$CF_3PhCH_2CH_2$ | $EtO^-/EtOH$ | H | 1.267 ± 0.012 | |
| | | D | 1.032 ± 0.003 | 7.52 ± 0.10 |
| $PhCHCH_3$ | $t$-$BuO^-/t$-$BuOH$ | H | 1.224 ± 0.005[b] | |
| | | D | 1.029 ± 0.003[b] | 7.05 ± 0.10 |
| $p$-$ClPhCH_2CHPh$ | $EtO^-/EtOH$ | H | 1.238 ± 0.004 | |
| | | D | 1.031 ± 0.003 | 6.95 ± 0.10 |

[a] See eq 6. [b] At 54.5 °C.

implicates tunneling. We have pointed out previously that $A_{aH}/A_{aT}$ values near 0.9 are consistent with sizable tunneling contributions, as shown by model calculations.[2,3]

Turning now to Table 3, eq 6 should be satisfied in the absence of tunneling with $R = 3.26$.[2,3] Actually this exponent raises the

$$k_H/k_T = (k_D/k_T)^R \tag{6}$$

D/T effects only to 1.10–1.11, far short of the H/T effects. Exponents of 7.0–7.5 are necessary to satisfy eq 6. This finding is in accord with significant tunneling, for the tunnel correction should be reduced when the transferred atom is deuterium rather than protium, so that $k_H^H/k_H^T > (k_D^D/k_D^T)^{3.26}$ is expected. It is clear that $R$ is greater for **1** than for **2** or **3**, but no reliable distinction can be made between the latter two.

Since **1** is expected to react via a more carbanion-like transition state than the other two, the fact that all three criteria indicate the most tunneling in its reaction implicates carbanion character as a factor favoring tunneling. We had also expected that **3** should display more carbanion character than **2**, but the necessity of using a different solvent for **2** makes the distinction less clear. Of the three criteria, the Arrhenius parameters seem to provide the least ambiguous order of propensity for tunneling: **1** > **3** > **2**. It is not surprising that the temperature dependence of the secondary isotope effect should provide the best measure of tunneling, for such has been the case with the much larger body of primary deuterium and tritium isotope effects.[6]

Comparisons with literature data support the argument that a carbanion-like transition state is conducive to tunneling. All three of the criteria used here have been applied in only two other cases we are aware of.[3] Unsubstituted (2-phenylethyl)trimethylammonium ion with ethoxide in ethanol gives a smaller $k_H^H/k_H^T$ and a larger $A_{aH}/A_{aT}$ and requires a smaller exponent to convert $k_D^D/k_D^T$ to $k_H^H/k_H^T$ than the $p$-$CF_3$ compound **1** of the present investigation. These are clear indications that the lesser carbanion character in the reaction of the unsubstituted substrate is accompanied by more normal behavior of the secondary isotope effects. Comparison of **1** with 2-($p$-chlorophenyl)ethyl tosylate ($t$-$BuO^-/t$-$BuOH$) also shows more normal behavior for the latter. Again, less carbanion character would be expected in the reaction of the $p$-Cl derivative, though the fact that it differs from the reaction of **1** in substituent, leaving group, and base/solvent makes the comparison less direct.

It should be emphasized that a single criterion for the contribution of tunneling to secondary isotope effects can be misleading. For 2-phenylethyl bromide with *tert*-butoxide/*tert*-butyl alcohol, $A_{aH}/A_{aT}$ is not far below unity (0.927), even though the magnitude of the secondary tritium isotope effect (1.27) clearly points to tunneling.[3] As noted above, an observed $A_{aH}/A_{aT}$ in this range is not inconsistent with significant tunneling. This example illustrates another point, namely that the magnitude of the isotope effect alone is not necessarily a reliable indicator of the extent of tunneling. The secondary isotope effect with the bromide (1.27) is comparable to that found for **1** in the present work, yet the transition state for the bromide is by various criteria almost certainly less carbanion-like and closer to central. The more normal temperature dependence suggests that tunneling is indeed less important and that the large secondary isotope effect is the product of moderate tunneling and a larger normal (zero-point energy) isotope effect, which could plausibly result from more rehybridization in the transition state.

Secondary kinetic isotope effects in hydride as well as proton transfers can exceed the equilibrium isotope effects.[7-11] Model calculations analogous to ours pointed to tunneling as the likely cause.[12] More recently, the criteria described above have been applied to several enzymatic hydride transfers.[13,14] In the first case, compelling evidence for tunneling was afforded by both primary and secondary isotope effects. Evidence was more mixed in the second case, but the secondary isotope effect results were not inconsistent with tunneling.[15] The effect itself was at the upper end of the range that could be explained without tunneling, and $A_{aH}/A_{aT}$ was 0.81, which is low enough to suggest at least some tunneling. Thus the magnitudes of secondary isotope effects, their temperature dependences, and the relation between the H/T and D/T effects appear to be generally useful criteria for tunneling in hydrogen-transfer reactions, especially when two or all three of them are applied to the same reaction.

## Experimental Section

**Solvents and Reagents.** Ethanol was refluxed over magnesium and a catalytic amount of iodine for 12 h and distilled. *tert*-Butyl alcohol was refluxed for several hours over Union Carbide type 3-Å molecular sieves

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(6) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley-Interscience, New York, 1980; pp 140–151.

(7) Kurz, L. C.; Frieden, C. *J. Am. Chem. Soc.* **1980**, *102*, 4198–4203.

(8) Cook, P. F.; Oppenheimer, N. J.; Cleland, W. W. *Biochemistry* **1981**, *20*, 1817–1825.

(9) Cook, P. F.; Blanchard, J. S.; Cleland, W. W. *Biochemistry* **1980**, *19*, 4853–4858.

(10) Cook, P. F.; Cleland, W. W. *Biochemistry* **1981**, *20*, 1797–1805, 1905–1916.

(11) Ostovic, D.; Roberts, M. G.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1983**, *105*, 7629–7631.

(12) Huskey, W. P.; Schowen, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 5704–5706.

(13) Cha, Y.; Murray, C. J.; Klinman, J. P. *Science* **1989**, *243*, 1325–1330.

(14) Grant, K. L.; Klinman, J. P. *Biochemistry* **1989**, *28*, 6597–6605.

(15) Saunders, W. H., Jr. *Croat. Chim. Acta* **1992**, *65*, 505–515.

(Fluka) and distilled. The alkoxide bases were obtained by dissolving the clean metal in the appropriate alcohol under nitrogen. Saturated solutions of potassium *tert*-butoxide were diluted to the desired concentration prior to use. Sodium deuteroxide was prepared by dissolving clean metallic sodium in deuterium oxide (99.9%) chilled in an ice bath and surmounted by a condenser. Tritiated water (1 Ci/mL) was diluted to 1 mCi/mL in distilled water or in deuterium oxide. Alkoxide concentrations were determined by titration with standard hydrochloric acid to the bromthymol blue end point.

**Syntheses.** The quaternary ammonium salts were all known compounds whose melting points agreed with literature values. Identities of key intermediates were confirmed by $^1$H NMR and/or solid derivatives. The protium contents of deuterated species were determined by $^1$H NMR.

**(2-(*p*-(Trifluoromethyl)phenyl)ethyl-*2-t*)trimethylammonium Bromide.** 2-(*p*-(Trifluoromethyl)phenyl)acetic acid (4.8 g, 0.024 mol) was refluxed with 10 mL of tritiated water (1 mCi/mL) and 2.5 g (0.062 mol) of sodium hydroxide for 48 h. The mixture was cooled and acidified with 10% sulfuric acid, the precipitate collected and washed with water. Recrystallization from ethanol gave material of mp 84–85 °C (6.8 mCi/mol). Reduction with lithium aluminum hydride in ether, quenching with water, and acidification by 10% sulfuric acid were followed by extraction with ether and drying of the ether extract over $Na_2SO_4$. Distillation gave 93% yield of 2-(*p*-(trifluoromethyl)phenyl)ethanol-*2-t*, bp 75.5–77.0 °C (0.55–0.60 mm). This was converted to the tosylate in 96% yield by treatment with tosyl chloride (mole ratio 1.2:1) in dry pyridine at –5 °C. The product had mp 90.5–91.0 °C. The tosylate in anhydrous ether was treated with an excess of anhydrous dimethylamine and allowed to stand at room temperature for 48 h. A little absolute ethanol was added occasionally to keep the mixture homogeneous. Concentration to about one-sixth of the original volume, addition of water, and extraction with 10% HCl gave an acid solution which was made basic with sodium hydroxide pellets and extracted with ether. Distillation of the extract gave 88% of *N,N*-dimethyl-2-(*p*-(trifluoromethyl)phenyl)ethylamine-*2-t*, bp 60–61 °C (0.95 mm) (lit.[16] bp 108–108.5 °C (23 mm) for the $d_2$ compound). The amine was treated with excess methyl bromide in nitromethane at 0 °C. The reaction mixture was allowed to stand for 24 h as the bath slowly rose to room temperature. Removal of solvent under reduced pressure and three recrystallizations from ethanol–ether gave 95% of (2-(*p*-(trifluoromethyl)phenyl)ethyl-*2-t*)trimethylammonium bromide, mp 226–226.5 °C (lit.[17] 228–228.5 °C for the $d_2$ compound).

**(2-(*p*-(Trifluoromethyl)phenyl)ethyl-*2-d-2-t*)trimethylammonium Bromide**, mp 228–228.5 °C (lit.[8] 228–228.5 °C), was obtained by the same sequence of reactions as the *2-t* compound above, starting with four exchanges of 2-(*p*-(trifluoromethyl)phenyl)acetic acid with sodium deuteroxide in $D_2O$ followed by a final exchange with sodium deuteroxide in $D_2O$–DTO (5 mCi/mL). The resulting acid contained 1.6% ($^1$H NMR) of unexchanged protium in the $\alpha$-position.

**(1-Phenylethyl-*2-t*)trimethylammonium Bromide.** Acetophenone (21.8 g, 0.18 mol) was refluxed for 24 h with 10 mL of tritiated water (1 mCi/mL), 0.1 g of $K_2CO_3$, and 1 mL of Aliquat 336 (Aldrich). The mixture was extracted with ether, and the ether layer was isolated, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The light brown product was distilled to yield 21.4 g (98%) of colorless acetophenone, bp 45 °C (0.90 mm). This was reduced with $LiAlH_4$ in ether to yield 1-phenylethanol-*2-t*, bp 49 °C (0.95 mm). Acetyl bromide (21.3 g, 0.17 mol) was added to 16.0 g (0.13 mol) of this alcohol and the mixture shaken. A vigorous reaction set in. Acetic acid and excess acetyl bromide were removed under reduced pressure. The crude product was dissolved in 100 mL of benzene, and the solution was washed with 10% $NaHCO_3$ and dried over anhydrous $Na_2SO_4$. The resulting pale yellow oil (23.4 g) was dissolved in 150 mL of nitromethane, cooled to 0 °C, and trimethylamine from a cylinder added dropwise through a dry ice–acetone condenser. The mixture was allowed to stand in the ice bath for 24 h and then concentrated on a rotary evaporator. The residue was recrystallized three times from ethanol–ether to give 30.0 g (97%) of (1-phenylethyl-*2-t*)trimethylammonium bromide, mp 201 °C (lit.[9] 202–203 °C).

**(1-Phenylethyl-*2-t-2,2-d₂*)trimethylammonium Bromide.** Acetophenone-*2,2,2-d*$_3$ (Aldrich) was tritiated as described above, using NaOD in DTO–$D_2O$. The remainder of the synthesis was identical to that for the undeuterated material. The recrystallized product had mp 202–202.5 °C (lit.[18] 202–203 °C).

**(1-Phenyl-2-(*p*-chlorophenyl)ethyl-*2-t*)trimethylammonium Bromide.** 2-(*p*-Chlorophenyl)acetic acid (30.0 g) was refluxed with 50 mL of tritiated water and 28 g of NaOH pellets for 6 days. The product was worked up as for 2-(*p*-(trifluoromethyl)phenyl)acetic acid to give material of mp 106–107 °C (6.55 mCi/mol) after recrystallization from ethanol. The acid (30 g, 0.18 mol) was dissolved in 500 mL of benzene and treated with 31.5 g (0.25 mol) of oxalyl chloride. The mixture was stirred at room temperature for 0.5 h, then warmed to 50 °C for 10 h. The solution was concentrated to 250 mL by a rotary evaporator. It was cooled in an ice–salt bath and treated with 45 g of anhydrous aluminum chloride. The orange-brown mixture was stirred for 10 h, treated with 500 mL of ice water, and extracted with ether. The ether layer was washed with 15% $NaHCO_3$, then with saturated NaCl, and dried over anhydrous $Na_2SO_4$. Removal of the ether by a rotary evaporator left 43.7 g of a light yellow solid. Recrystallization from cold hexane and ether gave 36.8 g (82%) of white crystals, mp 139–139.4 °C. This product (36.8 g, 0.13 mol) was stirred for 120 h under nitrogen with a suspension of $NaCNBH_3$ (8.4 g, 0.13 mol), $NH_4OAc$ (110 g, 1.4 mol), powdered 3-Å molecular sieves (38 g), 600 mL of 2-propanol, and 150 mL of methanol. The mixture was filtered, the residue washed with methanol, and the filtrate concentrated to a viscous oil. The oil was taken up in ether and washed with 15% NaOH. The aqueous phase was extracted with ether, and the combined ether solutions were washed with water and saturated NaCl, dried over anhydrous $Na_2SO_4$, filtered, and concentrated to yield 28.2 g (76%) of 1-phenyl-2-(*p*-chlorophenyl)ethyl-*2-t*-amine. This amine (24.2 g, 0.10 mol) was dissolved in 300 mL of acetonitrile and stirred with 42 mL (0.52 mol) of 37% formaldehyde and 10.5 g (0.17 mol) of $NaCNBH_3$. The vigorous exothermic reaction was moderated by cooling with tap water, and stirring continued for 1.5 h. Glacial acetic acid was added until wet pH paper tested neutral; the solvent was evaporated at reduced pressure, and 400 mL of 2 M KOH was added. The resulting mixture was extracted with ether and the extract washed with 0.5 M KOH and extracted three times with 1 M HCl. The acid extracts were combined and neutralized with KOH pellets and extracted with ether. The combined ether extracts were dried over anhydrous $K_2CO_3$ and concentrated in vacuo to yield 26.2 g (97%) of (1-phenyl-2-(*p*-chlorophenyl)ethyl-*2-t*)-dimethylamine. The amine was dissolved in 400 mL of nitromethane, cooled to 0 °C, and treated dropwise with methyl bromide (200 drops) through a dry ice–acetone condenser. The mixture was allowed to stand for 24 h while the ice bath rose to room temperature. The solvent was removed in vacuo and the residue recrystallized from ethanol–ether to give 29.4 g (94%) of (1-phenyl-2-(*p*-chlorophenyl)ethyl-*2-*)trimethylammonium bromide of mp 137.5–138 °C (lit.[19] 136–138 °C).

**(1-Phenyl-2-(*p*-chlorophenyl)ethyl-*2-t-2-d*)trimethylammonium Bromide.** The sequence was in part the same as that for the undeuterated material, but exchanging the (*p*-chlorophenyl)acetic acid with NaOD in DTO–$D_2O$. Attempted reductive amination of (*p*-chlorophenyl)acetophenone-$\alpha,\alpha$-$d_2$ resulted in loss of deuterium, requiring a different approach. The ketone was instead reduced with $LiAlH_4$ in THF and the alcohol converted to the bromide by the addition of $PBr_3$ with stirring. After the vigorous reaction was moderated, the mixture was heated on the steam bath for 0.5 h and poured into ice water. The resulting mixture was extracted with ether, and the extracts were washed with 10% $Na_2CO_3$ and dried over anhydrous $Na_2SO_4$. The solution was concentrated and the crude bromide (8.0 g) treated directly with 3.6 g (0.055 mol) of sodium azide in 30 mL of ethanol and 5 mL of acetone with constant stirring for 20 h. The solvent was removed under reduced pressure, water was added, the mixture was extracted three times with ether, and the combined ether extracts were dried over anhydrous $Na_2SO_4$. The ether solution was concentrated and used directly in the next step. It was slowly added to excess $LiAlH_4$ in anhydrous ether, and the solution was refluxed for 10 h. Unreacted $LiAlH_4$ was destroyed by addition of water and the mixture filtered to remove inorganic salts. The ether solution was dried over anhydrous $K_2CO_3$ and concentrated to yield 6.0 g of crude product. The 1-phenyl-2-(*p*-chlorophenyl)ethyl-*2-t-2-d*-amine was then carried as before through reductive methylation with formaldehyde and $NaCNBH_3$ and treatment with methyl bromide to yield (1-phenyl-2-(*p*-chlorophenyl)ethyl-*2-t-2-d*)trimethylammonium bromide, mp 138.5–139 °C (lit.[10] 136–138 °C).

**Secondary Isotope Effects.** The procedures followed were essentially those of Amin, Price, and Saunders[3] and Subramanian and Saunders.[1] In all cases the reaction was stopped at the desired fraction of reaction by using an insufficiency of base and allowing the reaction to run at least overnight. Fractions of reaction were determined on a Varian DMS-200

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(16) Smith, P. J.; Bourns, A. N. *Can. J. Chem.* **1970**, *48*, 125–132.

(17) Smith, P. J.; Bourns, A. N. *Can. J. Chem.* **1974**, *52*, 749–760.

(18) Smith, P. J.; Tsui, S. K. *Tetrahedron Lett.* **1972**, 917–920.

(19) Wu, S. L. Ph.D. Thesis, University of Saskatchewan, 1984.

**Table 4.** Molar Absorbances of Reactants and Products

| compd | λ, nm | $\epsilon \times 10^{-4}$ |
|---|---|---|
| **1** | 249.9[a] | 1.73 |
| **2** | 248.0[a] | 1.62 |
| **3** | 298.4[a] | 1.52 |
| **4**[b] | 249.9 | 0.032 |
| **5**[b] | 248.0 | 0.014 |
| **6**[b] | 299.0 | <0.01 |

[a] Position of maximum absorbance. [b] Olefins from **1**, **2**, and **3**, respectively.

spectrophotometer using the absorbances for the pure reactants and products listed in Table 4. Styrene and *p*-(trifluoromethyl)styrene were converted to the dibromides for activity measurements, mp 73 and 47.5 °C, respectively. *p*-Chlorostilbene was isolated as such (recrystallization from ethanol), mp 129 °C. Counting was done on an LKB 1209 liquid scintillation counter using standard quenched samples to determine counting efficiency. Samples of 10–50 mg in 15 mL of scintillation cocktail were counted to 0.2% precision. Each vial was counted three times, and activities used in calculating isotope effects were based on two to five separate weighings. For each isotope effect at each temperature, the reaction was run on five different fractions of reaction ranging from 0.15–0.25 at the low up to 0.5–0.6 at the high end. The activity of the product at zero fraction of reaction was then evaluated by extrapolating a least-squares plot of measured activity vs fraction of reaction.

**Control Experiments.** The nontritiated quaternary ammonium salts underwent no reaction when heated at 70 °C in the absence of base for the time of the reaction. When the tritiated quaternary ammonium salts were treated in the same way, the distilled solvents from the reaction mixture were inactive. No substitution products could be detected by GC–MS in any of the reactions. No deuterium exchange was found in quaternary ammonium salts recovered from partial reaction of deuterated compounds. Treatment of the quaternary ammonium salts with excess base for 20 half-lives gave by spectrophotometric analysis olefin yields within experimental error of 100%.

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