Mechanisms of Elimination Reactions. 39. Steric and Electronic Effects on Stereochemistry in Eliminations from Primary Alkyltrimethylammonium Salts$^{1,2}$

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Abstract: Percentages of syn elimination have been determined by high-field NMR on the products of elimination from $R_1R_2$CHCHDX. The results for $X = OTs$ with $r$-BuO$^-$/r-BuOH at 60 °C were the following ($R_1$, $R_2$, % syn): $p$-MeOC$_6$H$_5$, C$_6$H$_5$, 3.7; $p$-ClC$_6$H$_4$, C$_6$H$_5$, 29; $p$-ClC$_6$H$_4$, C$_6$H$_5$, 0 in EtO$^-$/EtOH. For $X = NMe_3^+$ with OH$^-$ in 50 mol % Me$_2$SO–50 mol % H$_2$O at 60 °C, the results were as follows ($R_1$, $R_2$, % syn): $p$-MeOC$_6$H$_5$, C$_6$H$_5$, 60; $p$-ClC$_6$H$_4$, C$_6$H$_5$, 72. For Ar($i$-Pr)-CHCHDNMe$_3^+$ with OH$^-$ in 50 mol % Me$_2$SO–50 mol % H$_2$O at 80 °C, the results were as follows ($Ar$, % syn): $m$-ClC$_6$H$_4$, 78.6; $p$-ClC$_6$H$_4$, 69.5; C$_6$H$_5$, 59.6; $p$-EtC$_6$H$_4$, 58.3; $p$-t-BuC$_6$H$_4$, 60.3. Overall rates in this series were dissected into syn and anti rates, which fitted the Hammett equation to give $\rho_{syn} = 3.69 \pm 0.20$ and $\rho_{anti} = 3.02 \pm 0.22$. This result supports the conclusion that syn elimination has a more carbanionic transition state than anti. The lower percent syn with $X = OTs$ than with $X = NMe_3^+$ is ascribed to the lesser steric requirements of OTs.

The stereochemistry of bimolecular elimination reactions has been shown over the past 20 years or so to follow a complex pattern ranging from all anti to all syn, including cases where one stereoisomer is formed by anti and the other by syn elimination.$^{3,4}$ Quaternary ammonium salts are particularly prone to syn elimination, but primary alkyltrimethylammonium ions appeared to be exclusive or predominantly anti until it was shown that $\beta$ branching could cause syn elimination to become the major path.$^7$ The present research was undertaken to explore the role of the leaving group and of substituent effects in syn eliminations from $\beta$-branched primary alkyl derivatives.

The substrates used were all of the general formula $R_1R_2$CHCHDX. They were stereospecifically synthesized by the general procedure described earlier for similar compounds.$^7$ Base-promoted elimination reactions were performed on these substrates and the resulting mixtures of stereoisomeric deuterated olefins analyzed by high-field NMR.$^7$ The results are recorded in Tables I and II.

Table I. Stereochemistry of Elimination from ArPhCHCHDX at 60 °C

<table>
<thead>
<tr>
<th>$Ar$</th>
<th>$X$</th>
<th>base/solvent$^a$</th>
<th>% syn</th>
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<tbody>
<tr>
<td>$p$-ClC$_6$H$_4$</td>
<td>OTs</td>
<td>EtO$^-$/EtOH</td>
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<tr>
<td>$p$-ClC$_6$H$_4$</td>
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<td>r-BuO$^-$/r-BuOH</td>
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<td>$p$-MeOC$_6$H$_5$</td>
<td>OTs</td>
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<tr>
<td>$p$-MeOC$_6$H$_5$</td>
<td>NMe$_3^+$</td>
<td>OH$^-$/50%Me$_2$SO–50%H$_2$O</td>
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$^a$Solvent composition in mol %. $^b$Each value is the average of at least three determinations with standard deviation.

Table II. Rates and Sterechemistry of Elimination from (3-Methyl-2-(X-phenyl)-1-butyyl)-1-trimethylammonium iodides with Hydroxide Ion in 50% Me$_2$SO–50% H$_2$O at 80 °C

<table>
<thead>
<tr>
<th>$X$</th>
<th>$k_3 \times 10^3$ M$^{-1}$ s$^{-1}$</th>
<th>% syn</th>
<th>$k_{syn} \times 10^3$ M$^{-1}$ s$^{-1}$</th>
<th>$k_{anti} \times 10^3$ M$^{-1}$ s$^{-1}$</th>
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<td>175</td>
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<tr>
<td>p-Cl</td>
<td>96.6 ± 0.6</td>
<td>69.5</td>
<td>67.1</td>
<td>29.5</td>
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<tr>
<td>H</td>
<td>11.6 ± 0.02</td>
<td>59.6</td>
<td>6.79</td>
<td>4.61</td>
</tr>
<tr>
<td>p-Et</td>
<td>3.14 ± 0.003</td>
<td>58.3</td>
<td>1.83</td>
<td>1.31</td>
</tr>
<tr>
<td>p-i-Bu</td>
<td>3.08 ± 0.01</td>
<td>60.5</td>
<td>1.86</td>
<td>1.22</td>
</tr>
</tbody>
</table>

$^a$Solvent composition in mol %. $^b$Each value is the average of at least three determinations with standard deviation.

The effect of the leaving group can be readily understood in terms of our steric explanation of syn elimination from primary substrates.$^5$ The anti transition state, 2, should be less stable, the larger $R_1$, $R_2$, and $X$ thereby allowing syn elimination to compete more effectively. Trimethylammonium is a poorer leaving group than tosylate, a characteristic which could also promote syn elimination by increasing the carbanion character of the transition state.$^6$ The present research was undertaken to explore the role of the leaving group and of substituent effects in syn eliminations from $\beta$-branched primary alkyl derivatives.

The substrates used were all of the general formula $R_1R_2$CHCHDX. They were stereospecifically synthesized by the general procedure described earlier for similar compounds.$^7$ Base-promoted elimination reactions were performed on these substrates and the resulting mixtures of stereoisomeric deuterated olefins analyzed by high-field NMR.$^7$ The results are recorded in Tables I and II.

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<tr>
<td>$p$-ClC$_6$H$_4$</td>
<td>OTs</td>
<td>EtO$^-$/EtOH</td>
<td>0</td>
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<td>OTs</td>
<td>r-BuO$^-$/r-BuOH</td>
<td>29</td>
</tr>
<tr>
<td>$p$-MeOC$_6$H$_5$</td>
<td>OTs</td>
<td>r-BuO$^-$/r-BuOH</td>
<td>3.7</td>
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<tr>
<td>$p$-ClC$_6$H$_4$</td>
<td>NMe$_3^+$</td>
<td>OH$^-$/50%Me$_2$SO–50%H$_2$O</td>
<td>72</td>
</tr>
<tr>
<td>$p$-MeOC$_6$H$_5$</td>
<td>NMe$_3^+$</td>
<td>OH$^-$/50%Me$_2$SO–50%H$_2$O</td>
<td>60</td>
</tr>
</tbody>
</table>

$^a$Solvent composition in mol %. $^b$Each value is the average of at least three determinations with standard deviation.

between the percent syn values, for tert-butoxide in tert-butoxide alcohol is generally more effective in promoting syn elimination than is hydroxide in mixtures of dimethyl sulfoxide and water.$^5$ Second, tert-butoxide in tert-butoxide alcohol gives more syn elimination than ethoxide in ethyl alcohol. The superiority of tertiary over primary alkoxides in promoting syn elimination has been noted before.$^5$ Third, the electron-withdrawing $p$-chloro substituent increases the proportion of syn elimination from both the tosylate and the quaternary ammonium salt (1a and 1c) relative to the corresponding substrates (1b and 1d) with the electron-releasing $p$-methoxy substituent.

The effect of the leaving group can be readily understood in terms of our steric explanation of syn elimination from primary substrates.$^5$ The anti transition state, 2, should be less stable, the larger $R_1$, $R_2$, and $X$ thereby allowing syn elimination to compete more effectively. Trimethylammonium is a poorer leaving group than tosylate, a characteristic which could also promote syn elimination by increasing the carbanion character of the transition state (see below). We believe, however, that the steric difference

(1) This work was supported by the National Science Foundation.

0002-7863/86/1508-0245$1.50/0 © 1986 American Chemical Society
is so great that its effect predominates.

The different results with p-chloro and p-methoxy substituents indicate that electron withdrawal favors syn elimination. We tried to prepare a wider to of sterosepecifically deuterated substrates of the type of 1a-d, but difficulties in separating the stereoisomeric vinyl bromide precursors caused us to abandon this approach. We turned instead to 1e-f, where the vinyl bromides could be separated readily by chromatography on silica gel. The overall rates of elimination with hydroxide in 50% dimethyl sulfoxide-50% water at 80 °C were measured, and the stereochemistry of elimination was determined under the same conditions, enabling us to dissect the overall rate into rates of syn and anti elimination. The results are recorded in Table II.

It is qualitatively evident that both anti and syn elimination are facilitated by electron-withdrawing substituents, the latter more so than the former. When the rate constants are fitted to the Hammett equation, the resulting $\rho$ values are $3.50 \pm 0.18$ for the overall reaction, $3.02 \pm 0.22$ for the anti elimination, and $3.59 \pm 0.20$ for the syn elimination. These values at 80 °C may be compared to 2.4 at 60 °C for (2,2-diarylethyl)trimethylammonium ion* (probably mixed syn-anti) and 3.4 at 60 °C for (2-aryl-ethyl)trimethylammonium ion19 (probably all anti). We have previously suggested that the low value for the 2,2-diarylethyl system results from the inability of both aryl groups to attain the conformations necessary to interact effectively with the developing carbanionic center. That $\rho_{\text{anti}}$ in the present case is less than $\rho$ for the 2-aryl ethanol system may reflect a similar restrictive effect of the $\beta$-isopropyl group on the formation of the ary1 group.

The most significant comparison is that $\rho_{\text{anti}}$ is substantially larger than $\rho_{\text{anti}}$, indicating that the transition state for syn elimination has more carbanion character than the transition state for anti elimination. A similar result is reported for the reaction of 2-arylcyclopentyl tosylates with tert-butoxide in tert-butyl alcohol at 50 °C, where the trans series (syn elimination) gives a $\rho$ of 2.8 while the cis series (anti elimination) has a $\rho$ of only 1.5.11 Thus, greater carbanion character for syn than anti elimination seems to be found independent of the nature of the leaving group or the structure of the substrate.

The present results provide additional support for theoretical discussions which have emphasized the role of carbanion character in syn elimination. Ingold originally suggested that the E2 reaction could be viewed as an "$\Sigma_2^+$" displacement of the leaving group by the electrons of the $\beta$-C-H bond.12 Normally an anti-periplanar arrangement of the C-H and C-X bonds would be required for a smooth backside displacement (3). If the $\beta$-C-H bond is nearly broken and a carbanionic center nearly fully formed in the transition state, as in 4, the lobe of the developing $\beta$ orbital opposite the $\beta$-C-H bond could contain enough electron density for a "backside" displacement of the leaving group. The overall result would then be an syn-periplanar elimination. This idea has been taken up extended by a number of workers, including Zavada and Sicher,13,14 Lowe,15 and Bach.16

The molecular orbital approach of Bach16 has contributed several important insights. One is that the "displacements" in 3 and 4 can be viewed as interaction of the $\beta$-H bonding electrons with the vacant $\sigma^*$ orbital of the C-X bond. In order for this to occur efficiently in 4, inversion at $\text{C}_2$ must precede or accompany C-X bond breaking, implying either an E1cB or an E1cB-like E2 mechanism. The experimental results indicate that the E1cB character need not be extreme, for all $\rho$ values below those found (4-7) in typical carbanion-forming reactions.17-19

Experimental Section

Solvents. Ether was refluxed over sodium with benzophenone used as an indicator of dryness.16 It was then distilled. Dimethyl sulfoxide was stirred over calcium hydride for 2 days. It was distilled under reduced pressure and the first 10% discarded. Distilled water was refluxed over potassium permanganate for 2 h and then distilled. tert-Butyl alcohol was stirred over calcium hydride for 24 h and then distilled. The first 10% of distillate was discarded. Absolute ethanol was refluxed over magnesium turnings for 8 h and then distilled. The first 10% of distillate was discarded. Tetrabromoethylene was refluxed over sodium with benzo-phenone used as an indicator of dryness.15 It was then distilled.

General. All melting and boiling points are uncorrected. The NMR spectra were recorded on a Bruker WH-400 or a Nicolet QE 300 NMR spectrometer in all cases involving distinctions between or analyses of stereoisomeric olefins and their mixtures. A Varian EM-390 NMR spectrometer was used in some less critical cases. Chloroform-d and dimethyl-d$_2$ sulfoxide were used as NMR solvents. Mass spectra were determined on a VG 7035 mass spectrometer.

(R5R5)-2-Phenyl-2-(p-methoxyphenyl)ethyl-1-d tosylate was an intermediate in the synthesis of (R5R5)-(2-phenyl-2-methoxyphenyl)ethyl-1-dtrimethylammonium iodide, recrystallization from ethanol gave material of mp 59.0-62.5 °C.17 $^{1}H$ NMR 3.30 (s, 3 H), 4.33 (d, 1 H), 4.51 (d, 1 H), 6.7-8.7 (m, 13 H); MS 383 (M$^+$).

(R5R5)-(2-Phenyl-2-(p-methoxyphenyl)ethyl-1-d)-trimethylammonium iodide was obtained by the procedure previously used for the corresponding bromide,1 substituting methyl iodide for methyl bromide. $^{1}H$ NMR 3.01 (s, 9 H), 3.68 (s, 3 H), 4.12 (d, 1 H), 4.59 (d, 1 H), 7.15 (dd, 4 H), 7.28 (m, 5 H).

(Z)-1-Phenyl-1-(p-chlorophenyl)-2-bromoethylene was obtained by the same method used to prepare (E)-1-phenyl-1-(p-methoxyphenyl)-2-bromoethylene.1 The crude mixture of Z and E bromides was redistilled over potassium hydroxide in ethanol to ensure complete elimination from the precursor dibromide. The Z isomer crystallized when the mixture was left at room temperature for 48 h. Recrystallization from ethanol gave material of mp 88-89.5 °C (lit.1 mp 88-89 °C). $^{1}H$ NMR 6.71 (s, 1 H), 7.0-7.6 (m, 9 H).

(R5R5)-2-Phenyl-2-(p-chlorophenyl)ethyl-1-d tosylate was obtained from (Z)-1-phenyl-1-(p-chlorophenyl)-2-bromoethylene by the same sequence of reactions used to prepare (R5R5)-(2-phenyl-2-(p-methoxyphenyl)ethyl-1-dtrimethylammonium iodide (above and ref 7). It had mp 122-123 °C. $^{1}H$ NMR 3.01 (s, 9 H), 4.20 (d, 1 H), 4.79 (d, 1 H), 7.2-7.5 (m, 5 H), 7.50 (dd, 4 H). $^{13}C$ NMR 284.5. $^{13}C$ NMR 3.01 (s, 9 H), 4.20 (d, 1 H), 4.79 (d, 1 H), 7.2-7.5 (m, 5 H), 7.50 (dd, 4 H).

(R5R5)-2-Phenyl-2-(p-chlorophenyl)ethyl-1-d tosylate was an intermediate in the synthesis of (R5R5)-(2-phenyl-2-(p-chlorophenyl)-

ethyl-1-d-tetramethylammonium iodide (see above). Recrystallization from ethanol gave material of mp 66.0-66.8 °C; 'H NMR δ 2.48 (s, 3 H), 4.31 (d, 1 H), 4.50 (d, 1 H), 6.8-7.8 (m, 13 H).

p-Chloroisobutyrophenone was obtained by adding isobutyryl chloride (0.42 mol) dropwise to a mixture of aluminum chloride (0.28 mol) and chlorobenzene (1.27 mol). When the evolution of hydrogen chloride ceased, the mixture was poured into ice water and the product extracted with ether. The ether was dried over MgSO4 and removed. The resulting mixture (78% para and 22% ortho by NMR) was fractionally distilled in vacuum, to give ortho isomer, bp 60 °C (ca. 0.5 torr), and para isomer, bp 87 °C (ca. 0.5 torr), the latter in 60% isolated yield: 'H NMR δ 1.20 (d, 6 H), 3.45 (m, 1 H), 7.60 (d, 4 H).

p-Ethylisobutyrophenone was obtained from ethylbenzene by the same procedure as for p-chloroisobutyrophenone. The product was 62% para, bp 107 °C (ca. 3 torr), and 38% ortho, bp 90 °C (ca. 3 torr). The para isomer had 'H NMR δ 1.19 (d, 6 H), 1.38 (s, 9 H), 3.52 (m, 1 H), 7.69 (ddd, 4 H). After removal of the pentane and distillation, the product was obtained in 93% yield: 'H NMR δ 1.19 (d, 6 H), 1.38 (s, 9 H), 3.52 (m, 1 H), 7.69 (ddd, 4 H).

m-Chloroisobutyrophenone was obtained by the chlorination of isobutyrophenone according to the procedure used by Pearson, Pope, Hargrove, and Stampler for the chlorination of acetophenone.22 The product, bp 60 °C, was obtained in 50% yield from (RR,SS)-3-methyl-2-(p-chlorophenyl)-2-butyl-1-d)trimethylammonium iodide and had mp 169-171 °C: 'H NMR δ 0.71 (d, 3 H), 0.90 (d, 3 H), 1.17 (t, 3 H), 1.82 (m, 1 H), 2.61 (m, 3 H), 2.95 (s, 9 H), 3.05 (m, 1 H), 3.90 (t, 1 H), 7.25 (dd, 4 H).

(RS,SR)-(3-Methyl-2-(p-chlorophenyl)-1-butyl-1-d)trimethylammonium iodide was obtained by the sequence of reactions used to prepare (RS,SR)-(3-methyl-2-(p-chlorophenyl)-1-butyl-1-d)trimethylammonium iodide and had mp 169-171 °C: 'H NMR δ 0.70 (d, 3 H), 0.90 (d, 3 H), 1.17 (t, 3 H), 1.82 (m, 1 H), 2.61 (m, 3 H), 2.95 (s, 9 H), 3.05 (m, 1 H), 3.90 (t, 1 H), 7.25 (dd, 4 H).

1.25 (s, 6 H), 1.82 (m, 1 H), 2.95 (s, 9 H), 3.13 (m, 1 H), 3.91 (s, 1 H), 7.39 (m, 4 H).

(RS,SR)-(3-Methyl-2-(p-chlorophenyl)-1-butyl-1-d)trimethylammonium iodide was obtained by the sequence of reactions used to prepare (RS,SR)-(3-methyl-2-(p-chlorophenyl)-1-butyl-1-d)trimethylammonium iodide and had mp 149-150 °C: 'H NMR δ 0.70 (d, 3 H), 0.88 (d, 3 H), 1.28 (s, 9 H), 1.80 (m, 1 H), 2.93 (s, 9 H), 3.02 (m, 1 H), 3.87 (m, 1 H), 7.33 (dd, 4 H).

(RS,SR)-(3-Methyl-2-(p-chlorophenyl)-1-butyl-1-d)trimethylammonium iodide was obtained by the sequence of reactions used to prepare (RS,SR)-(3-methyl-2-(p-chlorophenyl)-1-butyl-1-d)trimethylammonium iodide and had mp 199-200 °C: 'H NMR δ 0.70 (d, 3 H), 0.90 (d, 3 H), 1.82 (m, 1 H), 2.95 (s, 9 H), 3.13 (m, 1 H), 3.91 (s, 1 H), 7.43 (m, 4 H).

Steroechemistry of Elimation. The substrate (ca. 15 mg) was dissolved in 2 mL of solvent, heated to the desired temperature, and mixed with 2 mL of base solution at the same temperature. The reaction was followed to completion by TLC, and the reaction mixture was poured into water. The product was extracted with petroleum ether, the solution was dried over magnesium sulfate, and the solvent was removed. The residue was obtained by the sequence of reactions used to prepare (RS,SR)-(3-methyl-2-(p-chlorophenyl)-1-butyl-1-d)trimethylammonium iodide and had mp 179-180 °C: 'H NMR δ 0.71 (d, 3 H), 0.91 (d, 3 H), 1.84 (m, 1 H), 2.98 (s, 9 H), 3.09 (m, 1 H), 3.91 (s, 1 H), 7.39 (m, 5 H).

(RS,SR)-(3-Methyl-2-(m-chlorophenyl)-2-butyl-1-d)trimethylammonium iodide was obtained by the sequence of reactions used to prepare (RS,SR)-(3-methyl-2-(p-chlorophenyl)-1-butyl-1-d)trimethylammonium iodide and had mp 39-40 °C: 'H NMR δ 0.71 (d, 3 H), 0.91 (d, 3 H), 1.84 (m, 1 H), 2.98 (s, 9 H), 3.09 (m, 1 H), 3.91 (s, 1 H), 7.39 (m, 5 H).

Stereochemistry of Elimination. The substrate (ca. 15 mg) was dissolved in 2 mL of solvent, heated to the desired temperature, and mixed with 2 mL of base solution at the same temperature. The reaction was followed to completion by TLC, and the reaction mixture was poured into water. The product was extracted with petroleum ether, the solution was dried over magnesium sulfate, and the solvent was evaporated. The 400 or 300 mHz 'H NMR spectrum of the residue was recorded. The vinyl proton NMR absorptions of the R,R,C=C=CHD stereoisomers are listed in Table III.

Kinetics of Elimination Reactions of (3-methyl-2-aryl-1-butyl-1-d)-trimethylammonium Iodides. The substrate (20 mg) in 2.5 mL of 50% dimethyl sulfoxide-water was brought to 80 °C in a constant-temperature bath and mixed with 2.5 mL of an equilibrated solution of 0.083 M sodium hydroxide in 50% dimethyl sulfoxide-water. Aliquots (0.15 mL) were withdrawn periodically and diluted to 25 mL with 95% ethanol, and the UV absorbance at the absorption maximum of the olefinic product (Table IV) was determined. The data were fitted to the second-order rate law for unequal initial concentrations with use of a linear least-squares program. Each rate constant recorded in Table II is the mean of at least three separate determinations. Standard deviations were less than 4% in all cases.

Table III. 'H NMR Chemical Shifts of the Vinyl Protons in R,R,C=C=CHD.

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>δ(E)</th>
<th>δ(Z)</th>
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<tbody>
<tr>
<td>C6H5</td>
<td>p-CIC6H4</td>
<td>5.45</td>
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<td>C6H5</td>
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* Determined in chloroform. δ(E) is the chemical shift of the E isomer and δ(Z) the chemical shift of the Z isomer.