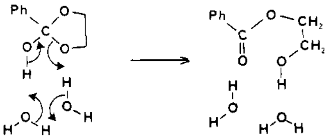
reaction of eq 11 does not make a significant contribution to k_0. The possibility has been raised[1,2] of a concerted process for this reaction, with solvent water molecules acting as acid and base to transfer protons to and from the neutral hemiorthoester.



(12)

Acknowledgment. The continued financial support of the National Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Registry No. 1, 4353-38-2; **2**, 59700-73-1; **3**, 92544-12-2.

Supplementary Material Available: Table SI listing observed rate constnts for the breakdown of 2-phenyl-2-hydroxy-1,3-dioxolane in acetic and formate buffers (1 page). Ordering information is given on any current masthead page.

Mechanisms of Elimination Reactions. 38. Why Is the Effect of Successive β-Alkyl Substitution on the Rates of Elimination from Quaternary Ammonium Salts Nonadditive?[1]

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Abstract: Possible reasons are examined for the nonadditivity of the effect of successive β-methyl substitution on the rates of elimination reactions of quaternary ammonium salts. The temperature dependences of the deuterium isotope effects in E2 reactions of $R_1R_2NMe_2^+$ show that tunneling is not a significant source of nonadditivity. Neither is a change of gross mechanism or stereochemistry, for studies with $C_4H_9CHDCHDNMe_3^+$ and $C_4H_9(CH_3)CHCHDNMe_3^+$ show the reactions to be very predominantly (>88%) anti-E2 in both cases. Secondary tritium isotope effects with $R_1R_2CHCHTNMe_3^+$ increase, however, in the order ethyl (1.108 ± 0.002), propyl (1.150 ± 0.015), isobutyl (1.216 ± 0.012). This result suggests increasing rehybridization at the α-carbon in the transition state and therefore a shift toward less E1cB and more central-E2 character. Since methyl substitution is expected to favor a developing double bond, the much smaller rate-depressing effect of the second β-methyl is accounted for by such a shift in transition-state character.

Substituent effects on rates and equilibria in organic reactions are usually assumed to be approximately additive. This assumption is often valid for remote substituents; e.g., the Hammett σ for 3,4-dichlorophenyl is well represented by $\sigma_{p\text{-Cl}} + \sigma_{m\text{-Cl}}$.[3] When substituents are closer to the reaction center, saturation effects may be observed. Chloroacetic acid is 79 times as acidic as acetic acid, but dichloroacetic acid is only 37 times as acidic as chloroacetic acid.[4] This saturation effect is still modest. When successive substituents affect each other's ability to undergo resonance interaction with the reaction center, dramatic effects often result. Diphenylmethane is 10^8 times as acidic as toluene, but triphenylmethane is less than 10^2 times as acidic as diphenylmethane.[4]

We have been intrigued for some time by a pattern of nonadditive substituent effects for certain E2 reactions. In the Hofmann elimination at 85–150 °C of quaternary ammonium hydroxide, $R_1R_2NMe_2^+OH^-$, the ethylene/propylene ratio when R_1 = Et and R_2 = n-Pr is 41, but the propylene/isobutylene ratio when R_1 = n-Pr and R_2 = i-Bu is only 2.7.[5] In other words, the effect of the second β-methyl group is only one-fifteenth that of the first. A similar, though somewhat less dramatic effect persists in direct rate measurements. The relative rates of the elimination reactions of $RNMe_3^+$ with ethoxide in ethanol at 104.2 °C run Et/n-Pr = 13.8 and n-Pr/i-Bu = 3.1.[6] To get the true chemical effects, the above values should be corrected for symmetry number differences. The corrections can most simply be understood from the fact that there are three indistinguishable anti-E2 transition states for loss of ethyl, two enantiomeric ones for loss of propyl, but only one for loss of isobutyl. The ratios from $R_1R_2NMe_2^+OH^-$ then become ethylene/propylene 27.3 and propylene/isobutylene 1.35, while the relative rates from $RNMe_3^+$ become Et/n-Pr 9.20 and n-Pr/i-Bu 1.55.

Table I. Temperature Dependence of the Product Ratios for the Reactions of $R_1R_2NMe_2^+Br^-$ with Sodium 1-Butoxide in 50% 1-Butanol–Dimethyl Sulfoxide

	ethylene/propylene		propylene/isobutylene		
T, °C	**1**[a]	**2**[a]	**3**[a]	**4**[a]	**5**[a]
50	68.12				
60	59.80	19.88	2.594	0.7072	11.59
70	49.65	16.20			
80			2.696	0.8458	10.80
90	38.42	13.20	2.764	0.8748	10.65
100		12.50	2.892	0.9059	10.12

[a] See text for structures of these compounds. Each product ratio is the average of two runs. Derivations from mean ran usually 1–2% and never above 4%.

Even more interesting is the fact that this nonadditivity is almost completely absent in the reactions of the corresponding sulfonium ions, $RSMe_2^+$. Here the relative rates of reaction with ethoxide

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[1] This work was supported by the National Science Foundation.

[2] Sherman Clarke fellow, 1979–1981.

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Table II. Relative Activation Parameters for the Reactions of $R_1R_2NMe_2^+Br^-$ with Sodium 1-Butoxide in 50% 1-Butanol–Dimethyl Sulfoxide

substrate-(s)[a]	product ratio, X/Y[b]	ΔE_a,[c] kcal mol^{-1}	A_{aX}/A_{aY}[c]	k_H/k_D[d] (70 °C)
1	E/P	−3.40 ± 0.18	0.344 ± 0.094	
2	E/P	−2.81 ± 0.22	0.273 ± 0.087	
3	P/I	0.64 ± 0.07	6.75 ± 0.69	
4	P/I	1.55 ± 0.14	7.49 ± 1.47	
5	P/I	−0.80 ± 0.07	3.50 ± 0.34	
1/2	E_H/E_D	0.59 ± 0.06	1.26 ± 0.53	3.0
3/4	P_H/P_D	0.91 ± 0.13	0.90 ± 0.20	3.4
5/3	I_H/I_D	1.43 ± 0.20	0.52 ± 0.07	4.2

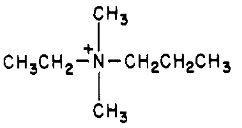
[a] See text for structures of these compounds. [b] E = ethylene, P = propylene, I = isobutylene, E_D = deuterioethylene, etc. [c] From least-squares fit of individual measurements (not averages in Table I) to Arrhenius equation. Not statistically corrected for differing numbers of β-hydrogens in R_1 and R_2. See text for corrections. [d] Calculated from Arrhenius parameters.

in ethanol at 64.08 °C run Et/n-Pr = 2.7 and n-Pr/i-Bu = 2.9 (1.80 and 1.45 corrected for symmetry). Thus, the nonadditivity observed in the quaternary ammonium salt eliminations does not arise from any inherent electronic or steric effect of successive β-methyl substitution. It depends on the nature of the leaving group, even when both sets of substrates follow the Hofmann rule.

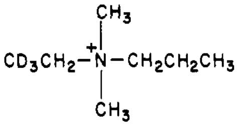
We have tested experimentally three possible explanations of this interesting effect and have found only one to be viable.

The first was suggested by our earlier observations on the contribution of tunneling to relative reactivity in E2 reactions of 3-methyl-2-butyl p-nitrobenzenesulfonate.[7] The temperature dependences of the deuterium isotope effects on elimination toward the methyl and the isopropyl groups suggested that tunneling made an approximately threefold greater contribution to the rate of the former than of the latter.

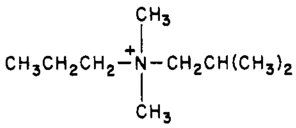
In the context of the present problem, it seemed reasonable to suppose that the normal electronic and/or steric effects of successive β-methyl substitution might be roughly additive, but that the rate of elimination of the ethyl group might be further enhanced by a contribution from tunneling that was absent from or much smaller in the eliminations of the n-propyl and isobutyl groups. To test this hypothesis, we studied product compositions as functions of temperature in E2 reactions of **1**–**5**. The deuterium isotope effects can then be determined competitively. For example, k_H/k_D for loss of ethyl is given by the ethylene/propylene ratio from **1** divided by that from **2**, assuming that the rate of loss of propylene is the same from both **1** and **2**. The product ratios are given in Table I, and the isotope effects and activation parameters in Table II.


$CH_3CH_2-\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}-CH_2CH_2CH_3$

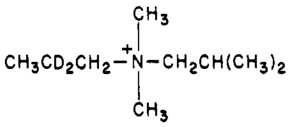
1


$CD_3CH_2-\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}-CH_2CH_2CH_3$

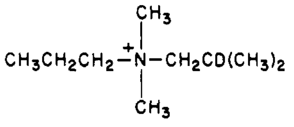
2


$CH_3CH_2CH_2-\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}-CH_2CH(CH_3)_2$

3


$CH_3CD_2CH_2-\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}-CH_2CH(CH_3)_2$

4


$CH_3CH_2CH_2-\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}-CH_2CD(CH_3)_2$

5

We will discuss later the relative activation parameters for the unlabeled substrates **1** and **3**. The temperature dependence of the isotope effects for the formation of ethylene and propylene clearly gives no reason for suspecting that tunneling contributes significantly to either process.[8] A_{aH}/A_{aD} is within experimental error of unity in both cases, and $E_{aD} - E_{aH} < 1.2$ kcal mol^{-1}. The temperature dependence of the isotope effect for the formation of isobutylene suggests a modest contribution from tunneling, but fitting the observed temperature dependence to the Bell equation by our usual procedure[9] suggests that the tunnel correction, Q_{tH} ~ 2.0 at 70 °C. The rate of isobutylene formation thus cannot be sufficiently enhanced by tunneling to explain why the propylene/isobutylene ratio is more than an order of magnitude smaller than the ethylene/propylene ratio. We have no explanation of why tunneling in this case is more important in elimination toward the more substituted β-carbon rather than the less substituted one as was found with 3-methyl-2-butyl p-nitrobenzenesulfonate.[7]

We next turned to the possibility that the nonadditivity of the β-methyl effect resulted from a change in mechanism. More specifically, we suspected that the elimination could be wholly or predominantly anti-E2 for the loss of ethylene and propylene, but syn-E2 for the loss of isobutylene. In such a case the β-methyl effect could be additive for the anti-E2 mechanism, but the overall rate of production of isobutylene would be substantially greater than the anti-E2 rate because of the incursion of the syn-E2 mechanism. We had in hand at that time evidence that the syn-E2 mechanism could be important for β-branched primary alkyltrimethylammonium salts.[10]

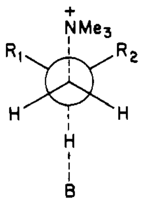
Determination of the stereochemistry of elimination of an ethyl group as ethylene could in principle be done by double labeling with deuterium and tritium. In the light of the results below, however, we felt it safe to assume that ethylene production occurred entirely by an anti-E2 mechanism.

When stereospecifically labeled **6** and **7** were treated with sodium 1-butoxide in 50% 1-butanol–dimethyl sulfoxide at 80 °C, the proportion of syn-E2 reaction was found to be <5% for **6** and only 12% for **7**.[10] While the trend is in the direction we predicted,

$C_4H_9CHDCHDNMe^+$ **6** $C_4H_9CH(Me)CHDNMe_3^+$ **7**

there is still not enough syn-E2 reaction with **7** to make the overall E2 rate exceed by very much the anti-E2 rate. The (unobservable) percentage of syn-E2 loss of an isobutyl group should, if anything, be less than the 12% found for the 2-methyl-1-hexyl group of **7**.

With our first two hypotheses excluded, we turned to the third. This was based on our observation that β-branching in a primary alkyltrimethylammonium ion promotes syn elimination, which we explained by arguing that the transition state for anti elimination suffered significant nonbonded interactions between the leaving group and the β-alkyl groups (**8**).[10] One way of relieving these interactions is to go over to a syn-E2 transition state, where R_1 and R_2 interact only with the α-hydrogen atoms. Another way, however, would be to adopt a transition state in which the C---N bond is more extended and the α- and β-carbon atoms closer to sp^2 hybridization. Such a transition state would have more



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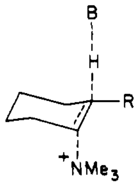
central-E2 or double-bond character than the E1cB-like transition state that normally seems to be involved in E2 reactions of quaternary ammonium salts.[11]

If the transition state for elimination of isobutylene has more double-bond character and less carbanion character than the transition states for elimination of propylene or ethylene, the rate-retarding inductive effect of β-methyl substitution would be diminished and partially counteracted by the stabilizing effect of the β-methyl groups on the developing double bond. As a result, the elimination of isobutylene would be faster than expected. Support for this hypothesis has been in the literature for some time. *cis*-2-Alkylcyclohexyltrimethylammonium ions yield, in E2 reactions, predominantly the Saytzev-rule product, the 1-alkylcyclohexene, rather than the expected Hofmann-rule product, the 3-alkylcyclohexene.[12,13] This was explained as resulting from a lengthening of the C---N bond in the transition state (**9**) for anti-E2 reaction so as to relieve the steric strain caused by forcing the bulky trimethylammonio group into an axial position. Here the effect is so large that it reverses the usual orientation effect, rather than just attenuating it as in the isobutylene elimination.



9

In order to test this hypothesis, we chose to determine the α-tritium isotope effect in eliminations from the appropriate alkyltrimethylammonium ions. A complicating factor in the study was that the reactions are not pure eliminations but are accompanied by substitution. The possible reactions are shown in eq 1–3. Gas chromatographic analysis (see Experimental Section for details) revealed that the k_S' process (eq 3) was negligible in all cases. The k_S process (eq 2) was not, however, and constituted some 78% of the overall reaction with isobutyltrimethylammonium ion. The product analyses are recorded in Table III.

$$R_1R_2CHCH_2NMe_3^+ \xrightarrow{RO^-,\ k_E} R_1R_2C{=}CH_2 + NMe_3 \quad (1)$$

$$R_1R_2CHCH_2NMe_3^+ \xrightarrow{RO^-,\ k_S} R_1R_2CHCH_2NMe_2 + ROMe \quad (2)$$

$$R_1R_2CHCH_2NMe_3^+ \xrightarrow{RO^-,\ k_S'} R_1R_2CHCH_2OR + NMe_3 \quad (3)$$

The overall tritium isotope effect was determined on **10** by

$$R_1R_2CHCHTNMe_3^+$$

10a, $R_1, R_2 = H$
10b, $R_1 = H$; $R_2 = CH_3$
10c, $R_1 = R_2 = CH_3$

reisolating unreacted starting material after fraction of reaction F_H and using its activity (R) and the activity of the original starting material (R_0) to calculate $(k_H/k_T)_{obsd}$ from eq 4.[14] The results are given in Table IV.

$$\left(\frac{k_H}{k_T}\right)_{obsd} = \frac{\log\,(1 - F_H)}{\log\,[(1 - F_H)R/R_0]} \quad (4)$$

These overall isotope effects are defined by eq 5, which can be

$$\left(\frac{k_H}{k_T}\right)_{obsd} = \frac{k_{H(E)} + k_{H(S)}}{k_{T(E)} + k_{T(S)}} \quad (5)$$

recast as eq 6 for purposes of calculating the isotope effect on the elimination process, $k_{H(E)}/k_{T(E)}$. The ratio $k_{H(S)}/k_{H(E)}$ is simply the substitution/elimination ratio (Table III), determined as described above. The ratio $k_{T(S)}/k_{H(S)}$ is the reciprocal of the tritium isotope effect on the substitution reaction.

Table III. Substitution and Elimination Products in the Reaction of $R_1R_2CHCH_2NMe_3^+$ with Sodium 1-Butoxide in 50% 1-Butanol–Dimethyl Sulfoxide at 70 °C

R_1	R_2	substitution,[a] %	elimination,[a] %	$k_{H(S)}/k_{H(E)}$[b]
H	H	2.06 ± 0.05	97.94 ± 2.25	0.0210 ± 0.0007
		1.93 ± 0.01	98.07 ± 5.25	0.0197 ± 0.0011
		2.00 ± 0.01	98.00 ± 1.99	0.0204 ± 0.0004
			mean	0.0204 ± 0.0007
H	CH_3	51.54 ± 1.91	48.46 ± 3.17	1.064 ± 0.080
		51.63 ± 1.07	48.37 ± 2.22	1.067 ± 0.053
		52.45 ± 0.50	47.55 ± 3.28	1.103 ± 0.077
			mean	1.08 ± 0.02
CH_3	CH_3	78.50 ± 0.30	21.50 [illegible] 0.23	3.651 ± 0.047
		78.37 ± 0.30	21.63 ± 0.30	3.623 ± 0.052
		78.20 ± 1.77	21.80 ± 0.16	3.587 ± 0.085
			mean	3.62 ± 0.03

[a] Each is the mean of three analyses with standard deviation of the mean. Errors are combined errors. [b] Errors in the mean values are standard deviations of the mean.

$$\frac{k_{H(E)}}{k_{T(E)}} = \frac{(k_H/k_T)_{obsd}}{1 + (k_{H(S)}/k_{H(E)})[1 - (k_{T(S)}/k_{H(S)})(k_H/k_T)_{obsd}]} \quad (6)$$

We could find in the literature no isotope effects on substitution reactions that are directly relevant to our system, although there is evidence that non-negligible effects result from deuteration of a trimethylammonio leaving group in E2 and E1 reactions.[15] Similarly, small (ca. 2% per D) inverse isotope effects are observed in quaternization of *N*,*N*-dimethyl-d_6-aniline.[16,17] The origin of these effects is uncertain. One recent suggestion is that the trimethylammonio group, whose protons bear partial positive charges, hydrogen bonds to solvent molecules but that this solvation is diminished as the group departs and loses its positive charge.[18] If that is the case, solvation of an ethyl, propyl, or isobutyl group in an NMe_2R leaving group should be less than that of a methyl group because of steric hindrance of solvation and (probably less important) an electron-releasing inductive effect. The isotope effect from α-tritium substitution in R then should be smaller than that for tritium substitution in methyl. In view of the uncertainties over the proper value for $k_{H(S)}/k_{T(S)}$, we have chosen a value of unity (no isotope effect) to calculate the $k_{H(E)}/k_{T(E)}$ values in Table V. Small values of $k_{H(S)}/k_{T(S)}$ (1.01 or less) would not affect the qualitative trend.

The figures for $k_{H(E)}/k_{T(E)}$ in the last column of Table V clearly support our hypothesis that the extent of C–N cleavage and of rehybridization at the α-carbon in the E2 reaction increases in the order ethyl < propyl < isobutyl. While the hypothesis can hardly be regarded as proved by this one set of isotope effects, it remains the one viable explanation of the three we have explored in this investigation, and no other plausible explanations have occurred to us.

Additional support is furnished by several observations. More importantly, the nonadditivity is *not* observed with the corresponding sulfonium salts,[6] where the steric requirements of the leaving group are less and where the C–S bond is longer than the C–N bond, further diminishing steric interactions.

The activation parameters in Table II also provide evidence of a change in transition-state character. The greater rate of loss

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Table IV. Counting Data and $(k_H/k_T)_{obsd}$ Values for the Reaction of $R_1R_2CHCHTNMe_3^+$ with Sodium 1-Butoxide in 50% 1-Butanol–Dimethyl Sulfoxide at 70 °C

R_1	R_2	F_H[a]	R_0[a]	R[a]	$(k_H/k_T)_{obsd}$[b,c]
H	H	0.7182 ± 0.0030	5.358 ± 0.014	6.040 ± 0.047	1.105 ± 0.007
		0.7308 ± 0.0046		6.065 ± 0.050	1.104 ± 0.010
		0.7504 ± 0.0001		6.136 ± 0.034	1.109 ± 0.007
				mean	1.106 ± 0.002
H	CH_3	0.4211 ± 0.0024	4.260 ± 0.019	4.396 ± 0.016	1.061 ± 0.012
		0.4678 ± 0.0029		4.413 ± 0.038	1.059 ± 0.016
		0.4951 ± 0.0032		4.457 ± 0.030	1.071 ± 0.014
		0.5201 ± 0.0007		4.470 ± 0.011	1.070 ± 0.008
		0.5349 ± 0.0037		4.483 ± 0.019	1.072 ± 0.009
				mean	1.067 ± 0.006
CH_3	CH_3	0.4629 ± 0.0028	8.617 ± 0.025	8.817 ± 0.040	1.039 ± 0.009
		0.5708 ± 0.0041		8.913 ± 0.009	1.042 ± 0.009
		0.6406 ± 0.0031		8.964 ± 0.097	1.040 ± 0.012
				mean	1.040 ± 0.002

[a] Each is the mean of three measurements with standard deviation of the mean. [b] Calculated from eq 4. Deviations are calculated from the standard deviations of F_H and R/R_0 (ref 8, pp 319–322). [c] Errors in the mean values are standard deviations of the mean.

Table V. Tritium Isotope Effects in the Reaction of $R_1R_2CHCHTNMe_3^+$ with Sodium 1-Butoxide in 50% 1-Butanol–Dimethyl Sulfoxide at 70 °C

R_1	R_2	$k_{H(S)}/k_{H(E)}$[a]	$(k_H/k_T)_{obsd}$[b]	$k_{H(E)}/k_{T(E)}$[c]
H	H	0.0204 ± 0.0007	1.106 ± 0.002	1.108 ± 0.0002
H	CH_3	1.08 ± 0.02	1.067 ± 0.006	1.150 ± 0.015
CH_3	CH_3	3.62 ± 0.03	1.040 ± 0.002	1.216 ± 0.012

[a] See Table III. [b] See Table IV. [c] Errors calculated from errors in $k_{H(S)}/k_{H(E)}$ and $(k_H/k_T)_{obsd}$ by standard methods of error analysis (ref 19). It is assumed in the calculation that $k_{H(S)}/k_{T(S)} = 1.00$. See text for discussion of this assumption.

of ethyl than of propyl (**1**) is dominated by the activation energy difference, with the preexponential factor (0.229 corrected for symmetry) actually unfavorable to ethylene production. The greater rate of loss of propyl than of isobutyl (**3**) is, in contrast, the result of a favorable preexponential factor (3.38 corrected for symmetry), which is partly counteracted by a higher energy of activation for propyl loss. Detailed analysis of these numbers is scarcely justified, but they at least emphasize that a quite different mix of effects governs the ethylene/propylene and propylene/isobutylene ratios. The results with **3** are consistent with the idea that the transition state for isobutyl loss has more double-bond character than that for propyl loss. The transition state for propyl loss should then be less rigid than that for isobutyl loss, and consequently be favored entropically (larger preexponential factor). Greater double-bond character of the transition state for isobutyl loss suggests more effective stabilization by the two β-methyl groups than by the one β-methyl group of propyl, which would explain the direction of the activation energy difference.

Experimental Section

Solvents. Distilled water was refluxed over potassium permanganate for 2 h and distilled. Absolute ethanol was refluxed with magnesium turnings for at least 8 h and distilled. *n*-Butyl alcohol was refluxed over sodium *n*-butoxide and distilled, or stirred over and distilled twice from calcium hydride. Fisher ACS grade dimethyl sulfoxide was stirred over calcium hydride for at least 2 days and distilled at reduced pressure. Diglyme was refluxed over lithium aluminum hydride and distilled. The first 10% of distillate from each solvent was discarded.

Ethanol-*1,1-d*$_2$ was obtained in 81% yield by the reduction of acetyl chloride with lithium aluminum deuteride in dry diglyme.[20]

Propionitrile-*α,α-d*$_2$. Ethanol-*1,1-d*$_2$ was converted to the tosylate in 75% yield by the usual procedure.[21] The tosylate was stirred for 5 h at 90 °C with 11.3 g of sodium cyanide in 180 mL of dimethyl sulfoxide. Distillation yielded 66% of product, bp 93–96 °C (lit.[22] bp 97 °C).

1-Propylamine-*2,2-d*$_2$ was obtained in 41% yield by reducing propionitrile-*α,α-d*$_2$ with lithium aluminum hydride in diglyme by the same procedure as for ethanol-*1,1-d*$_2$.[20] The product had bp 44–48 °C (lit.[22] bp 48 °C).

***N*-1-Propyl-*2,2-d*$_2$-isobutyramide** was obtained by the reaction of 1-propylamine-*2,2-d*$_2$ (0.059 mol), isobutyryl chloride (0.065 mol), and triethylamine (0.12 mol) in 20 mL of benzene with cooling. The mixture was stirred overnight, water added, and the amide extracted with methylene chloride. Evaporation of the solvent afforded 7.6 g of crude product which was used directly in the next step without further purification.

Isobutyl-1-propyl-*2,2-d*$_2$-amine was obtained in 65% yield by reducing *N*-1-propyl-*2,2-d*$_2$-isobutyramide with lithium aluminum hydride by Moffett's procedure.[23] The product had bp 123–30 °C (lit.[5] bp 123–125 °C).

Isobutyl-1-propyl-*2,2-d*$_2$-dimethylammonium iodide was obtained by methylating isobutyl-1-propyl-*2,2-d*$_2$-amine with formaldehyde and formic acid,[24] followed by treatment of the resulting tertiary amine with methyl iodide in dry ether. The hygroscopic product was recrystallized from ethanol–ether and dried under vacuum. It had mp 193–194 °C (lit.[5] mp 194–194.6 °C). Unlabeled material, prepared as above, had mp 194–194.6 °C.

2-Propanol-*2-d* was obtained in 97% yield by the reduction of acetone with lithium aluminum deuteride by using the same procedure as for ethanol-*1,1-d*$_2$ above.

2-Bromopropane-*2-d* was obtained in 67% yield from 2-propanol-*2-d* by treatment with HBr.[25] The product had bp 59 °C (lit.[22] bp 59 °C).

2-Methylpropanoic-*2-d* acid was obtained by carbonation of the Grignard reagent of 2-bromopropane-*2-d* according to a standard procedure.[26] The product was obtained in 41% yield, bp 153–159 °C (lit.[22] bp 153–154 °C).

***N*-Propyl-2-methylpropanamide-*2-d*.** The 2-methylpropanoic-*2-d* acid (0.067 mol) was refluxed with 0.067 mol of thionyl chloride for 2 h and then cooled in an ice bath and treated with 0.20 mol of propylamine in 50 mL of toluene. The toluene was removed by distillation and the amide purified by vacuum distillation, bp 144–148 °C (45 mm). The yield was 79%.

(2-Methyl-1-propyl-*2-d*)-1-propyldimethylammonium iodide was obtained from *N*-propyl-2-methylpropanamide-*2-d* by the procedure used for isobutyl-1-propyl-*2,2-d*$_2$-dimethylammonium iodide (above). The product had mp 193–194.5 °C (lit.[5] mp 194–196 °C).

***N,N*-Dimethyl-1-propylamine** was obtained by treating 1-propylamine with formic acid and formaldehyde.[24] The ethereal solution was used directly in the next synthesis.

Ethyl-*2,2,2-d*$_3$-1-propyldimethylammonium Iodide. Ethanol-*2,2,2-d*$_3$ was obtained by reduction of acetic-*d*$_4$ acid.[20] The tosylate was made[21]

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and converted to ethyl-*2,2,2-d_3* iodide.[27] The acetone solution of the iodide was refluxed with 1-propyldimethylamine (see above). The hygroscopic product was precipitated with ether and dried under vacuum at 78 °C. Unlabeled material was prepared by the same procedure. NMR (in Me_2SO-d_6) δ 0.96 (t, 3 H), 1.32 (t, 3 H), 1.52–2.0 (m, 2 H), 3.16 (s, 6 H), 3.2–3.6 (m, 4 H).

Ethanol-*1-t* was obtained by reducing 0.3 mol of acetyl chloride with sodium borohydride-*t*. The chloride in 10 mL of diglyme was first added to 0.1 mol of the borohydride-*t* in 60 mL of diglyme, the mixture heated at 50 °C for 2 h and cooled in an ice bath, and an additional 0.2 mol of unlabeled borohydride in 100 mL of diglyme added. The mixture was refluxed for another 2 h and cooled in ice and 165 g of 2-(2-ethoxyethoxy)ethanol added. The crude product was distilled from the mixture and redistilled through a 10-cm column: bp 78.6–79 °C (lit.[22] bp 78.5 °C); yield 65%; molar activity 20.63 mCi mol^{-1}.

1-Propanol-*1-t* was obtained from propionyl chloride and sodium borohydride-*t* in the same manner as above: bp 97 °C (lit.[22] bp 97.4 °C), yield 87%; molar activity 7.00 mCi mol^{-1}.

2-Methyl-1-propanol-*1-t* was obtained from isobutyryl chloride and sodium borohydride-*t* in the same manner as above: bp 108–109 °C (lit.[28] bp 106–108 °C (748 mm)); yield 70%; molar activity 8.35 mCi mol^{-1}.

Ethyl-*1-t* Bromide. Ethanol-*1-t* was diluted with unlabeled ethanol and treated with phosphorus tribromide by the procedure of Noller and Dinsmore.[29] The product had bp 36–37 °C (lit.[22] by 38–39 °C), yield 53%, and molar activity 5.63 mCi mol^{-1}.

1-Propyl-*1-t* bromide was prepared from 1-propanol-*1-t* by the same procedure as above.[29] The product had bp 66–67 °C (lit.[29] bp 70–73 °C), yield 51%, and molar activity 6.98 mCi mol^{-1}.

2-Methyl-1-propyl-*1-t* bromide was prepared from 2-methyl-1-propanol-*1-t* by the same procedure as above.[29] The product had bp 90–92 °C (lit.[29] bp 91–93 °C), yield 64%, and molar activity 8.03 mCi mol^{-1}.

Ethyl-*1-t*-trimethylammonium Bromide. Ethyl-*1-t* bromide (0.18 mol) in 20 mL of dry ether in a pressure bottle was cooled to °C and 0.20 mol trimethylamine added. The bottle was sealed and the mixture stirred for 2 days. The precipitate was filtered and recrystallized repeatedly from ethanol–ether to constant molar activity (5.358 mCi mol^{-1}). The yield was 87% and the mp 334 °C dec (lit.[6] mp 338 °C (sealed, evacuated tube)).

1-Propyl-*1-t*-trimethylammonium bromide was prepared from 1-propyl-*1-t* bromide by the above procedure to give 82% of product: mp 265 °C dec (lit.[6] mp 265 °C dec); molar activity 4.260 mCi mol^{-1}.

(2-Methyl-1-propyl-*1-t*)-trimethylammonium bromide was prepared from 2-methyl-1-propyl-*1-t* bromide by the above procedure to give 82% of product: mp 237–237.5 °C (lit.[6] mp 240 °C); molar activity 8.617 mCi mol^{-1}.

Eliminations from Deuterium-Labeled Quaternary Ammonium Salts. The substrate (ethyl-1-propyldimethylammonium iodide or (2-methyl-1-propyl)-1-propyldimethylammonium iodide and their labeled analogues) was dissolved in 50 mol % 1-butanol–dimethyl sulfoxide, and the base was prepared by dissolving sodium in 1-butanol and diluting with dimethyl sulfoxide to a 50 mol % mixture. The solutions were equilibrated separately before mixing, and concentrations were such as to give 10 mL of final solution 0.4 M in base and 0.04 M in substrate. The reaction vessel was a three-neck, round-bottom flask with a magnetic stirrer in a constant-temperature bath. A syringe needle for nitrogen bubbling was fitted through a septum in one side neck, and the other side neck was closed. The center neck carried a condenser, and the gases passing through the condenser were led through a calcium chloride drying tube, an ice–water trap, and finally a liquid nitrogen trap. The reaction was allowed to proceed 2–12 h (depending on temperature) with nitrogen bubbling through the mixture. The reaction mixture was then quenched with 20 mL of water, and nitrogen bubbling was continued for 40 min to 2 h (depending on temperature). The liquid nitrogen trap was evacuated to 0.5–1.0 torr and connected to the gas-sampling valve of the Hewlett-Packard Model 5730A gas chromatograph. After warming to room temperature, the gaseous olefin mixture in the trap was expanded into the 0.125-mL sample loop, and 3–4 injections were made. A 6-ft Poropak N column was used with helium carrier gas and a flame ionization detector.

Control Experiments. Response factors for the different olefins were determined by making synthetic mixtures of known composition by vacuum-line techniques. These were expanded into the sample loop as in the product analyses, and the percentages determined by GC showed that response factors were proportional to the number of carbon atoms.[31] To ensure that all olefinic reaction products were carried into the liquid nitrogen trap for analysis, an experiment was performed in which a new trap was placed in the line after the nitrogen bubbling as described above was complete, and bubbling was continued for another 2 h. No detectable amount of product was found in the second trap.

Kinetics of Reaction of Alkyltrimethylammonium Salts. The times required to achieve the desired fractions of reaction in the isotope-effect studies (below) were determined as follows. Into each of eight stainless-steel ampules was pipetted 5 mL each of 0.302–0.304 M alkyltrimethylammonium salt in 50 mol % 1-butanol–dimethyl sulfoxide and 0.338–0.360 M sodium 1-butoxide in the same solvent. The ampules were sealed and placed in a thermostatted oil bath at 70 ± 0.2 °C. Two ampules were withdrawn after 10 min and cooled in dry ice–acetone. Three 1-mL aliquots from each ampule were pipetted into three 30-mL volumes of 50% by volume 2-propanol–pyridine and titrated with standard hydrochloric acid. Thymolphthalen in pyridine (1%) was used as indicator. Results from the 10-min samples were taken as initial base concentration (10 min is negligible compared to half-lives of 8–120 h). Ampules were withdrawn periodically thereafter and aliquots titrated in the same way. Titration of a base-substrate solution kept at room temperature for 4 h showed no significant change in concentration. Titration of base solution kept at 70 °C for 156 h showed no significant change, indicating no attack of base on the stainless steel ampule.

Determination of $(k_H/k_T)_{obsd}$. Ampules prepared as above, using tritium-labeled alkyltrimethylammonium salt, were thermostated at 70 ± 0.2 °C for a time sufficient to give 50–75% reaction. Three aliquots (1 mL) from each ampule were titrated as above to determine the fraction of reaction. The remainder of the solution in each ampule was treated with 2 equiv of sodium tetraphenylborate in 100 mL of water. The precipitated ethyltrimethylammonium and 1-propyltrimethylammonium tetraphenylborates were recrystallized from acetonitrile–dioxane at least three times, while the 2-methyl-1-propyltrimethylammonium tetraphenylborate was similarly recrystallized from acetone–water. The precipitates were ground to fine powders and dried at 100 °C for at least 10 h. Three samples of each precipitate were weighed into scintillation counter vials and dissolved in 1 mL of acetonitrile, and 15 mL of Ready-Solv HP scintillation cocktail (Beckman) was added. Initial activities (R_0) were similarly determined on the tetraphenylborates of the unreacted alkyltrimethylammonium salts. Counting was to 0.2% (2σ) precision, and quench corrections were determined as before.[32]

Determination of Substitution/Elimination Ratio. Substitution and elimination products were determined on two separate ampules withdrawn at the same time when the reaction was >98% complete. The substitution products were analyzed on a Hewlett-Packard 5730A gas chromatograph using a 12 ft × 0.125 in. column of Chromosorb 101 at 175 °C and a flame ionization detector. The alkyl 1-butyl ethers used as standards were prepared by Vogel's procedure[33] and the tertiary amines by Caspe's procedure.[34] Only substitution products from attack on CH_3 of $RN(CH_3)_3^+$ were found; none from attack on R were detected. Quantitative analysis for methyl 1-butyl ether was performed by using *n*-hexane as an internal standard. For the elimination products, the ampule was cooled in liquid nitrogen, opened, and connected to a bubbler containing 50 mL of ca. 0.125 M bromine in dichloromethane. Nitrogen gas was gently bubbled through the reaction mixture for 2 h as the ampule was gradually heated to 50 °C. Part of the dichloromethane (ca. 30 mL) was distilled off and the rest of the solution transferred quantitatively to a 50-mL volumetric flask and diluted to the mark with more dichloromethane. The dibromides were analyzed by gas chromatography with use of a 6 ft × 0.125 in column of Carbowax 20 M on 60/80 mesh Chromosorb P-AW at 100 °C. Purified diglyme was used as internal standard. As a control, tetraethylammonium bromide was subjected to the procedure and 101.1 ± 2.1% of 1,2-dibromoethane obtained. The column was changed after each analysis to avoid contamination by residual bromine in the solution of dibromides.

Registry No. 1, 44657-87-6; **1** (bromide), 84697-18-7; **2**, 92623-05-7; **2** (bromide), 92623-28-4; **3**, 92623-06-8; **3** (bromide), 92623-29-5; **4**, 92623-07-9; **4** (bromide), 92623-30-8; **5**, 92623-08-0; **5** (bromide),

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Asymmetric Synthesis via Acetal Templates. 10.[1] Aldol-Type Reactions. Preparation of a Nonactic Acid Intermediate

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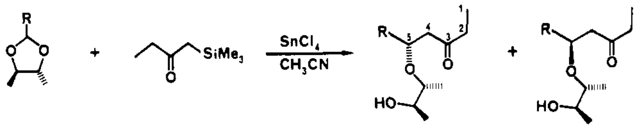
Abstract: A procedure has been developed for the coupling of acetals **4**–**7** derived from (*R*,*R*)-2,4-pentanediol with α-silyl ketones or enol silyl ethers to give aldol ethers **8**/**9** in excellent yield and high diastereoselectivity, **8**:**9** = >95:5. This methodology has been applied to a total asymmetric synthesis of (2*S*,4*R*)-2,4-dihydroxyoct-7-ene, a key intermediate in the Bartlett synthesis of nonactic acid.

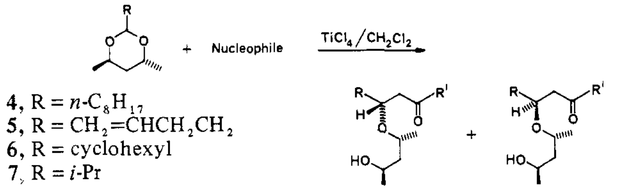
McNamara and Kishi[2] were the first to disclose the use of chiral acetals in aldol-type reactions.[3] Thus for the coupling **1** + **2**, the diastereoselectivity of **3a**:**3b** was excellent (91:9–94:6) with aromatic acetals **1** (R = aryl), while it was lower (50:50–76:24) with aliphatic acetals. The absolute configuration of the major aldol products **3a** was the same as that observed by us for a variety of asymmetric acetal coupling reactions.[1,4]



1 2 3a 3b

The present paper includes an account of some of our work in this area which differs from the Harvard study[2] in that excellent diastereoselectivity (>95:5) can now be realized with aliphatic acetals. We have used six-membered ring acetals derived from 2,4-pentanediol which affords the advantage of being readily available in the *S*,*S* as well as the *R*,*R* forms.[5] These acetals have already been shown to react highly diastereoselectively with a variety of nucleophilic partners to give products from which the chiral auxiliary is easily removed.[1,4] Some of our studies of the $TiCl_4$-catalyzed aldol reaction are summarized in Table I.

Table I. Aldol Coupling of Chiral Acetals



4, R = *n*-C_8H_{17}
5, R = CH_2=$CHCH_2CH_2$
6, R = cyclohexyl
7, R = *i*-Pr

8 **9**

a, R = *n*-C_8H_{17}; R′ = Me
b, R = *n*-C_8H_{17}; R′ = *t*-Bu
c, R = CH_2=$CHCH_2CH_2$; R′ = Me
d, R = cyclohexyl; R′ = Me
e, R = *i*-Pr; R′ = Et
f, R = *n*-C_8H_{17}; R′ = Et

entry	acetal[4a,b,6]	nucleophile[7,8]	% yield[9]	product[10]	ratio[11]
1	**4**	$CH_3COCH_2SiMe_3$ (**10**)	92	**8a**/**9a**	97:3
2	**5**	$CH_3COCH_2SiMe_3$	93	**8c**/**9c**	97:3
3	**6**	$CH_3COCH_2SiMe_3$	93	**8d**/**9d**	98:2
4	**5**	CH_2=$C(OSiMe_3)Me$	89	**8c**/**9c**	97:3
5	**7**[10]	**2**	48	**8e**/**9e**	95:5
6	**7**	CH_2=$C(OSiMe_3)Et$	84	**8e**/**9e**	96:4
7	**4**	CH_2=$C(OSiMe_3)Et$	95	**8f**/**9f**	97:3
8	**4**	CH_2=$C(OSiMe_3)$-*t*-Bu	96	**8b**/**9b**	96:4

After extensive experimentation a procedure has been developed for obtaining excellent results using enol silyl ethers as the nucleophile (entries 4 and 6–8). Trimethylsilylacetone (**10**) is just as effective in the condensations (entries 1–3) as the enol silyl ether of acetone (entry 4), and it is easier to prepare, handle, and store. No attempt was made to optimize the yield of the coupling with trimethylsilylbutanone (entry 5), which is a slower process than with the corresponding enol silyl ether (entry 6). Use of the latter

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