A Stereochemical Approach toward a More Detailed Understanding of Electron Impact Induced Elimination Reactions[1,2]

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Abstract: Electron impact induced elimination reactions involving the loss of small molecules, such as water and hydrogen chloride from alcohols and chlorides, possess considerable potential for the application of mass spectrometry to stereochemical problems. In the present work the elimination of water and hydrogen chloride has been found to obey identical steric driving forces in acyclic systems following the observation of equivalent propensity for the abstraction of the *pro-R* over the *pro-S* hydrogen at C-4 in (*S*)-2-pentyl alcohol and chloride. This similarity is not extended entirely in cyclohexanol and cyclohexyl chloride. Diastereotopic deuterium labeling has revealed that 1,4 elimination in both compounds is stereospecific while the 1,3 process is only stereospecific in the chloride. Ring opening has been proposed as a prerequisite to 1,3 elimination in cyclohexanol and this hypothesis allows correlation of the apparently dissimilar behavior of cyclic and acyclic alcohols and as well explains such anomalous results as a 90/1 difference for loss of water from the stereoisomers of 4-*t*-butylcyclohexanol while the derived chlorides exhibit stereoinsensitive loss of hydrogen chloride. Deuterium scrambling is found not to intervene in both low and high voltage measurement in these systems and thus offers a counterpoint to recent examples in ketones. A general theory is proposed connecting site selective hydrogen abstracting elimination reactions to the size of the heteroatom involved and findings on the model compounds studied here suggest that ground-state interatomic distances may be extrapolated to the ionized states in the mass spectrometer and thereby used to predict the positions of hydrogen abstraction.

The mass spectra of aliphatic alcohols and chlorides appear straightforward. Elimination of the functional group as HX is a highly favored fragmentation[4] as might be assumed, resting on analogy with thermal processes.[5] This seeming analogy breaks down on detailed examination. Deuterium labeling studies[6-8] have demonstrated, in contrast to pyrolysis,[5] that loss of water and hydrogen chloride do not occur by a 1,2 elimination. Even more striking is the fact that the hydrogen involved in the loss of water from acyclic alcohols comes unexpectedly and with high specificity from C-4 while loss of hydrogen chloride from acyclic chlorides[8] occurs predominantly by hydrogen abstraction from C-3 (Figure 1). Additional interest in these eliminations arises from the behavior of the diastereomers of 4-*t*-butylcyclohexanol and its derived chloride. That is, while the alcohols demonstrate high stereospecificity for water loss, the chloride isomers (Figure 2)[9] exhibit little difference for elimination of hydrogen chloride.

Following the expectation that bond-forming reactions (*i.e.*, rearrangements) will best allow the application of mass spectrometry to stereochemical problems,[10,11] and noting the common occurrence of these simple eliminations, we were prompted to investigate these processes in more detail.

Results

Pentyl Alcohol and Pentyl Chloride. The reason for the difference in site selectivity for loss of hydrogen chloride and water is not readily apparent. Both fragmentations are not a function of source pressure,[12] and thus are unimolecular, and as well likely take place in one step from the respective molecular ions, since corresponding metastable peaks are observed.[13]

Study of the elimination of water from the secondary alcohol 2-pentanol allows a new kind of insight into the mechanism. By virtue of the chiral carbon in 2-pentanol, each methylene group now presents to the hydroxyl function stereochemically distinguishable (diastereotopic) hydrogens for abstraction and formation of water. These arguments apply identically to the 2-pentyl chlorides. If one could substitute deuterium in turn for the diastereotopic hydrogens on the methylene group of interest (*e.g.*, C-4), the details of the approach of the X group might be revealed by observing the relative propensity for abstraction of the diastereotopic deuteriums. This goal may be reached

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[1] This work was supported by grants from the Petroleum Research Fund of the American Chemical Society, Research Corporation and the National Institute of General Medical Sciences.

[2] Portions of this work have been reported: M. M. Green and J. Schwab, *Tetrahedron Lett.*, 2955 (1968); M. M. Green, *J. Amer. Chem. Soc.*, 90, 3872 (1968); M. M. Green and R. J. Cook, *ibid.*, 91, 2129 (1969).

[3] (a) National Science Foundation Summer Fellow, 1968; (b) visiting professor on leave from B. S. College, Dinapore, Magadh University, Bihar, India.

[4] For early studies discussing these fragmentations, see F. W. McLafferty, *Anal. Chem.*, 34, 2 (1962); R. A. Friedel, J. L. Schultz, and A. G. Sharkey, Jr., *ibid.*, 28, 926 (1956).

[5] A. Maccoll, *Chem. Rev.*, 69, 33 (1969).

[6] W. Benz and K. Biemann, *J. Amer. Chem. Soc.*, 86, 2375 (1964).

[7] S. Meyerson and L. C. Leitch, *ibid.*, 86, 2555 (1964).

[8] A. M. Duffield, S. D. Sample, and C. Djerassi, *Chem. Commun.*, 193 (1966).

[9] The alcohols have been reported by (a) C. E. Brion and L. D. Hall, *J. Amer. Chem. Soc.*, 88, 3661 (1966); (b) L. Dolejš and V. Hanuš, *Coll. Czech. Chem. Commun.*, 33, 332 (1968); (c) M. M. Green, R. J. Cook, W. Rayle, E. Walton, and M. F. Grostic, *Chem. Commun.*, 81 (1969). We have measured the spectra of the chlorides in the present work.

[10] S. Meyerson and A. W. Weitkamp, *Org. Mass. Spectrosc.*, 1, 659 (1968).

[11] R. B. Roy and M. M. Green, 158th National Meeting of the American Chemical Society, New York, N. Y., 1969, Abstract O-64.

[12] There is no significant change in the relative intensity of the M − HX peaks as a function of pressure in the source on either the MS-902 or the CEC-103C. In addition the relative intensity of metastable peaks for loss of water from cyclohexanol is independent of the pressure in both the source and the analyzer region of the MS-902 mass spectrometer.

[13] See F. W. McLafferty and R. B. Fairweather, *J. Amer. Chem. Soc.*, 90, 5915 (1968), for a discussion of metastable abundances including the systems of interest here.

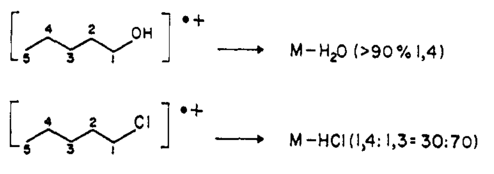
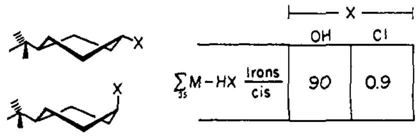


Figure 1.



ΣM-HX $\frac{\text{trans}}{\text{cis}}$	OH	Cl
	90	0.9

Figure 2. Numerical values are the percentages of total ionization above *m/e* 35.

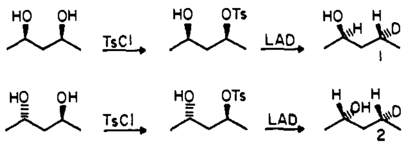


Figure 3. All compounds are racemic. Only one enantiomer is shown. LAD(H) stands for lithium aluminum deuteride (hydride).

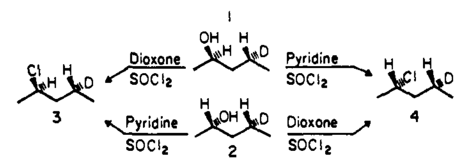


Figure 4.

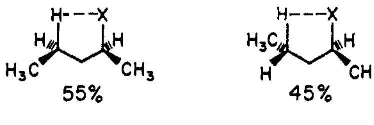


Figure 5. X = Cl, OH. The percentages shown are derived from Table I and have been corrected for the expected[16] 10–20% nonstereospecific deuterium incorporation in the displacement of tosylate by lithium aluminum deuteride.

utilizing the available isomers of 2,4-pentanediol.[14] Figure 3 summarizes the preparation of the necessary epimers (**1** and **2**) of 4-deuterio-2-pentanol in this manner.

Each isomer (**1** and **2**) in turn has been converted[15] to the additionally desired chloride diastereomers, thereby precluding the intervention of artifacts of preparation in these measurements. Figure 4 outlines these stereospecific conversions to the chlorides while Table I presents the mass spectral data for elimination of H(D)X from these materials.

Table I[a,b]

	1	2	3	4
[M − DX]/([M − DX] + [M − HX]) × 10²	3.3	3.9	26	30

[a] X = OH, Cl on CEC-103C mass spectrometer. [b] Data taken with source near ambient temperature and voltage near threshold. The differences between the isomers was about 50% of above under 70-eV conditions. The spectra were indistinguishable on various runs and the difference between **3** and **4** prepared by the alternative routes (Figure 4) was the same. For **3** and **4** the loss of chlorine radical (M − Cl) was the same relative intensity for both isomers and again was independent of precursor (**1** or **2**, Figure 4).

It is at first apparent from inspection of Table I that the overall difference in site selectivity (see above) is maintained in the secondary alcohols and chlorides. The high abstraction of the deuterium label at C-4 in the chlorides (**3** or **4**) follows the preferred 1,3 elimination in acyclic primary chlorides,[8] while the much lower loss of DOH from **1** and **2** corresponds to the favored 1,4 elimination from alcohols.[6,7] More significantly the results reveal that in spite of the markedly different site selectivities, both X groupings (OH or Cl) prefer the same face of the C-4 methylene and further that this preference is quantitatively similar in the alcohol and chloride (3.3/3.9 ≅ 26/30, Table I). In the abstraction step, these data (Table I) strongly suggest that the steric relationships are the same for the two functional groups. The simplest and most straightforward representation of these facts is shown in Figure 5.

It is remarkable that the difference between the diastereotopic deuteriums[17] is measurable at all. Indeed, if we proposed a structural connection between the hypothesized electron impact transition states and the isomers of *cis*- and *trans*-1,3-dimethylcyclopentane, we would be rewarded by the apparent correspondence. Thus, the *cis* isomer of 1,3-dimethylcyclopentane is stabilized over the *trans* by a few hundred calories per mole[18] matching the favored state exhibited in Figure 5. Whatever the efficacy of such arguments of correspondence,[19] it is clear that elimination of water and hydrogen chloride takes place by an identical mechanism in spite of the disparity in site selectivity.

Cyclohexanol and Cyclohexyl Chloride. Site Selectivity. The elimination of water from cyclohexanol has been found[20] to occur by essentially equal abstraction of hydrogens from C-4 and C-3(5). In order to determine the limits for the difference in site selectivity in chlorides and alcohols, we have prepared the deuterated compounds needed to gauge the positions of hydrogen abstraction in cyclohexanol and cyclohexyl chloride under identical conditions. Table II summarizes our findings while Figure 6 outlines the synthetic route to the labeled molecules.

The results (Table II) demonstrate first that 1,2 elimination is not the route to loss of HX. Further inspection reveals a fact of more immediate significance.

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[14] J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, **28**, 1545 (1963).

[15] C. E. Boozer and E. S. Lewis, *J. Amer. Chem. Soc.*, **75**, 3182 (1953); W. A. Cowdrey, E. D. Hughes C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937).

[16] G. K. Helmkamp and B. F. Rickborn, *J. Org. Chem.*, **22**, 479 (1957); W. A. Sanderson and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 4185 (1966).

[17] Diastereotopic by external comparison: see K. Mislow and M. Raban, "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967, p 1 *ff.*

[18] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 202.

[19] Research is in progress utilizing diastereotopic deuterium incorporation, to probe a range of 1,*n*-abstraction reactions in both condensed phase (*e.g.*, Barton, Hofmann-Loeffler) and mass spectrometry.

[20] H. Budzikiewicz, Z. Pelah, and C. Djerassi, *Monatsh. Chem.*, **95**, 158 (1964).

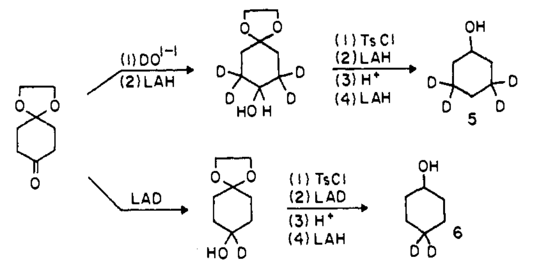
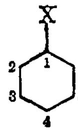


Figure 6. The compounds deuterated at C-1 and C-2 were prepared from cyclohexanone in a straightforward manner. See Experimental Section for details. The chlorides were prepared from the alcohols with phosphorus pentachloride.

Whereas the pentyl system (Figure 1) allowed substantially different paths for loss of water and hydrogen chloride, the cyclohexyl ligand appears to draw the two elimination mechanisms together.[21] This result could be imagined to arise from some restrictive influence of the ring (*e.g.*, conformation) forcing the similar site selectivities. In fact, this argument appears more reasonable in the light of experiments on substituted alicyclic alcohols showing stereoisomeric effects[22] and thus suggesting that the ring does not suffer cleavage prior to elimination. The experiments described below reveal that the fundamental mechanisms for the eliminations from cyclohexanol and cyclohexyl chloride are different and that the similarity in the site selectivities is a coincidence.

Table II[a,b]



$\longrightarrow [C_6H_{11}X]^{+\cdot} \longrightarrow HX + [C_6H_{10}]^{+\cdot}$

	Abstraction site			
	1	2	3	4
OH	0	≤6	41	55
Cl	0	0	44	46

[a] Spectra taken at 70 eV on a CEC-103C mass spectrometer with inlet at ambient temperature and source at ~125°. The difference between the totals in each case and 100% is due to the operation of a small isotope effect (*ca.* 0.9). [b] Elimination from C-3 involved loss of DOH and D_2O (32%:9%).

Stereochemistry of Elimination in Cyclohexanol and Cyclohexyl Chloride. A possible factor, excluded for the acyclic cases, in the site selectivity of cyclohexyl compounds is for elimination of HX to be preceded by cleavage of the ring.[23] Since stereospecific deuterium labeling offers a means of detecting such behavior, we have prepared the compounds outlined in Figure 7 to determine the ring integrity in the 1,4 elimination. The mass spectral data for the abstraction of HX and DX from these labeled materials (**7–10**) are exhibited in Table III.

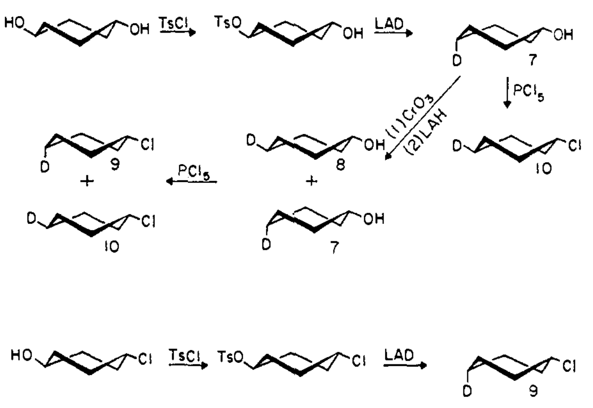


Figure 7. Details in the Experimental Section.

Table III[a,b]

	OH		Cl		
	7	7 and 8	9	10	9 and 10
M − HX/M − DX	49/39	65/24	39/32	67/4	56/15
Σ[(M − HX) + (M − DX)]	88	89	71	71	71

[a] All data taken at 70 eV and 125° on a CEC-103C mass spectrometer. [b] The numerical values are the calculated percentages of the total ionization of the group of peaks (peak group) surrounding the ion for H(D)X loss.

The first important feature in Table III is the invariance of the summation (Σ) of the competing processes. This value, which is lower for the chlorine ligand because of significant contribution to the peak group from M − Cl, demonstrates not only the absence of extraneous ions in these measurements but also that the abstraction of more or less isotope does not affect the intensity of other competing fragmentations. The data also reveal that the 1,4 elimination in both cyclohexanol and cyclohexyl chloride is highly stereospecific. In both cases, conversion of the *cis*-deuterio compounds (**7** or **9**) to the mixture of epimers (**7** and **8** or **9** and **10**) decreases the loss of DX substantially. In addition, in the case of *trans*-4-deuteriocyclohexyl chloride (**10**) the loss of DCl is lowered significantly further as would be expected if the elimination had a stereospecific requirement for a *cis* C-4 hydrogen. In fact, these data allow us to be quantitative about these processes. Since averaging the observed values of M − HX and M − DX for **9** with 71/0 yields the observed value for the mixture **9** and **10** (Table III), we may conclude first that the 1,4 elimination of hydrogen chloride from cyclohexyl chloride is 100% stereospecific and second that **10** (M − HX/M − DX = 67/4) is formed in less than epimeric purity.

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(21) The absence of significant scrambling of deuterium in the eliminations described is evidenced by measurements at low electron voltage. At a nominal 9 eV on the CEC-103C the data show an increase of abstraction from C-4 from 55% (Table II) to 61% or in other words, an increased loss of DOH from the molecule (**6**) with less deuterium. Abstraction from C-3(5) decreases from 41 to 34%. Scrambling should increase, if present, at lower beam energies. See A. N. H. Yeo and D. H. Williams, *J. Amer. Chem. Soc.*, **91**, 3582 (1969), for an enlightening discussion and demonstration of a system which exhibits such scrambling.

(22) (a) See ref 9, 10, and 11 and references therein as well as C. G. MacDonald, J. S. Shannon, and G. Sugowdz, *Tetrahedron Lett.*, 807 (1963); H. Egger and G. Spiteller, *Monatsh. Chem.*, **97**, 579 (1966); V. I. Zaretskii, N. S. Wulfson, V. G. Zaikin, V. N. Leonov, and I. V. Torgov, *Tetrahedron*, **24**, 2339 (1968), and previous papers in that series; R. F. Chandler, R. G. Coombe, and T. R. Watson, *Tetrahedron Lett.*, 1729 (1968); A. F. Thomas, B. Willhalm, and J. H. Bowie, *J. Chem. Soc., B*, 392 (1967); A. F. Thomas and B. Willhalm, *ibid.*, 219 (1966); (b) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day Publishers, San Francisco, Calif., 1967, p 107 ff, and references therein.

(23) Ample precedent exists for this cleavage in alcohols while little evidence can be found for it in chlorides. See ref 22b, Chapters 2 and 12.

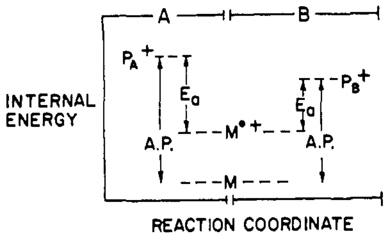

Figure 8. Energetic competition involving differing energies of activation leading to change in relative rates with beam energy. A and B represent two competitive reactions; A.P. is the appearance potential; E_a is the activation energy. These drawings are idealized. They actually represent a range of energy states.

Indeed, since a small isotope effect does operate, the diastereomeric composition of sample **10** may be calculated to be at best 90% *trans*-4-deuterio (**10**) and 10% *cis*-4-deuteriocyclohexyl chloride (**9**). Since **10** is derived from **7**, and if one assumes 100% stereospecificity in the phosphorus pentachloride reaction,[24] the epimeric compositions may be equated. Since the mixture of **7** and **8** must be essentially 50:50 (Figure 7), the ratio one would obtain for pure **7** if the 1,4 process in cyclohexanol were 100% stereospecific would be 41/47. The value experimentally determined for **7** (49/39) demonstrates that we are observing 80% *cis* and 20% *trans* elimination from C-4. Since **7** is a mixture (see above) of at best 90% *cis*-4-deuterio and 10% *trans*-4-deuteriocyclohexanol this requires a minimum stereospecificity of 80% (90% *cis*:10% *trans*) for the 1,4 elimination of water from cyclohexanol.

In any competitive kinetic situation the competing reactions must wane and wax as a function of energy if their activation energies are different.[25] It follows that measurement of the ratio of the abundances of two ions as a function of beam energy must reveal which has the higher appearance potential. If the two ions of interest arise from the same precursor, the data necessarily tell us the relative absolute energies of the transition states for reaction.[26] Figures 8 and 9 exhibit these relationships, and show why two such reactions with respectively differing and identical absolute energies of their activated states must possess respectively different and identical appearance potentials. Brown[27] has neatly circumvented the problem of reactions from different precursors in studies concerning the intervention of position scrambling in aromatics, by choosing starting *meta* and *para* positional isomers. The latter compounds have essentially identical heats of formation and thus lead to the energetic situations comparable to those discussed above (Figures 8 and 9). This technique, used by Brown,[27] has been termed "wide range electron energy kinetics." In the competitive reactions of interest here, *i.e.*, 1,4 *vs.* 1,3 elimination or 1,4 stereospecific *vs.* 1,4 nonstereospecific elimination, fragmentation occurs from a common ion, namely the molecular ion and thus as discussed above, the change in ratio of relative abundance of these competing reactions as a function of electron energy must reveal the relative heights of the intervening transition states. The low voltage data on the deuterated cyclohexanols[21] therefore require that the transition state for the 1,4 elimination be energetically favored over that for the 1,3 process. We have further taken the low electron voltage spectra of the stereospecifically deuterated compounds (**7–10**). These data are presented in Table IV.

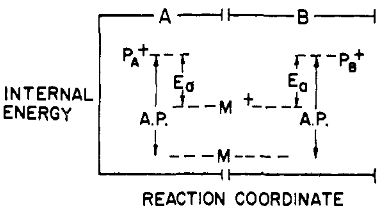

Figure 9. Energetic competition involving identical energies of activation leading to no change in relative rates with beam energy; see caption to Figure 8.

Table IV[a,b]

	OH		Cl		
	7	**7** and **8**	**9**	**10**	**9** and **10**
M − HX/M − DX	50/47	69/30	48/43	82/7	69/20
Σ[(M − HX) + (M − DX)]	97	99	91	89	89

[a] All spectra were taken at a nominal 9 eV and 125° on a CEC-103C mass spectrometer. [b] See footnote *b* to Table III.

First, these data reinforce our earlier conclusions about lack of significant scrambling as a factor in these measurements.[21] The high stereospecificity observed in the high energy measurements is maintained here. In quantitative detail, the values for **9** (48/43) and **9** and **10** (69/20) demonstrate that **10** is formed in about 90% steric purity (see discussion following Table III). Thus, in the change from 70 to 9 eV the stereospecificity of 1,4 elimination of hydrogen chloride from cyclohexyl chloride remains at 100%. In the cyclohexanol case the elimination of water at 70 eV appeared to involve a competition between *cis* (90%) and *trans* (10%) elimination. This figure (80% stereospecificity) was shown to be a minimum since it was derived using a correction based on the ratio of isomers in **10**. The latter correction rests on the intervention of no isotope effect on the loss of DCl from **10**. The presence of such an isotope effect would raise the stereospecificity for water loss from **7**. Calculations on **7** and the mixture of **7** and **8**, using the data at low energy input (Table IV), show no change from the results at 70 eV. Since the two processes (stereospecific *vs.* nonstereospecific) would likely possess transition states differing in energy (Figure 8) it is reasonable that the apparent lowered

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(24) This reaction is known to be highly stereospecific. For a general discussion and leading references, see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, pp 91, 92.

(25) For an especially clearcut demonstration of this phenomenon in mass spectrometry, see S. Meyerson, *Appl. Spectrosc.*, 22, 30 (1968). See examples throughout ref 22b and especially p 25 in that work.

(26) Even if each competing fragmentation took place from isolated electronic states of the molecular ion, the observation of a constant ratio with change in electron energy would require transition states of identical energy. Notwithstanding this fact, we have measured the ratio of metastable peaks for the competitive eliminations in cyclohexanol (1,4 *vs.* 1,3) and find that this ratio is independent of beam energy indicating the absence of such isolated electronic states. For an excellent qualitative discussion of the general theory of mass spectrometry including the relationship of isolated states to metastable behavior, see R. G. Cooks, I. Howe, and D. H. Williams *Org. Mass Spectrosc.*, 2, 137 (1969), and the numerous references therein. See also A. N. H. Yeo, R. G. Cooks, and D. H. Williams, *J. Chem. Soc.*, *B*, 149 (1969).

(27) P. Brown, *J. Amer. Chem. Soc.*, 90, 4459, 4461 (1968); see also R. H. Shapiro and K. B. Tomer, *Org. Mass Spectrosc.*, 2, 579 (1969).

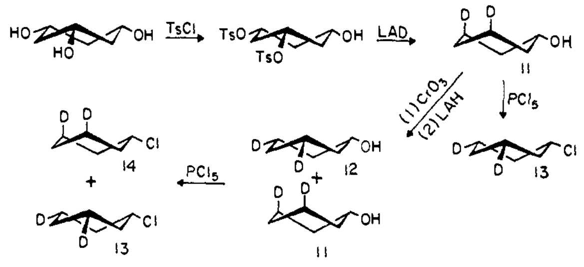

Figure 10. Details in the Experimental Section.

stereospecificity for 1,4 water loss from cyclohexanol is actually due to the lack of steric purity of 7.[28]

Figure 10 outlines the synthesis of the deuterated compounds needed to probe the stereochemistry of the 1,3 elimination in cyclohexanol and cyclohexyl chloride. The derived mass spectral data for these materials are presented in Table V.

Table V[a,b]

		HO		Cl	
		11	**11** and **12**	**13**	**13** and **14**
70 eV	M − HX/M − DX	69/23	69/23	47/27	58/18
	Σ[(M − HX) + (M − DX)]	92	92	74	76
9 eV	M − HX/M − DX	82/17	82/17	61/34	75/21
	Σ[(M − HX) + (M − DX)]	99	99	95	96

[a] Data taken on a CEC-103C mass spectrometer at ~125° at the beam energies noted (70 and 9 eV nominal). [b] See footnote *b* to Table III.

After noting the required lack of deviation in the sets of summation terms (Σ) in Table V (see discussion following Table III) it is apparent that there exists a fundamental difference between these results and those for the 1,4 elimination. That is, the relative loss of DOH and HOH is unchanged in the stereospecifically labeled material (**11**) and the mixture (**11** and **12**). That this coincidence does not arise from lack of steric integrity in **11** is demonstrated by the result for **13** (Table V). Since **13** is prepared from **11**, the stereochemical purity of **11** must be at least as good as that for **13**. The data in Table V allow us to calculate the minimum epimeric composition for **13** assuming 100% stereospecificity for the 1,3 elimination of hydrogen chloride. That is, at 70 eV, one finds a minimum ratio close to 80% *cis*:20% *trans* or making the alternative assumption that **13** is sterically pure, one concludes that the 1,3 elimination in cyclohexyl chloride is ~60% stereospecific. Either way, the data unequivocally demonstrate that **11** is not sterically equivalent to the mixture of **11** and **12** and thus, that the 1,3 elimination of water from cyclohexanol occurs without stereospecificity.

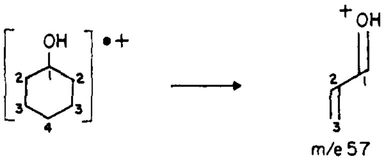

Figure 11.

We may in fact proceed further quantitatively since the data at 9 eV calculate to show that even at this low beam energy, the ratio of *cis* to *trans* elimination remains close to 80:20 for **13**. Since it seems unlikely that two competitive reactions differing in their stereochemical consequences would have identical transition state energies (Figure 9) we conclude that **11** is formed in less than epimeric purity but at least 60% stereospecifically[28] (80% **11** and 20% **12**) and that the 1,3 elimination in cyclohexyl chloride occurs by one mechanism, namely 100% stereospecifically. At any rate the data (Table V) clearly demonstrate that at any energy input, 1,3 water loss is nonstereospecific while the apparently similar loss of hydrogen chloride is highly stereospecific.

Site of Deuterium Before and After Electron Impact. In order to draw firm conclusions from the preceding data, any questions concerning the position of the label (deuterium) in compounds **5–14** must be put to rest.

As discussed above with regard to Table II[21] significant scrambling is ruled out in these measurements since lowered beam energies do not affect the results as would be expected for such goings on. These conclusions are reinforced by the low voltage data taken on the stereospecifically labeled materials (Tables IV and V).[29]

Djerassi and his coworkers[30] have cleanly dissected the electron impact induced fragmentation of the ring in cyclohexanol and demonstrated that the fragment of *m/e* 57 arises as shown in Figure 11. These results[30] allow us to check on the deuteration site of our labeled materials. Examination of the mass spectra in the region of *m/e* 57 exhibited no shift in *m/e* 57 for compounds **6**, **7**, **7** and **8**; shift to *m/e* 59 for **5**; shift to *m/e* 58 for **11**, **11** and **12**. These results are in agreement with the sites of deuteration proposed and as well, fix the deuterium in the derived chlorides since phosphorus pentachloride is an unlikely candidate for rearrangement.[24] We have further confirmed the deuteration sites in both **6** and **11** by oxidation to the derivative adipic acids[31] followed by esterification and nmr analysis (Figure 12).

The nmr of the labeled adipate from 6 (Figure 12) showed δ 3.6 (6 H), 2.2 (4 H), 1.6 (2 H), while the ester from 11 exhibited 6 H, 3 H, 3 H, at these respective chemical shifts as expected for the label sites in **6** and **11**. The combination of the nmr data and the *m/e* 57 shift in the various mass spectra unequivocally fix the site of deuteration in all the deuterated materials both prior to and at least up to 70 eV electron impact fragmentation to *m/e* 57.

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(28) Reactions of lithium aluminum hydride (deuteride) are known to be subject to anchimeric assistance. Such behavior would lead to some retention in the production of 7. See D. S. Noyce and B. N. Bastian, *J. Amer. Chem. Soc.*, **82**, 1246 (1960), for a discussion of the assisted solvolysis of 4-substituted cyclohexyl tosylates. E. L. Allred and S. Winstein [*ibid.*, **89**, 4008 (1967), and references therein] discuss this behavior in certain reactions of this type. For an additional example of lack of stereospecificity in a lithium aluminum deuteride displacement, see F. R. Jensen and B. H. Beck, *Tetrahedron Lett.*, 4523 (1966). Even unassisted displacement of tosylate by lithium aluminum deuteride may occur with less than 100% stereospecificity. See ref 16.

(29) Work in collaboration with Dr. A. Duffield of Stanford University is in progress to determine the behavior of these and related labeled molecules in the kinetic slice leading to metastable decompositions. Preliminary data suggest scrambling mechanisms intervening in this region, at least for the alcohols.

(30) See ref 23, p 107 ff and references therein.

(31) We thank Mrs. Ruth Reingold for carrying out these oxidations.

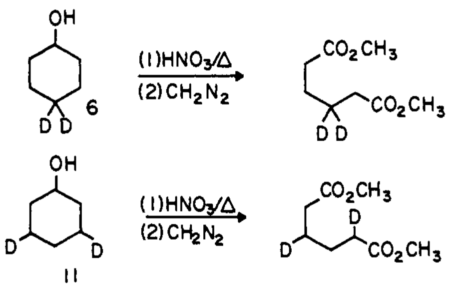

Figure 12.

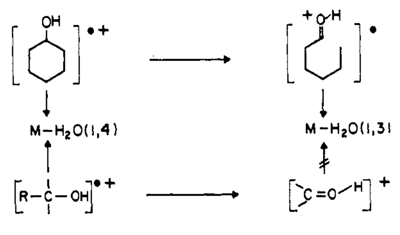

Figure 13. The α-cleaved ion of an acyclic alcohol may go on to eliminate water by a 1,3 process[32] but not to give an ion at the molecular weight minus eighteen.

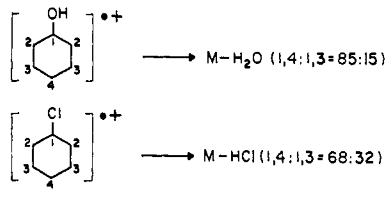

Figure 14. Statistically corrected site selectivity in cyclohexanol and cyclohexyl chloride.

Discussion of Results

The results presented here demonstrate that all loss of hydrogen chloride from cyclohexyl chloride is stereospecific while only the 1,4 loss of water from cyclohexanol shows stereochemical dependence. The only reasonable mechanism to account for the absence of specificity in the 1,3 elimination in cyclohexanol is cleavage of the carbon–carbon bond adjacent to the hydroxyl group. This type of α-cleavage is well documented in the mass spectra of alcohols[23] and in fact accounts for a sizable percentage of the total ionization in cyclohexanol.[30] Indeed, if we accept such a mechanism for the nonstereospecificity, the bias against 1,3 elimination in acyclic alcohols becomes intelligible. That is, while α-cleavage may precede 1,3 elimination in ring compounds it must necessarily preempt such an elimination in acyclic counterparts.[32] Figure 13 exhibits these concepts.

In the case of cyclohexyl chloride both 1,4 and 1,3 eliminations occur stereospecifically thereby not offering any similar interruption in the acyclic chlorides and, as found, the pentyl chlorides exhibit significant amounts of both modes of elimination.[8] These arguments find considerable support in the low voltage behavior of cyclohexanol and cyclohexyl chloride. Thus, as noted,[21] 1,4 elimination of water increases over 1,3 as the beam energy is lowered corresponding to a situation in which the transition state for 1,4 loss is lower in energy (refer to Figure 8). If the 1,3 loss involves energy input necessary to break a carbon–carbon bond, as proposed here, this low voltage behavior follows expectation.[33] In contrast, similar measurements on deuterated cyclohexyl chloride show essentially no change on lowering the energy from 70 to 9 eV. This situation would be described by the energetic configuration exhibited in Figure 9 and would follow from the similar mechanism (stereospecific) for the two processes. In fact it is now apparent that the site selectivities in the cyclic alcohol and chloride are not similar at all. Whereas a statistical correction to compensate for the excess C-3(5) hydrogens (Table II) would be 1,3 loss/2 in the halide it should be 1,3 loss/4 in the alcohol. When these corrections are applied the results shown in Figure 14 are obtained. It is interesting to speculate that the increased 1,3 elimination in cyclohexanol over that observed in acyclic alcohols (between 5 and 10% from C-3)[6,7] may be in fact 1,5 elimination.[34] That is, after α-cleavage one of the C-3 methylene groups now possesses a 1,5 relationship to the carbinol carbon. Further this newly designated C-5 methylene may be adjacent to a radical site, stimulating the abstraction of the adjacent hydrogen atom.

These new insights into the behavior of elimination reactions of alcohols and chlorides shed light on the otherwise anomalous behavior of the epimers of 4-*t*-butylcyclohexanol[9a] and the derived isomeric chlorides (Figure 2). Thus, the proposed[9c] cleavage of the *t*-butyl group preempting 1,3 elimination of water from the molecular ion in *cis*-4-*t*-butylcyclohexanol gains stature with the knowledge that carbon–carbon cleavage precedes this elimination normally.[35] Further, such preemptive activity with regard to 1,3 elimination of hydrogen chloride in *cis*-4-*t*-butylcyclohexyl chloride should be much less efficient in the light of the behavior of cyclohexyl chloride and, as found, the overall stereochemical difference in the chloride epimers is lowered (Figure 2). That is, the *trans* isomer may eliminate 1,4 while the *cis* epimer may also readily eliminate hydrogen chloride utilizing the two available hydrogens on C-3(5).

Although we can now describe the eliminations encountered in these simple alcohols and chlorides, the question of the disparity in site selectivity still remains. The simplest and most attractive hypothesis to account

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[32] Water loss can be observed from acyclic ions after α-cleavage. Such experiments have been carried out. See ref 6 as well as M. Kraft and G. Spiteller, *Monatsh. Chem.*, **99**, 1839 (1968).

[33] Research is in progress with Professor J. L. Franklin on the appearance potentials for loss of DOH from **6** and **11**.

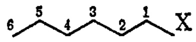
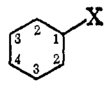
[34] Elimination of water through a 1,5 process has been observed from acyclic molecular ions of alcohols. See ref 6. We have observed predominant 1,5 elimination of water in *cis*-4-isopropylcyclohexanol.[11] Kraft and Spiteller[32] have observed 1,5 elimination from an α-cleaved ion of 8-pentadecanol. Abstraction of hydrogens over rather long distances has been observed in mass spectrometry. See, for one example, R. E. Wolff, M. Greff, and J. A. McCloskey, *Advan. Mass Spectrom.*, **4**, 193 (1968). In unpublished work in this laboratory by J. M. Schwab elimination of water through transition states with as many as 16 atoms has been observed. It should also be noted that only formal 1,3 abstraction involves both ring opening and in part retention of the hydroxyl hydrogen for water loss (Table II). Therefore, Djerassi's suggestion of rearrangement to a hexanal for loss of H_2O from cyclohexyl-O-D finds considerable support. See M. K. Strong and C. Djerassi, *Org. Mass Spectrosc.*, **2**, 631 (1969), and references therein.

[35] We have determined the mass spectra of the C-4 deuterated epimers of 4-*t*-butylcyclohexanol (unpublished research by R. B. Roy) and find that the water loss in the trans isomer occurs entirely by abstraction of the C-4 tertiary hydrogen. Water loss from the *cis* epimer is insignificant.

for this behavior invokes the variation in bond length encountered in bonds to the two elements involved.[36]

Inspection of any conformationally mobile molecular model will reveal the fact that groupings pendant to a carbon chain may approach each other most closely when the groups are furthest away along the backbone of the chain. Table VI lists the distances of closest approach between an X group and the hydrogens on the various carbons in a hexyl and cyclohexyl ligand.

Table VI.[a] Distance of Closest Approach in Ångströms

		
C-2	2.4	2.4
C-3	1.8	2.3
C-4	0.8	1.7
C-5	0	

[a] The differences found between the chlorides and alcohols were within the accuracy of the measurements. The distances were measured with a ruler (0.4 Å/cm) on Dreiding models by making only torsional movements and without noticeably introducing strain.

The behavior of various functional groups X which are eliminated as HX on electron impact point out a likely connection between the relative sizes[37] or bonding radii of X and the hydrogen abstraction site. In acyclic alcohols and chlorides studied [6–8] one finds loss of water preceding by abstraction of the nearby hydrogen on C-4 while loss of hydrogen chloride involves abstraction over the longer distance required for approach to hydrogens on C-3 (Table VI). This behavior would be expected following the relative bonding radii for chlorine and oxygen.[36] The hypothesis receives further support since studies of labeled acyclic bromides[38] and mercaptans[39] show substantial abstraction by the 1,3 process. That is, the longer range hydrogen abstraction follows from the longer bonding radii for bromine (1.11 Å) and sulfur (1.04 Å).[40] Moreover, loss of hydrogen fluoride from acyclic fluorides[41] takes place by a competition between hydrogen abstraction from C-4 and C-5 as might be expected considering the shorter bonding radius for fluorine (admittedly not much smaller than oxygen at 0.64 Å).[40]

The exact bonding radii of the various atoms cannot reasonably be directly used to predict the allowable distance for abstractable hydrogen. Even if these radii could be extrapolated to the ionized state involved in mass spectrometry, and there is no reason to allow such an extrapolation, one is still faced with a reaction coordinate in which the atoms to be bonded will attract each other in a transition state with a necessarily longer bond than that of the product (HX). If one does allow use of the approximate geometry of the neutral molecule in the ionized state, and there is very little choice at present but to do so, we could attempt to derive, from our observations on the hydrogen site selectivity, a correlation between distance and abstraction propensity. Indeed, this is a useful endeavor since success or failure in such speculations may be the only way to determine the efficacy of such extrapolations of structural parameters. On our first attempt at such an approach we are immediately met with success. Thus, we know that acyclic alcohols exhibit >90% abstraction from C-4 and a small (~5%) loss of hydrogen from C-3.[6,7] Inspection of Table VI would therefore lead us to conclude that 0.8 Å is well within the distance required while 1.8 Å is just barely competitive.[42] Immediately testing these new quantities on cyclohexanol we are rewarded by the experimental verification of our tentative prediction. That is, loss of water by abstraction from C-4 should be allowed while abstraction from C-3 should be out of bounds (as discussed earlier in this paper, all the C-3 hydrogen loss in cyclohexanol involves prior ring rupture and thereby intervention of a new mechanism). Following our speculative path we would conclude from the results on the acyclic chlorides[8] that 1.8 Å is well within the required distance while 2.4 Å is too distant for loss of hydrogen chloride. Again, experiment supports us (Figure 14) since change from the acyclic chloride to cyclohexyl chloride where the C-3 distance has increased to almost the prohibitive value, moves the hydrogen abstraction site propensity from about 70% C-3 to nearly 70% C-4.[43,44]

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(36) In all cases known oxygen forms stable bonds with shorter bond length than those for chlorine. It is reasonable that this should also be so for the ions of interest here. See L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, Chapters 7 and 12. For example, the O–H distance in water is 0.96 Å while in hydrogen chloride the H–Cl distance is 1.27 Å. The covalent bonding radius for oxygen is 0.66 Å and for chlorine 0.99 Å.

(37) W. Benz has independently come to similar conclusions regarding the connection between atomic size and abstraction site. See W. Benz, "Massenspektrometrie Organischer Verbindugen," Akademische Verlagsgesellschaft, Frankfurt am Main, 1969, p 142 ff.

(38) W. H. McFadden and M. Lounsbury, *Can. J. Chem.*, **40**, 1965 (1962). Only the *sec*-butyl bromide was studied by labeling and this molecule allows no 1,4 contribution.

(39) A. M. Duffield, W. Carpenter, and C. Djerassi, *Chem. Commun.*, 109 (1967).

(40) See ref 36, Chapter 7. Recently, 1,2-hydrogen transfer to silicon has been uncovered. See T. H. Kinstle, P. J. Ihrig, and E. J. Goettert, *J. Amer. Chem. Soc.*, **92**, 1780 (1970).

(41) W. Carpenter, A. M. Duffield, and C. Djerassi, *Chem. Commun.*, 1022 (1967).

(42) In situations involving equivalent C–H bond strengths at C-4 and C-3, hydrogens at 1.8 Å are poor competitors. When the closer C-4 hydrogens are primary and thus more expensive energetically, the C-3 abstraction becomes substantial. See ref 22a, C. G. MacDonald, *et al.* In a series of studies on rigid steroidal ketones, Djerassi and his coworkers arrived at a similar figure of 1.8 Å for the maximum distance for hydrogen abstraction in the McLafferty rearrangement. See ref 22b, p 157. Studies on intramolecular hydrogen abstraction by alkoxy radicals in steroids (see K. Heusler and J. Kalvoda, *Angew. Chem. Intern. Ed. Engl.*, **3**, 525 (1964)) suggested a maximum carbon (bearing abstractable hydrogen) to oxygen distance of about 2.8 Å. It appears more than a coincidence that the distance from the mass spectral inaccessible C-3 to the hydroxyl oxygen in cyclohexanol is 2.8 Å. J. Deutsch and A. Mandelbaum [*J. Amer. Chem. Soc.*, **91**, 4809 (1969)] have recently used distances extrapolated from molecular models to explain the mass spectra of the adducts of bi-1-cycloalken-1-yls and *p*-benzoquinone.

(43) For any heteroatom in the acyclic cases there are numerous hydrogen atoms further along the chain which easily approach within bonding distance (*e.g.*, C-5, closest approach is 0 Å). Although it seems reasonable to invoke a probability term to account for lowered abstraction through larger rings it should be noted that change of beam energy from 70 eV to near-threshold does not affect the relative competition between C-4 and C-3 abstraction in pentyl chloride.[8] The quasi-equilibrium theory (ref 26, R. G. Cooks, *et al.*, and references therein) predicts that the more probable (higher frequency factor) of two competitive reactions will be favored at high energies while the reaction of lower endothermicity will be favored at low energies.

(44) The values in Table VI show that the unstrained C-2 and C-3 distances in the cyclic ligand are nearly the same and further C-2 is the same in both the acyclic and cyclic case. If chlorine is large enough to eliminate by a 1,3 abstraction of hydrogen in cyclohexyl chloride the larger sulfur and bromine atoms might be expected to eliminate 1,2. In the acyclic series such 1,2 elimination is absent for loss of H_2S[39] but the results on the acyclic bromide are less definite.[38] It is important in this regard, that movement of the C-3 hydrogen toward X is softer energetically than equivalent movement of the hydrogen on C-2 since the Bayer strain is spread over more atoms in the former situation.

Experimental Section

The mass spectral data reported here were taken on a CEC-103C mass spectrometer[45] under standard conditions with a room temperature inlet and the source at equilibrium with the heater off (~125°). The electron voltages are uncorrected. In every case the compounds reported were run numerous times at intervals over as long as months and in no cases were there deviations in relative abundance greater than a few per cent of the measured ion intensity. Many of the materials were also measured on an MS-902[46] mass spectrometer and the data taken in this manner differed somewhat from that on the CEC but were nevertheless internally consistent with the conclusions drawn from the data on the CEC-103C.

The *cis* and *trans* isomers of 4-*t*-butylcyclohexanol were prepared following Eliel.[47] They were separable under many gas chromatographic conditions but we found a 10-ft 20% Carbowax 20M on Chromosorb W 60–80 column to be best. In our hands the 4-*t*-butylcyclohexyl chloride epimers were prepared in high yield by the action of phosphorus pentachloride in chloroform on a mixture of isomers of the precursor alcohols. The chloride epimers were separated by vapor phase chromatography on a 10-ft aluminum column of 30% QF-1 on Chromosorb W 60–80 and identified by comparison with authentic infrared spectra.[48]

meso- and *dl*-2,4-pentanediol were prepared and separated following known procedures.[14] The monoethylene ketal of 1,4-cyclohexanedione was prepared by known routes.[49]

The isomers of 1,4-cyclohexanediol and the derived monotosylates were prepared by available methods.[50] *cis*-1,3,5-Trihydroxycyclohexane is a known compound, and our preparation followed that described.[51] *trans*-4-Chlorocyclohexanol was prepared from 1,4-epoxycyclohexane as described.[52]

All preparations of chlorides from alcohols using phosphorus pentachloride followed a published procedure.[53] Displacement of tosylate by lithium aluminum deuteride[54] was accomplished in each case by the cautious addition of a 1 molar equiv of solid deuteride[55] to the tosylate in ether. After stirring at room temperature for at least 12 hr the workup followed addition of saturated aqueous sodium sulfate and magnesium sulfate. Deuterium exchange of the α-hydrogens in cyclohexanone and the monoethylene ketal of cyclohexanone was carried out by stirring the ketone overnight in a sealed flask with deuterium oxide and a pinch of sodium carbonate. Workup involved extraction with dry ether. This procedure repeated twice led to deuterium incorporation of >90% d_4 (by mass spectrometry). In all cases involving lithium aluminum deuteride the isotopic incorporation was quantitative. All deuterated materials reported in this paper have been shown to be identical with authentic proteum compounds by gas chromatography under at least two different conditions. Mass spectra were taken on samples purified by preparative gas chromatography (Varian 90-P). Each tosylate prepared for this work was synthesized by the slow (5 hr) addition of the appropriate equivalency of *p*-toluenesulfonyl chloride in pyridine (distilled from barium oxide) to the alcohol at 0° stirring in pyridine.[56] In the preparation of the epimeric mixtures **7** and **8** as well as **11** and **12** complete conversion to a 50:50 mixture was assured by vpc collection of the intermediate ketone before reduction to the alcohol mixture. The oxidations were carried out in the standard manner utilizing Jones reagent.[57]

The stereospecifically deuterated chlorides **3** and **4** were prepared as described in detail below for one of them. The high stereochemical integrity of this procedure is attested to by the results exhibited in Figure 4 and detailed in Table I.

Preparation of Racemic 2(*S*),4(*R*),2-Chloro-4-deuteriopentane (4) from Racemic 2(*R*),4(*R*),4-Deuterio-2-pentanol (1). Pyridine, which was freshly distilled from barium oxide, was mixed with the alcohol (**1**) in the proportions of 5 ml to 200 mg, respectively. Thionyl chloride (0.27 ml) was added quickly with stirring at ice temperature causing the deposition of crystals. This mixture was heated at about 60° for 24 hr and the resulting dark paste was washed with pentane. The remaining intractable paste was dissolved in dilute hydrochloric acid and extracted with pentane. The combined pentane layers were washed and dried and concentrated to a few milliliters volume. Gas chromatography showed this concentrate to be a solution containing at least 100 mg of a material identical with authentic 2-pentyl chloride. Mass spectral analysis of the M − 15 ion demonstrated the quantitative incorporation of one deuterium as also found by mass spectrometry on the ketone derived from the precursor (**1**).

Preparation of Racemic 2(*S*),4(*R*),2-Chloro-4-deuteriopentane (4) from Racemic 2(*S*),4(*R*),4-Deuterio-2-pentanol (2). In pentane at −8°, 200 mg of **2** was cautiously added to excess thionyl chloride. The hydrogen chloride produced was pulled off with the aspirator and the solution was stoppered and allowed to set over two nights in the freezer (−15°). At that time the volatiles were evaporated at room temperature or below and the remaining liquid was taken up in 7 ml of dioxane (freshly distilled from lithium aluminum hydride). This solution was heated overnight at 60° followed by extraction with pentane. The pentane extracts were washed with water and base, dried, and concentrated to a few milliliters volume. Gas chromatography showed a major component (> 100 mg) identical with authentic 2-pentyl chloride while mass spectral analysis of vpc collected material showed it to be identical with **4** as prepared by the pyridine route (see above).

Thus, the equivalent distances for hydrogens on C-2 and C-3 in Table VI may be misleading.

(45) We are indebted to Mr. Frank Drogosz for his expert technical assistance.

(46) The University of Michigan is grateful for funds from the NSF for help in purchasing the MS-902.

(47) E. L. Eliel and M. N. Rerick, *J. Amer. Chem. Soc.*, **82**, 1367 (1960).

(48) F. D. Greene, C. C. Chu, and J. Walia, *J. Org. Chem.*, **29**, 1285 (1964). We wish to thank Mssrs. P. Kuneck and J. Krakower for carrying out these transformations

(49) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949); H. Plieninger and H. J. Grasshoff, *Chem. Ber.*, **90**, 1973 (1957); D. A. Prins, *Helv. Chim. Acta*, **40**, 1621 (1957).

(50) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 320 (1949).

(51) H. Stetter and K. H. Steinacker, *Chem. Ber.*, **85**, 451 (1952).

(52) E. L. Bennett and C. Niemann, *J. Amer. Chem. Soc.*, **74**, 5076 (1952). For more recent work describing both isomers, see D. S. Noyce, B. N. Bastian, P. T. S. Lau, R. S. Monson, and B. Weinstein, *J. Org. Chem.*, **34**, 1247 (1969).

(53) H. L. Goering and F. H. McCarron, *J. Amer. Chem. Soc.*, **78**, 2270 (1956).

(54) Purchased from either Stohler Isotopes or Merck of Canada.

(55) Only one of the hydrogens is known to be efficient in this reaction. See J. E. Johnson, R. H. Blizzard, and H. W. Carhart, *J. Amer. Chem. Soc.*, **70**, 3664 (1948).

(56) The tosylates were used without analytical characterization.

(57) See L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 142.