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Stereochemistry of Electron-Impact and Lead Tetraacetate Induced Hydrogen-Abstraction Reactions

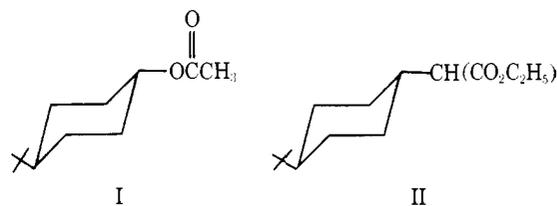
George Eadon

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Abstract: The stereochemistry of the hydrogen-abstraction step in the electron-impact induced dehydration of a series of β -*trans*-4-*tert*-butylcyclohexyl alcohols is consistent with reaction through a chair or half-chair-like six-membered transition state and a chair conformation of the 4-*tert*-butylcyclohexyl ring system. The hydrogen-abstraction step in the lead tetraacetate induced cyclization of these alcohols exhibits parallel stereochemistry, providing further support for these conclusions. Steric arguments exclude a boat or a planar conformation of the cyclic transition state for hydrogen abstraction in either reaction. Since the lead tetraacetate induced reaction proceeds with significant *trans* hydrogen abstraction in every case, these observations confirm the utility of the stereochemistry of hydrogen abstraction from the 4-*tert*-butylcyclohexyl system as a probe into the concerted or nonconcerted nature of elimination reactions proceeding through six-membered cyclic transition states.

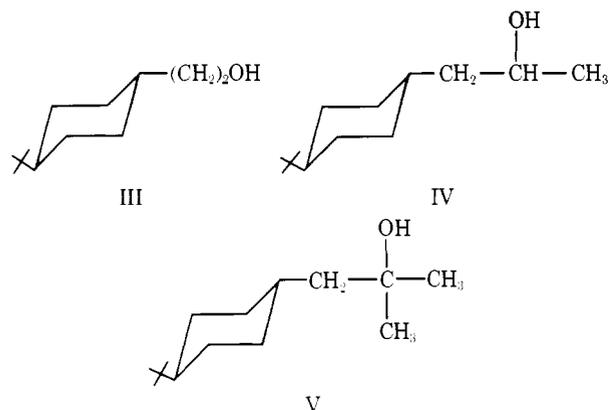
The application of mass spectrometry to stereochemical problems is made difficult by at least two factors. Most obviously, the detailed stereochemical prerequisites of most electron-impact induced fragmentations remain unknown. Of comparable importance, however, is the current dearth of knowledge concerning the prevalence of high-energy conformations after ionization. Unless the latter problem is better understood, knowledge of the former will have limited predictive value.

An effort to investigate both factors involved a study of the stereochemistry of the McLafferty rearrangements of *trans*-4-*tert*-butylcyclohexyl acetate (I) and diethyl (*trans*-4-*tert*-butylcyclohexyl)malonate (II).¹ Both reactions exhibited a clear preference for elimination of the *trans* equatorial hydrogen. It was tentatively suggested that this result was attributable to steric effects in the competing transition states for hydrogen abstraction from the chair form of the 4-*tert*-butylcyclohexyl ring system. Further, it was suggested that extensive *trans* elimination might be characteristic of a non-



concerted elimination proceeding through a cyclic six-membered transition state.

The importance of these mechanistic proposals makes it desirable to establish more firmly the causes for and the generality of *trans* hydrogen abstraction in eliminations proceeding from the *trans*-4-*tert*-butylcyclohexyl ring system and to better define the conformation of the ring after electron impact. Therefore, the stereochemistry of the electron-impact induced dehydration of 2-(*trans*-4-*tert*-butylcyclohexyl)ethanol (III), 1-(*trans*-4-*tert*-butylcyclohexyl)-2-propanol (IV), and 2-methyl-1-(*trans*-4-*tert*-butylcyclohexyl)-2-propanol (V) has



been determined and compared with the stereochemistry of the lead tetraacetate induced hydrogen-abstraction reaction of these compounds. The results obtained provide strong support for the mechanistic proposals already advanced and shed considerable light on the preferred transition-state geometry for electron-impact induced dehydration.

Electron-Impact Induced Dehydration Reaction. The stereochemistry of the electron-impact induced elimination of water has been a subject of interest since the initial observation by Biemann² that ground-state stereochemical differences between cyclic alcohols are often reflected in the $M^+ / M^+ - H_2O$ ratio in their mass spectra. The reaction is highly regioselective for 1,4-hydrogen abstraction, at least for alicyclic molecules.^{3,4} There is a clear geometric requirement for approach of the oxygen atom to the hydrogen atom to be abstracted;⁵⁻⁷ a realistic estimate for the upper limit for the $H \cdots OH$ distance in the hydrogen-transfer step is 1.8 Å.^{4,8} The elegant studies of Green^{9,10} have demonstrated the reaction's sensitivity to subtle steric interactions and confirmed the similarity between the geometries of reacting ion-molecules and their neutral precursors. Based on these precedents, it seemed likely that the preponderant source of eliminated hydrogens from the alcohols III, IV, and V would be C-2' and C-6', and that stereospecific reaction might be observed. Both assumptions were correct, as the data in Table I demonstrate.

The stereochemistry of the electron-impact induced dehydration of alcohols III-V was assessed from the mass spectra of the equatorial-deuterated alcohols III_E-V_E and the axial deuterated alcohols III_A-V_A. The relative intensities of the $M^+ - DOH$ and the $M^+ - HOH$ peaks for each pair of compounds can be converted into k_A/k_E , the relative "rate constants" for axial and equatorial hydrogen elimination, by analogy to the procedure of Green et al.^{9,10,12} For example, for compound III_E, $(M^+ - DOH)/(M^+ - HOH) = (k_E/I)/(k_E + 2k_A + k_i)$, where I is the isotope effect, and k_E and k_A are, respectively, rate constants for abstraction of an equatorial and

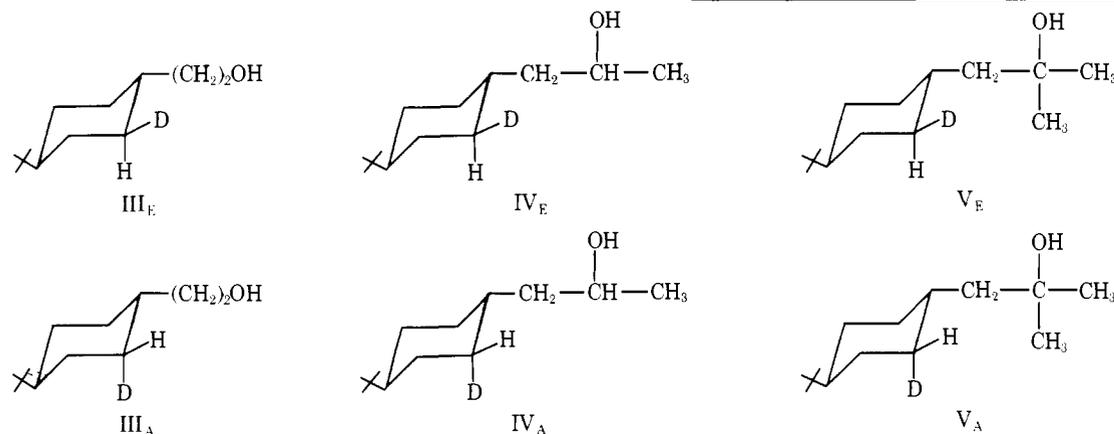


Table I.^a Stereochemistry of the Electron-Impact Induced Dehydration

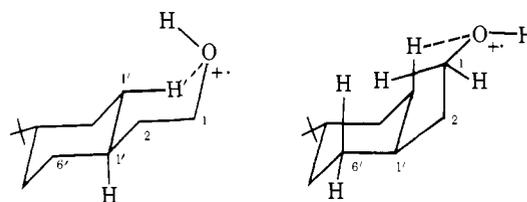
Compd	$\frac{(HOD \text{ loss})^b}{(HOH \text{ loss})}$	$(k_A/k_E)^c$
III _E	0.29 ± 0.01	0.77 ± 0.03
III _A	0.21 ± 0.01	
IV _E	0.45 ± 0.03	0.02 ± 0.03
IV _A	0.20 ± 0.03	
V _E	0.79 ± 0.03	
V _A	0.01 ± 0.01	

^a Error limits represent extreme values observed in four runs.

^b Determined at 70 eV ionizing voltage using a direct insertion probe and a source temperature of 30-40 °C. ^c Calculated assuming an isotope effect of 1.

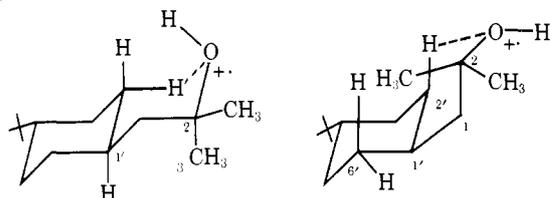
an axial hydrogen atom, and k_i is the rate constant for dehydration reactions not involving abstraction from C-2' or C-6'. Similarly, for compound III_A, $(M^+ - DOH)/(M^+ - HOH) = (k_A/I)/(k_A + 2k_E + k_i)$. There is now abundant experimental evidence that electron-impact induced dehydration proceeds with isotope effects near unity.^{4,13} If it is assumed that I equals 1, these equations can be solved for k_E/k_A ; these results appear in Table I. (The validity of this assumption was confirmed by estimating $k_i/(k_E + k_A)$ from the mass spectra of the 2',2',6',6'-d₄ alcohols. Substitution for k_i and solution of the simultaneous equations gave, in each case, $I \approx 1$.)

An economical explanation of the data in Table I postulates a chair conformation of the 4-*tert*-butylcyclohexyl ring system and a chairlike conformation of the six-membered cyclic transition state for hydrogen abstraction. If the 4-*tert*-butylcyclohexyl ring system is in a perfect chair conformation, an equatorial carbon-carbon bond bisects the H_E-C-H_A bond angle of the adjacent carbon atom. Thus, the hydroxyl oxygen atom can approach the trans axial hydrogen and the cis equatorial hydrogen equally closely (well within the requisite 1.8 Å distance,^{4,8} with an angle strain-free chairlike transition state, and without distortion of the 4-*tert*-butylcyclohexyl ring). Explanation of the modest preference for equatorial hydrogen abstraction in the dehydration of 2-(*trans*-4'-*tert*-butylcyclohexyl)ethanol (III) requires close inspection of the two competing transition states. The transition state for trans



equatorial hydrogen abstraction resembles a strain-free *trans*-decalin system; conversely, the transition state for *cis* equatorial hydrogen abstraction requires a skew-butanelike interaction (C-1-C-2-C-1'-C-6') and resembles the higher energy *cis*-decalin isomer.

If the preference for equatorial hydrogen abstraction in compound III is in fact attributable to steric interaction between the hydrogens at C-1 and C-6', it is predictable that as the substituents at C-1 become bulkier, even less *cis* axial abstraction will be observed. The data in Table I confirm this prediction. For 2-methyl-1-(*trans*-4-*tert*-butylcyclohexyl)-2-propanol (V), equatorial hydrogen abstraction predominates over axial hydrogen abstraction by at least 20 to 1. Inspection of the transition state for *trans* hydrogen abstraction shows a single skew-butane interaction (C-3-C-2-C-1-C-1');



trast, the transition state for axial hydrogen abstraction requires a severe interaction between a methyl group at C-2 and the C-6' methylene group. (An accepted value for a skew-butane interaction is 0.8–0.9 kcal/mol.¹⁴ If the transition state for axial hydrogen abstraction were rigidly chairlike, the steric interaction would approximate a 1,3-diaxial methyl–methyl interaction, estimated at 3.7 kcal/mol.^{14,15}) In view of the large differences in energy between the two competing transition states, the remarkable stereospecificity observed here is explicable.

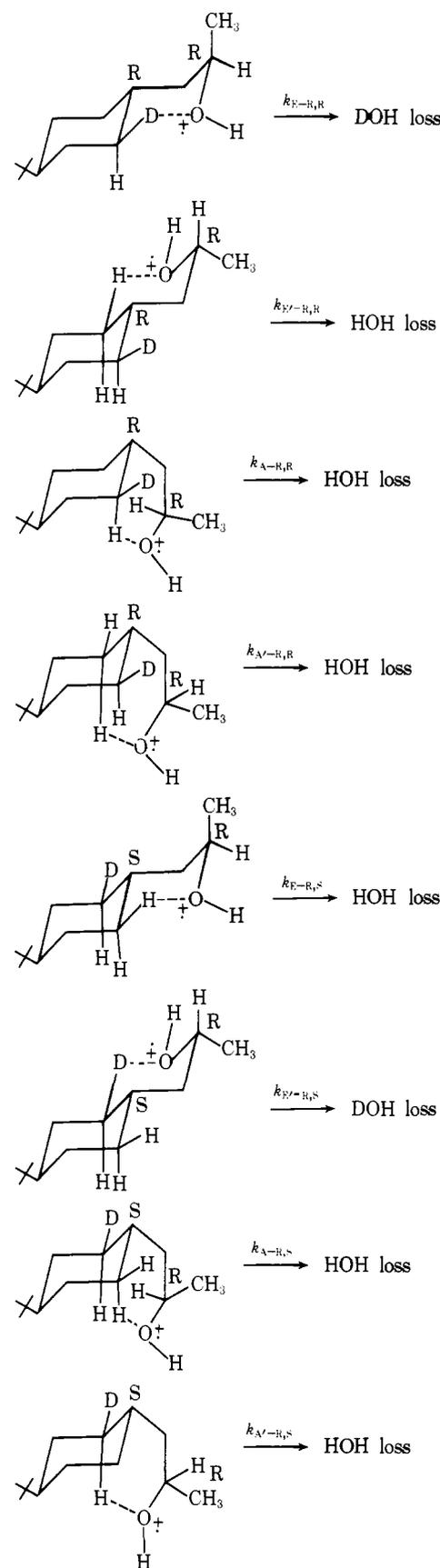
The stereochemistry of the dehydration of 1-(*trans*-4-*tert*-butylcyclohexyl)-2-propanol (IV) is complicated by the presence of an asymmetric center at C-2. Because of their method of synthesis, both IV_E and IV_A must contain equal amounts of the 2*R*,1'*R* and 2*R*,1'*S* diastereomers and their mirror images 2*S*,1'*S* and 2*S*,1'*R*. A simplification is possible since the mirror images must react identically. Nevertheless, prediction of the relative magnitudes of eight rate constants (cf. Scheme I) is required. Fortunately, in the absence of isotope effects, symmetry requires that $k_{E-R,R} = k_{E-R,S}$, $k_{E'-R,R} = k_{E'-R,S}$, $k_{A-R,R} = k_{A-R,S}$, and $k_{A'-R,R} = k_{A'-R,S}$. Thus, the expression for (DOH loss)/(HOH loss) (eq 1) can be simplified considerably (eq 2).

$$\frac{(\text{DOH loss})}{(\text{HOH loss})}_{\text{IVe}} = \frac{k_{E'R,R} + k_{E'RS}}{k_{E,R,R} + k_{E'RS} + k_{A,RR} + k_{A'RR} + k_{A,RS} + k_{A'RS}} \quad (1)$$

$$\frac{(\text{DOH loss})}{(\text{HOH loss})}_{\text{IVe}} = \frac{k_{E'R,R} + k_{E'RS}}{k_{E,R,R} + k_{E'RS} + 2k_{A,RR} + 2k_{A'RS}} \quad (2)$$

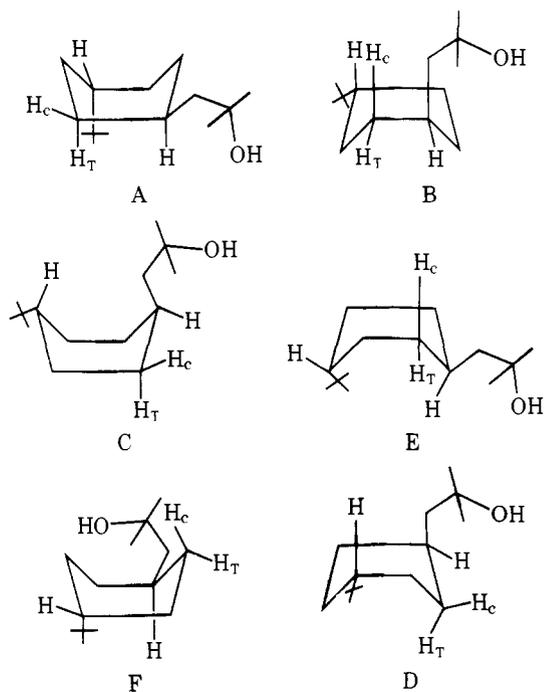
A numerical value for (DOH loss)/(HOH loss) can be estimated for IV_E, if it is assumed that the analysis of the causes of the stereospecificities of hydrogen elimination from III and V is correct. For example, the absence of axial hydrogen abstraction in the dehydration of the tertiary alcohol V was attributed to steric interaction between a methyl group at C-2 and the C-6' methylene group; the same interaction will express itself in the transition state corresponding to $k_{A'-R,R}$. Thus, it will be assumed that $k_{A'-R,R} = 0$. Secondly, in the dehydration of the primary alcohol III, the value of 0.77 for the ratio k_A/k_E was attributed to a single skew-butanelike interaction in the transition state for axial hydrogen abstraction. The transition state corresponding to $k_{E'RR}$ appears strain-free; the transition states corresponding to $k_{A,RR}$ and $k_{E,R,R}$ each contain a single skew-butane interaction. Thus, it will be assumed that 0.77

Scheme I



$k_{E'RR} = k_{ARR} = k_{ERR}$. These assumptions lead to the prediction (D loss)/(H loss) = 0.53, in reasonable agreement with the experimentally determined value of 0.45 ± 0.03 . The same assumptions lead to the prediction that (D loss)/(H loss) =

Scheme II



0.18 for the axial-labeled alcohol IVa; experimentally, a value of 0.20 ± 0.03 was obtained.

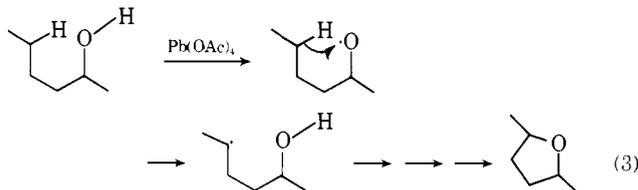
Thus, these results are fully consistent with the postulates that hydrogen abstraction occurs with a chairlike six-membered transition state and a chair conformation of the 4-*tert*-butylcyclohexyl ring system. Other formulations to explain these data are less satisfactory, but cannot be rigorously excluded. In particular, the implication of boatlike conformers in the dehydration of certain cyclohexanols^{13,16-18} demands that the possibility of alcohols III-V reacting through a high-energy boatlike conformer of the 4-*tert*-butylcyclohexyl ring be examined. A priori, there are six boat conformations possible for the 4-*tert*-butylcyclohexyl ring system; in addition, of course, there are "flexible" or skew-boat conformers derivable from each true boat conformer. Inspection of models indicates that for four of the six families of boatlike conformers (depicted as the true boat conformer in Scheme II) abstraction of a trans hydrogen is impossible, based on the distance criterion;^{4,8} in contrast, cis hydrogen abstraction appears feasible from conformers A-D. On the other hand, in conformers E and F, both cis and trans hydrogens appear accessible. Inspection of models indicates no discernible reason why fragmentation should occur preponderantly from conformers related to E and F (and not from A, B, C, or D) and no plausible reason for predominant trans elimination from E and F, even if reaction occurs largely from these conformers.

If it is assumed that fragmentation occurs predominantly from the chair conformation of the 4-*tert*-butylcyclohexyl ring, the stereochemical results expected for various geometries of the six-membered cyclic transition state can be considered. For example, the highly stereospecific trans elimination observed from the tertiary alcohol V is inconsistent with a boatlike transition state. No seriously destabilizing steric interactions exist in the boatlike transition state for cis hydrogen abstraction, since the closest approach of a C-2' hydrogen and a C-2 methyl hydrogen in such a transition state is estimated at ca. 2.6 Å. Further, a planar cyclic transition state is inconsistent with the predominant trans elimination observed; the cyclohexyl ring structure precludes a cis-coplanar relationship for trans equatorial groups, but does permit such a geometry for cis groups.^{1,19} As already indicated, these results are consistent

with a chairlike transition state; they do not permit a distinction between a chairlike and a half-chair transition-state geometry.

In order to provide further support for these mechanistic proposals, the stereochemistry of a better understood, more easily investigated hydrogen-abstraction reaction was investigated.

Lead Tetraacetate Induced Cyclizations. The mechanism of the lead tetraacetate induced oxidation of alcohols to tetrahydrofurans has been extensively investigated.²⁰ The reaction proceeds through the intermediacy of an alkoxy radical, which abstracts a hydrogen atom via an intramolecular (usually six-membered) cyclic transition state; oxidation followed by ring closure and proton loss generates the tetrahydrofuran product (eq 3).



Several features of the intramolecular hydrogen-abstraction step make the reaction a useful probe into the steric interactions in electron-impact induced dehydration. The geometric requirements of the hydrogen abstraction are fairly well characterized; studies on rigid molecules have demonstrated that the alkoxy radical requires an oxygen-carbon distance of 2.5-2.7 Å for facile hydrogen abstraction²⁰ and that the six-membered transition state for hydrogen abstraction is chairlike.²⁰⁻²² Inspection of models indicates that both requirements can be fulfilled for either axial or equatorial hydrogen abstraction from III, IV, or V without distortion of the 4-*tert*-butylcyclohexyl ring system from the chair conformer and without angle strain. On this basis alone, it would be surprising if appreciable hydrogen abstraction occurred from the high-energy boat or skew-boat forms of the 4-*tert*-butylcyclohexyl ring, in view of the relatively low temperature under which the reaction occurs. More tellingly, however, there is considerable evidence that tetrahydrofuran formation proceeds only in very low yield when the hydrogen-abstraction step requires conversion of a cyclohexyl ring into a high-energy form.²³ Isolated yields of tetrahydrofuran products from the reactions of compounds III-V ranged from 10 to 35%, well in excess of the yields reported for reactions proceeding through high-energy cyclohexyl ring conformations. Thus, the lead tetraacetate induced tetrahydrofuran formation reaction provides a model for the steric interactions present in hydrogen-abstraction reactions proceeding through a six-membered chairlike transition state with a cyclohexyl ring in a chair conformer. If the electron-impact induced dehydration is proceeding similarly, and if the dehydration stereochemistry is determined primarily by steric interactions, the two reactions should exhibit similar stereochemistry.

Treatment of the stereospecifically labeled alcohols 2-(*trans*-4'-*tert*-butylcyclohexyl-*trans*-2'-*d*)ethanol (IIIe) and 2-(*trans*-4'-*tert*-butylcyclohexyl-*cis*-2'-*d*)ethanol (IIIa) with lead tetraacetate gave both *cis*- and *trans*-fused tetrahydrofurans. The isomers were readily separable by column or gas chromatography, and their isotopic composition was determined from the relative heights of the $M^+ - CH_3$ peaks in their mass spectra. The isotopic composition of the product was independent of tetrahydrofuran stereochemistry, consistent with a long-lived alkyl radical or carbonium ion intermediate.²⁰ Within experimental error, the labeled alcohols lost identical amounts of deuterium in the cyclization process (Table II).

Similar treatment of 2-methyl-1-(*trans*-4'-*tert*-butylcyclohexyl-*trans*-2'-*d*)-2-propanol (Ve) and 2-methyl-1-

Table II.^a Stereochemistry of the Lead Tetraacetate Induced Hydrogen Abstraction

Compd	(D loss) ^b (H loss)	k_A/k_E	k_H/k_D
III _E	0.060 ± 0.005 ^c	0.9 ± 0.2 ^f	6.2 ± 1.4
III _A	0.055 ± 0.005 ^c		
IV _E	0.11 ± 0.01 ^d		
IV _A	0.06 ± 0.01 ^d		
V _E	0.165 ± 0.02 ^e		
V _A	0.0 ± 0.005 ^e	0 ± 0.04 ^f	6.0 ± 1

^a Error limits represent extreme values observed in at least three cyclization reactions. ^b Determined by mass spectral analysis of the tetrahydrofuran product. ^c Both *cis*- and *trans*-fused octahydrobenzofurans were isolated. Deuterium content was independent of stereochemistry. ^d Two stereoisomers were produced, with differing isotopic composition. The numbers quoted are weighted averages. ^e Only a single stereoisomer was observed. ^f Calculated assuming that isotope effects for equatorial and axial hydrogen abstraction are identical and that secondary isotope effects can be ignored.

(*trans*-4'-*tert*-butylcyclohexyl-2'-*d*)-2-propanol (Va) produced a single tetrahydrofuran isomer in isolable amounts. Strikingly, this reaction was highly stereospecific; equatorial deuterium loss occurred at least 30 times as frequently as axial deuterium loss (Table II).

Transposition of the ratios of deuterium loss to protium loss into the relative rates of axial and equatorial hydrogen abstraction can be accomplished by analogy to the procedure of Curtin²⁴ if it is assumed that the isotope effects for axial and equatorial hydrogen abstraction are identical and that secondary isotope effects can be ignored. For example, (D loss/H loss)_{Ve} = (k_E/I)/ $k_E + 2k_A$, and for the axial-labeled isomer, (D loss/H loss)_{Va} = (k_A/I)/($k_A + 2k_E$). These equations can be solved for the ratio k_A/k_E ; the results also appear in Table II. The observed rate ratios in this well-studied reaction are in good agreement with the relative rate ratios for the less well-understood electron-impact induced dehydration and with the results expected for hydrogen abstraction in a chairlike transition state with a chairlike cyclohexyl ring system. Although appreciable *trans* hydrogen abstraction is observed in the reaction of III, the data do not suffice to demonstrate the expected small preference for *trans* abstraction. The appreciable uncertainties in the value of k_A/k_E are attributable to unfavorable statistical effects and the large isotope effects observed here; small uncertainties in the isotopic composition of the tetrahydrofuran products lead to appreciable errors for the relative rate ratio. The data do demonstrate that the hydrogen-abstraction step for the alcohol V is highly stereospecific; k_E is at least 20 times as large as k_A .

Analysis of the data obtained from the cyclization of labeled analogues of 1-(*trans*-4'-*tert*-butylcyclohexyl)-2-propanol (IV) is complicated by the asymmetric carbon at C-2; because of the large isotope effects observed in these reactions, the various diastereomers present will react with appreciable difference. In fact, reaction of the alcohol IV with lead tetraacetate generates only two of the four possible stereoisomeric furans. Deuterium labeling experiments demonstrate that the major product (60% of the mixture) is formed with predominant loss of the equatorial deuterium (for IV_E, (D loss)/(H loss) = 0.16 ± 0.01; for IV_A, (D loss)/(H loss) = 0.02 ± 0.01). Conversely, the minor isomer is formed with predominant loss of the axial deuterium (for IV_E, (D loss)/(H loss) = 0.04 ± 0.01, for IV_A, (D loss)/(H loss) = 0.12 ± 0.10). The value listed in Table II is the weighted average of the isotopic composition of the two stereoisomeric products.

Conclusions

The lead tetraacetate induced hydrogen-abstraction step in the formation of tetrahydrofurans is an obvious model for the hydrogen-abstraction step in a nonconcerted elimination proceeding through a cyclic transition state. These results provide a second example²⁵ of a hydrogen abstraction from the *trans*-4-*tert*-butylcyclohexyl ring system that proceeds with significant *trans* hydrogen abstraction. These data provide the first clear evidence that the stereochemistry of the hydrogen-abstraction step is determined by steric interactions and, thus, that *trans* abstraction should be a general result for simple hydrogen abstractions proceeding through a six-membered transition state of the 4-*tert*-butylcyclohexyl system. The proposal^{1,25} that the stereochemistry of such eliminations may permit distinction between concerted and nonconcerted eliminations is therefore supported by these results.

These results provide strong evidence that the 4-*tert*-butylcyclohexyl ring is predominantly in the chair conformation among the population of ions undergoing electron-impact induced dehydration. The stereochemistry of the dehydration is in good accord with a priori predictions based on this hypothesis and closely parallels the stereochemistry of the lead tetraacetate induced hydrogen abstraction; there is strong evidence that the latter reaction would only be successful if the cyclohexyl ring is in a stable chair conformation. The conclusion that the cyclohexyl ring is predominantly fragmenting from a low-energy conformer is important for the application of mass spectrometry to stereochemical problems; differentiation between stereoisomers or the basis of their mass spectrometric behavior will usually be a much more complex process if high-energy conformers predominate among the fragmenting ions.

The results of these experiments are completely consistent with the generally accepted chair or half-chair-like cyclic transition state for alkoxy radical hydrogen abstraction; they provide strong evidence against boatlike or planar transition state for these reactions. The results of these experiments are fully consistent with a chair or half-chair-like transition state for the electron-impact induced dehydration; they appear less consistent with a boatlike or planar transition state for this reaction. A detailed knowledge of the preferred transition-state geometry is of obvious importance for the application of mass spectrometry to stereochemical problems. Further experiments are clearly necessary to rigorously define these parameters for electron-impact induced dehydration.

Experimental Section²⁶

trans-4'-*tert*-Butylcyclohexylacetic-*cis*-2'-*d* and -*trans*-2'-*d* acid were prepared from diethyl *trans*-4'-*tert*-butylcyclohexylmalonate-*cis*-2'-*d* and -*trans*-2'-*d*¹ according to the procedure of Stork and White.²⁷ The resulting acids exhibited mp 95–96 °C (lit.²⁷ mp 95.5–96 °C); NMR and ir spectra were in excellent agreement with those already reported for the unlabeled compound, except the ir exhibited an additional absorption (*cis*-2'-*d* at 2130 cm⁻¹, *trans*-2'-*d* at 2155 cm⁻¹) corresponding to C–D stretch.

(*trans*-4'-*tert*-Butylcyclohexyl)-2-propanone-*cis*-2'-*d* and -*trans*-2'-*d* and 2-methyl-(*trans*-4'-*tert*-butylcyclohexyl)-2-propanol-*cis*-2'-*d* (V_A) and -*trans*-2'-*d* (V_E) were prepared by analogy to the procedure of House²⁸ from the corresponding labeled acids. For example, to a cold (0 °C) solution of 200 mg (1 mmol) of *trans*-4'-*tert*-butylcyclohexylacetic-*cis*-2'-*d* acid in 20 ml of Et₂O was added dropwise with stirring 4 ml of a 2.0 M solution of MeLi (purchased from Ventron). The resulting solution was stirred for 1 h at room temperature and then added dropwise to a vigorously stirred solution of 5% HCl. The neutral products were isolated by Et₂O extraction, dried, and concentrated. Column chromatography gave 106 mg (ca. 0.538 mmol, 54%) of a colorless liquid, *trans*-(4'-*tert*-butylcyclohexyl)-2-propanone-*cis*-2'-*d*. The ketone exhibited M⁺ at 197 (97% *d*₁), and NMR and ir spectra were in excellent agreement with those described in the literature, except for an additional ir absorption at 2130 cm⁻¹ (C–D stretch).

Further elution with benzene gave 81 mg (0.38 mmol, 38% yield) of a white solid, mp 69–71 °C, 2-methyl-1-(*trans*-4'-*tert*-butylcyclohexyl)-2-propanol-*cis*-2'-*d* (Va): ir (CCl₄) 3640 (OH), 2130 cm⁻¹ (C-D); NMR δ 0.82 (9 H, S, (CH₃)₃C), 1.21 (6 H, S, (CH₃)₂C(OH)), 0.8–1.92 (12 H, OH and aliphatic C-H); mass spectrum, no molecular ion, intense peaks at *m/e* 198 (M⁺ - 15), 195 (M⁺ - H₂O), and 194 (M⁺ - HOD).

2-(*trans*-4'-*tert*-Butylcyclohexyl)ethanol-*trans*-2'-*d* (III_E) and -*cis*-2'-*d* (III_A) were prepared by LiAlH₄ reduction of the corresponding labeled acids. For example, to a solution of 100 mg (2.64 mmol) of LiAlH₄ in Et₂O was added 200 mg (1 mmol) of 4-*tert*-butylcyclohexylacetic-*trans*-2'-*d* acid. The resulting mixture was stirred for 2 h at room temperature. The excess hydride was decomposed by the addition of 25 ml of 10% HCl. The neutral fraction was isolated by Et₂O extraction. Column chromatography gave 160 mg (0.86 mmol, 86% yield) of the clear liquid, III_E: ir (CCl₄) 3640 (free OH), 3600–3100 (associated OH), 2155 cm⁻¹ (C-D); NMR δ 0.82 (9 H, S, (CH₃)₃C), 3.25 (2 H, d, CH-CH₂O), 0.8–2.0 (10 H, OH and aliphatic C-H); mass spectrum, M⁺ at 185. Analysis was obtained by exact mass measurements on the unlabeled molecule. Anal. Calcd for C₁₂H₂₄O: mol wt 184.1827. Found: 184.1825.

1-(*trans*-4'-*tert*-Butylcyclohexyl)-2-propanol-*trans*-2'-*d* (IV_E) and -*cis*-2'-*d* (IV_A) were prepared by LiAlH₄ reduction of the appropriate ketone. For example, *trans*-(4'-*tert*-butylcyclohexyl)-2-propanone-*cis*-2'-*d* (100 mg, 0.53 mmol) was added to a suspension of 100 mg (2.64 mmol) of LiAlH₄ in 20 ml of Et₂O. The resulting solution was treated with 25 ml of 10% HCl after stirring for 1 h at room temperature. The neutral fraction was isolated by extraction. Column chromatography gave 89 mg (0.45 mmol, 85% yield) of the crystalline alcohol, 1-(*trans*-4'-*tert*-butylcyclohexyl)-2-propanol-*cis*-2'-*d* (IV_E), mp 56–57 °C (lit.²⁸ mp 55–57 °C). The NMR and ir spectra were in excellent agreement with those described with the unlabeled compound,²⁸ except for an additional absorption at 2130 cm⁻¹ in the ir. The mass spectrum exhibited a molecular ion at *m/e* 199.

Reaction of Unlabeled and Labeled 2-(*trans*-4'-*tert*-Butylcyclohexyl)ethanols III, III_A, and III_E with Lead Tetraacetate. Reactions were carried out by treatment of the alcohols III, III_A, and III_E with 1.0 equiv of Pb(OAc)₄ in refluxing benzene for 4 h, in accord with standard literature procedures. After isolation of the neutral fraction by benzene extraction, column chromatography (on silica gel with a hexane eluent) yielded two isomeric octahydrobenzofuran products. The unlabeled major product, a clear oil (21% isolated yield), exhibited the higher *R_f* in TLC and column chromatography and the shorter retention time in gas chromatography. The major tetrahydrofuran product from the unlabeled alcohol III exhibited: ir, only C-H stretch above 1500 cm⁻¹; NMR δ 0.86 (9 H, S, (CH₃)₃C), 3.6–4.2 (3 H, O-CH₂ and O-CH), and 0.8–2.1 (10 H, aliphatic C-H). The mass spectrum exhibits a molecular ion at *m/e* 182, small peaks at *m/e* 181, 167, and 149. Anal. Calcd for C₁₂H₂₂O: mol wt 182.1670. Found: 182.1671.

The minor product, also a clear oil (14% isolated yield), exhibited a lower *R_f* in TLC and column chromatography and the larger retention time in gas chromatography. The ir and NMR spectra of this isomer (unlabeled) were in close accord with that of the other isomer: mass spectrum, molecular ion at 182, small peaks 181, 167, and 149. The M⁺ - 1 peak was markedly more intense for this isomer, however. Anal. Calcd for C₁₂H₂₂O: mol wt 182.1670. Found: 182.1672.

Additional corroboration for the tetrahydrofuran structure of these compounds was obtained by treatment of 2-(*trans*-4'-*tert*-butylcyclohexyl)ethanol-2',2',6',6'-*d*₄ with Pb(OAc)₄. Mass spectrometric analysis of the isotopic composition of both isomers established that each contained three deuterium atoms.

Reaction of Unlabeled and Labeled 1-(*trans*-4'-*tert*-Butylcyclohexyl)-2-propanols (IV, IV_A, and IV_E). Reactions were carried out by treatment of the alcohols IV, IV_A, and IV_E with 1.0 equiv of lead tetraacetate in refluxing benzene for 8 h, in accord with standard literature procedures. After isolation of the neutral fraction by benzene extraction, column chromatography yielded only two of the four possible isomeric octahydrobenzofuran products. The minor product, a clear oil (8% isolated yield), exhibited the higher *R_f* in TLC and column chromatography and the lower retention time in gas chromatography. The minor tetrahydrofuran product from the unlabeled alcohol IV exhibited: ir, only C-H stretch above 1500 cm⁻¹; NMR δ 0.88 (9 H, S, (CH₃)₃C), 1.25 (3 H, d, *J* = 6.5 Hz, CH₃CH-O), 3.8–4.6 (2 H, CH-O) and 0.88–2.5 (10 H, aliphatic C-H); mass

spectrum, molecular ion at *m/e* 196, significant peaks at 195, 181, and 163. Anal. Calcd for C₁₃H₂₄O: mol wt 196.1827. Found: 196.1822.

The major product (12% isolated yield) exhibited the lower *R_f* in TLC and column chromatography and the longer retention time in gas chromatography. The major tetrahydrofuran product from the unlabeled alcohol IV exhibited NMR and ir spectra similar to those of the minor isomer already described. The mass spectrum exhibited a molecular ion at *m/e* 196, significant peaks at 195, 181, 178, and 163. Anal. Calcd for C₁₃H₂₄O: mol wt 196.1827. Found: 196.1830.

Treatment of 1-(*trans*-4'-*tert*-butylcyclohexyl)-2-propanol-2',2',6',6'-*d*₄ with lead tetraacetate generated both compounds with clean *d*₃ isotopic composition, confirming their tetrahydrofuran structure.

Reaction of Unlabeled and Labeled 2-Methyl-1-(*trans*-4'-*tert*-butylcyclohexyl)-2-propanols (V, V_A, and V_E). Reactions were carried out by treatment of the alcohols V, V_A, and V_E with 1.0 equiv of Pb(OAc)₄ in refluxing benzene for 24 h, in accord with standard literature procedures. After isolation of the neutral fraction by benzene extraction, column chromatography gave a single octahydrobenzofuran product in 10% isolated yield: ir, C-H stretch only above 1500 cm⁻¹; NMR δ 0.87 (9 H, S, (CH₃)₃C), 1.21 (3 H, S, CH₃), 1.36 (3 H, S, CH₃), 3.8–4.6 (1 H, m, H-C-O), 0.8–2.2 (10 H, aliphatic C-H).

Cyclization of 2-methyl-1-(*trans*-4'-*tert*-butylcyclohexyl)-2-propanol-2',2',6',6'-*d*₄ generated a compound with identical TLC and gas chromatographic behavior; mass spectral analysis indicated a clean *d*₃ isotopic composition.

Acknowledgment. The author gratefully acknowledges support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

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Mechanism of the Acid- and General-Base-Catalyzed Conjugation of 3-Cyclopentenone and 3-Cyclohexenone; Electrostatic Effects in the Conjugation of β,γ -Unsaturated Ketones

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Received March 3, 1976

Abstract: The rates of isomerization of 3-cyclohexenone and 3-cyclopentenone by a variety of general bases were determined. It was found that the α -hydrogens of 3-cyclopentenone were exchanged for deuterium by a given general base in D_2O at a rate slower than that for exchange of the α -hydrogens in 3-cyclohexenone. However, the rates of conjugation of 3-cyclopentenone were considerably faster than the rates of conjugation of 3-cyclohexenone. It was determined that for isomerization of 3-cyclohexenone, protonation of the intermediate dienolate ion was solely rate determining, whereas for isomerization of 3-cyclopentenone, formation of the dienolate ion was partially rate determining. The rate-limiting step for the acid-catalyzed conjugation of 3-cyclopentenone was shown to be formation of the intermediate dienol. This result differs from that obtained in the acid-catalyzed conjugation of 3-cyclohexenone, where published data show that protonation of the intermediate dienol is the rate-limiting step. The observed results in the acid- and base-catalyzed conjugation of 3-cyclopentenone and 3-cyclohexenone are interpreted in terms of different geometries of the intermediate dienols and dienolate anions. The rates of isomerization of 3-cyclohexenone and 3-cyclopentenone were found to depend markedly on the charge type of the general base. Neutral tertiary amines were much more effective catalysts than negatively charged bases. This difference in catalytic effectiveness was attributed to electrostatic interactions at the transition state.

The conjugation of β,γ -unsaturated ketones to their conjugated isomers has received considerable attention. The isomerization of $\Delta^{5(6)}$ -3-ketosteroids¹ and the deconjugation of prostaglandins in the A series² are catalyzed by enzymes. Because of the importance of these reactions, the mechanisms for conjugation of the parent β,γ -unsaturated ketones, 3-cyclohexenone and 3-cyclopentenone, take on added significance. Although the acid-catalyzed isomerizations of 3-cyclohexenones have been thoroughly studied,³ and mechanisms for the acid- and base-catalyzed conjugation of $\Delta^{5(6)}$ -3-ketosteroids have been reported,⁴ no systematic studies of the conjugation of cyclopentenones have appeared.

Protonation of the γ -position of an intermediate dienolate ion is generally assumed to be the rate-limiting step in the base-catalyzed conjugation of β,γ -unsaturated ketones (i.e., $k_2 \ll k_{-1}$, Scheme I).⁵ In this paper, however, it is shown that enolization (k_1) is partially rate determining in the general-base-catalyzed isomerization of 3-cyclopentenone (IV). The rates of conjugation of I and IV by a given general base were also found to depend markedly on the charge of the catalytic species, in addition to its strength as a base.

Results and Discussion

The rate constants for isomerization of I and IV at pH > 6 in solutions of constant buffer ratio but varied buffer concentrations fit the rate expression given by the equation

$$k_{\text{obsd}} = k_{\text{OH}^-}[\text{OH}^-] + k_{\text{B}}[\text{B}] \quad (1)$$

where B represents the base form of the buffer. The values for the rate constants are listed in Table I.

The isomerization of I with $\text{HPO}_4^{2-}(\text{H}_2\text{O})$ and $\text{DPO}_4^{2-}(\text{D}_2\text{O})$ solutions exhibited a normal isotope effect ($k_{\text{HPO}_4^{2-}}/k_{\text{DPO}_4^{2-}}$) of 7.7, which indicated a pre-equilibrium formation of a dienolate ion followed by rate-determining protonation of the dienolate ion by the buffer acid ($k_2 < k_{-1}$, Scheme I).⁶ This mechanism is consistent with the observation that the exchange of α -hydrogens in I, catalyzed by DPO_4^{2-} in D_2O , occurred at a rate 575 times greater than the isomerization of I to III.⁷

In contrast to the isomerization of I, the isomerization of IV in $\text{DPO}_4^{2-}-\text{D}_2\text{O}$ solutions did not exhibit pseudo-first-order kinetics throughout the reaction. An initial value of the isotope effect ($k_{\text{HPO}_4^{2-}}/k_{\text{DPO}_4^{2-}}$) for the isomerization of IV through 4% reaction in $\text{HPO}_4^{2-}(\text{H}_2\text{O})$ and $\text{DPO}_4^{2-}(\text{D}_2\text{O})$ solutions was measured to be 0.9. As the reaction in $\text{DPO}_4^{2-}-\text{D}_2\text{O}$ solution proceeded, however, the instantaneous value for $k_{\text{DPO}_4^{2-}}$ decreased until it became significantly less than $k_{\text{HPO}_4^{2-}}$ for

Scheme I

