1976

Cyclohexanones Halogenation: Stereochemistry And Mechanisms

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CYCLOHEXANONES HALOGENATION: STEREOCHEMISTRY AND MECHANISMS

by

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Submitted in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

Faculty of Graduate Studies

The University of Western Ontario

London, Ontario

November, 1975

Abstract

It has been generally accepted that there is a stereoelectronic effect operating which favors the initial formation of axial halo chair conformers in the halogenation of cyclohexanones. Much of the evidence available for this proposal is of uncertain validity because of the presence of opposing or reinforcing steric effects of unknown magnitude. This study concerned the stereoelectronic effect in a system where the steric effects have been minimized. The halogenation of the enol, enol acetate, and lithium enolate of 4-t-butylcyclohexanone was examined under a variety of conditions. The results show that there is a clear preference for axial entry of halogen in the kinetically controlled halogenation of the enol acetate. Chlorination gave a ratio of 2:1 for axial:equatorial halo ketones or a ratio of 4:1 for axial:equatorial entry when the side product was taken into account; and bromination gave a ratio of 4:1 for axial:equatorial halo ketones or a ratio of 5.6:1 for axial:equatorial entry when the side product was taken into consideration. Kinetically controlled halogenation of the enol shows no preference for axial or equatorial entry: both chlorination and bromination gave a ratio of 1:1 for axial:equatorial entry. Similarly, kinetically controlled halogenation of the lithium enolate shows no preference for axial over equatorial entry: both chlorination and bromination gave a ratio of 1:1 for axial:equatorial entry. No solvent effect was observed.

The above results have been rationalized by suggesting that in the halogenation of the enol acetate, the transition state was reached later along the reaction coordinate, and after the substrate had undergone

substantial change in geometry to resemble the product halo ketone in the chair-form. The stereoelectronic effect would then favor the formation of the axial halo ketone. However, for the more reactive enol, the transition state is reached earlier before any significant change in geometry has occurred, and because stereoelectronic factors on either side of the double bond of the flat enol are comparable, equal amounts of axial and equatorial halo ketones were formed. Similarly, with the even more reactive enolate, attack on either side of the flat enolate is equally probable and hence no preference is given to the formation of either axial or equatorial halo ketone.

trans-6-Chloro-1-acetoxy-4-t-butylcyclohexene was isolated and characterized. The kinetically controlled chlorination of this chloro enol acetate under a variety of conditions gave only cis,trans-2,6-dichloro-4-t-butylcyclohexanone indicating that only the equatorial entry of chlorine took place. This presumably is due to the steric effect exerted by the quasi-axial chlorine already present in the molecule which prevents further chlorine from occupying the axial position.

In aprotic solvents of low dielectric constants (chloroform and carbon tetrachloride), a new mechanism was established which could account for the formation of the disubstitution product without the intervention of the monosubstitution product in the chlorination of 4-t-butylcyclohexanones at low temperatures (0-5°).

Equilibration studies on epimeric monohalo and dihalo ketones show that the amount of the epimer with the higher dipole moment increases as the dielectric constant of the solvent increases.

Finally, 2,2,6-trichloro- and 2,2,6,6-tetrachloro-4-t-butylcyclohexanones were prepared and characterized.

Acknowledgements

I would like to acknowledge my sincere gratitude to Dr. E. W. Warnhoff for his support, guidance, and encouragement throughout the course of this work. His kindness and friendliness are unforgettable.

I would also like to thank Dr. J. B. Stothers for recording the ^{13}Cmr spectra, Dr. P. de Mayo for the loan of his photochemical equipment, and Dr. A. N. Starratt for numerous suggestions concerning the thesis. The financial support of the National Research Council of Canada is also gratefully acknowledged.

Finally, I thank my wife, Lin, for her help at every step of the way.

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CHAPTER 1

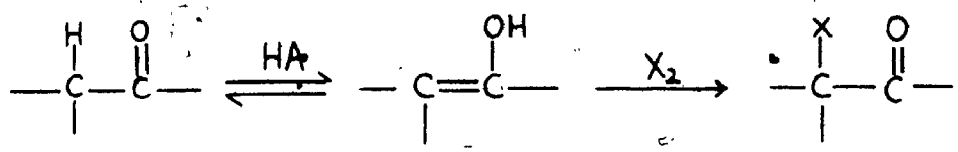
INTRODUCTION

1.1 General

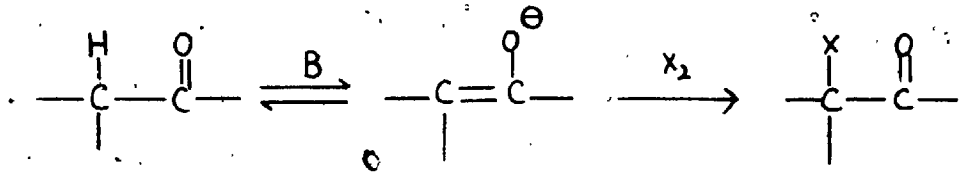
The halogenation of ketones may take place via ionic or radical mechanisms depending on the halogenating agent as well as the reaction conditions. In general, an ionic halogenation takes place more efficiently in a polar solvent and is subject to acid and base catalysis. On the other hand, a radical halogenation usually requires light or heat to start the reaction, which may be accelerated by the presence of a radical initiator and quenched by a radical inhibitor.

1.1.A Ionic Halogenation

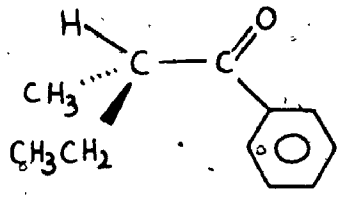
The generally accepted ionic mechanism is due to Lapworth[1] who advanced the proposition in 1904 that the reaction involves a two-step sequence. Thus, in the acid-catalyzed bromination of acetone, the first step is the rate-determining formation of the reactive intermediate enol while the second step is the fast attack of the halogen on the enol. This proposition survived rigid kinetic tests which show that the rate of halogenation is proportional both to the concentration of the ketone and the concentration of hydrogen ion and is independent of the concentration of the halogen used. Thus, the mechanism for acid-catalyzed halogenation is illustrated by the accompanying equation:



In base-catalyzed halogenation, instead of the enol, the formation of the enolate ion is the rate-determining step and the mechanism could be represented as follows:



Studies undertaken by different groups of workers confirmed these conclusions.[2,3] Moreover, for the optically active ketone 1 the rate of the reaction is the same for chlorination, bromination, iodination,[4] racemization and deuteration[5] under the same conditions.



1

The reactions are subject to general acid[6] or general base[7] catalysis. It was then later discovered by Bell[8] and Yates[9] that although the zero order dependence in halogen operates over a wide range of concentrations, the relation deviates and breaks down when a very low concentration of halogen (10^{-5}-10^{-8} M) is employed. In those cases the halogenation step becomes the rate-determining step and the rate is first order with respect to the enol or the enolate as well as the halogen used.

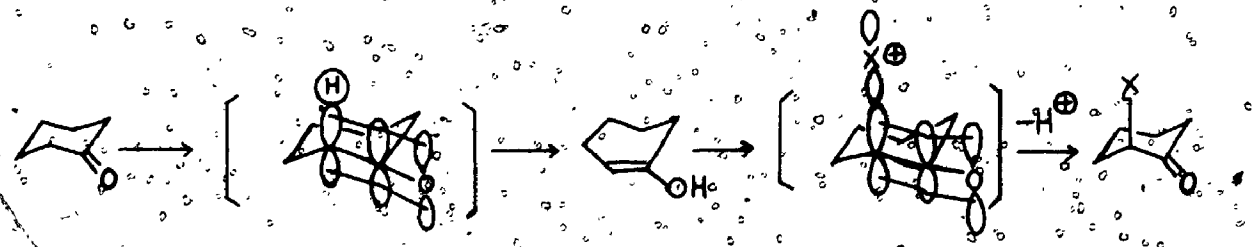
After the development of conformational analysis, the

stereochemistry of halogenation of cyclohexanones became a topic of interest. The orientation of the halogen in the product appears to be controlled by two important factors: (a) a stereoelectronic effect[10] which guides the incoming halogen to the axial position and (b) a steric effect[11] which diverts the attacking species to the less crowded equatorial side. These two factors determine the regioselectivity of the electrophilic attack of the halogen on the enolic double bond which in turn decides which stereoisomeric halo ketone will be predominant. The two factors may oppose or reinforce one another depending upon the circumstances.

In general, the following extreme cases exist:[12,13]

(1) Chair-like Transition State

Considering only the more stable chair-form of cyclohexanone, Corey[10] suggested that it is energetically more favorable to remove an axial hydrogen or to add an axial halogen (see 2a and 2b) rather than an equatorial one since this pathway allows a continuous maximum overlap of all p-orbitals involved. This is the so-called stereoelectronic effect. Therefore, when no serious steric factor is



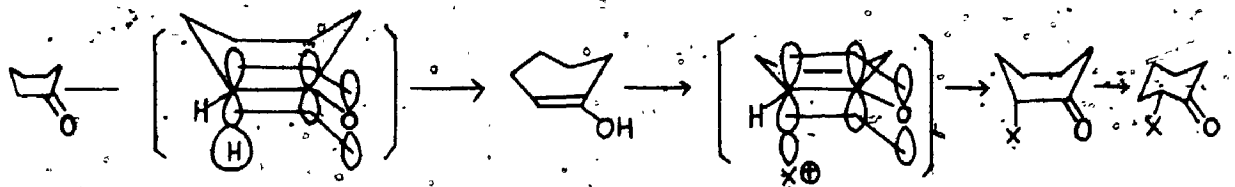
2a 2b

encountered, the stereoelectronic effect favors the formation of axial halo ketone in the chair conformation.

(2) Boat-like Transition State

However, the actual situation is more complicated than what (1) implies. For steric reasons the starting ketone may be more stable in

the boat-form,[14] in which case, the transition state for axial proton removal and axial halogen addition would still allow continuous p-orbital overlap (see 3a and 3b). Also in certain other cases, there are steric interactions between the entering group and the groups already present in the molecule such that the molecule may be forced to take the boat-like transition state. This ends up with the formation of an axial halo boat ketone which could ring-flip to give the equatorial halo chair ketone.[15,16] Support for such a proposition is the isolation of an axial halo boat ketone so stable that it is

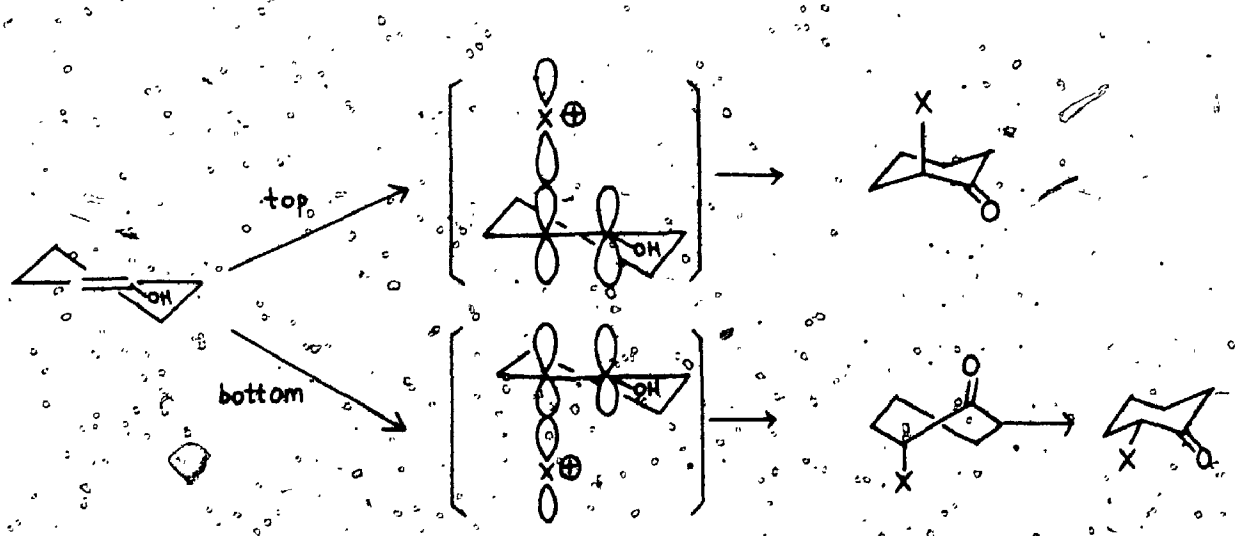


3a 3b

unable to flip back to the chair-form.[15,17]

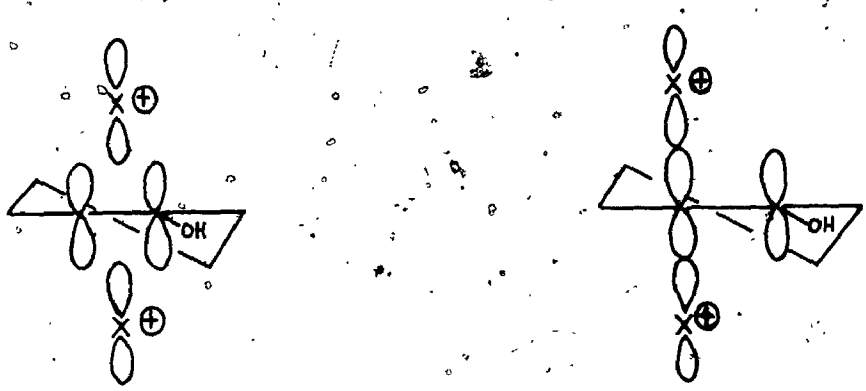
(3) Planar Transition State

When the transition state resembles the planar enol, Valls and Toromanoff[18a] as well as Barton and Morrison[18b] suggested that the attack could be from either side: attack from one side leads to an axial halo



chair ketone whereas attack from the other side leads to an equatorial

halo chair ketone. The stereoelectronic effect offers little or no preference for one attack over another since both routes permit continuous maximum overlap of the p-orbitals of the enolic double bond and that of the halogen. Steric factors on both sides of the double bond will be exactly or nearly the same depending on whether the halogen approaches toward the center (see 4) or the reacting end (see 5) of the double bond. Therefore, the two routes are equally probable in the limiting case if there is little or no change in the geometry of the ring before the transition state is reached.



4 5

1.1.B Radical Halogenation[19,20]

Radical halogenation of a ketone is initiated by a radical initiator, which could be any radical or a halogen atom. The reaction is a substitution reaction which is outlined in the general form below.

$$X_2 \longrightarrow 2X\cdot \qquad \text{(initiation)}$$

$$\left\{ \begin{array}{l} X\cdot + RH \longrightarrow HX + R\cdot \\ R\cdot + X_2 \longrightarrow RX + X\cdot \end{array} \right. \qquad \text{(propagation)}$$

$$\left\{\begin{array}{ll} 2X\cdot \longrightarrow X\text{-}X & \\ 2R\cdot \longrightarrow R\text{-}R & \text{(termination)} \\ R\cdot + X\cdot \longrightarrow RX & \end{array}\right.$$

Chlorine or bromine atoms could be generated by thermolysis at high temperatures (> 200°) or more conveniently at lower temperatures by photolysis using light of approximately 365 nm. A chlorine atom is more reactive than a bromine atom since the abstraction of a hydrogen from a C-H bond by a chlorine atom is a strongly exothermic, low activation energy process whereas the same abstraction by bromine is endothermic with a higher activation energy except for the very weakest C-H bonds.

Studies of chlorination of hydrocarbons led to the formulation of the chlorination rules[21] summarized below. These rules should be applicable to the chlorination of any carbon chain.

(1) Carbon skeleton rearrangements do not occur during chlorination.

(2) Every possible monochloride is formed.

(3) Hydrogen atoms are substituted at rates in the order tertiary > secondary > primary.

(4) At increasing temperatures these relative rates approach 1:1:1.

(5) Liquid phase chlorination gives higher rates than vapor phase chlorination at any given temperature.

(6) Moisture, surfaces, and light have no effect on these ratios.

Radical bromination is more selective than radical chlorination. The reason resides mainly in the difference in bond energies between

H-Cl and H-Br, the former being 16 kcal/mol stronger than the latter. The reaction requires elevated temperature except for the most activated C-H bonds.

The bromination rules are summarized as follows:[18]

(1) Except for reactions producing very stable radicals, kinetic chains will be short.

(2) Stability of the resulting radical is important in determining the point of attack of bromine atoms.

(3) Compared with chlorine, bromine atoms will be highly selective.

(4) In most cases the reverse reaction

$$R\cdot + HBr \longrightarrow R\text{-}H + Br\cdot$$

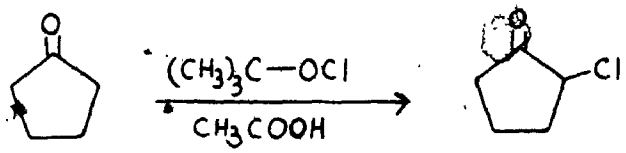
will be detectable and important.

Radical chlorination is very strongly inhibited by oxygen which, however, affects bromination less seriously. Efficient radical scavengers commonly used to quench a radical reaction are iodine, p-benzoquinone, galvinoxyl, nitrobenzene, and dinitrobenzenes.

1.1.C Dichotomy: Ionic versus Radical

Although the carbonyl group activates the α-position toward ionic halogenation, Walling[22] observed that it deactivates both the α- and β-positions for radical halogenation. It has also been made clear that ionic halogenation leads only to α-halogenation whereas radical halogenation gives random products. This is exemplified by using cyclopentanone (6) as a substrate. Thus, the acid-catalyzed ionic chlorination of cyclopentanone with t-butylhypochlorite in the dark with acetic acid as solvent led to 2-chlorocyclopentanone as the exclusive product. However, the radical

halogenation of cyclopentanone (6) with t-butylhypochlorite at 0° under irradiation gave the two possible chlorides, 2-chlorocyclopentanone and 3-chlorocyclopentanone, in almost equal amounts.



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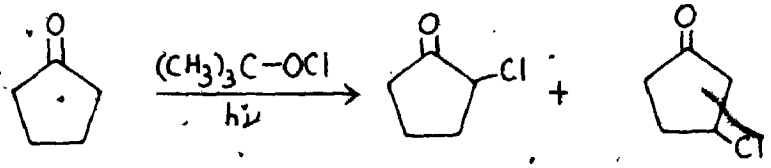
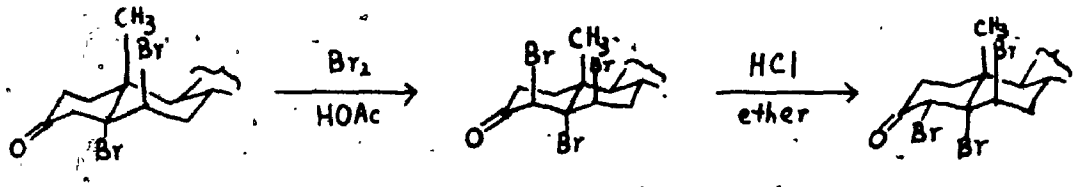


6 48% 52%

Hence, as a simple working diagnosis without going into complicated detail to judge whether the reaction is ionic or radical, the product is to be subject to close analysis. Formation of only α-halo ketone indicates very likely an ionic halogenation has occurred while a mixture of products with chlorine introduced at random along the chain is a sign of radical halogenation.

1.2 Review of Related Works

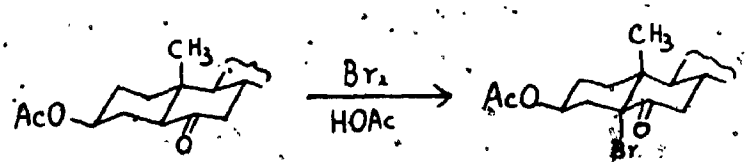
Corey[10] has proposed the generalization that in kinetically controlled bromination of cyclohexanones the first formed product is always the axial halo ketone in the chair conformation due to the stereoelectronic effect discussed earlier. This prediction agrees with the result obtained from the bromination of 5α,6β-dibromocholestan-3-one (7) in acetic acid to give the thermodynamically less stable axial 4β-bromo ketone 8 as the only product.[10] Treatment of this bromo ketone 8 with hydrogen chloride in ether solution led to the thermodynamically more



7 8 9

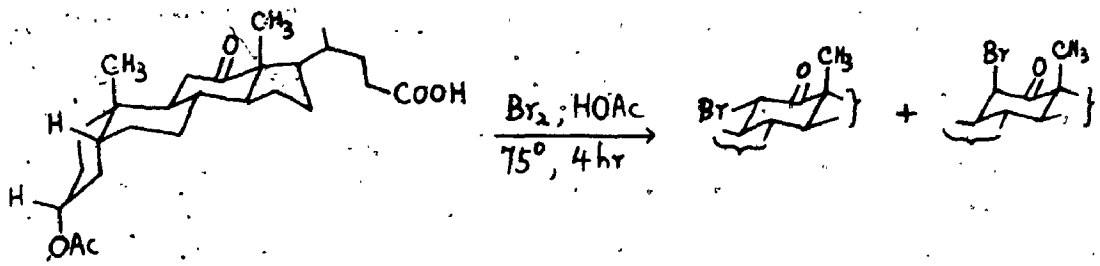
stable equatorial 4α-bromo ketone 9.

Similarly, the bromination of 3β-acetoxycholestan-6-one (10) afforded the axial 5α-bromo ketone 11 as the product of kinetic control.[10]



10 11

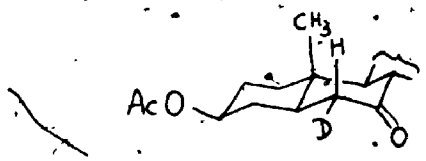
Corey was able to find a number of examples in the literature to establish his point. In some cases where the reported product was predominantly equatorial halo ketone, the epimeric axial halo ketone was shown to be the less stable epimer under the reaction conditions. For instance, the bromination of 12-keto-3α-acetoxycholanic acid (12) under vigorous conditions afforded a mixture of 11α- and 11β-epimeric



12 13 14

bromo ketones 13 and 14 in which the 11α-epimer 13 predominated.[23] The 11β-epimer 14 was shown to epimerize at room temperature to give 13 which implied that the latter was probably formed from the former during bromination.[10]

To further substantiate his point that there is a stereo-electronic effect operating which favors the initial formation of axial halo chair conformers, a detailed study of enolization and ketonization reactions using a deuterium tracer was carried out.[24] The stereochemistry of enolization was studied employing 6α- and 6β-deuterio-3β-acetoxycholestan-7-one (15 and 16) as the substrates. The individual deuterated ketone was allowed to enolize in the presence of excess of bromine so as to ensure an irreversible process by trapping the enol



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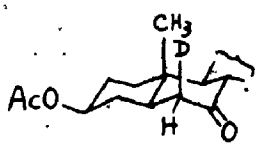
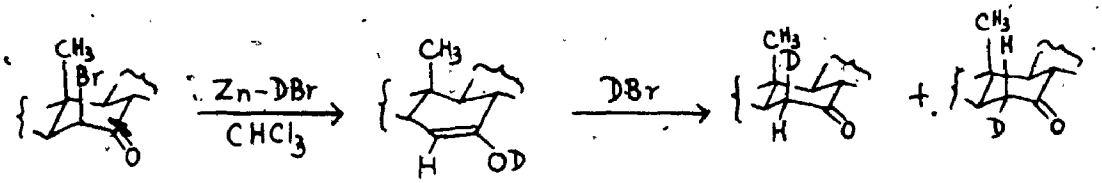


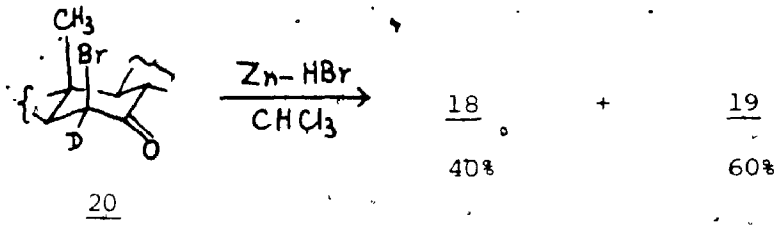
16

as soon as it was formed. From the deuterium content of the product bromo ketones, the ratio of axial:equatorial loss was found to be only 1.2:1 in chloroform after the correction for a deuterium isotope effect.

The stereochemistry of ketonization was studied with 6β-bromo- and 6α-deuterio-6β-bromo-3β-acetoxycholestan-7-one (17 and 20) as the substrates. The non-deuterated bromo ketone was debrominated by Zn-DBr-$CHCl_3$ to give the corresponding enol which was then ketonized by the deuterio acid generating α-deuterated ketones 18 and 19. The deuterated bromo ketone 20 was reduced by Zn-HBr-$CHCl_3$ which led to the same deuterated ketones 18 and 19 as products but in a reverse proportion.



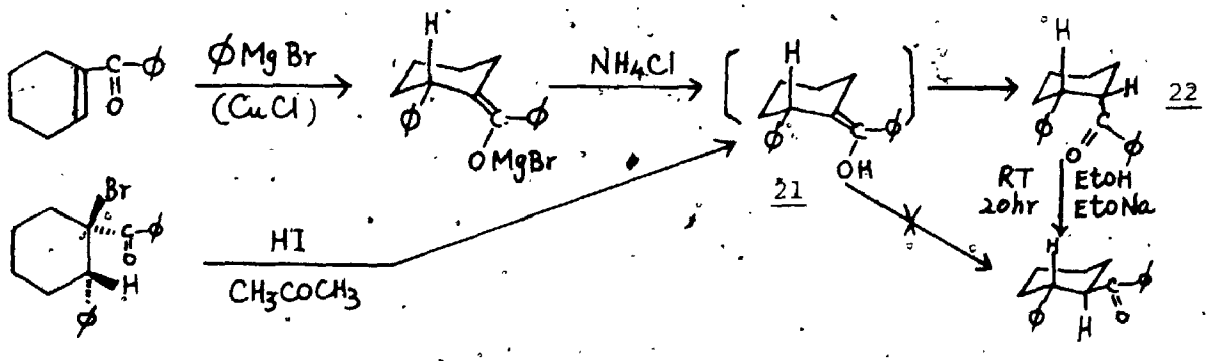
17 18 (60%) 19 (40%)



20 18 40% + 19 60%

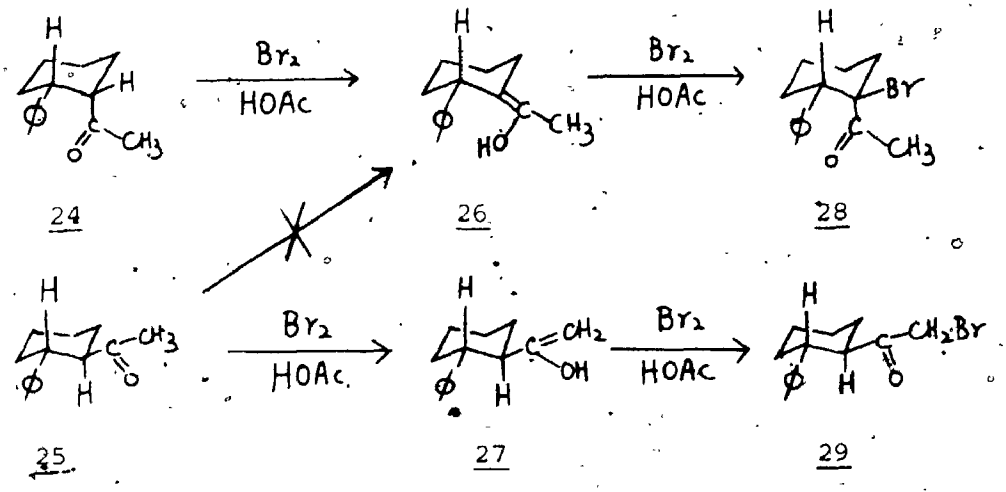
From the ratio of the two epimeric deuterated ketones 18 and 19, the ratio of axial to equatorial protonation was found to be 1.5 which is in reasonably close agreement with the value of 1.2 for the reverse reaction. Corey concluded that, after the correction for an assumed steric effect due primarily to the presence of the angular methyl group at C-10, the stereoelectronic factor favors the axial over the equatorial attack by a factor of 12-15.

In the ketonization of exocyclic cyclohexane enols, Zimmerman[11,25] pointed out that the steric effect is the deciding factor determining the stereochemical course since the stereoelectronic factors are equal on both sides of the double bond.



This is illustrated by the ketonization of the enol 21 which could be obtained either from the conjugate addition of phenylmagnesium bromide to benzoylcyclohexene followed by an acidification or the acetone-dilute hydriodic acid debromination of 1-bromo-2-phenyl-1-benzoylcyclohexane.[25a] The proton is prevented from assuming an axial orientation due to the non-bonded interactions with the axial hydrogens as well as the phenyl group.[26] The kinetically controlled product was almost exclusively cis-1-benzoyl-2-phenylcyclohexane (22) which could undergo an epimerization caused by sodium ethoxide in ethanol to give the thermodynamically more stable trans-1-benzoyl-2-phenylcyclohexane (23).

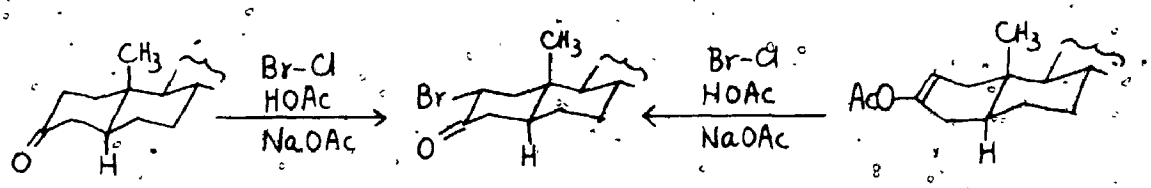
In the bromination[25b] of cis- and trans-1-acetyl-2-phenylcyclohexanes (24 and 25) similar steric factors operate. The cis-isomer 24 which possesses an equatorial α-hydrogen could enolize toward the ring to give the desired enol 26 which then brominated to give the



equatorial bromo ketone 28. However, the trans-isomer 25 in which the hydrogen to be removed is axial fails to give the enol 26, but instead enolizes toward the methyl carbon to give the isomeric enol 27 which upon bromination furnished 29. The explanation offered is that the enolization toward the tertiary α-carbon atom in this case is hampered

by the high energy transition state leading to the enol 26. In fact the most important reason why the compound 24 enolizes to the compound 26 seems to be the relief of the interactions between the acetyl group and the two axial hydrogens as well as the equatorial phenyl group.

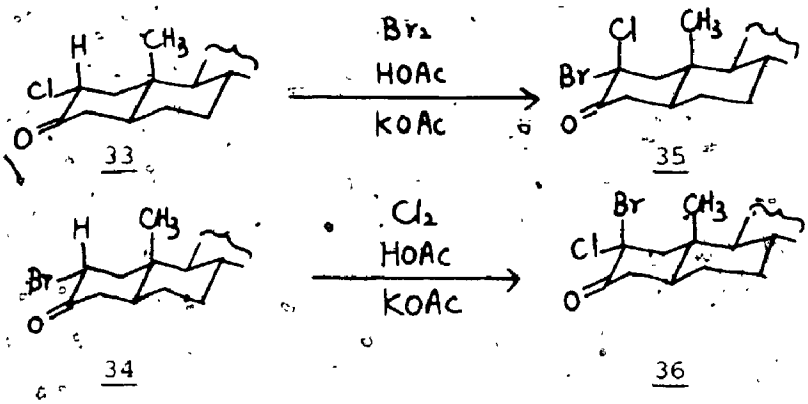
The importance of steric factors was further stressed by Djerassi[15] who found that when the formation of an axial bromo ketone is sterically hindered Corey's rule no longer applies; the principal product of a kinetically controlled bromination is then the equatorial epimer. This point is clearly illustrated by the bromination of 17β-acetoxy-5α-androstan-3-one (30) or its enol acetate 31. The attack from the β-side of the molecule leading to the axial bromo ketone is strongly



30 32 31

hindered by the angular methyl group and hence is energetically unfavorable. This resulted in the formation[15] of the equatorial bromo ketone 32. Similarly, the enol acetate 31 afforded the same bromo ketone 32 almost exclusively under the same conditions.[15]

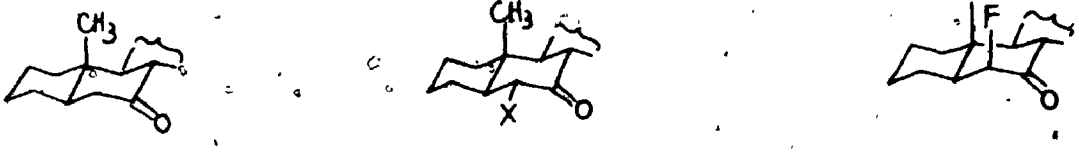
Further evidence supporting this view was provided by Warnhoff[16] who studied the halogenation of 2α-chloro- and 2α-bromo-cholestan-3-one (33 and 34). In each case the β-side of the molecule is too crowded to be attacked. The entering halogen attacks predominantly (85-90%) from the less hindered α-side forcing the erstwhile equatorial halogen already present in the molecule into the axial β-configuration. The equilibrium ratio of 35:36 was estimated to be 4:1.



33 35

34 36

The tangled relationship between stereoelectronic and steric effects was further revealed by the work of Nickon and Castle.[27] Rate-controlled bromination of cholestan-7-one (37) in acetic acid gave a ratio of equatorial:axial halogenation of 1.5-1.2:1 whereas chlorination led exclusively to equatorial 6α-chloro ketone with no evidence of an axial product. This led to the conclusion that the relative importance



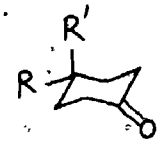
37 38 a, x=Br b, x=Cl 39

of stereoelectronic and steric effects is different for different halogens. In the chlorination of 6α-bromo-cholestan-7-one (38a) and 6β-fluorocholestan-7-one (39) at the carbon bearing the halogen atom no axial chlorination product was observed. However, bromination of 6α-chlorocholestan-7-one (38b) introduced the incoming bromine preferentially at the axial position whereas bromination of 6β-fluorocholestan-7-one (39) led to a predominance of equatorial bromination. It was claimed that the initial halogen plays a role in determining the relative importance of stereoelectronic and steric effects.

The results gathered so far led to the question of whether there really is a stereoelectronic effect favoring the initial axial attack on a cyclohexenol. Bordwell[28] has attempted to answer this question.

The rate of deuterium exchange of a number of 4,4-disubstituted cyclohexanones was studied and compared with that of the unsubstituted cyclohexanone itself. The results are listed below:

Methoxide ion catalyzed exchange of cyclohexanone and 4',4-disubstituted cyclohexanones in methanol-O-d at 25°



R	R'	Relative Rate
H	H	1
Ph	Ph	3.2
Ph	Me	0.82
Me	Me	0.54

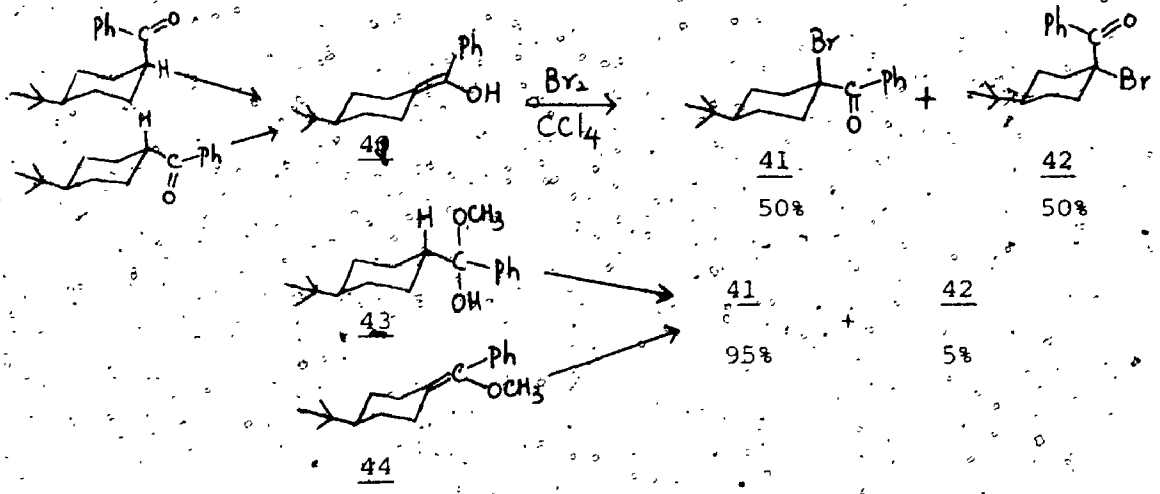
The data above show that 4-axial substitutents exhibit very little, if any, effect on the rate of proton abstraction at the α-carbons. The 3.2 fold faster rate for 4,4-diphenylcyclohexanone, as compared with cyclohexanone, could be accounted for by the inductive effect of the phenyl groups. These experiments show that no steric effect is present in retarding the deuterium exchange at the α-carbons and the effect seems to be negligible in the other ketones studied. Bordwell concluded that at least in the methoxide-catalyzed enolization-ketonization reaction no significant stereoelectronic effect favoring axial removal or uptake exists. This may or may not be applicable to other base-catalyzed or

acid-catalyzed enolization-ketonization reactions.

Now, Corey's original results on the enolization-ketonization reaction showed that the ratio of axial:equatorial attack is 1.2-1.5:1. Based on the assumption that the steric hindrance due to the angular methyl group at C-10 is severe, the ratio was then scaled up to 12-15:1 in favor of the axial attack. Since the axial phenyl group at C-4 fails to retard the rate of exchange at C-2, as has been verified,[28] the correction factor due to the steric effect applied by Corey is no longer valid. The ratio of 1.2-1.5:1 would then hardly indicate any stereoelectronic preference for the axial attack.

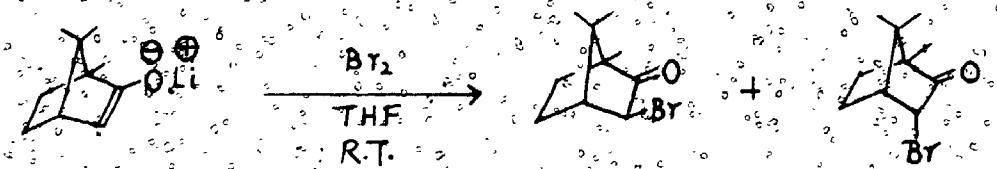
Although there were reports that enol and enol derivatives react in a similar manner,[15] Charpentier[29] found that the stereochemical outcome of the bromination of an enol derivative may be different from that of the corresponding enol. The evidence for this statement came from the bromination study of enol 40, hemiketal 43 and enol ether 44.

Bromination of enol 40 derived either from cis- or trans-4-t-butylcyclohexyl phenyl ketone gave two brominated ketones 41 and 42 in a 1:1 ratio under non-equilibrating conditions. However, under the same conditions bromination of the hemiketal 43 and the enol ether 44 led principally to the halo ketone 41 (95%).



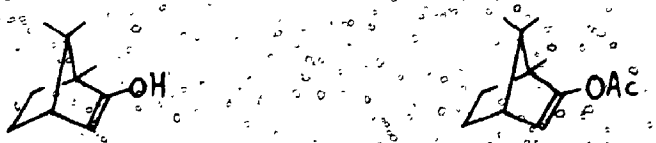
Joshi and Warnhoff[30,31] have suggested that the geometry of the transition state is of primary importance in determining the ratio of the two possible epimeric halo ketones. By varying the reactivity of the substrate, the ratio of the two epimers changes, a result which could be satisfactorily accounted for by a change in geometry at the transition state. Thus, in the halogenation of camphor derivatives the strong tendency for exo-attack inherent in the bornane system predominates with the most reactive substrates and is overcome almost completely by endo-attack with the least reactive substrates. The experimental results giving rise to this conclusion are summarized below.

Kinetically controlled bromination of the lithium enolate of camphor at room temperature gave predominantly exo-bromo-camphor 46 (70%). The preferential exo attack no longer prevailed in the bromination of camphor enol 48 which resulted in almost equal amounts of exo- and endo-bromo-camphor (53% of 46 and 47% of 47). As the reactivity of the



45 → 46 (70%) + 47 (30%)

substrate decreases further the main product became endo-bromo-camphor 47 (64%) in the bromination of camphor enol acetate 49. A similar trend was observed in the chlorination of camphor enol and its derivatives.



48 49

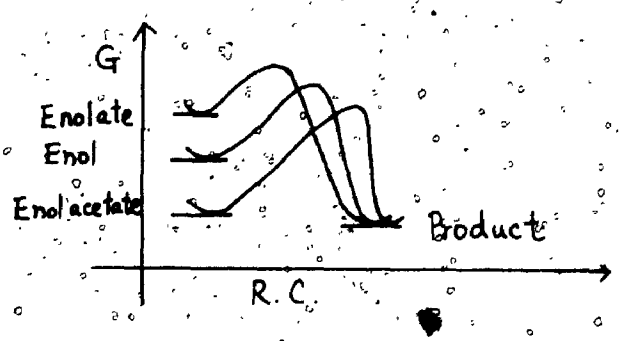
The bromination of the enolate, enol and enol acetate derived

from 3-chloro-camphor and the chlorination of the same derivatives from 3-bromo-camphor fit into the general picture described above. The change was dramatic: for instance, a switch from predominantly exo-bromination (64%) to almost exclusively endo-bromination (95%) was observed in brominating the lithium enolate and the enol acetate of 3-chloro-camphor respectively. Again, bromination of the enol of 3-chloro-camphor gave about 1:1 exo:endo attack (43% of exo and 57% of endo).

1.3 Purpose of this Research

From the results of the halogenation of the camphor system discussed above, Joshi and Warnhoff advanced the view that in the halogenation of camphor enol derivatives, the less reactive the substrate is, the later the transition state lies along the reaction coordinate, as expected according to Hammond's postulate.[32] In other words, the less reactive the substrate is, the more developed the carbon-halogen bond will be and the more severe the steric interference by the syn-8-methyl group, which disfavors the preferential exo-halogenation, will be.

If this is true, the transition state for halogenation of the less reactive enol acetate should bear more resemblance to the product halo ketone than the enol, followed by the enolate as depicted in the following diagram.



The fundamental mechanism for the halogenation of all three enol derivatives was the same as far as the available evidence indicated.[15,30] There was no reason to think that a three-membered halonium ion was involved in some of the reactions. This point has been established by different workers.[15,27,9]

Since the earlier work on halogenation has been done on those substrates with reinforcing and opposing steric factors, and since there also exists uncertainty as to whether kinetically controlled conditions were established, it was the purpose of the present research to assess the magnitude of any stereoelectronic effect favoring the initial axial halo ketone formation in those substrates with no or minimized steric factors. Based on the assumption that all of the halogenation reactions are fundamentally the same but with variation in the transition state position along the reaction coordinate, it was also intended to examine the effect of changing transition state geometry on the product stereochemistry. The compound, 4-t-butylcyclohexanone, fulfills the requirement that the steric factors are minimized, and moreover it is anchored by the t-butyl group in a single chair form. The method used was to investigate the stereochemistry of the product in kinetically controlled halogenation of 4-t-butylcyclohexanone, its enol acetate, and enolate derivative.

Applying the theory described earlier, one would expect any stereoelectronic effect favoring the axial halo ketone formation to operate most effectively in the enol acetate, less in the enol, and least in the most reactive enolate.

With these premises in mind, it was planned to perform the following experiments at the onset of this research project.

(1) To prepare both the known and unknown pure α-halo-4-t-butylcyclohexanones and characterize their identities by physical methods so that the presence of a pair of epimers in the crude reaction mixture could be qualitatively detected and quantitatively estimated without ambiguity.

(2) To check how stable they are and to do equilibration studies and obtain their equilibrium ratios in various solvents.

(3) To find the best possible mild halogenation conditions to suppress any other side reactions except monohalogenation.

(4) To obtain the kinetically controlled ratio of the two epimeric halo ketones from the halogenation of enol acetate, enol and enolate.

(5) To see whether different conditions such as different reagents, different solvents, and different temperature ranges would change the ratio of the two epimers.

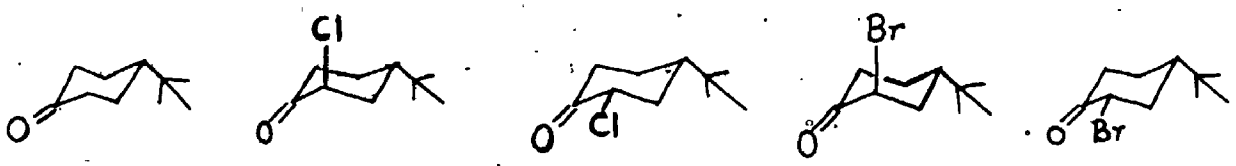
In the course of the study, it became necessary to establish whether any free radical reaction was complicating the halogenation reaction. In solvents of low dielectric constant a new mechanism which could account for disubstituted product was discovered. A few runs on kinetically controlled chlorination of a chloro enol acetate were also carried out.

CHAPTER 2

MONOHALO-4-t-BUTYLCYCLOHEXANONES

2.1 Preparation

In this project, two pairs of epimers (51, 52, 53, and 54) were required for performing control experiments as well as equilibration studies. All of the four monohalo ketones (51, 52, 53, and 54) are

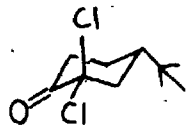


50 51 52 53 54

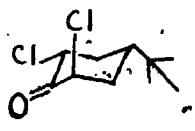
known compounds. The trans isomers (51 and 53) with axial halogen are liquids and the cis isomers (52 and 54) with equatorial halogen are crystaline solids. These two pairs of epimers were prepared, isolated and purified, and their physical properties were studied and compared with the values reported in the literature.

In our hands, attempts to prepare the chloro ketones 51 and 52 by the published procedure of Allinger and coworkers[33,34] led to undesired products. The method involves suspending 4-t-butylcyclohexanone in acetic acid-water (9:1) solution and allowing chlorine gas to pass through the reaction mixture. The failure was due to the difficulty in estimating the amount of chlorine gas absorbed by the reaction mixture. The reaction invariably led to an oily material containing mainly

dichloro ketones, which had a tendency to decompose upon distillation if the pressure was not low enough. However, under very carefully controlled reduced pressure conditions, the crude product upon distillation through a spinning band column gave a crystalline solid in the foreruns which was later shown to be a mixture containing gem-dichloro ketone 55 and cis,trans-2,6-dichloro ketone 56, and a thick syrupy residue which on trituration with n-pentane afforded a solid containing 57 and a trichloro ketone.



55



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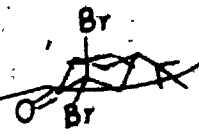
57

A different method was developed later by chlorinating the enol acetate of 4-t-butylcyclohexanone with only slightly more than one mole of chlorine dissolved in carbon tetrachloride or formic acid. The strength of the chlorine solution was determined by adding an aliquot of the solution to aqueous potassium iodide to liberate the equivalent amount of iodine, which was then titrated against a standard solution of sodium thiosulfate. The crude product was subjected to a distillation through a spinning band column under reduced pressure. Pure isomers were obtained by further purification with column chromatography on silica gel.

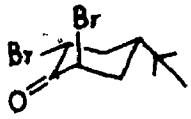
The same epimers 51 and 52 were also prepared from the controlled chlorination of 4-t-butylcyclohexanone with a 1:1 molar ratio of chlorine: ketone in carbon tetrachloride or formic acid and followed by a column separation on silica gel.

The published procedure[35] for preparing the bromo ketones 53 and

54 used the method of suspending the parent ketone in water, and adding bromine dropwise while the reaction flask was immersed in an ice-bath. More than a 1:1 molar ratio of bromine:ketone was used. Attempts to reproduce the preparation were unsuccessful due to the fact that the crude reaction mixture decomposed fairly readily either when the pressure was not low enough or the distillation was not done fast enough. Hence, the crude reaction mixture was directly separated on a silica gel column. This led to a mixture containing 53, 58 and 59 in the earlier fractions and a white crystalline solid 60 in the later fractions.



58



59

60

Preparation of the bromo ketones 53 and 54 was then accomplished by brominating the enol acetate of 4-t-butylcyclohexanone with a carefully controlled 1:1 molar ratio of bromine:enol acetate in formic acid.

The crude mixture contained mainly 53 and 54, together with some unreacted starting enol acetate. This crude product was separated into pure trans 53 and cis 54 isomers by column chromatography without any prior distillation. The physical data obtained for trans 53 and cis 54 agree with the reported data.

2.2 Properties

2.2.A Thin Layer Chromatography (tlc)

On tlc with silica gel as the adsorbent, the trans isomers gave R_f values higher than the cis isomers. One reason presumably is that

the polar carbonyl group can more readily get to the adsorbent when the substituent is equatorial rather than axial.[36,37] It may well be simply because the equatorial halo ketones have greater dipole moments and are therefore more polar and more strongly adsorbed than the axial epimers. On tlc both trans isomers isomerize to a certain extent to the respective cis isomers and vice versa.

2.2.B Gas-Liquid Partition Chromatography (glpc)

The behavior of all four compounds on glpc is very similar to that on tlc. Trans isomers have shorter retention times compared to the cis isomers and both interconvert on the glass columns packed with 1% or 5% DEGS on Chromosorb P; 1% XE-60 on Gas-Chrom Q; 1% BDS on Neutraport "S" or Chromsorb W; and 1% Carbowax 20M on siliconized Chromosorb W. Isomerization occurs to a lesser extent on the column packed with 1% SE-30 on Chromosorb W. The temperature range used was 80-160° and the optimum temperature was 120°.

2.2.C Dipole Moments

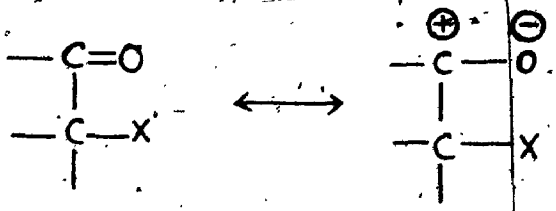
The dipole moments of trans- and cis-2-chloro-4-t-butylcyclohexanones (51 and 52) as well as those of trans- and cis-2-bromo-4-t-butylcyclohexanones (53 and 54) have been reported by Allinger and coworkers.[38] The dipole moments of the cis isomers (52 and 54) in which both the C-X and C=O bond moments are nearly in the same plane and pointing in the same direction exhibit higher dipole moments whereas the trans isomers (51 and 53) where the C-X and C=O bond moments are pointing in different directions tend to have lower dipole moments. The value reported for trans-2-chloro-4-t-butylcyclohexanone (51) is 3.17D and

that for cis-2-chloro-4-t-butylcyclohexanone (52) is 4.29D in benzene solution.[33] The corresponding values for the bromo ketones 53 and 54 in benzene are 3.20D and 4.27D, respectively.[38]

2.2.D Infrared Absorption (ir)

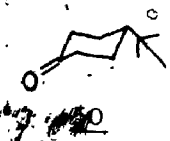
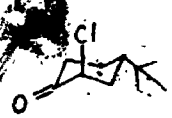
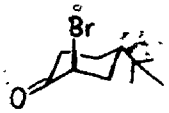
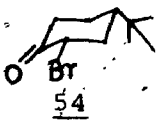
The most informative and characteristic absorption band in the infrared spectrum of an α-halo ketone is the carbonyl stretching band. Jones and coworkers[39] have studied the carbonyl stretching band in α-halogenated ketosteroids of known configuration and concluded that an axial halogen has essentially little or no effect on the position of the carbonyl absorption frequency whereas an equatorial halogen shifts the carbonyl absorption band to higher frequency by 16-21 cm^{-1} relative to the unsubstituted ketone.

The reason is probably that it would be more difficult to stretch the carbonyl group when two dipoles oriented in the same direction are eclipsed in the same plane, i.e., syn periplanar or almost so.[39] The picture will be clear if the two principal resonance forms of the carbonyl group are considered. The existence of C-X decreases the relative significance of the ionic cannonical form and hence the carbonyl group



would be stronger and less easily stretched.[39] The infrared spectra of 51-54 are in agreement with this general trend. The carbonyl absorption maxima for compounds 51-54 are compared with the parent ketone 50 in Table 1 (p. 26).

Table 1. Infrared Data of Monohalo Ketones

Compounds	$\nu_{C=O}$ (CCl_4) in cm^{-1}			
	This Work	Allinger Ref 33 & 35	Stothers Ref 34	Casadevall Ref 40
	1720			
 51	1730	1736	1730	1725
 52	1740	1748	1745	1740
 53	1725	1724	1730	1720
 54	1735	1739	1742	1730

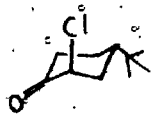
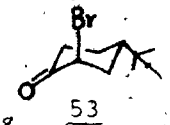
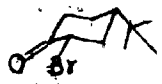
2.2.E Ultraviolet Spectroscopy (uv)

The n-π* absorption band for a simple ketone usually occurs at approximately 280 nm. This absorption band corresponds to the excitation of an electron from a non-bonding orbital on the carbonyl oxygen to an antibonding π* orbital of the carbonyl group.

The introduction of a halogen alpha to the carbonyl group affects the absorption as shown in Table 2 (p 28). As observed, an equatorial halogen has virtually no effect on the carbonyl absorption, whereas an axial halogen shifts the absorption maxima to the longer wavelength region. This could be rationalized by the explanation offered by Cookson[74] as well as Kosower[41] for a similar system. A chlorine or bromine atom has unfilled upper orbitals and, due to its axial position, could overlap slightly with the antibonding oribital of the carbonyl carbon. The excited state is therefore stabilized by this partial overlap.[41] This stabilization is absent in the ground state because the axial halogen is too far away from the non-bonding orbital on oxygen. Since an axial halogen stabilizes the excited state but not the ground state, the transition energy for the n-π* transition decreases as compared to that for the unsubstituted ketone. This results in a shift of the n-π* absorption band to the longer wavelength region.

The situation reverses itself when the halogen is in an equatorial position. The empty orbitals of equatorial halogen are in a favorable position to overlap with the non-bonding orbital on oxygen and hence stabilize the ground state but not the excited state. This stabilization is presumably small and hence no significant shift was observed.

Table 2. Ultraviolet Data of Monohalo Ketones

Compounds	λ_{max} in nm (ε) This Work*	Casadevall Ref 40	Allinger# Ref 33 & 35
 50	285 (16)		
 51	305 (35)	303 (48)	306 (49)
 52	280 (17)	280 (20)	283 (15)
 53	308(94)	310 (104)	310 (128)
 54	281 (13)+	283 (22)	286 (25)

* in MeOH

\+ in EtOH

\# 51 and 52 in dioxane, 53 and 54 in 95% EtOH.

2.2.F Proton Magnetic Resonance Spectra (pmr)

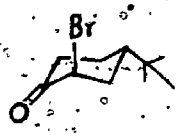
The pmr spectra of all four isomers 51, 52, 53 and 54 are displayed in Fig. 1-4 (p 31-34). The CHX protons absorb in the region δ 4-5 in deuteriochloroform. The collected data are shown in Table 3 (p 30). The region in which the CHX proton appears for trans-2-chloro ketone 51 does not overlap with the region in which the CHX proton is found for cis-2-chloro ketone 52. Similarly, no overlap of CHX proton absorptions occurs for trans-2-bromo 53 and cis-2-bromo 54.

2.3 Quantitative Measurement

After a thorough examination of the physical properties of the monohalo ketones 51-54, a good method for identification and estimation of the relative epimeric ratio may be chosen. Tlc and glpc are good analytical methods but not good enough for quantitative determinations since the isomers epimerize to some extent on the adsorbent or the packing material. Although dipole moment measurements have been used to determine the relative ratio of two epimers upon equilibration,[33,38] this method is not likely to be useful here. The reason is that the method is not highly accurate and at the same time it is impossible to have the crude reaction product from halogenation to be completely free from the starting material or any other impurities which would certainly affect the observed dipole moment. Allinger and coworkers[33,35] have used the fingerprint region of the infrared spectra to estimate the equilibrium ratio of epimeric halo ketones. However, the method is very tedious and inaccurate. Similarly, uv spectroscopy is equally inaccurate.

The proton magnetit resonance method seemed to be the most promising method for identification of the isomers and estimation of the

Table 3. Proton Chemical Shifts of Monohalo Ketones

Compounds	CHX ($CDCl_3$)					
	This Work		Stothers Ref 34		Casadevall Ref 40	
	δ	J*	δ	J*	δ	J*
 51	4.22	5.3	4.23	5.9	4.25	5.0
 52	4.55	17.8	4.50	18.0	4.53	19.0
 53	4.37	5.7	4.35	5.6	4.38	5.0
 54	4.70	18.1	4.67	18.6	4.69	15.0

* Vicinal coupling $|J_{AX}+J_{BX}|$ in Hz

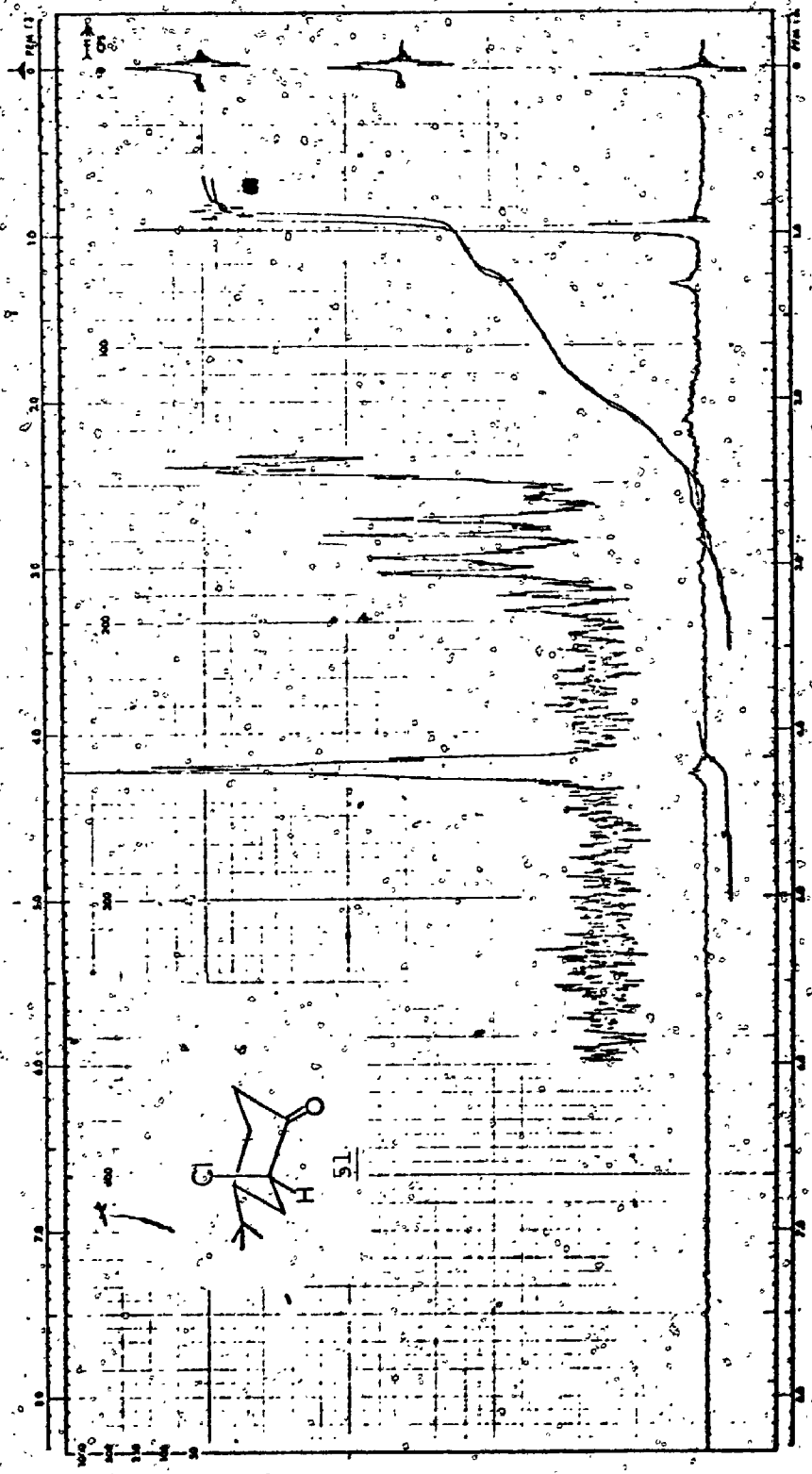


Fig. 1. Pmr Spectrum of trans-2-Chloro-4-t-butylcyclohexanone (51)

Fig. 2. Pmr Spectrum of cis-2-Chloro-4-t-butylcyclohexanone (52)

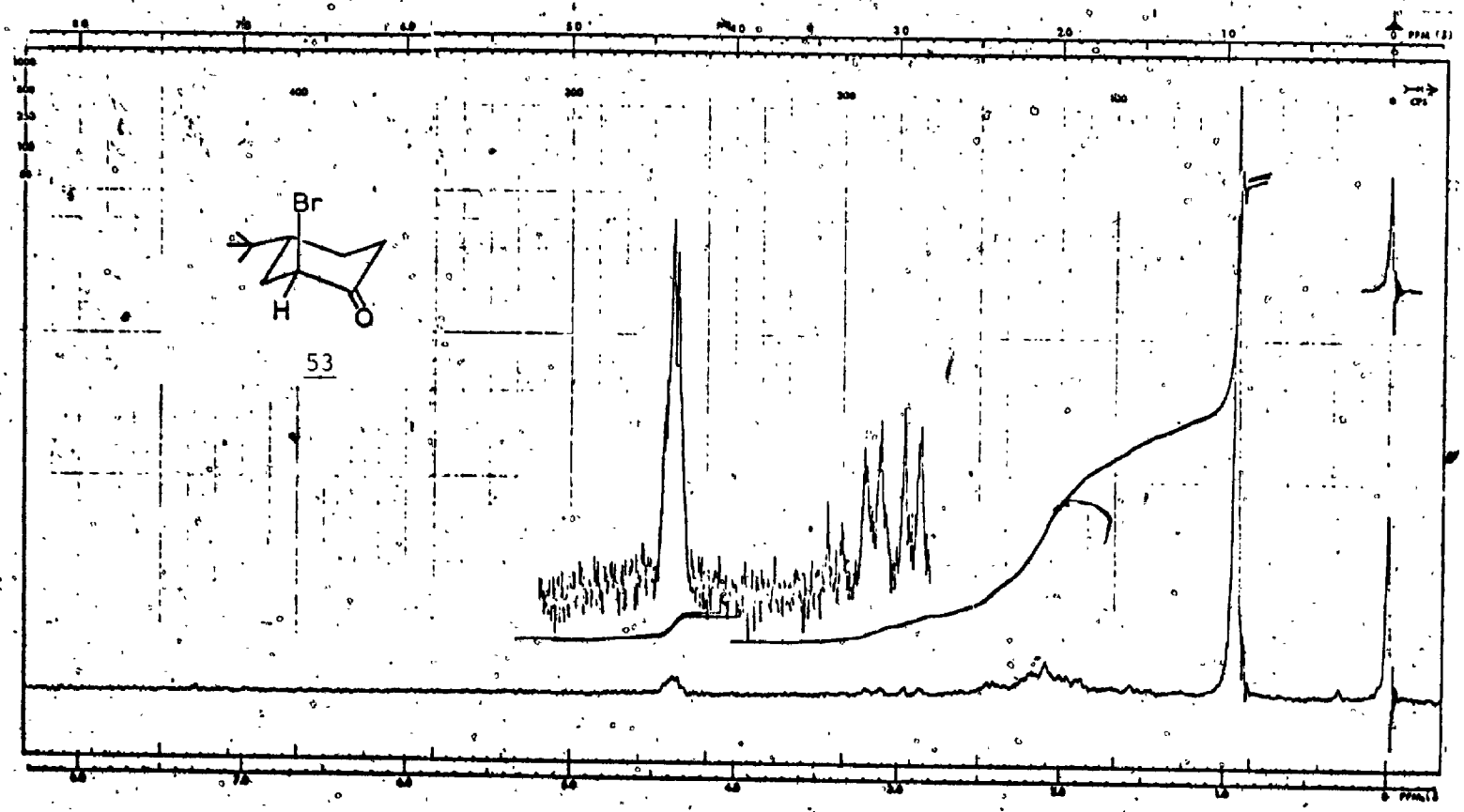


Fig. 3. Pmr Spectrum of trans-2-Bromo-4-t-butylcyclohexanone (53)

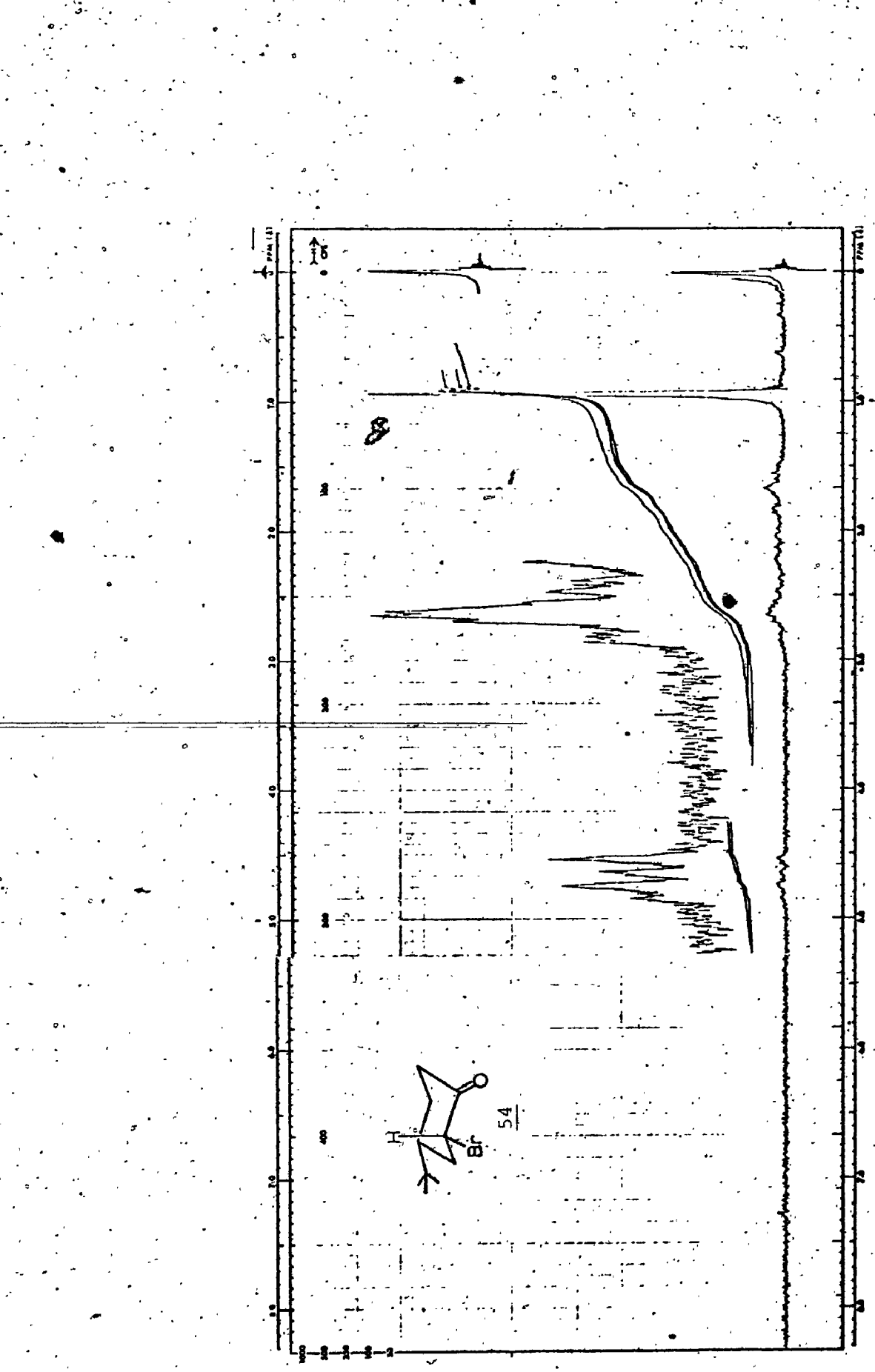


Fig. 4. Pmr Spectrum of cis-2-Bromo-4-t-butylcyclohexanone (54)

epimeric ratio. One advantage is that the chemical shift of the proton on the carbon bearing the halogen atom is very much downfield from the rest of the protons in the molecule. At the same time, a study by Pan and Stothers[34] had covered the proton magnetic resonance of α-halocyclohexanones thoroughly. Moreover, one can be relatively sure that what is being measured belongs to a specific halo ketone. The accuracy of this method is fairly high since it could detect 2% of an isomer in the presence of 98% of the other epimer. This method was therefore chosen for estimating the epimeric ratio in the reaction mixture.

CHAPTER 3

EQUILIBRATION STUDIES OF MONOHALO-4-t-BUTYLCYCLOHEXANONES

3.1 Equilibrium Ratio

In order to make sure that the ratio of the epimeric halo ketones from halogenation was indeed the first-formed ratio, each of the epimeric halo ketones was subjected to the same reaction conditions to test its stability. If both epimers are stable, then the ratio from halogenation must be the kinetic ratio. At the same time, it was necessary to compare the ratio from halogenation with the equilibrium ratio in the same solvent to see how far they differ from each other. If they are very far apart, then we would have more confidence that the ratio from halogenation is the true kinetic ratio.

3.2 Equilibration Studies

Equilibration studies were carried out in a series of six solvents ranging from highly polar and protic to nonpolar and aprotic. The method used was to treat the crude halogenation mixture containing only the monohalo ketones with a saturated solution of halogen acid HX in the solvent required. The pmr spectra of the reaction mixture in the nmr tube was periodically recorded and integrated until the equilibrium was attained and the ratio remained constant. Equilibrium usually was established in 5-7 days at 25°. From tests with cis- and

Table 4. Equilibrium Composition of Monochloro Ketones

Solvent	Dielectric constant (D_2O)*	Percentage of cis- and trans-2-chloro-4-t-butylcyclohexanones					
		This study (pmr)		Allinger (ir) ref 33		Casadevall (pmr) ref 40	
		cis	trans	cis	trans	cis	trans
HCOOH	47.9	76	24				
CF_3COOH	40.0†	72	28				
CH_3CN	38.8	77	23				
CH_3COOH	7.1	70	30			68	32
$CHCl_3$	5.0	65	35				
CCl_4	2.2	57	43	43	57	46	54

* From ref 42.

† From ref 43.

Table 5. Equilibrium Composition of Monobromo Ketones

Solvent	Dielectric constant (D_2O)*	Percentage of cis- and trans-2-bromo-4-t-butylcyclohexanones					
		This study (pmr)		Allinger (ir) ref 35		Casadevall (pmr) ref 40	
		cis	trans	cis	trans	cis	trans
HCOOH	47.9	55	45				
CF_3COOH	40.0†	48	52				
CH_3CN	38.8	53	47				
CH_3COOH	7.1	43	57			47	53
$CHCl_3$	5.0	43	57				
CCl_4	2.2	31	69	22	78	32	68

* From ref 42.

† From ref 43.

trans-2-chloro-4-t-butylcyclohexanones (52 and 51) it was found that the equilibrium ratio of 51:52 does not change significantly over a temperature range of 0-40°. For instance, the equilibrium ratio of 51:52 is roughly 1:1 molar in CCl_4 at 0°, 25°, and 40°.

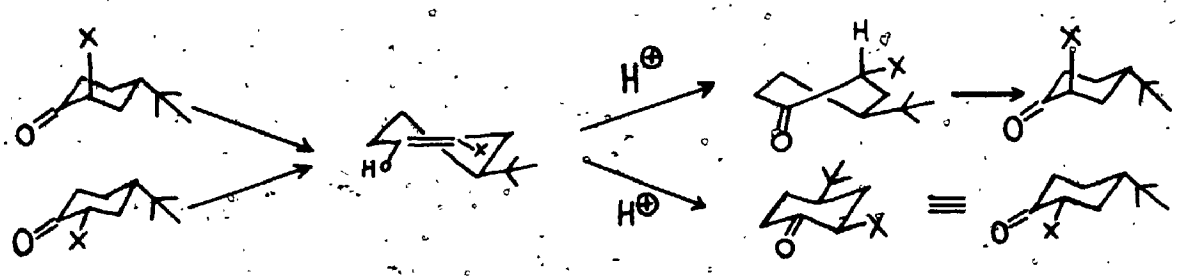
The behavior of both chloro and bromo ketones is quite similar. The general trend being that the percentage of equatorial halo ketone increases as the dielectric constant of the solvent increases. The results are listed in Tables 4 and 5 (p 37-38). In mixed solvents, the ratio seems to be affected only by the solvent having the higher dielectric constant. Results for bromo ketones are shown in Table 6.

Table 6. Equilibrium Composition of Monobromo Ketones in Mixed Solvents

Solvent mixture (1:1)	Percentage of cis- and trans-2-bromo-4-t-butylcyclohexanones	
	cis	trans
CH_3CN-HCOOH	55	45
$CHCl_3$-HCOOH	45	55
CCl_4-HCOOH	44	56

3.3 Solvent Dielectric Constant vs. Percentage of cis Isomers

The equilibrium between axial and equatorial halo ketones was attained by an enolization-ketonization sequence as shown in the equations below.



As was mentioned in the previous chapter, cis isomers have higher whereas trans isomers have lower dipole moments. The experimental results show that as the solvent dielectric constant increases the percentage of cis isomers also increases. This could be rationalized by applying the mathematical expression shown below

$$E_{\mu} = \frac{\mu_1 \mu_2}{Dr^3} (\cos x - 3\cos\alpha_1 \cos\alpha_2)$$

where E_{μ} is the classical electrostatic interaction energy of the two dipoles μ_1 and μ_2, r is the distance between them, D is the dielectric constant of the medium, and x, α_1 and α_2 are angular terms defining their relative orientation.

This equation was first applied by Smyth and coworkers[44] by adaptation from a theoretical relationship originally derived by Jeans.[45,69] Since the interaction energy is inversely proportional to the dielectric constant of the solvent, cis isomers become more stable as the dielectric constant of the solvent increases. This then operates to favor the equatorial form in a highly dielectric medium. As the dielectric constant increases from carbon tetrachloride to formic acid, it is therefore logical to expect the percentage of cis isomer to increase in the same direction.

Another point which deserves comment is that at 0-40° the ratio

of the epimers stays quite constant. This is probably an indication that the balance of polar and steric factors is not affected very much by temperature. Although the bulk dielectric constant does vary a bit with temperature, the change probably is not great enough to exert any significant effect. Solvents of higher dielectric constant dominate the scene when a mixture of solvents was used because solvents of higher dielectric constants tend to stabilize the equatorial isomers more than those of lower dielectric constants.

CHAPTER 4

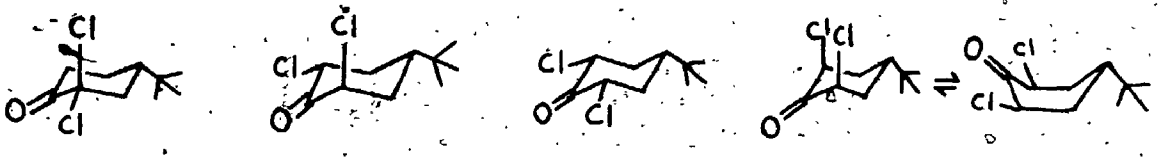
STUDIES ON DI-, TRI-, AND TETRACHLORO KETONES

4.1 Polychlorination

In the course of studying monochlorination, dichloro ketones have inevitably been encountered as by-products in low dielectric media (e.g. CCl_4 and $CHCl_3$) even with a 10:1 molar ratio of substrate:chlorine. Dichlorination also occurred in acidic medium (e.g. CH_3COOH-H_2O (9:1)) with an excess of chlorine. Trichloro- and tetrachloro-ketones were obtained in cases where a three to four fold excess of chlorine and a higher reaction temperature were employed. These products have been isolated and their spectroscopic and chromatographic properties and isomeric equilibration studied. The main purpose is to study a complete series of halo ketones so that their presence in the crude product of halogenation could be detected unambiguously.

4.2 Dichloro Compounds

There are four possible α-dichloro ketones, i.e., 55, 56, 57, and 79, of which 79 has never been isolated. This is not difficult to explain since obviously non-bonded interaction between the two axial chlorine atoms is so severe that isomer 79 is not the favored isomer under either kinetic or thermodynamic conditions. The boat form with equatorial halogens would of course have higher energy content than 56



55 56 57 79

or 57. The other three known isomers 55, 56, and 57 were isolated and purified.

4.2.A Preparation

As was mentioned earlier, direct chlorination in CH_3COOH-H_2O (9:1) by passing chlorine through the solution containing 4-t-butylcyclohexanone (50) invariably led to the formation of dichloro compounds as the major products. Other reactions, with 2-2.5:1 molar ratio of sulfuryl chloride in methylene chloride-dioxane (1:1) or methylene chloride alone also furnished dichlorinated products. The problem in the preparation of pure 55, 56, and 57 resides mainly in the separation. Among the three dichloro ketones 55, 56, and 57, cis,cis-2,6-dichloro ketone 57, is the easiest one to isolate. This is because its solubility in n-pentane is rather low and its melting point and boiling point are relatively high. Chlorination of 4-t-butylcyclohexanone (50) with a 2:1 molar ratio of sulfuryl chloride in methylene chloride-dioxane (1:1) at 25-35° for 12.5 hr led to a mixture containing a small amount of monochloro ketones and mainly dichloro ketones 55, 56, and 57. Distillation of the crude product under carefully controlled reduced pressure conditions provided a nonvolatile brown oil as the residue in the distillation pot. Trituration of this brown oil with n-pentane furnished the desired cis,cis-2,6-dichloro ketone 57.

It was not too difficult to get gem-dichloro ketone 55 since it has a relatively low boiling point. In the chlorination reaction carried out in methylene chloride-dioxane (1:1) or methylene chloride alone, compound 55 was present in the crude product. Upon fractional distillation on a spinning band column under reduced pressure, gem-dichloro ketone 55 was obtained in the first few fractions right after trans-2-chloro ketone 51. The collected fraction crystallized after standing in the refrigerator overnight.

The isolation of cis,trans-2,6-dichloro ketone 56 is most touchy. Upon spinning band distillation under reduced pressure, compound 56 appeared after trans-2-chloro ketone 51 and gem-dichloro ketone 55. However, a trace of either trans-2-chloro ketone 51, or cis-2-chloro ketone 52, or cis,cis-2,6-dichloro ketone 57 present was sufficient to prevent it from crystallizing. For instance, in a fraction containing mainly cis,trans-2,6-dichloro ketone 56 with ~10% of cis-2-chloro ketone 52, cooling in a refrigerator overnight gave white crystals of 52. Removal of 52 by suction filtration enriched the mother liquor to cis,trans-2,6-dichloro ketone 56 almost completely judging from the pmr spectrum. However, 56 refused to crystallize. In another fraction containing mainly cis,trans-2,6-dichloro ketone 56 and a small amount of cis,cis-2,6-dichloro ketone 57, a separation of 56 from 57 on a thick plate (silica gel) furnished almost pure 56 but it still did not crystallize. Finally, crystalline cis,trans-2,6-dichloro ketone 56 was obtained as described below.

Chlorination of 4-t-butylcyclohexanone (50) in CH_3COOH-H_2O (9:1) with chlorine gas furnished a crude product containing dichloro ketones 55, 56, and 57, and trichloro ketone 61. Upon fractional distillation on

a spinning band column, a fraction containing a mixture of a few white crystals suspended in a colorless oil was shown by the pmr spectrum to contain mainly cis,cis-2,6-dichloro ketone 56 with only a trace of gem-dichloro ketone 55. The colorless oil from this fraction was carefully pipetted out and triturated with n-pentane. After standing in the refrigerator overnight, white crystals were obtained. The pmr, ir, and mass spectra all agreed with the structure 56 and with the reported data.[47] The best way to obtain 56 seems to be the chlorination of chloro enol acetate 67 which furnished 56 as the only product (see Chapter 6).

4.2.B Properties

All three dichloro ketones 55, 56, and 57 are white crystalline solids. It is not unexpected to find that the melting point of 57 is the highest since 57 is symmetrical[48] whereas 55 and 56 are not.

On tlc, both gem-dichloro ketone 55 and cis,trans-2,6-dichloro ketone 56 have the same R_f value which is much higher than that of cis,cis-2,6-dichloro ketone 57 (see Table 7, p 46). This is in agreement with the polarity of the molecules which should fall in the order 55~56<57. The reason is that 57 has two equatorial chlorine atoms pointing in almost the same direction as the carbonyl group and thus increases the resultant dipole moments whereas in 55 or 56, each has an axial chlorine which points in a different direction from the equatorial chlorine as well as the carbonyl group and hence reduces the resultant dipole moment and thefefore lowers the polarity.

With 1% SE-30 on Chromosorb-W at 120°, both gem-dichloro ketone 55 and cis,trans-2,6-dichloro ketone 56 have the same retention time, whereas cis,cis-2,6-dichloro ketone 57 has a longer retention time. (see

Table 7. Physical Constants of Polychloro Ketones

Compds / Data	gem-di-Cl 55	c,t-di-Cl 56	c,c-di-Cl 57	tri-Cl 61	tetra-Cl 62
mp (^{o}C)	38.5-40	41-42	148-150	102-103	66-68
R_f PE-$CHCl_3$ (1:1)	0.65	0.65	0.26	0.24	0:24
t_r (min), 120^{o} 1% SE-30 on Chromosorb W	2.8	2.8	3.4	7.1	7.8
t_r (min), 120^{o} 1% XE-60 on Gas-Chrom Q	2.95	5.4	5.15		
ir $\nu_{C=O}$ in cm^{-1} (CCl_4)	1745	1751	1755	1768	1764
pmr δ ($CDCl_3$)	no peak at	4.50 H_e J=6.0	4.63	5.23	no peak lower field than
$J=\lvert J_{AX}+J_{BX}\rvert$ (Hz)	3.5-5.5	5.20 H_a J=19.5	J=18.0	J=20.0	3.67
pmr δ (Benzene)	no peak at	4.10 H_e J=6.0	3.87		
$J=\lvert J_{AX}+J_{BX}\rvert$ (Hz)	3.5-5.5	4.83 H_a J=19.0	J=19.0		

Table 7). The difference of 0.6 min is not sufficient for unambiguous analytical purposes especially since the peaks are relatively broad. When the column was packed with 1% XE-60 on Gas-Chrom Q at 120°, compounds 56 and 57 have very close retention times whereas the peak due to 55 is relatively well separated (see Table 7). This column was employed to detect gem-dichloro ketone 55 in the crude chlorination product.

The ir spectra of 55, 56, and 57 revealed that the main carbonyl absorption frequencies are quite close (see Table 7). These absorption frequencies do not range too far away from the cis-2-chloro ketone 52 which absorbs at 1740 cm^{-1}.

The pmr spectra of 55, 56, and 57 are shown in Figs. 5, 6, and 7 (p 48-50). The CHCl protons absorb in the region between δ 4-5 and are listed in Table 7.

The CHCl peak position of 57 in benzene is very much different from that in deuteriochloroform. The proton exhibits an upfield shift from δ 4.63 to δ 3.87. The absorption peak (δ 3.87) is also 0.23 ppm from the absorption peak of cis-2-chloro ketone 52 (δ 4.10). Hence, the chemical shift in benzene reveals whether 57 is present even in the presence of 52 (see Fig. 15, p 117).

4.2.C Equilibration Studies

The equilibration of cis,trans-2,6-dichloro ketone 56 and cis,cis-2,6-dichloro ketone 57 was studied in four different solvents. The ratio was obtained by integrating the CHCl signal in the pmr spectra. The results are tabulated in Table 8. These results serve as a reference for the kinetically controlled chlorination of chloro enol acetate 67.

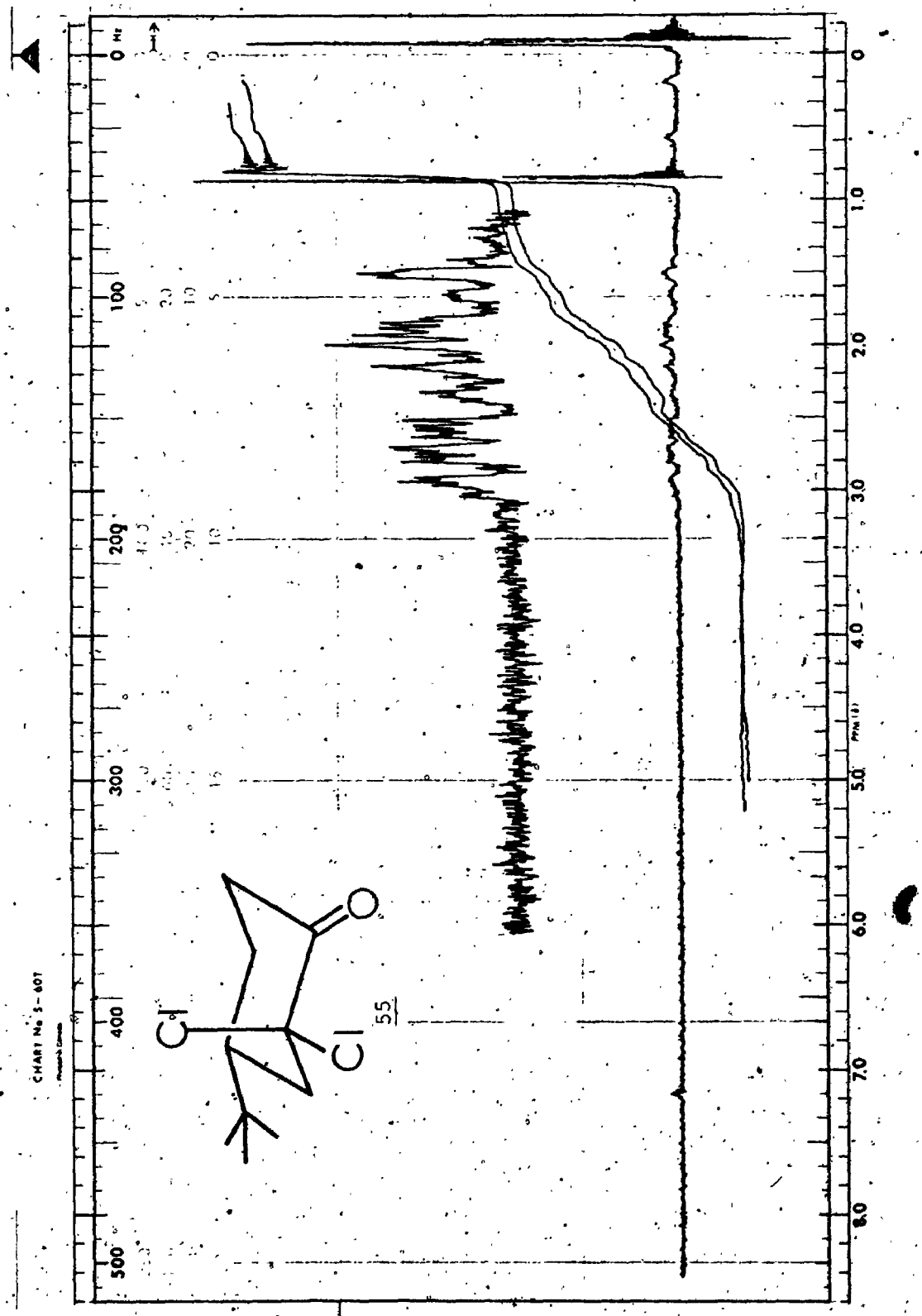


Fig.5. Pmr Spectrum of 2,2-Dichloro-4-t-butylcyclohexanone (55)

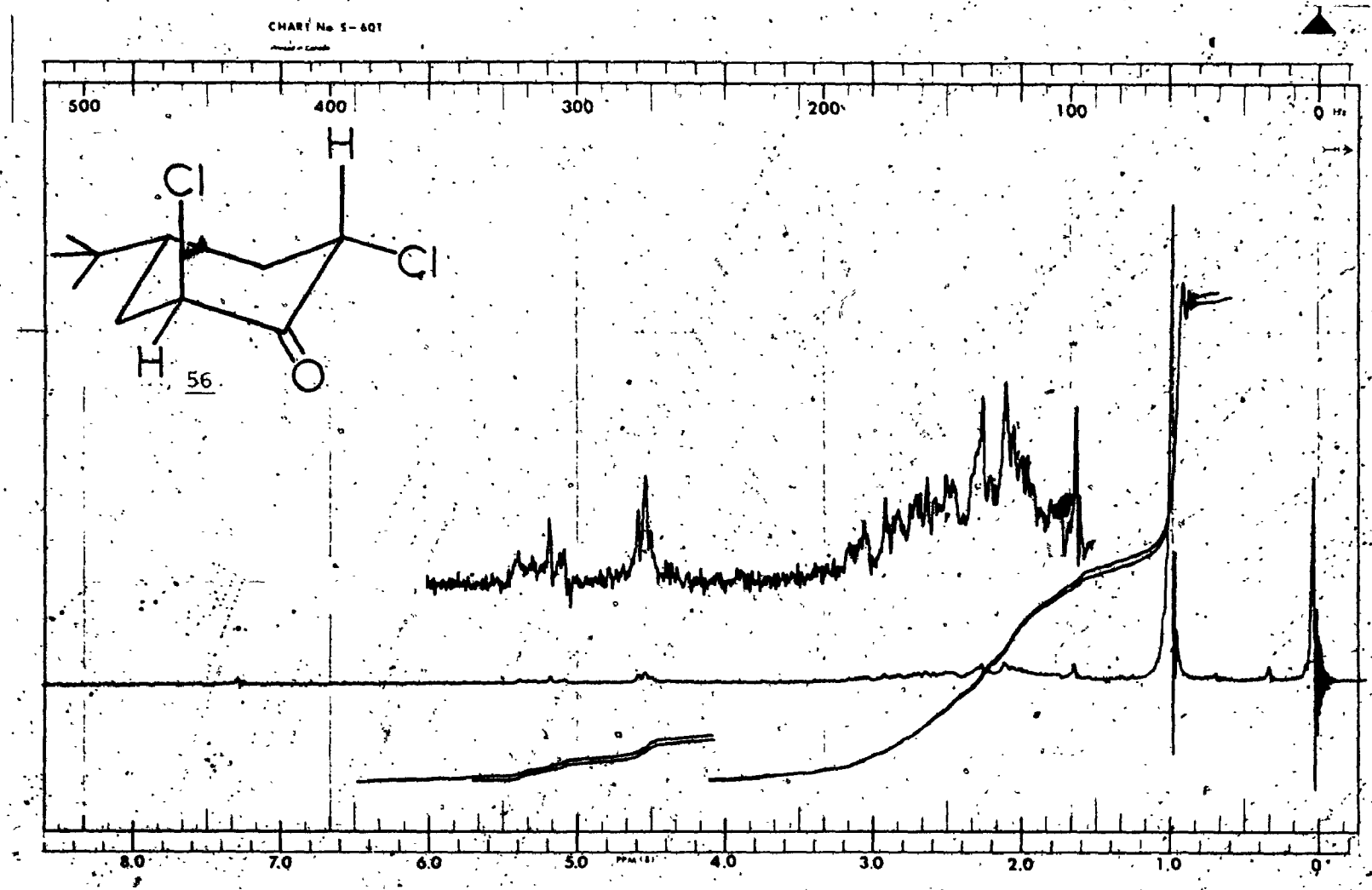


Fig. 6. Pmr Spectrum of cis,trans-2,6-Dichloro-4-t-butylcyclohexanone (56)

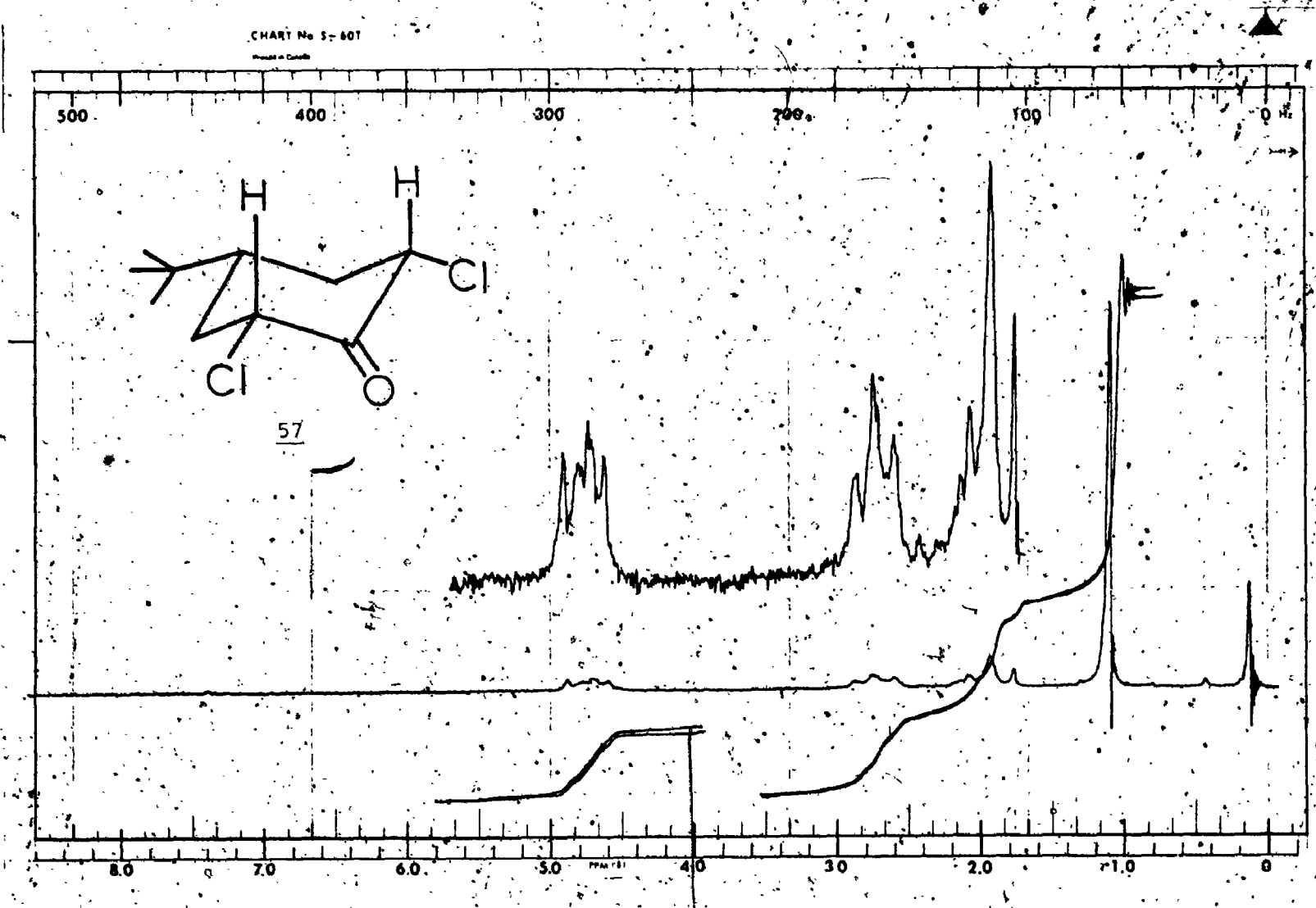


Fig. 7. Pmr Spectrum of cis,cis-2,6-Dichloro-4-t-butylcyclohexanone (57)

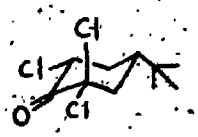
Parallel to the study mentioned in the previous chapter on the equilibration of monohalo ketones, the percentage of the more polar component increases as the dielectric constant of the solvent employed increases.

Table 8. Equilibration of Dichloro Ketones

Solvent	Dielectric Const. D_{20°	% 57 in equil. mixt. at 25°	Equil. Const. at 25° (C_{57}/C_{56})
HCOOH	47.9	61	1.56
CH_3COOH	7.1	43	0.75
$CHCl_3$	5.0	31	0.42
CCl_4	2.2	28	0.39

4.3 Trichloro and Tetrachloro Compounds

Of the two possible trichloro ketones 61 and 61a, only 61 has been isolated. This previously unknown trichloro ketone was obtained accidentally during the preparation of dichloro ketones. It was obtained



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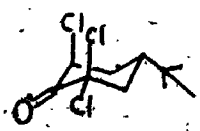
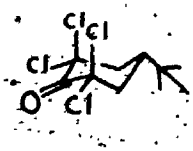


61a



62

pure from the residue after all the volatile components were removed. Trituration of the residual oil with n-pentane followed by recrystallization furnished pure trichloro ketone 61. A better way of preparing 61 is the polychlorination of the parent ketone 50 in acetic acid at 80-90° with 2:1 molar ratio of chlorine:ketone followed by rechlorination

of the crude product again with the same amount of chlorine used before. The crude product contained mainly trichloro ketone 61 and a small amount of tetrachloro ketone 62. The crude oil crystallized after standing in the refrigerator overnight. The crystals were washed and recrystallized from n-pentane to give the previously unknown tetrachloro ketone 62. The filtrate after 62 was removed was treated with methylene chloride and n-pentane to give white needles of trichloro ketone 61. The carbonyl absorption of 61 and 62 occurs at 1768 cm^{-1} and 1764 cm^{-1} respectively. The further introduction of chlorine into the molecules had little effect on the carbonyl absorption compared with the dichloro ketones. For more accessible comparison all physical data for 61 and 62 are listed in Table 7 along with those of the dichloro ketones. The pmr spectrum of trichloro ketone 61 is shown in Fig. 8 (p 53).

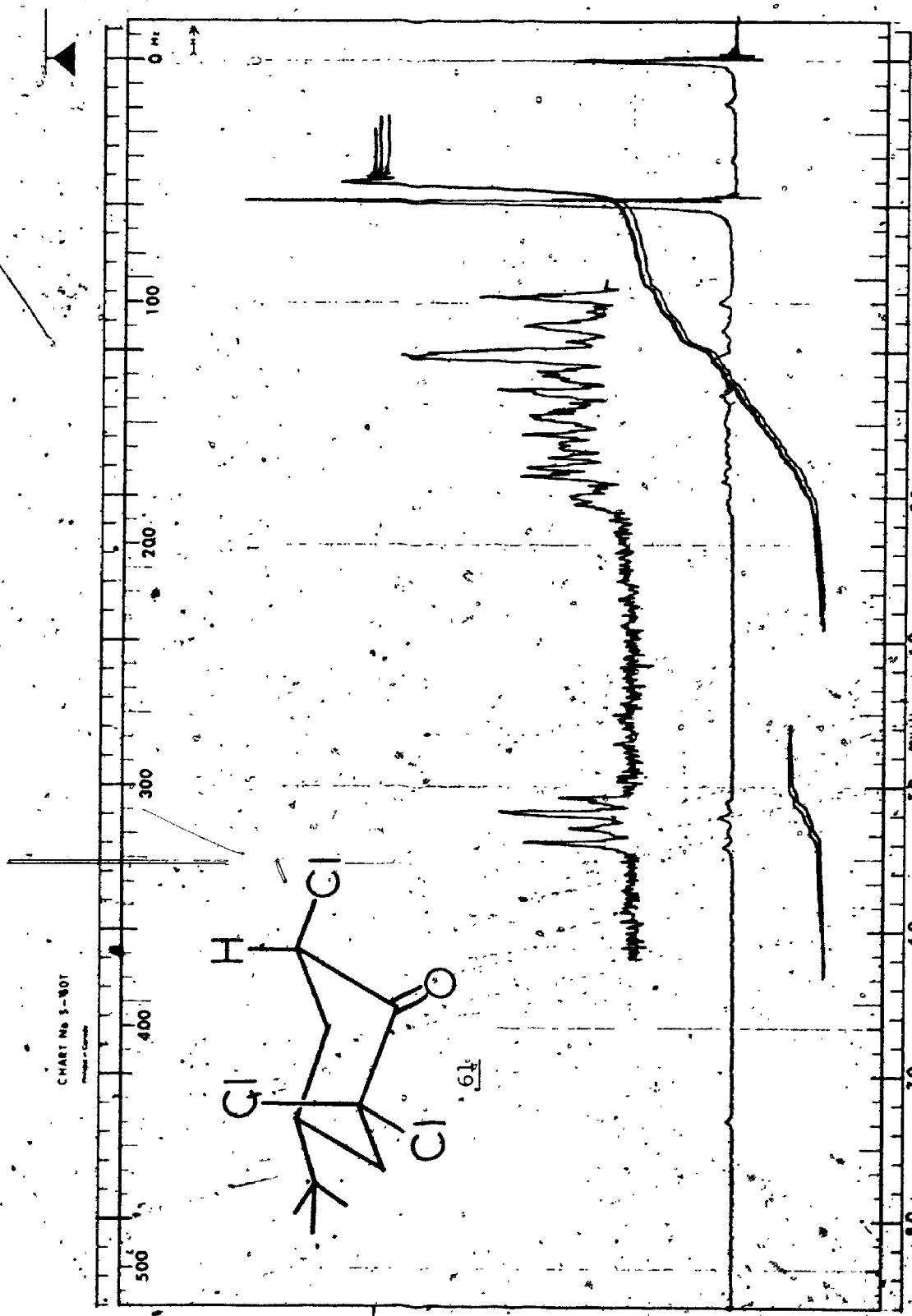


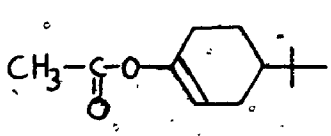
Fig. 8. Pmr Spectrum of 2,2,6-Trichloro-4-t-butylcyclohexanone (61)

CHAPTER 5

HALOGENATION OF 4-t-BUTYLCYCLOHEXANONE ENOL DERIVATIVES

5.1 General

The enol derivatives of 4-t-butylcyclohexanone chosen for detailed halogenation study were its enol acetate 63, enol 64, and lithium enolate 65. The enol silyl ether 66 from which the lithium enolate was prepared was not suitable for study under either acidic or neutral conditions. This conclusion arose from the fact that enol silyl ether 66 was unstable



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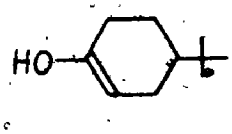

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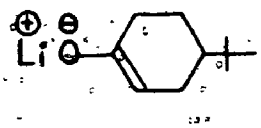

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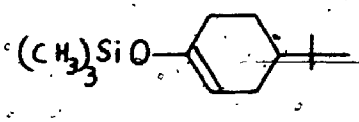

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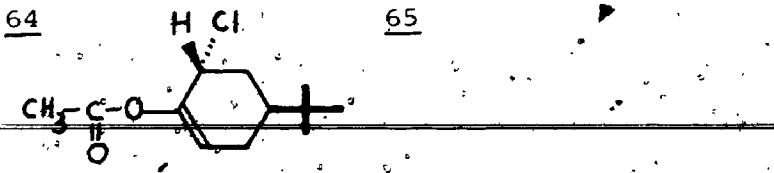
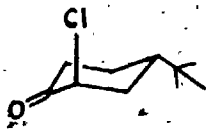


67

under acidic medium: a quantitative conversion to the parent ketone 50 was observed when 66 was treated with formic acid and stirred at 0-5° for 5 min. Under neutral conditions, in dimethoxyethane-carbon tetrachloride solution, both chlorination and bromination of 66 at 0-5° for 5 min resulted not only in the formation of the monohalo ketones 51-54 but also cis,trans-2,6-dihalo ketones 56 and 59 respectively. Therefore, halogenation of 66 was not studied further. Chlorination of chloro enol acetate 67 was studied in a variety of solvents and the results will be



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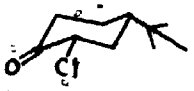

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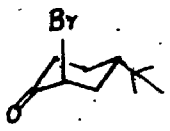

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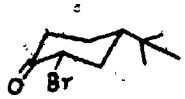

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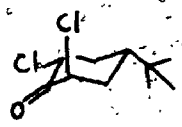

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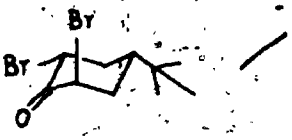

59

discussed in Chapter 6.

Enol acetate 63 was prepared from ketone 50 by adapting the methods of Rogic[66] and Lamaty.[67] The ketone and isopropenyl acetate were refluxed in the presence of p-toluenesulfonic acid with continuous removal of acetone to drive the reaction to completion. Pure 63 was obtained by distillation through a spinning band column under reduced pressure. The purity of 63 was checked by tlc, ir, and pmr (Fig. 9, p56).

Enol silyl ether 66 was prepared by adapting Stork's[50,68] method. Ketone 50 was treated with sodium hydride followed by trimethylchlorosilane in the presence of triethylamine to ensure a basic condition. Pure 66 was obtained by distillation through a spinning band column under reduced pressure. Its purity was checked by tlc, ir, pmr (Fig. 10, p57) and an elemental analysis.

Lithium enolate 65 was generated *in situ* by treating enol silyl ether 66 with methyllithium under a nitrogen atmosphere. The identity of the lithium enolate was confirmed by quenching the enolate anion with NH_4Cl to give ketone 50. In halogenation of the lithium enolate, a solution or a suspension of the lithium enolate was added to a solution of molecular halogen with vigorous stirring provided jointly by a

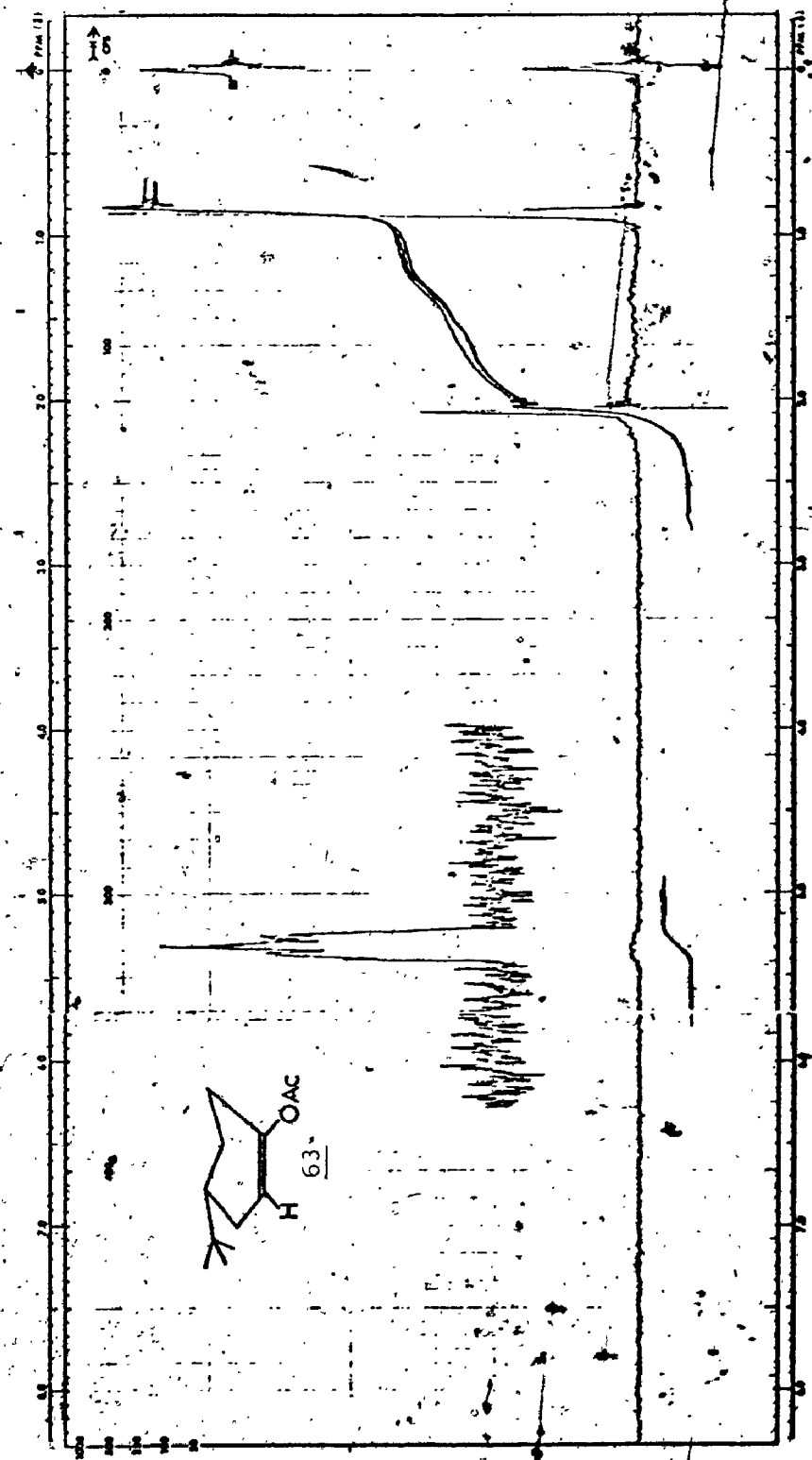

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Fig. 9. Pmr Spectrum of Enol Acetate 63

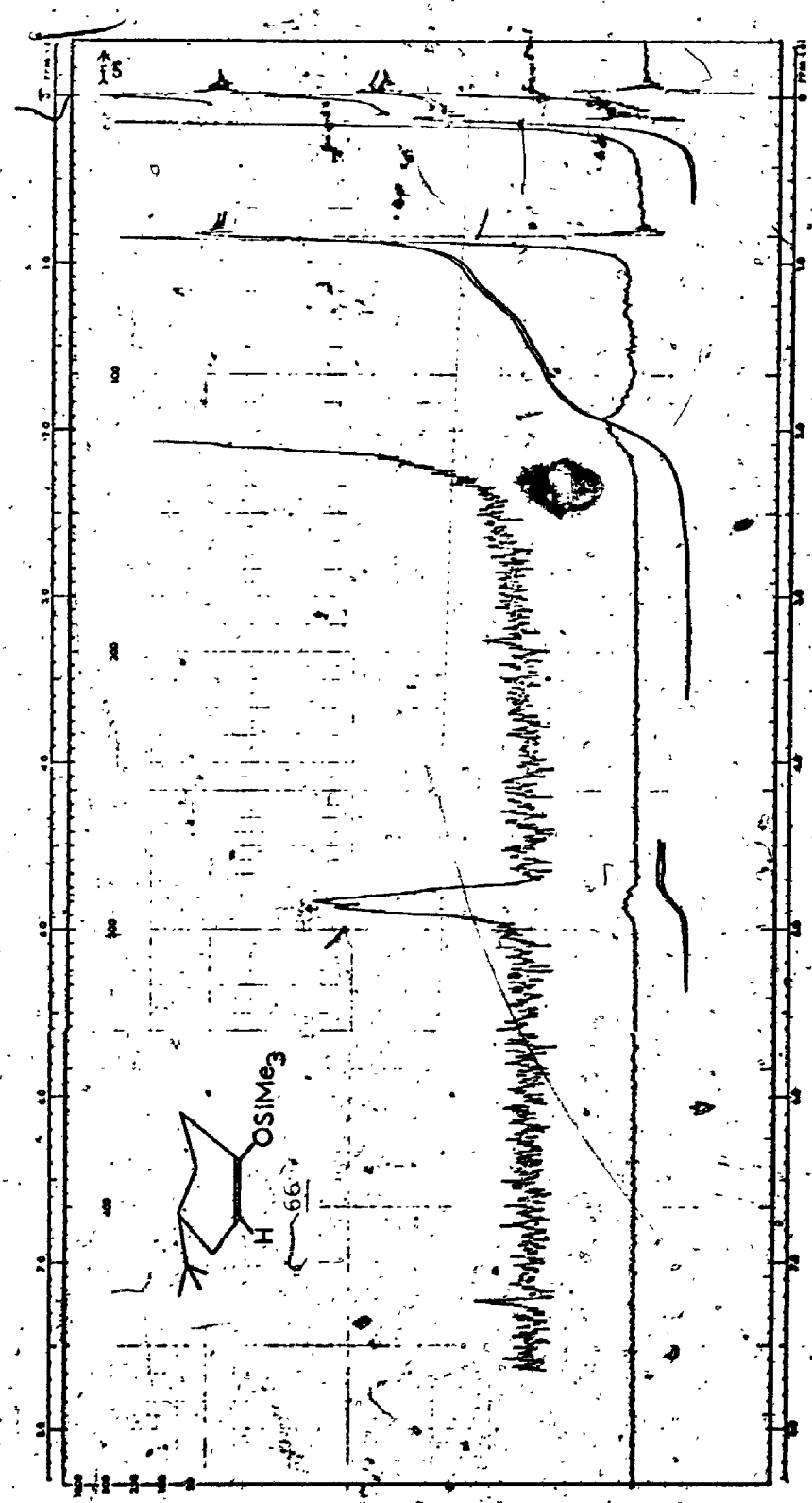


Fig. 10. Pmr Spectrum of Enol Silyl Ether 66

Vibromixer and [illegible] ensured that halogen was always pres[illegible] chances of epimerization of the first-form[illegible]

Chlori[illegible] were studied under a variety of [illegible] different polarity, and over the temperat[illegible] The main purpose of changing solvent was to find out whether there was any solvent effect on the stereochemistry of halogenation.

The conditions employed for halogenation were the mildest possible ones. To avoid undesired epimerization during the work-up procedure, the dried extracts of crude reaction product were evaporated in vacuo with the temperature of the heating bath set no higher than 40°. Control experiments on pure 51 and 52 were carried out to ensure that no epimerization occurred during the work-up procedure.

None of the reactions reported in this chapter are of radical nature since only the α and/or α' substituted halo ketones were obtained. This point was checked when chlorination was carried out in carbon tetrachloride solution. In light-initiated (λ 350-390 nm) radical chlorination, ketone 50 gave not only α-chloro ketones but also unidentified product(s) with pmr absorption peaks ~δ3.43. This signal presumably is due to the product(s) with chlorine attached to positions other than the α or α' position along the carbon skeleton. Under conditions not favoring radical halogenation, e.g., in the dark, in the presence of radical scavenger, and under an inert atmosphere, this side product was not formed.

5.2 Chlorination of 4-t-Butylcyclohexanone Enol Acetate (63)

5.2.A Chlorination in Formic Acid

In the course of this study, we found that formic acid is one of the best solvents for clean monohalogenation. Formic acid is a reducing agent, and it may be oxidized by chlorine. Therefore, before undertaking chlorination in this solvent, it was required to test the stability of chlorine in formic acid.

Formic acid was purified by standing overnight with anhydrous copper sulfate and then distilled. The pmr spectrum showed a singlet at δ8.10 due to the aldehydic proton and a singlet at δ10.75 due to the carboxylic acid proton. The separation of the two peaks was 159 Hz. When water was added to formic acid the acidic proton signal moved upfield. When 0.4 ml of water was added to 0.3 ml of formic acid the peak due to the acidic proton (δ6.33) surpassed the aldehydic proton (δ8.10) and increased in intensity. The position of the peak due to the carboxylic acid proton with reference to that due to the aldehydic proton was therefore a good indication whether an undesired amount of water was present.

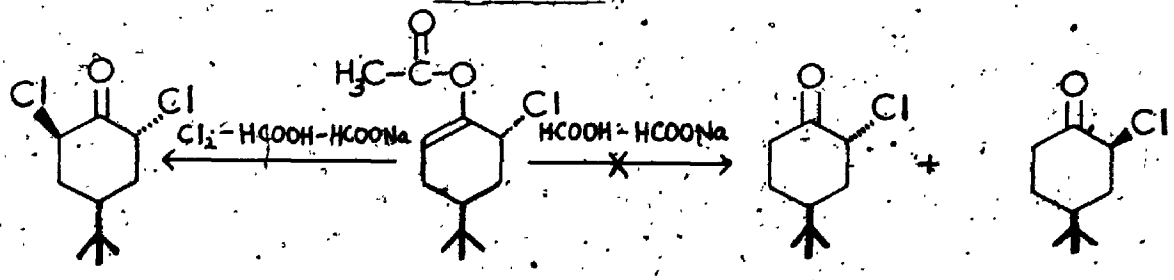
To find out whether chlorine reacts with formic acid, a standardized solution of chlorine in acetic acid was added to formic acid and allowed to stand at room temperature for 3 hr. Titration revealed that no change of titer had occurred. This indicated that chlorine did not react with formic acid at 25° within 3 hr. However, the solubility of chlorine was low in formic acid and chlorine escaped when the solution was left at room temperature overnight. Therefore, the solution had to be prepared immediately before use.

The enol acetate 63 was chlorinated for 5 min in the temperature range of 5-15° with an equivalent amount of chlorine dissolved in formic acid (Table 9, entry 1, p 69). This reaction gave very cleanly monochloro

ketones 51 and 52 together with 10-30% of unreacted starting enol acetate 63. The epimeric ratio of cis 52:trans 51 was 36:64 (see Fig. 11, p 61). A control experiment showed that enol acetate 63 was stable in a formic acid-sodium formate mixture for at least 1 hr at 25° in the absence of chlorine. This implied that the reaction product came directly from the reaction of enol acetate 63 with chlorine. To test whether the ratio is in fact the kinetically controlled one, the same reaction was carried out in the presence of an equivalent amount of sodium formate at 5-10° for 5 min (Table 9, entry 2). The result was found to be almost the same. Control experiments showed that each of the pure cis- and trans-2-chloro ketones, 52 and 51, was recovered unchanged when treated with a HCOOH-HCOONa-CH_3COCl mixture at 0-25° for at least 5 hr. The equilibrium ratio of cis 52:trans 51 in formic acid was 76:24 (see Chapter 3), quite different from the kinetic ratio.

In carbon tetrachloride solution a side reaction took place giving rise to chloro enol acetate 67. Since chloro enol acetate 67 was not formed in the formic acid solution, it was required to check the possibility that 67 was indeed formed in the reaction but was converted to chloro ketones 51 and 52 under acidic condition by solvolysis (Scheme 5-1). A control experiment showed that chloro enol acetate 67 was stable in a formic acid-sodium formate mixture in the absence of chlorine at

Scheme 5-1



56 67 52 51

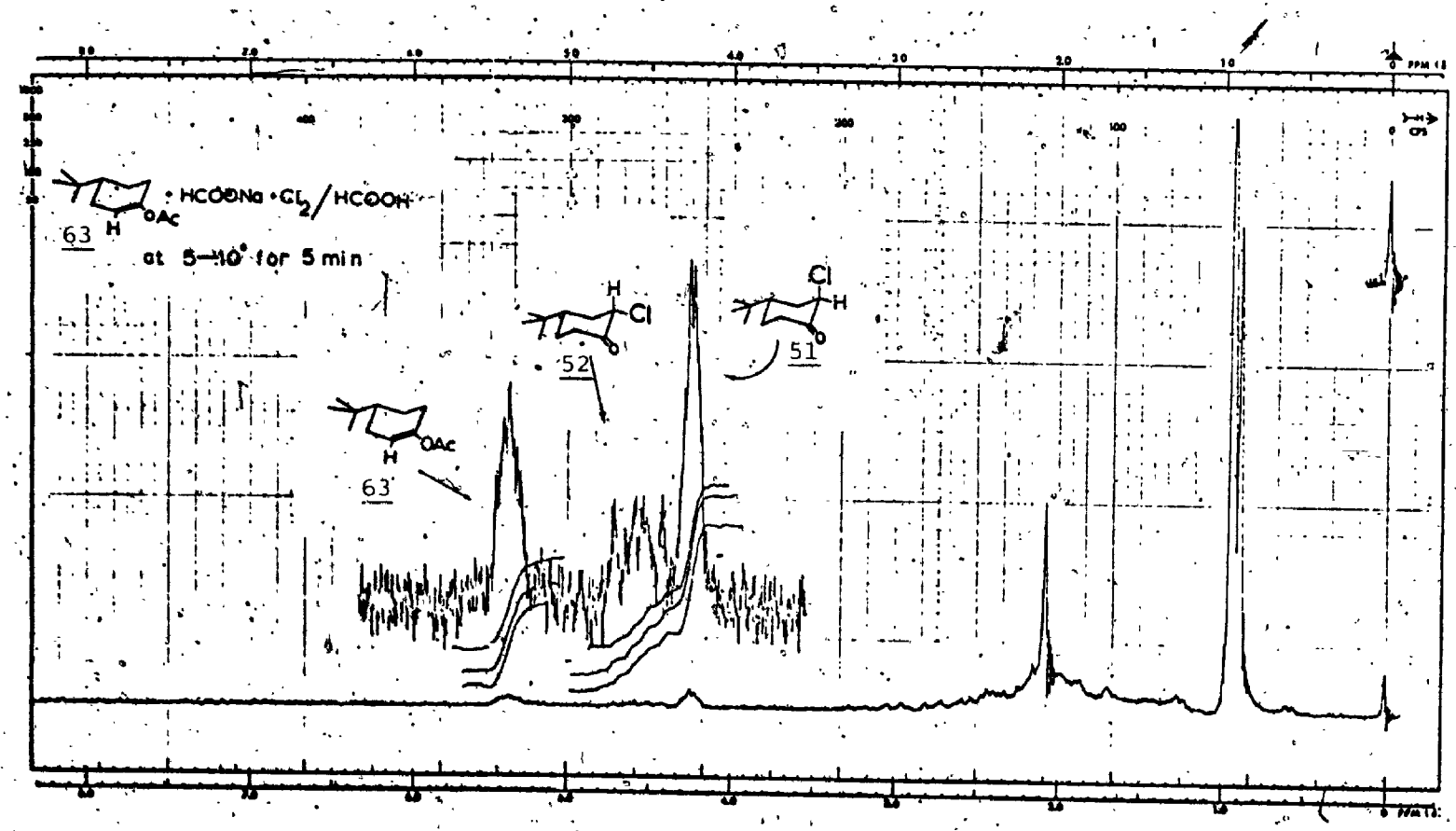


Fig. 11. Pmr Spectrum of the Chlorination Products from Enol Acetate 63

5-10° for at least 5 min with no detectable amount of solvolysis (see Chapter 6). In the presence of chlorine, chlorination of 67 is faster than protonation in formic acid as revealed from the final product whereby only cis,trans-2,6-dichloro ketone 56 and no trace of cis 52 or trans 51 was obtained (see Chapter 6). The fact that chloro enol acetate 67 was stable in a formic acid-sodium formate mixture and no cis,trans-2,6-dichloro ketone 56 was obtained in the crude chlorination product in formic acid ruled out the possibility of chloro enol acetate 67 being involved at any stage of the reaction in this solvent.

5.2.B Chlorination in Trifluoroacetic Acid

Besides formic acid, trifluoroacetic acid is also a good solvent for monochlorination. Chlorination of enol acetate 63 in trifluoroacetic acid was carried in the presence of two equivalents of sodium trifluoroacetate at 0-5° for 3 min (Table 9, entry 3, p 69). The crude product contained monochloro ketones 51 and 52, and about 30% of unreacted enol acetate 63. The epimeric ratio was again roughly the same as that obtained with formic acid as solvent.

Evidence that the result was actually kinetically controlled came from the equilibration experiment (see Chapter 3). The crude product was treated with a saturated solution of hydrogen chloride in trifluoroacetic acid and allowed to stand at room temperature. The equilibrium was established after 7 days, and the equilibrium ratio of cis 52:trans 51 was 72:28.

Since the ratio obtained in trifluoroacetic acid was similar to the kinetically controlled ratio in formic acid, and also very much different from the equilibrium ratio, we were confident that the result

obtained represented the true kinetically controlled ratio.

5.2.C Chlorination in Carbon Tetrachloride

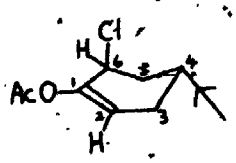
Chlorination reactions by molecular chlorine and N-chlorosuccinimide were studied under a variety of conditions. In the temperature range of 0-15°, enol acetate 63 was chlorinated to a mixture containing 55% of cis- and trans-2-chloro ketones 52 and 51, 35% of chloro enol acetate 67, and 10% of unreacted enol acetate 63. The ratio of cis 52:trans 51 was found to be 33±4:67±4. Unidentified by-products (δ4.10 and δ4.85) were estimated to be <10% by glpc (5% or 10% DEGS on Chromosorb P at 160°, and 1% XE-60 on Gas-Chrom Q at 120°). It was also checked by glpc (e.g., Table 9, entry 8, p 69) that no trace of gem-dichloro 55 or trichloro ketone 61 was present. No cis,trans-2,6-dichloro ketone 56 was detected by pmr in deuteriochloroform solution and no cis,cis-2,6-dichloro ketone 57 was detected by pmr in benzene solution. This reaction was thoroughly investigated, ten runs have been carried out, all of them gave similar results (Table 9, entries 4-13, p 69). Attempts to reduce the side product, chloro enol acetate 67, by lowering the reaction temperature to -4° (entry 4), by working up the reaction mixture immediately after mixing (entry 5), or adding water (entries 12 and 13) to decrease the nucleophilicity of chloride anion failed to produce any significant change.

Control experiments showed that both cis- and trans-2-chloro ketones 52 and 51 were stable under the simulated reaction conditions in the presence of one equivalent of hydrogen chloride. Treatment of each of the two monochloro ketones 51 and 52 with a CH_3COCl-HCl-CCl_4 mixture produced no unidentified products and also no trace of chloro enol acetate 67 indicating that both 67 and the unidentified products (δ4.10 and δ4.85)

were not derived from further reaction of monochloro ketones 51 and 52. Furthermore, the equilibrium ratio of cis 52:trans 51 (47:53) was far from the ratio we obtained which is therefore, most likely to be the kinetic ratio.

The isolation of chloro enol acetate 67 was a tedious process. The crude product from the reaction of enol acetate 63 and one equivalent of chlorine in carbon tetrachloride was fractionated on a spinning band column under reduced pressure. The later fractions gave fairly pure 67 containing ~10% of cis 52. Further purification was done on a silica gel column. Pure 67 was eluted from the column by petroleum ether-benzene (75:25) mixture. The analytical sample was further purified by another clean-up distillation. Ir, pmr and mass spectra all supported the structure of 67. The evidence supporting the chlorine being quasi-axial came from (1) the pmr half-height band-width, $W_{\frac{1}{2}}$, (2) the hydrolytic study, (3) the glpc analysis, and (4) the chlorination study.

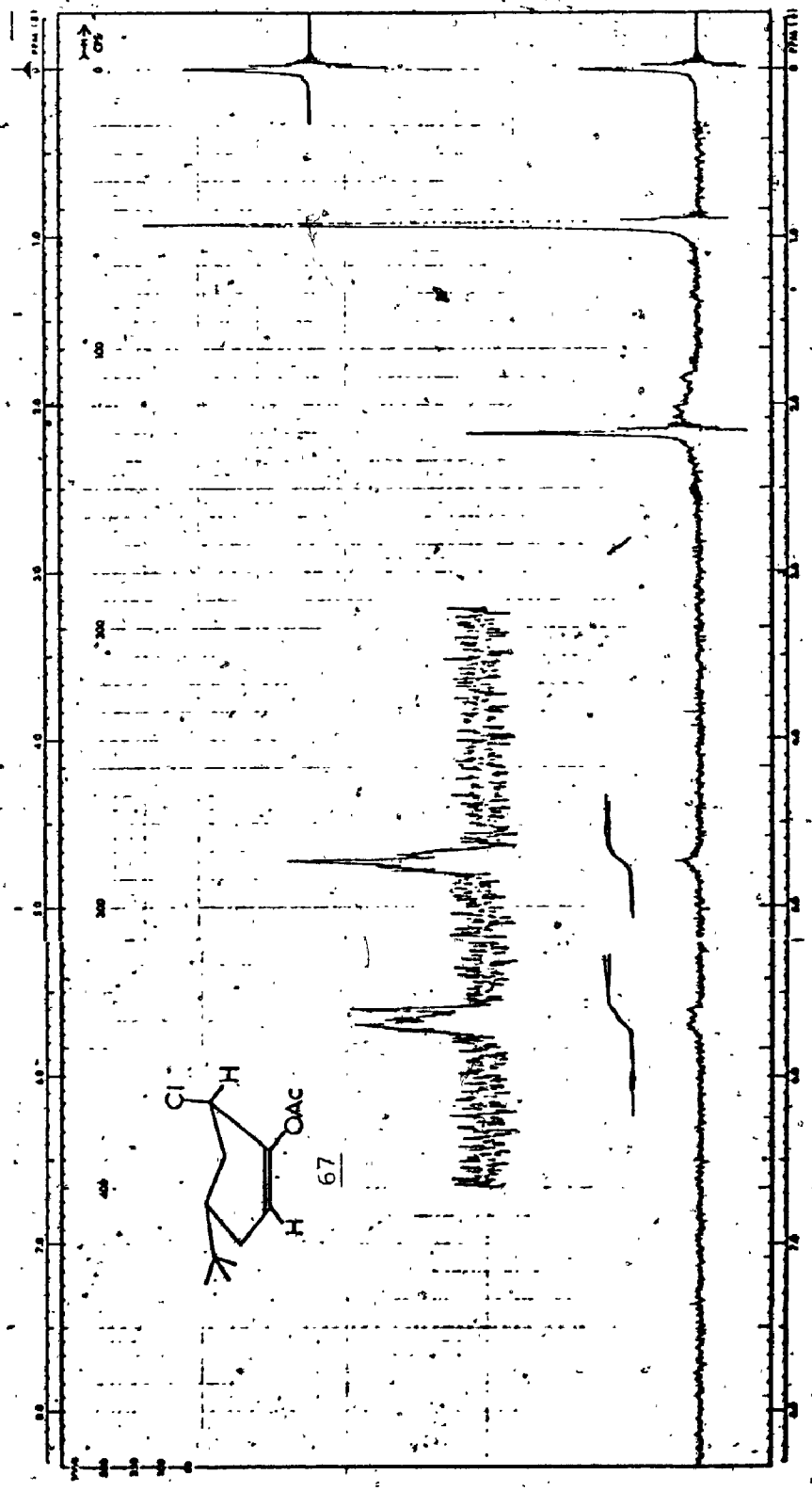
The pmr spectrum of chloro enol acetate 67 is shown in Fig. 12 (p 65). The two low field signals are assigned to the proton at C-6 (δ 4.72, 1 H, m, $W_{\frac{1}{2}}$ 5 Hz) and the proton at C-2 (δ5.63, 1H, m) respectively.



67

It is well established that an axial proton in a cyclohexane ring has a half-height band-width, $W_{\frac{1}{2}}$, of ~20 Hz and an equatorial proton has a $W_{\frac{1}{2}}$ of ~5 Hz.[71] This supported our assignment for the proton at C-6 to be quasi-equatorial and the chlorine atom to be quasi-axial.

A hydrolytic study showed that chloro enol acetate 67 was very



67

Fig. 12. Pmr Spectrum of Chloro Enol Acetate 67

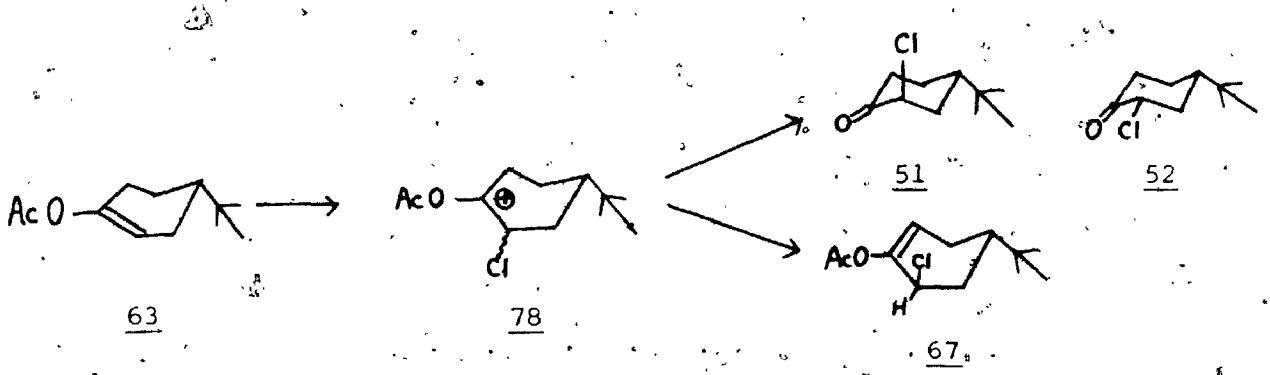
stable under several different conditions (see Chapter 6). Under drastic conditions, hydrolysis leads to a mixture of trans 51 and cis 52. For instance, stirring 67 at 25° for 24 hr in dioxane-water (3:1) with four equivalents of hydrogen chloride present gave an equilibrium mixture of 2-chloro ketones containing 27% of trans 51 and 73% of cis 52. Using deuterated solvent, e.g. CD_3COOD-$CDCl_3$-D_2O with a 5:1 molar ratio of deuterium chloride (from PCl_5+D_2O), no hydrolysis occurred in 1 hr at 25°. A small peak in the pmr spectrum due to trans-2-chloro ketone 51 started to appear only after 20 hr. After 68 hr, the peak due to 51 disappeared presumably due to a deuterium exchange process. The major portion of 67 remained unreacted. Since 67 hydrolyzed to 51 and since 51 was stable enough to be detected by pmr, the stereochemistry of chlorine in 67 and 51 must be the same. This supported the quasi-axial assignment of the chlorine atom.

The glpc result also supported this assignment. The analytical sample, which gave good ir, pmr, mass spectra, and elemental analysis showed two peaks on glpc with 1% XE-60 on Gas-Chrom Q. The tiny peak corresponded to trans-2-chloro ketone 51 which possesses an axial chlorine atom. The only explanation for the presence of two peaks is that some chloro enol acetate 67 hydrolyzed on the column to give trans-2-chloro ketone 51. Therefore, the chlorine atom should be quasi-axial in chloro enol acetate 67. Further chlorination of chloro enol acetate 67 (Chapter 6) gave cis,trans-2,6-dichloro ketone 56 as the only product. This result proved that the positions of the double bond and the chlorine are correct.

The reaction leading to the formation of chloro ketones 51 and 52 and that leading to the formation of chloro enol acetate 67 appeared to be two independent competing processes. The formation of 67 is best

accounted for by a concerted mechanism (see Chapter 7) similar to that suggested by Newman[75] since chloro enol acetate 67 was not formed in a highly polar, protic solvent such as formic acid where chloro ketones 51 and 52 were the only two products. Moreover, 67 was not formed from either 51 or 52 under the same reaction conditions giving rise to 67 and not formed from 63 under radical chlorination conditions by N-chlorosuccinimide. However, a step-wise mechanism such as that given in Scheme 5-2 could not be completely ruled out. As far as the initial attack of chlorine on enol

Scheme 5-2



63 78 51 52 67

acetate 63 is concerned, we have to include 67 with 51 when we consider the axial chlorination product. Therefore, two sets of ratios are given in Table 9: the first set gives the ratio of equatorial:axial chloro ketones, the chlorination ratio ignoring the side product 67, and the other set gives the ratio of equatorial:axial chlorination taking into consideration the side product 67. The ratio of equatorial:axial chlorination was 20±3:80±3 in carbon tetrachloride when the side product 67 was taken into consideration.

Chlorination of enol acetate 63 with N-chloro-succinimide (Table 9, entries 14-18, p 70) did not give any reaction whether the reaction was performed at 25° for 1 hr or at reflux temperature in carbon terachloride for 17 hr. Similarly, no reaction took place when benzoyl

peroxide was added as a radical initiator and the mixture refluxed for 14-42 hr (entries 16 and 17). When enol acetate 63 was chlorinated in dioxane-water with N-chloro succinimide under reflux for 33 hr the enol acetate was hydrolyzed to ketone 50 (entry 18). These results apparently indicate that chloro enol acetate 67 was not formed from the reaction of chlorine atoms and enol acetate 63.

5.2.D Chlorination in Mixed Solvents

Enol acetate 63 was also chlorinated in mixed solvents to examine whether a mixture of solvents would have any effect on the stereochemistry of chlorination. The substrate was dissolved in acetonitrile containing suspended sodium formate. A solution of chlorine in a formic acid-sodium formate mixture was added and the mixture allowed to react at $-2\pm1^{\circ}$ for 1 min. The reaction proceeded to the extent of only 42% from pmr spectrum of the crude product and the ratio of cis 52:trans 51 was 33:67 (Table 9, entry 19, p71). Similarly, when a solution of 63 in carbon tetrachloride with suspended sodium formate was treated with a solution of chlorine in a formic acid-sodium formate mixture, a similar ratio of cis 52:trans 51 (38:62) was obtained (entry 20). No side product was observed in either run.

The two reactions again gave a cis 52:trans 51 ratio similar to those obtained in the previous runs in other solvents. This gave us more confidence that the results represented the kinetic ratio.

5.3 Bromination of 4-t-Butylcyclohexanone Enol Acetate (63).

5.3.A Bromination in Formic Acid

Bromination in formic acid was studied at temperatures ranging

Table 9. Halogenation of 4-t-Butylcyclohexanone Enol Acetate (63)

No.	63 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 52 : trans 51		Chlorination ratio eq(52) : ax(51+67)		% of side prod in Cl-prod
1	1	1 mmol Cl_2 9.4 ml HCOOH	5-15° 5 min	36	64			0
2	1	1 mmol Cl_2 1 mmol HCOONa 13.35 ml HCOOH	5-10° 5 min	34	66			0
3	1	1 mmol Cl_2 2 mmol CF_3COONa 10 ml CF_3COOH	0-5° 3 min	36	64			0
4	1	1 mmol Cl_2 6.86 ml CCl_4	-4° 0.5 min	36	64	21	79	40 67 <10 unidtfd
5	1	1 mmol Cl_2 9.1 ml CCl_4	0-5° 0.5 min	35	65	23	77	34 67 <10 unidtfd
6	25.5	25.5 mmol Cl_2 87.6 ml CCl_4	0-5° 2 min	37	63	22	78	40 67 <10 unidtfd
7	100	100 mmol Cl_2 163 ml CCl_4	5° 2 min	34	66	22	78	36 67 <10 unidtfd
8	100	100 mmol Cl_2 120 ml CCl_4	0-5° 5 min	33	67	22	78	34 67 <10 unidtfd

Table 9. (cont.)

No.	63 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 52 : trans 51		Chlorination ratio eq(52) : ax(51+67)		% of side prod in Cl-prod
9	1	1 mmol Cl_2	0-5°	31	69	20	80	35 67
		9 ml CCl_4	15 min					<10 unidtfd
10	5.1	5.1 mmol Cl_2	0-10°	36	64	22	78	39 67
		15.83 ml CCl_4	45 min					<10 unidtfd
11	70.6	70.6 mmol Cl_2	-5-15°	29	71	18	82	39 67
		440 ml CCl_4	5 min					<10 unidtfd
12	1	1 mmol Cl_2 6.53 ml CCl_4 0.02 ml H_2O	2-5° 3 min	29	71	20	80	33 67 <10 unidtfd
13	1	1 mmol Cl_2 7 ml CCl_4 0.5 ml H_2O	2-5° 2 min	31	69	19	81	38 67 <10 unidtfd
14	1	1 mmol NCS 8 ml CCl_4	25° 1 hr	N.R.				0
15	1	1 mmol NCS 8 ml CCl_4	reflux 17 hr	N.R.				0
16	1	1 mmol NCS 6 mg BZ_2O_2 10 ml CCl_4	reflux 14 hr	N.R.				0

Table 9. (cont.)

No.	63 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 52 : trans 51	Chlorination ratio eq(52) : ax(51+67)	% of side prod in Cl-prod
17	1	1 mmol NCS 6 mg Bz_2O_2 5 ml CCl_4	reflux 42 hr	N.R.		0
18	1	1 mmol NCS 5 ml H_2O 5 ml dioxane	reflux 33 hr	hydrolyzed to ketone 50		0
19	1	1 mmol Cl_2 2 mmol HCOONa 4.49 ml HCOOH 5.5 ml CH_3CN	-2±1° 1 min	33	67	0
20	1	1 mmol Cl_2 2 mmol HCOONa 7.8 ml HCOOH 2.2 ml CCl_4	0±2° 2 min	38	62	0

Table 9. (cont.)

No.	63 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 54:trans 53		Bromination ratio eq(54):ax(53+69)	% of side prod in Br-prod	
21	1	1 mmol Br_2 11.85 ml HCOOH	0-5° 5 min ($Na_2S_2O_3$ washed)	33	67		11	68
22	1	1 mmol Br_2 1 mmol HCOONa 10.6 ml HCOOH	0-5° 5 min ($Na_2S_2O_3$ washed)	36	64		10	68
23	1	1 mmol Br_2 1 mmol HCOONa 11.27 ml HCOOH	0-5° 30 min ($Na_2S_2O_3$ washed)	25	75		11	68
24	1	1 mmol Br_2 1 mmol HCOONa 10.9 ml HCOOH	0-5° 30 min (HCOONa washed)	18	82		9	68
25	10	10 mmol Br_2 10 mmol HCOONa 60.1 ml HCOOH	0-5° 5 min (HCOONa washed)	21	79		11	68
26	1	1 mmol Br_2 9.9 ml HCOOH	0-5° 5 min ($NaHSO_3$ washed)	21	79		9	68

Table 9. (cont.)

No.	63 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 54:trans 53		Bromination ratio eq(54):ax(53+69)		% of side prod in Br-prod	
		1 mmol Br_2	-5-0°						
27	1	1 mmol HCOONa 9.25 ml HCOOH	2 min ($NaHCO_3$ washed)	20	80			10	68
28	1	1 mmol Br_2 10 ml CF_3COOH	0-5° 5 min	44	56			0	
29	1	1 mmol Br_2 2 mmol CF_3COONa 10 ml CF_3COOH	0-5° 3 min	23	77			0	
30	2	0.5 mmol Br_2 2 mmol $CaCO_3$ 30.5 ml CH_3CN	0-5° 4 min	18	82	15	85	14 <5	69 unidtfd
31	1	1 mmol Br_2 1 mmol HCOONa 1 drop HCOOH 10 ml CH_3CN	0-5° 5 min	21	79	18	82	14	69
32	1	1 mmol Br_2 1 mmol CH_3COONa 8.49 ml CH_3COOH	10±2° 3 min	12	88	11	89	15	69

Table 9. (cont.)

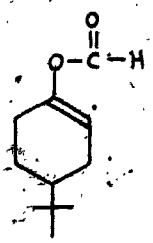
No.	63 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 54	Epimeric ratio trans 53	Bromination ratio eq(54)	Bromination ratio ax(53+69)	% of side prod in Br-prod	
33	2	0.5 mmol Br_2 2 mmol $CaCO_3$ 28.7 ml CCl_4	1±1° 5 min	26	74	22	78	15	69
34	2	0.4 mmol Br_2 2 mmol $CaCO_3$ 44 ml CCl_4	0±1° 5 min	28	72	21	79	25	69
35	1	1 mmol Br_2 1 mmol HCOONa 3.4 ml HCOOH 6.6 ml CH_3CN	0-5° 5 min	14	86			4	68
36	1	1 mmol Br_2 2 mmol HCOONa 4 ml HCOOH 6 ml CH_3CN	-4±1° 2 min	15	85			4	68
37	1	1 mmol Br_2 1 mmol HCOONa 4 ml HCOOH 6 ml $CHCl_3$	-1° 2 min	14	86	13	87	4 3	69 68

from -5° to 5° from 5 min to 0.5 hr. As with chlorination, the reaction gave only monobromination. With no sodium formate present (Table 9, entry 21, p 72) the ratio of cis 54:trans 53 in the crude bromination product was 36:64. Repetition with one equivalent of sodium formate added gave about the same result (entry 22). Another run with a slightly different volume of formic acid gave the ratio of 25:75 for cis 54:trans 53 (entry 23). In all three runs, potassium iodide was added at the end of the reaction to react with any unreacted bromine followed by the addition of sodium thiosulfate solution to react with the liberated iodine. However, sulfur was deposited from the reaction between sodium thiosulfate and formic acid as indicated in the following equation:

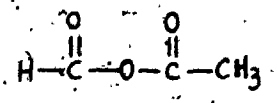
$$Na_2S_2O_3 + 2HCOOH \rightarrow 2HCOONa + H_2O + SO_2\uparrow + S\downarrow$$

Two more runs were carried out at 0-5° for 5 min and 30 min respectively and worked up by using 1% sodium formate solution to wash the extracts (entries 24 and 25). The ratios of cis 54:trans 53 were fairly consistent (18:82 and 21:79).

In these reactions, there was an unidentified product which showed pmr absorption at δ8.10; this is unlikely to be 78 but more likely to be 68. The reason is that this absorption peak did not appear in the crude product when enol acetate 63 was treated with a formic acid-sodium formate mixture for 1 hr at 25°. Compound 68 is a known compound; one



78



68

of its reported preparations is the reaction of acetyl chloride and sodium formate at 0°.[49] Since bromine is a better leaving group than chlorine, it is logical to expect acetyl bromide to react with sodium formate within a shorter reaction period (5-30 min). It is quite surprising to see that the mixed anhydride could survive aqueous work-up, nevertheless, there are reports in the literature[72a] that mixed anhydrides from many different carboxylic acids and ethyl chloroformate survive aqueous work-up.

In order to determine more certainly which ratio is in fact the kinetically controlled one, the reaction was carried out without sodium formate, and 5% sodium bisulfite solution was used to wash the extracts. This experiment gave a ratio of 21:79 for cis 54:trans 53. A final run was performed at an even lower temperature range from -5° to 0° for even shorter time (2 min), and worked up in the shortest possible time with 5% sodium bisulfite solution to wash the extracts. The result showed a ratio of 20:80 for cis 54:trans 53. The general agreement of several of these runs provides us confidence that the kinetically controlled ratio of cis 54:trans 53 is 20±1:80±1.

As a control experiment, each pure isomer was dissolved in formic acid-sodium formate containing the maximum amount of hydrogen bromide that could be present in the bromination reaction conditions. Both CHX signals of cis (δ4.87) and trans (δ4.37) appeared at lower field than they appeared in deuteriochloroform. The lack of change in the pmr spectra showed that both epimers were stable for at least 68 hr. The equilibrium ratio of cis 54:trans 53 was 55:45 determined in a different experiment (Chapter 3).

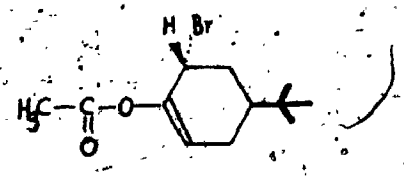
5.3.B Bromination in Trifluoroacetic Acid

Bromination of enol acetate 63 was attempted in trifluoroacetic acid at 0-5° for 5 min. Only monobromo ketones were present in the crude product. The ratio of cis 54:trans 53 was 44:56 (Table 9, entry 28, p 73) which was close to the equilibrium ratio of 48:52.

In order to get the initial ratio, bromination was attempted in trifluoroacetic acid at 0-5° for 3 min in the presence of two equivalents of sodium trifluoroacetate to act as an internal base to trap hydrogen bromide formed in the reaction. The result showed a ratio of 23:77 for cis 54:trans 53 (entry 29). This must be the kinetically controlled ratio since control experiments showed that both isomers 53 and 54 were stable for 10 min at 31-32° in CF_3COOH-CF_3COONa-HBr in a nmr tube.

5.3.C Bromination in Acetonitrile

Bromination of enol acetate 63 proceeded to about 25% completion in acetonitrile containing calcium carbonate to ensure a neutral condition. The ratio of the two isomers cis 54:trans 53 was 18:82 (Table 9, entry 30, p 73). A side product which exhibited absorption peaks at δ4.76 and δ5.60 was tentatively assigned the structure 69 with reference to chloro enol acetate 67. Again the half-height band-width of the peak at δ4.76 was 5 Hz indicating that the bromine is most likely to be quasi-axial. This product was not isolated. The major portion in the crude



69

product was the unreacted enol acetate 63. An unidentified product with pmr absorption in the region δ3.80-4.00 (estimated to be less than 5%)

was also formed. Similarly to the chlorination reaction when the side product 69 was taken into account, the ratio of axial:equatorial bromination was 85:15.

Bromination in acetonitrile with one drop of formic acid as catalyst and one equivalent of sodium formate gave a similar result (Table 9, entry 31, p 73). The close agreement of both runs coupled with the fact that the ratios are far different from the equilibrium ratio (53:47 for cis 54:trans 53) built up our confidence that these ratios represent the kinetic ratio. When the side product 69 was taken into account the ratio of axial:equatorial bromination was 82:12.

5.3.D Bromination in Acetic Acid

Bromination of enol acetate 63 was carried out at 10±2° in the presence of sodium acetate for 3 min. The ratio of cis 54:trans 53 was 12:88. The only side product was bromo enol acetate 69 which was present to the extent of 15% in the bromihated product (Table 9, entry 32, p 73). This ratio is far different from the equilibrium ratio of 54:53 (43:57). When the side product 69 was taken into account the ratio of axial: equatorial bromination was 89:11.

5.3.E Bromination in Carbon Tetrachloride

Similarly to the chlorination of enol acetate 63 in carbon tetrachloride, bromination led to the corresponding side product, bromo enol acetate 69, beside monobromo ketones 53 and 54. Two independent runs (Table 9, entries 33 and 34, p 74) at a temperature around 1° with one equivalent of calcium carbonate to mop up any hydrogen bromide formed gave similar results. The amount of bromine employed was intentionally

reduced to 0.25 or 0.20 mole per mole of the substrate present in order to reduce the side product 69. However, 69 was still formed to the extent of 15-25%. Both runs showed a clear predominance in the axial bromination. The ratio of cis 54:trans 53 was 26-28:74-72. The ratio of axial:equatorial bromination was 78-79:22-21 when 69 was taken into account. The equilibrium ratio of cis 54:trans 53 in this solvent was 31:69.

5.3.F Bromination in Mixed Solvents

Bromination of enol acetate 63 in CH_3CN-HCOONa-HCOOH at 0-5° for 5 min gave predominantly (86%) trans-2-bromo ketone 53 (Table 9, entry 35, p 74). Another run at a lower temperature range -4±1° for 2 min (entry 36) gave a similar result. No bromo enol acetate 69 was detected in either run. Compound 68 again showed up as shown by the absorption peak at δ8.10. The equilibrium ratio of cis 54:trans 53 in CH_3CN-HCOOH-HBr was 55:45.

In $CHCl_3$-HCOOH-HCOONa at -1° for 2 min (entry 37) reaction furnished monobromo ketones cis 54:trans 53 in the ratio of 14:86 with 4% of bromo enol acetate 69 present in the crude product. When 69 was taken into consideration, the ratio of axial:equatorial bromination was 87:13. Compound 68 was also present showing an absorption peak at δ8.10. The equilibrium ratio of cis 54:trans 53 in the same mixed solvent was 45:55.

5.4 Chlorination of 4-t-Butylcyclohexanone (50)

5.4.A Chlorination in Formic Acid

Three independent runs at temperatures within the range 0-10° were performed and the results are collected in Table 10 (p 84). All

three runs (entries 1, 2, and 3) gave similar results and the ratio of cis 52:trans 51 was 52-57:48-43. Control experiments showed that both cis-2-chloro ketone 52 and trans-2-chloro ketone 51 were stable in HCl-HCOOH-HCOONa solution at 0-25° for at least 1 hr. The equilibrium ratio of cis 52:trans 51 in the same solvent was found to be 76:24. No by-product was formed in all these runs. Control experiments, reproducible results, and the equilibrium ratio all indicated that these runs represented the kinetically controlled chlorination.

5.4.B. Chlorination in Trifluoroacetic Acid

Chlorination of 4-t-butylcyclohexanone (50) in trifluoroacetic acid was done at a higher temperature (31-32°) than the same reaction in acetic acid 63 taking into consideration that no reaction occurred when ketone 50 was treated with bromine in trifluoroacetic acid at 0-5°. As in the chlorination in formic acid, only monochlorinated products 51 and 52 were obtained. No other by-product was formed. The ratio of cis 52:trans 51 was 51:49 (Table 10, entry 4, p 84) and the equilibrium ratio of cis 52:trans 51 in this solvent was 72:28.

5.4.C. Chlorination in Acetic Acid

Chlorination of 4-t-butylcyclohexanone (50) in acetic acid was investigated thoroughly. At 7-8°, passing chlorine gas into acetic acid-water (9:1) solution containing 4-t-butylcyclohexanone (50) for 30 min led to cis- and trans-2-chloro ketones 52 and 51 in the ratio of 49:51 (Table 10, entry 5, p 84). Under buffered conditions in the presence of one equivalent of potassium acetate, the reaction was sluggish, a temperature range of 18-25° and reaction time from 5 min-2 hr failed to

give any trace of reaction (entries 6, 7, and 8). Two runs at 52±3° for 2 and 4 hr, respectively, led to a mixture of cis- and trans-2-chloro ketones 52 and 51 in the ratio of 50-51:50-49 (entries 9 and 10). A compromise between 25° and 53° was the chlorination at 37-38° for 3.5 hr. This led to 46% of cis 52 and 54% of trans 51 (entry 11). All three runs described above gave similar ratio of cis 52:trans 51 which was very much different from the equilibrium ratio of 70:30 for cis 52:trans 51 in this solvent.

5.4.D Chlorination in Chloroform

Chlorination of 4-t-butylcyclohexanone (50) in chloroform was performed at a temperature range of 0-5° and a reaction time from 5-20 min. Results are collected in Table 10 (p 85). The ratios of cis 52: trans 51 are consistently 48-59:52-41. The general agreement for all runs gave us confidence that they reflect the kinetically controlled reaction. The equilibrium ratio of cis 52:trans 51 in this solvent was found to be 65:35. In chloroform as well as carbon tetrachloride which will be described in the next section, cis,trans-2,6-dichloro ketone 56 was also formed to the extent of 11-16% ($CHCl_3$) and 20-32% (CCl_4). The isolation, identification and spectroscopic properties of 56 have been discussed in Chapter 4. In no way, did decreasing the amount of chlorine help in diminishing the dichloro ketone 56.

5.4.E Chlorination in Carbon Tetrachloride

Chlorination of 4-t-butylcyclohexanone (50) in carbon tetrachloride was investigated in detail in the temperature range from -2° to 49° in air as well as in an inert argon atmosphere in the dark. Results are listed

in Table 10 (p 86). No reaction was observed at temperatures below 0° (entry 20) in the absence of hydrogen chloride gas. With added calcium carbonate at 0-5° (entry 22) again no reaction was observed. In the absence of calcium carbonate (entries 22-29), reactions took place in carbon tetrachloride at various molar ratios of ketone:chlorine. From a 1:1 to 10:1 ketone:chlorine ratio, the reaction invariably led to 19-30% of cis,trans-2,6-dichloro ketone 56 as the by-product. The pmr spectrum of the crude reaction product from one of the typical runs is shown in Fig. 14 (p115). In all runs, the ratio of cis 52:trans 51 was quite reproducible in the range 41-57:59-43. Control experiments showed that both cis-2-chloro ketone 52 and trans-2-chloro ketone 51 were stable in hydrogen chloride-carbon tetrachloride solution and thus indicated that the ratios are kinetically controlled. Lowering the ratio of chlorine decreases the yield of cis,trans-2,6-dichloro ketone 56 slightly but the formation of this compound could not be prevented entirely. Compound 56 was not formed from monochloro ketones 51 and 52 by an ionic or a radical pathway (see Chapter 7). For compound 56 we have no evidence indicating which chlorine was introduced first. Whichever goes in first, an argument can be made that the second halogen introduced should be in the opposite configuration: if the 2-axial chlorine goes in first, the second chlorine would have to go in equatorial because there would be too much hindrance for the second chlorine to go in axial too. On the other hand, if the first chlorine goes in equatorial, there is nothing to stop the second chlorine from going in axial, particularly since the chloro enol will be less reactive. Perhaps the best one could do would be to assume that the 2,6-dichloro ketone 56 is formed about equally by initial axial and equatorial attack (see Chapter 7). Consequently, the ratio of axial to equatorial

halogenation would be the same as that calculated by ignoring the 2,6-dichloro ketone 56.

That the chlorination of ketone 50 is not of radical nature was supported by the three runs (Table 10, entries 31, 32, and 33, p 88) in the dark and under an inert argon atmosphere. The ratios were again quite reproducible with cis 52:trans 51 in the range of 49-53:51-47. These results indicate that there is no preference for the axial entry as against the equatorial entry for the formation of 2-chloro ketones 51 and 52.

In the presence of radical scavengers, e.g., m-dinitrobenzene (entry 34) or galvinoxyl (entry 35), the reaction was completed within 5 min giving again a similar product mixture with the ratio of cis 52:trans 51 in the range of 54-57:46-43. Dichloro ketone 56 was also formed to the extent of 21-23%.

A radical chlorination of ketone 50 initiated by photochemically (λ350-390 nm) generated chlorine atoms[73] was carried out (Table 10, entry 36, p 88) at -14° at which temperature the products 51, 52, and 56 were stable in the reaction medium. Ten equivalents of calcium carbonate were added to mop up the hydrogen chloride generated during the reaction. In addition to the monochloro ketones, 51 and 52, and the dichloro ketone 56, the crude product contained also an unidentified product(s) showing pmr absorption γ3.43. The same product(s) was also obtained in the radical chlorination of cis 52 or trans 51 which will be discussed in Chapter 7. This compound(s) presumably contained chlorine at a position other than α or α' to the carbonyl group.

3.5 Bromination of 4-t-Butylcyclohexanone (50)

Table 10. Halogenation of 4-t-Butylcyclohexanone (50).

No.	50 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 52 : trans 51		% of side prod in Cl-prod
1	1	1 mmol Cl_2 8 ml HCOOH	0-10° 5 min	52	48	0
2	1	1 mmol Cl_2 1 mmol HCOONa 8.9 ml HCOOH	5-10° 5 min	57	43	0
3	1	1 mmol Cl_2 1 mmol HCOONa 7.3 ml HCOOH	5-10° 1 hr	52	48	0
4	1	1 mmol Cl_2 2 mmol CF_3COONa 10 ml CF_3COOH	31-32° 20 min	51	49	0
5	1.5	30 min passage Cl_2 10 ml CH_3COOH-H_2O (9:1)	7-8°	49	51	0
6	1	1 mmol Cl_2 1 mmol CH_3COOK 7.2 ml CH_3COOH	18-19° 5 min	N.R.		
7	1	1 mmol Cl_2 1 mmol CH_3COOK 7.35 ml CH_3COOH	21±3° 1 hr	N.R.		

Table 10. (cont.)

No.	50 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 54 : trans 53		% of side prod in Br-prod
44	1	1 mmol Br_2 3 mmol CH_3COONa 10 ml CH_3COOH	32±3° 2 hr	47	53	0
45	1	1 mmol Br_2 10 ml $CHCl_3$-EtOH (99.5:0.5)	25±1° 5 min	46	54	9 59
46	1	1 mmol Br_2 7.65 ml CCl_4	0-5° 5 min	50	50	13 59
47	2	0.5 mmol Br_2 2 mmol $CaCO_3$ 28.7 ml CCl_4	30±1° 10 min	47	53	4 59
48	1	1 mmol Br_2 1 mmol HCOONa 1 drop HCOOH 10 ml CH_3CN	20-25° 5 min	55	45	0
49	1	1 mmol Br_2 1 mmol HCOONa 4 ml HCOOH 6 ml CH_3CN	38±1° 10 min	53	47	0

Table 10. (cont.)

No.	50 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 52 : trans 51		% of side prod in Cl-prod	
8	1	1 mmol Cl_2 1 mmol CH_3COOK 7.5 ml CH_3COOH	25±2° 2 hr	N.R.			
9	1	1 mmol Cl_2 1 mmol CH_3COOK 10.95 ml CH_3COOH	52±3° 2 hr	50	50	0	
10	1	1 mmol Cl_2 1 mmol CH_3COOK 8.15 ml CH_3COOH	52±3° 4 hr	51	49	0	
11	1	1 mmol Cl_2 1 mmol CH_3COOK 7.54 ml CH_3COOH	37-38° 3.5 hr	46	54	0	
12	1	1 mmol Cl_2 10 ml $CHCl_3$	0-5° 10 min	54	46	15	56
13	1	0.5 mmol Cl_2 10 ml $CHCl_3$	0-5° 12 min	54	46	11	56
14	1	0.5 mmol Cl_2 10 ml $CHCl_3$	0-5° 15 min	56	44	15	56

Table 10. (cont.)

No.	50 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 52 : trans 51		% of side prod in Cl-prod	
15	1	0.5 mmol Cl_2 10 ml $CHCl_3$	0-4° 20 min	54	46	16	56
16	1	0.25 mmol Cl_2 10 ml $CHCl_3$	1±1° 10 min	54	46	12	56
17	1	0.2 mmol Cl_2 10 ml $CHCl_3$	0-5° 5 min	59	41	13	56
18	4	0.4 mmol Cl_2 15 ml $CHCl_3$	1±1° 5 min	48	52	14	56
19	2	0.2 mmol Cl_2 20 ml $CHCl_3$	0-5° 5 min	50	50	14	56
20	1	1 mmol Cl_2 7 ml CCl_4	-3±1° 3 min	N.R.			
21	1	1 mmol Cl_2 1 mmol $CaCO_3$ 6.6 ml CCl_4	0-5° 30 min	N.R.			
22	1	1 mmol Cl_2 7 ml CCl_4	0±1° 6 min	56	44	28	56

Table 10. (cont.)

No.	50 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 52 : trans 51		% of side prod in Cl-prod	
23	1	1 mmol Cl_2 7.1 ml CCl_4	0-5° 5 min	52	48	31	56
24	1	0.5 mmol Cl_2 5 ml CCl_4	0-5° 5 min	47	53	32	56
25	1	0.25 mmol Cl_2 4 ml CCl_4	3±2° 20 min	48	52	32	56
26	2	0.4 mmol Cl_2 8.4 ml CCl_4	-1±1° 25 min	53	47	27	56
27	4	0.4 mmol Cl_2 14.4 ml CCl_4	2±1° 5 min	59	41	20	56
28	4	0.4 mmol Cl_2 14.4 ml CCl_4	0±2° 35 min	53	47	20	56
29	4	0.4 mmol Cl_2 14.4 ml CCl_4	1±1° 5 min	57	43	20	56
30	1	0.5 mmol Cl_2 1 mmol $CaCO_3$ 4.47 ml CCl_4	27±2° 2 hr	52	48	23	56

Table 10. (cont.)

No.	50 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 52	Epimeric ratio trans 51	% of side prod in Cl-prod
31	1	1 mmol Cl_2 7.1 ml CCl_4	0-5° 10 min Ar gas, dark	49	51	25 56
32	3	3 mmol Cl_2 21.5 ml CCl_4	0-5° 5 min Ar gas, dark	52	48	24 56
33	3	3 mmol Cl_2 21.5 ml CCl_4	0-5° 5 min Ar gas, dark	53	47	22 56
34	6	6 mmol Cl_2 100 mg m-DNB* 36 ml CCl_4	0-5° 5 min Ar gas	57	43	21 56
35	6	6 mmol Cl_2 10 mg GVNX† 42 ml CCl_4	0-5° 5 min Ar gas	54	46	23 56
36	1.5	1.5 mmol Cl_2 15 mmol $CaCO_3$ 42 ml CCl_4	-14° hν 70 min	72	28	17 56 10 unidtfd

* m-DNB m-dinitrobenzene

† GVNX galvinoxyl

Table 10. (cont.)

No.	50 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 54	trans 53	% of side prod in Br-prod
37	1	1 mmol Br_2 10.2 ml HCOOH	5-10° 1 hr ($NaHSO_3$ washed)	48	52	0
38	1	1 mmol Br_2 1 mmol HCOONa 10.14 ml HCOOH	0-5° 3 hr	52	48	0
39	1	1 mmol Br_2 1 mmol HCOONa 9.25 ml HCOOH	0-5° 4 hr	46	54	0
40	1	1 mmol Br_2 2 mmol CF_3COONa 10 ml CF_3COOH	31-32° 10 min	47	53	0
41	2	0.5 mmol Br_2 2 mmol $CaCO_3$ 51 ml CH_3CN	26±1° 10 min	messy		
42	2	0.5 mmol Br_2 2 mmol $CaCO_3$ 53 ml CH_3CN	25-26° 8 min	messy		
43	1	1 mmol Br_2 10 ml CH_3COOH	31±1° 5 min	47	53	18 59

Table 10. (cont.)

No.	50 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 54	Epimeric ratio trans 53	% of side prod in Br-prod
44	1	1 mmol Br_2 3 mmol CH_3COONa 10 ml CH_3COOH	32±3° 2 hr	47	53	0
45	1	1 mmol Br_2 10 ml $CHCl_3$-EtOH (99.5:0.5)	25±1° 5 min	46	54	9 59
46	1	1 mmol Br_2 7.65 ml CCl_4	0-5° 5 min	50	50	13 59
47	2	0.5 mmol Br_2 2 mmol $CaCO_3$ 28.7 ml CCl_4	30±1° 10 min	47	53	4 59
48	1	1 mmol Br_2 1 mmol HCOONa 1 drop HCOOH 10 ml CH_3CN	20-25° 5 min	55	45	0
49	1	1 mmol Br_2 1 mmol HCOONa 4 ml HCOOH 6 ml CH_3CN	38±1° 10 min	53	47	0

Table 10. (cont.)

No.	50 (mmol)	Reagent and solvent	Conditions	Epimeric ratio cis 54	Epimeric ratio trans 53	% of side prod in Br-prod
50	1	1 mmol Br_2 2 mmol HCOONa 3 ml HCOOH 7 ml $CHCl_3$	26±1° 10 min	50	50	0
51	1	1 mmol Br_2 1 mmol HCOONa 7 ml HCOOH 3 ml CCl_4	0-5° 5 min	49	51	0

5.5.A Bromination in Formic Acid

No reaction took place between bromine and 4-t-butylcyclohexanone (50) at 0-5° for 5 min. When the reaction was allowed to proceed for 20 min, traces of brominated product were observed in the pmr spectrum. Since they were too weak for integration the ratio was not estimated. At 5-10° for 1 hr (Table 10, entry 37, p 89), reaction proceeded smoothly leading to a mixture containing 48% of cis 54 and 52% of trans 53. In the presence of added sodium formate to react with hydrogen bromide formed, the reaction at 0-5° for 3 hr (entry 38) led to a crude product containing 52% of cis 54 and 48% of trans 53. With very similar conditions, at 0-5° for 4 hr (entry 39), the ratio of 54:53 was 46:54. Both of the bromo ketones, 53 and 54, were found to be stable in formic acid for at least 68 hr in the presence of the amount of hydrogen bromide that could have been formed under the reaction conditions, thus proving that all the ratios obtained are those of the true kinetically controlled bromination.

5.5.B Bromination in Trifluoroacetic Acid

When a 1:1 molar ratio of bromine:4-t-butylcyclohexanone (50) was allowed to react in trifluoroacetic acid at 0-5° for 5 min, no reaction took place. The reaction was then carried out at 31-32° for 10 min in the presence of two equivalents of sodium trifluoroacetate (Table 10, entry 40, p 89). The epimeric ratio of cis 54:trans 53 was 47:53. No by-product was obtained. Control experiments showed that both cis- and trans-2-bromo ketones, 54 and 53, were stable in $HBr-CF_3COOH-CF_3COONa$ under the reaction conditions for at least 10 min. This showed that the ratio obtained is the kinetic ratio.

5.5.C Bromination in Acetonitrile

Bromination of 4-t-butylcyclohexanone (50) in acetonitrile was studied at 25-27° with a quarter mole of bromine added per mole of ketone 50 present. With one mole of calcium carbonate suspended in acetonitrile (magnetic stirring) to react with hydrogen bromide as soon as it was formed during bromination, the crude reaction product (Table 10, entry 41, p 89) showed tlc spots corresponding to the starting ketone 50, cis-2-bromo ketone 54, and trans-2-bromo ketone 53. However, the pmr spectrum was messy. Beside vaguely identified peaks due to cis 54 and trans 53, there were many unidentified peaks appearing from δ3.80 to 5.20. Hence, determination of the ratio of cis 54:trans 53 could not be undertaken. Another run (entry 42) carried out at 25-26° for 8 min gave a similar result. Acetonitrile does not appear to be a suitable solvent for bromination. The side products probably were due to the reaction between bromine, acetonitrile, and the parent ketone 50.

5.5.D Bromination in Acetic Acid

Bromination of 4-t-butylcyclohexanone (50) in acetic acid was studied at 30-35°. With a 1:1 molar ratio of bromine:ketone, the bromination of ketone 50 at 31±1° for 5 min (Table 10, entry 43, p 89) led to a crude product in which the ratio of cis 54:trans 53 was 47:53. There was also present 18% (from pmr) of cis,trans-2,6-dibromo ketone 59. The ratio remained the same when the reaction was carried out in the presence of three equivalents of sodium acetate at 32±3° for 2 hr (entry 44). No dibromo ketone 59 was observed in this run. The general agreement of the results obtained with or without added sodium acetate as buffer showed that the ratios obtained are kinetically controlled.

5.5.E Bromination in Chloroform

With 1:1 molar ratio of chlorine:ketone 50 in chloroform-ethanol (99.5:0.5) at 25° for 5 min (Table 10, entry 45, p 90), the ratio of cis 54:trans 53 was found to be 46:54. Dibromo ketone 59 was present in the crude brominated product to the extent of 9%. This ratio is likely to be kinetically controlled since it is similar to the kinetic ratio obtained in acetic acid.

5.5.F Bromination in Carbon Tetrachloride

Bromination of 4-t-butylcyclohexanone (50) with bromine in carbon tetrachloride at -5±1° gave no detectable brominated product. At 0-5° for 5 min in a more concentrated solution (Table 10, entry 46, p 90), the ratio of cis 54:trans 53 was found to be 50:50. This reaction also gave 13% of cis,trans-2,6-dibromo ketone 59 in the brominated product. The formation of dibromo ketone 59 was depressed to 4% when the reaction (entry 47) was carried out in the presence of one equivalent of calcium carbonate and a quarter mole of bromine per mole of ketone present. The ratio of cis 54:trans 53 was found to be 47:53. The equilibrium mixture in this solvent consisted of 31% of cis 54 and 69% of trans 53. This showed that the ratio obtained is likely to be kinetically controlled.

5.5.G Bromination in Mixed Solvents

Bromination of 4-t-butylcyclohexanone (50) at 20-25° for 5 min in acetonitrile containing a drop of formic acid as catalyst and one equivalent of sodium formate (Table 10, entry 48, p 90) gave a ratio of 55:45 for cis 54:trans 53. No detectable brominated product was formed when the reaction was carried out in formic acid-acetonitrile (2:1) at

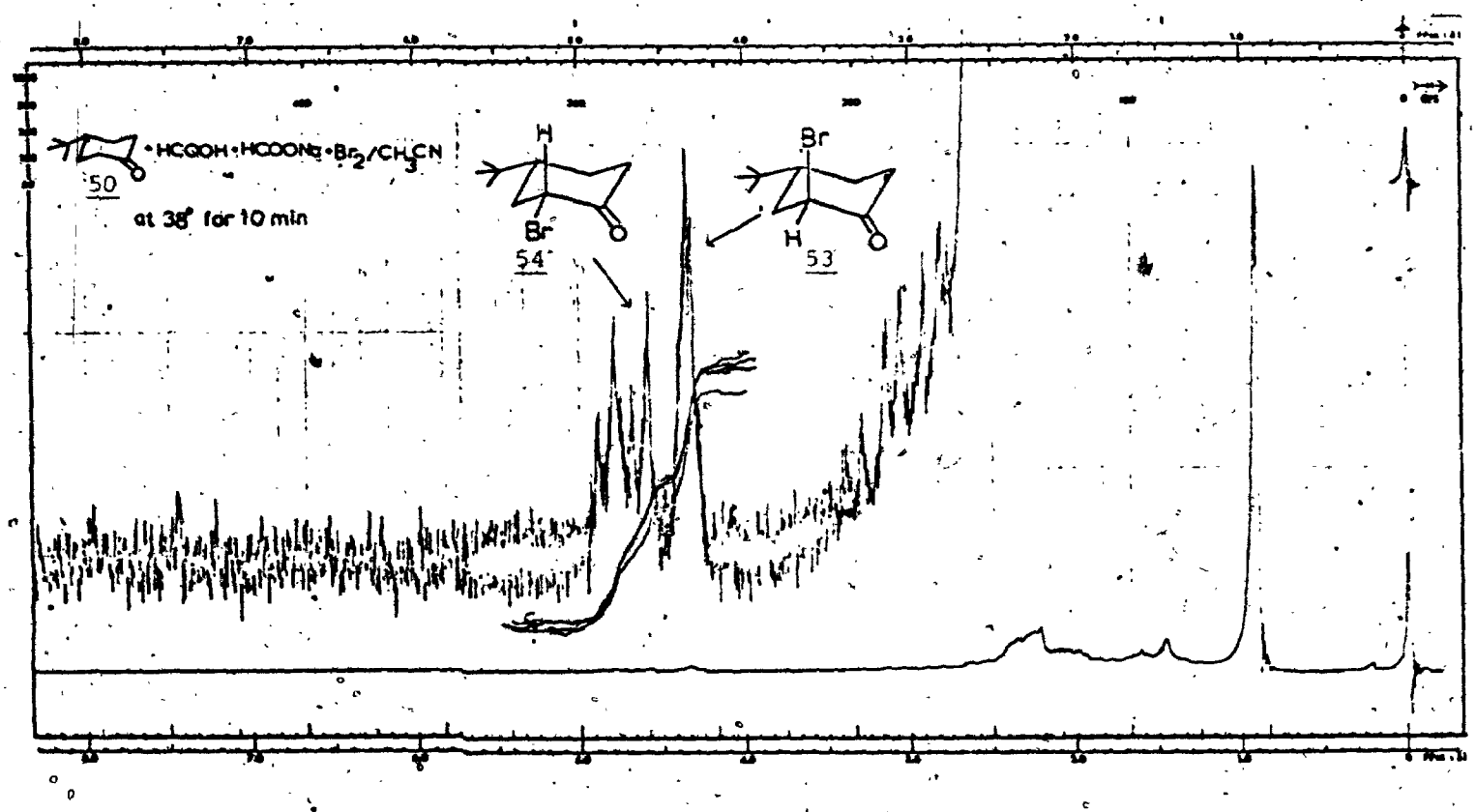


Fig. 13. Pmr Spectrum of the Bromination Products from Ketone 50

0-5° for 5 min. At 38±1° for 10 min (entry 49), the ratio of 53:47 (cis 54:trans 53) was obtained (see Fig. 13, p 95). No cis,trans-2,6-dibromo ketone 59 was detected in the crude brominated product.

When bromination was done at 26° in chloroform-formic acid (2:1) containing two equivalents of sodium formate present (entry 50), the ratio of cis 54:trans 53 was 50:50. In formic acid-carbon tetrachloride (2:1), a similar result was also obtained in which the ratio of cis 54:trans 53 was 49:51 (entry 51). Again, no dibromination occurred in both runs described above. The reproducibility of the ratios under different conditions and different mixed solvents gave us confidence that these ratios are kinetically controlled and the change of solvent does not seem to have any significant effect on the stereochemistry of bromination.

5.6 Chlorination of 4-t-butylcyclohexanone Lithium Enolate (65)

Chlorination of 4-t-butylcyclohexanone lithium enolate (65) was studied in dimethoxyethane-carbon tetrachloride, dimethoxyethane-ether and benzene. Results are listed in Table 11 (p 98).

The lithium enolate of 4-t-butylcyclohexanone was generated in situ using Stork's procedure[50,55] for the cleavage of trimethylsilyl enol ether 66 by methyl lithium in dimethoxyethane at 25° in the "dropper-cooler" (see Fig. 18, p181) under a nitrogen atmosphere. The almost clear enolate solution was then cooled to 0° and added to a solution of chlorine in carbon tetrachloride at 0-5° with vigorous stirring (Vibromixer and magnetic bar together). Three runs (Table 11, entries 1-3, p 98) were attempted and the results did not indicate any preference in the formation of cis- or trans-2-chloro-4-t-butylcyclohexanone (52 or 51). The three runs gave ratios of cis 52:trans 51 in the range of 44-53:56-47

or 49±5:51±5.

The presence of cis- and trans-2-chloro ketones 52 and 51 in the crude product was confirmed by tlc as well as glpc analysis. However, there were some unidentified side products which had broad pmr absorption peaks at δ6.01 and also in the aromatic region at δ7.20. These absorption bands changed shape and position on standing. After standing at room temperature for two days in the nmr tube, the pmr spectrum of the solution no longer showed peaks due to cis 52 and trans 51 but a broad peak at δ4.50 and also two broad peaks at δ6.85 and δ7.25. This was probably because the crude product was being converted to some other products on prolonged standing.

It was originally thought that one of the side products could have arisen from the reaction of enolate 65 and the solvent carbon tetrachloride since it was reported in the literature that enol ethers could react with carbon tetrachloride[51] so enolates might also react. However, a control experiment showed that in the absence of chlorine but with the rest of the reagents present and the conditions exactly the same, lithium enolate 65 gave mainly the parent ketone 50 on work-up as confirmed by tlc and ir absorption, although there were side products (~5% from tlc) showing pmr absorption peaks at δ5.00-6.00. Quenching the lithium enolate 65 in dimethoxyethane with aqueous ammonium chloride gave only the parent ketone 50 shown by tlc, ir, and pmr. The organic layer from the reaction of methyl lithium and water did not show any functional group in the ir spectrum except C-H stretching. Control experiments showed that both cis 52 and trans 51 were stable in LiCl-DME-Cl_2-CCl_4 solution under the same reaction conditions. The general agreement of the three runs (entries 1-3) with ratio estimation made immediately after the isolation of the

Table 11. Halogenation of 4-t-Butylcyclohexanone Lithium Enolate (65)

No.	Generated from	Reagent and solvent	Conditions	Epimeric ratio cis 52 : trans 51		% of side prod in Cl-prod
1	4.4 mmol 66 2.7 mmol CH_3Li 2 crystals Ph_3CH 21.5 ml DME 25°, N_2, 5 min	4.4 mmol Cl_2 27.5 ml CCl_4	0-5° 5 min N_2	53	47	15 unidtfd
2	4.4 mmol 66 4.4 mmol CH_3Li 2 crystals Ph_3CH 25 ml DME 25°, N_2, 15 min	4.4 mmol Cl_2 12 ml CCl_4	0-5° 5 min N_2	49	51	20 unidtfd
3	4.4 mmol 66 4.4 mmol CH_3Li 2 crystals Ph_3CH 25 ml DME 25°, N_2, 15 min	4.4 mmol Cl_2 12 ml CCl_4	0-5° 5 min N_2	44	56	20 unidtfd
4	4.4 mmol 66 4.4 mmol CH_3Li 2 crystals Ph_3CH 25 ml Benzene 25°, N_2, 1 hr	4.4 mmol Cl_2 27.5 ml Benzene	0-5° 5 min N_2	N.R.		

Table 11. (cont.)

No.	Generated from	Reagent and solvent	Conditions	Epimeric ratio cis 52:trans 51	% of side prod in Cl-prod
5	14 mmol 66 14 mmol CH_3Li 8 ml EtOEt 2 crystals Ph_3CH 30 ml DME 25°, N_2, 15 min	14 mmol Cl_2 35 ml CCl_4	0-5° 5 min N_2	N.R.	
6	14 mmol 66 14 mmol CH_3Li 8 ml EtOEt 2 crystals Ph_3CH 30 ml DME 25°, N_2, 15 min	14 mmol Cl_2 35 ml CCl_4	0-5° 5 min N_2	N.R.	

No.	Generated from	Reagent and solvent	Conditions	Epimeric ratio cis 54:trans 53		% of side prod in Br-prod
7	4.4 mmol 66 4.4 mmol CH_3Li 25 ml DME 2 crystals Ph_3CH 25°, N_2, 15 min	4.4 mmol Br_2 20.47 ml CCl_4	0-5° 5 min N_2	48	52	15 unidtfd

Table 11. (cont.)

No.	Generated from	Reagent and solvent	Conditions	Epimeric ratio cis 54:trans 53		% of side prod in Br-prod
8	4.4 mmol 66 4.4 mmol CH_3Li 25 ml DME 2 crystals Ph_3CH 25°, N_2, 15 min	4.4 mmol Br_2 20 ml CCl_4	0-5° 3 min N_2	50	50	15 unidtfd
9	8.8 mmol 66 8.8 mmol CH_3Li 2 crystals Ph_3CH 40 ml DME 25°, N_2, 15 min	8.8 mmol Br_2 42.9 ml CCl_4	0-5° 3 min N_2	40	60	20 unidtfd

crude reaction product and also the result of the control experiments showed that the ratio 49±5:51±5 (52:51) must be the kinetically controlled ratio.

Chlorination of lithium enolate 65 generated in benzene (Table 11, entry 4, p 98) and ether (entries 5 and 6) was unsuccessful since no chlorination took place; 4-t-butylcyclohexanone (50) was the major product in these cases with some unidentified products with absorption peaks at δ4.00-5.00. Since lithium enolate 65 was not soluble in benzene or ether, failure to react was probably due to the heterogenous system involved.

5.7 Bromination of 4-t-Butylcyclohexanone Lithium Enolate (65)

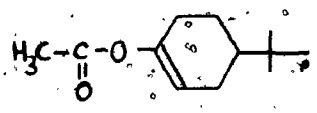
Results from brominating lithium enolate 65 are listed in Table 11 (p 99).

Lithium enolate 65 was generated in the same way as described in section 5.6. The dimethoxyethane solution of lithium enolate 65 was added dropwise to a solution of bromine in carbon tetrachloride with high-speed stirring (Vibromixer and magnetic stirrer together). This was done to ensure that an excess amount of enolate was not accumulated which might cause epimerization of the initially formed bromo ketones 53 and 54. Three runs under similar conditions were carried out. The first two runs gave similar results and the ratios of cis 54:trans 53 were 48:52 (entry 7) and 50:50 (entry 8). Unidentified side products (~15% from tlc) showing pmr absorption peaks at δ5.00 and δ7.20 were also present. Another run with slightly higher concentration of lithium enolate 65 gave a corresponding ratio of 40:60 (entry 9). Since all three runs were carried out under similar conditions, they are taken together. An average of these runs gives the ratio of 45±5:55±5 for cis 54:trans 53. Since this ratio is far from the equilibrium ratio of 31:69 (cis 54:trans 53) in the same

solvent, it is most likely the kinetically controlled ratio. Similar to chlorination, the crude product darkened and underwent changes on standing in nmr tube. Taking into consideration the highly reactive nature of an enolate ion, we are not as confident in the results from enolate halogenation compared with those obtained from enol and enol acetate halogenation. Nevertheless, our approach by the reverse addition of the enolate to an excess of halogen with vigorous mixing appears to be the best possible approach toward obtaining the true kinetically controlled ratio.

5.8 Discussion

After a detailed study of the halogenation of 4-t-butylcyclohexanone enol derivatives 63, 64, and 65, a general trend for the stereochemical



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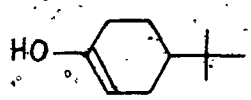

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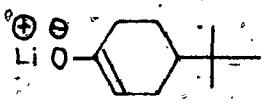

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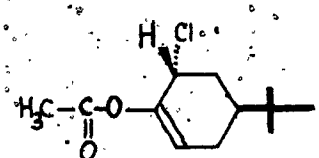

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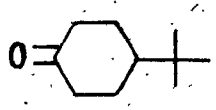

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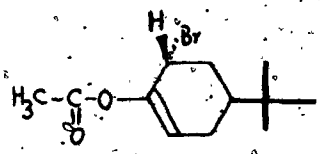

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outcome was revealed. Under kinetically controlled conditions, there is a clear preference for axial entry of halogen in the halogenation of enol acetate 63. The degree of preference is somewhat different for different halogens: axial entry of chlorine took place to the extent of 67±4 compared to 33±4 for equatorial entry whereas axial entry of bromine took place to the extent of 80±8 compared to 20±8 for equatorial entry. Moreover, when the side products 67 and 69 were taken into consideration, the ratio of axial:equatorial chlorination increased to 80±3:20±3 and the ratio of axial:equatorial bromination increased to 84±6:16±6. In the

kinetically controlled halogenation of ketone 50, no preference for either axial or equatorial entry was observed. Kinetic chlorination of 50 gave a ratio of 50±9:50±9 for axial:equatorial entry of chlorine. Kinetically controlled bromination gave a ratio of 50±5:50±5 for axial:equatorial entry. Similarly, kinetically controlled halogenation of lithium enolate 65 did not show any preference for axial entry over equatorial entry. The ratio for kinetically controlled chlorination of 65 was 51±5:49±5 for axial entry as against equatorial entry. Kinetically controlled bromination of 65 provided a similar ratio, i.e., 55±5:45±5 for axial vs. equatorial entry. These results are summarized in Table 12 in ratios of simple numbers.

Table 12. The Axial:Equatorial Ratio in Halogenation

enol derivative	ax:eq ratio in chlorination	ax:eq ratio in bromination
enolate	1:1	1:1
enol	1:1	1:1
enol acetate	2:1* or 4:1	4:1* or 5-6:1†

* Cl (Br) ketone only.

† Cl (Br) ketone + Cl (Br) enol acetate.

Perhaps surprisingly, no solvent effect on the relative epimeric ratio was observed in all three cases since the ratio of axial to equatorial halogenation remains constant whether the solvent used was highly polar formic acid or nonpolar carbon tetrachloride.

Considering the reactivity of the various enol derivatives, although there are no complete kinetic data, it is reasonable to believe

that the reactivity of the substrate increases in the order: enol acetate 63<enol 64<enolate 65. There is no doubt that enolates are more reactive than enols toward halogenation which is an electrophilic reaction. Concrete evidence on this point came from Bell's work[54] who showed that enolate ions react about 10^5 times as fast as enols with halogen. The rate of enolate halogenation is equal to or larger than the rate of diffusion control and is in the order of 10^9-10^{11} M^{-1} sec^{-1} whereas the rate of enol halogenation is in the order of 10^4-10^6 M^{-1} sec^{-1}.

The question of whether an enol is more reactive than an enol acetate deserves more comment. The available data on acetone show that the rate of bromination of the enol of acetone ($k=4\times10^6$ M^{-1} sec^{-1} in H_2O at 25°)[76] is faster than that of enol acetate of acetone ($k=4.9\times10^2$ M^{-1} sec^{-1} in CH_3OH at 25°).[9] Unfortunately, the two reactions were not carried out in the same solvent system. An ionic reaction might be 10^4 times faster in water than in methanol. Therefore, this set of numbers was not very helpful.

However, a study of the relative reactivities of a ketone (cyclohexanone), an olefin (cyclohexene), and an enol acetate (cyclohexenyl acetate) towards bromination in tetrahydrofuran by the "pyrrolidone-bromine" complex has established the order of the reactivity to be enol>olefin>enol acetate.[77] A mixture containing a 1:1 molar ratio of cyclohexanone:cyclohexene upon bromination gave a ratio of 199:1 for bromocyclohexanones:dibromocyclohexane whereas a mixture containing a 1:1 molar ratio of cyclohexene:cyclohexenyl acetate gave only dibromocyclohexane. The results showed that the enol is more reactive than the olefin which is in turn more reactive than the enol acetate at least in tetrahydrofuran. We would have to assume that the same reactivity holds

in other solvents.

Other data are also available in the literature which leads to the inference that the order of reactivity is enol>olefin>enol acetate. For example, the enol of acetone reacts faster with bromine ($k=4\times10^{6}$ M^{-1} sec^{-1} in H_2O at 25°) than 1-butene ($k=<6\times10^{6}$ M^{-1} sec^{-1} in H_2O at 25°; what was measured was $k=6\times10^{6}$ M^{-1} sec^{-1} for the reaction $(CH_3)_2C=CH_2 + Br_3^-$ and also $k_{Br_3^-}/k_{Br_2}$ was "large.")[70] At the same time, 1-butene halogenates faster ($k=2.7\times10^{3}$ M^{-1} sec^{-1} in CH_3OH at 25°) than the enol acetate of acetone ($k=4.9\times10^{2}$ M^{-1} sec^{-1} in CH_3OH at 25°).[76]

In short, by indirect comparison, we arrive at the conclusion that the relative reactivities fall in the order: enolate>enol>enol acetate. The results could then easily be rationalized that in the halogenation of the enol acetate, the transition state was reached later along the reaction coordinate and after the substrate has undergone substantial change in geometry to resemble the product halo ketone in the chair-form. Stereoelectronic effect would then operate to favor the formation of axial halo ketone. However, for the more reactive enol, the transition state is attained earlier before any (or as much change) in geometry has occurred, stereoelectronic factors on either side of the double bond of the flat enol are comparable and therefore equal amounts of axial and equatorial α-halo ketones were formed. Similarly, with the even more reactive enolate, attacks on either side of the flat enolate are equally probable and hence no preference is given to the formation of either axial or equatorial α-halo ketone.

In the halogenation of enol acetate 63, kinetic bromination gave more axial halo ketone than kinetic chlorination although bromine has a greater van der Waals radius (r_{Br} 1.95 Å)[52] than chlorine (r_{Cl} 1.8 Å).[52]

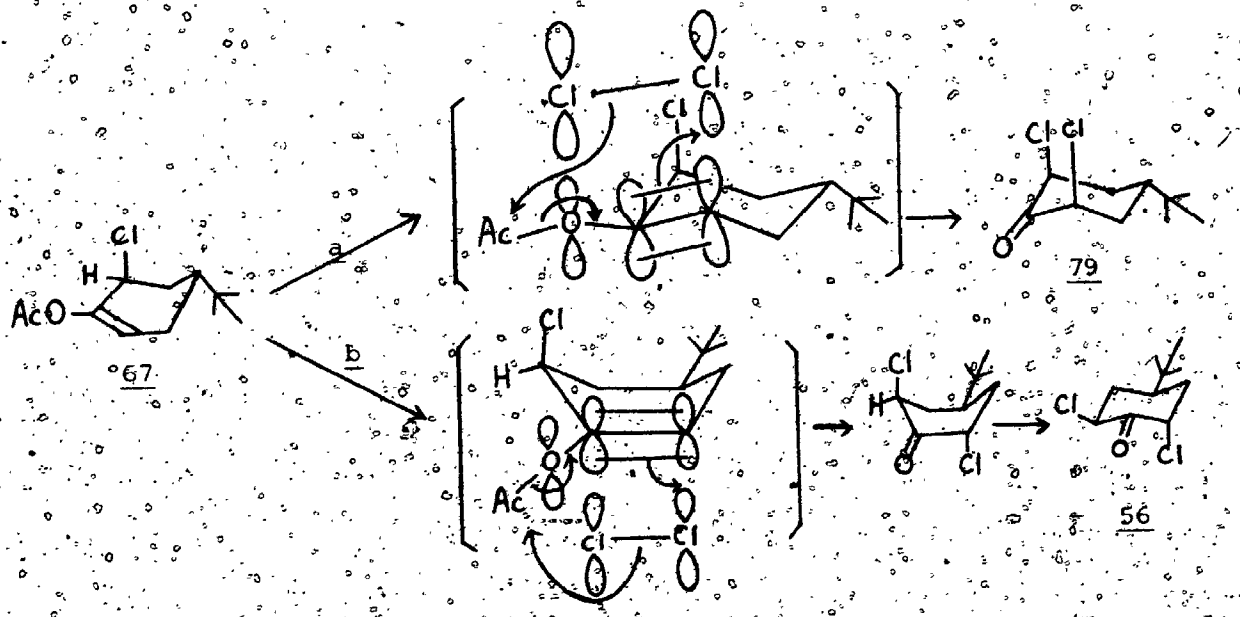
Perhaps steric factors were not important here. Greater stereochemical preference for axial entry of bromine than that of chlorine was also found in the study of cholestan-7-one halogenation carried out by Nickon and Castle.[27]

In enolate halogenation, one assumption was made i.e. the cation has no effect on the stereochemistry of halogenation. This is reasonable because previous investigations from our laboratory on the camphor halogenation[30] revealed that a change of cation from Na^+ to Li^+ did not have any effect on the stereochemistry of halogenation.

attack than the electron-poor counterpart in 67.

Applying the same principle we have elaborated earlier, with a less reactive substrate, the attacking species, in this case chlorine, has to approach closer to the substrate at the transition state. Now, comparing the two possible routes, a and b (Scheme 6-2), route a involves a diaxial interaction between two chlorine atoms whereas route b does not involve this type of interaction. Instead, route b approaches a

Scheme 6-2



boat-like transition state which is not implicated in route a. The result obtained seems to indicate that a diaxial 1,3-interaction between two chlorine atoms is severe enough to force the reaction to take the alternative pathway. This is in agreement with the earlier work of Djerassi[15] and Warnhoff[16] in which it was found that the equatorial halo ketone was formed when there would be serious interactions if axial halogenation leading to the chair conformer occurred. However, we do not know how far along toward a boat the transition state is.

Solid evidence for its stability came from some control experiments as well as those futile attempts in the hydrolytic study. For instance, attempts to hydrolyze chloro enol acetate 67 in dioxane-water in the presence of hydrogen chloride in the range 15-20° for 5-6 hr failed to give any trace of monochloro ketones.

In a formic acid-sodium formate mixture, chloro enol acetate 67 was stable at 5-10° for at least 5 min with no detectable hydrolysis. In CD_3COOD-$CDCl_3$-D_2O with deuterium chloride present at 25°, no hydrolysis occurred in 1 hr. Similarly, in acetone-d_6-deuterium oxide containing deuterium chloride at 25°, no hydrolysis took place until one-half hour after mixing. In CCl_4-D_2O-DCl at 10° for 10 min no noticeable hydrolysis occurred. Finally, in CH_3COCl-Cl_2-CCl_4 in the presence of hydrogen chloride at 0-5° for 15 min, no hydrolysis nor chlorination took place. With the reluctance of chloro enol acetate 67 toward hydrolysis in mind, this compound should be a good substrate for a stereochemical halogenation study.

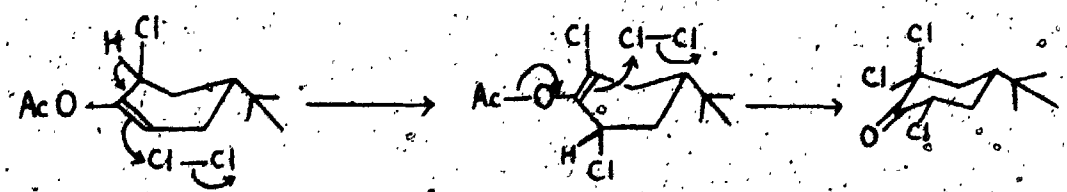
6.2 Chlorination

Chlorination of chloro enol acetate 67 was carried out in four different solvents at temperatures ranging from 0-30°. The results are gathered in Table 13 (p_{111}). As a control run to check the stability of chloro enol acetate 67, the substrate was subjected to the treatment of Cl_2-HCl-CH_3COCl-HCOOH buffered with sodium formate at 0-5° for 5 min. Chloro enol acetate 67 reacted with chlorine to give cis,trans-2,6-dichloro ketone 56 as the only product, judging from the pmr spectra in deuteriochloroform and benzene solutions as well as the glpc analysis with 1% XE-60 on Gas-Chrom Q. No unreacted starting material, monochloro ketones 51 or 52, cis,cis-2,6-dichloro ketone 57, or other unidentified

products were detected by pmr in deuteriochloroform and benzene solutions. The reaction was then repeated with a 1:1 molar ratio of chlorine:67 in formic acid buffered with sodium formate. Again, cis,trans-2,6-dichloro ketone 56 was found to be the only product with no starting chloro enol acetate 67 left over and no cis,cis-2,6-dichloro ketone 57 present judging from the pmr spectrum of the crude reaction product in benzene. This showed that the trapping of chloro enol acetate 67 with chlorine was a very efficient process. Since chloro enol acetate 67 did not hydrolyze first to monochloro ketones 51 or 52 (it has been mentioned earlier that 67 was stable at 5-10° for at least 5 min in formic acid-sodium formate) the possible intermediacy of monochloro ketones 51 or 52 in the formation of the final product, cis,trans-2,6-dichloro ketone 56, is ruled out. In other words, the dichloro ketone 56 must come directly from chloro enol acetate 67. An equilibration study revealed that the equilibrium mixture contained 39% of cis,trans-2,6-dichloro ketone 56 and 61% of cis,cis-2,6-dichloro ketone 57 in formic acid-hydrogen chloride solution. Since the crude reaction product contained only cis,trans-2,6-dichloro ketone 56, the product must be the kinetically controlled one.

Glpc analysis with 1% XE-60 on Gas-Chrom Q at 120° showed no trace of gem-dichloro ketone 55 or 2,2,6-trichloro ketone 61, thus ruling out the further extension of the S_E pathway as shown in Scheme 6-1.

Scheme 6-1



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When chlorination was carried out in acetic acid with sodium acetate as buffer at 27±2° for 40 min, again complete reaction took place. Exactly the same crude product was obtained as in the case of chlorination in formic acid. cis,trans-2,6-Dichloro ketone 56 was the only product. The crude product did not contain any trace of monochloro ketones, 51 or 52; gem-dichloro ketone 55, cis,cis-2,6-dichloro ketone 57, or 2,2,6-trichloro ketone 61. The equilibrium ratio of cis,cis-:cis,trans-2,6-dichloro ketone, i.e., 57:56, in this solvent system is 43:57. Therefore, this reaction is also a kinetically controlled chlorination.

With a 1:1 molar ratio of chlorine:67 in chloroform, reaction took place at 20° after 40 min furnishing only cis,trans-2,6-dichloro ketone 56. Again, no other product nor unidentified product was obtained. The equilibrium ratio of 57:56 in chloroform is 31:69.

In HCl-CH_3COCl-CCl_4 with a 4:1 molar ratio of chlorine at 0-5° for 15 min, no reaction took place. This also served as a control experiment showing that chloro enol acetate 67 was stable under the reaction conditions in which it was formed during the chlorination of enol acetate 63. When the same reaction was carried out at 0-5° for 1.5 hr, incomplete chlorination took place. The crude product contained 72% of the starting chloro enol acetate 67 and 28% of cis,trans-2,6-dichloro ketone 56. No other product was detected by the same type of analysis described earlier. At higher temperature (30±1°) and for a longer time (15 hr) complete reaction took place. The crude product contained no starting chloro enol acetate 67 but only cis,trans-2,6-dichloro ketone 56 with an unidentified product exhibiting a sharp singlet absorption peak at δ3.40. Glpc analysis with 1% XE-60 on Gas-Chrom Q showed that the side product was about 10% of the chlorinated product. The equilibrium mixture in this solvent system contained 28% of cis,cis-2,6-dichloro

Table 13. Chlorination of Chloro Enol Acetate 67

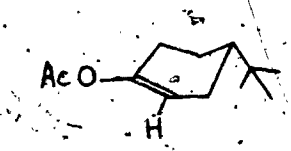
Entry	Substrate in mmol	Reagent and Solvent	Conditions	Product composition: Starting material 67(%)	 56(%)	Unidentified product
1	0.2	1 mmol Cl_2 1 mmol HCl 1 mmol CH_3COCl 1 mmol HCOONa 13.3 ml HCOOH	0-5° 5 min	0	100	absent
2	0.1	0.1 mmol Cl_2 0.1 mmol HCOONa 1 ml HCOOH	0-5° 5 min	0	100	absent
3	0.1	0.1 mmol Cl_2 0.1 mmol CH_3COONa 1 ml CH_3COOH	27±2° 40 min	0	100	absent
4	0.1	0.1 mmol Cl_2 0.625 ml $CHCl_3$	20° 40 min	0	100	absent
5	0.25	1 mmol Cl_2 1 mmol HCl 1 mmol CH_3COCl 9 ml CCl_4	0-5° 15 min	N.R.		
6	0.25	1 mmol Cl_2 1 mmol HCl 1 mmol CH_3COCl 9 ml CCl_4	0-5° 1:5 hr	72	28	absent
7	0.25	1 mmol Cl_2 9 ml CCl_4	30±1° 15 hr	0	90	10% present

ketone 57 and 72% of cis,trans-2,6-dichloro ketone 56.

6.3 Discussion

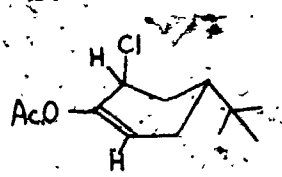
These studies carried out in solvents of widely different polarity revealed that, while the rate of chlorination changes, the stereochemistry of the kinetically controlled chlorination of chloro enol acetate 67 is not affected by the dielectric constant of the solvents employed. Except in carbon tetrachloride where an unidentified product was formed, in all other solvents studied, a clean reaction leading to cis,trans-2,6-dichloro ketone 56 as the only kinetically controlled product was observed.

It is beyond any doubt that chloro enol acetate 67 is less reactive than enol acetate 63 towards electrophilic attack by chlorine. The best evidence is that the reaction conditions required for chlorinating 67 are more drastic than those needed for chlorinating 63.* The pmr data collected



δ5.35

63



δ5.63

67

also support this point. Comparing the chemical shift of the vinylic protons of 63 and 67, it is obvious that the vinylic proton of 63 is more shielded than that of 67. This implies that the vinylic position in 63 has higher electron density than that in 67.[56,57] Naturally, the relatively electron-rich vinylic position in 63 will be more susceptible towards electrophilic

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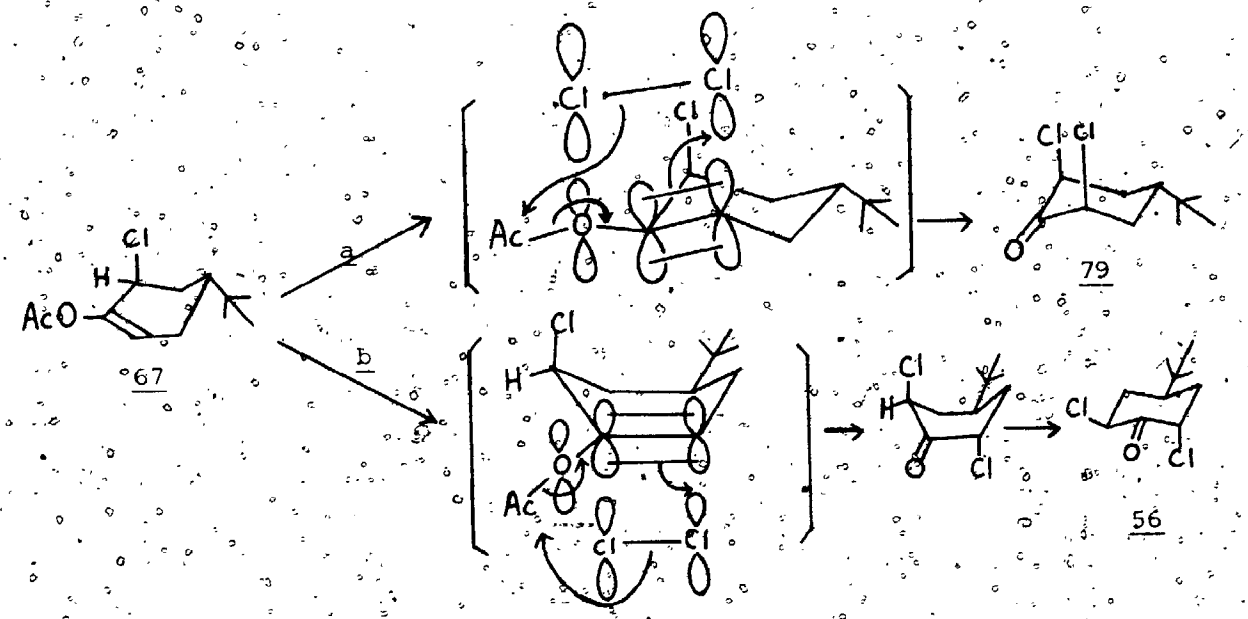
* Both 63 and 67 react equally fast with chlorine in formic acid. However, in carbon tetrachloride solution, chlorination of 67 requires 15 hr for a complete reaction to take place whereas chlorination of 63 takes only 5 min for almost a complete reaction to occur.

attack than the electron-poor counterpart in 67.

Applying the same principle we have elaborated earlier, with a less reactive substrate, the attacking species, in this case chlorine, has to approach closer to the substrate at the transition state. Now, comparing the two possible routes, a and b (Scheme 6-2), route a involves a diaxial interaction between two chlorine atoms whereas route b does not involve this type of interaction. Instead, route b approaches a

Scheme 6-2



boat-like transition state which is not implicated in route a. The result obtained seems to indicate that a diaxial 1,3-interaction between two chlorine atoms is severe enough to force the reaction to take the alternative pathway. This is in agreement with the earlier work of Djerassi[15] and Warnhoff[16] in which it was found that the equatorial halo ketone was formed when there would be serious interactions if axial halogenation leading to the chair conformer occurred. However, we do not know how far along toward a boat the transition state is.

CHAPTER 7

HALOGENATION WITH ALLYLIC REARRANGEMENT

7.1 Mechanism of Disubstitution Reaction

In the course of gathering kinetically controlled ratios of mono-halo ketone epimers in the halogenation of 4-t-butylcyclohexanone (50), the monosubstituted product was found to be accompanied by varying amounts of disubstitution product in nonpolar aprotic solvents even in the presence of a large excess of the ketone. Detailed investigation reveals that disubstitution product is not necessarily formed by further reaction of the monosubstituted ketone as would have been expected. Instead, the α,α'-disubstitution can occur by a mechanism with the basic feature as depicted in Scheme 7-1 (p123). This mechanism was found to be common with both the ketone 50 itself as well as its enol acetate 67.[58]

7.2 Origin of Disubstitution Product

The chlorination of 4-t-butylcyclohexanone (50) in carbon tetrachloride solution at 0-5° gave cis,trans-2,6-dichloro ketone 56 (19-30% of the chlorinated product), in addition to the mixture of cis- and trans-2-chloro ketones 52 and 51. Quantitative analyses of the mixture of the possible products 51, 52, 55, 56, and 57 were carried out by a combination of integration of the δ3.5-5.5 region of 100-MHz and 60-MHz spectra of benzene and deuteriochloroform solutions (e.g., see Fig. 14, p115)

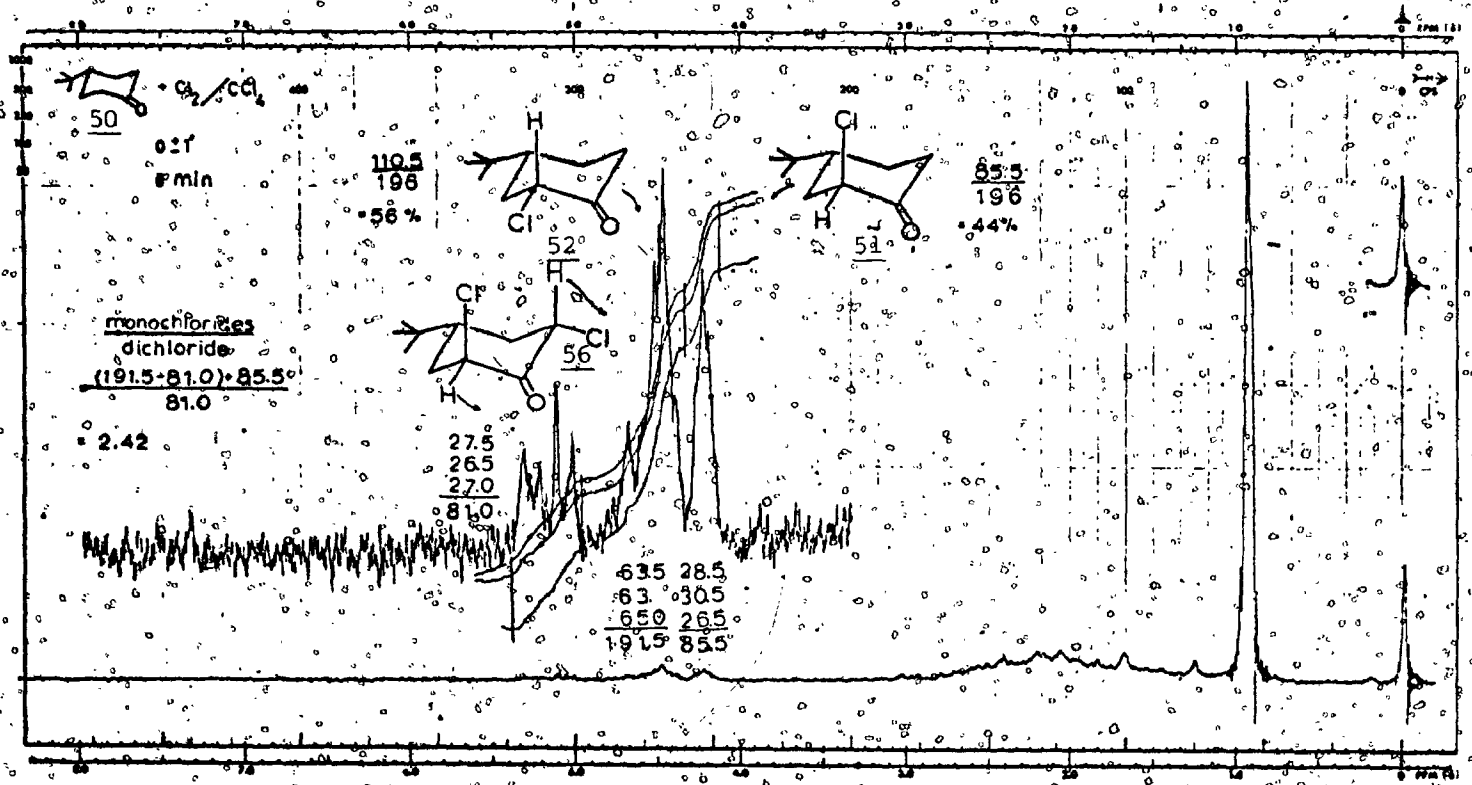
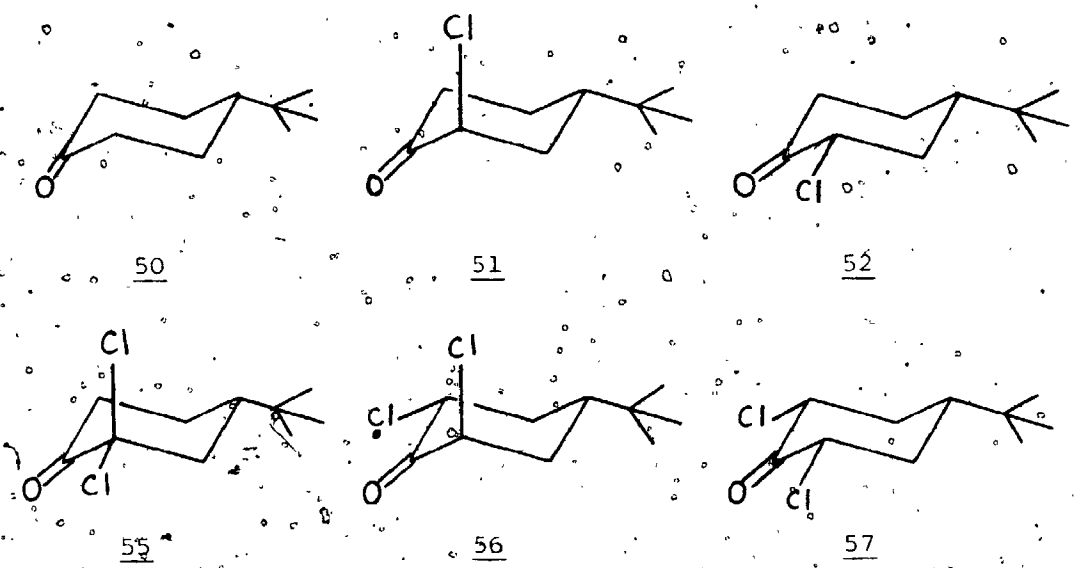


Fig. 14. Pmr Spectrum of the Chlorination Products from Ketone 50



50 51 52

55 56 57

and glpc analyses. No cis,cis-2,6-dichloro ketone 57 was detected by comparing the pmr spectra of the crude reaction product with each of the pure 51, 52, 56, and 57. Partial spectra proving this point are shown in Fig. 15 (p. 117). The partial spectra on the left-hand side are 60-MHz spectra run with deuteriochloroform as solvent. The signals due to cis-2-chloro ketone 52 and cis,cis-2,6-dichloro ketone 57 both appear at almost the same place (δ4.55 for 52 and δ4.63 for 57). It is very difficult to know whether the crude product contains any cis,cis-2,6-dichloro ketone 57. However, in benzene solution, the signals due to the -CHCl protons of 52 and 57 are clearly distinguishable (δ4.10 for 52 and δ3.87 for 57). It is now obvious that the crude chlorinated product contained no detectable amount* of cis,cis-2,6-dichloro ketone 57 as shown by the partial 100-MHz pmr spectra on the right-hand side (Fig. 15). Should there be any gem-dichloro ketone 55 present, it would certainly be less than 0.5% of the

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* In the 100-MHz spectrum of the crude reaction product with increased spectrum amplitude, a signal with an area corresponding to 0.5% of 57 in the dichlorinated product 56 could be easily detected. This set the upper limit for 57 to be <0.5%.

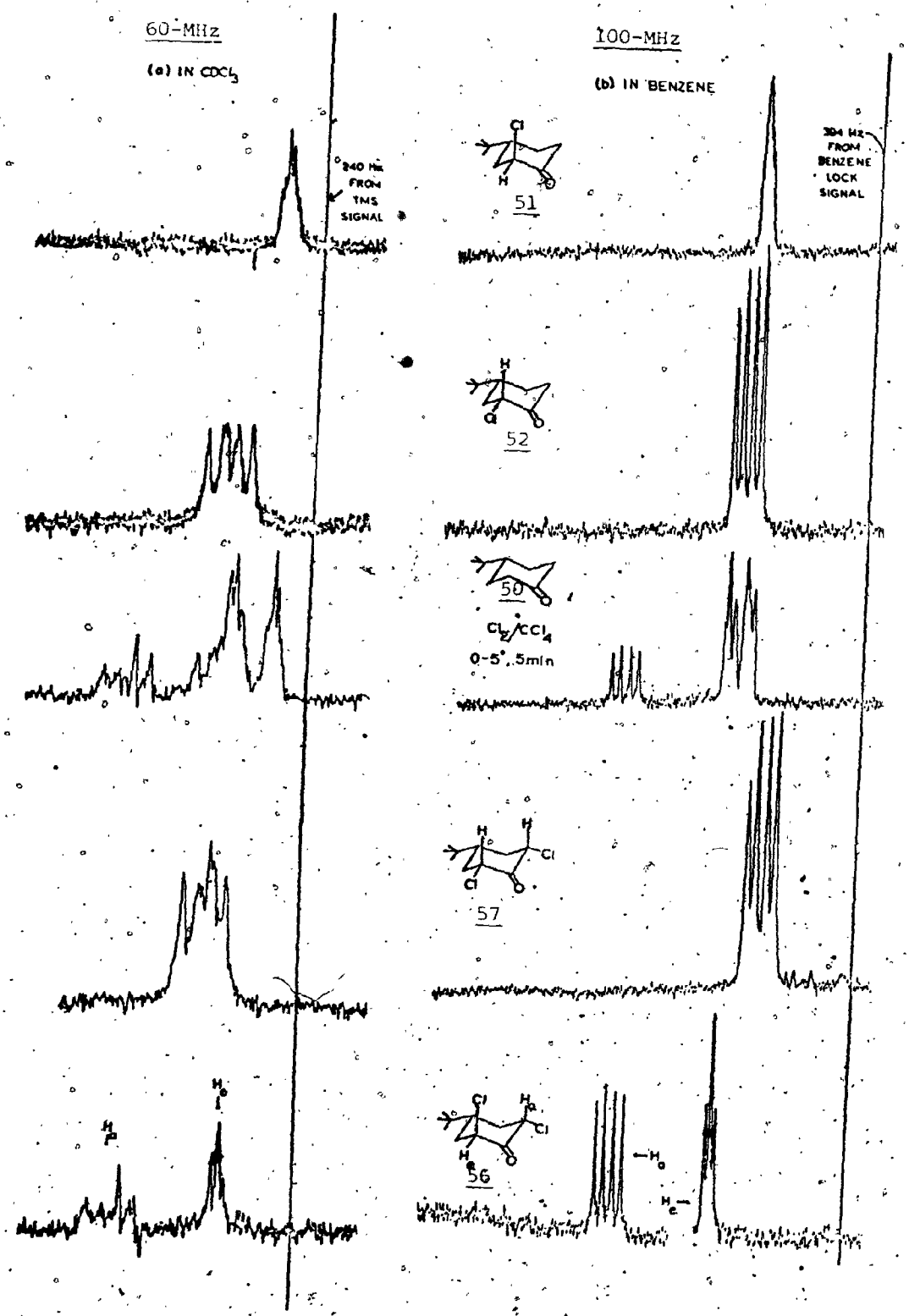

Fig. 15. Comparison of Pmr Spectra in Deuteriochloroform and Benzene Solutions

dichloro portion of the product as determined by glpc comparison with an authentic mixture using 55 as the internal standard (see Experimental). Attempts to minimize the formation of dichloro ketone by increasing the ketone:chlorine ratio produced some change* (Table 14, p119), but the roughly twofold decrease in the dichloro:monochloro ketone ratio for a tenfold increase in ketone:chlorine ratio is not compatible with the dichloro ketone being formed from monochloro ketone by either an ionic or a radical mechanism. For an ionic mechanism this is even more evident when the $\sim 10^3$ weaker basicity[59] of the carbonyl oxygen in the monochloro ketone and its consequent slower rate of acid-catalyzed enolization[60] are taken into account. A radical disubstitution reaction was ruled out because the reaction could not be quenched by radical quenchers such as m-dinitrobenzene or galvinoxyl and the reaction proceeded in an argon atmosphere even in the dark. Conclusive evidence on the point came from the control experiments in which pure cis- and pure trans-2-chloro-4-t-butylcyclohexanone (51 and 52) were each treated with Cl_2-HCl-CCl_4 under the chlorination conditions at 0-5°. No dichloro ketone was produced over a period of 1 hr nor was there any epimerization of the monochloro ketones, even with a larger amount of hydrogen chloride present than would have been formed during chlorination of 50. At 30°, chlorination of 51 and 52 occurred slowly to

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* Due to the decreasing amount of chloro ketones formed when the ratio of ketone:chlorine increases, it is necessary to use more starting material in order to get strong enough chloro ketone pmr signals. Therefore, the total volume of the solvent has to be changed and it varies over a factor of 1-3. However, the assumption is made that this change should not have any effect on the ratio of monochloro:dichloro ketones.

† Chlorination was allowed to proceed for 6 hr (no reaction occurs at the end of 2 hr) in the case of 51 and 2 hr in the case of 52. At the end of the stirring period, the color of chlorine still persisted. Less than (for 51) or close to (for 52) half the equivalent of chlorine was estimated to have been used up judging from the amount of starting material recovered by glpc analyses.

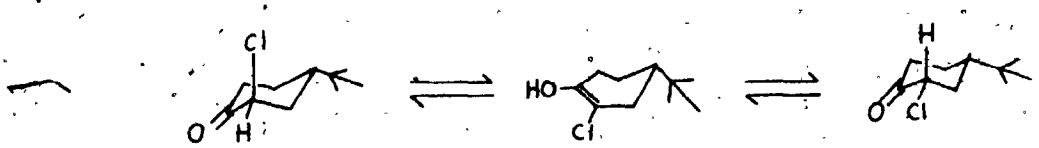
Table 14. Chlorination in Carbon Tetrachloride

Concn. of 50 in CCl_4, M	Molar ratio ketone:Cl_2	Monochloro:dichloro ketones
0.14	1	2.2-2.4
0.20	2	2.1
0.25	4	2.2
0.24	5	2.7
0.28	10	4.1

Table 15. Chlorination in Chloroform

Concn. of 50 in $CHCl_3$, M	Molar ratio ketone:Cl_2	Monochloro:dichloro ketones
0.1	1	5.7
0.1	2	5.1-5.9
0.1	4	7.1
0.1	5	6.6
0.1	10	6.3 (2 runs)

produce a mixture of 2,6- and 2,2-dichloro ketones (54-57% cis,trans-2,6 56 and 43-46% 2,2- 55) each of which was stable under the reaction conditions as shown by control experiments.* During the chlorination of trans-2-chloro ketone 51, 16% of the chloro ketone 51 was also epimerized to cis-2-chloro ketone 52, i.e., enolization of 51 to 73 without the enol being trapped by chlorine but instead by hydrogen chloride. This may be due to an equilibration between 51 and 52 at a longer reaction time. Finally, light-catalyzed (λ350-390 nm) radical chlorination of both the trans- and cis-2-chloro ketones 51 and 52 at -14° introduced chlorine at other points in



51 73 52

the carbon skeleton but gave no dichloro ketones 55, 56 and 57. The pmr spectra of the crude reaction product showed a sharp singlet absorption peak at δ3.43 (see Fig. 16 and 17, p121) which may be due to the chlorinated product(s) with chlorine substituted at the carbon atom(s) other than that α or α' to the carbonyl group. ^{13}Cmr (Table 18, p206) showed that no gem-dichloro ketone 55 was present since the strong peak at δ49.3 in 55 was missing from the crude reaction product. An unidentified carbonyl carbon at δ208.2 presumably belongs to the compound which is responsible for the singlet absorption peak in the pmr spectrum. Also present was a series of minor peaks which belong to the minor products.

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* Wayne Yerhoff of this laboratory has been looking at the α→α' rearrangement of 2,2-dichloro-4-t-butylcyclohexanone (55). His results showed that in CH_3COOH saturated with HCl, there is very little rearrangement (2,2→2,6) after 1 hr at room temperature. It is also known that rearrangements in CH_3COOH are considerably faster than rearrangements in $CHCl_3$ or CCl_4. This is a surprising result.

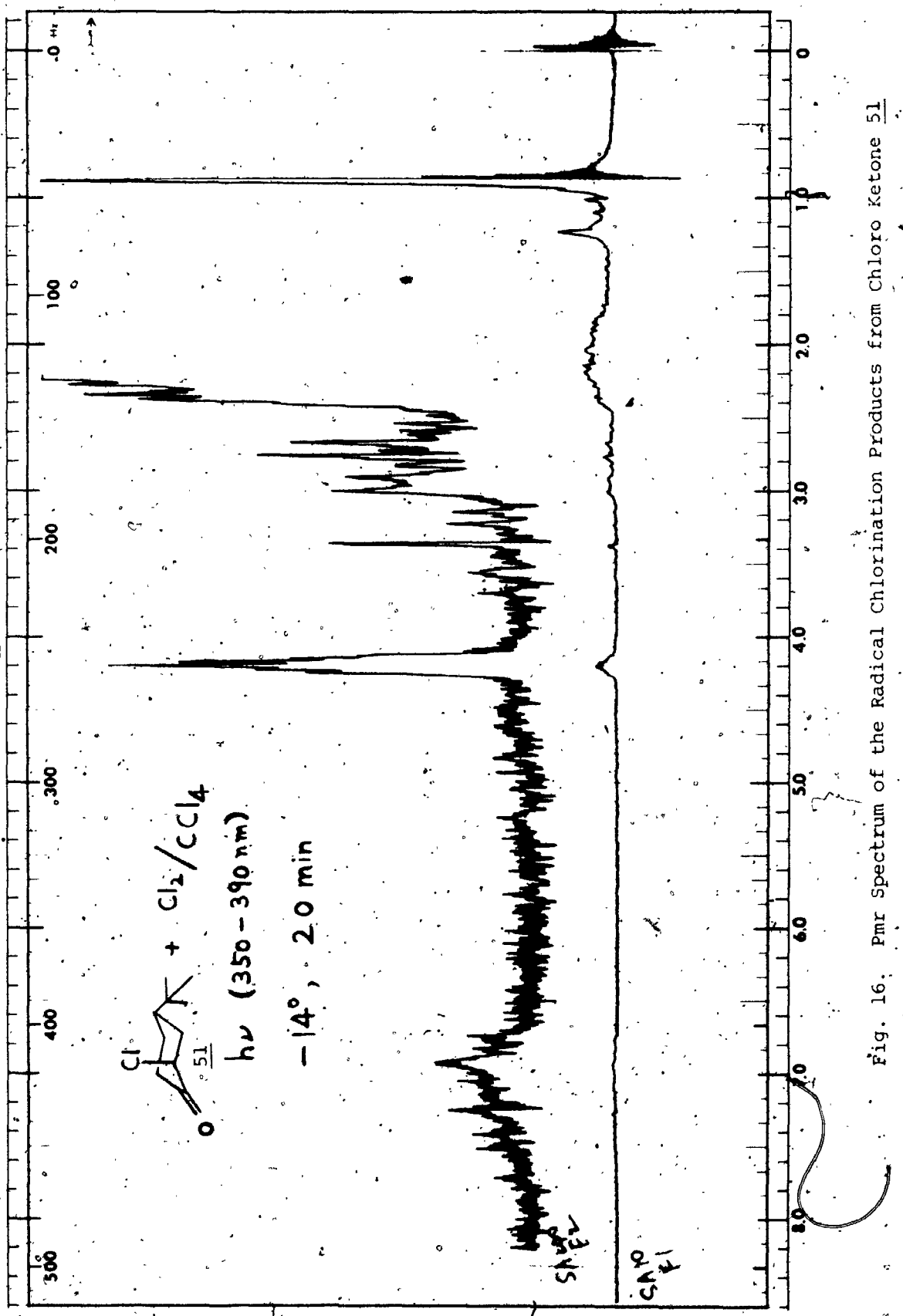


Fig. 16. Pmr Spectrum of the Radical Chlorination Products from Chloro Ketone 51

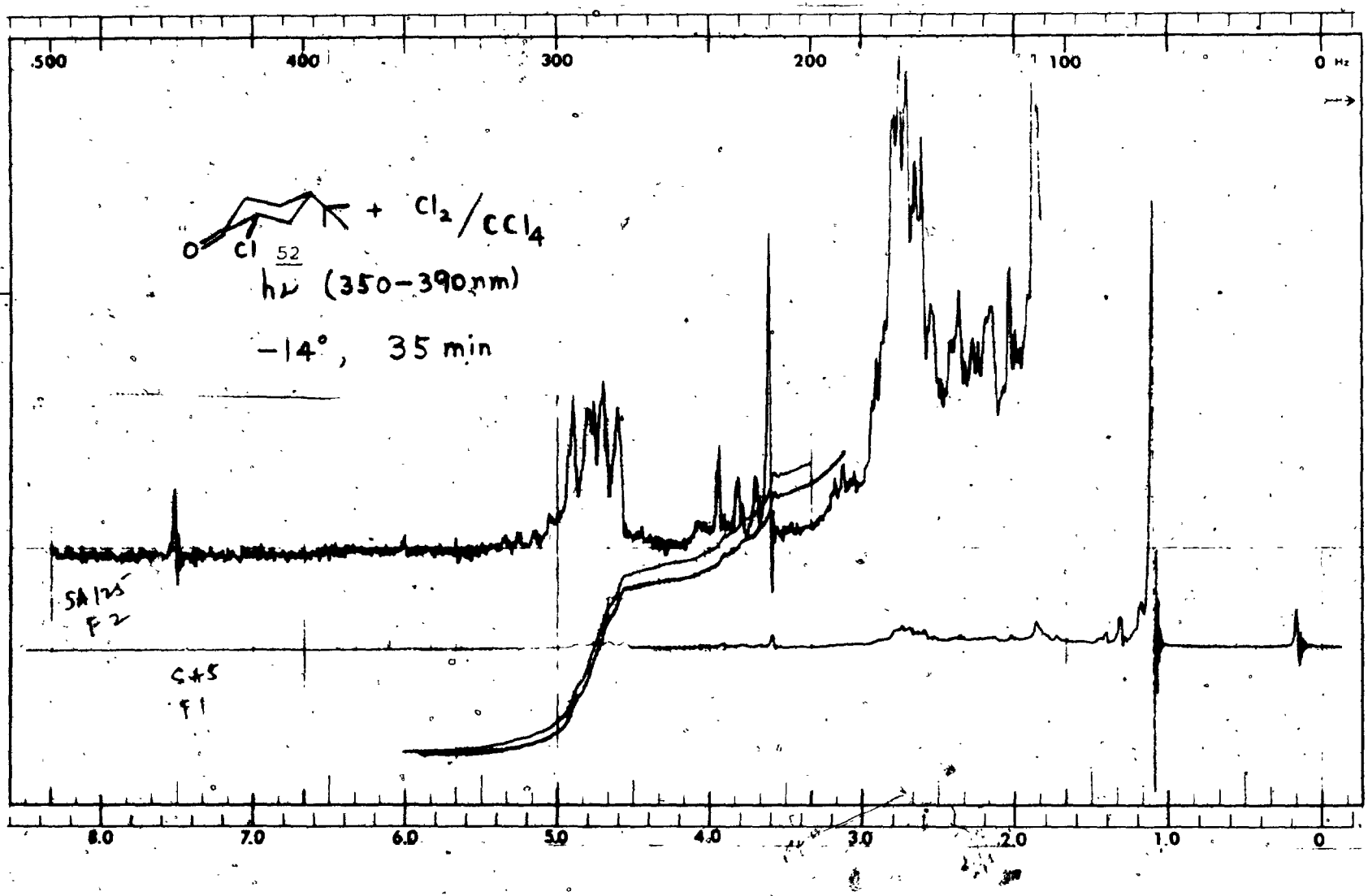
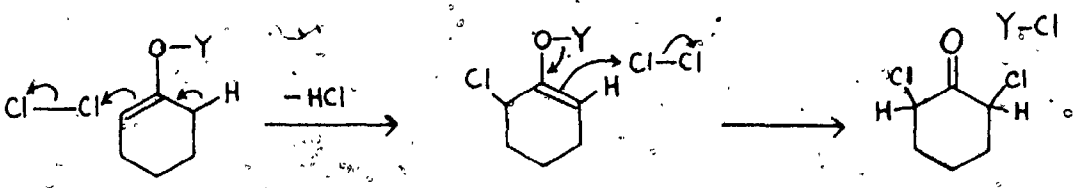


Fig. 17. Pmr Spectrum of the Radical Chlorination Products from Chloro Ketone 52

7.3 Discussion

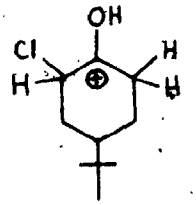
Since chlorination of 4-t-butylcyclohexanone produces 56 under conditions not yielding this compound from either monochloro ketone 51 or 52 by ionic or radical paths and since ionic chlorination of either 51 or 52 at only 25° higher temperature produces not only 56 but an equal amount of 2,2-dichloro ketone 55, the 2,6-dichloro ketone 56 from the reaction with 4-t-butylcyclohexanone (50), must arise without the intervention of the monochloro ketone itself. The most reasonable alternative is the chloroenol path 70→71→72 (Y=H) in which the step 70→71 is concerted. The concertedness of this step agreed well with the fact that the disubstitution

Scheme 7-1

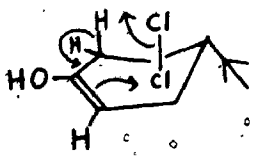


70 (Y=H, Ac) → 71 → 72

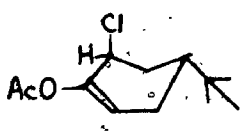
reaction took place in nonpolar aprotic solvents ($CHCl_3$, CCl_4) whereas the same reaction was not observed in polar protic solvents (HCOOH, CF_3COOH, and CH_3COOH). The carbonium ion 74 cannot be an intermediate on the way from 70→71; 74 would deprotonate from oxygen instead since 51 and 52 do not in fact enolize in the presence of HCl-Cl_2-CCl_4 under the conditions



74



75



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used although their carbonyl oxygens must be protonated to some extent in this medium. For reaction 70→71 to be concerted would require favorable orientation of the available incipient chloride base at the α' C-H instead of nearer the hydroxyl hydrogen, perhaps as in 75 which has analogy in the reaction of singlet oxygen with allylic system.[61]

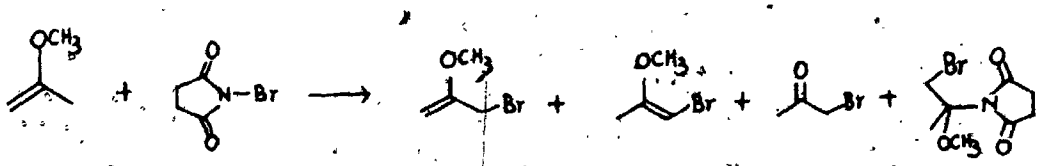
Support for such a mechanism was provided by the isolation of the chloroenol derivative when Y=Ac (Scheme 7-1). As pointed out earlier chlorination of enol acetate 63 in carbon tetrachloride at 5° gave, in addition to monochloro ketones 51 and 52, as much as 30% of trans-6-chloro-1-acetoxy-4-t-butylcyclohexene (67). The survival of 67 in the presence of some chlorine must be a consequence of the decreased nucleophilic character of the enolic double bond caused by the combined effect of the acetyl and allylic chlorine groups which have already been discussed in Chapter 6. Treatment of 51 and 52 with AcCl-HCl-CCl_4 at 5° gave no 67 thus ruling out the possibility of 67 being formed from either 51 or 52.

Similarly, this mechanism presumably operates during the chlorination of 4-t-butylcyclohexanone (50) in chloroform solution (Table 15, p119). The dielectric constant of chloroform (5.0) is not far from that of carbon tetrachloride (2.2).[42] Again, the change of the monochloro:dichloro ketone ratio was not compatible with ketone being formed from monochloro ketone.

Two factors which appear to be equally important are the polarity measured by the dielectric constant and the solvation power of the solvent. Chlorination of ketone 50 in formic acid (D 47.9),[42] trifluoroacetic acid (D 40.0)[43] and acetic acid (D 7.1)[42] led to only monochlorination (see Chapter 4) with no trace of 2,6-dichloro ketone 56 formed. This could be rationalized that in these protic solvents, the halogen molecules are polarized and the incipient halide anion presumably are effectively

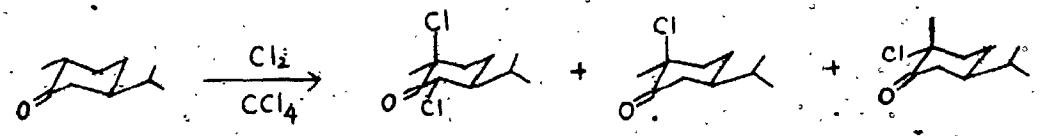
solvated through hydrogen bonding by the solvent to the negative end of the chlorine molecule. Thus the halide base is solvated and is not available or basic enough for α' C-H removal. However, in aprotic solvents such as $CHCl_3$ (D 5.0),[42] and CCl_4 (D 2.2),[42] the solvent molecules presumably could not solvate the incipient base which for some reactive collisions is likely to lie close to the α' C-H and thus α' C-H cleavage effectively competes with the O-H cleavage.

In the chlorination of enol acetate 63, it is not surprising to see that the α' C-H cleavage is closely competitive with the O-Ac cleavage in an aprotic solvent (CCl_4). The effectiveness might well be due to the incipient non-solvated chloride base which facilitates the removal of the α' C-H proton. The C-H cleavage can no longer compete with O-Ac cleavage when the reaction was carried out in protic solvents (HCOOH, CF_3COOH) because the solvated (through hydrogen bonding) chloride anion could no longer act as a base to remove the α' C-H proton. Bromination gave less α' C-H cleavage product. Decreasing the bromine:ketone ratio to 0.25:1 depresses the formation of bromo enol acetate 69 to ~4% in carbon tetrachloride. This could well be the consequence of the weakening basicity of the incipient bromide compared to the chloride base. The formation of bromo enol derivative was also reported recently in the literature in another system, e.g., in the bromination[62] of enol ether 76:



76

In carbon tetrachloride, α,α'-dichlorination has been reported recently by Yasuhara[63] to occur in (+)-carvomenthone furnishing 1,3-dichlorocarvomenthone 77.



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The surprising implication of the mechanism in Scheme 7-I is that, at least in an aprotic solvent in which proton removal from the enolate OH during halogenation is not facilitated by the solvent, electrophilic attack on an enol or its derivative with cleavage of an α' C-H bond to yield the α'-enol derivative 71 can be closely competitive with cleavage of the O-X bond of 70 to form the monosubstituted ketone.

CHAPTER 8

EXPERIMENTAL

GENERAL

Melting points (mp) were determined on a Reichert-Kofler microscope hot stage and are corrected. Infrared spectra (ir) were taken on a Beckman IR-5A, IR-10, or IR-20A spectrophotometer in carbon tetrachloride solutions unless otherwise specified. Absorption maxima, ν_{max}, are reported as wave numbers in cm^{-1}. Ultraviolet spectra (uv) were recorded on a Cary Model 14 spectrophotometer in methanol solutions. Absorption maxima, λ_{max}, are reported as wavelengths in nm with extinction coefficients in parentheses. Proton magnetic resonance spectra (pmr) were run on a Varian A-60, T-60, or HA-100 instrument in deuteriochloroform solutions with tetramethylsilane (TMS) as internal reference unless otherwise stated. Chemical shifts are reported as values in ppm downfield from TMS (δ=0). The complete pmr spectra are reported for pure materials and, in these cases, the number of protons is included in the pmr data. Otherwise, only the major signals and their interpretations are given. The area under each absorption peak was integrated and is reported in area units (au). Mass spectra were obtained on a Varian M-66 instrument with perfluoroalkane for calibration.

Gas-liquid partition chromatographic analysis (glpc) was done on 2 m spirally wound glass column (OD 4 mm) in a Glowall Model 400

instrument with hydrogen flame detector.

Silica gel GF-254 (E. Merck) was used for thin layer chromatography (tlc) and thick layer chromatography (20 g of silica gel per 20 cm×20 cm plate). Petroleum ether-ethyl acetate 70:30 (eluent A) or petroleum ether-chloroform 50:50 (eluent B) was used for developing the tlc plate. Petroleum ether refers to the fraction boiling at 60-80°. A GE G15T8 uv lamp was employed to detect uv-visible spots before spraying the plate with a 30% sulfuric acid solution and charring in an oven at 170°. In column chromatography, silica gel refers to the type with particle-size of 60-120 mesh (BDH).

Microanalyses were carried out by J. F. Alicino, Metuchen, N. J., U. S. A., or the A. Bernhardt Laboratory, West Germany, or Chemalytics, Tempe, Arizona, U. S. A.

Fractional distillation was done with a Nestor-Faust 18" semi-micro spinning band column under reduced pressure.

Extracts with organic solvent, after being washed to neutrality, were dried by washing with saturated brine and standing over anhydrous magnesium sulfate before filtration. Organic solvent was removed by a rotary evaporator under the reduced pressure provided by the house vacuum line with the flask heated in a water bath at temperature below 40°. Last trace of solvent was removed by oil pump.

For halogenation in neutral solvent, the standard work-up procedure consisted of quenching the reaction with 10% potassium iodide solution followed by 10% sodium thiosulfate solution, extraction with methylene chloride, and washing the organic solution to neutrality with 5% sodium bicarbonate solution followed by water. For halogenation in acidic solvent, the standard work up procedure means dilution with

water, extraction with methylene chloride, washing the extracts to neutrality with 5% sodium bisulfite solution, 5% sodium bicarbonate solution, and finally with water. This organic solution was then subjected to the standard solvent drying and removing procedure mentioned earlier.

The following abbreviations for the solvents indicated are in use:

PE	Petroleum ether
Bz	Benzene
DME	Dimethoxyethane

PREPARATION OF COMPOUNDS

4-t-Butylcyclohexanone (50)

4-t-Butylcyclohexanone was prepared by oxidation of 4-t-butylcyclohexanol. The procedure of Sicher, et. al.,[64] was followed. 4-t-Butylcyclohexanof (Matheson, Coleman, and Bell, or Aldrich Chemical Co., Inc., 97.0 g, 0.62 mol) was suspended in glacial acetic acid (J. T. Baker Chemical Co., 200 ml) and treated at 10° with concentrated sulfuric acid (J. T. Baker Chemical Co., 35 ml). To this solution was then added a solution of chromium trioxide (Shawingigan, 47.4 g, 0.48 mol) in water (200 ml) and acetic acid (100 ml) in portions over a period of 4 hr with stirring and external cooling, at such a rate that the temperature of the reaction mixture did not rise above 15°. Stirring was then continued for another 2 hr, the mixture was diluted with water (500 ml) and extracted four times with 200-ml portions of petroleum ether (30-60°). The combined extracts were washed to neutrality with 5% sodium bicarbonate solution followed by water. After drying and removal of solvent, the residue was distilled at reduced pressure. The fraction (93.5 g, 98%) boiling at 50-52° (0.5 mm) which was collected rapidly crystallized. Repeated recrystallization from petroleum ether gave white needles of 50, mp 50-50.5° (lit.[65] mp 49-50°).

Tlc: single spot (eluent A or eluent B).

Ir: 1720 (C=O) {lit.[34a] 1720 (C=O)}.

In CS_2 solution: 1718 (C=O).

Pmr: 0.91 {9H, s, $(CH_3)_3C$-}, 1.2-1.9 {4H, m, CH_2(C-3 and C-5)}, 1.9-2.2 {1H, m, CH(C-4)}, 2.2-2.5 {4H, m, CH_2(C-2 and C-6)}.

Semicarbazone derivative: white crystals recrystallized from methanol-benzene, mp 209-209.5° (lit.[65] 210-211°).

4-t-Butylcyclohexanone enol acetate (63)

The methods of Rogic[66] and Lamaty[67] were adapted.

A mixture of 4-t-butylcyclohexanone (15 g, 97 mmol), isopropenyl acetate (Eastman Organic Chemicals, freshly distilled at 95-97° (760 mm), 27.5 g, 30.0 ml, 275 mmol), and p-toluenesulfonic acid (Eastman Organic Chemicals, 90 mg) was placed in a 50-ml round-bottomed flask equipped with an 18" spinning band column and refluxed for 72 hr with continuous removal of acetone (11 ml). Unreacted isopropenyl acetate {bp 45° (70-80 mm)} was distilled off on the water bath (70-80°). Ether (100 ml) was then added to the residue. The ethereal solution was washed twice with saturated sodium bicarbonate solution, alcoholic sodium bisulfite solution and water. After drying and removal of ether, the light brown liquid (19 g, 99%) was distilled through the same column. Two fractions were collected: the first fraction weighing 1.02 g, bp 58-63° (0.3 mm), contained a trace of the starting ketone and the second fraction weighing 16.06 g (84%), bp 63-63.5° (0.3 mm) was the pure enol acetate 63.

Tlc: single spot (eluent A or eluent B).

n_D^{27}: 1.4610 (lit.[66] n_D^{20} 1.4641).

Ir: 1755 (C=O), 1698 (C=C), 1220(C-O-C), {lit.[66] 1755 (neat)}.

In CS_2 solution: 1755(C=O), 1695 (C=C), 1220 (C-O-C).

Pmr: 0.88 {9H, s, $(CH_3)_3C$-}, 2.1 {3H, s, CH_3-C=O}, 1-2.2 {7H, m, CH_2(C-3, C-5 and C-6) also CH(C-4)}, 5.35 {1H, m, C=C-H}.

4-t-Butylcyclohexanone enol trimethylsilyl ether (66)

Stork's method[50,68] for preparing enol silyl ethers was adapted to prepare 66.

Dimethoxyethane (DME, Aldrich Chemical Co., Inc.) was dried by refluxing with lithium aluminum hydride (Alfa Products) for 2 hr and was distilled at 83.5-84° (760 mm). Triethylamine (Eastman Organic Chemicals) was dried by refluxing with calcium hydride (BDH) for 2 hr and was distilled at 89-90° (760 mm). Nitrogen gas was purified by passage through two bottles of Fieser's solution,[72b] two bottles of Drierite and one bottle of sodium hydroxide pellets before it was used in this preparation.

A solution of 4-t-butylcyclohexanone (10 g, 65 mmol) in DME (150 ml) was placed in a 500-ml two-necked round-bottomed flask fitted with a reflux condenser, the top of which was connected to the purified nitrogen source. The other neck was fitted with a rubber septum tightly fastened by copper wire on the outside. Sodium hydride (56%, Metal Hydrides Inc., weight before washing 8.30 g, 0.19 mol) was washed twice with 15 ml of DME and then transferred to the flask along with 50 ml of DME. By alternately applying suction and filling with nitrogen gas, the system was cut off from the atmosphere. A positive nitrogen pressure was maintained throughout the experiment. The mixture was then refluxed for 3 hr with stirring provided by a heavy egg-shaped magnetic stirring bar. At the end of the stirring period the mixture became a thick white cream. This mixture was then cooled with an ice-salt bath to -5° before chlorotrimethylsilane (Aldrich Chemical Co., 14.1 g, 16.5 ml, 0.13 mol) and triethylamine (13.1 g, 18.0 ml, 0.13 mol) were added alternately in portions. The mixture was stirred at -5° for 15 min before the white cream was taken up with petroleum ether (30-60°). The organic

solution was washed three times with 5% hydrochloric acid and twice with water to neutrality. After drying and solvent removal, the crude yellow oil (15.31 g, 61.6% from pmr) was then fractionally distilled. Four fractions were collected, each of which was analyzed by tlc, ir, and pmr methods.

Details of the four fractions collected are as followed: Fraction 1 {1.14 g, bp 40-45°(0.05 mm)} contained roughly 70% of the parent ketone and 30% of silyl ether 66. Fraction 2 {2.1 g, bp 45° (0.05 mm)} contained mainly silyl ether 66 with less than 5% of the parent ketone. Fraction 3 {1.44 g, bp 45° (0.05 mm), n_D^{27} 1.4517, n_D^{20} 1.4548} contained pure silyl ether 66. Fraction 4 {1.47 g, bp 45° (0.05 mm), n_D^{27} 1.4510, n_D^{20} 1.4542} containing pure silyl ether 66 with no trace of impurities was submitted for elemental analysis.

Tlc: single spot (eluent A or eluent B).

Ir: 1672 (C=C), and 847 and 737 ($Si-CH_3$).

Pmr: 0.15 {9H, s, $(CH_3)_3Si-$}, 0.87 {9H, $(CH_3)_3C-$}, 1.1-2.2 {7H, CH_2(C-3, C-5, and C-6), and CH(C-4)}, 4.83 (1H, m, C=C-H).

Analysis: Cald. for $C_{13}H_{26}OSi$: C, 68.95%; H, 11.58%; Si, 12.41%.

Found : C, 68.88%; H, 11.63%; Si, 13.59%.

cis- and trans-2-Chloro-4-t-butylcyclohexanone (52 and 51)

Isomers 51 and 52 were prepared by chlorination of 4-t-butylcyclohexanone enol acetate (63) or 4-t-butylcyclohexanone (50) in either carbon tetrachloride or formic acid. The crude product was either subjected to a clean-up distillation followed by a separation on a column of silica gel or directly separated on the column.

A typical preparation from 50 is as follows. In a 1-l three-necked round-bottomed flask was placed a solution of 50 (20.0 g, 130 mmol) in 20

ml of formic acid (Anachemia, dried over $CuSO_4$ and distilled at 54° (20 mm)). The solution was cooled with an ice-salt bath to maintain the temperature of the solution at 0-10°. A freshly prepared solution of dried chlorine in formic acid (680 ml, 0.21 M, 143 mmol, 10% excess) was added during one half hour at such a rate that the temperature remained below 10°. The solution was stirred for another half hour below 10° before the color of chlorine disappeared. This solution was then diluted with water (200 ml) and washed to neutrality with saturated sodium bicarbinate solution and water. After drying and solvent removal, a pale yellow oil (24.6 g) was obtained. This was an equilibrium mixture containing the isomeric 2-chloro ketones 52 and 51 in 3:1 ratio.

This crude mixture was then placed on the silica gel (500 g) which was washed and packed with petroleum ether in a 5 cm x 116 cm column. The column was then eluted with the following solvents in the order and quantity given: (1) PE, 500 ml; (2) PE-Bz (99:1), 500 ml; (3) PE-Bz (98:2), 500 ml; (4) PE-Bz (95:5), 500 ml; (5) PE-Bz (90:10), 5.71 l; (6) PE-Bz (85:15), 1.5 l; (7) PE-Bz (80:20), 7.75 l; (8) PE-Bz (70:30), 1.75 l; (9) PE-Bz (50:50), 4 l; (10) Bz, 3.5 l; (11) Bz-ether (50:50), 1 l; (12) ether, 1 l.

Fraction 7 contained nearly pure trans-2-chloro-4-t-butylcyclohexanone (51) (8.8 g) which was purified by distillation under reduced pressure to give a colorless liquid, bp 60-66° (0.6 mm), n_D^{27} 1.4710, n_D^{20} 1.4742 (lit.[34,69] n_D^{25} 1.4737; $n_D^{25.5}$ 1.4719).

Tlc: One intense spot at R_f 0.61 (eluent A) or 0.52 (eluent B) with a faint spot at R_f 0.53 (eluent A) or 0.33 (eluent B). The intense spot corresponded to the isomer 51 and the faint spot the isomer 52. There is evidence discussed in Chapter 2 that epimerization took place on the

tlc plate.

Glpc: 5% DEGS on Chromosorb P, 160°, t_r 1.38 min (intense peak, 51) and t_r 3.65 min (tiny broad peak 52). 1% SE-30 on Chromosorb-W, 100°, t_r 3.2 min. 1% XE-60 on Gas-Chrom Q, 120°, t_r 1.45 min.

Ir: 1730 (C=O) {lit.[34,33] 1736 (C=O); 1730 (C=O)}.

Uv: 305 (ε 35) {lit.[40] 303(ε 48)}.

Pmr: 0.97 {9H, s, $(CH_3)_3C$-}, 1.2-3.3 {7H, m, CH_2(C-3, C-5, and C-6) and CH(C-4)}, 4.22 {1H, m, narrow, equatorial CH(C-2), $|J_{AX}+J_{BX}|$=5.3 Hz}. {lit.[34] 4.23, equatorial CH(C-2)}.

In benzene solution: 0.61 {9H, s, $(CH_3)_3C$-}, 0.87-3.0 {7H, m, CH_2(C-3,C-5, and C-6) and CH(C-4)}, 4.06 {1H, dd, narrow, equatorial CH(C-2), $|J_{AX}+J_{BX}|$= 5 Hz}.

Fraction 9 and 10 furnished nearly pure cis-2-chloro-4-t-butylcyclohexanone (52) (11.2 g) which was recrystallized from n-pentane to give white needles, mp 59-60° (lit.[34,33] mp 58.5-59.5°, 56.5-57°).

Tlc: One intense spot at R_f 0.53 (eluent A) or 0.33 (eluent B) with a faint spot at R_f 0.61 (eluent A) or 0.52 (eluent B).

Glpc: 5% DEGS on Chromosorb P, 160°, t_r 1.38 min (tiny peak) (51) and t_r 3.65 min (broad peak) (52).

1% SE-30 on Chromosorb W, 100°, t_r 6.6 min.

1% XE-60 on Gas-Chrom Q, 120°, t_r 5 min.

Ir: 1740 (C=O) {lit.[34,40,33] 1748, 1745, 1740 (C=O)}.

Uv: 280 (ε 17). {lit.[40] 280 (ε 20)}.

Pmr: 0.94 {9H, s, $(CH_3)_3C$-}, 1.3-2.8 {7H, m, CH_2(C-3, C-5, and C-6) and CH(C-4)}, 4.55 {1H, dd, axial CH(C-2), $|J_{AX}+J_{BX}|$=17.80 Hz}. {lit.[34] 4.51, axial CH(C-2)}.

In benzene solution: 0.63 {9H, s, $(CH_3)_3C$-}, 0.83-2.53 {7H, m, CH_2(C-3

and C-5) and CH(C-6)}, 4.10 {1H, dd, axial CH(C-2), $|J_{AX}+J_{BX}|$=20 Hz}.

cis and trans-2-Bromo-4-t-butylcyclohexanone (54 and 53)

A solution of 4-t-butylcyclohexanone enol acetate (63) (2.0 g, 10 mmol) in formic acid {Anachemia, dried over anhydrous $CuSO_4$ and distilled at 54-55° (20 mm)} was placed in a two-necked 100-ml round-bottomed flask fitted with a thermometer. Freshly dried sodium formate (680 mg, 10 mmol) was added. This solution was cooled in an ice-salt bath to 0-5°. A solution of bromine (BDH AnalaR or Fisher, 1.6 g, 10 mmol) in formic acid (20 ml) was added at such a rate that the temperature of the reaction mixture remained at 0-5°. Immediate decoloration took place when the bromine solution came into contact with the enol acetate solution. Addition was completed in 5 min. The solution was then poured into a separatory funnel containing 60 ml of 1% sodium formate solution. The solution was extracted with methylene chloride, washed to neutrality, and dried. After removal of solvent, a pale yellow oil (2.55 g, 81% from pmr) was obtained. Its pmr spectrum showed it to be a mixture containing 21% of 53 and 79% of 54 (kinetic mixture).

Separation was accomplished on a column (2.5 cm x 6.0 cm) packed with 40 g of silica gel. The column was eluted with the following solvents in the order and quantity given: (1) PE, 120 ml; (2) PE-Bz (99:1), 120 ml; (3) PE-Bz (98:2), 120 ml; (4) PE-Bz (95:5), 120 ml; (5) PE-Bz (90:10), 120 ml; (6) PE-Bz (85:15), 120 ml; (7) PE-Bz (80:20), 240 ml; (8) PE-Bz (75:25), 1440 ml; (9) PE-Bz (70:30), 240 ml; (10) PE-Bz (60:40), 120 ml; (11) PE-Bz (50:50), 1.1 l; (12) PE-Bz (40:60), 240 ml; (13) PE-Bz (30:70), 240 ml; (14) PE-Bz (20:80), 240 ml; (15) Bz, 120 ml; (16) ether, 100 ml.

Fraction 7 contained trans-2-bromo-4-t-butylcyclohexanone 53 (0.2 g)

and fraction 8 contained 53 (0.79 g) mixed with a little unreacted enol acetate 63. For pure trans-2-bromo-4-t-butylcyclohexanone (53), the following data were recorded:

Tlc: One intense spot at R_f 0.47 (eluent B) with a faint spot at R_f 0.33 (eluent B). The intense spot corresponded to the isomer 53 and the faint spot the isomer 54. Epimerization took place on the tlc plate (see Chapter 2).

Ir: 1725 (C=O) {lit.[35] 1724 (C=O)}.

Uv: 308 (ε 94) {lit.[40] 310 (ε 104) in EtOH}.

Pmr: 0.92 {9H, s, $(CH_3)_3C$-}, 1.15-2.5 {7H, m, CH_2(C-3, C-5, and C-6) and CH(C-4)}, 4.37 {1H, m, narrow, equatorial CH(C-2), $|J_{AX}+J_{BX}|$=5.7 Hz}. {lit.[34] 4.35, equatorial CH(C-2)}.

Fraction 11 contained almost pure cis-2-bromo-4-t-butylcyclohexanone (54) (330 mg). After repeated recrystallizations from n-pentane, white needles, mp 68-69° (lit.[34,35] 67-68°) were obtained.

Tlc: One intense spot at R_f 0.33 (eluent B) with a faint spot at R_f 0.47 (eluent B).

Ir: 1735 (C=O) {lit.[40] 1730 (C=O)}.

Uv: 281 (ε 13) {lit.[40] 283 (ε 22) in EtOH}.

Pmr: 0.94 {9H, s, $(CH_3)_3C$-}, 1.4-2.9 {7H, m, CH_2(C-3, C-5, and C-6)}, 4.70 {1H, dd, axial CH(C-2), $|J_{AX}+J_{BX}|$=18.1 Hz}. {lit.[34] 4.67, axial CH(C-2)}.

2,2-Dichloro-4-t-butylcyclohexanone (55)

To a solution of 4-t-butylcyclohexanone (10.0 g, 64.8 mmol) in methylene chloride (20 ml) was added a solution of sulfuryl chloride (21.8 g, 14.0 ml, 162 mmol) in methylene chloride (50 ml) over a period of 0.5 hr

with stirring. The pale yellow solution was stirred for 4 hr at 27±2°. The reaction mixture was diluted with 80 ml of methylene chloride at the end of the stirring period. The methylene chloride solution was washed to neutrality three times with saturated sodium bicarbonate solution followed by water. After drying the extracts and removal of solvent, a pale yellow oil (12.34 g) was obtained. This was a mixture of monochloro ketones, 51 and 52 and dichloro ketones 55, 56, and 57. The pale yellow oil was then distilled fractionally on a spinning band column under reduced pressure. Six fractions were collected: (1) A colorless liquid weighing 640 mg, bp 40-56° (0.05-0.1 mm) contained mainly trans-2-chloro ketone 51, (2) a colorless liquid weighing 960 mg, bp 52° (0.05 mm) was the pure trans-2-chloro ketone 51 by pmr spectrum, (3) a colorless liquid (nearly pure 55) weighing 2.34 g, bp 63-70° (0.05 mm) crystallized after standing overnight in the refrigerator, (4) a mixture of white crystals suspended in colorless liquid weighing 1.9 g, bp 73-75° (0.05 mm) was a mixture of cis,trans-2,6-dichloro ketone 56 and cis-2-chloro ketone 52, (5) white solid weighing 2.12 g, bp 75° (0.05 mm) was a mixture of 56 with very little 52, and (6) a colorless liquid weighing 1.23 g, bp 75-77° (0.05 mm) was a mixture of cis,trans- and cis,cis-2,6-dichloro ketones 56 and 57. A residual brown oil (1.92 g) was enriched in 57.

White crystals of 55 from fraction 3 were washed with n-pentane and recrystallized several times from the same solvent to give white needles, mp 38.5-40° (lit.[46] 40°).

Tlc: single spot (eluent B).

Glpc: 1% SE-30 on Chromosorb W, 120°, t_r 2.8 min.

1% XE-60 on Gas-Chrom Q, 120°, t_r 2.95 min.

Ir: 1745 (C=O) {lit.[46] 1749 (C=O)}.

Pmr: 0.93 {9H, s, $(CH_3)_3C$-}, 1.2-3.2 {7H, CH_2(C-3, C-5, and C-6) and CH (C-4)}.

Mass spectrum: Molecular ions: 222 (calcd. for 2 ^{35}Cl: 222), 224 (calcd. for $^{35}Cl+^{37}Cl$: 224), and 226 (calcd. for 2 ^{37}Cl: 226).

cis,trans-2,6-Dichloro-4-t-butylcyclohexanone (56)

Chlorine gas was passed for 1.5 hr into a solution of 4-t-butylcyclohexanone (10 g, 65 mmol) in 30 ml of acetic acid-water (90:10) with constant stirring. The reaction mixture was cooled in an ice-bath to ~15°. At the end of the reaction period, the reaction mixture was diluted with 50 ml of water, extracted twice with 500-ml portions of ether. The ether extracts were washed to neutrality with 5% sodium bicarbonate solution and water. A pale yellow oil (16.55 g) was obtained after drying and removal of the solvent. This yellow oil was a mixture containing 2,2-dichloro ketone 55, cis,trans-2,6-dichloro ketone 56, cis,cis-2,6-dichloro ketone 57, and also 2,2,6-trichloro ketone 61.

Upon distillation on a spinning band column, seven fractions were collected. Fraction (1) bp 64-70° (0.1 mm), 577 mg, was almost pure gem-dichloro ketone 65 from the pmr spectrum. This fraction crystallized after standing overnight in the refrigerator. Fraction (2), bp 72-76° (0.075 mm), 301 mg, was also a crystalline solid after cooling overnight. This contained mainly gem-dichloro ketone 55 with a trace of cis,trans-2,6-dichloro ketone 56 as detected in the pmr spectrum. Fraction (3), bp 76-79° (0.075 mm), 400 mg, contained some crystals mixed with a colorless oil. This fraction was a mixture of cis,trans-2,6-dichloro ketone 56 and gem-dichloro ketone 55. Fraction (4), bp 79-81° (0.075 mm), 610 mg, was nearly pure cis,trans-2,6-dichloro ketone 56 with a little

at 52±3° was added a solution of chlorine (71 mg, 1 mmol) in acetic acid (5.15 ml). The mixture was then stirred at 52±3° for 4 hr and then worked up to give 140 mg of a light yellow oil.

Pmr: 4.22, 241 au; 4.55, 246 au. The ratio of cis 52:trans 51 was 246:241 or 51:49.

(vii) A solution of ketone 50 (155 mg, 1 mmol) and potassium acetate (198 mg, 1 mmol) in acetic acid (3 ml) was treated with a solution of chlorine (71 mg, 1 mmol) in acetic acid (4.54 ml) and allowed to stir at 37-38° for 3.5 hr. The reaction mixture was then worked up to give 178 mg of a light yellow oil.

Pmr: 4.22, 235 au; 4.55, 197 au. The ratio of cis 52:trans 51 was 197:235 or 46:54.

(d) Chlorination in chloroform

To a well stirred solution of ketone 50 (155 mg, 1 mmol) in chloroform (5 ml) at 0° was added a solution of chlorine (35 mg, 0.5 mmol) in chloroform (5 ml). The mixture was stirred at 0-5° for 12 min and then worked up to give 151 mg of a light yellow oil mixed with some white crystals.

Pmr: 4.22 (51, 1 ax H), 62 au; 4.55 (52, 1 ax H; 56, 1 eq H), 89 au; 5.20 (56, 1 ax H), 16 au. The ratio of cis 52:trans 51 was (89-16):62 or 54:46.

For all of the other runs see "Halogenation with allylic rearrangement."

(e) Chlorination in carbon tetrachloride

(i) A solution of ketone 50 (155 mg, 1 mmol) in carbon tetrachloride (3 ml) was cooled to -3°. To this solution was added a solution of chlorine (71 mg, 1 mmol) in carbon tetrachloride (4 ml). The mixture was stirred

pressure, there was always some residual brown oil remaining in the distillation pot. The brown oil upon trituration with n-pentane gave cis,cis-2,6-dichloro-4-t-butylcyclohexanone (57).

A typical preparation is as follows. Dioxane used in this preparation was dried over lithium aluminium hydride for 1 hr and distilled at 99-100° (760 mm). A solution of 4-t-butylcyclohexanone (10 g, 64.8 mmol) in 20 ml of methylene chloride-dioxane (1:1) was placed in a three-necked 250-ml flask fitted with a dropping funnel, a thermometer and a reflux condenser. To this mixture was added a yellow solution of sulfuryl chloride (18.9 g, 11.5 ml, 140 mmol) in 50 ml of methylene chloride-dioxane (1:1) over a period of 0.5 hr. The resulting pale yellow solution was stirred in a water bath for 12 hr at 25-35°. During the stirring period, the solution turned deep yellow. The solution was washed three times with water (100 ml each). After each washing, the aqueous layer was extracted once more with methylene chloride and added to the methylene chloride extracts. The combined extracts were then washed to neutrality with three 100-ml portions of saturated sodium bicarbonate solution and once with water. A yellow oil (15.13 g) was left after drying and solvent removal. The crude product was distilled at reduced pressure through a spinning band column. After collecting the distillate in four separate fractions, a residual brown oil was left which was triturated with n-pentane. White crystals (450 mg), mp 143.5-146°, immediately precipitated. These were recrystallized from methylene chloride-n-pentane to give white needles, mp 146-148°. A second recrystallization from the combined solvents raised the melting point to 148-150° (lit.[46] 149-150°).

Glpc: 1% SE-30 on Chromosorb W, 120°, t_r 3.4 min.

1% XE-60 on Gas-Chrom Q, 120°, t_r 5.15 min.

Ir: 1755 (C=O).

Pmr: 0.95 {9H, s, $(CH_3)_3C$-}, 1.57-2.93 {5H, m, CH_2(C-3 and C-5) and CH(C-4)}, 4.63 {2H, dd, CH(C-2 and C-6), $|J_{AX}+J_{BX}|$=18 Hz}.

In benzene solution: 0.50 {9H, s, $(CH_3)_3C$-}, 0.8-2.27 {5H, m, CH_2(C-3 and C-5) and CH(C-4)}, 3.87 {2H, dd, CH(C-2 and C-6); $|J_{AX}+J_{BX}|$=19 Hz}.

Mass spectrum: Molecular ion: 222 (calcd. for 2 ^{35}Cl: 222), 224 (calcd. for $^{35}Cl+^{37}Cl$: 224), 226 (calcd. for 2 ^{37}Cl: 226).

2,2,6-Trichloro-4-t-butylcyclohexanone (61) and 2,2,6,6-tetrachloro-4-t-butylcyclohexanone (62)

To a milky solution of 4-t-butylcyclohexanone (6.17 g, 40 mmol) and sodium acetate (6.56 g, 80 mmol) in 20 ml of acetic acid, was added a solution (0.82 M) of chlorine (6.42 g, 90.5 mmol) in acetic acid (110 ml). The mixed solution was heated at 80-90° for 20 min before the color of chlorine faded. The milky solution was diluted with 50 ml of water, cooled to room temperature, and extracted twice with 75-ml portions of petroleum ether (30-60°). The extracts were washed to neutrality with 5% sodium bicarbonate solution and water before drying. A pale yellow liquid (5.94 g) was obtained after the solvent was removed. This was a mixture of cis- and trans-2-chloro ketones 52 and 51 with no sign of dichlorination judging from the pmr spectrum. This crude oil was then dissolved in acetic acid (10 ml) and heated to 85°. A solution (0.845 M in Cl_2) of chlorine (90 mmol) in acetic acid (107 ml) was then added. The mixture was stirred at 85-90° for 1 hr until it decolorized. The acetic acid was then removed at 60° (110 mm). The residual oil was taken up in 100 ml of petroleum ether (30-60°), washed to neutrality with 5% sodium

bicarbonate solution and water. After the extracts were dried and the solvent was removed, a thick pale yellow oil (7.63 g) was obtained. Pmr spectrum showed that the mixture was mainly 61. After standing overnight in the refrigerator, the thick oil solidified. The solid was then recrystallized from n-pentane. White crystals (300 mg), mp 62-66°, were obtained. These crystals were recrystallized once from n-pentane followed by sublimation to give white crystals, mp 66-68°. This was 2,2,6,6-tetrachloro-4-t-butylcyclohexanone (62) judging from the glpc analysis.

Tlc: single spot (eluent B).

Glpc: 1% SE-30 on Chromsorb W, 140°, t_r 3.9 min; 120°, t_r 7.8 min; 110°, t_r 9.9 min; 100°, t_r 17.3 min; 90°, t_r 23 min.

Ir: 1764 (C=O).

Pmr: 1.02 {9H, s, $(CH_3)_3C$-}, 1.73-3.67 {5H, m, CH_2(C-3 and C-5) and CH(C-4)}.

Mass spectrum: Molecular ion: 289.988 (calcd. for 4 ^{35}Cl: 289.979), 292.020 (calcd. for 3 ^{35}Cl+^{37}Cl: 291.976), 294.020 (calcd. for 2 ^{35}Cl+ 2 ^{37}Cl: 293.973), 296.024 (calcd. for 3 ^{37}Cl+^{35}Cl: 295.971), 298.100 (calcd. for 4 ^{37}Cl: 297.967).

Analysis: Calcd. for $C_{10}H_{14}OCl_4$: Cl, 48.56%.

Found : Cl, 48.80%.

The filtrate, after the removal of 2,2,6,6-tetrachloro ketone 62, was evaporated to dryness, and methylene chloride was added to dissolve the crystals. This solution was evaporated to a thick yellow liquid, n-pentane was quickly added and the solution mixed thoroughly and allowed to stand in ice. White needles, 426 mg, mp 101.5-102°, were obtained. The sample was again disolved in methylene chloride, concentrated to a thick liquid, n-pentane was then added and the solution chilled.

White needles, 95 mg, mp 102-103°, gave ir and pmr spectra which fit the structure of 2,2,6-trichloro-4-t-butylcyclohexanone (61). One more recrystallization did not improve the mp. This sample was sent for an elemental analysis.

Tlc: single spot (eluent B). Same R_f as 62

Glpc: 1% SE-30 on Chromsorb W, 100°, t_r 10.5 min; 120°, t_r 7.1 min. 1% XE-60 on Gas-Chrom Q, 120°, t_r 11.5 min.

Ir: 1768 (C=O).

Pmr: 0.98 {9H, s, $(CH_3)_3C$-}, 1.6-3.2 {5H, m, CH_2(C-3 and C-5) and CH(C-4)}, 5.23 {1H, dd, CH(C-6), $|J_{AX}+J_{BX}|$=20 Hz}.

Mass spectrum: Molecular ion: 256 (calcd. for $3\ ^{35}Cl$: 256), 258 (calcd. for $2\ ^{35}Cl+^{37}Cl$: 258); 260 (calcd. for $^{35}Cl+2\ ^{37}Cl$: 260).

Analysis: Calcd. for $C_{10}H_{15}OCl_3$: C, 46.63%; H, 5.87%; Cl, 41.29%

Found : C, 46.90%; H, 6.04%; Cl, 42.51%.

trans-6-Chloro-1-acetoxy-4-t-butylcyclohexene (67)

A 250 ml two-necked round-bottomed flask was charged with a solution of 4-t-butylcyclohexanone enol acetate (63) (19.63 g, 0.1 mol) in carbon tetrachloride (20 ml). This solution was cooled in an ice-salt bath to 0° after which a cold solution (0°) of chlorine (7.1 g, 0.1 mol) in carbon tetrachloride (100 ml) was added over a period of 5 min with stirring. The temperature of the reaction mixture was maintained at 0-5°. After all chlorine solution has been added the reaction mixture was poured into water (150 ml), methylene chloride (50 ml) was added and the organic layer separated. After neutralizing and drying the organic layer, carbon tetrachloride and methylene chloride were removed to give 22.8 g light yellow liquid. This liquid was then

fractionated on a spinning band column under reduced pressure, twelve fractions were collected. The first seven fractions ($b_{0.05-0.2}$ 43-65°) contained trans-2-chloro ketone 51 mixed with enol acetate 63. Fraction 8 ($b_{0.05-0.075}$ 58-74°) contained the same mixture in decreasing amount together with chloro enol acetate 67 and cis-2-chloro ketone 52. Fraction 9, 10, 11, and 12 ($b_{0.05}$ 74-74.1°) contained mainly 67 and a small amount of 52 in approximately 8:1 ratio judging from the glpc analysis (1% XE-60 on Gas-Chrom Q, 120°). Fraction 12 (1.57 g) was placed on 45 g silica gel (20 mm x 40 cm column) and eluted with the following solvents in the order and quantity given. (1) PE, 1 l; (2) PE-Bz (99:1), 500 ml; (3) PE-Bz (98:2), 500 ml; (4) PE-Bz (97:3), 200 ml; (5) PE-Bz (95:5), 200 ml; (6) PE-Bz (90:10), 200 ml; (7) PE-Bz (85:15), 200 ml; (8) PE-Bz (80:20), 200 ml; (9) PE-Bz (75:25), 1 l; (10) PE-Bz (70:30), 200 ml; (11) PE-Bz (60:40), 200 ml; (12) PE-Bz (50:50), 200 ml; (13) Bz 200 ml.

Fraction 9 gave 168 mg of a colorless liquid which was determined to have the structure 67 by ir, pmr, mass spectrum, elemental analysis, and hydrolysis study. An analytical sample was purified by a bulb-to-bulb distillation at 0.05 mm and 75° (oven setting).

Tlc: single spot (eluent B), R_f for 67 is the same as that for 51.

Glpc: 1% XE-60 on Gas-Chrom Q, 120°, t_r 3.6 min. A tiny peak (t_r 1.45 min) corresponded to trans-2-chloro ketone 51 resulting from hydrolysis on column.

Ir: 1755 (enol ester C=O), 1682 (C=C).

Pmr: 0.95 {9H, s, $(CH_3)_3C$-}, 1.5-2.4 {8H, m, CH_2(C-3 and C-5) and CH(C-4) with singlet at 2.19 (CH_3-C-O-)}, 4.72 (1H, m, -CHCl, $W_{\frac{1}{2}}$=5 Hz), 5.63 (1H, m, -C=C-H).

Mass spectrum: Molecular ion: 230 (calcd. for ^{35}Cl: 230), 232 (calcd.

for ^{37}Cl: 232).

Analysis: Calcd. for $C_{12}H_{19}O_2Cl$: C, 62.47%; H, 8.30%; Cl, 15.37%.

Found : C, 62.47%; H, 8.58%; Cl, 15.37%.

EQUILIBRATION STUDIES

Equilibration of cis- and trans-2-chloro-4-t-butylcyclohexanone (52 and 51)

The equilibration between 51 and 52 was studied in a series of six solvents, namely, formic acid, trifluoroacetic acid, acetonitrile, acetic acid, chloroform, and carbon tetrachloride. A saturated solution of hydrogen chloride in each of the above solvents was prepared by a passage of hydrogen chloride gas through an ice-cold solvent to obtain maximum absorption. Each of the above solutions (0.3 ml) was then added to a pure isomer (~50 mg) or a mixture (80-150 mg) of 51 and 52 in a nmr tube. Two drops of TMS or a few crystals of sodium 3-trimethylsilylpropane-sulfonate were added. The tube was then allowed to stand at 25° with or without prior warming at 40° for 1 min. The pmr spectrum of the mixture in each tube was then periodically recorded and integrated over a period of several days until the epimeric ratio remained constant. These experiments are summarized in Table 16.

Equilibration of cis- and trans-2-bromo-4-t-butylcyclohexanone (54 and 53)

The general procedure for the equilibration study of the bromo ketones 53 and 54 was the same as that employed for the study of chloro ketones 51 and 52 except a saturated solution of hydrogen bromide in the required solvent was used. These experiments are summarized in Table 17.

Equilibration of cis,cis- and cis,trans-2,6-dichloro-4-t-butylcyclohexanone (57 and 56)

Table 16. Equilibration of Chloro Ketones 51 and 52 at 25°

Exp.	Solvent (0.3 ml)	Wt (mg) Cl-ketone	Composition of starting material	Time (days) to establish equilibrium	Pmr δ Value trans 51	Pmr δ Value cis 52	Pmr δ Value Ref peak	Equilibrium ratio cis 52:trans 51
(a)	(i) HCOOH	47#	pure 51	14	4.38	4.82	0.00*	78:22
	(ii) HCOOH	47#	pure 52	14	4.38	4.82		76:24
(b)	CF_3COOH	80	64% 51 36% 52	7	4.43	4.77	0.00 TMS	72:28
(c)	CH_3CN	150	20% 51 80% 52	5	4.31	4.75	1.98 CH_3CN	77:23
(d)	CH_3COOH	150	20% 51 80% 52	5	4.30	4.70	2.08 CH_3COOH	70:30
(e)	$CHCl_3$	150	20% 51 80% 52	5	4.22	4.55	0.00 TMS	65:35
(f)	(i) CCl_4	50	pure 51	60	4.13	4.41	0.00	57:43
	(ii) CCl_4	50	pure 52	21	4.13	4.41	TMS	57:43

* reference $Me_3Si(CH_2)_3SO_3Na$

also present 17 mg (0.25 mmol) of HCOONa

Table 17. Equilibration of Bromo Ketones 53 and 54 at 25°

Exp.	Solvent (0.3 ml)	Wt (mg) Br-ketone	Composition of starting material	Time (days) to establish equilibrium	Pmr δ Value			Equilibrium ratio
					trans 53	cis 54	Ref peak	cis 54:trans 53
(a)	HCOOH*	200	80% 53 20% 54	20	4.56	5.06	8.37 HCOOH	55:45
(b)	CF_3COOH	150	77% 53 23% 54	5	4.50	4.86	0.00 TMS	48:52
(c)	CH_3CN	150	80% 53 20% 54	5#	4.45	4.93	0.00 TMS	53:47
(d)	CH_3COOH	150	51% 53 49% 54	6#	4.45	4.83	0.00 TMS	43:57
(e)	$CHCl_3$	50	Pure 54	7	4.37	4.70	0.00 TMS	43:57
(f)	CCl_4	150	53% 53 47% 54	4#	4.33	4.66	0.00 TMS	31:69
(g)	CH_3CN-HCOOH (1:1)	150	51% 53 49% 54	5	4.53	5.00	0.00 TMS	44:56
(h)	$CHCl_3$-HCOOH (1:1)	150	85% 53 15% 54	5	4.50	4.86	0.00 TMS	45:55
(i)	CCl_4-HCOOH (1:1)	150	51% 53 49% 54	5#	4.40	4.63	0.00 TMS	44:56

* A volume of 0.38 ml was used. # prior warming at 40° for 1 min.

(a) In formic acid

Pure cis,trans 56 (40 mg) in a saturated solution (0.3 ml) of hydrogen chloride in formic acid was allowed to stand at 25°. The equilibrium was established after 3 days.

Pmr: 4.72 (cis,cis 57, 2 ax H's; cis,trans 56, 1 ax H), 29 au; 5.33 (cis, trans 56, 1 eq H), 7 au. Chemical shifts are reported with reference to the solvent peak at 8.23 for the formyl proton of formic acid. The ratio of 56:57 was 7.0:{(29-7.0)/2} or 39:61.

(b) In acetic acid

Pure cis,cis 57 (100 mg) was dissolved in a saturated solution (1 ml) of hydrogen chloride in acetic acid. The mixture was heated on a steam bath for 1 hr and then allowed to stand at 25° for 2 hr. The reaction mixture was then diluted with methylene chloride. After subjecting to the standard work-up procedure, a light yellow oil containing white crystals was obtained.

Pmr: 4.60 (cis,cis 57, 2 ax H's; cis,trans 56, 1 ax H), 15 au; 5.23 (cis,trans, 1 eq H), 6.0 au. The ratio of 56:57 was 6.0:{(15-6)/2} or 57:43.

(c) In chloroform

Pure cis,trans 56 (20 mg) was dissolved in a saturated solution (0.3 ml) of hydrogen chloride in chloroform. This solution was allowed to stand at 25° for 5 days before the equilibrium was established.

Pmr: 4.55 (cis,cis 57, 2 ax H's; cis,trans 56, 1 ax H), 23 au; 5.20 (cis,trans 56, 1 eq H), 12 au. Chemical shifts are reported with reference to the solvent peak at 7.26 for $CHCl_3$ proton. The ratio of 56:57 was

12:{(23-12)/2} or 69:31.

(d) In carbon tetrachloride

Pure cis,trans 56 (22 mg) was dissolved in a saturated solution (0.3 ml) of hydrogen chloride in carbon tetrachloride. The solution was warmed at 40° for 1 min and then allowed to stand at 25°. Two drops of TMS were added and the pmr spectrum was recorded periodically. The equilibrium was established after 4 days.

Pmr: 4.40 (cis,cis 57, 2 ax H's; cis,trans 56, 1 ax H), 35 au; 5.04 (cis,trans 56, 1 eq H), 20 au. The ratio of 56:57 was 20:{(35-20)/2} or 72:28.

HALOGENATION OF 4-t-BUTYLCYCLOHEXANONE ENOL DERIVATIVES

Chlorination of 4-t-butylcyclohexanone enol acetate (63)

The results are reported in Table 9 (p 69).

(a) Chlorination in formic acid

(i) Formic acid was dried by standing over anhydrous copper sulfate and distilled at 54-55° (20 mm).

To a well stirred (magnetic bar) solution of 63 (200 mg, 1 mmol) in formic acid (4 ml) was added a solution of chlorine (71 mg, 1 mmol) in formic acid (5.4 ml). The reaction mixture was stirred at 5-15° for 5 min. The color of chlorine disappeared. The reaction mixture was then diluted with water and extracted with methylene chloride. The methylene chloride extracts were washed free of acid and dried. The solvent was removed to give a yellow oil (165 mg). Tlc showed three spots corresponding to cis 52, trans 51, and enol acetate 63.

Pmr: 4.22 (51), 142 au; 4.55 (52), 79 au; 5.35 (63), 20 au. The ratio of cis 52:trans 51 was 79:142 or 36:64.

(ii) To a well stirred solution of enol acetate 63 (200 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (4 ml) was added a solution of chlorine (71 mg, 1 mmol) in formic acid (9.35 ml). The reaction mixture was stirred at 5-10° for 5 min and then worked up to give 180 mg of a faintly yellow oil. Tlc showed three spots corresponding to trans 51, cis 52, and enol acetate 63.

Pmr: 4.22, 116 au; 4.55, 60 au; 5.35, 83 au. The ratio of cis 52:trans 51 was 60:116 or 34:66.

Stability enol acetate 63 in formic acid

A solution of enol acetate 63 (200 mg, 1 mmol) and sodium formate (68 mg, 1mmol) in formic acid (4 ml) was stirred at 25° for 1 hr. The reaction mixture was worked up to give 195 mg of a light yellow oil. Tlc and glpc (5% DEGS on Chromosorb P, 160°) both showed that no detectable amount of ketone 50 was present.

Ir: 1755 (enol acetate C=O).

Pmr: 5.35 (olefinic proton).

Control experiment on trans 51

In a nmr tube was placed a solution of trans 51 (47 mg, 0.25 mmol) in 0.25 ml of formic acid. The tube was allowed to stand in an ice-bath (5-10°) for 5 min with frequent shaking. Pmr showed an absorption peak at 4.38 due to trans 51 but no peak at 4.82 due to cis 52 (reference peak: formyl proton at 8.10).

To the above solution was added 20 mg (0.25 mmol) of sodium formate. The mixture was allowed to stand at 5-10° for 5 min. Pmr showed an absorption peak at 4.38 implying no epimerization has taken place.

To the above solution was added 2 drops (28 mg, 0.36 mmol) of acetyl chloride and the tube was allowed to stand at 5-10° for 5 min. Pmr showed that no epimerization has occurred. The solution was allowed to stand at 25° for 5 hr. Pmr showed an absorption peak at 4.38 but no peak at 4.82.

Control experiment on cis 52

The same experiment described above was performed on 52 (47 mg, 0.25 mmol), mixing with sodium formate (20 mg, 0.25 mmol), and acetyl chloride (28 mg, 0.36 mmol) in 0.25 ml of formic acid. The mixture was stable at 25° for 8.5 hr. Pmr showed an absorption peak at 4.82 but no peak at 4.38 (reference peak: formyl proton at 8.10).

Equilibrium ratio of cis 52:trans 51 in formic acid

See "Equilibration studies."

Stability of chloro enol acetate 67

See "Chlorination of chloro enol acetate 67."

(b) Chlorination in trifluoroacetic acid

To a well stirred solution of enol acetate 63 (200 mg, 1 mmol) and sodium formate (272 mg, 2 mmol) in trifluoroacetic acid (6.9 ml) maintained at 0-5° was added a solution of chlorine (71 mg, 1 mmol) in trifluoroacetic acid (3.1 ml). Immediate decoloration was observed. The reaction mixture was worked up to give 190 mg of a faintly yellow oil. Tlc showed 3 spots corresponded to trans 51, cis 52, and enol acetate 63. Pmr: 4.22, 63 au; 4.55, 35 au; 5.35, 40 au. The ratio of cis 52:trans 51 was 35:63 or 36:64.

Equilibrium ratio of cis 52:trans 51 in trifluoroacetic acid

See "Equilibration studies."

(c) Chlorination in carbon tetrachloride

With molecular chlorine

General procedure: A solution of enol acetate 63 in carbon tetrachloride was cooled to 0° and stirred rapidly with a magnetic stirrer. A cold (0°) solution of chlorine was then added. The reaction mixture was stirred for a further period as specified until the color of chlorine has disappeared. The reaction mixture was then worked up and analyzed by tlc, glpc, ir, and pmr. In all of the following runs, tlc (eluent A) showed an elongated spot (R_f 0.61) corresponding to trans 51, enol acetate 63, and chloro enol acetate 67 and a spot (R_f 0.53) due to cis 52. The unidentified product was estimated to be < 10% by glpc using 5% or 10% DEGS on Chromosorb P at 160° or 1% XE-60 on Gas-Chrom Q at 120°.

(i) A solution of enol acetate 63 (200 mg, 1 mmol) in carbon tetrachloride (4 ml) was treated with a solution of chlorine (71 mg, 1 mmol) in carbon tetrachloride (2.86 ml) at -4°. The reaction mixture was worked up immediately (0.5 min) after mixing. A faintly yellow oil (190 mg) was obtained.

Pmr: 4.10 (unidentified); 4.22 (trans 51, 1 eq H), 27 au; 4.40-4.80 (cis 52, 1 ax H; chloro enol acetate 67, 1 eq H), 43 au; 4.85 (unidentified); 5.35 (enol acetate 63, 1 olefinic H), 5 au; 5.63 (chloro enol acetate 67, 1 olefinic H), 28 au. The ratio of cis 52:trans 51 was (43-28):27 or 36:64. The eq:ax chlorination ratio was (43-28):(27+28) or 21:79.

(ii) A solution of enol acetate 63 (200 mg, 1 mmol) in carbon tetrachloride (4 ml) was treated with a solution of chlorine (71 mg, 1 mmol) in carbon tetrachloride (5.1 ml) at 0-5°. The reaction mixture was worked up immediately (0.5 min) after mixing. A faintly yellow oil (65 mg) was obtained.

Glpc: 5% DEGS on Chromosorb P, 160°, t_r 0.94 (50, present in the starting

material), t_r 1.26 (63), t_r 1.38 (51), t_r 1.97 (unidentified, estimated by an area measurement to be ~ 10% of the chlorinated product), t_r 2.74 (67), and t_r 3.65 (52).

Pmr: 4.10 (unidentified); 4.22, 15 au; 4.40-4.80, 20 au; 4.85 (unidentified); 5.35, 3 au; 5.63, 12 au. The ratio of cis 52:trans 51 was (20-12):15 or 35:65. The eq:ax chlorination ratio was (20-12):(15+12) or 23:77.

(iii) A solution of enol acetate 63 (5 g, 25.5 mmol) in carbon tetrachloride (20 ml) was treated with a solution of chlorine (1.81 g, 25.5 mmol) in carbon tetrachloride (67.6 ml). The reaction temperature was maintained at 0-5° for 2 min and the reaction mixture worked up to give 5.07 g of a light yellow liquid.

Pmr: 4.10 (unidentified); 4.22, 9.5 au; 4.40-4.80, 15.5 au; 4.85 (unidentified); 5.35; 3.5 au; 5.63, 10.0 au. The ratio of cis 52:trans 51 was (15.5-10):9.5 or 37:63. The eq:ax chlorination ratio was (15.5+10):(9.5+10) or 22:78.

(iv) A solution of enol acetate 63 (19.63 g, 0.1 mol) in carbon tetrachloride (20 ml) was treated with a solution of chlorine (7.1 g, 0.1 mol) in carbon tetrachloride (143 ml). The reaction mixture was stirred at 5° for 2 min and then worked up to give 26.06 g of a yellow liquid.

Glpc: 10% DEGS on Chromsorb P, 160°, t'_r 3.1 (ketone 50, present in starting material), t_r 3.9 (enol acetate 63), t_r 4.70 (trans 51), t_r 6.00 (broad peak, unidentified, estimated by an area measurement to be < 10% of the chlorinated product), t_r 11.20 (chloro enol acetate 67) and 16.30 (cis 52).

Pmr: 4.10 (unidentified); 4.22, 61 au; 4.40-4.80, 85 au; 4.85 (unidentified); 5.35, 25 au; 5.63, 53 au. The ratio of cis 52:trans 51 was (85-53):61 or 34:66. The ratio of eq:ax chlorination was (85-53):(61+53) or 22:78.

(v) To a cold (0°) solution of enol acetate 63 (19.63 g, 0.1 mol) in carbon tetrachloride (20 ml) was added a solution of chlorine (7.1 g, 0.1 mol) in carbon tetrachloride (100 ml) over a period of 5 min at 0-5°. The reaction mixture was then worked up to give 22.8 g of a light yellow liquid.

Glpc: 1% XE-60 on Gas-Chrom Q, 120°, t_r 1.20 (50, present in the starting material), t_r 1.30 (63), t_r 1.45 (51), t_r 3.60 (67), t_r 5.00 (52), and t_r 5.80 (unidentified, estimated by an area measurement to be <10% of the chlorinated product). No gem dichloro 55 (t_r 2.95) or trichloro 61 (t_r 10.4) was detected.

Pmr: 4.10 (unidentified); 4.22, 29 au; 4.40-4.80, 36 au; 4.85 (unidentified); 5.35, 14 au; 5.63, 22 au. The ratio of cis 52:trans 51 was (36-22):29 or 33:67. The ratio of eq:ax chlorination was (36-22):(29+22) or 22:78.

(vi) A solution of enol acetate 63 (200 mg, 1 mmol) in carbon tetrachloride (4 ml) was treated with a solution of chlorine (71 mg, 1 mmol) in carbon tetrachloride (5 ml). The reaction mixture was stirred at 0-5° for 15 min and then worked up to give 189 mg of a light yellow oil.

Pmr: 4.10 (unidentified); 4.22, 18 au; 4.40-4.80, 22 au; 4.85 (unidentified); 5.35, 7 au; 5.63, 14 au. The ratio of cis 52:trans 51 was (22-14):18 or 31:69. The ratio of eq:ax chlorination was (22-14):(18+14) or 20:80.

(vii) A solution of enol acetate 63 (1 g, 5.1 mmol) in carbon tetrachloride (10 ml) was treated with a solution of chlorine (362 mg, 5.1 mmol) in carbon tetrachloride (5.83 ml). The reaction mixture was stirred at 0-10° for 45 min and then worked up to give 900 mg of a light yellow oil.

Pmr: 4.10 (unidentified); 4.22, 7 au; 4.40-4.80, 11 au; 4.85 (unidentified); 5.35, 6 au; 5.63, 7 au. The ratio of cis 52:trans 51 was (11-7):7 or

36:64. The ratio of eq:ax chlorination was (11-7):(7+7) or 22:78.

(viii) A solution of enol acetate 63 (13.86 g, 70.6 mmol) in carbon tetrachloride (100 ml) was treated with a solution of chlorine (5.01 g, 70.6 mmol) in carbon tetrachloride (340 ml). The reaction mixture was stirred at -5° to 15° for 5 min and then worked up to give 12.98 g of a light yellow oil.

Pmr: 4.10 (unidentified); 4.22, 34 au; 4.40-4.80, 45 au; 4.85 (unidentified); 5.35, 6 au; 5.63, 31 au. The ratio of cis 52:trans 51 was (45-31):34 or 29:71. The ratio of eq:ax chlorination was (45-31):(34+31) or 18:82.

(ix) A solution of enol acetate 63 (200 mg, 1 mmol) in carbon tetrachloride (4 ml) was treated with a solution of chlorine (71 mg, 1mmol) in carbon tetrachloride (2.53 ml) and 0.02 ml of distilled water. The mixture was stirred at 2-5° for 3 min and then worked up to give 200 mg of a light yellow oil.

Pmr: 4.10 (unidentified); 4.22, 91 au; 4.40-4.80, 100 au; 4.85 (unidentified); 5.35, 47 au; 5.63, 62 au. The ratio of cis 52:trans 51 was (100-62):91 or 29:71. The eq:ax chlorination ratio was (100-62): (91+62) or 20:80.

(x) A solution of enol acetate 63 (200 mg, 1 mmol) in carbon tetrachloride (4 ml) and 0.5 ml of distilled water was treated with a solution of chlorine (71 mg, 1 mmol) in carbon tetrachloride (3 ml) at 2-5°. The reaction mixture was then worked up immediately (2 min reaction time) to give 209 mg of a light yellow oil.

Pmr: 4.10 (unidentified); 4.22, 85 au; 4.40-4.80, 113 au; 4.85 (unidentified); 5.35, 21 au; 5.63, 75 au. The ratio of cis 52:trans 51 was (113-75):85 or 31:69. The ratio of eq:ax chlorination was (113-75):(85+75) or 19:81.

Control experiment on trans 51

(i) With acetyl chloride-hydrogen chloride-carbon tetrachloride: To a solution of trans 51 (94.4 mg, 0.5 mmol) in three drops of carbon tetrachloride was added a cold (0°) solution of hydrogen chloride (36.5 mg, 1 mmol) and acetyl chloride (78.5 mg, 1 mmol) in carbon tetrachloride (6.3 ml). The mixture was stirred at 0-5° for 1 hr and then worked up to give 94 mg of a colorless oil. Pmr showed that the starting material 51 was recovered unchanged.

(ii) With hydrogen chloride-chlorine-carbon tetrachloride: The compound trans 51 was stable at 0-5° for 1 hr in the presence of up to two equivalents each of hydrogen chloride and chlorine. See "Halogenation with allylic rearrangement."

Control experiment on cis 52

(i) With acetyl chloride-hydrogen chloride-carbon tetrachloride: A solution of cis 52 (94.4 mg, 0.5 mmol) in three drops of carbon tetrachloride was treated with a cold (0°) solution of hydrogen chloride (36.5 mg, 1 mmol) and acetyl chloride (78.5 mg, 1 mmol) in carbon tetrachloride (6.3 ml) at 0-5° for 1 hr. This was then worked up to give 92.9 mg of white crystals. Pmr showed that the starting material 52 was recovered unchanged.

(ii) With hydrogen chloride-chlorine-carbon tetrachloride: The compound cis 52 was stable at 0-5° for 1 hr in the presence of up to two equivalents each of hydrogen chloride and chlorine. See "Halogenation with allylic rearrangement."

Isolation of chloro enol acetate 67

See "Preparation of compounds."

Hydrolysis of chloro enol acetate 67

See "Chlorination of chloro enol acetate 67."

Chlorination with N-chlorosuccinimide

General procedure: A mixture of N-chlorosuccinimide, enol acetate 63 with or without radical initiator (benzoyl peroxide) in the solvent mentioned was stirred at 25° or under reflux for a specified period. The reaction mixture was then diluted with methylene chloride and washed five times with water, once with saturated brine and dried ($MgSO_4$). The solvent was removed and the crude product was analyzed by tlc and pmr.

(i) A suspension of N-chlorosuccinimide (134 mg, 1 mmol) in a solution of enol acetate 63 (200 mg, 1 mmol) in carbon tetrachloride (8 ml) was stirred for 1 hr at 25°. The mixture was then worked up to give 175 mg of a colorless oil. Tlc showed that no reaction has occurred and pmr showed an absorption peak at 5.35 due to enol acetate 63.

(ii) A suspension of N-chlorosuccinimide (134 mg, 1 mmol) in a solution of enol acetate 63 (200 mg, 1 mmol) in carbon tetrachloride (8 ml) was refluxed for 17 hr and then worked up to give 110 mg of a yellow liquid. Tlc showed that no reaction has occurred and pmr showed an absorption peak at 5.35 due to enol acetate 63.

(iii) A mixture of enol acetate 63 (200 mg, 1 mmol), N-chlorosuccinimide (134 mg, 1 mmol) and benzoyl peroxide (6 mg) in carbon tetrachloride (10 ml) were refluxed for 14 hr. The reaction mixture was worked up to give 137 mg of a colorless oil. Tlc and pmr showed that no

reaction has occurred.

(iv) A mixture of enol acetate 63 (200 mg, 1 mmol), N-chlorosuccinimide (72% available chlorine, 185 mg, 1 mmol) and benzoyl peroxide (6 mg) in carbon tetrachloride (5 ml) were refluxed for 42 hr. The reaction mixture was worked up to give 123 mg of a light yellow oil. Tlc and pmr showed that no reaction has occurred.

(v) A mixture of enol acetate 63 (200 mg, 1 mmol), N-chlorosuccinimide (134 mg, 1 mmol) and 10 ml of dioxane-water (1:1) was refluxed for 33 hr. The reaction mixture was then worked up to give 89 mg of a yellow oil. Tlc, glpc and pmr showed that enol acetate 63 has hydrolyzed to ketone 50.

(d) Chlorination in mixed solvents

(i) To a solution of enol acetate 63 (200 mg, 1 mmol) in acetonitrile (5.5 ml) was added 68 mg (1 mmol) of sodium formate. The solution was stirred at $-2\pm1^{\circ}$. A cold (0°) solution of chlorine (71 mg, 1 mmol) in formic acid (4.49 ml) containing 68 mg (1 mmol) of sodium formate was added. The mixture was stirred for 1 min and then worked up to give 189 mg of a light yellow oil.

Pmr: 4.22 (51), 93 au; 4.55 (52), 45 au; 5.35 (63), 193 au. The ratio of cis 52:trans 51 was 45:93 or 33:67.

(ii) A solution of enol acetate 63 (200 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in carbon tetrachloride (2.2 ml) was stirred at $0\pm2^{\circ}$. To this solution was added a cold (0°) solution of chlorine (71 mg, 1 mmol) in formic acid (7.8 ml) containing 68 mg (1 mmol) of sodium formate. The mixture was stirred for 2 min and then worked up to give 203 mg of a light yellow oil.

Pmr: 4.22, 38 au; 4.55, 23 au; 5.35, 127 au. The ratio of cis 52:trans 51

was 23:38 or 38:62.

Bromination of 4-t-butylcyclohexanone enol acetate (63).

The results are reported in Table 9 (p72).

(a) Bromination in formic acid

(i) To a cold (0°) solution of enol acetate 63 (200 mg, 1 mmol) in formic acid (4 ml) was added a cold (0°) solution of bromine (160 mg, 1 mmol) in formic acid (7.85 ml) and the mixture was stirred at 0-5° for 5 min. The reaction was quenched by adding 4 ml of 10% potassium iodide solution followed by 5 ml of 10% sodium thiosulfate solution. The crude product was then extracted with methylene chloride, washed with 5% sodium bicarbonate solution, water, and saturated brine. After drying, the solvent was removed to give a faintly yellow oil (198 mg).

Pmr: 4.37 (53), 72 au; 4.70 (54), 35 au; 5.35 (63), 54 au; 8.1 (68), 13 au. The ratio of cis 54:trans 53 was 35:72 or 33:67.

(ii) A solution of enol acetate 63 (200 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (4 ml) was treated with a cold (0°) solution of bromine (160 mg, 1 mmol) in formic acid (6.6 ml) at 0°. The reaction mixture was stirred for 5 min at 0-5°. The same work-up procedure as described in (i) was followed which led to a colorless oil (216 mg).

Pmr: 4.37, 105 au; 4.70, 58 au; 5.35, 29 au; 8.10, 18 au. The ratio of cis 54:trans 53 was 58:105 or 36:64.

(iii) A cold (0°) solution of enol acetate 63 (200 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (4 ml) was treated with a cold (0°) solution of bromine (160 mg, 1 mmol) in formic acid (7.27 ml).

The reaction mixture was stirred at 0-5° for 30 min. The same work-up procedure as described in (i) was applied. This led to 193 mg of a light yellow oil.

Pmr: 4.37, 113 au; 4.70, 38 au; 5.35, 45 au; 8.10, 18 au. The ratio of cis 54:trans 53 was 38:113 or 25:75.

(iv) To a cold (0°) solution of enol acetate 63 (200 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (4 ml) was added a cold (0°) solution of bromine (160 mg, 1 mmol) in formic acid (6.9 ml). The mixture was stirred at 0-5° for 30 min. The mixture was then poured into a separatory funnel containing a cold solution (40 ml) of 1% sodium formate. The crude product was extracted with methylene chloride, washed with 5% sodium bicarbonate solution, water, saturated brine and dried ($MgSO_4$). A light yellow oil (226 mg) was obtained after the solvent was removed.

Pmr: 4.37, 55 au; 4.70, 12 au; 5.35, 20 au; 8.10, 7 au. The ratio of cis 54:trans 53 was 12:55 or 18:82.

(v) A solution of enol acetate 63 (2 g, 10 mmol) and sodium formate (680 mg, 10 mmol) in formic acid (40 ml) was mixed with a solution of bromine (1.6 g, 10 mmol) in formic acid (20.1 ml) at 0°. The reaction mixture was stirred at 0-5° for 5 min and then worked up in the same manner as described in (iv) to give 2.55 g of a light yellow oil.

Pmr: 4.37, 124 au; 4.70, 32 au; 5.35, 20 au; 8.10, 19 au. The ratio of cis 54:trans 53 was 32:124 or 21:79.

(vi) A solution of enol acetate 63 (200 mg, 1 mmol) in formic acid (3 ml) was treated with a solution of bromine (160 mg, 1 mmol) in formic acid (6.9 ml) at 0° with magnetic stirring. The mixture was stirred at 0-5° for 5 min and then worked up by extracting with methylene chloride, washed with 5% sodium bisulfite solution, 5%

sodium bicarbonate solution, water, saturated brine and dried ($MgSO_4$). The solvent was removed to give a light yellow oil (218 mg).

Pmr: 4.37, 87 au; 4.70, 23 au; 5.35, 41 au; 8.10, 10 au. The ratio of cis 54:trans 53 was 23:87 or 21:79.

(vii) A solution of enol acetate 63 (200 mg, 1 mmol) in formic acid (4 ml) was treated with a solution of bromine (160 mg, 1 mmol) in formic acid (5.25 ml) at -5°. The mixture was stirred at -5° to 0° for 2 min and then worked up by diluting with water, extracting with methylene chloride and washing with 5% sodium bicarbonate, water, saturated brine and dried. The solvent was removed to give a light yellow oil (225 mg).

Pmr: 4.37, 272 au; 4.70, 69 au; 5.35, 70 au; 8.10, 38 au. The ratio of cis 54:trans 53 was 69:272 or 20:80.

Control experiment on trans 53

A solution of trans 53 (47 mg, 0.2 mmol) and sodium formate (13.6 mg, 0.2 mmol) in formic acid (0.3 ml) containing 16.2 mg (0.2 mmol) of hydrogen bromide was placed in a nmr tube at 0-5°. The pmr spectra were recorded periodically. The compound trans 53 was stable for at least 68 hr.

Pmr: 4.37 (trans 53), reference peak at 8.15 (formyl proton of formic acid).

Control experiment on cis 54

The same experimental procedure described above was repeated for cis 54 (47 mg, 0.2 mmol). The compound cis 54 was stable for at least 70 hr.

Pmr: 4.87 (cis 54), reference peak at 8.15 (formyl proton of formic acid).

Equilibrium ratio of cis 54:trans 53 in formic acid

See "Equilibration studies."

(b) Bromination in trifluoroacetic acid

(i) A solution of enol acetate 63 (200 mg, 1 mmol) in trifluoroacetic acid (3.75 ml) was treated with a solution of bromine (160 mg, 1 mmol) in trifluoroacetic acid (6.25 ml) at 0-5° and allowed to react for 5 min. The orange-brown solution was then worked up to give 191 mg of a light yellow oil.

Pmr: 4.37, 63 au; 4.70, 50 au. The ratio of cis 54:trans 53 was 50:63 or 44:56.

(ii) A solution of enol acetate 63 (200 mg, 1 mmol) and sodium trifluoroacetate (272 mg, 2 mmol) in trifluoroacetic acid (4.04 ml) was treated with a solution of bromine (16 mg, 1 mmol) in trifluoroacetic acid (5.96 ml) at 0-5° and allowed to react for 3 min. The reaction mixture was worked up to give 201 mg of a light yellow oil.

Pmr: 4.37, 48 au; 4.70, 14 au. The ratio of cis 54:trans 53 was 14:48 or 23:77.

Control experiment on trans 53

A mixture of trans 53 (30 mg, 0.1 mmol) and sodium trifluoroacetate (27.2 mg, 0.2 mmol) was treated with a solution of hydrogen bromide (8 mg, 0.1 mmol) in trifluoroacetic acid (0.3 ml). The mixture was allowed to stand for 10 min at 31-32°. No epimerization has taken place as revealed by pmr: 4.50 (trans 53).

Control experiment on cis 54

A mixture of cis 54 (30 mg, 0.1 mmol) and sodium trifluoroacetate (27.2 mg, 0.2 mmol) was treated with a solution of hydrogen bromide (8 mg, 0.1 mmol) in trifluoroacetic acid (0.3 ml). The mixture was allowed to stand for 10 min at 31-32°. No epimerization has taken place as revealed by pmr: 4.86 (cis 54).

Equilibrium ratio of cis 54:trans 53 in trifluoroacetic acid

See "Equilibration studies".

(c) Bromination in acetonitrile

(i) To a cold solution of enol acetate 63 (400 mg, 2 mmol) in acetonitrile (20 ml) was added 200 mg (2 mmol) of calcium carbonate. The heterogenous mixture was stirred at 0° while a cold (0°) solution of bromine (80 mg, 0.5 mmol) in acetonitrile (10.5 ml) was added. The reaction mixture was stirred for 4 min and then worked up to give 385 mg of a light yellow oil and some crystals.

Pmr: 3.80-4.00 (unidentified); 4.37 (trans 53, 1 eq H), 28 au; 4.50-4.90 (cis 54, 1 ax H; bromo enol acetate 69, 1 eq H), 11 au; 5.35 (enol acetate 63, 1 olefinic H); 130 au; 5.60 (bromo enol acetate 69, 1 olefinic H), 5 au. The ratio of cis 54:trans 53 was (11-5):28 or 18:82. The eq:ax bromination ratio was (11-5):(28+5) or 15:85.

(ii) A solution of enol acetate 63 (200 mg, 1 mmol), sodium formate (68 mg, 1 mmol), and formic acid (one drop) in acetonitrile (4 ml) was cooled to 0-5° with vigorous stirring. To this solution was added a solution of bromine (160 mg, 1 mmol) in acetonitrile (6 ml) over a period of 5 min. The resulting light yellow solution was worked up to

give 236 mg of a faintly yellow oil.

Pmr: 3.80-4.00 (unidentified); 4.37, 52 au; 4.50-4.90, 25 au; 5.35, 22 au; 5.60, 11 au. The ratio of cis 54:trans 53 was (25-11):52 or 21:79. The eq:ax bromination ratio was (25-11):(52+11) or 18:82.

Equilibrium ratio of cis 54:trans 53 in acetonitrile

See "Equilibration studies."

(d) Bromination in acetic acid

A solution of 200 mg (1 mmol) of enol acetate 63 and 82 mg (1 mmol) of sodium acetate in 4 ml of acetic acid was stirred at 10±2°. To this solution was added a solution of bromine (160 mg, 1 mmol) in acetic acid (4.49 ml). The mixture was stirred for 3 min and then worked up to give 248 mg of a light yellow oil.

Pmr: 4.37, 57 au; 4.50-4.90, 19 au; 5.35, 11 au; 5.60, 11 au. The ratio of cis 54:trans 53 was (19-11):57 or 12:88. The eq:ax bromination ratio was (19-11):(57+[illegible]) or 11:89.

Equilibrium ratio of cis 54:trans 53 in acetic acid

See "Equilibration studies."

(e) Bromination in carbon tetrachloride

(i) To a solution of enol acetate 63 (400 mg, 2 mmol) in carbon tetrachloride (20 ml) at 1±1° was added 200 mg (2 mmol) of calcium carbonate followed by a solution of bromine (80 mg, 0.5 mmol) in carbon tetrachloride (8.7 ml). The mixture was stirred at 1±1° for 5 min and then worked up to give 399 mg of a light yellow oil.

Pmr: 4.37, 52 au; 4.50-4.90, 30 au; 5.35, 204 au; 5.60, 12 au. The ratio of cis 54:trans 53 was (30-12):52 or 26:74. The eq:ax bromination ratio was (30-12):(52+12) or 22:78.

(ii) To a mixture of enol acetate 63 (400 mg, 2 mmol) and calcium carbonate (200 mg, 2 mmol) in carbon tetrachloride (30 ml) was added a solution of bromine (64 mg, 0.4 mmol) in carbon tetrachloride (14 ml). The mixture was stirred at 0-1° for 5 min and then worked up to give 399 mg of a light yellow oil.

Pmr: 4.37, 33 au; 4.50-4.90, 28 au; 5.35, 80 au; 5.60, 15 au. The ratio of cis 54:trans 53 was (28-15):33 or 28:72. The eq:ax bromination ratio was (28-15):(33+15) or 21:79.

Equilibrium ratio of cis 54:trans 53 in carbon tetrachloride

See "Equilibration studies."

(f) Bromination in mixed solvent

(i) A solution of enol acetate 63 (200 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (3.4 ml) was cooled to 0-5° with vigorous stirring. A solution of bromine (160 mg, 1 mmol) in acetonitrile (6.6 ml) was added over a period of 5 min. The reaction mixture was worked up to give 230 mg of a yellow oil.

Pmr: 4.37 (53), 65 au; 4.70 (54), 11 au; 5.35 (63), 20 au; 8.10 (68), 3 au. The ratio of cis 54:trans 53 was 11:65 or 14:86.

(ii) A solution of enol acetate 63 (200 mg, 1 mmol) and sodium formate (136 mg, 2 mmol) in formic acid (4 ml) was cooled to -4-1°. To this solution was added a solution of bromine (160 mg, 1 mmol) in acetonitrile (6 ml) over a period of 2 min. The reaction mixture was

worked up to give 229 mg of a light yellow oil.

Pmr: 4.37, 110 au; 4.70, 19 au; 5.35, 38 au; 8.10, 5 au. The ratio of cis 54:trans 53 was 19:110 or 15:85.

(iii) To a solution of enol acetate 63 (200 mg, 1 mmol), sodium formate (168 mg, 1 mmol) in formic acid (4 ml) at -1° was added a solution of bromine (160 mg, 1 mmol) in chloroform (6 ml) over a period of 2 min. Immediate decoloration took place. The reaction mixture was worked up to give 228 mg of a light yellow oil.

Pmr: 4.37, 176 au; 4.50-4.90, 36 au; 5.35, 39 au; 5.60, 7 au; 8.10, 6 au. The ratio of cis 54:trans 53 was (36-7):176 or 14:86. The eq:ax bromination ratio was (36-7):(176+7) or 13:87.

Equilibrium ratio of cis 54:trans 53 in mixed solvent

See "Equilibration studies."

Chlorination of 4-t-butylcyclohexanone (50)

The results are reported in Table 10 (p84).

(a) Chlorination in formic acid

(i) To a solution of ketone 50 (155 mg, 1 mmol) in formic acid (3 ml) at 0° was added a solution of chlorine (71 mg, 1 mmol) in formic acid (5 ml). The mixture was stirred at 0-10° for 5 min and then worked up to give 166 mg of a light yellow oil.

Pmr: 4.22, 266 au; 4.55, 284 au. The ratio of cis 52:trans 51 was 284:266 or 52:48.

(ii) To a solution of ketone 50 (155 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (3 ml) maintained at 5-10° was

added a solution of chlorine (71 mg, 1 mmol) in formic acid (5.9 ml). The mixture was stirred for 5 min and then worked up to give 160 mg of a light yellow oil.

Pmr: 4.22, 113 au; 4.55, 148 au. The ratio of cis 52:trans 51 was 148:113 or 57:43.

(iii) To a solution of ketone 50 (155 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (3 ml) at 5-10° was added a solution of chlorine (71 mg, 1 mmol) in formic acid (4.3 ml). The mixture was allowed to stir at 5-10° for 1 hr and then worked up to give 155 mg a light yellow oil.

Pmr: 4.22, 237 au; 4.55, 260 au. The ratio of cis 52:trans 51 was 260:237 or 52:48.

(b) Chlorination in trifluoroacetic acid

A solution of ketone 50 (155 mg, 1 mmol) and sodium trifluoroacetate (272 mg, 2 mmol) in trifluoroacetic acid (4.7 ml) was stirred rapidly at 31-32°. A solution of chlorine (71 mg, 1 mmol) in trifluoroacetic acid (5.3 ml) was added. The mixture was stirred for 20 min and then worked up to give 197 mg of a light yellow oil.

Pmr: 4.22, 61 au; 4.55, 63 au. The ratio of cis 52:trans 51 was 63:61 or 51:49.

(c) Chlorination in acetic acid

(i) Chlorine gas was allowed to bubble through a solution containing 230 mg (1.5 mmol) of ketone 50 in 10 ml of acetic acid-water (9:1) for a period of 30 min. The mixture was rapidly stirred at 7-8° and then worked up to give 212 mg of a light yellow oil mixed with

some white crystals.

Pmr: 4.22, 48 au; 4.55, 46 au. The ratio of cis 52:trans 51 was 46:48 or 49:51.

(ii) A solution of ketone 50 (155 mg, 1 mmol) and potassium acetate (98.2 mg, 1 mmol) in acetic acid (3 ml) was treated with a solution of chlorine (71 mg, 1 mmol) in acetic acid (4.21 ml) and stirred at 18-19° for 5 min. The reaction mixture was then worked up to give light yellow crystals (quantitative recovery). Pmr showed that no reaction has occurred.

(iii) A solution of ketone 50 (155 mg, 1 mmol) and potassium acetate (98.2 mg, 1 mmol) in acetic acid (3 ml) was treated with a solution of chlorine (71 mg, 1 mmol) in acetic acid (4.35 ml) and stirred at 21±3° for 1 hr. The reaction mixture was then worked up. Pmr showed that no reaction has occurred.

(iv) A solution of ketone 50 (155 mg, 1 mmol) and potassium acetate (98.2 mg, 1 mmol) in acetic acid (3 ml) was treated with a solution of chlorine (71 mg, 1 mmol) in acetic acid (4.5 ml) and stirred at 25±2° for 2 hr. The reaction mixture was then worked up. Pmr showed that no reaction has taken place.

(v) To a well stirred solution of ketone 50 (155 mg, 1 mmol) and potassium acetate (98.2 mg, 1 mmol) in acetic acid (3 ml) maintained at 52±3° was added a solution of chlorine (71 mg, 1 mmol) in acetic acid (7.95 ml). The mixture was stirred for 2 hr and then worked up to give 147 mg of a light yellow oil.

Pmr: 4.22, 212 au; 4.55, 209 au. The ratio of cis 52:trans 51 was 209:212 or 50:50.

(vi) To a well stirred solution of ketone 50 (155 mg, 1 mmol) and potassium acetate (98.2 mg, 1 mmol) in acetic acid (3 ml) maintained

at 52±3° was added a solution of chlorine (71 mg, 1 mmol) in acetic acid (5.15 ml). The mixture was then stirred at 52±3° for 4 hr and then worked up to give 140 mg of a light yellow oil.

Pmr: 4.22, 241 au; 4.55, 246 au. The ratio of cis 52:trans 51 was 246:241 or 51:49.

(vii) A solution of ketone 50 (155 mg, 1 mmol) and potassium acetate (198 mg, 1 mmol) in acetic acid (3 ml) was treated with a solution of chlorine (71 mg, 1 mmol) in acetic acid (4.54 ml) and allowed to stir at 37-38° for 3.5 hr. The reaction mixture was then worked up to give 178 mg of a light yellow oil.

Pmr: 4.22, 235 au; 4.55, 197 au. The ratio of cis 52:trans 51 was 197:235 or 46:54.

(d) Chlorination in chloroform

To a well stirred solution of ketone 50 (155 mg, 1 mmol) in chloroform (5 ml) at 0° was added a solution of chlorine (35 mg, 0.5 mmol) in chloroform (5 ml). The mixture was stirred at 0-5° for 12 min and then worked up to give 151 mg of a light yellow oil mixed with some white crystals.

Pmr: 4.22 (51, 1 ax H), 62 au; 4.55 (52, 1 ax H; 56, 1 eq H), 89 au; 5.20 (56, 1 ax H), 16 au. The ratio of cis 52:trans 51 was (89-16):62 or 54:46.

For all of the other runs see "Halogenation with allylic rearrangement."

(e) Chlorination in carbon tetrachloride

(i) A solution of ketone 50 (155 mg, 1 mmol) in carbon tetrachloride (3 ml) was cooled to -3°. To this solution was added a solution of chlorine (71 mg, 1 mmol) in carbon tetrachloride (4 ml). The mixture was stirred

at -3±1° for 3 min and then worked up to give 148 mg of white crystals. The pmr spectrum of the crude product showed that no reaction has occurred.

(ii) To a solution of ketone 50 (155 mg, 1 mmol) in carbon tetrachloride (3 ml) was added 100 mg (1 mmol) of calcium carbonate. The mixture was stirred at 0-5° while a cold (0°) solution of chlorine (71 mg, 1 mmol) in carbon tetrachloride (3.6 ml) was added all at once. The mixture was stirred for 30 min and then worked up to give quantitative recovery of ketone 50 judging from tlc and the pmr spectrum.

(iii) A solution of ketone 50 (618 mg, 4 mmol) in carbon tetrachloride (12 ml) was treated with a solution of chlorine (28 mg, 0.4 mmol) in carbon tetrachloride (2.4 ml) at 0°. The mixture was then stirred at 0±2° for 35 min and then worked up to give 607 mg of white crystals.

Pmr: 4.22, 29 au; 4.55, 48 au; 5.20, 15 au. The ratio of cis 52:trans 51 was (48-15):29 or 53:47.

(iv) To a rapidly stirred mixture of ketone 50 (155 mg, 1 mmol) and calcium carbonate (100 mg, 1 mmol) in carbon tetrachloride (3 ml) was added a solution of chlorine (35.5 mg, 0.5 mmol) in 1.47 ml of carbon tetrachloride. The mixture was stirred at 27±2° for 2 hr and then worked up to give 157 mg of a colorless oil.

Pmr: 4.22, 37 au; 4.55, 63 au; 5.20, 23 au. The ratio of cis 52:trans 51 was (63-23):37 or 52:48.

(v) A solution of ketone 50 (155 mg, 1 mmol) in 3 ml of carbon tetrachloride was treated with a solution of chlorine (71 mg, 1 mmol) in 4.1 ml of carbon tetrachloride at 0° under argon atmosphere in a dark room. The solution was stirred for 10 min and then worked up to give 160 mg of a light yellow oil.

Pmr: 4.22, 18.0 au; 4.55, 28.5 au; 5.20, 11.5 au. The ratio of cis 52:

trans 51 was (28.5-11.5):18.0 or 49:51.

(vi) The same reaction as described in (v) was carried out with 463 mg (3 mmol) of ketone 50 in 9 ml of carbon tetrachloride and a solution of chlorine (213 mg, 3 mmol) in 12.5 ml of carbon tetrachloride. The mixture was stirred at 0-5° for 5 min in argon atmosphere in a dark room and then worked up to give a colorless oil (495 mg).

Pmr: 4.22, 23 au; 4.55, 40 au; 5.20, 15 au. The ratio of cis 52:trans 51 was (40-15):23 or 52:48.

(vii) The same reaction (v) was repeated with the same amount of all reactants, the same reaction temperature and the same reaction time. The crude product obtained was a colorless oil (508 mg).

Pmr: 4.22, 46 au; 4.55, 79 au; 5.20, 28 au. The ratio of cis 52:trans 51 was (79-28):46 or 53:47.

(viii) A mixture of ketone 50 (232 mg, 1.5 mmol) and 1.5 g (15 mmol) of calcium carbonate in 18 ml of carbon tetrachloride was mixed with a solution of chlorine (106.5 mg, 1.5 mmol) in 24 ml of carbon tetrachloride at -14° under argon atmosphere. The mixture was irradiated with a medium pressure mercury lamp (λ 350-390 nm) for 70 min and then worked up to give 223 mg of a light yellow oil.

Pmr: 3.43 (unidentified, estimated ~10%); 4.22, 34 au; 4.55, 112 au; 5.20, 25au. The ratio of cis 52:trans 51 was (112-25):34 or 72:28.

For all of the other runs see "Halogenation with allylic rearrangement."

Bromination of 4-t-butylcyclohexanone (50)

The results are reported in Table 10 (p89).

(a) Bromination in formic acid

(i) To a well stirred solution of ketone 50 (155 mg,1 mmol) in formic acid (3 ml) maintained at 5° was added a cold (5°) solution of bromine (160 mg, 1 mmol) in formic acid (7.2 ml). The mixture was stirred for 1 hr at 5-10° and then worked up to give 162 mg of a light yellow oil. Pmr: 4.37, 16 au; 4.70, 15 au. The ratio of cis 54:trans 53 was 15:16 or 48:52.

(ii) To a well stirred solution of ketone 50 (155 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (3 ml) maintained at 0° was added a cold (0°) solution of bromine (160 mg, 1 mmol) in formic acid (7.14 ml). The mixture was stirred at 0-5° for 3 hr and then worked up to give 147 mg of a light yellow oil mixed with some white crystals. Pmr: 4.37, 59 au; 4.70, 65 au. The ratio of cis 54:trans 53 was 65:59 or 52:48.

(iii) To a well stirred solution of ketone 50 (155 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (3 ml) was added a cold (0°) solution of bromine (160 mg, 1 mmol) in formic acid (6.25 ml). The mixture was stirred at 0-5° for 4 hr and then worked up to give 180 mg of a light yellow oil mixed with some white crystals. Pmr: 4.37, 24 au; 4.70, 20 au. The ratio of cis 54:trans 53 was 20:24 or 46:54.

(b) Bromination in trifluoroacetic acid

A solution of ketone 50 (155 mg, 1 mmol) and sodium trifluoroacetate (272 mg, 2 mmol) in trifluoroacetic acid (4.04 ml) was stirred at 31° while a solution of bromine (160 mg, 1 mmol) in trifluoroacetic acid (5.96 ml) was added. The mixture was stirred at 31-32° for 10 min and then worked up to give 182 mg of a light yellow oil.

Pmr: 4.37, 58 au; 4.70, 51 au. The ratio of cis 54:trans 53 was 51:58 or 47:53.

(c) Bromination in acetonitrile

(i) A mixture of ketone 50 (309 mg, 2 mmol) and calcium carbonate (200 mg, 2 mmol) in acetonitrile (30 ml) was stirred at 26±1° during which a solution of bromine (80 mg, 0.5 mmol) in acetonitrile (21 ml) was added. The mixture was stirred at 26±1° for 10 min until decoloration took place and then worked up to give 280 mg of white crystals mixed with a light yellow oil.

Pmr: Absorption peaks due to trans 53 and cis 54 could be recognized in the midst of the other absorption peaks in the region 3.80-5.20. However, the ratio of cis 54:trans 53 could not be assessed accurately.

(ii) The reaction (i) was repeated with 309 mg (2 mmol) of ketone 50 and 200 mg (2 mmol) of calcium carbonate in 20 ml of acetonitrile. The mixture was stirred at 25-26° during the addition of a solution of bromine (80 mg, 0.5 mmol) in 33 ml of acetonitrile was added. The mixture was stirred for 8 min until decoloration took place and then worked up to give 322 mg of a mixture of white crystals and a light yellow liquid.

Pmr: Messy absorption peaks extended over 3.80-5.20. Although the absorption peaks due to trans 53 and cis 54 were vaguely recognizable, their ratio could not be assessed accurately.

(d) Bromination in acetic acid

(i) To a well stirred solution of ketone 50 (155 mg, 1 mmol) in acetic acid (10 ml) was added a solution of bromine (160 mg, 1 mmol) in acetic acid (6 ml). The mixture was then stirred at 31±1° for 5 min and

then worked up to give 213 mg of a light yellow oil.

Pmr: 4.37 (53, 1 eq H), 41 au; 4.70 (54, 1 ax H; 59, 1 eq H), 53 au; 5.43 (59, 1 ax H), 17 au. The ratio of cis 54:trans 53 was (53-17):41 or 47:53.

(ii) A solution of ketone 50 (155 mg, 1 mmol) and sodium formate (246 mg, 3 mmol) in acetic acid (4 ml) was stirred at 32±3° during which a solution of bromine (160 mg, 1 mmol) in 6 ml of acetic acid was added. The mixture was stirred at 32±3° for 2 hr and then worked up to give 151 mg of a mixture of white crystals and a light yellow oil.

Pmr: 4.37, 53 au; 4.70, 47 au. The ratio of cis 54:trans 53 was 47:53.

(e) Bromination in chloroform

A solution of ketone 50 (155 mg, 1 mmol) in 3 ml of chloroform-ethanol (99.5:0.5) was stirred at 25±1° during which a solution of bromine (160 mg, 1 mmol) in 7 ml of the same solvent system was added. The mixture was stirred at 25±1° for 5 min and then worked up to give 222 mg of a light yellow oil.

Pmr: 4.37, 174 au; 4.70, 178 au; 5.43, 31 au. The ratio of cis 54:trans 53 was (178-31):174 or 46:54.

(f) Bromination in carbon tetrachloride

(i) A solution of ketone 50 (155 mg, 1 mmol) in carbon tetrachloride (3 ml) was stirred rapidly and maintained at 0-5° while a cold (0°) solution of bromine (160 mg, 1 mmol) in carbon tetrachloride (4.65 ml) was added. The reaction mixture was stirred at 0-5° for 5 min and then worked up to give 213 mg of a faintly yellow oil.

Pmr: 4.37, 60 au; 4.70, 76 au; 5.43, 17 au. The ratio of cis 54:trans 53

was (76-17):60 or 50:50.

(ii) A mixture of ketone 50 (309 mg, 2 mmol) and calcium carbonate (200 mg, 2 mmol) in carbon tetrachloride (20 ml) was stirred at 30±1° while a solution of bromine (80 mg, 0.5 mmol) in carbon tetrachloride (8.7 ml) was added. The mixture was stirred at 30±1° for 10 min and then worked up to give 319 mg of a mixture of white crystals and a yellow oil.

Pmr: 4.37, 223 au; 4.70, 215 au; 5.43, 17 au. The ratio of cis 54: trans 53 was (215-17):223 or 47:53.

(g) Bromination in mixed solvents.

(i) A solution of ketone 50 (155 mg, 1 mmol) sodium formate (68 mg, 1 mmol) and one drop of formic acid in acetonitrile (4 ml) was stirred at 20-25° while a solution of bromine (160 mg, 1 mmol) in acetonitrile (6 ml) was added. The mixture was stirred at 20-25° for 5 min and then worked up to give 169 mg of a mixture of white crystals and a yellow oil.

Pmr: 4.37, 49 au; 4.70, 60 au. The ratio of cis 54:trans 53 was 60:49 or 55:45.

(ii) To a solution of ketone 50 (155 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (4 ml) maintained at 38±1° was added a solution of bromine (160 mg, 1 mmol) in acetonitrile (6 ml). The mixture was stirred at 38±1° for 10 min and then worked up to give 168 mg of a light yellow oil.

Pmr: 4.37, 204 au; 4.70, 230 au. The ratio of cis 54:trans 53 was 230: 204 or 53:47.

(iii) To a solution of ketone 50 (155 mg, 1 mmol) and sodium formate (136 mg, 2 mmol) in formic acid (3 ml) at 26° was added a solution

of bromine (160 mg, 1 mmol) in chloroform (7 ml). The mixture was stirred at 26±1° for 10 min and then worked up to give 160 mg of white crystals mixed with a light yellow oil.

Pmr: 4.37, 48 au; 4.70, 48 au. The ratio of cis 54:trans 53 was 50:50.

(iv) To a solution of ketone 50 (155 mg, 1 mmol) in carbon tetrachloride (3 ml) maintained at 0-5° was added a solution of bromine (160 mg, 1 mmol) and sodium formate (68 mg, 1 mmol) in formic acid (7 ml). The mixture was stirred at 0-5° for 5 min and then worked up to give 189 mg of a faintly yellow oil.

Pmr: 4.37, 210 au; 4.70, 204 au. The ratio of cis 54:trans 53 was 204:210 or 49:51.

Chlorination of 4-t-butylcyclohexanone lithium enolate (65)

The results are reported in Table 11 (p98).

(a) Chlorination in dimethoxyethane-carbon tetrachloride

General procedure: All of the halogenation reactions of lithium enolate 65 were carried out in the same manner. The ethereal solution of methyl lithium was standardized by withdrawing an aliquot (4 ml) and dissolving in xylene along with o-phenanthrolene (2 crystals). The brownish yellow solution was then titrated against a standard solution of 2-butanol in xylene to the permanent yellow end-point under a nitrogen atmosphere. Dimethoxy ethane (DME) was dried by refluxing with lithium aluminum hydride for 2 hr and then distilled at 83.5-84° (760 mm). The solution of methyl lithium in dried DME was prepared by evaporating an etheral solution of methyl lithium to dryness and then dissolving the residue in DME under a nitrogen atmosphere. A three-necked round-bottomed flask

was used as the reaction vessel (100 ml). The flask was fitted with a high speed vibromixer in the central neck, the other neck was mounted with a glass inlet tube leading to a 25 ml "dropper-cooler" (Fig. 18, p181) in which the lithium enolate was generated and cooled to the required temperature, and the third neck was fitted with a condenser inside which a thermometer was hung and sealed with a serum cap. The system was first flushed with nitrogen for 5 min and then the reaction vessel was charged with a solution of halogen and cooled with an ice-salt bath. The cooled enolate solution was stirred with a mechanical stirrer. This solution was then added to a vigorously agitated (Vibromixer and magnetic stirrer) solution of halogen with continous thorough mixing and the mixture was then allowed to react for a period specified. The reaction was then quenched by injecting 15 ml of 10% potassium iodide solution followed by 20 ml of 10% sodium thiosulfate solution and then extracted with methylene chloride. The methylene chloride extracts were washed with water followed by saturated brine and dried ($MgSO_4$). The solvent was removed in vacuo at 40°. The pmr spectrum of the crude product was immediately recorded and the epimeric ratio was calculated.

(i) A red solution containing methyl lithium (59 mg, 2.7 mmol) and triphenylmethane (2 crystals) in DME (1.5 ml) was prepared under nitrogen and stirred rapidly in the "dropper-cooler." To this solution was added a solution of silyl ether 66 (1 g, 4.4 mmol) in DME (20 ml) until the mixture turned colorless (about 10 ml was added). Stirring was continued for 5 min at 25°. The DME solution of lithium enolate 65 was then cooled to 0° and added to a cold (0°) solution of chlorine (312 mg, 4.4 mmol) in carbon tetrachloride (27.5 ml) with vigorous vibromixing and magnetic stirring. Reaction temperature was maintained at 0-5° and

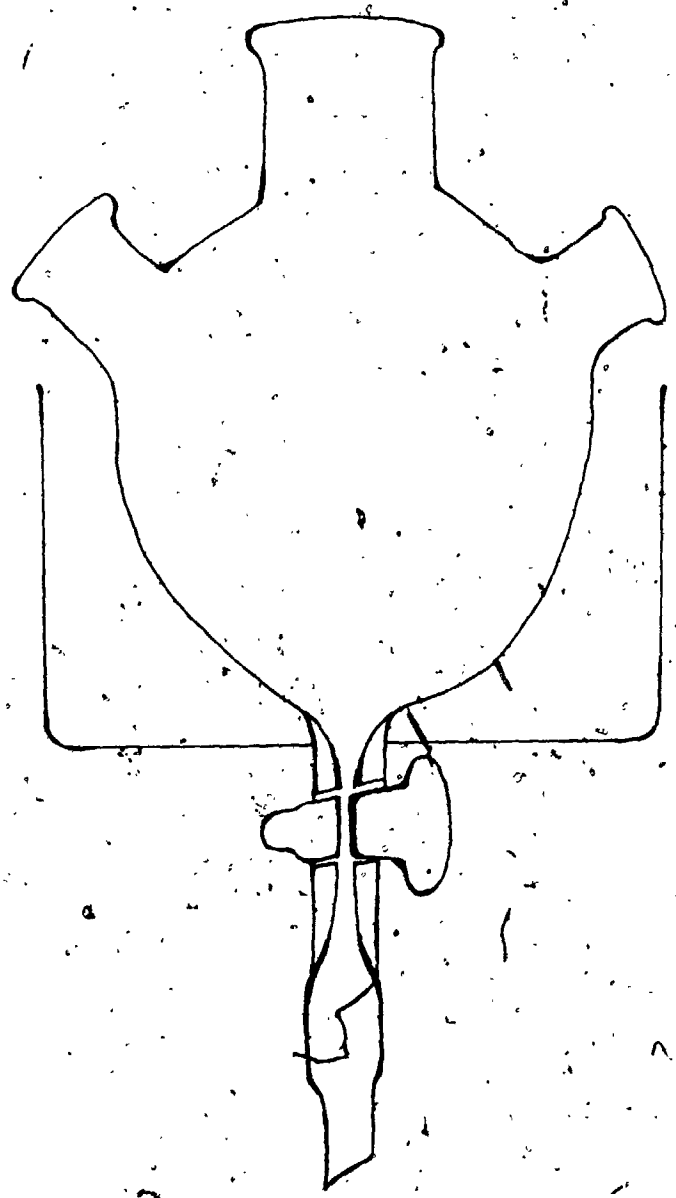

Fig. 18. The "Dropper-Cooler"

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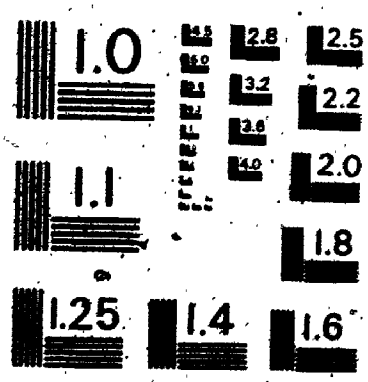

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the total reaction time elapsed was 5 min. The mixture was then worked up to give 510 mg of a reddish-brown oil.

Tlc: Two spots corresponded to trans 51 (R_f 0.61) and cis 52 (R_f 0.53) and also one unidentified less polar spot estimated to be ∿15% of the chlorinated product (eluent A).

Pmr: 4.25, 72 au; 4.55, 82 au; 6.01 (unidentified); 7.20 (unidentified). The ratio of cis 52:trans 51 was 82:72 or 53:47.

(ii) A red solution containing methyl lithium (97 mg, 4.4 mmol) and triphenylmethane (2 crystals) in dried DME (5 ml) was prepared under nitrogen and stirred rapidly in the "dropper-cooler." To this solution was added a solution of silyl ether 66 (1 g, 4.4 mmol) in DME (20 ml) until the solution turned colorless (almost all added). The mixture was stirred at 25° for 15 min and then cooled to 0°. This solution was then added dropwise to a solution of chlorine (312 mg, 4.4 mmol) in carbon tetrachloride (12 ml) with vigorous mixing and magnetic stirring at 0-5°. Total reaction time was 5 min. The mixture was worked up to give a reddish-brown oil (642 mg).

Tlc: two spots corresponded to trans 51 (R_f 0.61) and cis 52 (R_f 0.53) and one less polar spot estimated to be ∿20% of the chlorinated product (eluent A).

Glpc: 5% DEGS on Chromosorb P at 160°, two peaks corresponded to trans 51 (t_r 1.38) and cis 52 (t_r 3.65) and also an unidentified hump (t_r 4.50).

Ir: 1719-1727 (broad) shoulder at 1730.

Pmr: 4.25, 75 au; 4.55, 72 au; 6.01 (unidentified); 7.20 (unidentified). The ratio of cis 52:trans 51 was 72:75 or 49:51. On standing in the nmr tube for two days, broad peaks at 4.50, 6.85 and 7.25 replaced all of the other peaks. This is most likely due to the decomposition or the

further reaction of the primary product upon prolonged standing.

(iii) The solution of lithium enolate 65 was prepared by adding ether 66 (1 g, 4.4 mmol) in dried DME (20 ml) to a red solution of methyl lithium (97 mg, 4.4 mmol) and triphenyl methane (2 crystals) in 5 ml of dried DME until the solution turned colorless. The mixture was stirred at 25° for 15 min and then cooled to 0°. This solution was then added to a cold (0°) solution of chlorine (312 mg, 4.4 mmol) in carbon tetrachloride (12 ml) with vigorous vibromixing and magnetic stirring. The mixture was then worked up to give 903 mg of a reddish-brown oil.

Tlc: two spots corresponded to trans 51 (R_f 0.52) and cis 52 (R_f 0.33) and an unidentified less polar spot estimated to be ~20% (eluent B).

Ir: 1720 and shoulders at 1730 and 1740.

Pmr: 4.25, 44 au; 4.55, 34 au; 6.01 (unidentified); 7.20 (unidentified).

The ratio of cis 52:trans 51 was 56:44.

Control experiment in the absence of chlorine

This control experiment was carried out in the same manner as the chlorination reactions of lithium enolate 65 in dimethoxyethane-carbon tetrachloride with all the reagents present except chlorine.

A solution of lithium enolate 65 was prepared by adding a solution of silyl ether 66 (1 g, 4.4 mmol) in dried DME (20 ml) to a red solution containing methyl lithium (97 mg, 4.4 mmol) and triphenylmethane (2 crystals) in 5 ml of dried DME until the solution turned colorless. This solution was then stirred at room temperature for 15 min, cooled to 0°, and then added to 20 ml of carbon tetrachloride with vigorous vibromixing and magnetic stirring. After 5 min at 0-5°, the yellow solution was worked up in exactly the same manner as the chlorination mixture was treated.

A yellow oil weighing 573 mg was obtained.

Tlc: One spot corresponded to ketone 50 and one less polar spot estimated to be ~5% (eluent B).

Ir: 1720 (ketone 50, C=O).

Pmr: 5.00-6.00 (unidentified).

Quenching of lithium enolate 65 with aqueous ammonium chloride

A solution of lithium enolate 65 was prepared in exactly the same way as described in the chlorination reaction employing a solution of silyl ether 66 (1 g, 4.4 mmol) in dried DME (20 ml) and a solution of methyl lithium (97 mg, 4.4 mmol) and triphenylmethane (2 crystals) in dried DME (5 ml).

A solution of ammonium chloride (235 mg, 4.4 mmol) in 20 ml of distilled water was placed in the reaction vessel replacing the chlorine solution.

The generated lithium enolate 65 solution was added to the aqueous ammonium chloride solution with vigorous vibromixing and magnetic stirring and allowed to react for 5 min at 0-5° and then worked up to give 910 mg of faintly yellow oil.

Tlc: One spot corresponded to ketone 50 (eluent B).

Ir: 1720 (C=O, ketone 50).

Pmr: no peak at 4.00-8.00.

Control experiment of methyl lithium and water

Methyl lithium (97 mg, 4.4 mmol) in 2.5 ml of ether was injected into 20 ml of distilled water placed in a three-necked round-bottomed flask equipped with a thermometer under nitrogen. The mixture was stirred

at -5° for 5 min and then worked up to give 4.8 mg of organic material. The ir spectrum showed only the C-H stretching.

Control experiment on trans 51

To a well stirred solution of trans 51 (50 mg, 0.26 mmol) in dried DME (20 ml) at 0-5° was added a solution of chlorine (312 mg, 4.4 mmol) in carbon tetrachloride followed by lithium chloride (187 mg, 4.4 mmol). The mixture was stirred at 0-5° for 5 min and then worked up to give 46 mg of a light yellow oil. Pmr showed that no epimerization has taken place.

Control experiment on cis 52

Similarly, a solution of cis 52 (50 mg, 0.26 mmol) in dried DME (20 ml) at 0-5° was added to a solution of chlorine (312 mg, 4.4 mmol) in carbon tetrachloride followed by lithium chloride (187 mg, 4.4 mmol). The mixture was stirred at 0-5° for 5 min and then worked up to give 48 mg of a light yellow oil. Pmr showed that no epimerization has taken place.

(b) Chlorination in benzene

The same general procedure mentioned earlier for the chlorination of lithium enolate 65 was employed. The suspension of lithium enolate in dried benzene (standing over sodium) was prepared by injecting a solution of silyl ether 66 (1 g, 4.4 mmol) in dried benzene (20 ml) to a mixture of methyl lithium (97 mg, 4.4 mmol) and triphenylmethane (2 crystals) in benzene (5 ml) under nitrogen atmosphere in the "dropper-cooler." The white solid suspension was stirred for 1 hr and then cooled to 0°. The mixture was then added dropwise to a solution of chlorine

(312 mg, 4.4 mmol) in benzene maintained at 0-5° with high speed vibromixing and magnetic stirring. The reaction was allowed to proceed for 5 min and then worked up to give 1.2 g of a yellow oil.

Tlc: One spot corresponded to ketone 50 (eluent B), one unidentified less polar spot and one spot at the base line.

Ir: 1720 (ketone 50)

Pmr: 4.60 (broad, unidentified), no chloro ketone 51 or 52 were present.

(c) Chlorination in dimethoxyethane-ether-carbon tetrachloride

(i) A solution of silyl ether 66 (3.2 g, 14 mmol) in DME (30 ml) was added to a solution of methyl lithium (308 mg, 14 mmol) and triphenyl methane (2 crystals) in 8 ml of ether and stirred at 25° for 15 min under a nitrogen atmosphere. The solution of lithium enolate was then added to a solution of chlorine (994 mg) in carbon tetrachloride (35 ml) with high speed vibromixing and magnetic stirring. The reaction was allowed to proceed for 5 min at 0-5° and then quenched by a solution of potassium iodide followed by a solution of sodium thiosulfate and then worked up to give 2.16 g of a purple oil.

Ir: 1720 (ketone 50)

Pmr: 4.80 (broad, unidentified), no chloro ketones 51 or 52 were present.

(ii) The above reaction was repeated in exactly the same way to furnish 2.22 g of a purple oil.

Ir: 1720 (ketone 50)

Pmr: 4.80 (broad, unidentified), no chloro ketones 51 or 52 were present.

Bromination of 4-t-butylcyclohexanone lithium enolate (65)

The results are reported in Table 11 (p99).

Bromination in dimethoxyethane-carbon tetrachloride

General procedure: same as chlorination.

(i) A solution of lithium enolate 65 was prepared in the same way as in the chlorination reaction. A solution of silyl ether 66 (1 g, 4.4 mmol) in dried DME (20 ml) was added to a solution of methyl lithium (97 mg, 4.4 mmol) and triphenylmethane (2 crystals) in dried DME (5 ml) until the red solution turned colorless. The mixture was stirred at 25° for 15 min, cooled to 0°, and then added to a solution of bromine (704 mg, 4.4 mmol) in carbon tetrachloride (20.47 ml). The mixture was vigorously mixed by a Vibromixer and a magnetic stirrer at 0-5° for 5 min under a nitrogen atmosphere. The reaction mixture was then worked up in the same way as in the chlorination reaction. The crude product was a brownish-yellow oil (1.00 g).

Tlc: 3 spots corresponded to trans 53 (R_f 0.47), cis 54 (R_f 0.33) and an unidentified less polar spot estimated to be ~15% of the brominated product (eluent B).

Pmr: 4.37, 107 au; 4.70, 98 au; 5.00 (unidentified); 7.20 (unidentified). The ratio of cis 54:trans 53 was 98:107 or 48:52.

(ii) The same reaction was repeated as in (i) using all the same reagents in the same amount except the solution of bromine contained 704 mg (4.4 mmol) of bromine in 20 ml of carbon tetrachloride. The reaction was allowed to proceed at 0-5° for 3 min under nitrogen. The crude product was a browish purple oil (880 mg).

Tlc: 3 spots corresponded to trans 53 (R_f 0.47), cis 54 (R_f 0.33) and one unidentified less polar spot estimated to be ~15% (eluent B).

Pmr: 4.37, 44 au; 4.70, 44 au; 5.00 (unidentified); 7.20 (unidentified). The ratio of cis 54:trans 53 was 44:44 or 50:50.

(iii) A solution of lithium enolate 65 was prepared from a solution of silyl ether 66 (2 g, 8.8 mmol) in dried DME (30 ml) and a solution of methyl lithium (193 mg, 8.8 mmol) in 10 ml of dried DME. The solution of lithium enolate 65 was stirred at 25° for 15 min, cooled to 0°, and then added to a solution of bromine (1.41 g, 8.8 mmol) in 42.9 ml of carbon tetrachloride with vigorous vibromixing and magnetic stirring. After 3 min the reaction mixture was worked up to give 1.96 g of a brown oil.

Tlc: 3 spots corresponded to trans 53 (R_f 0.47) and cis 54 (R_f 0.33) and an unidentified less polar spot estimated to be ∿20% of the brominated product (eluent B).

Pmr: 4.37, 24 au; 4.70, 16 au; 5.00 (unidentified); 7.20 (unidentified). The ratio of cis 54:trans 53 was 16:24 or 40:60. After standing at 25° for one day the peak at 5.00 shifted to 5.40.

CHLORINATION OF CHLORO ENOL ACETATE 67

Stability of chloro enol acetate 67

(a) In dioxane-water

(i) A solution of hydrogen chloride (8.0 mg, 0.2 mmol) in water (5 ml) and dioxane (5 ml) was prepared. This solution was added to chloro enol acetate 67 (58.0 mg, 0.25 mmol) placed in a 25 ml-flask fitted with a thermometer. The mixture was stirred at 15° for 5 hr. The reaction mixture was then extracted with methylene chloride and worked up to give 56 mg of a colorless oil. Chloro enol acetate 67 was completely recovered.

Pmr: 4.72 (67), 5.63 (67).

(ii) A solution of chloro enol acetate 67 (58.0 mg, 0.25 mmol) was dissolved in dioxane (3 ml) and water (1 ml). To this solution was added 52.1 mg (0.25 mmol) of phosphorus pentachloride. Effervescence was observed. The mixture was then stirred at 20±1° for 6 hr. The organic material was extracted with methylene chloride and then subjected to the standard work-up procedure. The crude product was a colorless liquid weighing 56 mg.. This was chloro enol acetate 67 with 10% of trans-2-chloro ketone 51.

Pmr: 4.22 (51), 9 au; 4.72 (67), 81 au; 5.63 (67), 81 au.

(b) In formic acid

A solution of a mixture (200 mg) containing chloro enol acetate 67 in formic acid (4 ml) was mixed with 68 mg (1 mmol) of sodium formate. The mixture was stirred at 5-10° for 5 min and then diluted with methylene chloride, washed to neutrality and dried. The starting material was

completely recovered.

Pmr: 4.72 (67), 5.63 (67).

(c) In acetic acid-d_4-chloroform-d_1-deuterium oxide

Chloro enol acetate 67 (29.0 mg, 0.13 mmol) was placed in a 5 ml-flask, acetic acid-d_4 (0.2 ml) and deuterium oxide (0.05 ml) containing sodium 3-trimethylsilylpropanesulfonate (a few crystals) were added. This was then followed by the addition of phosphorus pentachloride (26.0 mg, 0.13 mmol). Effervescence was observed. The mixture was filtered into a nmr tube. Deuteriochloroform (0.1 ml) was then added. The mixture was allowed to stand at 25° for 1 hr, pmr did not show any new peak beside those given by the starting material, chloro enol acetate 67. After 20 hr, 10% of trans-2-chloro ketone 51 appeared.

Pmr: In CD_3COOD-$CDCl_3$-D_2O, at the end of 1 hr, 4.67 (67) and 5.63 (67). At the end of 20 hr, 4.22 (51), 14 au; 4.67 (67), 126 au; 5.63, 126 au.

(d) In acetone-d_6-deuterium oxide.

A solution of chloro enol acetate 67 (23 mg, 0.1 mmol) in acetone-d_6 (0.25 ml) and deuterium oxide (0.05 ml) containing sodium 3-trimethylsilylpropanesulfonate (10 mg) were placed in a nmr tube, thionyl chloride (12 mg, 0.1 mmol) was added. Pmr showed that no hydrolysis has taken place. After 30 min, pmr showed the appearance of a small peak (~10%) corresponded to trans-2-chloro ketone 51.

Pmr: In CD_3COCD_3-D_2O, immediately after mixing, 4.73 (67) and 5.63 (67). After 30 min, 4.43 (51), 8 au; 4.73 (67), 72 au; 5.63 (67), 72 au.

(e) In carbon tetrachloride-deuterium oxide

To an ice-cold solution of chloro enol acetate 67 (20 mg) in carbon tetrachloride (2 ml) was added a solution of phosphorus pentachloride (20 mg) in deuterium oxide (2 ml). The mixture was stirred at 10° for 10 min and then worked up to give 20 mg of a light yellow oil. Pmr showed no sign of the monochloro ketones 51 or 52 but only the recovered starting material.

Pmr: 4.72 (67), 5.63 (67).

Chlorination of chloro enol acetate 67

(a) In formic acid

(i) Chloro enol acetate 67 (46 mg, 0.2 mmol) and sodium formate (68 mg, 1 mmol) were placed in a 50-ml three-necked round-bottomed flask. An ice-cold solution of hydrogen chloride (36 mg, 1 mmol) in formic acid (8.3 ml) was added. This was then followed by the addition of a solution of chlorine (71 mg, 1 mmol) in formic acid (5.0 ml). Finally, two drops of acetyl chloride (78 mg, 1 mmol) were added. The mixture was stirred at 0-5° for 5 min. The solution was diluted with methylene chloride, washed to neutrality and dried. The solvent was removed to furnish 40 mg of a colorless oil. Pmr showed no sign of the starting material 67, no monochloro ketones 51 or 52, and no cis,cis 57. The only product was cis,trans 56.

Pmr: 4.50 (56), 5.20 (56).

In benzene solution, 4.10 (56), 4.83 (56).

(ii) A solution of chloro enol acetate 67 (23 mg, 0.1 mmol) in formic acid (0.5 ml) containing sodium formate (68 mg, 0.1 mmol) was

stirred at 0°. An ice-cold solution of chlorine (7.1 mg, 0.1 mmol) in formic acid (0.5 ml) was then added. The mixture was stirred for 5 min and then diluted with 5 ml of water. The organic material was extracted with methylene chloride, washed to neutrality and dried. The solvent was removed to give a colorless oil (21 mg). Pmr showed no monochloro ketones 51 or 52, no cis,cis 57 but only cis,trans 56 and glpc showed no sign of gem-dichloro 55 and trichloro 61.

Pmr: In benzene solution, 4.10 (56), 4.83 (56).

Glpc: 1% XE-60 on Gas-Chrom Q at 120°, single peak t_r 5.4.

(b) In acetic acid

Chloro enol acetate 67 (23 mg, 0.1 mmol) was dissolved in acetic acid (0.5 ml) buffered with sodium acetate (8.2 mg, 0.1 mmol). A solution of chlorine (7.1 mg, 0.1 mmol) in acetic acid (0.5 ml) was added. The mixture was then stirred at 27±2° for 40 min. At the end of the stirring period, the mixture was diluted with water (7 ml), and extracted with methylene chloride. The reaction mixture was worked up to give 21 mg of a colorless oil. Pmr showed no trace of monochloro ketones 51 or 52, no cis,cis 57 but only cis,trans 56. No gem-dichloro 55 and trichloro 61 were detected in glpc.

Pmr: 4.50 (56), 5.20 (56).

In benzene solution, 4.10 (56), 4.83 (56).

Glpc: 1% XE-60 on Gas-Chrom Q at 120°, single peak, t_r 5.4.

(c) In chloroform

To a solution of chloro enol acetate 67 (23 mg, 0.1 mmol) in chloroform (0.5 ml) was added a solution of chlorine (7.1 mg, 0.1 mmol)

in chloroform (0.125 ml). The solution was stirred at 20° for 40 min. The solution was then diluted with methylene chloride (8 ml) and worked up to give a colorless oil (22 mg). Pmr and glpc showed that cis,trans 56 was the sole product with no starting material left over and no detectable by-products.

Pmr: 4.50 (56), 5.20 (56).

In benzene solution, 4.10 (56), 4.83 (56).

Glpc: 1% XE-60 on Gas-Chrom Q at 120°, single peak, t_r 5.4.

(d) In carbon tetrachloride

(i) To an ice-cold solution of chloro enol acetate 67 (58 mg, 0.25 mmol) in carbon tetrachloride (2 drops) was added an ice-cold solution of chlorine (71 mg, 1 mmol) and hydrogen chloride (36 mg, 1 mmol) in carbon tetrachloride (9 ml) followed by two drops of acetyl chloride (78.5 mg, 1 mmol). The solution was stirred at 0-5° for 15 min. Ice-cold water (20 ml) was then added. The organic material was extracted with methylene chloride. The methylene chloride extracts were washed free of acid and dried. The solvent was removed to give 54 mg of a colorless oil. Pmr showed no sign of chlorination, the starting material was recovered.

Pmr: 4.72 (67), 5.63 (67).

(ii) To an ice-cold solution of chloro enol acetate 67 (58 mg, 0.25 mmol) in two drops of carbon tetrachloride was added an ice-cold solution of chlorine (71 mg, 1 mmol) and hydrogen chloride (36 mg, 1 mmol) in carbon tetrachloride (9 ml) made up of 2.7 ml of 0.37 M chlorine solution and 6.3 ml of 0.16 M hydrogen chloride solution in carbon tetrachloride. The mixture was stirred at 0-5° for 1.5 hr. At the end

of the stirring period, the color of chlorine had not been fully discharged. The solution remained light yellow. Cold water was then added and the organic material extracted with methylene chloride and worked up to give 62 mg of a colorless liquid. Pmr showed that the crude product contained 28% of cis,trans 56 and 72% of chloro enol acetate 67. Glpc showed that no side product was present.

Pmr: 4.50 (56), 24 au; 4.72 (67), 62 au; 5.20 (56), 24 au; 5.63 (67), 62 au.

In benzene solution, 4.10 (56), 4.70 (67), 4.83 (56), 5.50 (67). No peak at 3.87 due to cis,cis 57 was detected.

Glpc: 1% XE-60 on Gas-Chrom Q, one major peak (t_r 3.6) and one minor peak (t_r 5.4).

(iii) A solution of chloro enol acetate 67 (58 mg, 0.25 mmol) in two drops of carbon tetrachloride was mixed with a solution of chlorine (71 mg, 1 mmol) and hydrogen chloride (36 mg, 1 mmol) in carbon tetrachloride (9 ml) and allowed to stir at 30±1° for 15 hr. The mixture was then diluted with methylene chloride and worked up to give 42.7 mg of a colorless liquid. Pmr showed the presence of cis,trans 56 and an unidentified product. No other product was detected.

Ir: 1751 (C=O for 56).

Pmr: 3.40 (unidentified); 4.50 (56), 5.20 (56).

In benzene solution, 2.77 (unidentified), 4.10 (56), 4.83 (56).

Glpc: 1% XE-60 on Gas-Chrom Q, 120°, one major peak (t_r 5.4, 90%) with a tiny peak (t_r 8.3, 10%).

HALOGENATION WITH ALLYLIC REARRANGEMENT

Chlorination of 4-t-butylcyclohexanone (50) in carbon tetrachloride.

A solution of 4-t-butylcyclohexanone (155 mg, 1 mmol) in carbon tetrachloride (3 ml) was cooled in an ice-salt bath to 0° and stirred vigorously with a magnetic bar. To this solution was added a cold (0°) solution of chlorine (71 mg, 1 mmol) in carbon tetrachloride (4.1 ml). The yellow solution was allowed to stir for 5 min and the reaction temperature was controlled at 0-5°. At the end of the stirring period, the reaction was quenched by adding an ice-cold solution (10 ml) of 10% potassium iodide followed immediately by an ice-cold solution (15 ml) of 10% sodium thiosulfate. The carbon tetrachloride layer was separated and the aqueous solution was extracted twice with methylene chloride. The combined organic extracts were washed to neutrality and dried. A faintly yellow oil (178 mg) was obtained after the solvent was removed.

Tlc: 3 spots corresponded respectively to trans 51, cis 52, and cis, trans 56.

Glpc: 1% XE-60 on Gas-Chrom Q, 120°, two sharp peaks and a broad hump: t_r 1.20 (ketone 50), t_r 1.45 (51), t_r 5.00-5.60 (52 and 56), and no peak at t_r 2.95 (gem-dichloro 55).

To check the lower limit of gem-dichloro ketone 55 that could be detected in the reaction mixture, gem-dichloro ketone 55 (1 mg) was added to 100 mg of the crude product and the relative amounts of all the four halo ketones were estimated by the cut- and -weigh method. An area amounting to 0.5% of 55 in the dichlorinated product would have been detected without any difficulty. Therefore, any 55, if at all present, would be less than 0.5%.

Ir: 1720-1740 (broad, C=O).

Pmr: 4.22 (51, 1 eq H), 57 au; 4.55 (52, 1 ax H; 56, 1 eq H), 117 au; 5.20 (56, 1 ax H), 54 au. The ratio of cis 52:trans 51 was (117-54):57 or 48:52. The ratio of monochlorides:dichloride was (57+63)/54 or 2.2. In benzene solution, no peak at 3.87 (cis,cis 57) was detected. It was estimated from the 100 MHz spectrum with increased spectrum amplitude that an area amounting to 0.5% of 57 in the dichlorinated product could have been detected with no difficulty.

Dilution study in carbon tetrachloride

A series of experiments for the chlorination of 50 in carbon tetrachloride was carried out with varying molar ratios ketone:chlorine. The general procedure followed was exactly the same as that described above for the chlorination of 50 in carbon tetrachloride except varying molar ratios of ketone:chlorine were used.

(a) Molar ratio of ketone 50:chlorine=1

The solution of ketone was made up using 155 mg (1 mmol) of ketone 50 and 3 ml of carbon tetrachloride. The solution of chlorine contained 71 mg (1 mmol) of chlorine in 4 ml of carbon tetrachloride. The reaction was controlled within the temperature range of 0±1° and allowed to proceed for 6 min.

Pmr: 4.22 (51, 1 eq H), 85 au; 4.55 (52, 1 ax H; 56, 1 eq H), 191 au; 5.20 (56, 1 ax H), 81 au. The ratio of cis 52:trans 51 was (191-81):85 or 56:44. The ratio of monochlorides:dichloride was (85+110)/81 or 2.4. A similar run at 0-5° for 5 min reported earlier gave a ratfo of 2.2 for monochlorides:dichloride.

(b) Molar ratio of ketone 50:chlorine=2

The solution of ketone 50 contained 155 mg (1 mmol) of ketone 50 in 3 ml of carbon tetrachloride. The solution of chlorine was made up of 35.5 mg (0.5 mmol) of chlorine in 2 ml of carbon tetrachloride. The reaction was carried out within the temperature range 0-5° and the time elapsed was 5 min.

Pmr: 4.22, 24 au; 4.55, 42 au; 5.20, 21 au. The ratio of cis 52:trans 51 was (42-21):24 or 47:53. The ratio of monochlorides:dichloride was (24+21)/21=2.1.

(c) Molar ratio of ketone 50:chlorine=4

A solution of ketone 50 (155 mg, 1 mmol) in 3 ml of carbon tetrachloride was treated with a solution of chlorine (17.8 mg, 0.25 mmol) in 1 ml of carbon tetrachloride. The mixture was stirred at 3±2° for 20 min.

Pmr: 4.22, 91 au; 4.55, 165 au; 5.20, 81 au. The ratio of cis 52:trans 51 was (165-81):91 or 48:52. The ratio of monochlorides:dichloride was (91+84)/81 or 2.2.

(d) Molar ratio of ketone 50:chlorine=5

The solution of ketone 50 was made up using 309 mg (2 mmol) of ketone 50 in 6 ml of carbon tetrachloride. The solution of chlorine contained 28.4 mg (0.4 mmol) of chlorine in 2.4 ml of carbon tetrachloride. The reaction temperature was -1±1° and the reaction time was 25 min.

Pmr: 4.22, 20 au; 4.55, 39 au; 5.20, 16 au. The ratio of cis 52:trans 51 was (39-16):20 or 53:47. The ratio of monochlorides:dichloride was (20+23)/16 or 2.7.

(e) Molar ratio of ketone 50:chlorine=10

The solution of ketone contained 618 mg (4 mmol) of ketone 50 in 12 ml of carbon tetrachloride. The solution of chlorine in carbon tetrachloride contained 28.4 mg (0.4 mmol) of chlorine in 2.4 ml of carbon tetrachloride. The reaction was carried out in the temperature range of 2±1° for 5 min.

Pmr: 4.22, 7.5 au; 4.55, 15.5 au; 5.20, 4.5 au. The ratio of cis 52:trans 51 was (15.5-4.5):7.5 or 59:41. The ratio of monochlorides:dichloride was (7.5+11)/4.5 or 4.1.

The same reaction was repeated at 1±1° for 5 min. The ratio of cis 52: trans 51 was 57:43 and the ratio of monochlorides:dichloride was 4.1.

Control experiments on trans 51

(a) A solution of trans 51 (189 mg, 1 mmol) was dissolved in 2 drops of carbon tetrachloride and cooled in an ice-salt bath to 0°. While stirring with a magnetic stirrer, a cold (0°) solution containing 71 mg (1 mmol) of chlorine and 36.5 mg (1 mmol) of hydrogen chloride in 8.02 ml of carbon tetrachloride (made by mixing 6.25 ml of 0.16 M HCl-CCl_4 and 0.77 ml of 1.3 M Cl_2-CCl_4) was added dropwise maintaining the temperature of the reaction mixture at 0-5°. The mixture was stirred for 1 hr. At the end of the stirring period, the color of chlorine persisted. The reaction was then quenched by adding an ice-cold solution (10 ml) of 10% potassium iodide followed by an ice-cold solution (15 ml) of 10% sodium thiosulfate. The organic layer was separated and the aqueous layer was extracted twice with methylene chloride. The combined organic extracts were washed to neutrality and dried. A colorless oil (180 mg) was obtained after the solvent was removed.

Pmr: 4.22 (trans 51), no peak due to cis 52, cis,trans 56 or cis,cis 57 were detected.

Glpc: single peak, t_r 1.45 (trans 51) no peak due to gem-dichloro 55 was detected.

(b) Another control experiment was performed with 189 mg (1 mmol) of trans 51 in 2 drops of carbon tetrachloride and a solution containing 142 mg (2 mmol) of chlorine and 73 mg (2 mmol) of hydrogen chloride in 13.04 ml of carbon tetrachloride (made by mixing 12.5 ml of 0.16 M HCl-CCl_4 and 1.54 ml of 1.3 M Cl_2-CCl_4). The starting material trans 51 was recovered unchanged and the same pmr and glpc data as reported in (a) were obtained.

Control experiments on cis 52

The same procedure applied to trans 51 mentioned above was used. The cis 52 (189 mg) was dissolved in 2 drops of carbon tetrachloride. A solution containing 71 mg (1 mmol) of chlorine and 36.5 mg (1 mmol) of hydrogen chloride in 8.02 ml of carbon tetrachloride was added. After 1 hr at 0-5°, the starting material 52 was recovered unchanged.

Pmr: 4.55 (cis 52), no peak due to trans 51 or cis,trans 56 were detected.

In benzene solution, no peak at 3.87 (cis,cis 57) was detected.

Glpc: Single peak at t_r 5.00 (cis 52), no gem-dichloro 55 was detected.

Another control experiment employing 189 mg (1 mmol) of cis 52 in 2 drops of carbon tetrachloride, and a solution containing 142 mg (2 mmol) of chlorine and 73 mg (2 mmol) of hydrogen chloride in 13.04 ml of carbon tetrachloride was carried out. The starting material was recovered unchanged to judge from pmr and glpc (same as above).

Ionic chlorination of trans 51

A solution of 189 mg (1 mmol) of trans 51 was dissolved in 2 drops of carbon tetrachloride and stirred at 30±1°. A solution containing 73 mg (2 mmol) of hydrogen chloride and 144 mg (2 mmol) of chlorine in 13.5 ml of carbon tetrachloride was added dropwise. The mixture was then stirred at 30±1° for 6 hr. The color of chlorine persisted after the stirring period. The reaction mixture was diluted with methylene chloride (20 ml) and washed with 5% sodium bicarbonate solution, water, and saturated brine. After drying and evaporation of the solvent, a faintly yellow oil (205 mg) was obtained.

Pmr: 4.22 (trans 51, 1 eq H), 160 au; 4.55 (cis 52, 1 ax H; cis,trans 56, 1 eq H), 99 au; 5.20 (cis,trans 56, 1 ax H), 53 au. The ratio of cis 52:trans 51 was (99-53):160 or 23:77.

In benzene solution, no peak at 3.87 (cis,cis 57) was detected.

Glpc: 1% XE-60 on Gas-Chrom Q at 120°, t_r 1.45 (trans 51) t_r 2.95 (gem-dichloro 55), t_r 5.00 (cis 52) and t_r 5.40 (cis,trans 56). The ratio of gem-dichloro 55:cis,trans 56 was 43:57. The composition of the crude product was calculated to be: 53% of 51, 16% of 52, 13% of 55, and 18% of 56 (from pmr and glpc).

Ionic chlorination of cis 52

The same procedure described above for trans 51 was employed. The solution of 52 contained 377 mg (2 mmol) of cis 52 in 1 ml of carbon tetrachloride. The chlorinating reagent contained 146 mg (4 mmol) of hydrogen chloride and 284 mg (4 mmol) of chlorine in 26 ml of carbon tetrachloride. The reaction was allowed to proceed for 2 hr at 30±1°. The color of chlorine was still visible after the required stirring period.

The reaction was worked up in the same manner as described above for trans 51. This gave 417 mg of a faintly yellow oil.

Pmr: 4.55 (cis 52, 1 ax H; cis trans 56, 1 eq H), 20.5 au; 5.20 (cis,trans 56, 1 ax H), 8.5 au. The ratio of cis 52:cis,trans 56 was (20.5-8.5):8.5 or 59:41. No trans 51 was present.

Glpc: 1% XE-60 on Gas-Chrom Q at 120°, t_r 2.95 (gem-dichloro 55), t_r 5.00 (cis 52), and t_r 5.40 (cis,trans 56). The ratio of gem-dichloro 55:cis, trans 56 was 46:54. The composition of the crude product was calculated to be: 44% of 52, 26% of 55, and 30% of 56 (from pmr and glpc).

Control experiment on gem-dichloro ketone 55

A solution of gem-dichloro 55 (50 mg, 0.2 mmol) was dissolved in 2 drops of carbon tetrachloride and stirred at 30±1°. To this solution was added a solution of hydrogen chloride (73 mg, 2 mmol) and chlorine (142 mg, 2 mmol) in 13.5 ml of carbon tetrachloride. The mixture was stirred at 30±1° for 6 hr. The color of chlorine persisted. The mixture was then diluted with methylene chloride (20 ml) and washed with 5% sodium bicarbonate solution, water, and saturated brine. After drying and evaporation of the solvent, a light yellow oil (46 mg) was obtained.

Glpc: 1% XE-60 on Gas-Chrom Q at 120°, single peak, t_r 2.95 (gem-dichloro 55). No peak due to cis,trans 56 or cis,cis 57 was detected.

Control experiment on cis,trans-dichloro ketone 56

A solution of cis,trans 56 (50 mg, 0.2 mmol) was dissolved in 2 drops of carbon tetrachloride and stirred at 30±1°. To this solution was added a solution of hydrogen chloride (73 mg, 2 mmol) and chlorine (142

mg, 2 mmol) in 13.5 ml of carbon tetrachloride. The mixture was stirred at 30±1° for 6 hr. The same work-up procedure as described above for 55 was used. This led to 46 mg of a light yellow oil.

Pmr: In benzene solution, 4.10 and 4.83 (cis,trans 56). No peak at 3.87 due to cis,cis 57 was observed.

Glpc: 1% XE-60 on Gas-Chrom Q at 120°, no peak due to gem-dichloro 55 was detected.

Control experiment on cis,cis-dichloro ketone 57

A solution of cis,cis 57 (50 mg, 0.2 mmol) in 2 drops of carbon tetrachloride was stirred at 30±1°. A solution containing 73 mg (2 mmol) of hydrogen chloride and 142 mg (2 mmol) of chlorine in 13.5 ml of carbon tetrachloride was added. The mixture was then stirred for 6 hr at 30±1° and worked up in the same manner as described earlier for gem-dichloro 55. The crude product was a faintly yellow oil (44 mg).

Pmr: In benzene solution, 3.87 (cis,cis 57), no peak due to cis,trans 56 was observed.

Glpc: 1% XE-60 on Gas-Chrom Q at 120°, t_r 5.15 (cis,cis 57), no peak due to gem-dichloro 55 was detected.

Chlorination with radical scavenger

(a) With m-dinitrobenzene

A solution of 4-t-butylcyclohexanone (926 mg, 6 mmol) and 100 mg of m-dinitrobenzene in 18 ml of carbon tetrachloride was placed in a 100-ml three-necked round-bottomed flask equipped with an addition funnel sealed with a serum cap, a thermometer hung in a condenser and sealed with

a serum cap, and a gas inlet adaptor. A cold solution of chlorine (426 mg, 6 mmol) in 18 ml of carbon tetrachloride was introduced into the addition funnel. The system was flushed for 20 min with Argon purified by passage through the Fieser's solution, Drierite and sodium hydroxide pellets. The solution of chlorine was added all at once and the mixture stirred for 5 min at 0-5°. Decoloration of chlorine took place. The reaction was then quenched by injecting 20 ml of 10% potassium iodide solution followed by 30 ml of 10% sodium thiosulfate solution. The crude product was extracted with methylene chloride, washed to neutrality and dried. The solvent was removed to give 1.09 g of a light yellow oil.

Pmr: 4.22 (51, 1 eq H), 26 au; 4.55 (52, 1 ax H; 56, 1 eq H), 50 au; 5.20 (56, 1 ax H), 16 au. The ratio of cis 52:trans 51 was (50-16):26 or 57:43. The ratio of monochlorides:dichloride was (26+34)/16 or 3.7. In benzene solution, no peak at 3.87 (cis,cis 57) was present.

Glpc: 1% XE-60 on Gas-Chrom Q, 120°, no gem-dichloro 55 was detected.

(b) With galvinoxyl

The same procedure as described in (a) above was employed. The solution of ketone contained 926 mg (6 mmol) of 50 and 10 mg of galvinoxyl in 18 ml of carbon tetrachloride. This gave a brown solution. The system was flushed with argon for 5 min and a positive pressure of argon was maintained throughout the reaction period. The solution of chlorine contained 426 mg (6 mmol) of chlorine in carbon tetrachloride (24 ml). The mixture was stirred at 0-5° for 5 min. The same work-up procedure as described above for experiment (a) was used. This led to a yellow oil (1.01 g).

Pmr: 4.22, 23 au; 4.55, 42 au; 5.20, 15 au. The ratio of cis 52:trans

51 was (42-15):23 or 54:46. The ratio of monochlorides:dichloride was (23+27)/15 or 3.3.

In benzene solution, no peak at 3.87 (cis,cis 57) was observed.

Glpc: 1% XE-60 on Gas-Chrom Q, 120°, no gem-dichloro 55 was detected.

Radical chlorination of trans 51

A solution of trans 51 (142 mg, 0.75 mmol) in carbon tetrachloride (9 ml) was placed in a 100-ml three-necked round-bottomed flask equipped with a gas inlet adapter, a thermometer, and a 100-ml three-necked "dropper-cooler" (see Fig. 17, p181). A solution of chlorine (53 mg, 0.75 mmol) in carbon tetrachloride (12 ml) was then introduced into the "dropper-cooler". The contents of both the containers were cooled to -14° with Dry ice-methanol as the cooling agent and flushed with dried argon gas for 5 min. The cold solution of chlorine was then added at such a rate that the temperature remained at or slightly below -14°. The mixed solution was irradiated with a medium pressure mercury lamp fitted with a filter to cut off the light of wavelength outside the region 350-390 nm. Dry ice was added occasionally to the cooling bath and care was taken not to block the light with Dry ice-methanol slush. Irradiation was allowed to proceed for 20 min at -14° until decoloration took place. The reaction was quenched by adding a cold solution (30 ml) of 5% sodium bisulfite. After dilution with carbon tetrachloride, the organic layer was separated, washed to neutrality and dried. A colorless oil (145 mg) was obtained.

Glpc: 1% XE-60 on Gas-Chrom Q, 120°, two peaks: intense peak, t_r 1.45 (trans 51) and a tiny peak, t_r 1.98 (unidentified). No gem-dichloro 55 was detected.

Pmr: 4.22 (trans 51), 3.43 (unidentified). No cis 52 or cis,trans 56

were present (see Fig. 16, p 121).

In benzene solution, no peak at 3.87 (cis,cis 57) was observed.

Radical chlorination of cis 52

The same experimental procedure mentioned above for trans 51 was applied to cis 52. The solution of cis 52 was made up of 354 mg (1.88 mmol) of 52 dissolved in 22.5 ml of carbon tetrachloride. The solution of chlorine contained 133 mg (1.88 mmol) of chlorine in 30 ml of carbon tetrachloride. The reaction was carried out at -14° for 35 min until the color of chlorine disappeared. The same work-up procedure described for the radical chlorination of trans 51 led to a faintly yellow oil weighing 350 mg.

Glpc: 1% XE-60 on Gas-Chrom Q, 120°, two peaks: t_r 5.00 (cis 52) and a small hump at t_r 6.00 (unidentified). No gem-dichloro 55 was detected.

Pmr: 4.55 (cis 52), 3.43 (unidentified). No trans 51 and cis,trans 56 were detected (see Fig. 17, p 122).

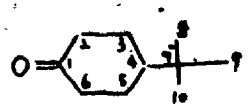
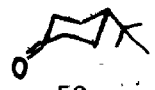
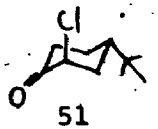
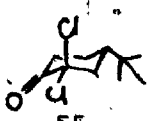
In benzene solution, no peak at 3.87 (cis,cis 57) was detected.

^{13}Cmr: See Table 18.

Chlorination of enol acetate 63 in carbon tetrachloride

One typical run was recorded as follows: A solution of 4-t-butylcyclohexanone enol acetate 63 (200 mg, 1 mmol) in 4 ml of carbon tetrachloride was cooled to 0°. A cold solution of chlorine (71 mg, 1 mmol) in carbon tetrachloride (5 ml) was added all at once. The mixture was stirred for 15 min at 0-5° until the color of chlorine disappeared. After the stirring period cold water was added and the mixture was diluted with methylene chloride. The organic layer was separated, washed free

Table 18. Comparison of ^{13}Cmr Data*

	8, 9, 10	2	6	3	5	4	7	1
								
 50	27.5	41.0	41.0	27.5	27.5	46.6	32.2	209.4
 52	27.4	64.2	40.0	40.0	27.7	47.1	32.1	200.2
 51	27.3	60.8	35.8	35.8	27.3	40.0	31.5	203.1
 55	27.4	89.1	35.7	49.3	27.4	44.3	31.8	193.7
 52 $+Cl_2+h\nu$	Major peaks 27.2, 27.3, 27.6, 31.6, 32.8, 35.7, 39.9, 46.9, 60.5, 64.1, 197.8, 204.8, 208.2.							
	minor peaks 21.0, 22.4, 22.7, 25.8, 42.1, 43.9, 45.5, 52.0, 54.4, 60.2, 60.8, 61.2, 61.7, 63.7.							

* Obtained in the Fourier transform mode at 25.2 MHz with a Varian XL-100-15 system using 5-10% solutions in $CDCl_3$; the peak positions are given relative to the internal TMS.

of acid and dried. The solvent was removed to give a light yellow oil (189 mg).

Ir: 1730° (51) and 1755 (63 and 67).

Pmr: 4.10 (unidentified), 3 au; 4.22 (trans 51, 1 eq H), 18 au; 4.40-4.80 (cis 52, 1 ax H; chloro enol acetate 67, 1 eq H), 22 au; 4.85 (unidentified), 4 au; 5.35 (enol acetate 63, 1 olefinic H), 7 au; 5.63 (chloro enol acetate 67, 1 olefinic H), 14 au. The ratio of cis 52:trans 51 was (22-14):18 or 31:69. The amount of 67 present in the chlorinated product was 14/(18+22) or 35%.

Glpc: 5% DEGS on Chromosorb-P at 160°, 5 peaks and a broad hump corresponding to ketone 50 (t_r 0.94), enol acetate 63 (t_r 1.26), trans 51 (t_r 1.38), a broad hump (t_r 1.97, unidentified), chloro enol acetate 67 (t_r 2.74) and cis 52 (t_r 3.65).

Control experiment on chloro enol acetate 67

A solution of chloro enol acetate 67 (58 mg, 0.25 mmol) in 2 drops of carbon tetrachloride was cooled to 0°. A cold (0°) solution of chlorine (71 mg, 1 mmol), hydrogen chloride (36.5 mg, 1 mmol) and acetyl chloride (78.5 mg, 1 mmol) in 9 ml of carbon tetrachloride was added. The mixture was stirred for 15 min at 0-5°. Cold water (20 ml) was then added to destroy acetyl chloride and the aqueous solution was extracted with methylene chloride, washed free of acid by 5% sodium bicarbonate solution, water, and saturated brine. After drying the solvent was removed to give an oil (54 mg).

Pmr: 4.67, 5.63 (chloro enol acetate 67), no peaks due to trans 51 or cis 52 were detected.

Control experiment on trans 51

A solution of trans 51 (94 mg, 0.5 mmol) in 2 drops of carbon tetrachloride was placed in a 50 ml two-necked round-bottomed flask. The solution was cooled to 0°. A solution containing 78.5 mg (1 mmol) of acetyl chloride and 36.5 mg (1 mmol) of hydrogen chloride in 6.3 ml of carbon tetrachloride was added. The mixture was stirred for 1 hr at 0-5°. Cold water was then added to the reaction mixture and the aqueous solution was extracted with methylene chloride, washed free of acid and dried. The solvent was removed to give 94 mg of a colorless oil.

Pmr: 4.22 (trans 51), no peaks due to cis 52 or chloro enol acetate 67 were detected.

Control experiment on cis 52

The same procedure described above for 51 was used here. The solution of cis 52 was made up of 94 mg (0.5 mmol) of cis 52 dissolved in 2 drops of carbon tetrachloride. A solution of acetyl chloride (78 mg, 1 mmol) and hydrogen chloride (36.5 mg, 1 mmol) in 6.3 ml of carbon tetrachloride was prepared. The latter solution was added to the former solution and the mixture was allowed to stir at 0-5° for 1 hr. The same work-up procedure as described above for trans 51 was used. This led to 92 mg of white crystals.

Pmr: 4.55 (cis 52), no trans 51 or chloro enol acetate 67 was detected.

Dilution study of chlorination of 4-t-butylcyclohexanone (50) in chloroform

Fisher spectrograde chloroform was allowed to pass through a column of 60-120 mesh silica gel to remove any ethanol present. The

absence of ethanol was checked by pmr. The general procedure for chlorination is to add a cold (0°) solution of chlorine in chloroform to a well-stirred (magnetic bar) cold (0°) solution of ketone 50 in chloroform in an ice-salt bath. The reaction was quenched by adding a cold solution (30 ml) of 5% sodium bisulfite solution, and the crude reaction product was extracted with chloroform. The chloroform extracts were washed free of acid and dried. The pmr spectrum of the crude product was recorded immediately after the solvent was evaporated. No peak at 3.87 (cis,cis 57) was detected in benzene solution. Glpc showed no trace of gem-dichloro 55 or trichloro 61 using the column packed with 1% XE-60 on Gas-Chrom Q at 120°.

(a) Molar ratio of ketone 50:chlorine=1

The solution of ketone 50 was made up of 155 mg (1 mmol) of ketone 50 in 5 ml of chloroform. The solution of chlorine contained 71 mg (1 mmol) of chlorine in 5 ml of chloroform. The reaction was maintained at the temperature range 5±1° for 10 min.

Pmr: 4.22 (51, 1 eq H), 42 au; 4.55 (52, 1 ax H; 56, 1 eq H), 66 au; 5.20 (56, 1 ax H), 16 au. The ratio of cis 52:trans 51 was (66-16):42 or 54:46. The ratio of monochlorides:dichloride was (42+50)/16 or 5.7.

(b) Molar ratio of ketone 50:chlorine=2°

The solution of ketone 50 contained 155 mg (1 mmol) of ketone 50 dissolved in 5 ml of chloroform. The solution of chlorine was made up of 35.5 mg (0.5 mmol) of chlorine in 5 ml of chloroform. The reaction was run for 15 min at 0-5°.

Pmr: 4.22, 48.0 au; 4.55, 79.0 au; 5.20, 18.5 au. The ratio of cis 52:

trans 51 was (79.0-18.5):48.0 or 56:44. The ratio of monochlorides:dichloride was (48+60.5)/18.5 or 5.9.

This reaction was repeated at 0-4° for 20 min. The ratio of cis 52:trans 51 was 54:46 and the ratio of monochlorides:dichloride was 5.1.

(c) Molar ratio of ketone 50:chlorine=4

The solution of ketone 50 contained 155 mg (1 mmol) of ketone 50 dissolved in 5 ml of chloroform and the solution of chlorine contained 17.8 mg (0.25 mmol) of chlorine in 5 ml of chloroform. The reaction was allowed to proceed at 1±1° for 10 min.

Pmr: 4.22, 125 au; 4.55, 182 au; 5.20, 38 au. The ratio of cis 52:trans 51 was (182-38):125 or 54:46. The ratio of monochlorides:dichloride was (125+144)/38 or 7.1.

(d) Molar ratio of ketone 50:chlorine=5

The solution of ketone 50 contained 155 mg (1 mmol) of ketone 50 in 5 ml of chloroform and the solution of chlorine was made up of 14.2 mg (0.2 mmol) of chlorine in 5 ml of chloroform. The reaction was allowed to proceed for 5 min at 0-5°.

Pmr: 4.22, 54 au; 4.55, 97 au; 5.20, 20 au. The ratio of cis 52:trans 51 was (97-20):54 or 59:41. The ratio of monochlorides:dichloride was (77+54)/20 or 6.6.

(e) Molar ratio of ketone 50:chlorine=10

The solution of ketone 50 contained 618 mg (4 mmol) of ketone 50 in 12 ml of chloroform and the solution of chlorine contained 28.4 mg (0.4 mmol) of chlorine in 3 ml of chloroform. The reaction was carried

out at 1±1° for 5 min.

Pmr: 4.22, 23 au; 4.55, 28 au; 5.20, 7 au. The ratio of cis 52:trans 51 was (28-7):23 or 48:52. The ratio of monochlorides:dichloride was (23+21)/7 or 6.3.

This reaction was repeated at 0-5° for 5 min. The ratio of cis 52:trans 51 was 50:50 and the ratio of monochlorides:dichloride was 6.3.

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