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LYCOPODIUM ALKALOIDS

(PART ONE)

CONFORMATIONAL STUDIES BY N.M.R. SPECTROSCOPY

(PART TWO)

By

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A thesis submitted in partial fulfillment
of the requirements of the degree of
Doctor of Philosophy.

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PREFACE

The elucidation of the unusual structure of annotinine, the principal alkaloid of Lycopodium annotinum, L., in 1957 has created a great interest in the studies of other Lycopodium alkaloids. The structure and stereochemistry of a number of other Lycopodium alksloids have since been elucidated. The first part of this thesis deals, in part, with the structure and stereochemistry of lycofoline, an alkaloid of Lycopodium annotinum L., first isolated by Anet and Khan of this laboratory in 1959. This part also deals with the stereochemistry of dihydrolycofoline (the hydrogenated product of lycofoline), some attempted reactions on annofoline (an alkaloid of Lycopodium annotinum L.), and equilibration studies on two Lycopodium alkaloids.

The second part of this thesis is concerned with the application of Nuclear Magnetic Resonance (N.M.R.) spectroscopy to (i) ring inversion of cyclohexane, (ii) restricted rotation in some aromatic aldehydes, (iii) spin-spin splittings in some cyclohexene derivatives, and (iv) conformational analysis of cyclohexyl acetate.

The author wishes to express his sincere thanks to Prof. F.A.L. Anet for his stimulating guidance and enlightening discussions at every stage of the work. Thanks are also due to

Prof. F.A.L. Anet and Dr. L.D. Hall for operating the N.M.R. spectrometer, to Dr. Ragini Anet for helpful criticism on the manuscript, to Othman bin Md. Nor for proofreading a part of the thesis.

Finally, the author wishes to thank the Canadian Commonwealth Scholarship Committee for the award of a scholarship to him.

This work was financially supported by the National Research Council of Canada.

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ABSTRACT

Part I

The structure and stereochemistry of lycofoline, an alkaloid of Lycopodium annotinum L., have been deduced by relating the alkaloid to acrifoline, another Lycopodium alkaloid, whose structure and stereochemistry are known. The stereochemistry of dihydrolycofoline, the hydrogenated product of lycofoline, has also been deduced.

Attempts to dehydrate, as well as to enol-acetylate, annofoline have been unsuccessful. Baeyer-Villiger oxidation of annofoline has been found to yield a complicated mixture of a number of minor components.

Treatment of dihydroacrifoline, the hydrogenated product of acrifoline, with strong base has yielded an α,β-unsaturated ketone. The structure of the conjugated ketone has been deduced from its molecular formula and spectroscopic evidences.

Anhydrodehydrodeacetylfawcettiine, the chromium trioxide oxidation product of anhydrodeacetyl-fawcettiine, has been found to be stable in the presence of a base.

Part II

The N.M.R. spectra of cyclohexane-d_{11} ($C_6D_{11}H$) in CS_2 solution has been studied over a range of temperatures, -32° to -94°, in order to follow the kinetics of the inversion of cyclohexane ring. The parameters for the ring inversion of $C_6D_{11}H$ have been calculated and discussed in the light of possible reaction pathway.

Low temperature N.M.R. studies on some aromatic aldehydes have revealed the presence of appreciable barrier to rotation about the C_{ald}-C_{ar} bond of these compounds. The free energy of activation, $\Delta F^{\neq}$, for rotation about the C_{ald}-C_{ar} bond in benzaldehyde, p-N,N-dimethylaminobenzaldehyde, 9-julolidinecarboxaldehyde, and p-anisaldehyde have been determined and discussed in the light of resonance theory.

Several suitably deuterated monosubstituted cyclohexane derivatives have been synthesized in order to determine the vicinal coupling constants of the homoallylic protons. The values of the vicinal coupling constants obtained for these derivatives have been compared and attempts have been made to explain the differences on the basis of conformational equilibria.

2,2,3,3,4,4,5,5-Octadeuteriocyclohexyl acetate has been synthesized to determine the vicianl coupling constants

and conformational equilibrium of this compound. The results have been compared with the results already reported in the literature.

LYCOPODIUM ALKALOIDS

PART ONE

INTRODUCTION

Scope of the Problem

A considerable amount of work has been carried out recently on the elucidation of structure and stereochemistry of *Lycopodium* alkaloids. The contribution to this field from this laboratory has aided considerably in the understanding of chemistry of these alkaloids. This part of the thesis is concerned with some aspects of a few *Lycopodium* alkaloids and can be classified under three heads.

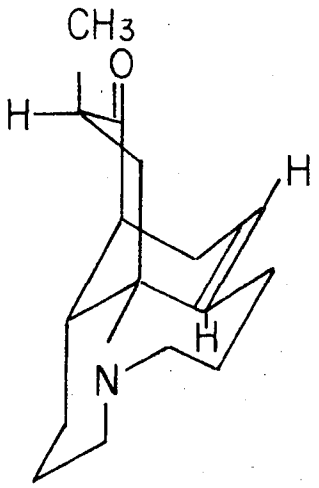
I. The first part of the present work deals with the elucidation of structure and stereochemistry of lycofoline, an alkaloid of *Lycopodium annotinum L.*, isolated by Anet and Khan (1) in 1959. Preliminary studies on lycofoline were carried out by Khan (2) in this laboratory.

II. Annotinine, the principal alkaloid of *Lycopodium annotinum L.*, has a carbon skeleton different from other *Lycopodium* alkaloids and has not been so far related to any of the other alkaloids. Annotinine like annofoline and other related alkaloids has the same hexahydrojulolidine system, but its fourth ring is four-membered instead of six-membered as found in annofoline and other related alkaloids. One point of attachment of the fourth ring to the hexahydrojulolidine system is the same in all these alkaloids. The second part of our work was aimed at preparing a suitable intermediate to interrelate annofoline and annotinine.

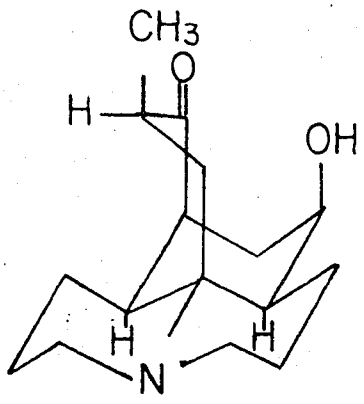
III. Several Lycopodium alkaloids, on treatment with base, have been found (see pages 26,27) to undergo inversion of configuration at the carbon atom (C-14), next to the carbonyl group in the D ring of these molecules. This finding has proved to be important in the elucidation of structure and stereochemistry of some Lycopodium alkaloids. The inversion of configuration at C-14 has been assumed to be influenced by the surroundings of ring D. In order to verify this assumption an equilibration study of Lycopodium alkaloids was proposed. Anhydroannofoline, I (the dehydration product of annofoline), dihydroacrifoline, II, and anhydrodehydrodeacetylfawcettiine, III (chromium trioxide oxidation product of anhydrodeacetyl-fawcettiine), were chosen for this purpose. They were suitable representatives for this study as the environment of the carbonyl group in these compounds (Fig. 1) are different. If the inversion of configuration at C-14 really depends on the surroundings of ring D then one would expect no or very little isomerisation in I and III and considerable isomerisation in II. Attempts to prepare I, anhydroannofoline, have been so far unsuccessful, and therefore, our equilibration study was limited to II and III.

Review of Pertinent Literature

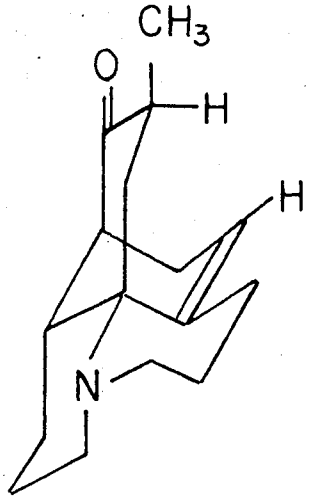
Lycopodium annotinum L. is one of about a hundred



I



II



III

Fig.1

species of the Lycopodium genus. They belong to the group pteridophyla and occupy an intermediate position in the evolution of plant life, linking the algae and fungi with the highly evolved flowering plants.

Investigations for alkaloidal constituents in various Lycopodium plants have been reported since the nineteenth century (3,4,5), but the first reports on the alkaloids of Lycopodium annotinum L. appeared only in 1943 (6). In this year, Manske and Marion reported the isolation of annotinine ($C_{16}H_{21}O_3N$), the principal alkaloid of this species, the previously known lycopodine ($C_{16}H_{25}ON$) (3,4), the obscurines, and several other alkaloids which were not well characterised, hence designated by the letter L. followed by a number e.g. L-8 ($C_{16}H_{25}O_2N$). Other alkaloids have been isolated from certain sub-species of Lycopodium annotinum L., and these include acrifoline ($C_{16}H_{23}O_2N$), annotine ($C_{16}H_{21}O_3N$), nicotine ($C_{10}H_{14}N_2$) and isolycopodine ($C_{16}H_{25}ON$), (7,8,9).

In the past, the alkaloids were mainly isolated and purified by the tedious and difficultly reproducible methods of fractional distillation and fractional crystallisation of the bases or of their salts. Recently a combination of counter current distribution and suitable paper chromatographic procedures was very efficiently utilized for the isolation

of a few new alkaloids in this laboratory. In 1958, Anet and Eves (10) isolated lycodine and in 1959, Anet and Khan (1) succeeded in isolating four other alkaloids, annofoline ($C_{16}H_{25}O_2N$), lycofoline ($C_{16}H_{25}O_2N$), lofoline ($C_{18}H_{29}O_3N$) and fawcettine ($C_{18}H_{29}O_3N$). Exhaustive reviews on the distribution, isolation and characterisation of alkaloids of various Lycopodium species are available (5,8,11).

Chemistry of Lycopodium Alkaloids

The chemistry of Lycopodium alkaloids was fairly well developed before this work was undertaken. The structure and stereochemistry of several Lycopodium alkaloids were already established and interrelation amongst several of them was also achieved. The structural and stereochemical features of some of the Lycopodium alkaloids have proved to be of key importance in the elucidation of structure and stereochemistry of other related alkaloids. The chemistry of some of these alkaloids is relevant to the present work and therefore in the following pages a brief discussion of the structural and stereochemical studies of these alkaloids is presented.

Acrifoline, $C_{16}H_{23}O_2N$, m.p. 99-104°, was first isolated by Manske and Marion (7) from the plant Lycopodium annotinum var. acrifolium Fern and has since been reported by others (8,9).

Earlier reports (8,9) on the functional groups in acrifoline were based mainly on negative findings and have since been proved to be erroneous in some respects. However, Bertho and Stoll (8) positively showed the presence of a keto group with no adjacent methylene group in acrifoline. This followed from their observation that acrifoline reacted with phenyllithium to give a C_{22} compound and yet did not show any tendency to form a benzylidene derivative. Acrifoline also formed a methiodide.

Perry and MacLean (12,13) have studied the nature of the functional groups in acrifoline. The infrared spectrum of acrifoline in nujol showed very strong absorption in the hydroxyl region, but very weak absorption in the carbonyl region. However, in chloroform solution acrifoline exhibited a strong band at 1700 cm^{-1} and another band at 1675 cm^{-1}, and they were assigned to a carbonyl group and to an unsaturated linkage respectively. Catalytic hydrogenation of acrifoline gave dihydroacrifoline ($C_{16}H_{25}O_2N$). Lithium aluminum hydride reduction of dihydroacrifoline yielded dihydroacrifolinol ($C_{16}H_{27}O_2N$) and the latter showed hydroxyl absorption (3300 cm^{-1}), but no carbonyl absorption or unsaturation in the infrared spectrum. The same compound was obtained by catalytic hydrogenation of acrifolinol, the lithium aluminum hydride reduction product of acrifoline (14). However, earlier work

of Perry and MacLean (12) erroneously reported them to be not identical but stereoisomers. Acetylation of acrifoline gave monoacetylacrifoline ($C_{18}H_{25}O_3N$), the infrared spectrum of which showed bands at 1740 cm^{-1} (acetoxy group) and 1700 cm^{-1} (ketone) but no band in the hydroxyl region. These studies confirmed the presence of a double bond, a hydroxyl group, a tertiary nitrogen, and a keto group in acrifoline and indicated that acrifoline was tetracyclic.

Dihydroacrifoline (pKa 9.13) is a considerably stronger base than acrifoline (pKa 8.34). This difference in basic strengths has been regarded (12) to be due to the presence of an allylamine (-C=C-C-N-) structure in acrifoline.

The application of nuclear magnetic resonance (N.M.R.) spectroscopy has provided (13,14) further information on the nature of the functional groups of acrifoline. The N.M.R. spectrum of acrifoline showed absorptions of area equivalent to one proton at displacements of 3.35 and 2.04 p.p.m. (from chloroform), and were attributed to $>CH-O-$ and $>C=C<^{H}$ groups respectively. A doublet of area equivalent to three protons, occurring at a displacement of 6.20 p.p.m. (from chloroform), indicated the presence of a $>CHCH_3$ group. The presence of one C-methyl group was also shown (13) by Kuhn-Roth analysis of acrifoline. The N.M.R. spectrum of acetylacrifoline (14) confirmed the above results. Its N.M.R. spectrum showed

absorptions attributable to $>C=C<^{H}$, $>CH-O-$, and $>CHCH_3$ at displacements of 1.97, 2.64 and 6.30 p.p.m. respectively. A sharp peak at a displacement of 5.50 p.p.m. was assigned to the $-COCH_3$ group. The absence of absorption at low field in both of the above N.M.R. spectra ruled out the presence of an aldehyde group, and therefore the carbonyl group in acrifoline must be ketonic. The hydroxyl group must be secondary since the signal area of the $>CH-O-$ group corresponded to one proton only.

The infrared spectrum of acrifoline provided a clue to the spatial relationship of the carbonyl and the hydroxyl groups. As mentioned earlier, acrifoline in Nujol mull showed strong hydroxyl absorption and weak or no carbonyl absorption in its infrared spectrum, but in solution (chloroform) showed strong absorption at 1700 cm^{-1}, as well as the usual hydroxyl absorption. Both spectra showed (14) ether absorption near 1100 cm^{-1}. This difference in behaviour in the solid state and in solution has been taken as evidence for the presence of a hemiketal form in the solid state. Since only five- and six-membered cyclic hemiketals form spontaneously, the carbonyl group and the carbon atom bearing the hydroxyl group must be separated by two or three atoms.

Acrifoline methiodide ($C_{17}H_{26}O_2NI$) underwent Hofmann elimination on treatment with potassium tertiary butoxide in

boiling tertiary butanol yielding a crystalline base, $C_{17}H_{25}O_2N$(I), in 70% yield. Strong absorption at 900 cm^{-1} in the infrared spectrum of I indicated the presence of a terminal methylene group in it. The ultraviolet spectrum of I exhibited strong absorption at 2400 Å (ϵ = 24,000) and suggested I to be a conjugated diene. The enhanced double-bond absorption in the infrared at 1625 cm^{-1} also supported this. The structural feature of I therefore indicated that the double bond introduced during Hofmann reaction was in conjugation with the original double bond in acrifoline. Barring rearrangement, the original double bond in acrifoline must have occupied a γ, Δ position relative to a nitrogen as in $>\overset{\Delta}{C}=\overset{\gamma}{C}H-\overset{\beta}{C}H_2-\overset{\alpha}{C}H_2-N<$ sequence, so that the sequence in I would be $>\overset{\Delta}{C}=\overset{\gamma}{C}H-\overset{\beta}{C}H=\overset{\alpha}{C}H_2$. Ozonolysis of compound I yielded formaldehyde and this confirmed the presence of a terminal methylene group in it.

Catalytic hydrogenation of I apparently resulted in a mixture of partially reduced and fully reduced compounds. Oxidation of this mixture by modified Kuhn-Roth method yielded butyric acid as well as propionic and acetic acids. Therefore, a n-propyl group was present in the product of complete hydrogenation of compound I.

Reduction of diene I with sodium borohydride gave a diol (II), $C_{17}H_{27}O_2N$, and 1,2-reduction of the latter with

sodium in alcohol yielded $C_{17}H_{29}O_2N$(III). A modified Kuhn-Roth oxidation of compound III gave acetic acid and propionic acid. This showed the presence of an ethyl group in III.

The N.M.R. spectrum of acrifoline established that the double bond in acrifoline was trisubstituted. The above Hofmann degradation and the oxidation studies on the degraded product showed that the double bond must occupy a γ,Δ-position relative to nitrogen with the ΔC-atom disubstituted.

Acrifoline reacted with cyanogen bromide to yield two isomeric cleavage products, α- and β-cyanobromoacrifoline, IV and V, respectively. The former, compound IV, was shown to be formed by the cleavage at the same C-N bond as in the Hofmann degradation, as its quaternary trimethylammonium bromide ($C_{20}H_{32}O_2N_3Br$) gave a conjugated diene ($C_{17}H_{22}O_2N_2$) upon treatment with potassium tertiary butoxide. Kuhn-Roth oxidation studies on the hydrogenated product of the diene substantiated the presence of the sequence $>C{=}CHCH_2CH_2N<$ in acrifoline.

β-Cyanobromoacrifoline (V) reacted with trimethylamine to yield a non-crystalline quaternary ammonium bromide, which in turn gave an oily neutral product with potassium tertiary butoxide. The neutral product had two isolated double bonds; the infrared spectrum of the compound indicated

that one of them was in the form of a terminal methylene group. Ozonolysis of the neutral compound gave formaldehyde and this confirmed the presence of a terminal methylene group. Catalytic hydrogenation of the neutral product followed by modified Kuhn-Roth oxidation yielded butyric, propionic and acetic acids. The presence of butyric acid among the oxidation products proved that the hydrogenated product of the neutral compound had a n-propyl side chain, and therefore, that the sequence $-\overset{|}{C}-CH_2CH_2CH_2\overset{|}{N}<$ was present in acrifoline.

The von Braun reaction of acrifoline, thus, not only confirmed the results of the Hofmann degradation but in addition, allowed the extension of the peripheral structure to $-CH_2CH_2CH_2-\overset{|}{N}-CH_2CH_2CH=C<$.

Selenium dioxide oxidation of acrifoline gave two products (13,14). The major product, $C_{16}H_{21}O_2N$, of this reaction proved to be an α,β-unsaturated ketone. The infra-red spectrum of its perchlorate showed carbonyl absorption at 1690 cm^{-1} and enhanced double-bond absorption at 1627 cm^{-1}, and the ultraviolet spectrum of its perchlorate exhibited a maximum at 2430 Å (ϵ = 5330). Hydrogenation of the compound gave dihydroacrifoline and therefore the possibility of skeletal rearrangement was ruled out. The N.M.R. spectrum of the conjugated carbonyl compound had two peaks of area equivalent to one proton at displacements of 1.96 and 3.37 p.p.m.

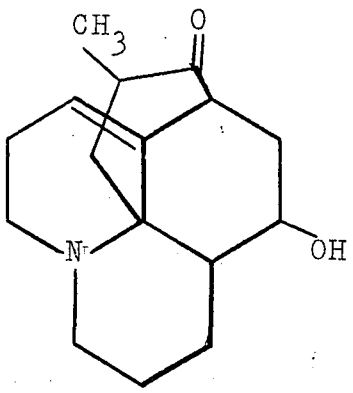
representing the isolated double-bond proton and the >CH-O-group respectively. A single, sharp peak at a displacement of 5.50 p.p.m. indicated that the methyl group was located on the double bond α,β to the carbonyl group. A singlet of area equivalent to one proton at δ = 0.23 was attributed to a proton on the β-carbon of the α,β-unsaturated ketone. These observations suggested the presence of $-CO-\overset{CH_3}{\overset{|}{C}}=CH-$ grouping in the conjugated ketone and of the sequence $-C\overset{CH_3}{\overset{|}{C}}H=CH_2-$ in acrifoline.

The minor product of selenium dioxide oxidation of acrifoline was isomeric to the major product but was not a conjugated ketone. This compound showed a carbonyl absorption at 1725 cm^{-1} in the infrared spectrum, but no hydroxyl absorption. The major product of selenium dioxide oxidation could be converted to its minor product by treatment with base and this indicated that the minor product was formed in the reaction medium by intramolecular addition of the hydroxyl group to the conjugated double-bond system. The ease of this addition implied that a five- or six-membered cyclic ether was formed, and that the carbon atom β to the carbonyl group and the carbon atom bearing the hydroxyl group are separated by two or three atoms. The N.M.R. spectrum of this compound supported a cyclic ether structure for it. Its N.M.R. spectrum had a doublet at δ = 6.22 representing the $>CHCH_3$ group, and a

peak of area equivalent to one proton at $\delta = 1.99$ for the single proton on the double bond. Two peaks, each of area equivalent to one proton at displacements of 3.19 and 3.54 p.p.m., were attributed to absorption by the two -CH-O-groups, one group at either end of the ether linkage. These N.M.R. data suggested the presence of the sequence $-CO-\underset{O}{\overset{CH_3}{C}}H-$ in the minor product of selenium dioxide oxidation of acrifoline.

Dihydroacrifolinol ($C_{16}H_{27}O_2N$) underwent Oppenauer oxidation to yield a diketone ($C_{16}H_{23}O_2N$). The infrared spectrum showed strong carbonyl absorption at 1705 cm^{-1}, but no hydroxyl absorption. The carbonyl frequency indicated that both carbonyl groups were located in rings that are six-membered or larger. Absorption at 1420 cm^{-1} in the infrared spectrum of the diketone and none in this region in the spectrum of acrifoline implied that a $-CH_2CO-$ group is present in the ketone but is absent in acrifoline. Thus the $-CH_2CO-$ group in the diketone must have arisen from a $-CH_2-CH(OH)-$group in acrifoline. The hydroxyl group in acrifoline does not appear to be allylic since attempts to replace it by halogen were unsuccessful.

The following structure for acrifoline has been proposed by French and MacLean (13,14) in accordance with the above findings.



Acrifoline

This structure can explain the existence of the hemiketal formed by interaction between the carbonyl and the hydroxyl functions. The facile conversion of the α,β-unsaturated ketone (major product of selenium dioxide oxidation of acrifoline) to its saturated isomer, the cyclic ether (minor product of selenium dioxide oxidation of acrifoline), is readily accomodated by this structure. The structure is biogenetically feasible and is compatible with the proposal recently put forward by Conroy (15). Furthermore, this structure is corroborated by the work of Anet (see later) in this field.

Annofoline, $C_{16}H_{25}O_2N$, m.p. 156-157°, was isolated by Anet and Khan from Lycopodium annotinum L. (1). It is a strong base, pKa 9.15. Annofoline yielded a methiodide indicating that the nitrogen atom in it was tertiary. It analysed for a

single C-methyl group.

The infrared spectrum of annofoline (16) in nujol showed absorptions for hydroxyl group (band at 3400 cm^{-1}) and a ~~and a~~ carbonyl group (band at 1700 cm^{-1}), probably a ketone in a six- or larger-membered ring. However, the intensity of the carbonyl band in the infrared spectrum (CCl_4 solution) of annofoline was abnormally low and resembled that of the alkaloid acrifoline (13). This behaviour has been explained to be due to the existence of an equilibrium between the hydroxyketone and the hemiketal forms in annofoline solution. The N.M.R. spectrum of annofoline showed a doublet at 8.93 τ indicating that the methyl group was present as a >CHMe group.

Reduction of annofoline with sodium borohydride (16) gave two isomeric diols, $C_{16}H_{27}O_2N$, α-dihydroannofoline, m.p. 264-265°, and β-dihydroannofoline, m.p. 200-203°. Later work (17) has shown, however, that β-dihydroannofoline is not a genuine reduction product of annofoline, but of an isomeric ketone.

Selenium dioxide oxidation of annofoline (16) yielded an α,β-unsaturated ketone, $C_{16}H_{23}O_2N$, ($\lambda_{max.}$(EtOH) 241 mμ; log ϵ = 3.8; $\nu_{max.}$ (CCl_4) 1685 cm^{-1}). The N.M.R. spectrum of the compound in $CDCl_3$ showed a sharp band at 2.74 τ of intensity corresponding to one proton and was

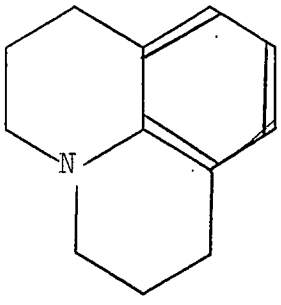
attributed to an olefinic proton β to the keto group. The singlet at 8.18 τ was assigned to the methyl group. Therefore it was concluded that there was a -CO-C(Me)=CH- system in the compound. The band for the olefinic proton was unsplit and this indicated that probably there was a quaternary carbon atom adjacent to the =CH group. The above results suggested the presence of the sequence -CO-CH(Me)-CH_2-C^*- (where C^* is a quaternary center) in annofoline.

Annofoline reacted with ethanethiol (16) to give an ethyl thioenol ether, $C_{18}H_{29}ONS$. The infrared spectrum showed a weak band at 1625 cm^{-1} (double bond) and a band at 3600 cm^{-1} (hydroxyl), but no band in the carbonyl region. The N.M.R. spectrum showed that there were no olefinic protons, but that the C-methyl group was now attached to a double bond. Hence the group EtS-C=C-Me must be present. Thus both in this reaction and in the selenium dioxide oxidation the keto group in annofoline preferred to enolise in the direction of the methyl group.

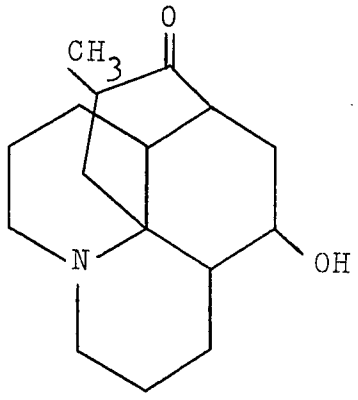
Wolff-Kishner reduction of annofoline gave dihydrodeoxyannofoline, $C_{16}H_{27}ON$, which no longer contained a carbonyl group. The reduction product gave an O-acetyl derivative showing that the oxygen atom in this compound was present as a hydroxyl function. Chromic acid oxidation gave a ketone, deoxyannofoline, $C_{16}H_{25}ON$, m.p. 88-92°, isomeric with lycopodine, but not identical with it. Selenium dioxide

oxidation of this ketone gave a base with weakly acidic properties and had the characteristics of an enolic α-diketone. (λ_{max} (EtOH) 282 mμ, shifting to 335 mμ with base). Thus, the presence of a $-CH_2-CH(OH)-CH$ or a $-CH-CH_2-CH(OH)-$ group in annofoline was indicated.

Annofoline reacted with t-butylnitrite in t-butanol (16) in the presence of potassium hydroxide to give an amphoteric compound. This compound underwent smooth dehydrogenation in the presence of palladium-charcoal to give julolidine (I). The formation of the amphoteric compound proceeds via an intermediate nitrosoketone which is cleaved by base at the -CO-CH(Me) bond. It was therefore concluded that annofoline contained a hexahydrojulolidine ring system, and that $-CO-CH(Me)-CH_2$ group present in annofoline was lost during the dehydrogenation step.



I



II

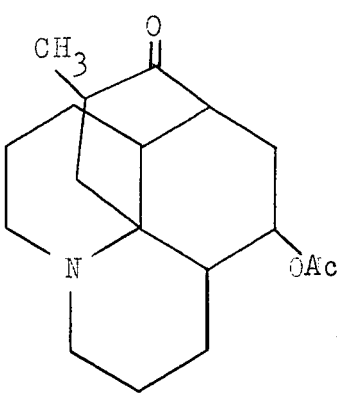
In order to accomodate the above reactions Anet and Khan (16) have proposed structure (II) for annofoline. The structure resembles the structures of acrifoline and

lycopodine, and to some extent that of annotinine. Annofoline should therefore be a diastereoisomer of dihydroacrifoline. The structure is also compatible with Conroy's scheme (15) for the biogenesis of Lycopodium alkaloids. Further, annofoline has since been related directly to acrifoline and indirectly to lycopodine; this will be discussed in detail in a later section.

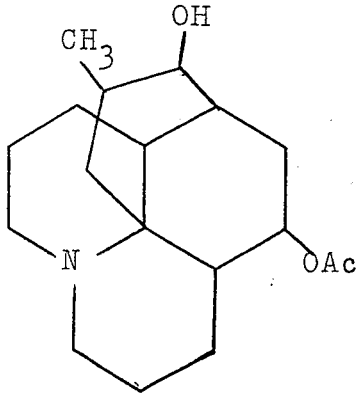
Fawcettiine; $C_{18}H_{29}O_3N$, is the major alkaloid of L. fawcetti (18), and a minor component of L. annotinum (1,19) and Jamaican L. clavatum (20). It has been shown to be a tetracyclic tertiary base possessing a hydroxyl group, an O-acetyl group, and one C-methyl group apart from the one in the acetyl group.

Mild hydrolysis of the base yielded a diol, deacetylfawcettiine, $C_{16}H_{27}O_2N$, which on dehydration with thionyl chloride lost only one molecule of water to give anhydrodeacetylfawcettiine, $C_{16}H_{25}ON$ (18). The latter, although it contained a hydroxyl group, was resistant to further dehydration. Oxidation of fawcettiine with chromium trioxide gave a ketoacetate, dehydrofawcettiine, $C_{18}H_{27}O_3N$, which could be hydrolysed by base to annofoline (21,22). However, it was shown later (17) that this was not a simple hydrolysis but one in which isomerisation accompanied deacetylation. Since the structure of annofoline was known (16) the gross structures of dehydrofawcettiine and fawcettiine must be

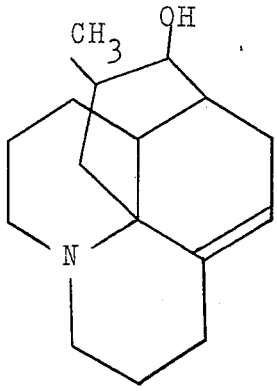
I and II respectively.



I



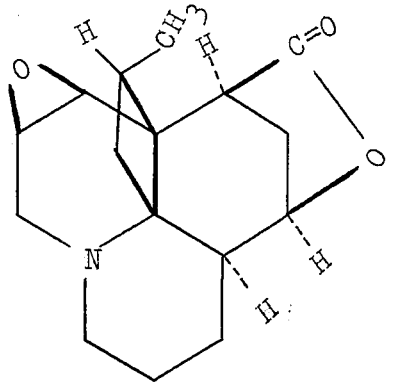
II



III

The N.M.R. spectrum of anhydrodeacetylfawcettiine (21,22) indicated the presence of only one olefinic proton (τ, 4.45) and also that the grouping CH_3-C-H is preserved (τ, 9.00; J 5.9 c.p.s.). These data can be accommodated by structure III for anhydrodeacetylfawcettiine.

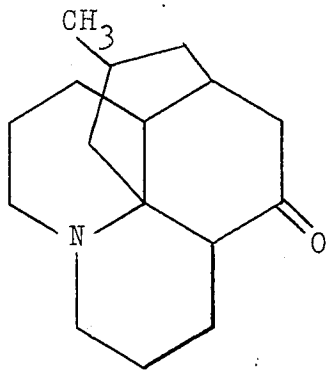
Annotinine, $C_{16}H_{21}O_3N$, is the principal alkaloid of Lycopodium annotinum L., and was first isolated by Manske and Marion (6). Much attention was centered on its chemistry for a number of years. The degradation studies on annotinine (23), as well as the X-ray crystallographic studies of Przybylska and Marion (24) on annotinine bromohydrin have led to the following structure for annotinine.



I

The relative stereochemistry implied in the above structure for annotinine has been established by the X-ray crystallographic work. Wiesner and his co-workers have recently deduced the absolute configuration (I) of annotinine (25). The chemistry, as well as the stereochemistry of annotinine has recently been summarized by Wiesner in an article in "Progress in the chemistry of organic natural products" (26).

Lycopodine, $C_{16}H_{25}ON$, m.p. 116°, is the major alkaloid of many Lycopodium species and has been detected in almost all of the species. Extensive degradation studies on lycopodine have led MacLean and Harrison (27) to propose the following structure for lycopodine.



Lycopodine

A full account of the degradation studies on lycopodine has been recently published by MacLean and his co-workers (28). The above structure for lycopodine has gained support from the subsequent work of Anet (17) in this field. He succeeded in relating lycopodine to annofoline whose structure has been arrived at by independent considerations (16). Anet's work has also established the relative stereochemistry of these alkaloids and is discussed in detail in a later section.

Lycofoline, $C_{16}H_{25}O_2N$, m.p. 144-145°, $[\alpha]_D$-75° was first isolated by Anet and Khan (1) from Lycopodium annotinum L., and later by Burnell and his co-workers (19) from L. fawcetti. Preliminary work on this alkaloid was carried out by Khan (2) in this laboratory. The infrared spectrum of lycofoline indicated the presence of a double bond and at least one hydroxyl group. A C-methyl group was found by Kuhn-Roth determination and the tertiary nature of the nitrogen atom was exhibited by the formation of a quaternary methiodide.

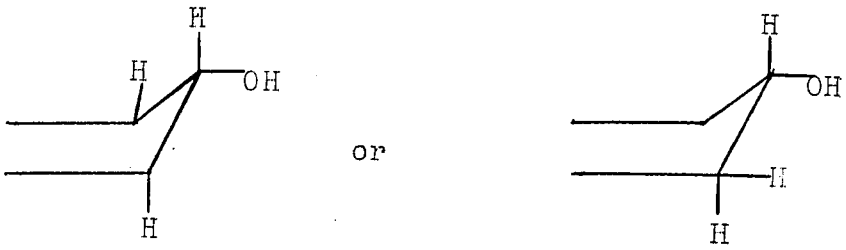
The nature of the oxygen atoms in lycofoline was determined by acetylation studies. Acetylation with acetic anhydride in pyridine solution at room temperature gave a monoacetyl derivative, $C_{18}H_{27}O_3N$, m.p. 159-160°. The infrared spectrum of the monoacetate showed bands at 3600 cm^{-1} (hydroxyl group) and 1730 cm^{-1} (acetate group), and thus indicated the presence of a second hydroxyl group in lycofoline. Acetylation of the second hydroxyl group was much more difficult, being incomplete even after seven hours at 80 to 90° with acetic anhydride-pyridine reagent. The diacetyl derivative, $C_{20}H_{29}O_4N$, m.p. 113-118°, was, however, easily separated from the monoacetyl derivative by chromatography on alumina. The acetylation studies, thus, showed the presence of two hydroxyl groups in lycofoline, one of which is quite strongly hindered.

Hydrogenation of lycofoline proceeded readily in the presence of Adam's catalyst to give dihydrolycofoline, $C_{16}H_{27}O_2N$, m.p. 146-147°. This confirmed the presence of a double bond in lycofoline.

The N.M.R. spectrum of lycofoline showed a doublet at 9.02 τ, the intensity corresponding to three protons and this confirmed the presence of a C-methyl group in the alkaloid. The position of this band showed that the C-methyl group was attached to a saturated carbon atom, and the splitting of 6 c.p.s., that this carbon carried just one

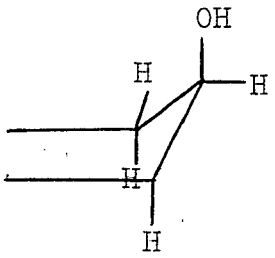
hydrogen atom. The triplet (splitting, 4 c.p.s.) of relative intensity 1:2:1 at 4.71 τ was attributed to one olefinic proton. The magnitude of the splitting showed that the grouping involved was $>C=CH-CH_2-$. Bands at 6.14 τ and 6.82 τ, each corresponding to one proton, could be assigned to $>CH-O-$ groups from their chemical shifts. The sharp band at 7.2 τ was probably due to the protons of the hydroxyl groups corresponding to the above two bands, and the absence of any coupling was probably due to fast exchange of the protons of hydroxyl groups caused by the basic nitrogen atom present in the alkaloid.

The band at 6.82 τ was a quartet with spacings of 10.8 and 5.4 c.p.s., showing that there was coupling to two protons. The magnitudes of the coupling constants suggested the following arrangement about the hydroxyl group:



The band at 6.14 τ was quite broad, with a half-band width of 10 c.p.s., indicating coupling to three or four protons. The coupling constants could not be very large and a structure of the following type appeared to be

consistent with the evidence:



The N.M.R. spectrum of acetyllycofoline showed the same features as that of the parent alkaloid except that the quartet at 6.8 τ was shifted to 5.66 τ . This was consistent with the assignment made earlier that the proton responsible for this band was attached to a carbon atom bearing an equatorial, and therefore unhindered, hydroxyl group. In diacetyllycofoline, the N.M.R. spectrum was further modified by a shift on the band at 6.14 τ to 4.94 τ . In both acetylated derivatives the protons of the acetyl groups gave rise to a sharp band at about 8.00 τ .

These were the available informations about lycofoline when the present work was undertaken. The present work deals in part with the structure and stereochemistry of lycofoline and of its hydrogenated product, dihydrolycofoline. After the preparation of the paper (29) on our results was completed for publication, a preliminary communication by Burnell and Taylor (30) appeared in which the same conclusions were reached, but based on different evidence. Recently, these people have

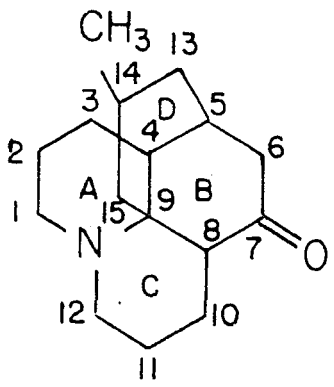
published (31) a full paper on lycofoline. Their evidences for structure and stereochemistry of lycofoline are discussed together with that of ours in a later section.

Interrelation and Stereochemistry

The elucidation of the gross structures of lycopodine (26), acrifoline (14), annofoline (16) and fawcettiine (21), I, II, III and IV respectively (Fig. 2), suggested their close relationship to each other. Interrelation of these alkaloids has since been accomplished (17). The stereochemistry of these alkaloids has been elucidated by Anet (17).

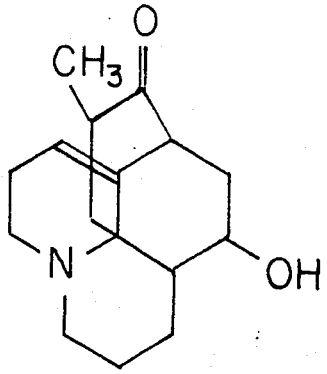
Catalytic hydrogenation of acrifoline (II) gave, in addition to the previously reported dihydroacrifoline, a small yield of annofoline (III) (17). Thus annofoline is a "dihydroacrifoline" and is epimeric with the previously known dihydroacrifoline at C_4 (see Fig. 2 for numbering used).

Attempts to interrelate annofoline (III) and lycopodine (I) directly had been unsuccessful. The Wolff-Kishner reduction of annofoline followed by chromic acid oxidation (16) yielded a compound, designated as deoxy-annofoline, $C_{16}H_{25}ON$, m.p. 88-92°, which had the gross structure I, but was not identical with lycopodine, m.p. 115°. This indicated that more than one stereochemical configuration was



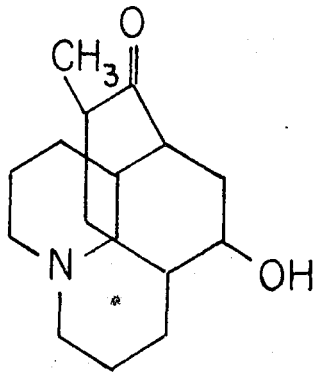
I

Lycopodine



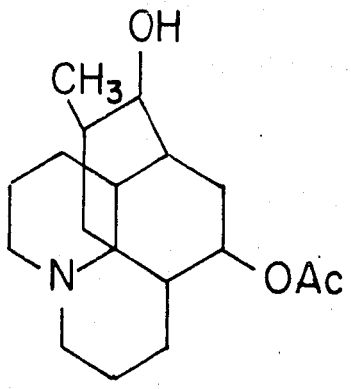
II

Acrifoline



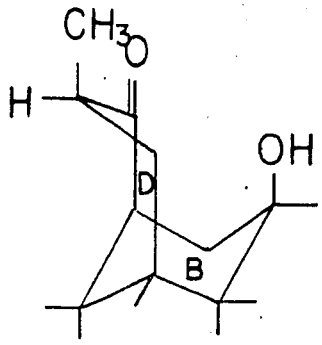
III

Annofoline

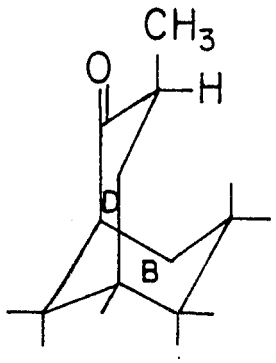


IV

Fawcettiine



V



VI

Fig. 2 Structure of some Lycopodium alkaloids.

involved. Later Anet has shown (17) that lycopodine and deoxy-annofoline differ only in the configuration of C_{14} atom bearing the methyl group.

The O-acetyl derivative of annofoline (III) has the same gross structure as dehydrofawcettiine, the chromium trioxide oxidation product of fawcettiine (IV); however, the nonidentity of their hydrobromides (17) has led to the conclusion that these two compounds are not identical. More recently (22) Burnell's observation that the methiodides of annofoline acetate and dehydrofawcettiine are different has confirmed the above conclusion. However, both O-acetyl-annofoline and dehydrofawcettiine, on hydrolysis with base, furnished annofoline (17,21,22). These surprising findings can be explained only if there was an isomerisation during the alkaline hydrolysis of dehydrofawcettiine, as it is known that during acetylation and chromium trioxide oxidation isomerisations are unlikely. These results indicated that annofoline and fawcettiine have opposite stereochemistry at C_{14} and also that annofoline is more stable than the hydrolysis product from dehydrofawcettiine, i.e. C_{14} epimer of annofoline (17).

Reduction of annofoline with sodium borohydride in boiling aqueous ethanol gave a mixture of two isomeric diols,

α- and β-dihydroannofoline (16). Later work showed that these two isomers were not merely epimeric alcohols at C_{13}, as might be assumed, but that they differed in the configuration at C_{14}. Reduction with lithium aluminum hydride or with sodium borohydride in neutral solution gave only the α-isomer. However, sodium borohydride reduction in the presence of sodium hydroxide gave as much as 50% of the β-isomer (17). Thus β-dihydroannofoline is not a genuine reduction product of annofoline, but of a ketone having the methyl group on C_{14} in the opposite configuration. This would also explain the observation (21) that β-dihydroannofoline and deacetylfawcettiine are identical. These results show that the reduction of annofoline proceeds in two steps; initial equilibration between annofoline and the less stable ketone by alkali, followed by faster reduction of the less stable ketone. The difference in the rates of reduction of the two isomers can be understood on the basis of the proposed stereochemistry of these compounds. The stereochemistry of these compounds are discussed below.

Lycopodine has been related to annofoline by the following series of reactions and these have allowed the assignment of the configuration at C_{14} in lycopodine (17). Dehydration of deacetylfawcettiine (identical to β-dihydroannofoline) yielded anhydrodeacetylfawcettiine, which on chromic acid oxidation gave an oily ketone. Wolff-Kishner

reduction of the ketone gave an oily base, $C_{16}H_{25}N$, proved to be anhydrodihydrolycopodine (naturally occurring alkaloid L-14), previously prepared from lycopodine (32) by reduction with lithium aluminum hydride followed by dehydration. Lycopodine, therefore, resembles fawcettiine in the configuration at C_{14} and not annofoline.

Both annofoline and acrifoline exist as mixtures of hemiketal and internally hydrogen bonded hydroxy ketone forms. This is only possible if in these compounds ring D assumes predominantly the boat conformation. Also for the same reason the hydroxyl group on C_7 must be axial. The conformation with the D ring in the chair form would be unfavourable due to strong repulsion between C_{14} and the axial hydroxyl group on C_7. Since, annofoline is the more stable one of the two C_{14}-epimers, the methyl group would have to be equatorial on ring D in the boat form. The partial conformation shown (V) (Fig. 2) should therefore be appropriate for both annofoline and acrifoline. However if the interaction between C_{14} and C_7 substituent is sufficiently relieved, the chair form of ring D should become the preferred conformation and, in such a case, the isomer with the C_{14} methyl group equatorial on ring D would be more stable. This situation would be attained in compounds where the hydroxyl group on C_7 is absent and even more so if a double bond were present at 6,7 or 7,8. The

partial conformation can be represented as VI (Fig. 2) where the methyl group on C_{14} has the opposite configuration to that in V. The stability of configuration on C_{14} depends on whether the ring D is in a chair or boat form and this in turn is determined by the bulk of the substituents on C_7.

The stability of lycopodine and deoxyannofoline to base indicates that the rings B and C are fused trans. The ready dehydration of dihydrolycopodine to the $\Delta^{7,8}$ isomer confirmed this conclusion. Rings A and B must be fused cis to allow formation of a cyclic compound from α-cyanobromo-lycopodine (27) by internal alkylation at C_8. The catalytic hydrogenation of acrifoline gave dihydroacrifoline in major yield and annofoline in smaller yield. This observation is understable since hydrogenation from the less hindered site is expected to give trans fusion of rings A and B and therefore, annofoline being the C_4 epimer, would have rings A and B cis fused.

The above evidence have led Anet (17) to assign the stereochemistry of lycopodine and annofoline as VII and VIII (Fig. 3) respectively. The interrelation of fawcettiine, annofoline and lycopodine is shown in Figure 3. The proposed stereochemistry also explains several other observations. As anticipated, Wolff-Kishner reduction of dehydrofawcettiine gave largely the isomerised product and no detectable amounts

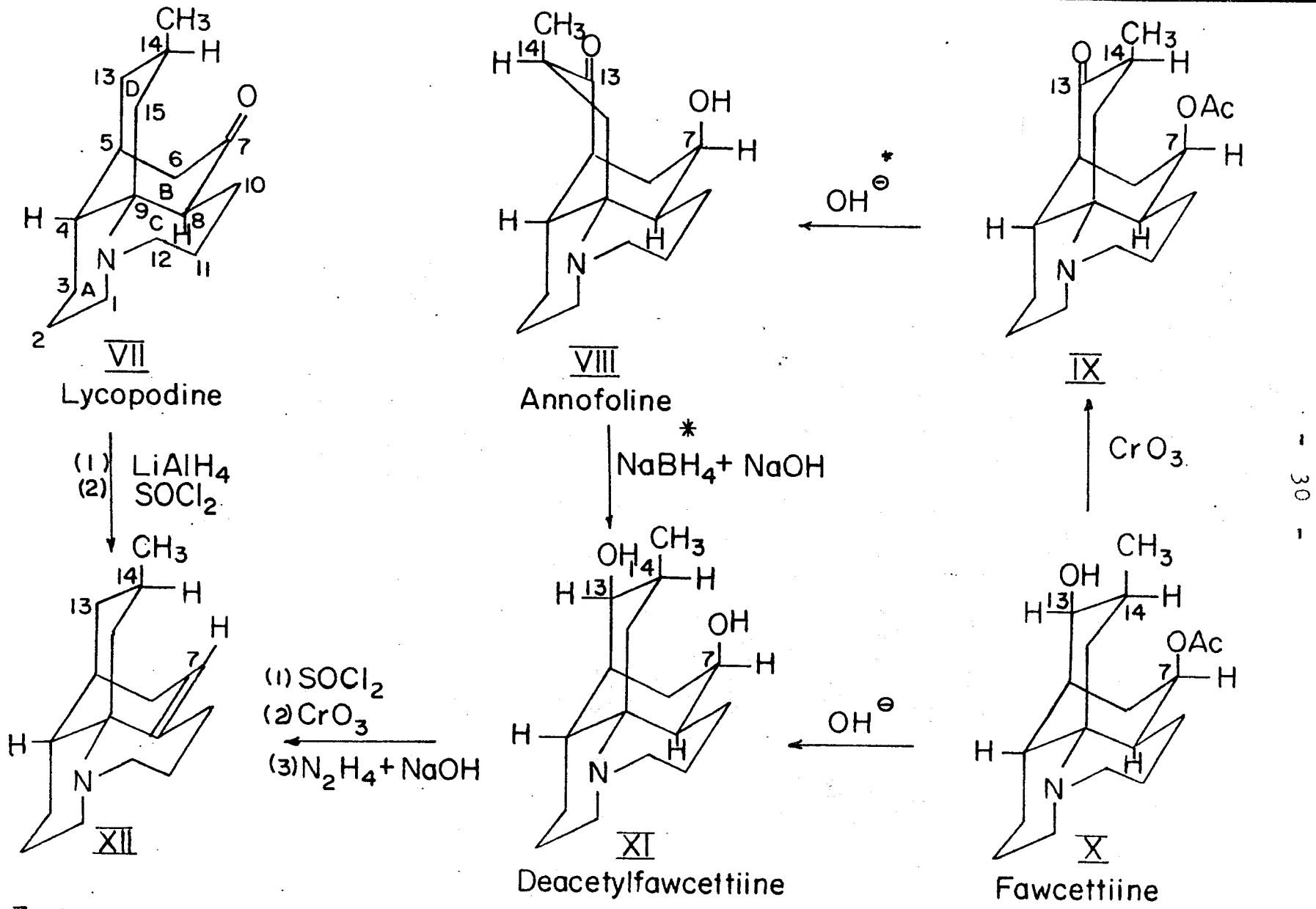


Fig. 3 Interrelation and stereochemistry of some Lycopodium alkaloids.
* indicates that the step involves isomerization at C-14.

of dihydrolycopodine. Ring D in fawcettiine (X) and therefore in deacetylfawcettiine (XI) has been represented by Anet in the chair form, as the methyl group would be in the extremely unfavorable flag-pole position if the D ring existed as a boat. This is consistent with the observations (17) that neither fawcettiine (X) nor lofoline, which are epimeric alcohols at C_{13} and have the 7-hydroxyl group acetylated are hydrogen bonded in dilute carbontetrachloride solutions. Anhydrodeacetyl-fawcettiine was resistant to further dehydration (18) and therefore the hydroxyl group at C_{13} must be trans to the methyl group, in agreement with the proposed stereochemistry for deacetylfawcettiine (XI).

The absolute configurations of lycopodine and its related alkaloids have been shown (25) to have the same absolute configuration as annotinine.

Leete (33) and Conroy (15) have proposed possible biogentic schemes for annotinine. Conroy's scheme which also explains the biogenesis of other Lycopodium alkaloids like the obscurines, lycodine, lycopodine, selagine, appears to be more attractive.

EXPERIMENTAL

Description of the General Methods

The melting points were determined on a Leitz hot-stage apparatus. The infrared spectra of solutions were measured in a micro-cavity cell (ca. 1 mm path length; 0.04 ml volume) on a Perkin Elmer "Infracord" double beam instrument. The ultraviolet spectrum reported in this thesis was recorded using a Beckmann DK-2 spectrophotometer in ethanol solution in 1 cm. cells.

Elementary analysis of a compound reported here was kindly performed by Mrs. Patricia Revelle.

Paper chromatography, unless otherwise stated, was carried out according to Anet and Khan (1), on Whatmann No. 1 paper impregnated with a citrate-phosphate buffer. The chromatogram was developed by n-butanol saturated with water and the spots were revealed by spraying with a modified Draggendorf reagent (34). Buffer of different pH values (as mentioned within the text) were used depending on the nature of the alkaloidal mixture under investigation. At times the same reaction mixture was subjected to paper chromatography at different pH values and the ones giving the best separation are presented in the text. The absolute R_f values of the different alkaloids and their degradation products

varied appreciably but their relative values were constant.

Appreciable amounts of acrifoline, annofoline that were needed for the present work were available in this laboratory from previous investigations.

Conversion of Acrifoline into Lycofoline

(a) Attempted Reduction of Acrifoline Hydrobromide with Sodium and Wet Ether

Metallic sodium, in excess, was added in small pieces to a well stirred solution of acrifoline hydrobromide (7 mg) in wet ether (10 ml) and the stirring was continued until all sodium went in solution. The reaction mixture was diluted with water and the aqueous portion was rejected. The ether extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The infrared spectrum of the product in carbon tetrachloride solution showed intense bands at 3600 cm^{-1}, 3500 cm^{-1} and 1700 cm^{-1}.

(b) Attempted Reduction of Acrifoline Hydrobromide with Sodium and n-Butyl Alcohol

A solution of acrifoline hydrobromide (6 mg) in n-butyl alcohol (3 ml) was heated to boiling; small pieces of sodium (184 mg) were added and the reflux was continued until all sodium went in solution. The solution was cooled and most of the liquid was removed at reduced pressure. The residue

was dissolved in water and the alkaloid material was extracted with methylene chloride. The methylene chloride extract was dried over anhydrous sodium sulfate and evaporated to dryness. The infrared spectrum of the product (in CCl_4) exhibited bands at 3600 cm^{-1}, 3500 cm^{-1} and 1700 cm^{-1}.

(c) Reduction of Acrifoline Hydrobromide with Lithium and Alcohol in Liquid Ammonia

A suspension of acrifoline hydrobromide (55 mg) in ether was added to methanol (5 ml) dissolved in liquid ammonia (50 ml); metallic lithium (410 mg) in small slices was added to the well stirred solution. The blue colour which appeared after the addition of each piece of lithium disappeared after a few seconds. After the addition of lithium was completed, ammonium chloride (2.7 g) was added to the mixture while stirring was continued. Excess of liquid ammonia was allowed to evaporate. The residue was dissolved in water; the solution was made strongly basic and the alkaloid was extracted with chloroform. The infrared spectrum of the product (in CCl_4) did not show any absorption in the carbonyl region but exhibited bands at 3600 cm^{-1} and 3500 cm^{-1}. Paper chromatography (pH 7.0) indicated the presence of two compounds [R_f 0.28 (very strong), 0.34 (very weak)]. In the same chromatogram acrifoline and lycoforline had R_f values of 0.56 and 0.41 respectively.

The crude reaction product was purified by sublimation under vacuum, m.p. 258-260°.

(d) Reduction of Acrifoline with Lithium Aluminum Hydride (12)

A solution of lithium aluminum hydride (10 mg) in dry ether (2.5 ml) was added to a stirred solution of acrifoline (9 mg) in dry ether (3 ml) and the contents were refluxed for seven hours. The mixture was cooled and unreacted lithium aluminum hydride was destroyed by careful addition of wet ether. The reaction product was filtered and the ether solution was dried over anhydrous sodium sulfate. The residue obtained on removal of ether did not show any infrared absorption (in CCl_4) in the carbonyl region; strong bands at 3600 cm^{-1} and 3500 cm^{-1} were present. Paper chromatography (pH 7.0) showed the presence of one compound with R_f value of 0.60 compared to 0.53 and 0.42 for acrifoline and lycofoline respectively.

(e) Reduction of Acrifoline with Sodium Borohydride

Sodium borohydride (25 mg) in small portions was added to a boiling solution of acrifoline (6 mg) in ethanol (0.4 ml). After the addition of sodium borohydride was complete, the contents were refluxed for another two hours. The mixture was then cooled; excess of sodium borohydride was decomposed with dilute acetic acid (1:1) and most of the liquid

was then removed at reduced pressure. The residue was dissolved in water; the solution was made alkaline and extracted several times with chloroform. The infrared spectrum of the reaction product in carbon tetrachloride solution showed bands at 3600 cm^{-1} and 3500 cm^{-1} but no band in the carbonyl region. A paper chromatogram (pH 7.0) on the product revealed the presence of two compounds corresponding to R_f values of 0.35 (very weak) and 0.60 (very strong); the R_f value for acrifoline in the same experiment was 0.56.

Reduction of acrifoline with sodium borohydride in buffer (pH 8.0) was carried out in the same way as above. Paper chromatography (pH 7.0) indicated the presence of two compounds [R_f, 0.49 (very weak), 0.74 (very strong)], corresponding R_f values for acrifoline and lycofoline were 0.69 and 0.52 respectively.

(f) Reduction of Acrifoline Hydrobromide with Sodium Borohydride in the Presence of Sodium Hydroxide

Acrifoline hydrobromide (205 mg), ethanolic sodium hydroxide (6.1 g in 150 ml), and sodium borohydride (712 mg) were refluxed for two hours. The alkaloidal material was isolated in the same way as in the preceding experiment. Paper chromatography (pH 7.0) revealed two spots at R_f values of 0.50 (weak) and 0.73 (strong); the R_f values of acrifoline

and lycofoline were 0.69 and 0.52 respectively.

Isolation of the two compounds was carried out by preparative paper chromatography on Whatmann No. 3MM paper buffered to pH 7.0 and developed with butanol saturated with water. The strip corresponding to the compound with lower R_f value was cut from the rest of the paper and was eluted with 1% hydrochloric acid. The acid solution was well shaken with chloroform and the chloroform layer was rejected. The acid solution was then made basic with dilute sodium hydroxide solution and the alkaloidal content was extracted with chloroform. The product obtained on removal of chloroform from the extract was sublimed at 105-115° under vacuum.

The sublimed product (25 mg, m.p. 140-144°) was crystallised from ether, m.p. 143-145°. A mixed melting point with an authentic sample of lycofoline did not show any depression. The infrared spectrum of the product in Nujol mull was identical with that of lycofoline. The product had $[\alpha]_D$-74.5° (C, 2.0 in ethanol). $[\alpha]_D$ for lycofoline -75° (C, 2.0 in ethanol) (1).

Small scale reduction of acrifoline hydrobromide with sodium borohydride in sodium ethoxide in ethanol, sodium isopropoxide in isopropanol, and sodium tertiary butoxide in t-butanol were carried out in the same way as above. Paper chromatographic results did not show any noticeable change in the amount of lycofoline formed.

Attempts to Interrelate Dihydrolycofoline with known Lycopodium Alkaloids

(a) Reduction of Annofoline with Lithium and Alcohol in Liquid Ammonia

Annofoline (50 mg) was reduced with lithium and methanol in liquid ammonia according to the procedure described on page 34. The infrared spectrum of the reaction product in chloroform did not show any absorption in the carbonyl region. Paper chromatography (pH 7.0) indicated the presence of one compound at R_f value 0.17; the corresponding R_f values of annofoline and dihydrolycofoline were 0.30 and 0.27 respectively. The crude product was purified by sublimation under vacuum, m.p. 256° (m.p. of α-dihydroannofoline 264-265°, m.p. of β-dihydroannofoline 200-203°; mixed m.p. of the product with α-dihydroannofoline showed depression).

(b) Reduction of Dihydroacrifoline with Lithium Aluminum Hydride

Dihydroacrifoline (5 mg) was reduced with lithium aluminum hydride (20 mg) in dry ether in the same way as described on page 35. The infrared spectrum of the product did not show any band in the carbonyl region. Paper chromatography (pH 7.0) on the reaction product revealed the presence of two compounds [R_f 0.53 (very strong), 0.36 (very weak)];

R_f value for dihydroacrifoline 0.47 and that for dihydrolycofoline 0.27.

(c) Reduction of Dihydroacrifoline with Lithium and Alcohol in Liquid Ammonia

Dihydroacrifoline (6 mg) was reduced with lithium and methanol in liquid ammonia in the same way as described for a similar reduction of acrifoline hydrobromide on page 34 . Paper chromatography (pH 7.0) indicated the presence of only one compound at R_f value 0.18; the R_f values for dihydroacrifoline and dihydrolycofoline were 0.47 and 0.27 respectively.

(d) Reduction of Dihydroacrifoline with Sodium Borohydride in the Presence of Sodium Hydroxide

Dihydroacrifoline (4 mg) was reduced with sodium borohydride (16 mg) in ethanolic sodium hydroxide in the same way as described on page 36 . The carbonyl band at 1700 cm^{-1} present in dihydroacrifoline was missing in the infrared spectrum of the reaction product but a band of medium intensity was present at 1740 cm^{-1}. Paper chromatography (pH 7.0) revealed three spots (R_f 0.25, 0.51, 0.84 (weak)), R_f value for dihydroacrifoline 0.47 and that for dihydrolycofoline 0.27.

Some Reactions of Annofoline

A. Attempted Preparation of Annofoline Enol-Acetate

1. Treatment of Annofoline with Isopropenyl Acetate

(a) A solution of annofoline (6 mg), isopropenyl acetate (1 ml), p-toluenesulfonic acid (8 mg), in methylene chloride (0.5 ml) was shaken for a period of twenty-four hours. Methylene chloride and unreacted isopropenyl acetate were removed at reduced pressure. The residue was dissolved in water; the aqueous solution was made basic with dilute sodium hydroxide solution, and the alkaloidal material was extracted with methylene chloride. The infrared spectrum of the reaction product (in CCl_4) showed strong absorptions at 1705 cm^{-1} and 1740 cm^{-1}, but no band in the hydroxyl region. Paper chromatography (pH 7.0) indicated the presence of two compounds (R_f values 0.41 and 0.55) and showed that there was no unchanged annofoline (R_f 0.22).

(b) A solution of annofoline (8 mg), isopropenyl acetate (1 ml), p-toluenesulfonic acid (7 mg), in methylene chloride (3 ml) was refluxed for two hours. The alkaloidal material was worked up in the same way as before. The infrared spectrum of the product in CCl_4 exhibited strong bands at 3600 cm^{-1}, 3450 cm^{-1}, 1740 cm^{-1} and 1705 cm^{-1}.

The above reaction product was dissolved in methylene

chloride and subjected to reflux for another four hours with additional amount of isopropenyl acetate (1 ml) and p-toluene-sulfonic acid. The infrared spectrum (in CCl_4) of the free base isolated at the end of the reaction showed intense absorptions at 1740 cm^{-1} and 1705 cm^{-1}, and weak absorptions at 3600 cm^{-1} and 3450 cm^{-1}.

2. Treatment of Annofoline with Acetic Anhydride

A mixture of annofoline (6 mg), acetic anhydride (0.2 ml) and dry triethylamine (0.3 ml) was refluxed for two hours. The mixture was cooled, unreacted acetic anhydride was decomposed with methanol and most of the liquid was removed at reduced pressure. The residue was dissolved in water; the solution was basified with dilute sodium hydroxide solution and was extracted several times with chloroform. The infrared spectrum of the reaction product showed strong bands at 1740 cm^{-1} and 1705 cm^{-1}. Paper chromatography (pH 7.0) showed the presence of three compounds in the reaction product (R_f 0.61, 0.73, 0.83) and also that there was no unchanged annofoline (R_f 0.27).

The same reaction was carried out for a reflux period of four hours, but however, did not show any additional change than that observed with the above reaction.

3. Treatment of Annofoline with a Mixture of Acetyl Chloride and Acetic Anhydride

A mixture of annofoline (6 mg), acetyl chloride

(0.3 ml) and acetic anhydride (0.3 ml) was heated on a water-bath for two hours during which time a few drops of acetyl chloride distilled off. The mixture was then refluxed for an hour, cooled and excess of acetic anhydride was decomposed with methanol. The liquid was removed at reduced pressure and the residue was dissolved in water. The aqueous solution was cooled in an ice-bath, made basic with sodium hydroxide solution and the free organic base was quickly extracted with chloroform. The infrared spectrum of the reaction product did not show any absorption in the hydroxyl region but exhibited strong bands at 1745 cm^{-1} and 1710 cm^{-1}. Paper chromatography (pH 7.0) of the reaction product revealed four spots, two of them being very strong (R_f 0.65, 0.73) and the other two being very faint (R_f 0.28, 0.84). The one with the R_f value of 0.28 may be due to unchanged annofoline (R_f 0.31).

B. Attempted Baeyer-Villiger Oxidation of Annofoline

1. Treatment with Peroxytrifluoroacetic Acid

A solution of peroxytrifluoroacetic acid was prepared (35) by the dropwise addition of trifluoroacetic anhydride (0.4 ml) to a stirred and ice-cooled suspension of hydrogen peroxide (90%, 0.05 ml) in methylene chloride (0.4 ml). The solution thus obtained was then added slowly to a vigorously stirred solution of annofoline (5 mg) in methylene chloride

(0.3 ml). After standing at room temperature in the dark for forty-eight hours, the contents were evaporated to dryness at reduced pressure. The residue was dissolved in water; the aqueous solution was cooled in an ice-bath and made basic with 10% sodium carbonate solution. The cold solution was extracted several times with chloroform, dried over anhydrous sodium sulfate and the solvent was removed. The infrared spectrum of the product in carbon tetrachloride solution did not show any absorption in the hydroxyl region, but showed intense bands at 1750 cm^{-1} and 1790 cm^{-1}. Paper chromatography (pH 6.0) on the reaction product showed it to be a mixture of six components.

The above reaction was repeated by decreasing the reaction time to twenty-four hours. The infrared spectrum (in CCl_4) again did not show any absorption for hydroxyl group, but exhibited bands at 1750 cm^{-1} and 1790 cm^{-1}.

2. Treatment with Peracetic Acid

Peracetic acid (90%; 0.02 ml) was added to a solution of annofoline (6 mg) and p-toluenesulfonic acid (5 mg) in methylene chloride (0.4 ml), and the mixture was allowed to stand at room temperature in the dark for four days. The alkaloid was worked up in the usual way. The infrared spectrum of the product exhibited weak bands at 3600 cm^{-1}, 3450 cm^{-1}, strong band at 1730 cm^{-1}, and a shoulder at 1705 cm^{-1}. Paper

chromatography (pH 7.0) of the product showed the presence of five compounds, one of them having the same R_f value as annofoline.

C. Attempted Dehydration of Annofoline

1. Treatment with Thionyl Chloride

A mixture of annofoline (7 mg) in dry benzene (1 ml) and freshly distilled thionyl chloride (0.2 ml) was refluxed for two hours, cooled and evaporated to dryness at reduced pressure. The residue was dissolved in dilute hydrochloric acid (1%) and the acidic solution was washed with chloroform. The solution was then made alkaline with sodium hydroxide solution and the free alkaloidal material was extracted with chloroform. The infrared spectrum (in CCl_4) of the reaction-product showed bands at 3625 cm^{-1}, 3400 cm^{-1} and 1700 cm^{-1}. Paper chromatography (pH 7.0) revealed three spots with R_f 0.29 (strong), 0.65 (weak), 0.92 (weak). The major product (R_f 0.29) had the same R_f value as annofoline.

The above reaction was repeated with an increased reflux period of eight hours but the infrared spectrum, as well as the paper chromatogram of the reaction product, did not indicate any difference from those of the preceding one.

2. Treatment with Phosphorus Pentoxide

A mixture of annofoline (6 mg) in dry xylene (3 ml)

and phosphorus pentoxide (100 mg) was refluxed for two hours and then cooled. Excess of phosphorus pentoxide was decomposed with careful addition of water and the resulting solution was evaporated to dryness. The solid residue was taken up in water, basified with sodium hydroxide solution, and the free organic base was extracted with chloroform. The infrared spectrum of the product in carbon tetrachloride solution did not show any band above 3000 cm^{-1}, but showed a band at 1700 cm^{-1}. Paper chromatography (pH 6.0) indicated the presence of seven components with R_f 0.02 (weak), 0.16 (weak), 0.47 (strong), 0.54 (strong), 0.63 (strong), 0.83 (weak), 0.90 (weak). In the same chromatogram annofoline had a R_f value of 0.12.

The same reaction was carried out for a reflux period of thirty minutes. The infrared spectrum of the product (in CCl_4) showed bands at 3650 cm^{-1}, 3490 cm^{-1} and 1700 cm^{-1}. Paper chromatography (pH 6.0) revealed five spots (R_f 0.04, 0.20, 0.44, 0.52, 0.65). The most predominant spot (R_f 0.20) may be due to unchanged annofoline (R_f 0.17).

3. Treatment with Phosphorus Oxychloride and Pyridine

To a solution of annofoline (6 mg) in dry pyridine (0.5 ml), freshly distilled phosphorus oxychloride (0.2 ml) was added, and the mixture was then refluxed for two hours. Most of the pyridine was removed by evaporation under a stream

of nitrogen and water was added to decompose any phosphorus oxychloride left unreacted. The solution was made basic and the alkaloid material was extracted with chloroform. The infrared spectrum of the product exhibited bands at 3650 cm^{-1}, 3500 cm^{-1} and 1700 cm^{-1}. Paper chromatography (pH 6.0) indicated the presence of two compounds with R_f values 0.02 (faint) and 0.26 (very strong) respectively. In the same run annofoline was found to have a R_f value of 0.24.

4. Treatment with p-Toluenefulfonyl Chloride and Pyridine

A mixture of annofoline (4 mg) and p-toluenesulfonyl chloride (25 mg) in dry pyridine (0.4 ml) was refluxed for a period of one hour. The reaction product was worked up as described in the preceding experiment. The infrared spectrum of the product in carbon tetrachloride solution showed bands at 3650 cm^{-1}, 3500 cm^{-1} and 1700 cm^{-1}. Paper chromatography (pH 6.0) revealed four spots with R_f values 0.13 (weak), 0.25 (very strong), 0.71 (weak) and 0.85 (weak). The predominant product (R_f 0.25) may be due to unchanged annofoline (R_f 0.24).

Attempt to dehydrate annofoline with p-toluene-sulfonyl chloride/ in the presence of triethylamine was also made in the same way as above. The infrared spectra and the paper chromatogram (pH 6.0) of the reaction product were identical to those yielded by the reaction product of the foregoing reaction.

Preparation of Dihydroacrifoline

A solution of acrifoline hydrobromide (410 mg) in water was hydrogenated at atmospheric pressure in the presence of Adam's catalyst (38 mg). Required amount of hydrogen was absorbed in forty-five minutes. The catalyst was removed, the solution was made basic and the alkaloidal material was extracted with chloroform. Paper chromatography (pH 7.0) showed the presence of two compounds - the R_f values of these compounds corresponded to those of annofoline and dihydroacrifoline respectively. More than 90% of the product appeared to be dihydroacrifoline. Dihydroacrifoline was separated from annofoline by preparative paper chromatography (for procedure see page 37). The crude material was then purified by sublimation at 110-115° at 0.05 mm. pressure.

Attempted Equilibration of Dihydroacrifoline

1. Treatment with Sodium Hydroxide Solution

Sodium hydroxide solution (10%, 0.5 ml) was added to an alcoholic solution of dihydroacrifoline (6 mg in 0.2 ml). The resulting solution was refluxed for four hours, cooled and the free alkaloidal base was extracted with chloroform. Paper chromatography (pH 7.0) indicated that most of the dihydroacrifoline was unchanged [R_f dihydroacrifoline 0.32; R_f reaction product 0.29 (strong), 0.62 (faint), 0.72 (faint)].

2. Treatment with Sodium-t-butoxide in t-butanol

(a) Small Scale Experiment

A mixture of dihydroacrifoline (7 mg) and sodium tertiary butoxide solution (160 mg of sodium dissolved in 12.5 ml of dry t-butanol) was refluxed for two hours. The alkaloidal base was isolated from the reaction mixture in the usual way. The infrared spectrum of the reaction product in carbon tetrachloride solution exhibited bands at 3600 cm^{-1}, 3450 cm^{-1}, 1725 cm^{-1}, 1675 cm^{-1} and a shoulder at 1700 cm^{-1}. Paper chromatography (pH 6.0) on the reaction product revealed seven spots (R_f 0.09, 0.19, 0.35, 0.45, 0.54, 0.60, 0.88), of which, however, only one (R_f 0.35) appeared to be a major product; the rest being present in small quantities. The one with the R_f value 0.19 may be due to unchanged dihydroacrifoline (R_f 0.17).

(b) Larger Scale Experiment

A mixture of dihydroacrifoline (100 mg) and sodium t-butoxide in t-butanol (2.45 g of sodium dissolved in 185 ml of dry t-butanol) was refluxed for two hours. 10 ml of the reaction mixture was taken out and the alkaloidal material was isolated. The infrared spectrum (in CCl_4) of the product showed bands at 3600 cm^{-1}, 3450 cm^{-1}, 1725 cm^{-1}, 1700 cm^{-1} and shoulders at 1675 cm^{-1} and 1630 cm^{-1}. Paper chromatography

(pH 6.0) showed five spots (R_f 0.16, 0.34, 0.45, 0.53, 0.57), of which the component with R_f value 0.16 was most predominant. This was most probably due to unchanged dihydroacrifoline (R_f 0.18).

Therefore the residual reaction mixture was refluxed for an additional period of two hours and the alkaloidal material was isolated in the usual way. The infrared spectrum of the product exhibited bands at 3600 cm^{-1}, 3450 cm^{-1}, 1735 cm^{-1}, 1675 cm^{-1} and a shoulder at 1630 cm^{-1}. There was no recognisable absorption at 1700 cm^{-1}. Paper chromatography (pH 6.0) indicated the presence of six components (R_f 0.09, 0.24, 0.36, 0.47, 0.88, 0.91) and the one with R_f value 0.36 was the most predominant one. It appeared that there was no unchanged dihydroacrifoline (R_f 0.18).

The major product of the above reaction mixture was isolated in the following way. The crude reaction product was dissolved in minimum quantity of methanol and to this a methanolic solution of perchloric acid (70%) was added dropwise until the solution became slightly acidic. It was then followed by dropwise addition of ether accompanied with scratching, the perchlorate crystallised out. Paper chromatogram (pH 6.0) on the perchlorate indicated the presence of only one compound with the R_f value of 0.36. The infrared spectrum of the perchlorate in Nujol mull showed bands at 3600 cm^{-1} and 1675 cm^{-1},

and weak bands at 3100 cm^{-1} and 1640 cm^{-1}. The perchlorate was recrystallised from methanol ether and decomposed at 270-272°. The analysis on the perchlorate gave C, 53.13%; H, 6.98%; (calculated for $C_{16}H_{23}O_2N.HClO_4$ C, 53.11%, H, 6.72%). The ultraviolet spectrum of the perchlorate in ethanol showed an absorption at 244 mμ (log ϵ 3.7).

Preparation of β-Dihydroannofoline (Deacetylfawcettiine)(17)

Annofoline (300 mg), ethanolic sodium hydroxide solution (4.1 g in 100 ml) and sodium borohydride (660 mg) were refluxed for two hours. The contents were cooled and the excess of sodium borohydride was decomposed with dilute acetic acid (1:1). Most of the ethanol was evaporated at reduced pressure. The residue was dissolved in water, made basic with sodium hydroxide solution and the free organic base was extracted with chloroform. A crude reaction product was obtained on removal of chloroform. The infrared spectrum of the product did not show any absorption in the carbonyl region. Paper chromatography (pH 7.0) showed the presence of almost equivalent amounts of β-dihydroannofoline (R_f 0.28) and α-dihydroannofoline (R_f 0.53).

The crude reaction product was chromatographed on alumina (Fluka) deactivated with 5% water. The solvent used for elution was benzene and chloroform in various proportions;

20 ml fractions were collected. Every third fraction was checked for α-dihydroannofoline and β-dihydroannofoline by paper chromatography. The fractions containing only β-dihydroannofoline were combined and the residue left after removal of the solvent was dissolved in methanol-benzene. This solution on concentration gave crystals of β-dihydroannofoline (also known as deacetylfawcettiine), m.p. 201-4° (reported 200-203°).

Dehydration of Deacetylfawcettiine (18)

Deacetylfawcettiine (105 mg) was dissolved in benzene and treated with excess of thionyl chloride (5 ml) at room temperature for a period of two hours. The liquid was then removed at reduced pressure. The residue was dissolved in water, made basic and extracted with chloroform. Paper chromatography (pH 7.0) of the product indicated the presence of two compounds, one of them being the predominant one. There was no unchanged deacetylfawcettiine. No attempt was made for the purification of the dehydrated product (i.e. anhydrodeacetylfawcettiine), and the crude product was directly employed for the next step.

Oxidation of Anhydrodeacetylfawcettiine (17)

Crude anhydrodeacetylfawcettiine obtained from the foregoing reaction was dissolved in pyridine (1.5 ml) and

the solution was added to a freshly prepared solution of chromium trioxide (160 mg) in pyridine (1.5 ml). The mixture was shaken to ensure thorough mixing and was allowed to stand at room temperature for eighteen hours. A dark brown paste was obtained and the complex was decomposed with water. The solution was slightly basic and was made strongly basic to make sure that all the alkaloid material was present as free base. The alkaloid was extracted with methylene chloride. The infrared spectrum of the product in carbon tetrachloride solution showed a strong band at 1700 cm^{-1} and a weak band at 1650 cm^{-1}; there was no band in the hydroxyl region. Paper chromatography (pH 7.0) revealed two spots at R_f values 0.65 (very weak) and 0.85 (very strong); anhydrodeacetylfawcettiine had a R_f value of 0.61.

The crude material was then sublimed at reduced pressure, a pale yellow oil was obtained. The oily base, anhydrodehydrodeacetylfawcettiine was converted to its perchlorate in the usual way (see page 49). The perchlorate was recrystallised from methanol-ether, m.p. 195-196° (reported 190°C). Paper chromatography (pH 7.0) showed the homogeneity of the perchlorate.

Equilibration of Anhydrodehydrodeacetylfawcettiine

A solution of sodium hydroxide (18 mg) was made in methanol (0.5 ml) and water (0.8 ml). 0.5 ml of this

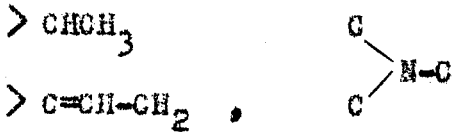
solution was added to anhydrodehydrodeacetylfawcettiine perchlorate (6 mg) dissolved in methanol. The solution was allowed to stand for seventeen hours and the alkaloidal material was extracted with chloroform. The infrared spectrum of the product in carbon tetrachloride solution was superimposable on that of the nonequilibrated anhydrodehydrodeacetylfawcettiine measured in carbon tetrachloride solution. Paper chromatography (pH 6.0) on the equilibrated product showed the presence of two compounds [R_f 0.43 (very weak) 0.66 (very strong), R_f of anhydrodehydrodeacetylfawcettiine 0.65)].

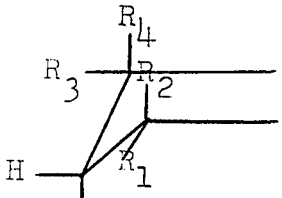
The reaction product was converted to its perchlorate, m.p. 205-212°. Paper chromatography of the perchlorate indicated the presence of a major product and a minor product. A mixture of the perchlorates of the equilibrated and the nonequilibrated base melted over a range of 190-195°.

DISCUSSION

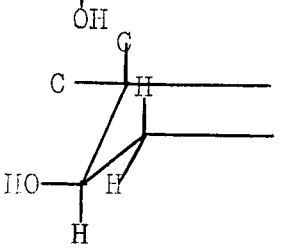
Structure and Stereochemistry of Lycofoline

Preliminary studies on lycofoline led Khan (2) to propose the following partial structure for lycofoline:

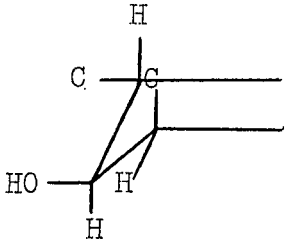




where more than two R's are hydrogen atoms,



or

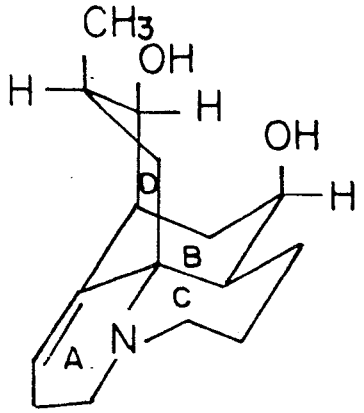


When the present work was undertaken the structures of acrifoline, annofoline, lycopodine and fawcettiine were already known. Anet's work (17) had also shown the close relationship existing between these alkaloids and had elucidated their relative stereochemistry. A possible biogenetic relationship of the Lycopodium alkaloids was also proposed by Conroy (15).

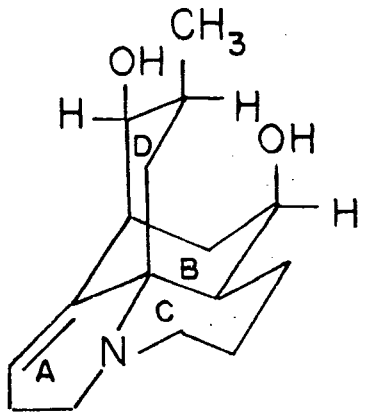
Since lycofoline was found together with annofoline and other related alkaloids in Lycopodium annotinum L. and,

moreover, that it was a C_{16} compound like annofoline, acrifoline, lycopodine, etc., it was speculated that lycofoline has a close structural relationship to these alkaloids. The amount of lycofoline available was too small to carry out any degradation studies on it. It was, therefore, proposed to interrelate lycofoline with one of the known Lycopodium alkaloids. This had the advantage that such an interrelation would not only provide the structure for lycofoline but also its relative stereochemistry.

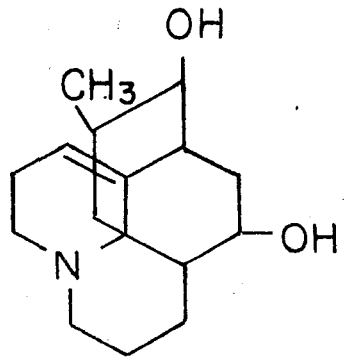
The structural and stereochemical features of Lycopodium alkaloids (see introduction), and the nature of the functional groups of lycofoline (2) led us to believe that lycofoline might have one of the two stereochemical structures, I and II (Fig. 4). Both of them have the same gross structure, III, but differ in the conformation of the bridge ring D and the configuration of the C-14 methyl group. Structure III is consistent with the biogenetic scheme of Lycopodium alkaloids forwarded by Conroy (15). It can be recalled here that the B and D rings of I have the conformational relationship as found in acrifoline and annofoline, whereas those in II have the conformational relationship as found in lycopodine and fawcettiine. Both I and II are consistent with the partial structure proposed by Khan (2), and the position of the double bond in these structures is the same as that found in acrifoline.



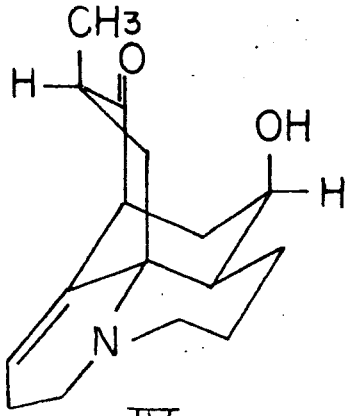
I



II

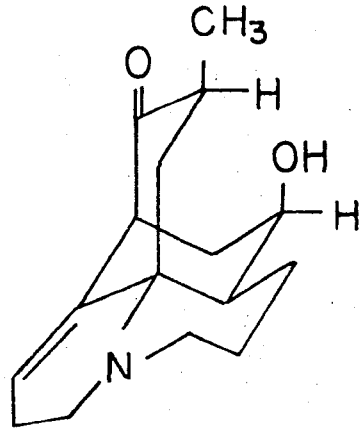


III

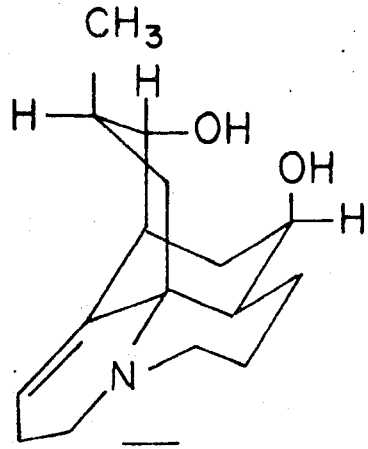


IV

Acrifoline



V



VI

Acrifolinol

Fig.4

Of all the known Lycopodium alkaloids, acrifoline, IV (Fig. 4), appeared to be the most suitable one to be interrelated to a compound having structure I directly, and to the one with structure II indirectly. The preparation of compound I from acrifoline would involve direct reduction of the ketonic group of acrifoline to an equatorial hydroxyl group. On the other hand, conversion of acrifoline to compound II would require initial isomerization of acrifoline to ketone V, and subsequent reduction of V to an equatorial alcohol. The latter reduction conditions might be achieved by carrying out reduction of acrifoline under isomerizing conditions, e.g. in the presence of a base. These reduction conditions had been successfully employed for obtaining deacetylfawcettiine (16,17) from annofoline.

Attempts were first made to prepare compound I from acrifoline. Acrifoline was subjected to reduction with various reducing agents which are known to yield equatorial alcohol from cyclic ketones.

Lithium aluminum hydride reduction of acrifoline was reported to yield acrifolinol (12), which is different from lycofoline. The ketonic group in acrifoline is highly hindered and, therefore, its reduction with metal hydrides should give an axial alcohol. Acrifolinol, must, therefore be represented by VI. We reinvestigated this reduction and

examined the reduction product by paper chromatography to see whether more than one reduction product was involved. However, only one product could be detected.

Attempted reductions of acrifoline hydrobromide with sodium and wet ether, as well as with sodium and n-butyl alcohol, proved to be unsuccessful. The infrared spectra of the products showed the presence of the carbonyl group originally present in acrifoline.

Reduction of acrifoline with lithium and methanol in liquid ammonia yielded mainly one product; the infrared spectrum of the product showed the absence of carbonyl absorption. Paper chromatography (pH 7.0) on the reaction mixture indicated the R_f values of the two products (0.28, 0.34) to be different from that of lycofoline (0.41). Furthermore, the crude product, on purification by sublimation yielded crystals which melted at 258-260° (m.p. of lycofoline 144-145°). This product was not further characterized. In the absence of analytical data nothing can be definitely said about the structure of this product. However, if it is a reduction product of acrifoline, structure I (Fig. 4) may be attributed to it, since it is known (36) that reduction with lithium and alcohol in liquid ammonia yields the more stable alcohol.

Sodium borohydride reduction of acrifoline hydrobromide indicated the formation of two compounds. The

infrared spectrum of the reaction product did not show any absorption for the carbonyl group, thus indicating that the reduction was complete. Paper chromatography on the reaction product showed that there was no unchanged acrifoline. The R_f value of the major component was the same as that of the lithium aluminum hydride reduction product of acrifoline. Therefore, the major component was probably acrifolinol. The second component, which was barely visible on the paper chromatogram, had an R_f value of 0.35 (pH 7.0), not much different from the R_f value of lycofoline.

Sodium borohydride reduction of acrifoline hydrobromide in buffer of pH 8.0 also revealed the presence of two components. The minor component had a R_f value (0.49) close to that for lycofoline (0.52). If the minor component was a second reduction product of acrifoline, it could not be I (Fig. 4), as sodium borohydride reduction of ketones is known (37) to be more stereospecific than lithium aluminum hydride reduction. Therefore, it was thought that the reduction was probably preceded by slight isomerization at C-14, caused by the weak basic medium of the reaction, and that the minor product was probably the reduction product of the isomerized ketone V.

That the above speculation was correct was proved by reduction of acrifoline hydrobromide with sodium borohydride

in ethanolic sodium hydroxide solution, when the yield of the minor component was considerably increased. The minor component was isolated by preparative paper chromatography and purified by sublimation followed by crystallization from ether. The crystals melted at 143-145° (m.p. of lycofoline 144-145°). A mixed melting point with an authentic sample of lycofoline did not show any depression. The infrared spectrum of the product in Nujol mull was identical with that of lycofoline. The product had $[\alpha]_D$ -74.5° (C, 2.0 in ethanol), $[\alpha]_D$ for lycofoline -75° (1). These physical properties thus proved the compound to be identical with lycofoline.

The above observations, hence, indicated that although acrifoline is certainly largely unchanged by base (14, 38), it must isomerize to give a small equilibrium amount of the less stable ketone, V (Fig. 4). Lycofoline was therefore not a reduction product of acrifoline, but of ketone V. The carbonyl group in V is unhindered, so on reduction with sodium borohydride, it should give rise to an equatorial alcohol. On these grounds, lycofoline must have structure II. The above results show that the initial equilibration between acrifoline and the less stable ketone by alkali is followed by faster reduction of the less stable ketone.

Sodium borohydride reduction of acrifoline hydrobromide in strong bases, like sodium ethoxide in ethanol,

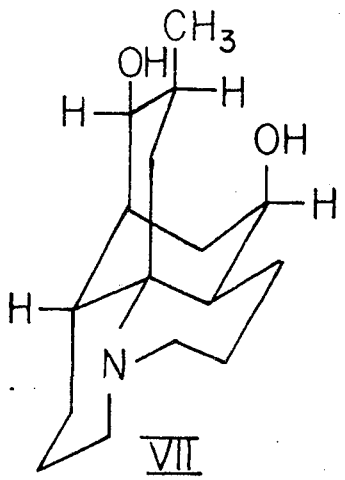
sodium iso-propoxide in iso-propanol, and sodium tertiary-butoxide in t-butanol, did not indicate any increase in the yield of lycofoline. This indicated that the equilibrium between acrifoline, IV (Fig. 4), and the isomerized ketone, V& (Fig. 4), favoured acrifoline, IV, rather than V&, even under strong basic conditions.

Stereochemistry of Dihydrolycofoline

The elucidation of the structure and the stereochemistry of lycofoline suggested one of the two structures, VII and VIII (Fig. 5) for dihydrolycofoline. However, VII represents deacetylfawcettiine whose structure and stereochemistry has been well established (16,17,18,22). Since dihydrolycofoline is not identical with deacetylfawcettiine, it must have structure VIII (Fig. 5).

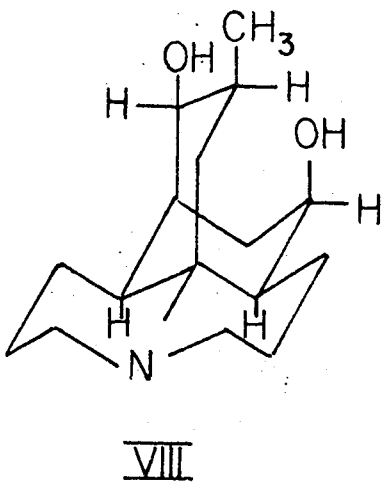
That the above conclusion is correct is also borne out by our experiments attempting to interrelate dihydrolycofoline with a known Lycopodium alkaloid. These reactions were carried out before the structure of lycofoline was established.

Reduction of annofoline IX, with lithium and methanol in liquid ammonia yielded only one product. Paper chromatography showed it (R_f 0.17) to be different from dihydrolycofoline (R_f 0.30). The purified product melted at 256°,

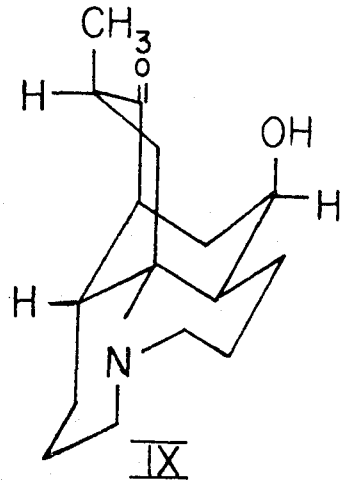


VII

Deacetylfawcettiine

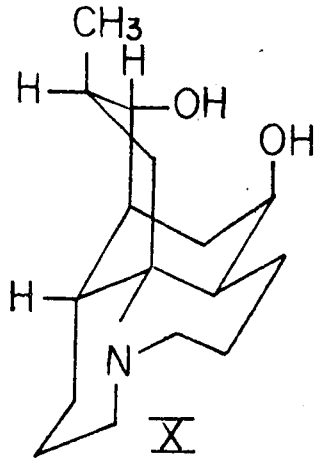


VIII



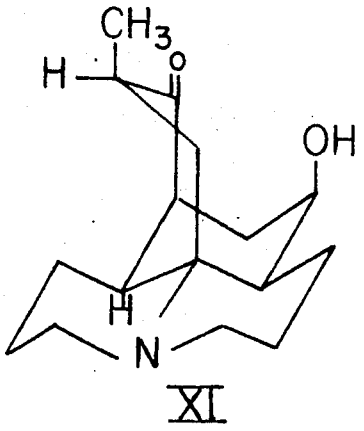
IX

Annofoline



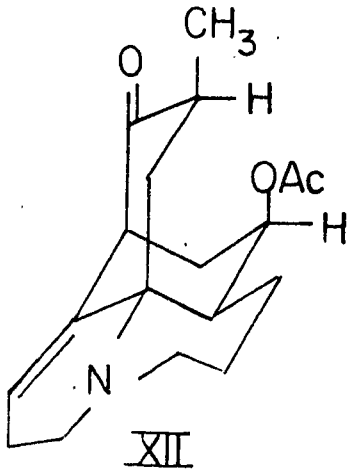
X

∝-dihydroannofoline

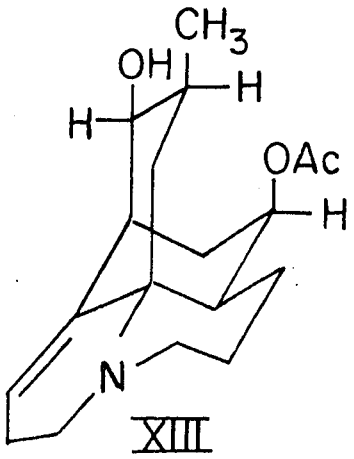


XI

Dihydroacrifoline



XII



XIII

Fig.5

which was different from the melting points of α-dihydroannofoline (m.p. 264-265°) and β-dihydroannofoline (m.p. 200-203°) (X and VII respectively in Fig. 5). The product was not further characterized.

Reduction of dihydroacrifoline, XI (Fig. 5), with lithium aluminum hydride and with lithium and alcohol in liquid ammonia, gave products which had R_f values different from that of dihydrolycofoline. These products presumably had the hydroxyl group at C-13 in axial and equatorial orientation respectively, with the skeleton of dihydroacrifoline unchanged. However, reduction of dihydroacrifoline with sodium borohydride in ethanolic sodium hydroxide solution yielded three products (paper chromatographic results), one of which had R_f value close to that of dihydrolycofoline. This component may very well be dihydrolycofoline. No further study on it, however, was carried out. It has been found (p. 48 of this thesis) that dihydroacrifoline undergoes changes in the presence of strong base; the infrared band at 1740 cm^{-1} found in the reaction product of sodium borohydride reduction of dihydroacrifoline might have arisen from one of these products.

Dihydrolycofoline is obtained by hydrogenation of lycofoline, the hydrogenation is expected to have taken place from the less hindered site of the double bond. This would lead to <u>trans</u> fusion of rings A and B which is consistent

with the proposed structure for dihydrolycofoline.

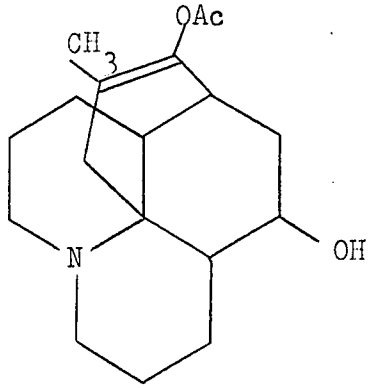
The contemporary work of Burnell and Taylor (30,31) in this field is in agreement with our conclusions about the structure of lycofoline. The two bases, M ($C_{18}H_{27}NO_3$) and N ($C_{20}H_{29}NO_4$), isolated from L. fawcettii (19), were shown by these authors to be a monoacetyl lycofoline and diacetyl-lycofoline respectively. However, they found that Base M was not identical with the monoacetate obtained by acetylation of lycofoline. Obviously Base M and lycofoline monoacetate differed only in the site of acetylation, and since acetylation of lycofoline gave preferentially lycofoline monoacetate, the acetyl group in the naturally occurring Base M must be in a hindered position, i.e., axially disposed. Confirmation for this came from cathylation reactions. Burnell and Taylor found that Base M, as well as lycofoline, yielded cathylates after room temperature treatment with ethyl chloroformate in pyridine; however, lycofoline monoacetate remained unchanged.

Burnell and Taylor (30,31) obtained a keto-acetate, $C_{18}H_{25}NO_3$, on oxidation of Base M with chromium trioxide-pyridine. On hydrolysis by dilute base, the ketoacetate yielded acrifoline. Therefore they proposed structure III (Fig. 4) for lycofoline. The acetyl derivative of acrifoline was, however, found (30,31) to be not identical with the keto-acetate obtained after oxidation of Base M. The hydrolysis of the

keto-acetate to acrifoline, thus, involved not only hydrolysis but also inversion of the configuration at C-14. The keto-acetate, was, therefore, represented by them as XII (Fig. 5), and lycofoline by II. (Fig. 4). Base M was given structure XIII (Fig. 5).

Attempted Preparation of Annofoline Enol-Acetate

It was realized that a suitable degradation product of annofoline, which would allow the rupture of its D ring, was essential for interrelating annofoline with annotinine. The enol-acetate (I) of annofoline appeared to be suitable for this purpose. Attempts were therefore made to prepare this compound.



I

Isopropenyl acetate has been found to react smoothly with enolizable ketones to yield enol-acetates and has frequently been used in the steroid field (39). Small scale reactions of annofoline with isopropenyl acetate in the presence of p-toluene-sulfonic acid, however, failed to yield any enol-acetate. The

infrared spectra showed that the ketonic carbonyl group was still present in the reaction products. The absence of any absorption in the hydroxyl region and the appearance of a new absorption at 1740 cm^{-1} indicated that the hydroxyl group of annofoline had undergone acetylation. This was expected from the known reactions of alcohols with isopropenyl acetate. It was, therefore, very likely that one of the components of the reaction product was annofoline acetate. No attempt was made to verify this expectation.

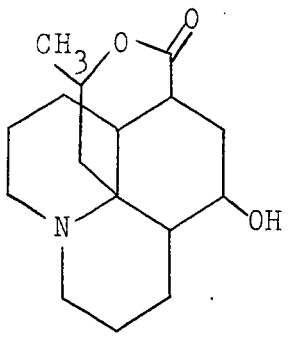
Attempts to enol-acetylate annofoline with acetic anhydride in the presence of triethylamine and also with a mixture of acetyl chloride and acetic anhydride were also unsuccessful. The latter method for preparing enol acetate has been used by several investigators (40,41). The infrared spectra of the reaction products indicated that the hydroxyl group of annofoline was no longer present and that it presumably had undergone acetylation.

The inability of annofoline to form enol-acetate must be due to its reluctance towards enolization. It was observed by Gynn and Degering (42) that the enol-acetylation of ketones by ketene depended on the number of hydrogen atoms α to the carbonyl group. All ketones with four or more α-hydrogen atoms underwent acetylation to an appreciable extent, but, as the number of α-hydrogen atoms dropped, the reaction

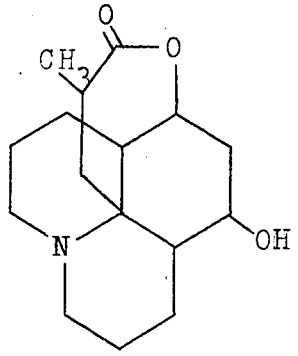
became very sluggish. Diisopropyl ketone, with only two α-hydrogen atoms, was found not to react at all. On these grounds the inability of annofoline to afford an enol-acetate is probably not surprising.

Baeyer-Villiger Oxidation of Annofoline

Peracid oxidation of ketones to esters or lactones, widely known as Baeyer-Villiger oxidation, has been used to synthesize a variety of steroid and terpene lactones, as well as lactones involving medium and large rings. We expected that Baeyer-Villiger oxidation of annofoline would give rise to either of the two ϵ -lactones, I and II, or a mixture of



I



II

both. We became interested in this reaction as it appeared to us that lactone I may be a good intermediate for interrelating annofoline with annotinine. Unfortunately, Baeyer-Villiger oxidations of annofoline with peroxytrifluoroacetic acid, as well as with peracetic acid, yielded complicated mixtures.

The infrared spectra of the reaction products obtained by "oxidation" of annofoline by peroxytrifluoroacetic acid did not show any absorption in the hydroxyl region, indicating that the hydroxyl group of annofoline had most probably participated in the reaction. Although the reaction product of the "oxidation" of annofoline with pedracetic acid exhibited hydroxyl band in its infrared spectrum, it cannot be ruled out that this was not due to unreacted annofoline.

The peracid oxidations were thus found to be unrewarding and were not, therefore, pursued. It should, however, be mentioned here that Baeyer-Villiger oxidation of dihydroacrifoline (a diastereoisomer of annofoline) has recently been reported (14) to yield an ether rather than a lactone.

Attempted Dehydration of Annofoline

Preliminary attempts by Khan (2) to dehydrate annofoline were unsuccessful. We reinvestigated this problem as we were interested to carry out an equilibration study on anhydroannofoline, the dehydration product of annofoline. However, our attempts in this field were also unrewarding. A number of dehydrating agents, under different conditions, were employed to affect dehydration of annofoline. In all of these cases, except the one using P_2O_5 under reflux for two

hours, the infrared spectra and the paper chromatograms of the reaction products indicated that annofoline remained mostly unchanged. Reaction of annofoline with P_2O_5 in dry xylene under reflux for two hours yielded a complicated mixture of seven components. The isolation of the individual components appeared to involve a lot of difficulties. Furthermore, the mixture may not contain any dehydration product of annofoline. This reaction was therefore abandoned.

The reluctance of annofoline towards dehydration is quite surprising in view of the fact that C-7 hydroxyl group of both dihydrolycopodine (lithium aluminum hydride reduction product of lycopodine) and deacetylfawcettiine undergo smooth dehydration under mild conditions (37,18). The steric environment of the C-7 hydroxyl group in annofoline is different from that in dihydrolycopodine (and also deacetylfawcettiine), as the D ring in the former is in the boat form, in contrast to the chair form in the latter. Introduction of a double bond between C-7 and C-8 in dihydrolycopodine and deacetyl-fawcettiine eliminates non bonded interaction between C-7 hydroxyl group and axial hydrogen atom on C-14 and thus causes a relief in the strain of the system. This may account for easy dehydration of these compounds. Dehydration of annofoline will also cause a relief of strain in annofoline, but to a lesser extent. The close proximity of the carbonyl

group of annofoline to its hydroxyl group may, also in part, be responsible for its reluctance towards dehydration.

Equilibration of Dihydroacrifoline

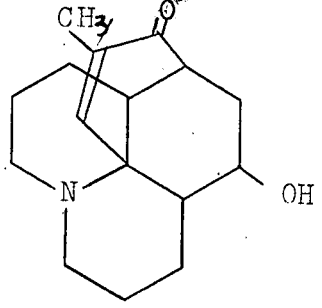
Dihydroacrifoline needed for this investigation was prepared by hydrogenation of acrifoline. The purity of this compound was ascertained by paper chromatography. Treatment of dihydroacrifoline with 10% sodium hydroxide solution for four hours under reflux conditions left most of the dihydroacrifoline unchanged (paper chromatographic results). However, when dihydroacrifoline was refluxed with sodium tertiary butoxide in t-butanol for two hours a complicated mixture was obtained. It was obvious that dihydroacrifoline had undergone some degradation. Without any detailed study on the individual components, it was not possible to predict whether or not one of the components constituted the equilibrated product. However, the separation of the minor components appeared to be unpracticable, and we proposed to study the major component only.

The major component (Base I) was easily isolated as its perchlorate from the crude reaction mixture and was purified by recrystallization from methanol-ether. Analysis on the perchlorate showed that it had the formula $C_{16}H_{23}O_2N.HClO_4$. The free base, thus, had two hydrogen atoms less than dihydroacrifoline. The infrared spectrum of the perchlorate in Nujol mull showed intense bands at 3600 cm^{-1} (free hydroxyl

group) and 1675 cm^{-1} (conjugated carbonyl group), and weak bands at 3100 cm^{-1} (-C-H) and 1640 cm^{-1} (-C=C-). The ultraviolet spectrum of the perchlorate showed absorption at 244 mμ (log ϵ 3.7). Thus, the spectroscopic data indicated that the free base was an α,β-unsaturated ketone. It was evident that we were dealing with an oxidation product of annofoline rather than an equilibrated product.

The amount of Base I obtained was very small, and its perchlorate in D_2O yielded a poor N.M.R. spectrum due to its low concentration. However, it was evident that the methyl group of Base I appeared as a single sharp peak in the middle of weak bands for the methylene protons of the molecule. The single peak for the methyl group indicated the absence of $>CHCH_3$ group originally present in dihydroacrifoline. The chemical shift of the singlet, which was almost the same as the methylene protons, suggested that the carbon atom bearing the methyl group was attached to a double bond.

The above observations can be accommodated if Base I is represented by the following structure:



Base I

The formation of Base I from dihydroacrifoline probably involves an intermediate hydroperoxide at C-15 (for numbering see Fig. 2) formed from the reaction between oxygen and the enol of dihydroacrifoline. Ketonization of the intermediate enolic hydroperoxide would lead to Base I. When the above reaction was carried out in an atmosphere of nitrogen the overall change of dihydroacrifoline was found to be greatly retarded. A much longer time (4 hrs. compared to 2 hrs.) needed for completion of a larger scale(see experimental) reaction between dihydroacrifoline and the base also indicated the importance of oxygen for the reaction. These observations are in accordance with our postulation of an intermediate hydroperoxide in the formation of Base I from dihydroacrifoline.

Equilibration of Anhydrodehydrodeacetylfawcettiine

Anhydrodehydrodeacetylfawcettiine needed for this study was obtained from annofoline through a series of known reactions. Annofoline, on reduction with sodium borohydride in sodium hydroxide solution (17), gave a mixture of almost equivalent amounts of α-dihydroannofoline and deacetylfawcettiine (β-dihydroannofoline). Deacetylfawcettiine underwent smooth dehydration of C-7 hydroxyl group to yield anhydrodeacetylfawcettiine (18); the latter on oxidation with chromium trioxide gave anhydrodehydrodeacetylfawcettiine (17).

The conditions which affected the hydrolysis (involving

inversion of configuration at C-14) of dehydrofawcettiine to annofoline (22) were employed for equilibration of anhydrodehydrodeacetylfawcettiine. The infrared spectrum of the equilibrated product in carbon tetrachloride solution was superimposable on that of the nonequilibrated base in carbon tetrachloride solution. Paper chromatography (pH 6.0) revealed the presence of two compounds and showed that the predominant product had the same R_f value as anhydrodehydrodeacetylfawcettiine.

The paper chromatographic, as well as the infrared, results tend to indicate that anhydrodehydrodeacetylfawcettiine remained mostly unchanged after base treatment. This suggests that anhydrodehydrodeacetylfawcettiine is the stable isomer and that isomerization of anhydrodehydrodeacetylfawcettiine to the ketone with the methyl group in the opposite configuration is not favoured. This is in agreement with Anet's (17) conclusion that when there is a double bond between C-7 and C-8 in these systems, the chair form of ring D should be the preferred conformation.

However, the perchlorate of the equilibrated base, still showing two spots on the paper chromatogram, melted over a range of 205-212°; its higher melting point compared to 195-196° for the perchlorate of anhydrodehydrodeacetylfawcettiine is unexpected. A mixture of the perchlorates of the equilibrated

and the non equilibrated base melted over a range of 190-195°.

A more rigid confirmation of our conclusions that anhydrodehydrodeacetylfawcettiine is the stable isomer, needs the isolation of the major product of equilibration. A larger scale equilibration of anhydrodehydrodeacetylfawcettiine was therefore necessary, but unfortunately, this could not be done due to lack of an adequate amount of the base.

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CONFORMATIONAL STUDIES BY N.M.R. SPECTROSCOPY

PART TWO

INTRODUCTION

The technique of Nuclear Magnetic Resonance (N.M.R.) spectroscopy has proved to be one of the most useful tools for structural organic chemistry. However, its application in the studies of dynamic properties of organic molecules has probably been even more interesting and exciting. Its success in the conformational analysis of organic compounds and in the studies of structural isomerism due to restricted internal rotation has already been immense.

The term "conformation" is used to denote any one of the infinite number of momentary arrangements of the atoms in space that result from rotation about single bonds. The conformations of the compounds dictate the thermodynamic properties, dipole moment, and spectral characteristics for the compounds and, consequently, the determination of these properties helps in the elucidation of their conformations.

"Chemical shifts" and "spin-spin splittings" data furnished by N.M.R. spectra have been of fundamental importance in the application of the N.M.R. technique to conformational analysis of organic compounds. The other factor which has been of importance in this field is the sensitivity of N.M.R. signals to time-dependent processes. These important aspects of N.M.R. spectroscopy will be discussed in brief in the

following few pages as they are relevant to the work that will be presented in this part of the thesis. A brief section on "double irradiation" has also been included. The present work deals with the application of N.M.R. spectroscopy to (i) ring inversion of cyclohexane, (ii) restricted rotation in some aromatic aldehydes, (iii) spin-spin splittings in some cyclohexene derivatives, and (iv) conformational analysis of cyclohexyl acetate.

Chemical Shift and Coupling Constant

The condition for nuclear magnetic resonance is given by the relation $\nu = \gamma H/2\pi$, where ν is the frequency of radiation in c.p.s., H the magnetic field at the nucleus in gauss, and γ the magnetogyric ratio of the nucleus. In order to observe a nuclear resonance, it is, therefore, necessary to adjust either the frequency of the radiation or the strength of the magnetic field at the nucleus until $\nu = \gamma H/2\pi$. Experimentally, it is most convenient to hold ν constant and to vary H continuously with time until the point, where the resonance occurs, is reached. The magnetic field at the nucleus is not, however, the same as the applied magnetic field, Ho, owing to diamagnetic and paramagnetic shielding effects produced by circulation of both bonding and non-bonding electrons in the neighbourhood of the nucleus (1).

The shielding, therefore, will depend on the electronic (chemical) environment of the nuclei, so that nuclei, which are chemically different will come into resonance at a different value of the magnetic field at a given frequency. These differences in resonance-line positions for nuclei of the same kind are called chemical shifts. The magnitude of a chemical shift is always taken in practice with reference to a standard; water, benzene, tetramethylsilane, which give only one sharp band, have been generally employed for this purpose.

The shielding effects are strictly proportional to the magnitude of the applied magnetic field so that the chemical shifts are directly proportional to the applied magnetic field. Since chemical shift is dependent on the Rf oscillator frequency, as well as on the applied field, any reported value should include both. Chemical shifts are, therefore, conveniently expressed in terms of a nondimensional parameter defined by

$$\delta \text{ (chemical shift)} = \frac{H - Hr}{Hr} \times 10^6,$$

where H is the resonant field of the signal being measured at a fixed frequency and Hr the corresponding resonant field for an arbritrary reference. In practice, the separation of the signals is generally represented in

frequency units (c.p.s.), which is readily obtained from the equation of the resonance condition, i.e., $\nu = \gamma H/2\pi$. In terms of frequency units chemical shifts are expressed as $\delta = \frac{n \times 10^6}{\nu_o}$, where n is the separation between the sample and reference peaks in c.p.s., and ν_o the rf oscillator frequency used.

"Spin-spin coupling" arises from magnetic interactions between groups of magnetic nuclei and takes place through the bonding electrons. The effect on a nucleus coupled to another nucleus, provided the resonances of the two nuclei are well separated, is to cause a splitting of the resonance line into two lines. The degree of spin-spin coupling is customarily designated by the coupling constant J and is expressed in c.p.s. Coupling constants are independent of the magnetic field but are dependent on the structural and stereochemical relationship of the interacting nuclei. Coupling constants are also dependent on the magneto-gyric ratio of the interacting nuclei. As for an example, the coupling constant between H and D nuclei in a molecule is $\gamma D/\gamma H$ (= 1/6.6) times that between two H nuclei in the same electronic environment. Splitting due to spin-spin coupling is often smaller than the chemical shift, but when it is not, the spectrum becomes quite complicated, especially when more than two or three nuclei are coupled together.

The theories behind chemical shifts and coupling constants are complicated and have been discussed by Pople, Schneider and Bernstein (1,2).

Double Irradiation

The technique of double irradiation (3,4) involves the removal of some spin coupling by the application of a second strong rf field in addition to the one used for observation. The frequency of the second rf field is adjusted close to the resonance frequency of a nucleus (or a group of nuclei) and this leads to frequent transitions between the states of the nucleus (or the group of nuclei), so that the nucleus (or the group of nuclei) becomes effectively decoupled from the remainder of the nuclear system. The method is applicable if the chemical shift is large compared with spin coupling constants and is, therefore, most conveniently used for removing coupling between unlike nuclei having a large difference in their resonance frequencies. In favourable cases, the technique has been successfully applied (5) to eliminate coupling between like nuclei.

Signal Shape and Rate Processes

As stated earlier, the N.M.R. signals are sensitive to time-dependent processes. The rate of exchange of a nucleus between two sites, chemically shifted from each other,

determines the shape and width of N.M.R. signals for the nucleus. The shape and width of the resonance signals undergo change in a regular fashion with the change in the exchange rate if the mean life times of the nucleus on the sites are of the order of magnitude of the inverse frequency separation which would be observed between the peaks in the absence of an exchange process. For rapid processes, i.e., if the life times on the sites are short, the spectra are determined by the time-average environment of the nucleus. On the other hand, if the rate of exchange is much smaller, the spectra consist of separate signals with their normal chemical shifts, and any fine structure due to spin-spin interactions. The rate process may involve intermolecular or interionic exchange of atoms, groups of atoms or electrons, or intramolecular rate processes such as hindered rotation and inversion. Both slow and fast passage conditions have been employed for the study of line shapes.

The slow passage conditions deal with the steady state lineshapes obtained when the spectrum is swept through slowly and has been so far extensively used. The most widely used approach to the evaluation of the relation between rates and lineshapes is based on a semi-classical treatment suggested by Gutowsky, McCall and Slichter (6). Their method involves the solution of the Bloch equations under conditions of

exchange. McConnell (7) has presented a simpler solution of the same problem. Their theoretical considerations succeeded in correlating the behaviour of the resonance lineshapes of nuclei with the conditions of their exchange between two sites. The expression for this relationship will be henceforth referred to as the lineshape equation. The method developed by Gutowsky and his co-workers (6) has been extended by others (8,9,10) to a number of reaction-rate lineshape problems. The general equation for a species has been given by Arnold (11), and by Piette and Anderson (12) as have equations for quadruplets (13) and triplets (14,15). The analysis for two types of sites has been extended to n types. The results for this more general problem have been discussed in detail by Anderson (16), Kubo (17) and Sack (18).

Other types of theoretical considerations have been used to interrelate the exchange phenomenon with the behaviour of N.M.R. signals. Solomon and Bloembergen (19) have considered chemical exchange as a relaxation mechanism, following the theory of relaxation times due to Bloembergen, Purcell and Pound (20). Kaplan (21) has proposed a general theory of exchange broadening, based on the time dependent equation of the density matrix which has been extended by Alexander (22).

The fast passage conditions are concerned with the lineshapes caused by sweeping quickly through the spectrum

and have been used to evaluate the line width of signals from the decay pattern of the wiggles.

The variation of the lineshape with the change in the mean life time (τ) at the different sites has been employed to measure τ . In most cases the broadest range of τ values is covered by solving numerically the appropriate lineshape equation for various values of τ , T_2 (line width), etc., and comparing the observed spectra with the calculated ones; when identity between the two is found τ is read directly. Analytical solutions have also been developed for evaluating τ in terms of measurable quantities. These were employed in our study on the ring inversion of cyclohexane and will be presented in the appropriate section. The mean life time of a species, τ , between exchanges has been related to the conventional rate equations and has been used to determine various thermodynamic data.

Applications of N.M.R. to Conformational Analysis

The observations of Lemieux and his co-workers (23), that the chemical shifts of substituents in polysubstituted six-membered rings depend on their conformational position and, furthermore, that the magnitude of the coupling of vicinal protons depend on the conformational relation between them, opened up new approaches towards tackling conformational aspects of organic compounds. Their finding that the axial and equatorial protons are chemically shifted from each other,

the former appearing at a higher field than the latter, has been explained on the basis of magnetic anisotropy in carbon-carbon single bonds (24,25). The above conclusion received immediate recognition and was used in the determination of the conformation of sugars (23,26), trioxanes (27), and isomeric hexachlorocyclohexanes (28). The finding suggested the possibility of determining the conformational equilibria of molecules which exist as mixture of conformers. However, in most simple cyclohexyl derivatives the interconversion between the conformers is so rapid that the N.M.R. spectra of these compounds at room temperature fail to show distinct signals for axial and equatorial protons.

Theoretical calculations of electron coupled spin interactions using approximate valence bond calculations by Karplus (29) have revealed interesting and important results. The magnitude of the vicinal coupling was found to vary with dihedral angle (Fig. 1); good agreement with the experimental data was obtained (30). Although anomalous observations have been made (31) in some cases, vicinal coupling data have been widely used to arrive at dihedral angles, and thus have helped in the elucidation of conformations of organic compounds. Unfortunately, the application of this method is limited to systems in which the vicinal coupling constants can be determined. The presence of too many hydrogens in simple cyclohexyl derivatives causes strong coupling among many protons of

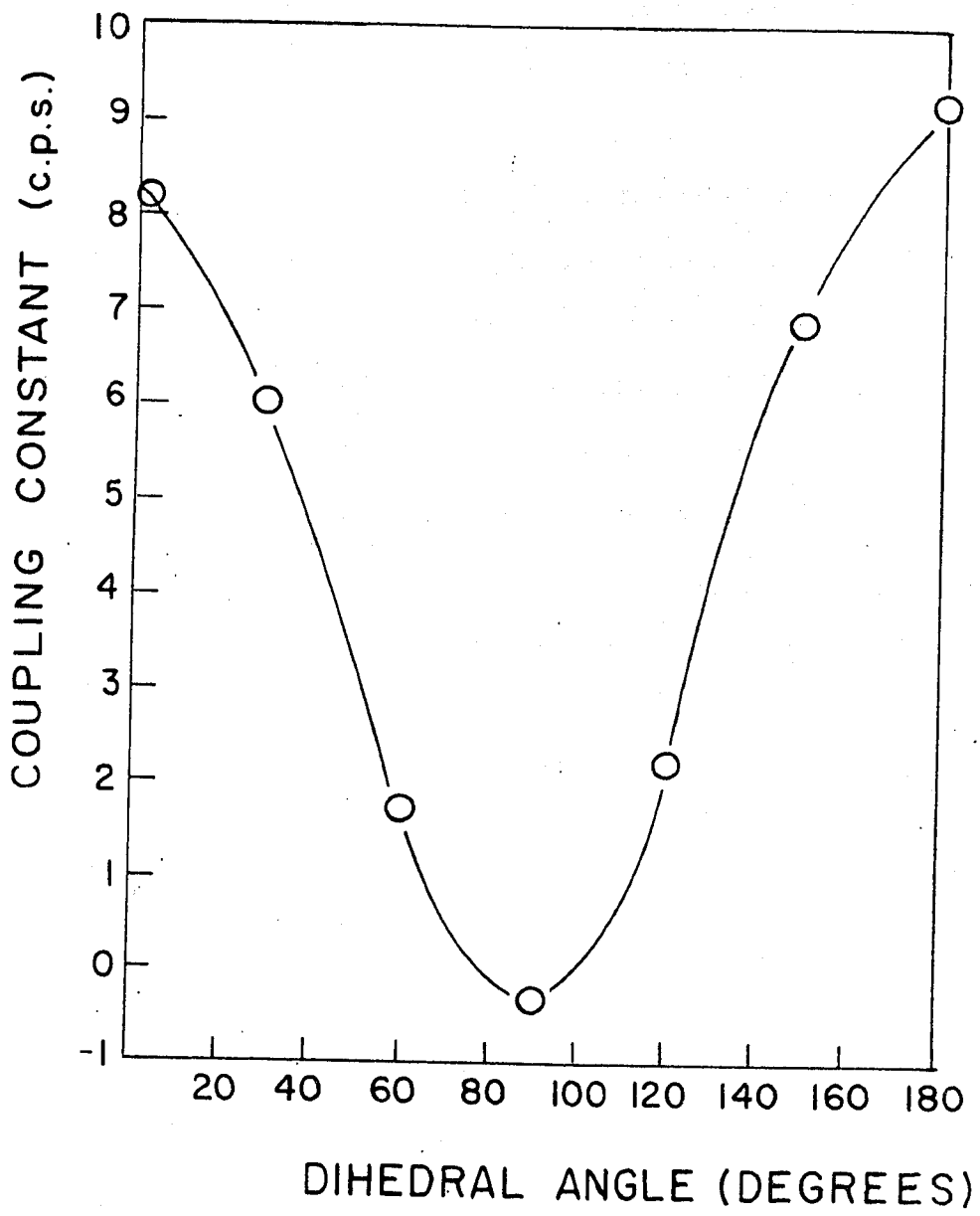


Fig. 1 The Karplus relationship

similar chemical shift and, in most cases, produces complex spectra. This difficulty has restricted the application of this method to molecules like sugar derivatives which contain relatively fewer and, often, well chemically shifted protons in the ring.

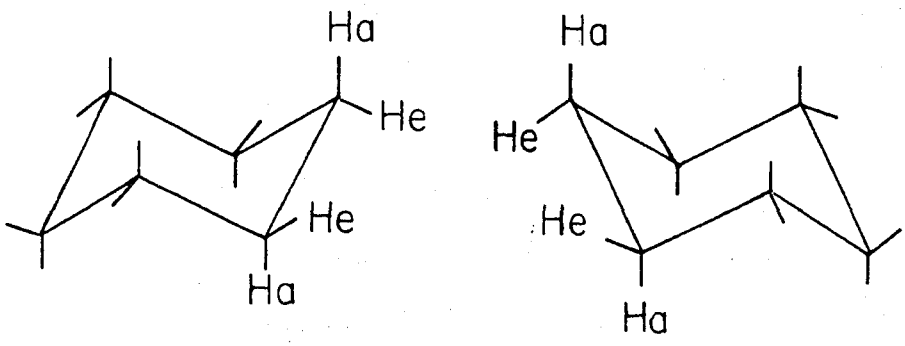
Two approaches have been utilized for the determination of conformational equilibria of substituted cyclohexane systems from a knowledge of chemical shift data. One of them is based on the determination of the average chemical shift of 1-H (proton attached to the carbon bearing the substituent), which in most cases is chemically shifted from the rest of the protons in the ring, from the spectrum of the compound at room temperature and relating it to the axial and equatorial proton chemical shifts obtained from related molecules with locked conformations. The other method involves the direct measurement of chemical shifts for axial and equatorial protons from spectra of frozen conformations. This method rests on the fact that lowering of temperature slows the rate of interconversion between conformers and that the mean life times of each conformer becomes sufficiently large to be detected by N.M.R. spectroscopy. In some cases, the relative peak areas for axial and equatorial protons available from low temperature spectra have been used to determine conformational equilibria. The parent compound, cyclohexane has also been subjected to low temperature investigation.

Methods have been sought to simplify complex spectra in an effort to determine the vicinal coupling constants of organic compounds. The technique of "double irradiation" has been introduced. This involves the removal of undesirable spin-spin interaction amongst nuclei, but unfortunately, is effective only when applied to a nucleus well chemically shifted from its neighbours. The most useful method in this respect is the technique of deuteration. The success of this technique is due to the fact that deuterium is "transparent" in the proton magnetic resonance spectra. Deuterium substitution introduces only small coupling and quadrupole relaxations, both causing broadening of the proton resonance signals, however, these minor effects can be removed by double irradiation at the deuterium resonance frequency. Deuterium does not change the nature of the compounds and also all properties associated with the electronic structure of the parent compound remain essentially unchanged. Suitable deuteration, therefore, can yield a very simple proton magnetic resonance spectrum for a compound otherwise yielding a highly complex one. An early application of this method was the practice of using D_2O as solvent for compounds containing exchangeable protons; the easy replacement of these protons by deuterium simplified the spectra. The difficulties involved in the syntheses of suitable deuterated

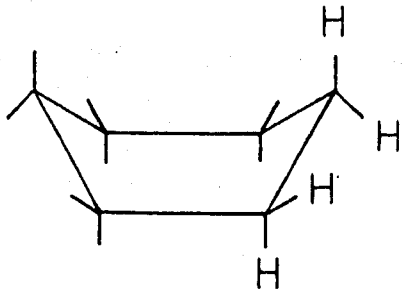
compounds have hindered the applicability of this technique to some extent. Nevertheless, in some cases, it has been possible to synthesize suitable deuterated compounds needed for conformational analysis; examples are discussed in a later section. The work presented in this part of the thesis also points towards the success of this technique.

(1) Ring Inversion in Cyclohexane

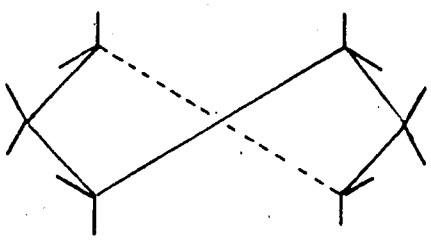
Considerable interest has centered around the conformational analysis of cyclohexane for a long time. Spectroscopic studies as well as thermodynamic data (32) established that the chair conformation for cyclohexane (Fig. 2a, 2a') is favoured over the alternative boat conformation (Fig. 2b). The decreased stability of the boat form was attributed to strong non-bonded interactions of eclipsed hydrogens. Several theoretical and semi-empirical estimates of the magnitude of the energy difference between the two conformations have been reported; however, the approximation and assumption implicit in these calculations have led to values ranging from as low as 1.31 to as high as 10.6 kcal./mole (32). The twist boat (Fig. 2c) is energetically more favoured than the ordinary boat form (Fig. 2b) since the severe non-bonded interactions between the eclipsed hydrogens operating in the latter is no longer present in the former. Recent theoretical calculations by Hendrickson (33) have estimated



2a 2a'



2b



2 c

Fig. 2 Conformations of cyclohexane.

the energy difference between the chair and the ordinary boat form as 6.93 kcal./mole, and that between the chair and the twist boat as 5.33 kcal./mole. The latter value is in good agreement with the values obtained from high temperature equilibration studies on cis- and trans-1,3-di-t-butyl-cyclohexane (34) and Johnson's (35) study on compounds with fused cyclohexane rings.

The chair form of cyclohexane possesses two types of bonds - axial and equatorial. Electron diffraction studies by Hassell and his co-workers (36) revealed the non-equivalence of the two types of bonds. This suggested the possibility of the existence of the chair form in two different chair conformations - the two differing from the fact that the axial bonds in one are equatorial in the other and vice versa (Figs. 2a, 2a'). Studies (32) on substituted cyclohexane systems and on fused six-membered rings provided evidence in this respect. However, the rapid interconversion between the two chair conformations in simple cyclohexane systems has precluded the isolation of separate conformers. The energy barrier involved in the interconversion of cyclohexane from one conformer to the other has been estimated by Shoppee (37) to be 9-10 kcal./mole from considerations of qualitative aspects of energetics, whereas spectroscopic studies led Beckett, Pitzer and Spitzer (38) to suggest a value of 14 kcal./mole

for the process. The most plausible transition state for the ring inversion of cyclohexane is believed (33,39b) to have a conformation which is half-way between that of the chair and the twist-boat (26). Careful theoretical calculations by Hendrickson (33) has shown it to be 12.66 kcal./mole more energetic than the chair form.

Recently the technique of N.M.R. spectroscopy has been employed to measure the rapid interconversion of cyclohexane. At room temperature, the N.M.R. spectrum of cyclohexane consists of a sharp single peak, in accordance with the expected rapid interconversion of the two chair conformers. The interconversion has been slowed down by lowering the temperature and the concomitant changes in the N.M.R. signal have been used to determine the energy barrier of the interconversion.

Jansen et al. (39) found that the single sharp peak for cyclohexane at room temperature (60 Mc/sec.) progressively broadened as the temperature was lowered and, at-70° separated into two peaks. At still lower temperatures, the spectrum showed two unsymmetrical bands, each of them being split into two broad peaks, indicating incompletely resolved spin-spin splittings. Moniz and Dixon (40), Harris and Sheppard (41) observed similar changes in the N.M.R. spectrum of cyclohexane with lowering of temperature in their studies at 40 Mc/sec. and reported the observation of an unsymmetrical broadened quartet at the lowest temperature studied (-77.5°

and -90° respectively).

From the coalescence temperature, T_c, of -66.5°, Jensen and his co-workers (39a) calculated a value of 9.7 kcal./mole for the free energy of activation, $\Delta F^{\neq}$, of the inversion process. The mean life time τ_c of the conformers at the coalescence temperature needed for the calculation of $\Delta F^{\neq}$ was evaluated from the relation $\tau_c = \sqrt{2}/2\pi\delta$, where δ is the chemical shift in c.p.s. Later (39b), they adopted an alternative procedure to determine $\Delta F^{\neq}$. Below coalescence, the peak separation changes most rapidly with temperature in the region of half the maximum separation and therefore they calculated the rate constant at the temperature of half separation (-66.7°) using the appropriate function (42). This method yielded a value of 10.1 ± 0.1 kcal./mole for $\Delta F^{\neq}$, an increase of 0.4 kcal. from the previous one.

Harris and Sheppard (41) questioned the applicability of the expression used by Jensen and his co-workers for the evaluation of τ at the coalescence temperature. They pointed out that the formula is only correct for averaging between two single uncoupled lines, and when the line widths in the absence of exchange are effectively zero. According to them the cyclohexane case approximates better to the averaging of the chemical shift of an AB system (1) with $J/\delta \approx 1/2$, where the correct equation is $\tau_c = 1/\pi\delta$. This change in the expression

for τ at coalescence temperature coupled with the consideration of line widths led Harris and Sheppard to suggest an estimated correction of + 0.5 kcal./mole to Jensen's value of 10.1 kcal./mole for the free energy of activation for the ring inversion of cyclohexane. They also carried out measurements of the rate of broadening of the single peak over the temperature range -20° to -70° at 40 Mc/sec. The values for the mean life times, τ, were determined by the fast exchange approximation method developed by Piette and Anderson (12). The values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were determined from a plot of log τT against 1/T for the appropriate Eyring's equation and were found to be 9.0 ± 0.2 kcal./mole and -7.9 ± 1.0 e.u. respectively. These results yielded a value of 10.6 kcal./mole for $\Delta F^{\neq}$ at -66.5°.

(ii) Ring Inversion in Substituted Cyclohexanes and other Six-membered Rings

Ring inversion studies on perfluorocyclohexane have been carried out by Tiers (43) by observation of the F^{19} resonance as a function of temperature. The free energy of activation, $\Delta F^{\neq}$, for the process has been determined to be 9.9 kcal./mole. The smaller barrier for perfluorocyclohexane compared with cyclohexane (10.1 to 10.6 kcal./mole) has been attributed to steric strain present in the chair form of the fluoro compound. Reeves and Strømme (44) have investigated

the rate of interconversion of the conformers of cyclohexyl chloride and cyclohexyl bromide by observing the changes of 1-H signal with temperature, and have estimated a value of 10.85 kcal./mole for the free energy of activation of the ring inversion processes involved. They have carried out (45) similar studies on 1,2-trans-dibromo- and 1,2-trans-dichloro-cyclohexanes. Calvin and his co-workers (46) have reported rate studies on the proton resonance of [4,5-d_4]-1,2-dithiane. Ring inversion studies on substituted 1,2-dithiane and 1,2-dioxane (47) have also been carried out by these investigators. Lüttringhaus et al. (48) have studied the rate of interconversion of the conformers of 4,5-cis-diacetoxy-1,2-dithiane and have estimated the free energy of activation to be 13.9 kcal./mole. Reeves and Strømme (49) have reported a $\Delta F^{\neq}$ value of 13.3 ± 0.3 kcal./mole for the ring inversion process in N,N'-dimethyl-piperazine. Recently, Roberts (50) has observed a very clear coalescence pattern in the F^{19} resonance spectrum of 1,1-di-fluorocyclohexane and has estimated the activation energy E_a for inversion of the ring to be 12 kcal./mole. Neikam and Dailey (51) have investigated the N.M.R. spectra of 1-H of several cyclohexyl derivatives at low temperatures and have calculated the activation energy for the ring inversion processes of chloro-, bromo-, iodo-cyclohexane and cyclohexanol to be about 11.7 kcal./mole.

(iii) Conformational Studies on Substituted Cyclohexane Systems

Eliel (52) determined the conformational equilibrium between axial and equatorial cyclohexyl bromide from the chemical shift of the proton attached to the carbon atom bearing the substituent group, henceforth designated as 1-H. The true chemical shifts for axial and equatorial 1-H were determined from the spectra of related compounds with locked conformations, e.g. trans- and cis-4-t-butyl cyclohexyl bromide respectively, and were related to the averaged chemical shift for 1-H furnished by cyclohexyl bromide in order to evaluate the conformational equilibrium. Reeves and Strømme (44) studied the low temperature N.M.R. spectra of cyclohexyl bromide and cyclohexyl chloride to determine the true chemical shift for axial and equatorial 1-H directly. They calculated the populations of conformers at different temperatures from the relative peak areas of the two conformers at low temperature and found that in both compounds the equatorial conformer of the halogen atom was favoured to some extent. Similar conformational studies on 1,2-trans-dibromo- and 1,2-trans-dichloro-cyclohexane have also been accomplished (45). More recently Eliel and Thill (53) investigated the conformational equilibrium of cyclohexyl mercaptan. A comparison of the chemical shifts of 1-H in cis- and trans-4-t-butylcyclohexyl-

mercaptan with the corresponding shift in cyclohexyl mercaptan showed that an equatorial sulfydryl group is more favoured than an axial one, contrary to the reports of Chiurdoglu et al. (54) made from infrared studies.

The signals for axial and equatorial 1-H of mono-substituted cyclohexanes at low temperatures are rather complex and broad. If the relative chemical shift between axial and equatorial 1-H is not large enough, the signals for the two conformers may overlap, and this makes conformational study difficult or impossible. Such is the case with cyclohexyl acetate. Anet (55) has used the technique of selective deuteration to overcome such difficulty. He synthesized 3,3,4,4,5,5-hexadeuteriocyclohexanol and its acetate; both of them yielded well-resolved $(AB)_2X$ patterns, slightly broadened in the AB part by coupling with deuterium. The X part of the $(AB)_2X$ pattern arose from resonance signal of 1-H and its interaction with other protons. Analyses by coupling constants were carried out. Cis- and trans-3,3,4,5,5-pentadeuterio-4-t-butyl cyclohexanol furnished models for the "pure" axial and equatorial hydroxyl conformers. Coupling constants in these compounds were much as expected from the Karplus relationship; these were related to the coupling constants in the simple alcohol to yield an estimate of the proportion of conformers. At low temperatures the 1-H of the acetate showed distinct signals for the two conformers; the coupling

constants obtained were related to the coupling constants supplied by the spectrum at room temperature to estimate the conformational equilibrium. Analysis of the acetate peak for conformational study of the acetate appears feasible since at low temperatures the acetate peak should separate into axial and equatorial components. Results on an analogous system have been reported (56). Selective deuteration technique has been utilized by Premuzic and Reeves (57) in their conformational studies on 1,2-trans-chloroiodocyclohexane.

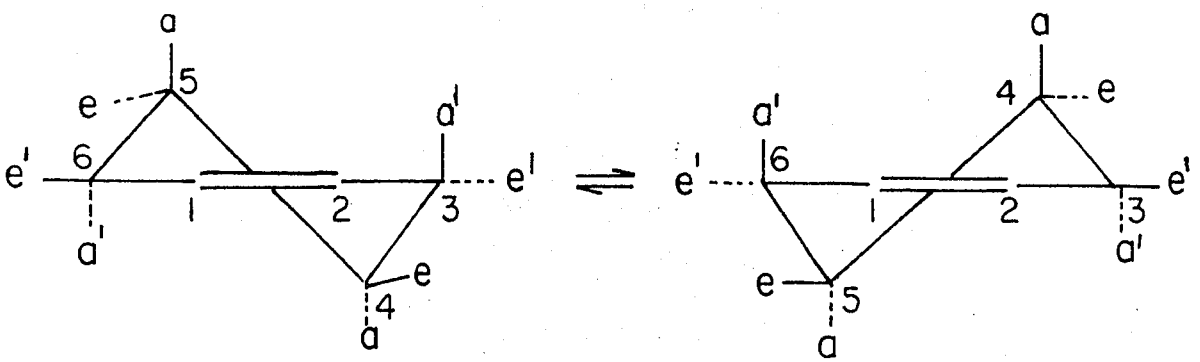
Lewin and Winstein (58) have introduced selective deuteration of a different nature. This involves deuteration of the adjacent positions of 1-H and thus strong coupling effects on its resonance signal are removed. In a series of cis- and trans-2,2,6,6-tetradeuterio-4-alkylcyclohexanols, the 1-H signal appeared as a sharp singlet. The chemical shift of this 1-H signal was then related to 1-H chemical shift data supplied by the cis- and trans-4-t-butyl model compounds in the estimation of the conformational equilibria in the series. More recently Reeves and his co-workers (59) have employed this method of adjacent deuteration in their low temperature studies on some cyclohexyl esters.

The application of N.M.R. spectroscopy in the conformational analysis of alkylcyclohexanes has not met with much success as yet. Methylcyclohexane (60) and several

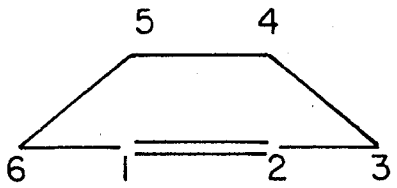
dimethylcyclohexanes (40,41,60) have failed to exhibit any appreciable change in their spectra with the lowering of temperature. This has been attributed to similar chemical shifts for 1-H and the other protons on the ring or/and to the rapid interconversion of the conformers even at low temperatures. However, Muller and Tosch (60) have reported the N.M.R. spectra of 1,1-, cis-1,2-, trans-1,3-, and cis-1,4-dimethylcyclohexane, and cis-decalin at 60 Mc/sec. to be temperature dependent as expected if ring inversion processes are involved in these compounds. The N.M.R. spectra of some of these compounds failed to show any temperature dependence when studied at 40 Mc/sec. (40,41). Recently Neikam and Dailey (51) have determined the conformational equilibrium of cyclohexanol from their low temperature N.M.R. spectra.

Conformation of Cyclohexene and Substituted Cyclohexenes

Theoretical calculations by Beckett, Freeman and Pitzer (61) have shown that the "half-chair" conformation (Fig. 3a, 3a') for cyclohexene is favoured by about 2.7 kcal./mole over the alternative 'half-boat' conformation (Fig. 3b). This geometry has been confirmed in the case of certain substituted cyclohexenes by X-ray and electron diffraction studies (62). The bonds of C-3 and C-6 are designated as 'quasi-equatorial' (e') and 'quasi-axial' (a') positions, as



3a 3a'



3b

Fig. 3 Conformations of cyclohexene.

shown. The bonds of C-4 and C-5 are almost normal equatorial and axial. The 'half-chair' conformations are expected to undergo rapid interconversion (3a $\rightleftharpoons$ 3a') like cyclohexane unless suitably locked into one conformation. Several 3:4-, 3:5- and 3:6-disubstituted cyclohexenes have been reported (63) to favour the diequatorial conformation. Sakashita has concluded recently (64) from infrared and Raman spectra that axial-3-halo- and axial-4-halo-cyclohexenes are more stable in the liquid state than their equatorial counterparts. Garbisch (65) has employed the technique of N.M.R. spectroscopy to determine the preferred conformations of C-6 substituents in a number of 6-substituted 1-phenyl (and methyl) cyclohexenes. No work in the literature is available as regards quantitative studies on conformational equilibria of substituted cyclohexenes.

Hindered Internal Rotation

The success of N.M.R. spectroscopy in the field of rotational isomerism has been due to the fact that the phenomenon mostly involves the reorientation of a particular atom or a group of atoms between two chemically shifted sites. In some cases, the spin-spin splitting data have contributed to the studies of rotational isomerism. When the energy barrier of internal rotation is very high, the rotamers are expected to be isolable. The cis- and trans-isomers of the olefinic compounds are examples of this type. In other cases,

where isolation is not possible, N.M.R. spectroscopy can be used for their detection as the nature of the N.M.R. spectra depends on the relative life times of the rotamers. The situation is the same as discussed in connection with the ring inversion studies on cyclohexane compounds. The role of restricted rotation has been observed in compounds where rotational isomerism is possible, due to (i) restricted rotation about a single bond, (ii) restricted inversion at nitrogen atom, and (iii) partial double bond character.

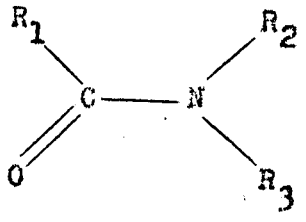
We have observed the phenomenon of restricted rotation in some aromatic aldehydes which falls into the third category. As such only a brief reference will be made to the first two types and a more detailed discussion of the third will be presented here.

The general types of spectra that may be expected in cases of fast and slow rotation in a variety of substituted ethanes have been discussed by Pople and others (66,67,68). The interconversion of the rotational isomers in saturated compounds is very rapid and the barrier is very small, and, consequently, the N.M.R. spectra of the compounds are essentially a weighted average of all the conformers. However, in favourable cases, the rates of rotation around a C-C bond has been found to be slow enough to allow the detection of the rotamers. The nonequivalence of the geminal fluorine atoms in compounds of the type $CF_2R-CFR'R''$ (69), and the temperature

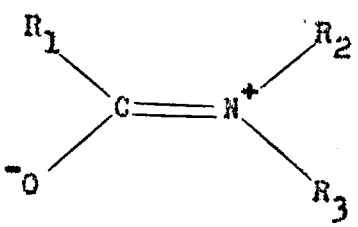
dependence of the F^{19} spectra of 1,1-difluoro-1,2-dibromo-2,2-dichloroethane (70), $CF_2Br\text{-}CBr_2\emptyset$ (70), $CF_2Br\text{-}CBr_2CN$ (71), $CFCl_2\text{-}CFCl_2$ (50) have been reported. The observations have been interpreted on the basis of restricted rotation about C-C bond. In a few cases isomer abundance ratios of substituted ethanes have been determined (67).

The temperature dependence of the N.M.R. spectra of N-ethylethylenimine (72) and N-ethylallenimine (72) has led to the detection of restricted inversion at nitrogen atom.

The existence of rotational isomers due to partial double bond character has been observed in quite a few types of compounds. Both qualitative and quantitative studies have been made on some of them. The first observation of this kind of restricted rotation was made in the amides. The principle of resonance led Pauling (73) to believe that in amides, there is a significant contribution of



I



II

resonance structure II, with a nitrogen-carbon double bond rather than a single bond. The structure II resembles that

of olefinic compounds and it would tend to bring the atoms attached to carbon and nitrogen in one plane. The contribution of resonance structure II would increase the energy barrier to the rotation about C-N bond and therefore would oppose the free rotation as expected from I. In structure II, the groups R_2 and R_3 are in different electronic environments, the former being <u>trans</u> and the latter <u>cis</u> to the oxygen atom respectively. This would cause R_2 and R_3 to experience different local magnetic fields and, hence, induce a chemical shift between them. This is contrary to the expectation from structure I where free rotation around C-N bond tends to make R_2 and R_3 magnetically equivalent. It is obvious, therefore, that the N.M.R. spectrum of an amide would depend on the relative contributions of the two structures.

The first compound studied in this aspect was <u>N</u>,<u>N</u>-dimethylformamide (R_1 = H, R_2 = R_3 = CH_3 in I and II). Philips (74) reported the qualitative results and later Gutowsky et al. (75) and Woodbrey and Rogers (76) carried out extensive studies on it. At room temperature, the compound exhibited a single line for the C-H proton but a chemically shifted doublet for the protons of the N-CH_3 groups. That this doublet was due to a chemical shift between the two nonequivalent N-CH_3 groups and not due to coupling with the formyl proton was evident from the fact that the resonance

signal for the latter was unsplit. Furthermore, the separation between the doublet was shown to be field dependent, the separation being 10 c.p.s. at 40 Mc. and dropping to 7 c.p.s. at 30 Mc., whereas the separation due to coupling would have been field independent. This observation could only be explained if a significant contribution of structure II to the resonance hybrid of the amide is possible. The spectrum of N,N-dimethylformamide was found to be temperature-dependent. At higher temperatures the rate of reorientation around C-N bond increases, and the separation between the doublet decreases until at a sufficiently high temperature the doublet coalesces to give a single line. Similar results have been obtained with other substituted amides, the complexity of spectra has sometimes been reduced by suitable isotopic substitution, such as the use of ^{15}N to eliminate quadrupole broadening of proton resonances in formamide (77). The changes in N.M.R. signal shapes with temperature have been used to determine the thermodynamic data involved with the rotation about C-N bond by various people; however, there are considerable discrepancies among the reported values. The values found for ΔE, the energy barrier to hindered internal rotation, vary from one amide to the other; Woodbrey and Rogers (76) have tried to explain this variation on the basis of the influence of the

substituents. Structure II suggests its possible stabilization in polar solvents and the dependence of energy barrier to internal rotation on the nature and concentration of the solvent when solutions are studied. This has been found to be true by Woodbrey and Rogers (78) in their studies on N,N'-dimethylpropionamide and N,N'-dimethylcarbamylchloride in different solvents at varied concentration. Table I lists some of the available data from internal rotation studies on the amides.

Our observations of restricted rotation in aromatic aldehydes are analogous to those of the amides. Recently Martin and Martin (80) have observed similar phenomenon in ethylenic aminoaldehydes. The $N-CH_3$ groups of $(CH_3)_2N-CH=CH-CHO$ were found to give rise to a chemically shifted doublet at 24° which broadened at higher temperatures and coalesced to give a single peak at about 30°. However, the following compounds

$(CH_3)_2N-\overset{*}{C}H=CH-CH=CH-CHO$

$(CH_3)_2N-\overset{*}{C}H=C(CH_3)-CHO$

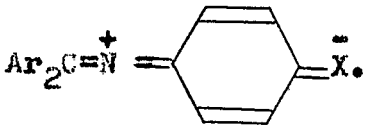
did not show similar trend in their N.M.R. spectra. Obviously, the rotation about the $\overset{*}{C}-N$ bond is sufficiently fast to make the $N-CH_3$ groups equivalent. Studies at low temperatures may indicate the nonequivalence of the $N-CH_3$ groups, no such experiments, however, have been reported by Martin and Martin.

Table I

Hindered Internal Rotation

Compound	ΔE kcal./mole	$\Delta F^{\neq}$ kcal./mole	Solvent	Ref.
N,N'-dimethylformamide	9.6 ± 1.5	-	Pure	(79)
	7 ± 3	22(99°)	Pure	(75)
	18.3 ± 0.7	21.0(25°)	-	(76)
N,N'-dimethylacetamide	12 ± 2	19(52°)	Pure	(75)
	10.6 ± 0.8	17.4(25°)		(76)
N,N'-dimethylpropionamide	6 to 10	16.7(25°)	Varying concns.	(78)
N,N'-dimethylcarbamylchloride	6 to 9	16.5(25°)	"	(78)
Formamide	18 ± 3	....	acetone	(77)
N,N'-dibenzylacetamide	7.3 ± 0.5	16.5(25°)	CH_2Br_2	(78)
	6.4 ± 0.6	16.7 (25°)	CCl_4	(78)

N.M.R. spectroscopic studies have also led to the detection of structural isomerism due to partial double bond in compounds like alkyl nitrites (81), aldoximes (81) and nitrosoamines (81). Recently (82) N.M.R. studies on a few N-phenylimines have led Curtin and McCarty to believe that isomerizations of these compounds are retarded due to contribution of resonance structures of the type



EXPERIMENTAL

Cyclohexane-d_{11} (minimum isotopic purity 98%) used for the investigation of the inversion of cyclohexane ring was purchased from Merck Sharp and Dohme of Canada Ltd. Julolidine needed for the preparation of 9-julolidine-carboxaldehyde was available from a previous investigation. Other chemicals used for the synthesis of the compounds described in this part of the thesis were commercially available. The purity of the compounds was checked by vapour phase chromatography (V.P.C.). The infrared spectra were measured on a Perkin Elmer "Infracord" double beam instrument.

All proton magnetic resonance spectra were obtained on a Varian V-4302 60 Mc/sec. high-resolution N.M.R. spectrometer. Tetramethylsilane (T.M.S.) was used as an internal standard and calibration for chemical shifts was carried out by the usual side-band modulation technique. Double irradiation at the deuterium resonance frequency was carried out by means of a spin decoupler manufactured by N.M.R. Specialties.

A temperature controlling device similar to that described by Shoolery and Roberts (83) was employed to carry put low temperature studies. An electric current was passed through a heating element in a large Dewar filled with liquid nitrogen, and the evolved cold nitrogen gas was

directed through a jacket around the spinning sample tube. The temperature desired for the sample was attained by adjusting the current in the heating element. A copper-constantan thermocouple, checked at the sublimation point of Dry Ice (-78.51°C) and found to be correct within 1°C, was placed inside the jacket and the temperature was monitored with a potentiometer calibrated from 0 to 5.0 mv. Corrections for the difference between the monitored temperature and the true sample temperature were determined by inserting a second thermocouple directly in the solution contained in the sample tube.

The spectra for cyclohexane-d_{11} were recorded on five different days. Sample heights of 3 cm. and 5 cm. in the sample tube, with the sample tube at the bottom and 1/4" raised in the probe insert respectively were used. Temperature corrections with the thermocouple 1/2" from the bottom of the sample tube in the first case and 1/4" in the latter case were made as the receiver coil is approximately 1/2" above the probe insert. Temperature corrections equivalent to 0.396 mv in the former case and 0.221 mv in the latter case were necessary. At each temperature several spectra were measured, half being recorded with increasing and half with decreasing linear sweep fields and a mean value of spectral data was used for calculation. The spectra were recorded at the best possible resolution of the spectrometer

and the field homogeneity was repeatedly adjusted by observing the decay of the wiggles on a rapid passage for the resonance signal of T.M.S. present in the sample solution. Rate calculations were made both above and below the coalescence point using the appropriate analytical solutions.

Synthesis

p-N,N-dimethylamino-3,3'-d_2-benzaldehyde

p-N,N-dimethylaminobenzaldehyde was first converted to its hydrochloride by adding dilute hydrochloric acid (1%) to an alcoholic solution of the aldehyde (0.5 g) until the solution became strongly acidic. The contents were then evaporated to dryness and the crystalline hydrochloride was obtained. The hydrochloride was dissolved in deuterium oxide (5 ml) and the solution was refluxed for 24 hours. On cooling, the hydrochloride crystallized out. The contents were then made basic with a solution of sodium hydroxide (20%) and the free organic base was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and the solvent was removed at reduced pressure. The yellow product obtained was purified by sublimation at 42° at 0.05 mm. pressure. The light grey compound was used for N.M.R. Studies.

9-Julolidinecarboxaldehyde

9-Julolidinecarboxaldehyde was prepared from julolidine following the method employed by Smith and Yu (84) for the synthesis of this compound. The method involved the introduction of a formyl group in the aromatic nucleus of julolidine according to the method of Vilsmeier and Haack (85).

Julolidine (205 mg) dissolved in a small amount of ether was added dropwise to a mixture of N-methylformanilide (240 mg) and phosphorous oxychloride (28 mg) cooled in an ice-bath. After standing overnight, the mixture was decomposed with water, made alkaline, and steam distilled to remove N-methylaniline. On cooling, the aldehyde crystallized in the distilling flask and was collected and recrystallized from aqueous ethanol, m.p. 81-82° (reported m.p. 83°). The infrared spectrum of the compound in Nujol mull exhibited a strong band at 1650 cm^{-1} indicating the presence of a conjugated carbonyl group.

Hexadeuterio-1,3-butadiene (butadiene-d_6) (86)

A freshly prepared mixture of sodium iodide (2.3 g) and cupric chloride (10.9 g, crystallized from deuterium oxide to exchange the water of hydration) in deuterium oxide (80 ml, 99.7%) was added to a mixture of zinc dust (240 g, Fisher) and dry dioxane (245 ml) contained in a two-liter

three-necked flask. The flask was equipped with a mechanical stirrer, a reflux condenser and an inlet for dry nitrogen gas. The reflux condenser was in turn connected to an air cooled trap and the latter to two Dry Ice-acetone cooled traps which served as receivers for the gaseous reaction products. Nitrogen was passed through the system, the mixture was stirred and heated to mild reflux. The nitrogen inlet was then replaced with a dropping funnel containing hexachloro-1,3-butadiene (130 ml, Eastman, practical grade) dissolved in dry dioxane (75 ml). Heating was discontinued and hexachlorobutadiene was added at a rate such that a steady reflux was maintained. After the addition of hexachlorobutadiene was complete (3 hrs. 30 min) nitrogen was flushed through the system for half an hour to ensure complete removal of the gaseous reaction products from the reaction vessel. Most of the product collected in the first Dry-Ice-acetone cooled trap as a clear, colourless liquid (15 ml at $\sim -70^{\circ}$). This was directly used for the synthesis of the deuterated compounds.

Δ^3-Tetrahydrobenzaldehyde-2,2,3,4,5,5-d_6 (cf 87)

A mixture of freshly distilled acrolein (5 g), butadiene-d_6 (4.5 ml), and hydroquinone (10 mg) was heated in a sealed tube for a period of 2 hrs. at 102-106°. A heavy yellow liquid was obtained and the unreacted acrolein,

as well as the impurities present in butadiene-d_6 were removed at reduced pressure. Distillation at 20 mm. pressure yielded a faintly yellow liquid (2.8 g) at 65.5° to 66.5°. A gummy residue was left in the distilling flask which most probably was a mixture of polymer and hydroquinone.

The infrared spectrum of the compound (liquid film) had strong absorptionsat 2090, 2150, 2190, and 2275 cm^{-1} indicating the presence of both -C-D and =C-D in the molecule. The infrared spectrum also exhibited absorptions for aldehydic -C-H (band at 2715 cm^{-1}) and carbonyl group (band at 1705 cm^{-1}). A V.P.C. analysis on the compound was carried out on a Perkin Elmer Vapor Fractometer with a Versamid column operating at 140° which indicated a single component.

Δ^3-Tetrahydrobenzoic Acid-2,2,3,4,5,5-d_6

The acid was prepared by the oxidation of the corresponding aldehyde made earlier from acrolein and butadiene-d_6. To a stirred slurry of silver oxide prepared from silver nitrate (7 g) in water (15 ml) and sodium hydroxide (3.4 g) in water (15 ml) was added Δ^3-tetrahydrobenzaldehyde-2,2,3,4,5,5-d_6 (1 g) in small portions. The addition was completed in 15 min. and the characteristic odour of aldehyde disappeared after 20 min. indicating the completion of oxidation. The precipitated silver was removed by filtration and washed with water. The aqueous alkaline filtrate was washed with

ether, made acidic with concentrated hydrochloric acid, and the free organic acid was extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and a very viscous liquid was obtained on removal of ether at reduced pressure. The liquid crystallized in the refrigerator. Yield 1.1 g. The infrared spectrum of the compound (liquid film) exhibited broad peak for hydroxyl group characteristic of carboxylic acids and a strong carbonyl band at 1690 cm^{-1}. The bands at 2090, 2150, 2190, and 2275 cm^{-1} present in the aldehyde were retained in the acid.

Δ^3-Tetrahydrobenzonitrile-2,2,3,4,5,5-d_6 (cf 88)

A mixture of freshly distilled acrylonitrile (3.4 ml), butadiene-d_6 (5 ml), hydroquinone (10 mg) in toluene (6 ml) was heated in a sealed tube for a period of 12 hrs. at 131-137°. This yielded a heavy deep brown liquid. Unreacted acrylonitrile and most of the toluene were removed by distillation at atmospheric pressure. The rest of the liquid was distilled at reduced pressure and a colourless liquid (2.8 g) distilled over at 76-77° at 10 mm. pressure. The infrared spectrum of the liquid showed five intense bands in the region between 2090-2280 cm^{-1}, the strongest one at 2250 cm^{-1} could be assigned to the C≡N and the rest to -C-D and =C-D stretchings. The spectrum also exhibited absorption above 3000 cm^{-1}, at 1600 cm^{-1}, and 1500 cm^{-1} and very intense bands at 732 cm^{-1}

and 695 cm^{-1} and thus indicated the presence of toluene. A V.P.C. analysis on the liquid on a Pye Argon chromatograph with an Apiezon column at 132° also revealed the presence of toluene. The liquid was then subjected to bulb to bulb distillation at reduced pressure and the liquid fraction coming last was found to be free from toluene by infrared as well as by V.P.C. This was used for N.M.R. studies.

Δ^3-Tetrahydroacetophenone-2,2,3,4,5,5-d_6 (cf 89)

A mixture of methyl vinyl ketone (5 ml), butadiene-d_6 (3.5 ml), and hydroquinone (10 mg) was pyrolyzed in a sealed tube for 10 hrs. 15 min. at 139-145°. A deep yellow liquid was obtained and this was subjected to distillation at reduced pressure. A colourless liquid (1.7 g) distilled over at 68° at 20 mm. pressure. The infrared spectrum of the product (liquid film) showed four bands in the region between 2090 to 2270 cm^{-1} for -C-D and =C-D stretchings; a strong band at 1700 cm^{-1} indicated the presence of carbonyl group in the compound. A V.P.C. analysis of the compound on Perkin Elmer Vapor Fractometer with a Versamid column operating at 174° showed a huge peak for the ketone and a very small peak with a lower retention time.

Hexahydroacetophenone-2,2,3,3,4,4,5,5-d_8

The addition of deuterium gas to Δ^3-tetrahydroacetophenone-2,2,3,4,5,5-d_6 (1 g) in ethanol was carried out at atmospheric pressure in the presence of Adam's catalyst (50 mg). The required amount of deuterium gas was taken up in 15 min. The catalyst was removed by filtration and ethanol was removed at reduced pressure. The infrared spectrum of the compound showed only two bands in 2090-2270 cm^{-1} region, showing the loss of two bands responsible for =C-D present in the unsaturated compound. It also exhibited a strong carbonyl absorption at 1700 cm^{-1}. The yield of hexahydroacetophenone was quantitative. A V.P.C. analysis on the compound on Perkin Elmer Vapor Fractometer with a Versamid column at 112° showed two little humps one on each side of the huge peak for the saturated ketone.

Cyclohexyl acetate-2,2,3,3,4,4,5,5-d_8

The acetate was prepared from the corresponding ketone hexahydroacetophenone-2,2,3,3,4,4,5,5-d_8 by Baeyer-Villiger oxidation. The procedure of Sauers (90) for the Baeyer-Villiger oxidation of camphor was applied. Hexahydroacetophenone-d_8 (425 mg) was dissolved in acetic acid (2 ml) containing sodium acetate (170 mg). To this mixture, peracetic acid (2.1 ml 40%) was added dropwise. After standing for five days at room temperature in the dark, the mixture

was neutralized by pouring into 20% aqueous sodium carbonate solution. The aqueous solution was then extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and ether was removed at reduced pressure. A colourless liquid with the characteristic fruity odor of an ester was obtained. The compound was then purified by bulb to bulb distillation at reduced pressure. Yield 200 mg. A V.P.C. analysis of the compound on Perkin-Elmer Vapor Fractometer with a Versamid column at 111° showed only one peak. The infrared spectrum of the compound showed two bands in 2090-2270 cm^{-1} region (-C-D), a carbonyl band at 1720 cm^{-1}, and a strong band at 1240 cm^{-1} (-OAc).

RESULTS

Inversion of the Cyclohexane Ring

The N.M.R. spectrum of cyclohexane-d_{11} in carbon disulfide solution (25%) was studied over a wide range of low temperatures -32° to -94° in order to follow the kinetics of the inversion of cyclohexane ring. At room temperature cyclohexane-d_{11} showed only one fairly broad peak which became very sharp on applying double irradiation at the deuterium resonance frequency of about 9.2 Mc/sec. (Fig. 4). The peak appeared at 8.64 τ . All spectra were recorded in the presence of deuterium decoupling frequency unless specifically mentioned. As the temperature was lowered, the sharp peak progressively broadened and ultimately at appreciably low temperature separated into a symmetrical doublet. The temperature at which the transition from the singlet to the doublet takes place on lowering the temperature will be referred to as the coalescence temperature. The signal shape for cyclohexane-d_{11} is very sensitive near the coalescence temperature and it is quite difficult to determine the coalescence temperature accurately. No attempt was made to determine the coalescence temperature from the change in signal shapes. Several signal shapes exhibited by cyclohexane-d_{11} around the coalescence point are shown in Fig. 5.

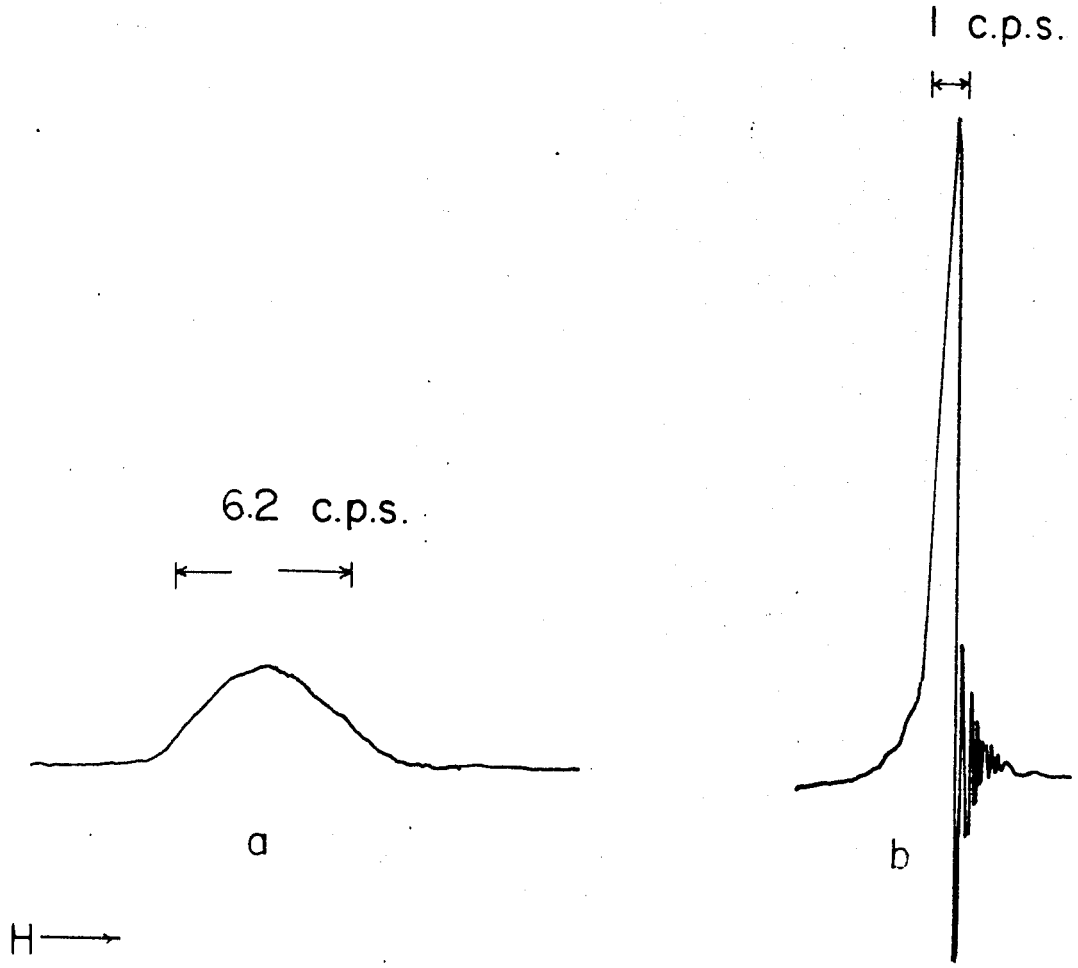


Fig. 4 Cyclohexane–d_{11} at room temperature

a) Without deuterium decoupling

b) With deuterium decoupling

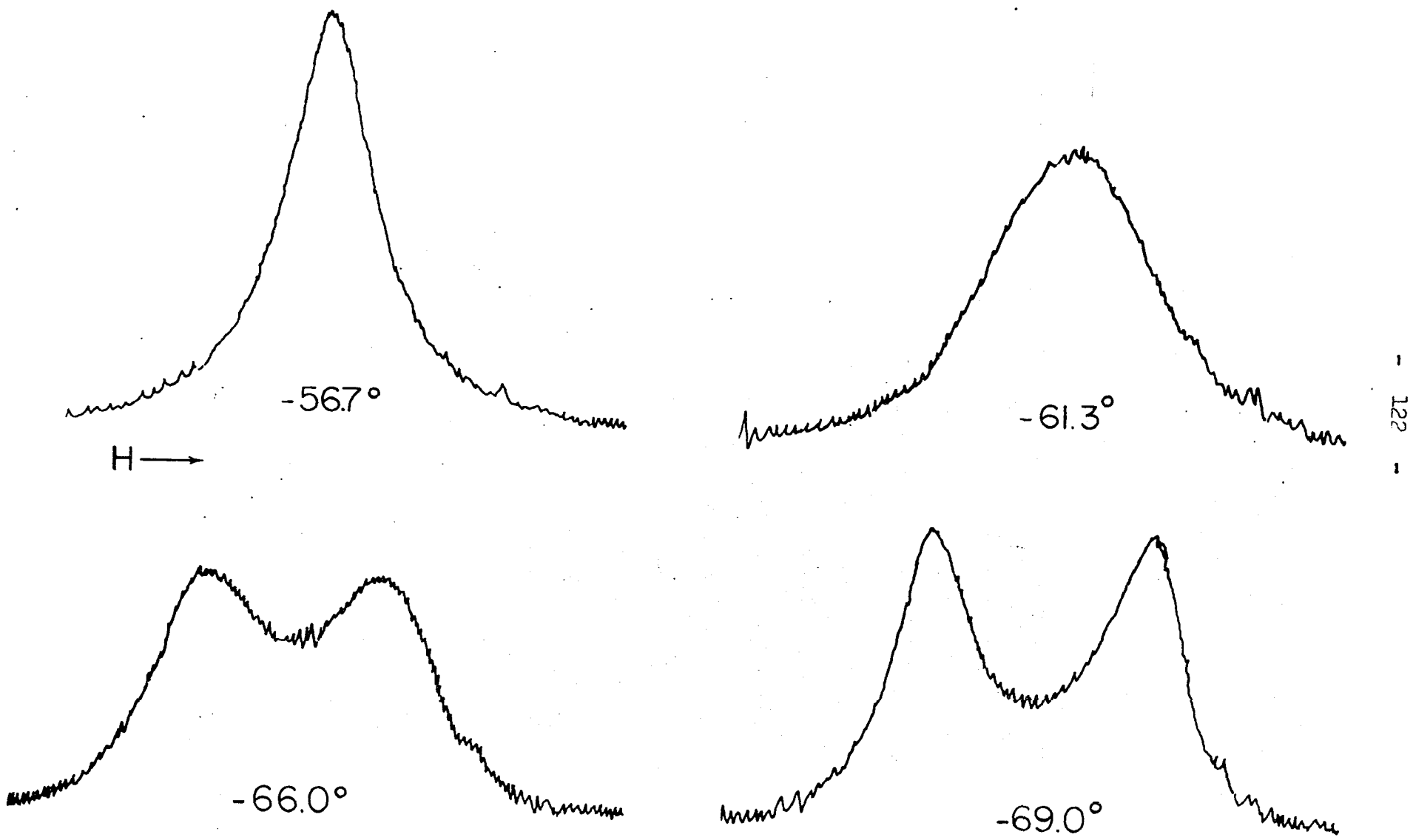


Fig. 5 Changes in the signal shape of cyclohexane-d_{11} near the c scence point

The changes in the N.M.R. signals corresponded to the simplest exchange process between two chemically shifted sites with equal populations and life time, and with no spin-spin coupling. The separation between the doublet increased on lowering of the temperature below the coalescence point and was accompanied by a sharpening of the peaks. The separation between the peaks i.e., the relative chemical shift, approached a constant value at appreciably lower temperatures. At six different temperatures, between -74.77 to -82.87°, the value for the apparent chemical shift ranged between 28.7 ± 0.1 c.p.s., the value of 28.7 c.p.s. was accepted as the true chemical shift between the doublet and was used in the calculations whenever necessary. Fig. 6 shows the doublet at a few low temperatures.

The high field signal of the doublet was assigned to the conformation with axial proton and the low field one to the conformation with the proton in the equatorial position in accordance with other (28) axial and equatorial assignments. Further evidence came from the spectrum at low temperature recorded in the absence of the deuterium decoupling frequency when the high field signal (band width at half height of the peak, 7.9 c.p.s.) appeared to be significantly broader than the low field one (band width at half height of the peak, 5.5 c.p.s.) (Fig. 6d). This is consistent with the observations

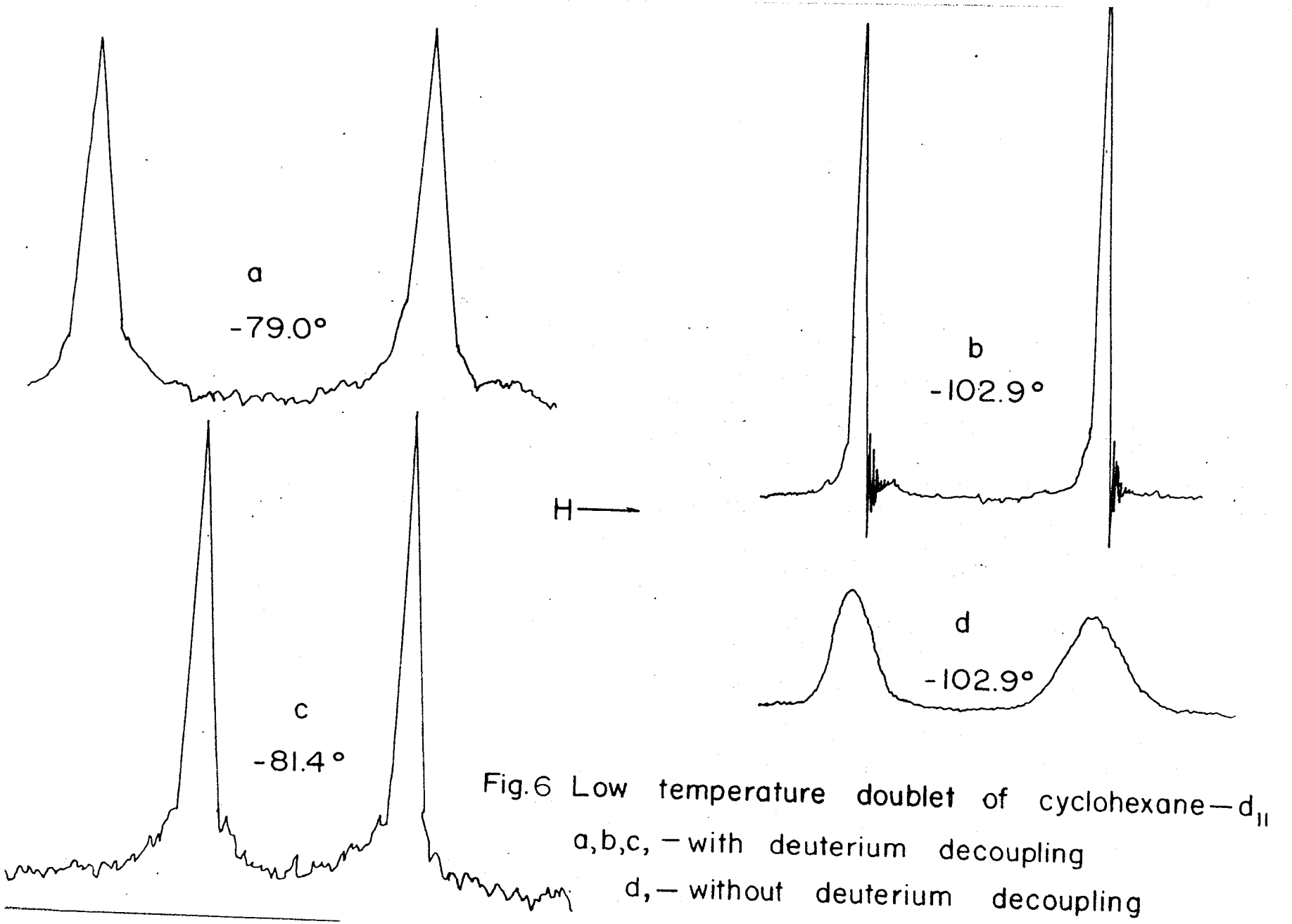


Fig.6 Low temperature doublet of cyclohexane—d_{11}

a,b,c, — with deuterium decoupling

d, — without deuterium decoupling

that axial-axial coupling constants are larger than equatorial-axial or equatorial-equatorial coupling constants (91).

Rate Calculations Below Coalescence Temperature

The line shape equation, equation (10-14) of reference (1), has been derived for two exchanging nuclei. Gutowsky and Holm (75) have modified this expression for calculating τ, the mean life time of a proton at each site, from separation of peak maxima near coalescence. The relevant equation, assuming negligible dipole-dipole broadening, equal population and equal mean life time at the two sites, is

$$\tau = \left[\frac{1}{2\pi^2 \nu_{AB}^2 \left[1 - \left(\frac{\nu e}{\nu_{AB}}\right)^2\right]}\right]^{1/2} \qquad [1]$$

in which

νe (c.p.s.) is the observed peak separation,

ν_{AB} (c.p.s.) is the peak separation at slow exchange (i.e., the true chemical shift), 28.7 c.p.s.

2τ is the life time of a proton on either site in the molecule.

Below coalescence temperature, rates were calculated by using this equation and the results are summarized in Table II.

Another method for determining τ below coalescence was used. Grunwald, Loewenstein, and Meiboom (13), and

Table II

Cyclohexane-d_{11} Ring Inversion Rates from Separation of Maxima

mv reading	corrected mv reading	T (°C)	$10^3/T°K$	ve c.p.s.	Rate $(\frac{1}{2\tau})$ sec^{-1}	$\log \frac{1}{2\tau}$	Number of spectra measured
-2.778	-2.557	-73.23	5.002	27.87	15.214	1.182	5
-2.648	-2.427	-68.98	4.898	25.93	27.314	1.436	5
-2.553	-2.332	-65.98	4.827	20.93	43.602	1.640	5
-2.940	-2.544	-72.81	4.991	28.22	11.840	1.073	6
-2.808	-2.412	-68.49	4.886	27.81	15.830	1.199	6
-2.755	-2.359	-66.81	4.846	27.0	21.610	1.335	6
-2.70	-2.304	-65.12	4.807	26.44	25.00	1.398	4
-2.652	-2.256	-63.64	4.773	26.04	26.990	1.431	3
-2.610	-2.214	-62.34	4.743	21.59	41.960	1.623	5
-2.540	-2.144	-60.18	4.695	19.54	46.770	1.670	4
-2.510	-2.114	-59.26	4.675	15.46	53.630	1.729	4

Loewenstein and Meiboom (92) have related the mean life time τ of exchangeable nuclei at a chemical site with r, the ratio of maximum to central minimum v-mode intensities. This method has been employed by Rogers and Woodbrey (76,78) for their kinetic studies on some substituted N,N-dimethylamides. The expression that deals with equal population and equal mean life time at the two sites and applicable in our case is

$$\tau \nu_{AB} = \pm \frac{1}{\pi \sqrt{2}} \sqrt{r \pm (r^2 - r)^{1/2}} \quad \text{for}$$

$$\pi \sqrt{2}\, \tau \nu_{AB} > 1 \qquad [2]$$

where ν_{AB} is the true chemical shift as before and

r is the ratio of maximum to central minimum v-mode intensities.

We have applied this expression for evaluating τ from a few spectra and the results are presented in Table III.

Below -73°, the widths of the cyclohexane-d_{11} signals were quite sharp and were only slightly broader than the T.M.S. resonance signal which corresponds to the natural line width. In this region, the line width method for slow exchange developed by Piette and Anderson (12) was applied. The relevant expression deals with the additional broadening of the individual signals to be due to exchange phenomenon and is represented as

$$\frac{1}{T_2'} = \frac{1}{T_2} + \frac{1}{\tau} \qquad [3]$$

Table III

Cyclohexane-d_{11} Ring Inversion Rates from Intensity Ratios

mv reading	Corrected mv reading	T(^{o}C)	$10^3/T^{o}K$	Ratio=r	$\sqrt{r_+(r^2-r)^{1/2}}$	$\frac{1}{2\tau}$ $sec.^{-1}$	log $\frac{1}{2\tau}$	Number of spectra measured
-2.778	-2.557	-73.23	5.002	6.55	3.547	17.91	1.253	5
-2.648	-2.427	-68.98	4.898	2.46	2.088	30.43	1.483	5
-2.553	-2.332	-65.98	4.827	1.40	1.466	43.34	1.637	5
-2.540	-2.144	-60.18	4.695	1.45	1.503	42.26	1.626	4
-2.610	-2.214	-62.34	4.743	1.49	1.530	41.54	1.618	5
-2.652	-2.256	-63.64	4.773	2.86	2.274	27.94	1.446	3
-2.70	-2.304	-65.12	4.807	3.60	2.581	24.62	1.391	4

where T_2' is the measured relaxation time and T_2 its magnitude in the absence of exchange i.e., the natural line width. The value of $2/T_2'$ was obtained (in c.p.s. and then converted into radians) from the width at one half of maximum intensity of peaks for cyclohexane-d_{11} and thus one spectrum yielded two values for T_2'; an average of the two values was taken to represent T_2' for the spectrum. The value for T_2 was taken as 1 second since the corresponding values both at very slow exchange and very fast exchange (see later) were estimated to be close to 1 second. The results are summarized in Table IV.

Below -81.4°, the line widths for cyclohexane-d_{11} signals became comparable with that of the T.M.S. signal. In this region T_2 and T_2' were measured by applying the method of Jacobsohn and Wangsness (93), where the exponential decay of the damping of the resonance line is taken as a direct measure of the effective transverse relaxation time T_2. This method was used by Piette and Anderson (12) with the help of a fast response Sanborn recorder in their kinetic studies on alkyl nitrites. Since no fast response recorder was available to us, an alternative method was adopted. The wiggle patterns of one of the cyclohexane-d_{11} signals and the T.M.S. signal at the same sweep rate were photographed directly from the oscilloscope using a Land Polaroid camera. A 20 c.p.s.

Table IV

Cyclohexane-d_{11} Ring Inversion Rates from Changes in Line Width

(Slow exchange)

mv reading	corrected mv reading	T (°C)	$10^3/T°K$	$\frac{2}{T_2}$ c.p.s.	$\frac{1}{T_2}$ sec.$^{-1}$	$\frac{1}{2\tau}$ sec.$^{-1}$	$\log \frac{1}{2\tau}$	Number of spectra measured
-3.110	-2.807	-81.4	5.215	2.53	7.94	3.47	0.540	5
-2.997	-2.694	-77.71	5.116	3.76	11.81	5.405	0.733	6
-2.952	-2.735	-79.04	5.151	2.21	6.94	2.97	0.473	6
-2.905	-2.688	-77.51	5.111	2.77	8.70	3.85	0.585	4

frequency was photographed on the same plate and was used for calibration purpose. Figure 7 show typical T_2 measurements at -92.4°. The signal shape under the fast passage condition has been shown (93) to be proportional to

$$e^{-t/T_2} \cos 1/2 \, at^2 \qquad [4]$$

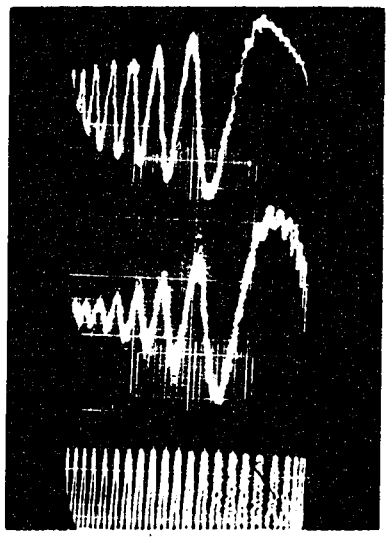
The ratio y of the maxima of two wiggles (where $\cos 1/2 \, at^2 = 1$) is therefore given by

$$y = e^{-t/T_2} \ldots\ldots \qquad [5]$$

in which t is the time elapsed between the passage of the two wiggles. The ratios of the maxima of all the well defined wiggles to the resonance signal (and in some cases to the first wiggle where the resonance signal was not well defined) were calculated and the time factor t involved in a particular ratio was directly taken from the exposure of the calibrating frequency. Thus a single exposure yielded a number of T_2 values for the appropriate signal, the average of the values was used for evaluating τ from equation [3]. The results are given in Table V.

Rate Calculations Above Coalescence Temperature

Gutowsky and Holm (75) have developed an analytical solution for determining τ above coalescence temperature. They extended the line shape equation for this



-92°.4

a). Cyclohexane - d_{11} resonance signal

b). T.M.S. resonance signal

c). 20 c.p.s. frequency (used for calibration).

Fig. 7 T_2 measurement from exponential decay of the resonance signal.

Table V

Cyclohexane-d_{11} Inversion Rates From Changes in Line Width. Slow exchange

(exponential decay method)

mv reading	corrected mv reading	T (°C)	$10^3/T^{\circ}K$	T_2' sec.	T_2 sec.	$\frac{1}{2\tau}$ $sec.^{-1}$	$\log \frac{1}{2\tau}$
-3.20	-2.980	-87.19	5.377	0.29	1.03	1.24	0.093
-3.35	-3.129	-92.39	5.532	0.44	1.07	0.67	$\bar{1}$.826
-3.40	-3.179	-94.13	5.585	0.52	0.96	0.44	$\bar{1}$.643

purpose and the solution involves the measurement of the width at half height of the single broad line. In the present simple case the relevant expression is

$$\tau = \left[\frac{2\nu^2}{\frac{1}{2}\pi^2\nu_{AB}^4 + 4\pi^2\nu_{AB}^2\nu^2 - 8\pi^2\nu^4}\right]^{1/2} \qquad [6]$$

where 2ν (c.p.s.) is the band width at half height. This equation was used by Hartman (94) to determine τ values for ring inversion in $C_8D_{15}H$ above coalescence temperature. The results are summarized in Table VI. This equation is also applicable immediately below the coalescence temperature, but was not used in the present case.

Above -47°, the exchange rate is quite high and the line widths of the cyclohexane-d_{11} signal decreased and were only slightly broader than the resonance signal due to T.M.S. In this region the fast exchange equation (10-22) of reference (1) was employed to determine τ. In our present simple case the equation simplifies to

$$\tau = \left[\frac{1}{T_2'} - \frac{1}{T_2}\right]\frac{4}{w^2} \qquad [7]$$

where w is the true chemical shift in radians per second. A general solution for the fast exchange conditions has been developed by Piette and Anderson (12). The equation [7] was applied to measure τ at two temperatures. $2/T_2'$ was

Table VI

Cyclohexane-d_{11} Ring Inversion Rates from Line Broadening

(Above coalescence)

mv reading	corrected mv reading	T (^{o}C)	$10^3/T^{o}K$	2ν c.p.s.	Rate $\frac{1}{2\tau}$ Sec.$^{-1}$	log $\frac{1}{2\tau}$	Number of spectra measured
-2.401	-2.180	-61.29	4.720	23.4	75.277	1.877	5
-2.252	-2.031	-56.69	4.620	12.4	120.963	2.083	7
-2.177	-1.956	-54.50	4.573	10.1	142.147	2.153	9
-2.437	-2.041	-57.0	4.626	20.3	84.34	1.926	4
-2.40	-2.004	-55.90	4.603	27.4	66.60	1.823	5
-2.37	-1.974	-55.02	4.584	15.3	102.895	2.012	5
-2.238	-1.842	-51.17	4.505	9.2	153.506	2.186	9
-2.11	-1.714	-47.22	4.426	6.51	208.325	2.319	5

obtained from the width at half height maxima of cyclohexane-d_{11} resonance signal. A value of 1 second for T_2 was used for calculation as the T_2 values determined at very slow exchange as well as very fast exchange processes were found to be close to 1 second. The results are given in Table VII (first two).

Above -40°, the method of Jacobsohn and Wangsness (93), p. 129 was employed for the determination of T_2 and T_2' and the expression for fast exchange approximation, equation [7], was used to evaluate τ . The results are shown in Table VII (last two).

The temperature dependence of the rate of inversion can be expressed in the familiar form of the Arrhenius Law:

$$k = \frac{1}{2\tau} = A\, e^{-E_a/RT} \qquad [8]$$

where k is the inversion rate constant (in this case $\frac{1}{2\tau}$), A is a frequency factor and E_a is the Arrhenius activation energy. Equation [8] can be rewritten as

$$\log \frac{1}{2\tau} = \log A - \frac{E_a}{2.3\ RT} \qquad [9]$$

The Arrhenius plot including all the rate data is shown in Figure 8. It was found that the rate data obtained from the spectra of a particular day yielded a good straight line for the Arrhenius plot and those of different days gave almost parallel straight lines. A least squares analysis was carried out for evaluating the Arrhenius activation energy,

Table VII

Cyclohexane-d_{11} Ring Inversion Rates from Line Broadening

(Fast exchange approximation)

mv reading	corrected mv reading	T (^{o}C)	$10^3/T^{o}K$	$1/T_2'$ Sec.$^{-1}$	$1/T_2$ Sec.$^{-1}$	$1/2\tau$ Sec.$^{-1}$	$\log \frac{1}{2\tau}$	Number of spectra measured
-1.850	-1.629	-44.64	4.376	11.99	1	369.498	2.568	6
-1.669	-1.448	-39.39	4.278	8.415	1	547.645	2.739	6
-1.56	-1.339	-36.37	4.223	3.23	0.97	1796.81	3.255	Exponential
-1.40	-1.179	-31.92	4.145	2.86	0.93	2104.04	3.323	decay

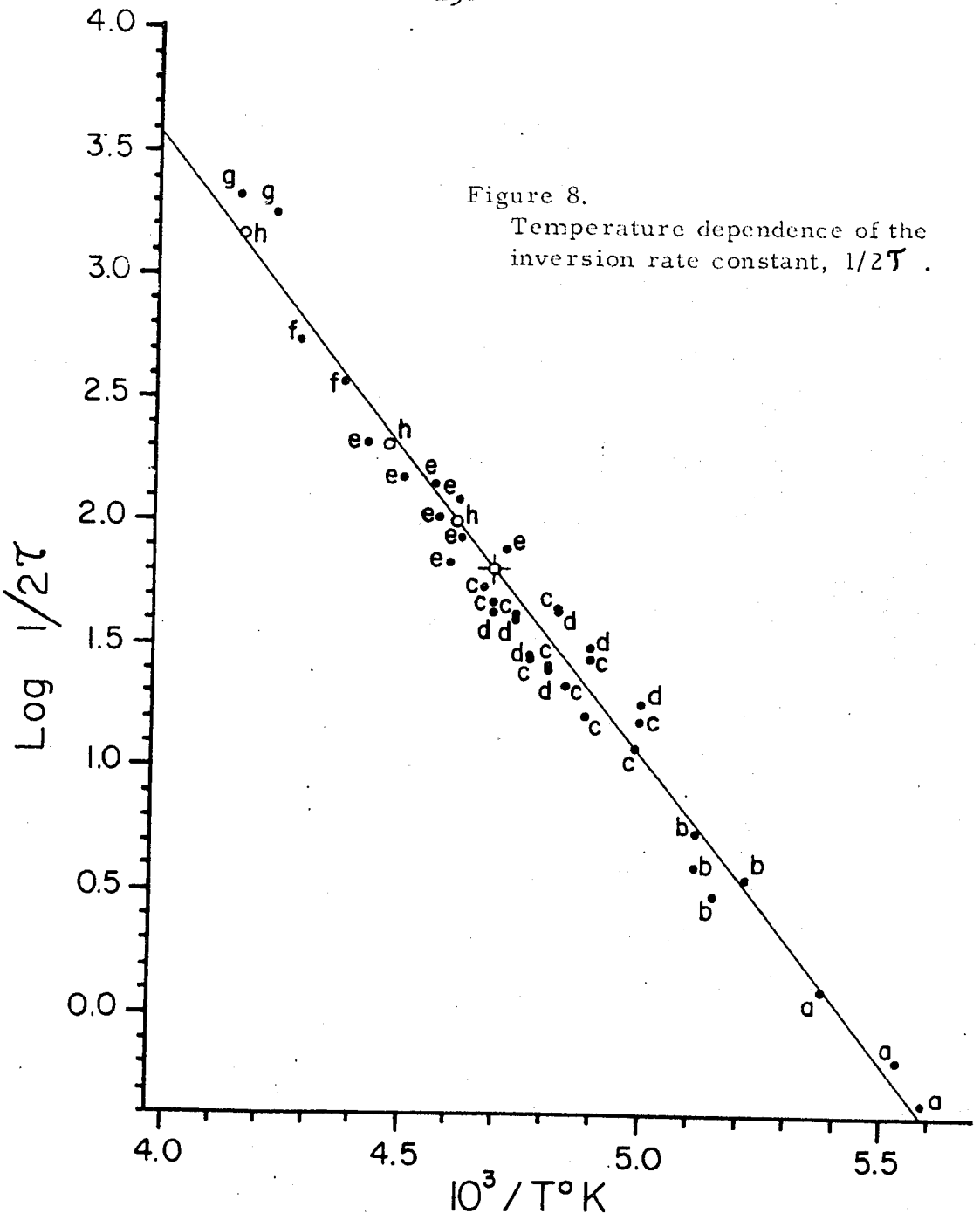


Figure 8.
Temperature dependence of the inversion rate constant, $1/2\tau$.

a Slow exchange, exponential decay method.
b Slow exchange, line width method.
c Below coalescence, peak-separation method.
d Below coalescence, intensity ratio method.
e Above coalescence, line broadening method.
f Fast exchange, line width method.
g Fast exchange, exponential decay method.
h Fast exchange for cyclohexane, C_6H_{12}.
⊹ Coalescence temperature.

E_a and the frequency factor A. The limits of E_a and log A were computed for 90% confidence using statistical methods described below. The limits were 11.29 ± 0.6 kcal./mole in E_a and 13.39 ± 0.5 in log A. The frequency factor A was therefore 2.45×10^{13} ~~± 3.2~~. The limits of 90% confidence in E_a were obtained from the following equation (95)

$$\beta = b \pm t_a \frac{b}{r} \left(1 - \frac{r^2}{N-2}\right)^{1/2} \qquad [10]$$

where β is the expected slope for the straight line, b is the slope calculated by the least squares method, r is the Pearson coefficient of correlation and t is a factor which depends on the number of degrees of freedom and the confidence limits. Equation (11.4.2) of reference 95 (page 287) was used for the evaluation of r and was found to be 0.986. The number of degrees of freedom is expressed as (N-2), where N is the number of points involved in the plot; the number of degrees of freedom in our case was (37-2) = 35. The value of t, 1.645, was taken from Table B.4 on page 422 of reference 95, for 90% confidence limits corresponding to 35 degrees of freedom. The limits of 90% confidence in log A were calculated from an appropriate expression given on page 295 of reference 95.

The coalescence temperature of the inversion process was determined from the Arrhenius plot using the relation

$$\tau_c = \frac{\sqrt{2}}{2\pi \nu_{AB}} \qquad [11]$$

and was found to be -60.3°. The free energy of activation, $\Delta F^{\neq}$ at the coalescence temperature (-60.3°) was calculated from Eyring's equation (96)

$$k = K. \frac{kT}{h} e^{-\Delta F^{\neq}/RT} \qquad [12]$$

assuming a transmission coefficient, K. of unity, as well as 1/2. Other parameters were calculated from appropriate expressions; these values are presented in Table VIII. The limits of $\Delta S^{\neq}$, shown in Table VIII, were calculated from the relation $A = K. \frac{kT}{h} e^{\Delta S^{\neq}/R}$, (where A is the frequency factor) for 90% confidence limits in A.

Table VIII

Parameters for Ring Inversions of Cyclohexane-d_{11}

E_a Kcal./mole	$\Delta F^{\neq}$ Kcal./mole	$\Delta H^{\neq}$ Kcal./mole	$\Delta S^{\neq}$ e.u.
11.29 ± 0.6^{i}	$10.55^{ii,iii}$	$10.87 \pm 0.6^{i,ii}$	1.5 ± 2.3^{iii}
11.29 ± 0.6^{i}	$10.26^{ii,iv}$	$10.87 \pm 0.6^{i,ii}$	2.9 ± 2.3^{iv}

i 90% confidence limit,

ii at the coalescence temp. (-60.3°),

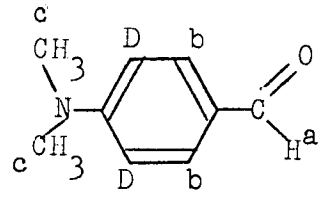
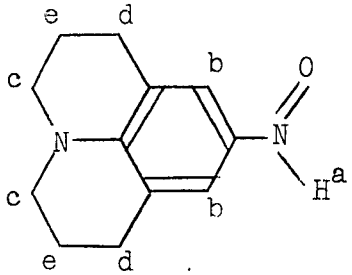
iii assuming transmission coefficient as unity,

iv assuming transmission coefficient as 1/2.

N.M.R. Studies of some Aromatic Aldehydes

The N.M.R. studies of 4-N,N-dimethylamino-3,3'-d_2-benzaldehyde and 9-julolidinecarboxaldehyde were carried out in methylene chloride solution (5%). All spectra of 4-N,N-dimethylamino-3,3'-d_2-benzaldehyde were measured with deuterium decoupling, in order to remove coupling between deuterium and hydrogen atoms. The resonance signal of the aromatic protons of this compound is shown in Figure 9. The spectrum of 9-julolidinecarboxaldehyde is shown in Figure 10. Table IX summarizes the results on the analyses of the spectra of 4-N,N-dimethylamino-3,3'-d_2-benzaldehyde and 9-julolidine-carboxaldehyde; the chemical shifts are expressed on the τ scale.

Table IX

Compound		τ_a	τ_b	τ_c	τ_d	τ_e
	room temp.	0.28	2.27	6.93	-	-
	low temp. (-92°)	0.33	2.20 2.34	6.84		
	room temp.	0.43	2.75	6.67	7.20	7.98
	low temp. (-92°)	0.50	2.66 2.88	6.75	7.30	8.11

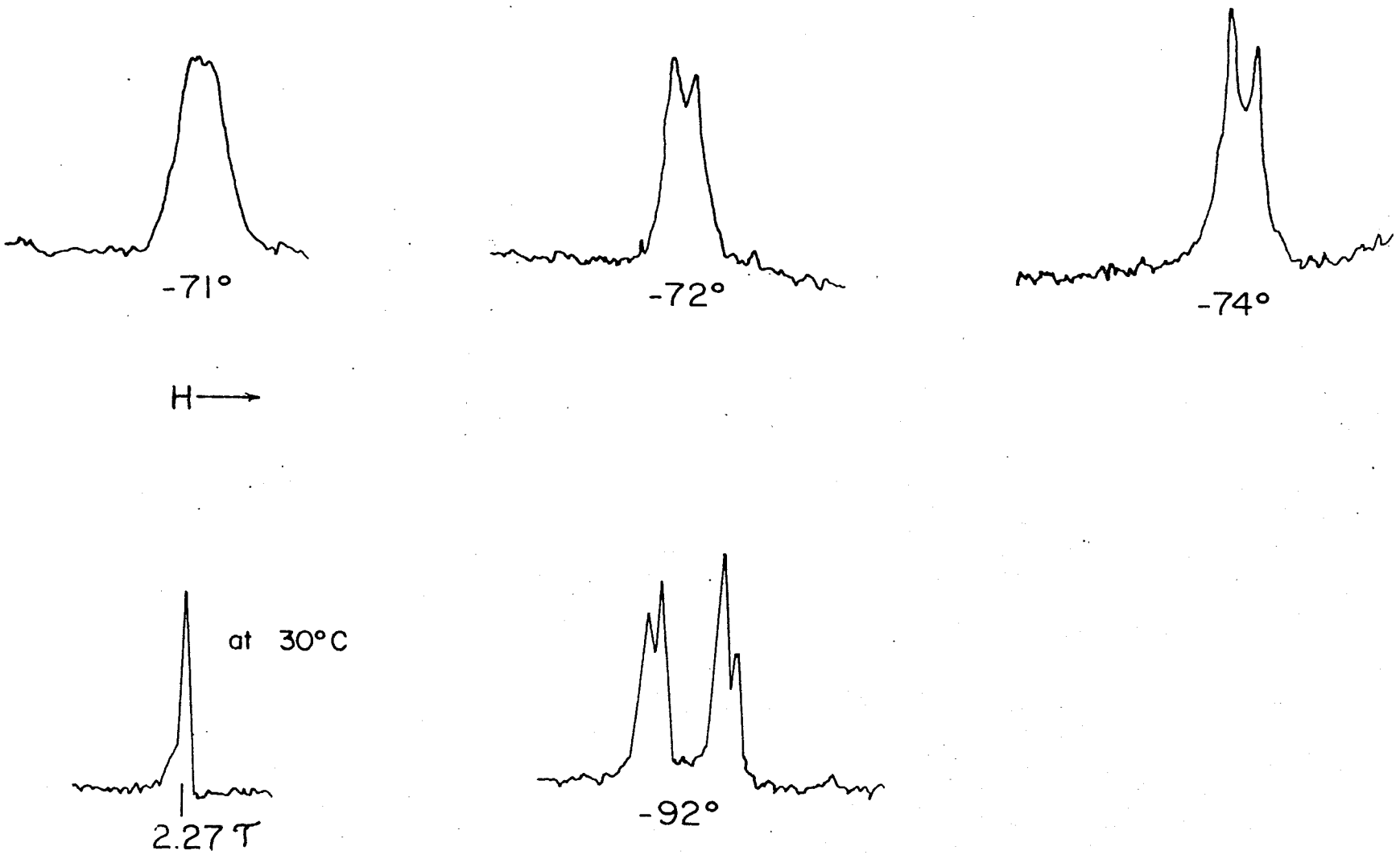


Fig.9 Changes in the spectrum of the ortho protons of 4,N,N-dimethylamino-3,3'-d_2-benzaldehyde in CH_2Cl_2 with temperature.

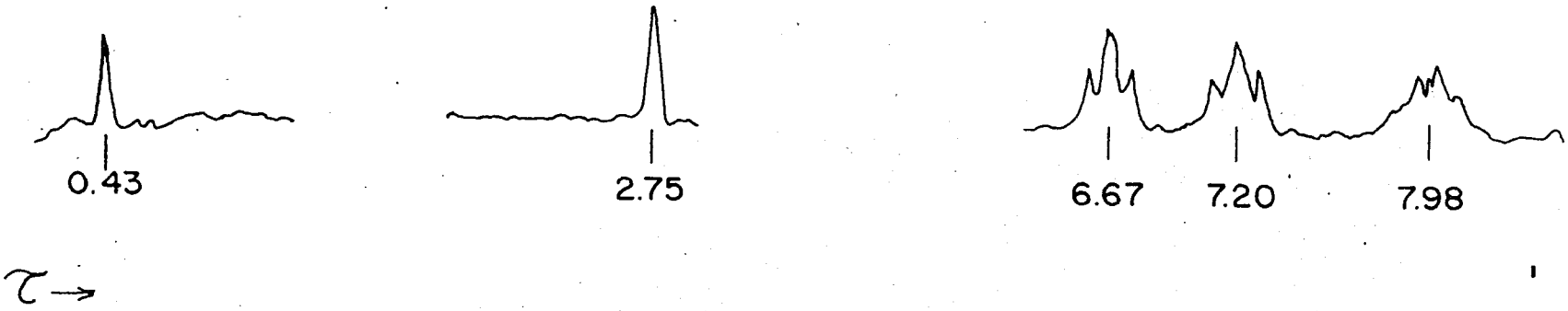


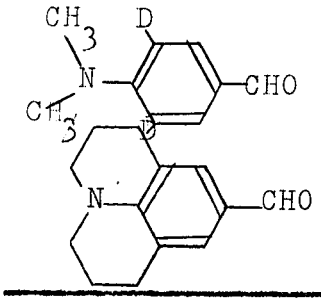
Fig. 10 N.M.R. Spectrum of 9-julolidinecarboxaldehyde in CH_2Cl_2 at 30°C

(solvent bands not shown)

The low temperature spectra for these compounds were examined, and it was found that the single sharp peak for the two ortho protons (marked as b) of both compounds at room temperature broadened with lowering of temperature, and yielded typical AB quartets at appreciably low temperatures. Figures 9 and 11 show the resonance signals of the ortho protons of 4-N,N-dimethylamino-3,3'-d_2-benzaldehyde and 9-julolidinecarboxaldehyde respectively at several low temperatures. The coalescence temperature for 4-N,N-dimethylamino3,3'-d_2-benzaldehyde and 9-julolidinecarboxaldehyde were determined to be -71° and -61° respectively. The chemical shifts for the various protons at -92° are given in Table IX. The chemical shifts between the ortho protons and their coupling constants were determined from low temperature spectra and are given in Table X.

Table X

Relative Chemical Shifts and Coupling Constants of the Aromatic Protons

Compound	Chemical shift between the ortho protons c.p.s.	Coupling constants c.p.s.
	8.4	2.5
	13.3	2.0

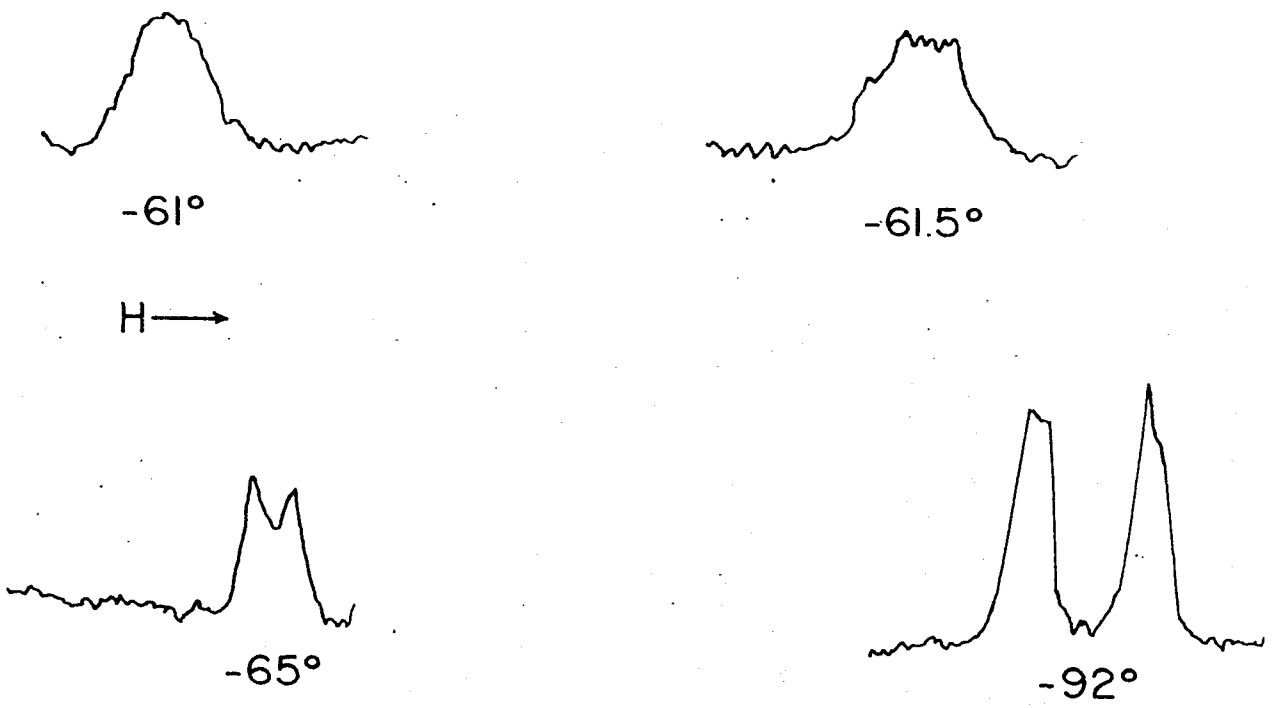


Fig. II Changes in the spectrum of the aromatic protons of 9-julolidinecarboxaldehyde in CH_2Cl_2 with temperature.

Preliminary low temperature studies were carried out on benzaldehyde and p-anisaldehyde in vinyl chloride solution. Figure 12 shows the spectrum of the aromatic protons of benzaldehyde at different temperatures. The spectrum was complex and assignment of the bands was difficult. However, broadening of the peaks and the appearance of new peaks on lowering of the temperature were evident. Below -136° the spectrum did not undergo any more change. The "coalescence" temperature was estimated to be around -123°.

The low field proton resonance signals for the ortho protons of p-anisaldehyde are shown in Figure 13 at several low temperatures. The doublet at high temperature broadened with the lowering of temperature and at appreciably low temperature yielded two overlapping doublets with other unresolved fine splittings. The separation of the high field doublet due to the meta protons (8.5 c.p.s. calculated from the spectrum given in the High Resolution N.M.R. Spectra catalog published by Varian Associates), was used to calibrate the low field spectrum. The chemical shift between the ortho protons was calculated to be 7.20 c.p.s. from the mean positions of the adjacent lines of the two overlapping doublets. The coalescence temperature was estimated to be around -99°.

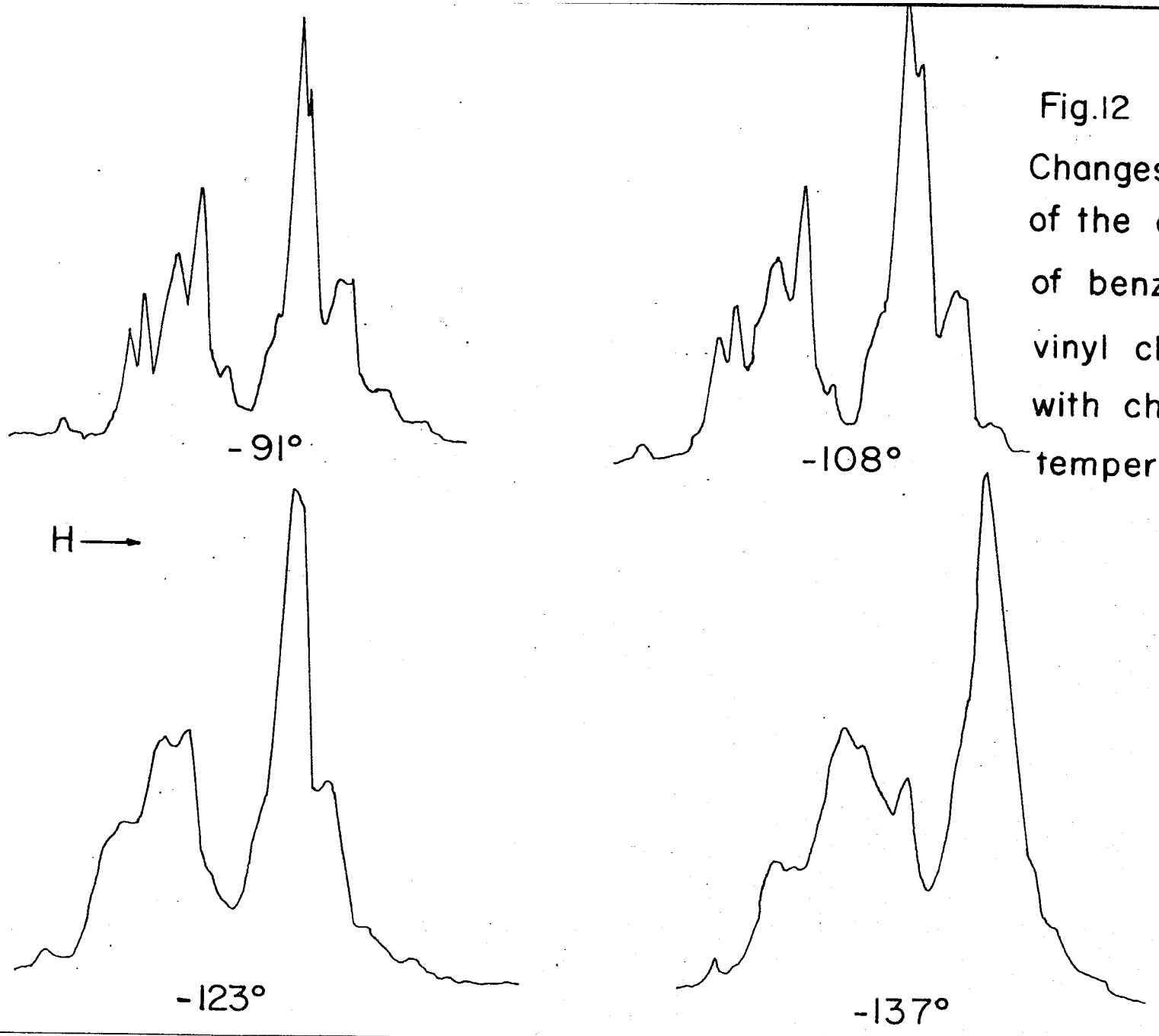


Fig.12

Changes in the spectrum of the aromatic protons of benzaldehyde in vinyl chloride solution with changes in temperature

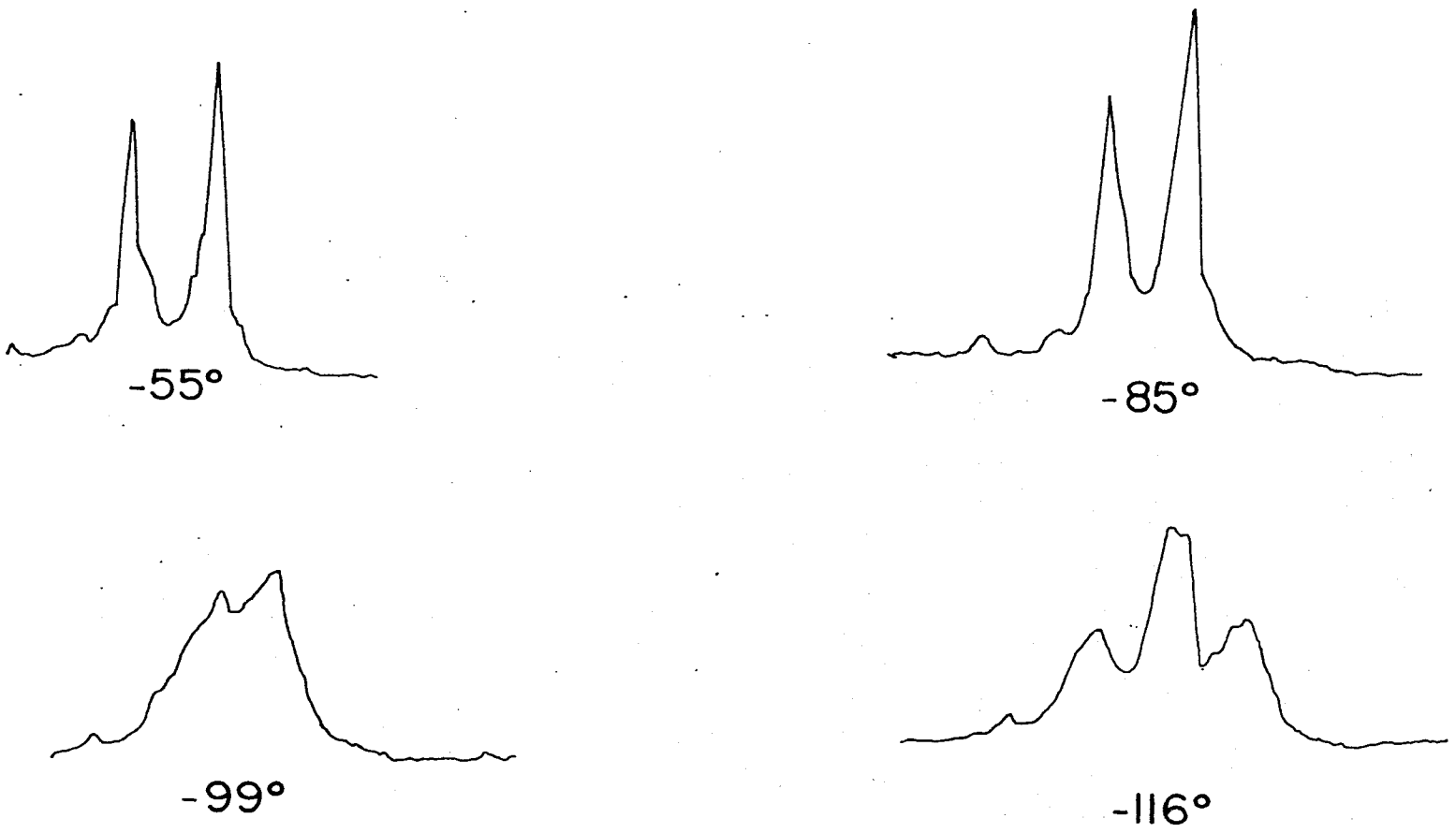


Fig. 13 Changes in the spectrum of the ortho protons of p-anisaldehyde in vinyl chloride solution with changes in temperature.

N.M.R. Studies of Substituted Cyclohexenes: Results and Analyses of the Spectra

The N.M.R. spectra of Δ^3-tetrahydrobenzaldehyde-d_6, Δ^3-tetrahydrobenzoic acid-d_6, Δ^3-tetrahydrobenzonitrile-d_6 and Δ^3-tetrahydroacetophenone-d_6 were studied in carbon disulfide solution (25%). In all these compounds the six deuterium atoms were occupying 2,2,3,4,5,5 positions of the ring. The isotopic purity, however, was not determined. The N.M.R. signals of 1-H of these compounds were chemically shifted from the rest of the proton signals, and exhibited considerable fine splittings. The methylene protons on C_6 appeared at a higher field and the signals were broad and incompletely resolved. The fine splittings in 1-H signals disappeared when double irradiation was applied at the deuterium resonance frequency; this also led to well resolved lines for the methylene protons. The spectrum of the ring protons of the aldehyde with and without deuterium decoupling are shown in Figure 14 for comparison. Figures 15, 16 and 17 show the spectra of the ring protons of the nitrile, the ketone and the acid respectively, recorded with deuterium decoupling.

In all the spectra of the substituted cyclohexene compounds, the low field signals for 1-H were easily recognised to be the X-part, and the high field ones for the methylene protons as the AB part, of an ABX system (97). The nitrile,

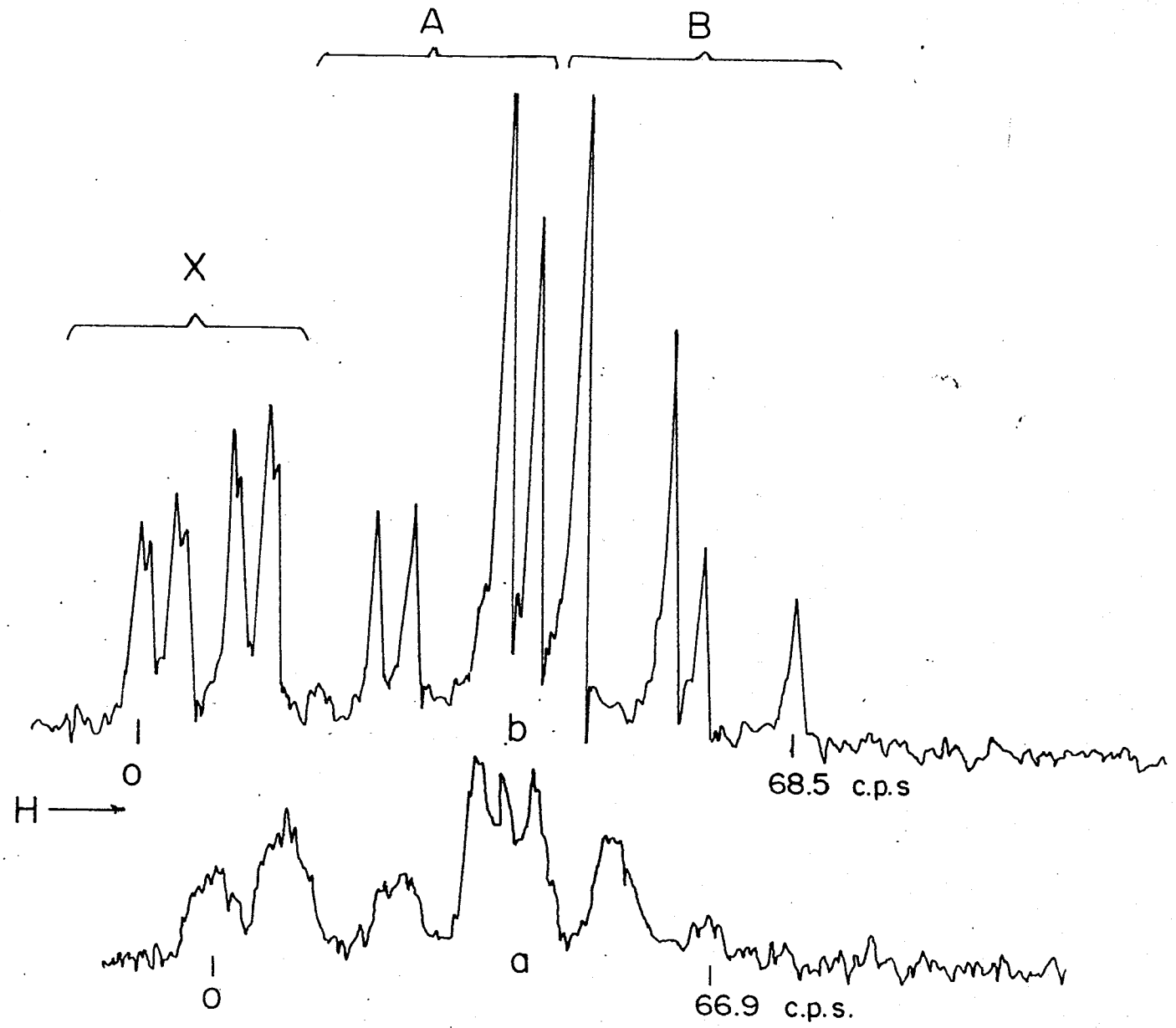


Fig. 14 Proton magnetic resonance spectra of Δ^3-tetrahydrobenzaldehyde-d6

a without deuterium decoupling

b with deuterium decoupling

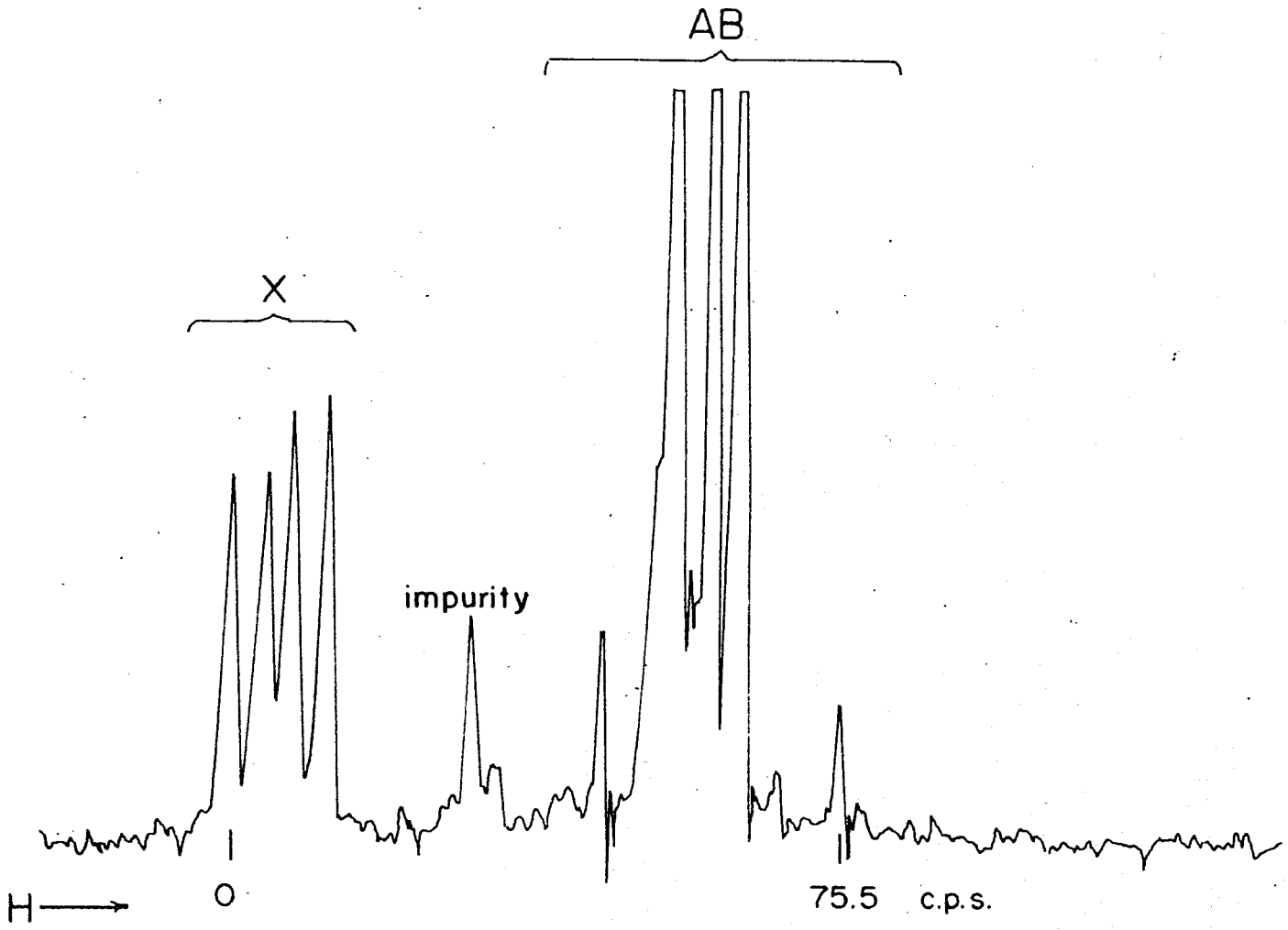


Fig. 15 Proton magnetic resonance spectrum of Δ^3-tetrahydrobenzonitrile-d_6

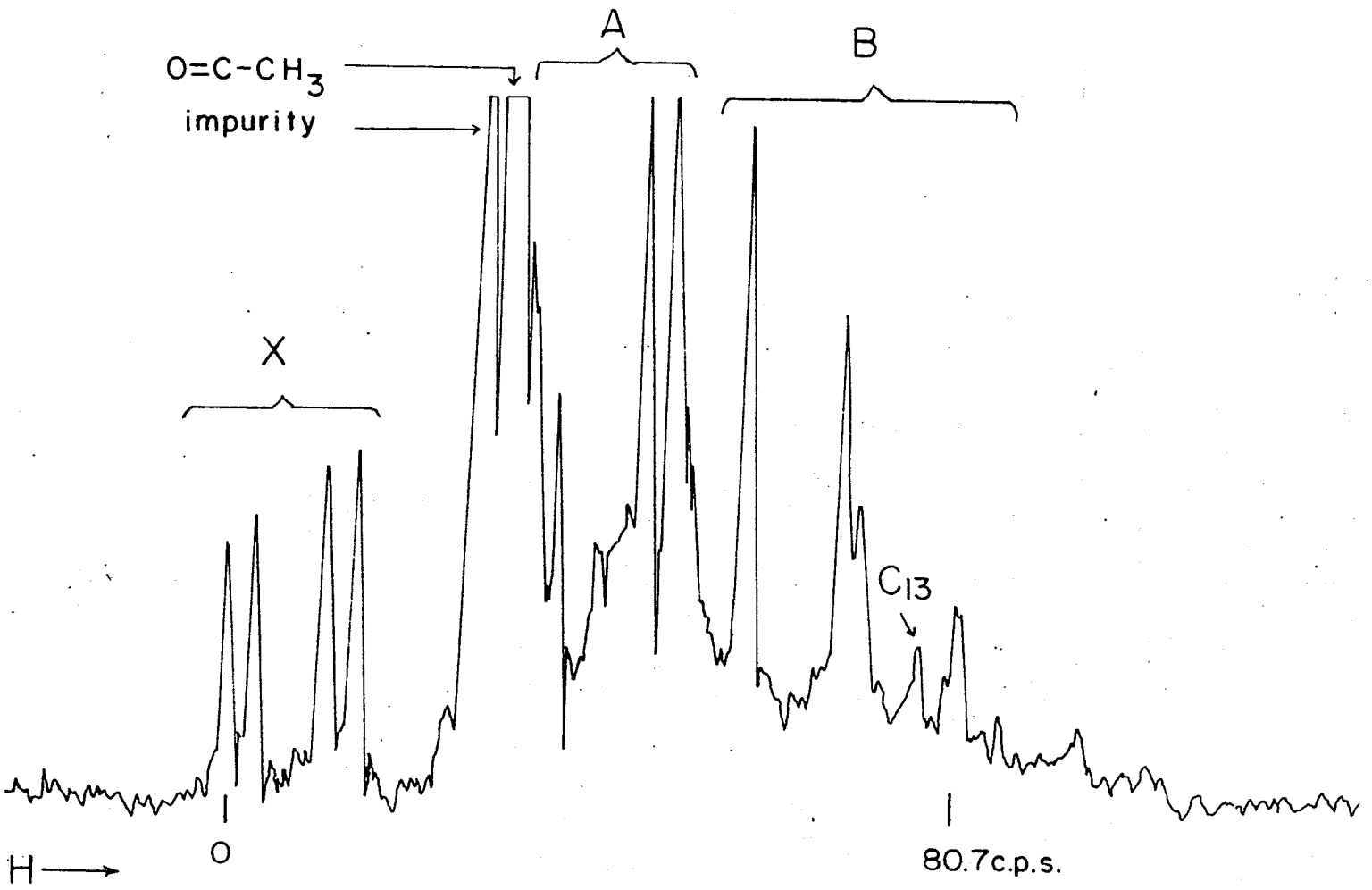


Fig. 16 Proton magnetic resonance spectrum of Δ^3-tetrahydroacetophenone-d6

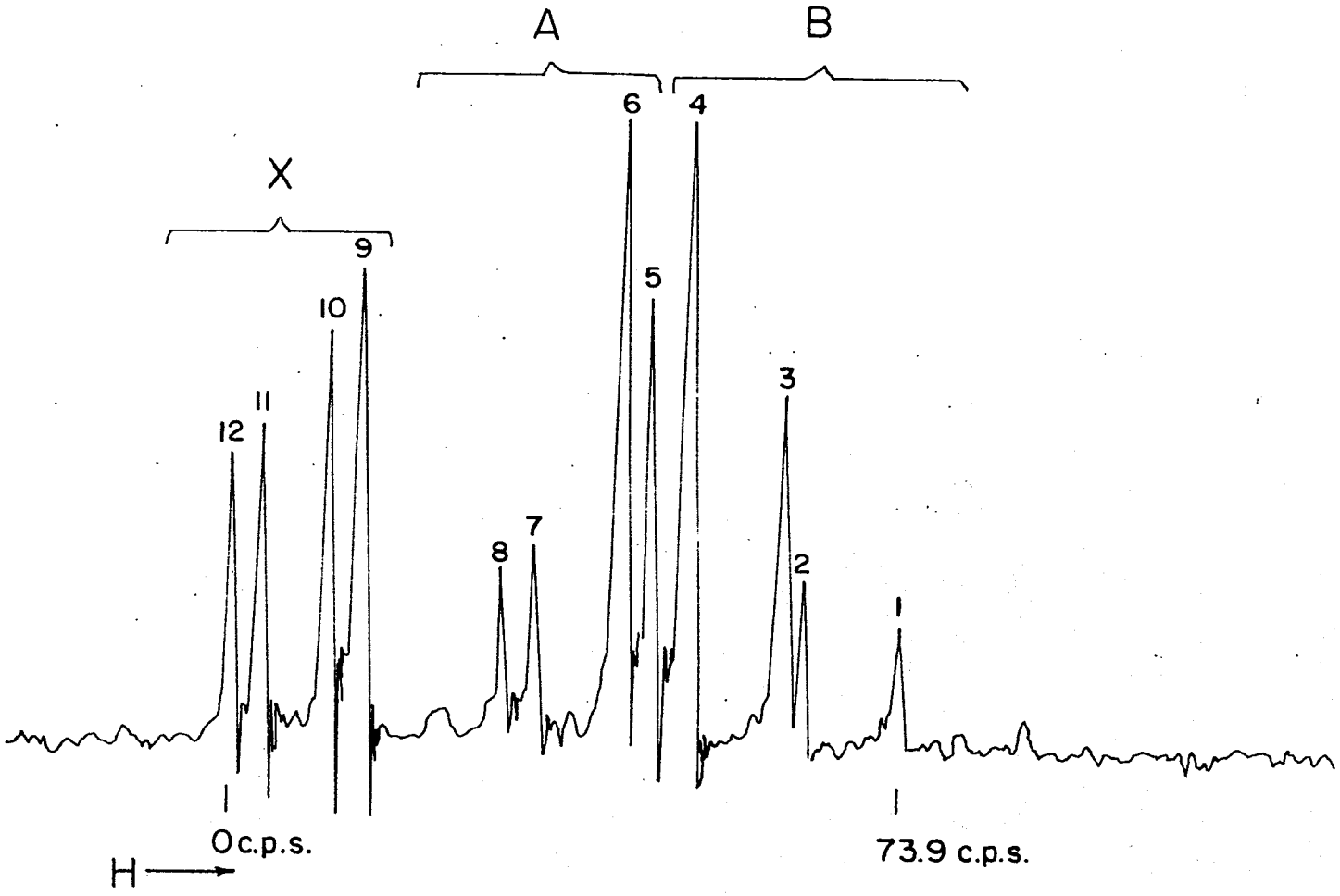


Fig. 17 Proton magnetic resonance spectrum of Δ^{3}-tetrahydrobenzoic acid $-d_6$

the acid and the ketone showed sharp quartets for the X-part, whereas in the aldehyde, each member of the quartet was split into a doublet of small separation (1.0 c.p.s.). This further splitting in the X quartet of the aldehyde arose from coupling between 1-H and the aldehyde proton; the resonance signal due to the aldehydic proton (not shown) was also split to the same extent. There was no trouble in picking up a high field and a low field quartet in the AB parts of the spectra of these compounds. The aldehyde and the acid exhibited eight distinct lines for the two quartets of the AB part; in the nitrile one line of the high field quartet was superimposed on a line of the low field quartet, and a line of the low field quartet of the ketone was hidden under the methyl resonance signal of the $O{=}C{-}CH_3$ group. A strong peak adjacent to the signal for the $O{=}C{-}CH_3$ group must have arisen from some impurity. The separation between the adjacent lines of the high field quartets was found to be larger than that in the low field quartets; the high field quartets were assigned to the B proton and the low field ones to the A proton, of the ABX system.

Four spectra were measured for each of these compounds and the average value of the spectral data obtained for each of these compounds were employed to carry out separate ABX analysis for all of them in the usual manner (97). As an example, the

lines 2 and 6, and 4 and 8; similarly the separation between the lines 1 and 5, and 3 and 7 yielded a pair of values for $2D_-$. The mean of the appropriate pair of values was accepted for $2D_+$ and $2D_-$. The mean position of the two centers of the lines 1 and 7, and 2 and 8 was determined to evaluate $\frac{1}{2}(\nu_A + \nu_B)$. All the foregoing spectral data were determined for four spectra and the mean values from these data (a to g) are presented in Table XI and were used to calculate $|J_{AX} - J_{BX}|$, $\frac{1}{2}(\nu_A - \nu_B)$.

Table XI

Analysis of the ABX Spectrum of Δ^3-tetrahydrobenzoic acid-d_6

a.	$\lvert J_{AX} + J_{BX} \rvert$	(from the X part of the spectrum)	14.2 c.p.s.
b.	$2 \lvert D_+ - D_- \rvert$	"	7.4 "
c.	$\lvert J_{AB} \rvert$	(from the AB part of the spectrum)	12.9 "
d.	$2 D_+$	"	20.3 "
e.	$2 D_-$	"	27.6 "
f.	$\frac{1}{2}(J_{AX} + J_{BX})$	"	7.0 "
g.	$\frac{1}{2}(\nu_A + \nu_B)$	"	107.3 "
h.	$J_{AX} - J_{BX}$	(calculated)	-8.6 "
i.	$\frac{1}{2}(\nu_A - \nu_B)$	"	20.0 "

The values of $\lvert J_{AX} + J_{BX} \rvert$ and $2 \lvert D_+ - D_- \rvert$ obtained from the X part of the spectrum are in good agreement with the corresponding values obtained from the AB part of the spectrum.

The values of sin $2\phi_+$ and sin $2\phi_-$ were calculated from equations 14 and 16 respectively; these were used to evaluate cos $2\phi_+$ and cos $2\phi_-$ respectively. The values for $|J_{AX} - J_{BX}|$, and $\frac{1}{2}(\nu_A - \nu_B)$ were calculated by solving equations 13 and 15 (h,i. in Table XI). The values of J_{BX}, J_{AX}, ν_A and ν_B are shown in Table XII. The chemical shift of the X proton, ν_x was determined from the mean position of the X-quartet. (Table XII). Similar analysis was carried out on the other cyclohexene compounds and the results are presented in Table XII.

A calculated spectrum for the nitrile with the values shown in Table XII was found to be consistent with the observed spectrum for the compound.

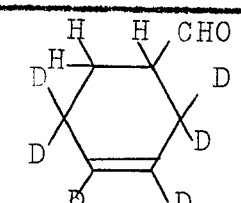
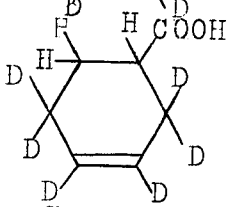
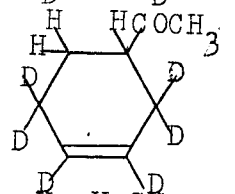
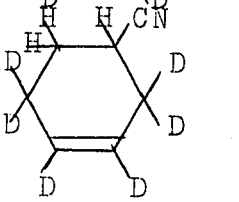
N.M.R. Study on Cyclohexylacetate

Results and Analyses of the Spectra

2,2,3,3,4,4,5,5-Octadeuteriocyclohexylacetate obtained by Baeyer-Villiger oxidation of hexahydroacetophenone-2,2,3,3,4,4,5,5-d_8 was used for N.M.R. studies in carbon disulfide solution (20%). The spectra were measured with deuterium decoupling to eliminate fine splittings caused by coupling between deuterium and hydrogen atoms. 1-H appeared at a low field as a quartet, as expected for the X proton of an ABX system (Fig. 18). The methylene protons on C_6 formed the AB part of the ABX system; however, only six lines could be

Table XII

Coupling Constants and Chemical Shifts of the Ring Protons of the Cyclohexene Derivatives

Compound	J_{AB} c.p.s.	J_{BX} c.p.s.	J_{AX} c.p.s.	ν_X c.p.s.	ν_A c.p.s.	ν_B c.p.s.
	13.1	10.2	3.0	143.1	115.0	94.6
	12.9	11.4	2.8	150.2	117.3	97.3
	12.7	12.9	3.4	148.0	112.1[a]	87.3[a]
	13.2	10.2	1.7	162.1	113.7	107.5

[a] The position of the line of the low field quartet (needed for determination of chemical shift of A proton) which was superimposed on the methyl resonance of $O=C-CH_3$ group was estimated.

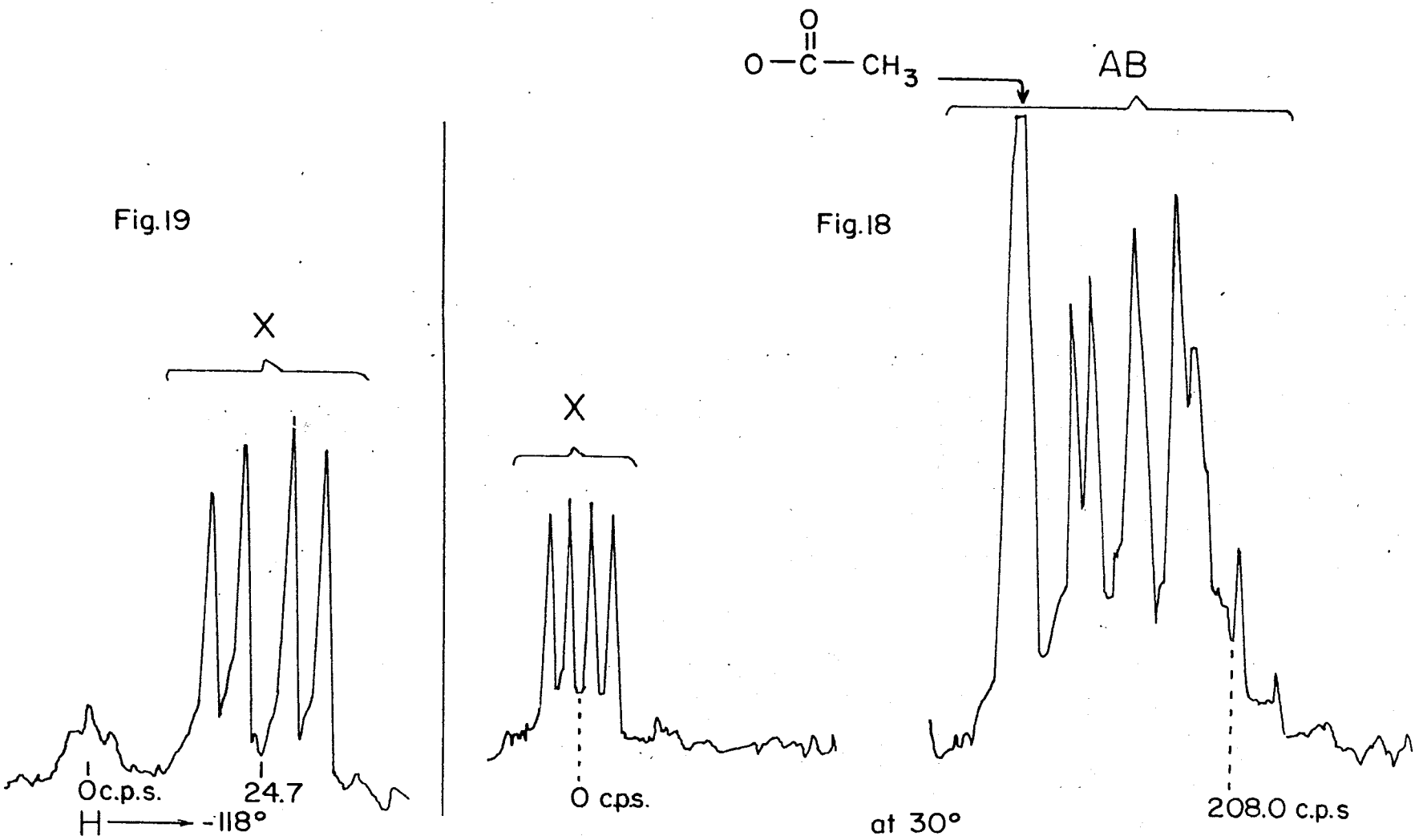


Fig. 18 N.M.R. spectra of cyclohexylacetate-2,2,3,3,4,4,5,5-d_8

Fig. 19 X part of spectrum of cyclohexylacetate at -118°

identified, the other two being hidden under the huge acetate peak. Signals arising from isotopic impurity were present in this region but it was not difficult to eliminate them from the known nature of an AB part of an ABX pattern. The spectral data furnished by the ABX system were used to carry out an analysis (97) for coupling constants; the calculated values are shown in Table XIII.

Low temperature spectrum of the compound was examined to find out the various vicinal coupling constants and the conformational equilibrium. At sufficiently low temperature 1-H yielded two sets of bands - a quartet at a higher field and a triplet at a lower field (Fig. 19). On the basis of the known observations (28,91), the quartet was attributed to the conformer with the 1-H in axial position (equatorial acetate), and the triplet to the one with the 1-H in equatorial (axial acetate) orientation. The triplet was poorly resolved, probably due to interference from isotopic impurity. The changes in the AB part of the spectrum at low temperature made the spectrum complex. This together with the signals for isotopic impurity precluded any simple analysis.

The value for geminal coupling constant (J_{AB}) obtained from room temperature spectrum, and the spectral data obtained from X part of the spectrum for the equatorial acetate conformer at low temperature were used to do an ABX analysis

Table XIII

Coupling Constants of Cyclohexyl Acetate-d_8

State of the acetate	J_{gem} c.p.s.	J_{large} (vicinal) c.p.s.	J_{small} (vicinal) c.p.s.	K
20% in CS_2 at				
Room temp.	12.34	9.28	4.07	3.3
		$J_{a,a}$	$J_{a,e}$	$J_{e,e}$
20% in CS_2 at -118°				
Equatorial acetate	-	11.66	4.03	-
Axial acetate	-	-	2.77	2.77

for calculating $J_{a,a}$ and $J_{a,e}$. The geminal coupling constant is expected to be independent of temperature variation and, therefore, the calculated values for $J_{a,a}$ and $J_{a,e}$ (Table XIII) should be of the right order of magnitude. The triplet for the 1-H proton of the axial acetate conformer at low temperature implies that $J_{a,e}$ and $J_{e,e}$ are of the same order of magnitude and therefore the values for $J_{a,e}$ and $J_{e,e}$ were taken as the mean value of the separation between the two extreme lines of the triplet. These results are shown in Table XIII. The

value of K shown in Table XIII refers to the ratio of the equatorial acetate conformer to the axial acetate conformer. It was calculated from the following relation

$$(J_{AX} + J_{BX})_{\text{at room temp.}} = P(J_{AX} + J_{BX})_{\text{equatorial acetate}} + (1-P)(J_{AX} + J_{BX})_{\text{axial acetate}}$$

which is

$$J_{large} + J_{small} = P(J_{a,a} + J_{a,e}) + (1-P)(J_{a,e} + J_{e,e})$$

where P and (1-P) are the fractions of the equatorial- and the axial-acetate conformers respectively.

The relative areas for the two X-pattern were measured at low temperature (-106°) with the help of a Varian V3521 Integrator and the ratio of the equatorial acetate conformer to the axial acetate conformer was found to be 4.5:1.

DISCUSSION

Ring Inversion in Cyclohexane

The N.M.R. studies on cyclohexane by Jensen et al (39), Moniz and Dixon (40), and Harris and Sheppard (41) exhibited the "freezing out" of the cyclohexane molecule into a rigid chair form at low temperature. Below -66.5°, cyclohexane yielded separate axial and equatorial proton resonance as broad bands with unresolved fine structure. The complex nature of the spectrum arose from coupling between the neighbouring hydrogen atoms. Figure 20 shows the spectrum of cyclohexane at several low temperatures, as observed by Jensen and his co-workers (39b). Below the coalescence temperature (-66.5°), the peaks are broad and rounded and the maxima are not clearly defined. At lower temperatures (below -70°), the centres of mass do not occur at the maxima and the peaks are not symmetrical. Thus an appreciable error must be involved in measuring the separation at any temperature specially at lower temperatures. The centres of the signals at low temperature were visually approximated by Jensen and his collaborators, and an uncertainty of about $\pm$ 3 c.p.s. was estimated for the value obtained for the maximum separation. This introduced an appreciable error in the rate constant for the inversion process of cyclohexane, and these authors have

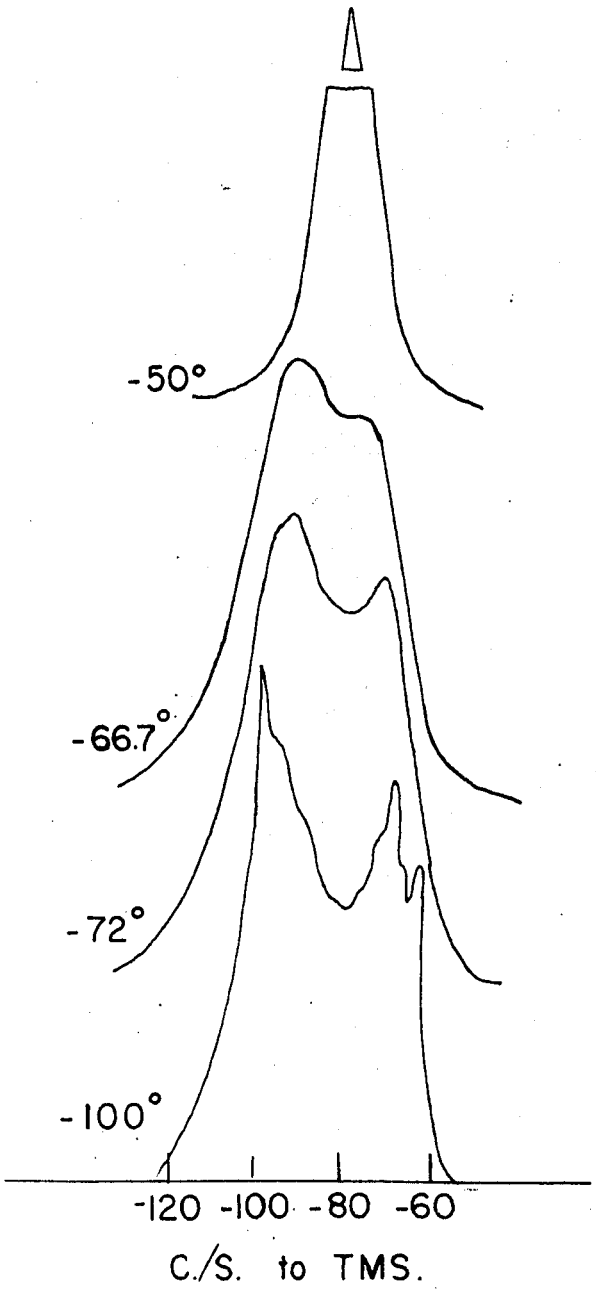


Fig. 20 Proton resonance spectrum of cyclohexane (39b)

estimated an error of less than 10% for the calculated rate constant. However, an error of 10% in the rate constant does not cause a great error in $\Delta F^{\neq}$. The rate constant was calculated from the expression $\tau_c = \sqrt{2}/2\pi\, \nu_{AB}$, where τ_c is the mean life time of each conformer at the coalescence temperature, and ν_{AB} is the chemical shift between the axial and equatorial protons in the absence of inversion of the cyclohexane ring (i.e., the maximum separation at low temperature). However, the applicability of this expression in the present case is questionable because the expression is valid for averaging between two single uncoupled lines and when the line widths in the absence of exchange are effectively zero. Harris and Sheppard (41) considered that the cyclohexane case approximates better to the averaging of the chemical shift of an AB system with $J/\nu_{AB} \approx 1/2$ and have derived and applied the expression, $\tau_c = 1/\pi\nu_{AB}$ for calculating the rate constant at the coalescence temperature. The expression used by Harris and Sheppard is also an approximation as the cyclohexane protons constitute an A_6B_6 system with unequal AB coupling constants.

The alternative method of Jensen et al. (39b) for calculating the rate constant at the temperature of half-peak separation, using equation 10-31 of reference 1 also suffers from inaccuracies due to the uncertainty involved in the chemical shift value, however, the $\Delta F^{\neq}$ value should not encounter

much error for this error in the rate constant. These methods could not be applied to evaluate $\Delta H^{\neq}$ and $\Delta S^{\neq}$. Harris and Sheppard have determined the values for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ from the rate constants of the line broadening of the single peak above coalescence by using the fast-exchange approximation formula of Piette and Anderson (12). The values 9.0 ± 0.2 kcal./mole, and -7.9 ± 1.0 e.u. determined by these workers for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ respectively should be correct, provided the fast-exchange approximation conditions were satisfied throughout the temperature range covered to determine the rate constants. Any error introduced due to uncertainty in the chemical shift will be small. The present work was undertaken in an effort to obtain more accurate parameters involved in the ring inversion of cyclohexane.

The inability of analyzing the N.M.R. spectrum of cyclohexane over a wide range of temperature limited the range of kinetic studies. A wide range of kinetic studies appeared to be essential for the determination of the kinetic data more accurately and a simple cyclohexane spectrum capable of being analyzed over a wide range of temperature was therefore desired. Cyclohexane-d_{11}, $C_6D_{11}H$, appeared to be the most suitable compound for this purpose. Under double irradiation at the deuterium resonance frequency, the single proton would be free of the effects of coupling and at low temperature

should yield only two lines, one for the axial-H- and the other for the equatorial-H- conformer. This would allow the kinetics to be followed over a wide range of temperature and increase the reliability of the kinetic data. Recently Anet and Hartman (98) have used $C_8D_{15}H$ successfully for determining the kinetic data for the ring inversion of cyclooctane. The availability of cyclohexane-d_{11} saved us from the trouble of synthesizing the deuterated compound.

As expected, cyclohexane-d_{11} gave two sharp peaks of equal intensity at low temperature (Fig. 6) and thus showed the population of the conformers to be the same. The high field peak was assigned to the axial-H conformer and the low field one to the equatorial-H conformer for reasons already stated (p. 123). Identical populations for the two conformers are expected from the similar energy content of the two conformers. The maxima of the peaks at low temperature were very well defined and the maximum separation could be measured with great accuracy. Rate data were calculated over a wide range of temperatures -32° to -94° using the appropriate analytical solutions and the results have been presented in an earlier section.

An important limiting factor in the rate measurements is T_2, the transverse relaxation time. $1/T_2$ is defined as $\nu/2$ where ν is the width at one-half of the full signal strength

and is determined by the magnetic field inhomogeneity. The magnetic field inhomogeneity causes broadening of all lines in the spectrum, regardless of whether additional broadening due to a rate process is involved. Therefore due consideration should be given to the effect of T_2 in the rate measurements.

As described in an earlier section (p. 129), T_2 was measured in our case from the exponential decay envelope of the sharp signal for T.M.S. at several temperatures. It was found that the magnitude of T_2 did not undergo any appreciable change with the variation in temperature; the value being close to 1 sec. both at high (Table VII) and low (Table V) temperatures. This observation showed that the effect of magnetic field inhomogeneity was not affected by variation in temperature, hence by the viscosity of the solution. The effect of T_2 on the rate constants is not of similar importance at all temperatures and its effect was neglected whenever justified.

Below the coalescence temperature, the rate data were determined from the separation of peak maxima according to the expression developed by Gutowsky and Holm (page 125). The terms in T_2 have been neglected in deriving this expression from the line shape equation because the line widths ($\approx 1/T_2$) are small compared to the separation of the maxima of the doublet. Any error encountered in the rate constants for this approximation will really be small. In order to verify this assumption,

corrected values of rate constants at three temperatures in this region were determined by using the graphical method presented by Gutowsky and Holm (Fig. 1 of reference 75), and assuming T_2 to be equal to 1 sec. The latter assumption should be quite appropriate as the T_2 values were determined to be close to 1 sec. both at higher and lower temperatures. Table XIV compares the corrected values of log $1/2\tau$ (obtained from the graph) with those of the uncorrected ones (obtained from equation 1, p125 ; $1/T_2 = 0$); the correction terms are negligible as expected.

Table XIV

Temperature °C	log $1/2\tau$ (corrected) T_2 = 1 Sec.	log $1/2\tau$ [a] (uncorrected) $T_2 = \infty$	Correction $T_2 \neq \infty$
-73.2	1.175	1.182	-0.007
-68.98	1.432	1.436	-0.004
-65.98	1.638	1.640	-0.002

[a] taken from Table II.

The rate data obtained from the ratios of the maximum to the central v-mode intensities (Table III) below coalescence temperature are in good agreement with those obtained from the separation of peak maxima (Table II). The expression used for

this method (equation 2) also neglects the effect of T_2 for the same reason as Gutowsky's and therefore the rate data obtained by this method do not need any correction for T_2.

Below -73°, the peak separation becames almost constant and the application of the method of Gutowsky and Holm, equation 1, needed accurate measurement of the peak separation. Any small error in measuring the peak separation was liable to cause a great error in rate constants.

Therefore, the line width method for slow exchange, equation 3, developed by Piette and Anderson (12) was applied at a few temperatures. The results have been presented in the appropriate section (Table IV). The assumption that T_2 = 1 sec. is appropriate for reasons already stated. However, below -81.4°, a direct comparison of T_2 and T_2', under identical conditions by the exponential decay method became essential as any attempt to measure the narrow line width of cyclohexane-d_{11} signals from the recorded spectrum would involve appreciable uncertainty. The values of T_2 and T_2' obtained from the decay envelope of the T.M.S. and cyclohexane-d_{11} signals respectively did not encounter any error due to interference between the wiggles of one signal with the resonance signal of the other. The wiggle patterns were photographed under the best possible resolution of the spectrometer. The actual decay envelopes were nearly but not exactly exponential and effective averages

for T_2 values were therefore essential.

Above the coalescence temperature, the rate constants were calculated by using equation 6 (page 134) and this involved the measurement of the line widths at half height of the single broad line of cyclohexane-d_{11}. Equation 6 does not take into consideration the effect of T_2 and, therefore, the results presented in Table VI are uncorrected for T_2. However, any correction for T_2 in this region is expected to be negligible; a comparison of the line widths of the cyclohexane-d_{11} signal with that of the T.M.S. signal reveals that the greater part of the line widths of the cyclohexane-d_{11} signal is caused by the inversion process. The calculation of τ values from the analytical solution which takes into consideration the effect of T_2 is a laborious job. A graphical solution, similar to that used by Takeda and Stejskal (99) to correct for T_2 in the collapse of a spin-spin doublet, would be suitable. In the present case the values of τ (corrected for T_2; T_2 = 1 sec.) were evaluated at two temperatures from the following complex expression 17, in order to compare with those obtained from equation 6 (uncorrected for T_2; $T_2 = \infty$) at the same temperatures.

$$\nu = -K \frac{[(1 + \tau/T_2)\ P + QR]}{P^2 + R^2} \qquad [17]$$

in which $P = \tau\left[\frac{1}{T_2^2} - w^2 + \frac{1}{4}\nu_{AB}^2\right] + \frac{1}{T_2}$.

$Q = -\tau w$

$R = -w - \frac{2w\tau}{T_2}$

ν is the intensity of absorption.

w is the frequency (radians per second) relative to an origin at the band centre

ν_{AB} is in radians per second.

Equation 17 is a modification of equation (10-23) of reference 1 and is suitable in our case. Application of equation 17 leads to equation 18, a quartic in τ :

$$\frac{\tau^2\left[\frac{1}{T_2^3} + \frac{w^2}{T_2} + \frac{\nu_{AB}^2}{4T_2}\right] + \tau\left[\frac{2}{T_2^2} + \frac{\nu_{AB}^2}{4}\right] + \frac{1}{T_2}}{\tau^2\left[\frac{1}{T_2^4} + w^4 + \frac{\nu_{AB}^4}{16} + \frac{2w^2}{T_2^2} + \frac{\nu_{AB}^2}{2T_2^2} - \frac{w^2\nu_{AB}^2}{2}\right] + \tau\left[\frac{2}{T_2^3} + \frac{2w^2}{T_2} + \frac{\nu_{AB}^2}{2T_2}\right] + \frac{1}{T_2^2} + w^2}$$

$$= \frac{\tau^2\left[\frac{1}{T_2^3} + \frac{\nu_{AB}^2}{4T_2}\right] + \tau\left[\frac{2}{T_2^2} + \frac{\nu_{AB}^2}{4}\right] + \frac{1}{T_2}}{2\tau^2\left[\frac{1}{T_2^4} + \frac{\nu_{AB}^4}{16} + \frac{\nu_{AB}^2}{2T_2^2}\right] + 2\tau\left[\frac{2}{T_2^3} + \frac{\nu_{AB}^2}{2T_2}\right] + \frac{2}{T_2^2}} \qquad [18]$$

Equation 18 reduces to equation 6 if $1/T_2 = 0$. Because of the difficulty of calculations involving equation 18, solutions were

obtained at only two temperatures. The correction factors, (log 1/2 τ) eq. 18- (log 1/2 τ) eq. 6 at the two temperatures are shown in Table XV and are small as expected. Thus no appreciable error was introduced by using equation 6 to evaluate the rate data in this region.

Table XV

Temperature °C	(log $\frac{1}{2\tau}$) eq.18 (T_2 = 1 sec.)	(log $\frac{1}{2\tau}$)[a] eq.6 ($T_2 = \infty$)	Correction ($T_2 \neq \infty$)
-61.29	1.882	1.877	+0.005
-56.69	2.090	2.083	+0.007

[a] Taken from Table VI.

Above -47°, the rate constants were calculated from the fast exchange formula, equation 7, page 134 . Equation 6 was inapplicable in this region as the effect of T_2 could not be neglected. Equation 7 is a modified form of equation 18, under the conditions of fast exchange and both of these equations should yield similar τ values at a particular temperature in this region. The solution of equation 18 needed to check this expectation is very laborious. However, the following expression 19, a quadratic in τ , derived from

equation 18 on neglecting the numerators and higher powers of T_2, was used.

$$\tau^2(w^4 - \frac{\nu_{AB}^4}{16} + \frac{2w^2}{T_2^2} - \frac{\nu_{AB}^2}{2T_2^2} - \frac{w^2\nu_{AB}^2}{2}) - \tau(\frac{2w^2}{T_2} - \frac{\nu_{AB}^2}{2T_2}) + (w^2 - \frac{1}{T_2^2}) = 0 \qquad [19]$$

Expression 19 is no doubt an approximation of equation 18, however, it is a nearer approach to equation 18 than is equation 7. Both equations 19 and 7 were used to calculate τ for various values of w (line width in radians) at constant values for T_2 and ν_{AB}. The results are compared in Table XVI.

Table XVI

ν_{AB} radians per second	T_2 sec.	w in radians	$(\frac{1}{2\tau})$ eq.19 $sec.^{-1}$	$(\frac{1}{2\tau})$ eq.7 $sec.^{-1}$
200	1	1	∞	∞
		5	1250	1250
		10	560	555
		20	273	263
		50	121	102
		100	71	50

The results in Table XVI indicate the validity of equation 7 at smaller values of w (fast exchange); the values yielded by two equations being in very good agreement when the ratio of w to ν_{AB} lies between 1:200 and 1:20 and fairly good agreement exists till the ratio becomes greater than 1:10. The results on Table VII, obtained by using equation 7, therefore, most likely do not include any inaccuracy due to the use of the fast exchange approximation formula. At higher temperatures (above -40°) more accurate measurements of T_2 and T_2' became essential as the difference in the widths of the signals for T.M.S. and cyclohexane-d_{11} was barely recognisable. Therefore, the method of Jacobsohn and Wangsness, p. 129 , was employed for the determination of T_2 and T_2' and τ was calculated from the expression for fast exchange approximation, equation 7. For reasons stated above, the fast exchange approximation formula is applicable in this region.

In principle, the rate constants for the inversion of cyclohexane ring could be evaluated from the spectrum of ordinary cyclohexane (C_6H_{12}) above the coalescence temperature, provided the true chemical shift (ν_{AB}) between the axial and equatorial protons is known accurately. Harris and Sheppard (41) employed the fast exchange approximation formula for determining the rate constants over the temperature range

-20° to -70°. We have determined several rate constants above the coalescence temperature from the spectrum of ordinary cyclohexane assuming the true chemical shift between the axial- and equatorial proton to be 28.7 c.p.s. The results are shown in Table XVII.

Table XVII

Cyclohexane (C_6H_{12}) Ring Inversion Rates from Line Broadening

(Fast exchange approximation)

$10^3/T$	Rate $\frac{1}{2\tau}$ $sec.^{-1}$	$\log \frac{1}{2\tau}$	Method
4.472	208.055	2.318	Line broadening method (equation 6)
4.618	107.225	2.030	"
4.145	1429.86	3.155	exponential decay method (equation 7).

These rate data are in good agreement (points marked as 'h' in Fig. 8) with the least squares line drawn for the rate data for cyclohexane-d_{11}.

The points in the Arrhenius plot are scattered above and below the least squares line. It was observed that the rate data calculated on a particular day yielded a good straight

line for the Arrhenius plot, but those of different days yielded parallel lines. This unexpected behaviour most probably arose from the temperature gradient existing along the length of the sample tube and thus making the temperature correction dependent on the height of the sample in the sample tube, as well as on the position of the sample tube in the insert probe. No reason could be found for excluding any of these rate data and, therefore, all of them were included in the Arrhenius plot. The scattering of the points should not change the slope of the line much, since the lines yielded by the rate data of different days were parallel to each other. The value of E_a was obtained from this plot and computed to 90% confidence limit (assuming a random scatter).

The coalescence temperature was evaluated from the Arrhenius plot and as stated earlier no attempt was made to determine it experimentally. The graphical method appeared to be more accurate, in view of the fact that it was quite difficult to locate the coalescence temperature experimentally, due to the rapid changes suffered by the spectrum around this critical point. The coalescence temperature in the present case was calculated to be -60.3°, compared to -66.5° for C_6H_{12} as reported by Jensen (39). The strong coupling effects operating in the latter case probably affect its coalescence temperature, and on this basis, a difference between the two

values is not unexpected. However, a difference of more than 6° appears to be quite large, and is probably, in part, due to different instrumental set-ups for measuring the temperatures. Table XVIII compares the energy parameters obtained by us with those reported earlier

Before discussing the values of the parameters (Table XVIII) obtained in the present work, we may mention about the possible sources of errors in the experimental data and in the calculations.

As previously mentioned, errors in the calculations through the use of approximate solutions of the line shape equation should be negligible.

Errors in the experimental data can arise from (a) deviations from slow-passage (where applicable) and non-saturation conditions, (b) magnetic field drifts, (c) measurements of intensities, line-widths, peak separations, and (d) temperature measurements.

In order to eliminate the errors encountered due to factor (a) special care was taken to measure the spectra of cyclohexane-d_{11} under slow-passage conditions and with radio-frequency power level well below saturation value. The errors due to points (b) and (c) were reduced by averaging out the characteristic parameters of a number of spectra, measured at

TABLE XVIII

Energy and Entropy Parameters for Ring Inversion of Cyclohexane

Compound	E_a kcal./mole	$\Delta F^{\neq}$ kcal./mole	$\Delta H^{\neq}$ kcal./mole	$\Delta S^{\neq}$ e.u.	Reference
C_6H_{12}	-	9.7(-66.5°)	-		(39a)
"	-	10.1±0.1 (-66.7°)	11.5±2	+4.9[a]	(39b)
"	-	10.6(-66.5°)	9.0±0.2	-7.9±1.0	(41)
$C_6D_{11}H$	11.29±0.6	10.55[b](-60.3°)	10.87±0.6	+1.5[b]±2.3	(present work)
"	11.29±0.6	10.26[c](-60.3°)	10.87±0.6	+2.9[c]±2.3	(")

[a] Theoretical estimate, based on symmetry considerations and assuming boat form as an intermediate; corresponds to $\Delta H^{\neq}$ = 11.1 kcal./mole.

[b] Based on transmission coefficient = 1 i.e. one barrier.

[c] Based on transmission coefficient = $\frac{1}{2}$; assuming boat form as an intermediate.

the same temperature.

Most of the uncertainties in our experimental data were expected to arise from the difficulty of measuring the temperature of the sample in the region of the sample coil. Furthermore, it is not possible to determine the true temperature of the sample during the actual measurement of a spectrum.

The parameters obtained by us, however, should be more reliable than any other experimental values reported in the literature, as the use of cyclohexane-d_{11} for this investigation has enabled us to follow the ring inversion process over a wide range of temperatures. The present work, thus, reveals the usefulness of suitably deuterated compound for kinetic studies. This is reminiscent to the use of $C_8D_{15}H$ (98) for studies on ring inversion of cyclooctane. The parameters for ring inversion of cyclohexane-d_{11} should reflect the parameters for ring inversion of cyclohexane (C_6H_{12}) because the inversion process does not involve any crowded transition state and therefore "conformational kinetic isotope effects" are expected to be small (100).

In the following section, our results are discussed in the light of possible reaction pathway and are compared with the results obtained by others.

It is recognized (101) that the chair-to-chair interconversion of cyclohexane and cyclohexane-like molecules

pass through a twist boat form as a metastable intermediate. The twist boat form, unlike the chair form, is flexible. It can undergo rapid conformational changes, and pass through "untwisted" boat forms of somewhat higher energy than the twist boat form itself. The boat forms are energetically less favoured than the chair form and therefore they have only a fleeting existence. The energy difference between the chair form and the twist boat is about 5 kcal./mole (33,34,35), much less than the observed inversion barrier (>10 kcal./mole) for cyclohexane ring. This indicates that the ring inversion process of cyclohexane effectively involves two barriers, the boat forms representing the valley between them (Fig. 21). Cyclohexane undergoes interconversion between two identical forms, and therefore, these barriers have the same height. For such a situation, it can be assumed that an intermediate boat form has an equal chance of passing over either barrier.

A transmission coefficient of unity, which assumes that no molecule moving along the reaction coordinate at the transition state is ever reversed in its path and returned to the starting form, therefore, does not represent the true picture for the ring inversion process of cyclohexane. A transmission coefficient of 1/2 is appropriate for this process, and the values 10.26 kcal./mole and 2.9 $\pm$ 2.3 e.u. for $\Delta F^{\neq}$ and $\Delta S^{\neq}$ respectively (Table XVIII) should be considered

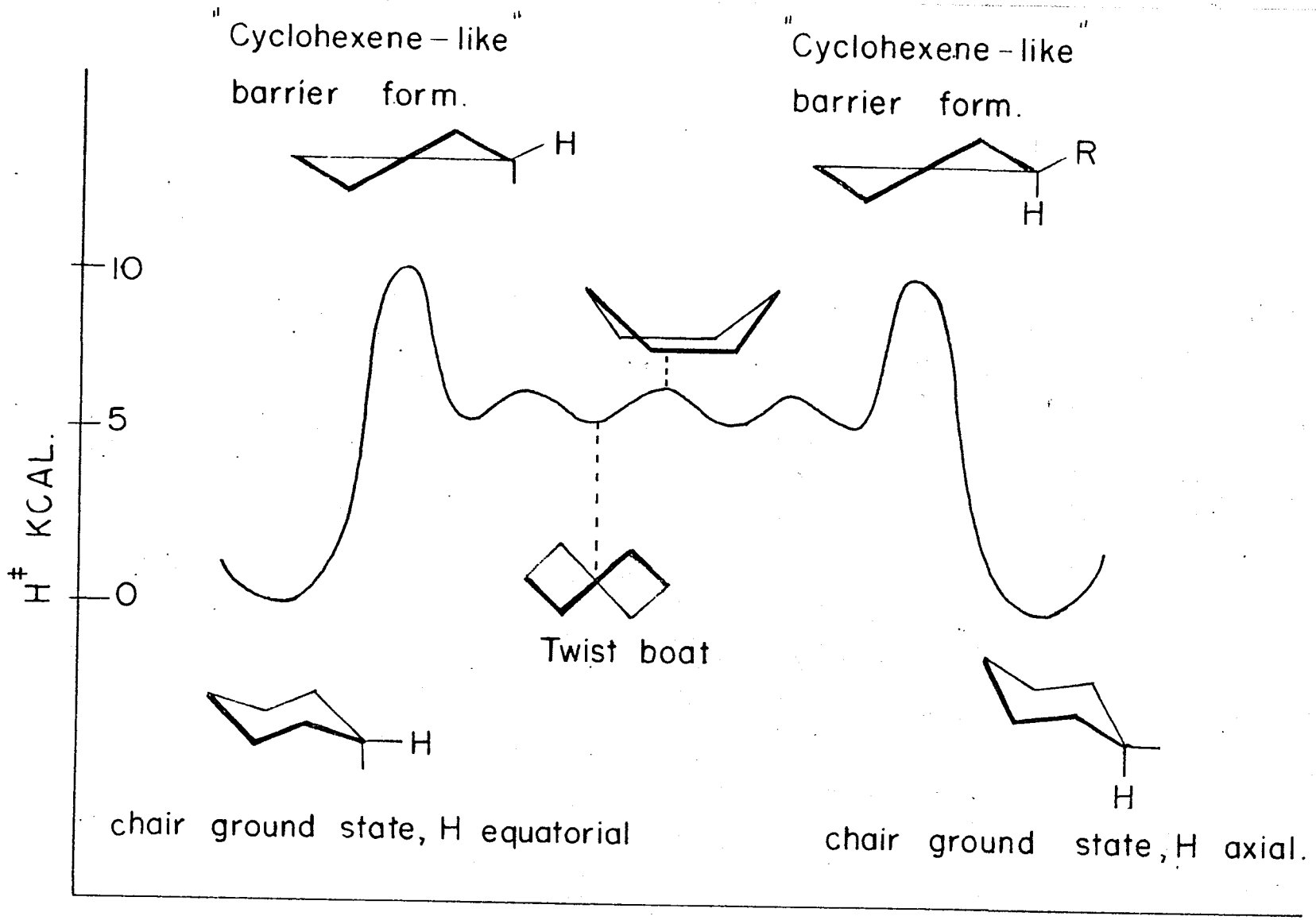

"Cyclohexene – like"
barrier form.
H
"Cyclohexene – like"
barrier form.
R
H
10
5
0
H‡ KCAL.
Twist boat
H
H
chair ground state, H equatorial
chair ground state, H axial.
Reaction coordinate

Fig. 21

as actual parameters for the ring inversion process of cyclohexane. However, these values of $\Delta F^{\neq}$ and $\Delta S^{\neq}$ differ by small amount from the corresponding values of $\Delta F^{\neq}$ and $\Delta S^{\neq}$, when transmission coefficient is unity (Table XVIII).

The most plausible molecular arrangement in the transition state for the ring inversion of cyclohexane has been visualized (33,39b) to be a structure approximately half-way between the chair and the twist boat. This model, with four carbon atoms in one plane, resembles the preferred conformation of cyclohexene, and has been calculated (33) to be 12.66 kcal./mole more energetic than the chair form. The calculations also show that the 'cyclohexene-like' transition state has the lowest energy requirement of any conceivable pathway for ring inversion of cyclohexane. Our value of 10.87 $\pm$ 0.6 kcal./mole for $\Delta H^{\neq}$ is in quite good agreement with Hendrickson's calculated value (33) of 12.66 kcal./mole.

Our finding of a positive $\Delta S^{\neq}$ is in disagreement with that of Harris and Sheppard (41). Jensen et al. (39b), assuming the "cyclohexene-like" activated form for the inversion process have calculated a $\Delta S^{\neq}$ (chair-to-boat) of +4.9 e.u. from symmetry considerations. A negative value of $\Delta S^{\neq}$, as found by Harris and Sheppard (41), is explainable on the basis of a planar form for the transition state. However, this is incompatible with the calculations of

Hendrickson (33), who has shown that the inversion process via a planar form probably requires an energy of at least 30 kcal./mole.

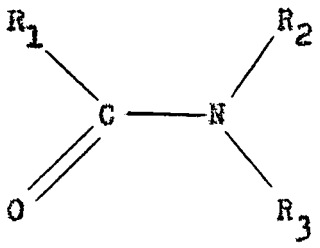
Kinetic studies by Harris and Sheppard (41) were limited to the temperature range of -20 to -70°. Rate data over such a small range of temperature must have limited the accuracy of the parameters calculated by these workers. Furthermore, their application of "fast exchange approximation" formula for evaluating τ throughout the temperature range of -20 to -70° is questionable. Our calculations (Table XVI) indicate that such an approximation is likely to introduce error in the rate constants, if applied at temperatures near the coalescence temperature. The $\Delta H^{\neq}$ value (11.5 ± 2 kcal./mole) determined by Jensen and his co-workers (39b) has a large uncertainty factor and did not enable them to determine $\Delta S^{\neq}$ from experimental data.

Our experimental value of $\Delta H^{\neq}$ is in good agreement with the proposed (33,39b) "cyclohexene-like" structure for the transition state of the inversion process of cyclohexane. A positive value of $\Delta S^{\neq}$ obtained by us is also consistent (39b) with the proposed transition state.

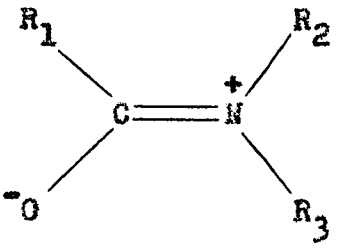
Our results are in agreement with the unpublished results ($\Delta H^{\neq}$ = 11.5 kcal./mole, $\Delta S^{\neq}$ = + 4.0 e.u.) of Meiboom (102), who has investigated the rate process of the ring inversion of cyclohexane (C_6H_{12}) by a pulse method. After the first draft of this thesis was completed, it was learnt that Dr. Bovey (103) has also investigated the ring inversion in $C_6D_{11}H$, and his approach has been in the same line as ours. The $\Delta H^{\neq}$ (10.7 kcal./mole) and $\Delta S^{\neq}$ (+ 1.4 e.u) values obtained by Shim are in excellent agreement with those obtained by us.

N.M.R. Studies on Some Aromatic Aldehydes

Rotational isomerism in amides (74,75,76) has been well established and has been attributed to the partial double bond character of the C-N bond arising from the contribution of resonance form II to the resonance hybrid of these molecules.



I



II

This finding led us to believe that similar isomerism may exist in p-aminobenzaldehydes. Several resonance structures are likely to contribute to the resonance hybrid of p-aminobenzaldehydes. These are shown in Fig. 22; the structures grouped as A and B arise from the resonance interaction of the benzene ring with the carbonyl group and the N< group respectively. The resonance structure C arises from the resonance interaction between these two groups through the benzene ring. This structure possesses a negatively charged oxygen atom and a positively charged nitrogen atom with eight electrons around it. Structure C is therefore energetically more favored than any member of the groups A and B, which is destabilized, either by a positively charged carbon atom with six electrons around it (Group A) or a negatively charged carbon atom with eight electrons around it (Group B). On this basis, resonance structure C is expected to make a greater contribution than any other resonance structure to the resonance hybrid of p-aminobenzaldehydes.

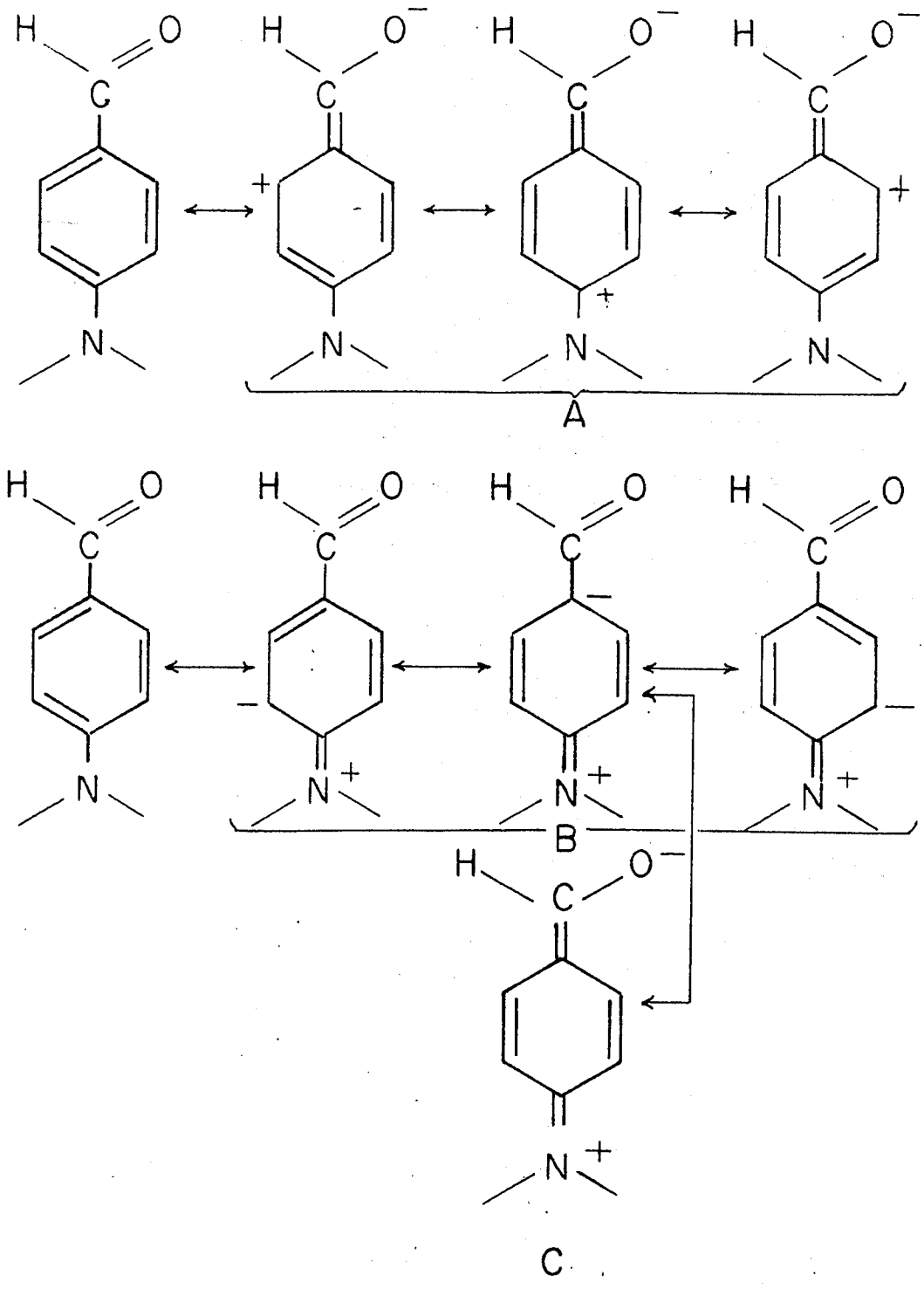


Fig. 22 Resonance structures of p-aminobenzaldehydes

The resonance structures indicate the presence of considerable double bond character in the bond connecting the aldehydid carbon atom (C_{ald}) with the aromatic ring (C_{ar}), as well as in the bond between the nitrogen atom and the aromatic ring. Therefore, appreciable barriers to free rotations about these bonds are to be expected.

A study on the restricted rotation about the C_{ald}-C_{ar} bond appears possible. The double bond character about this bond causes the ortho protons to be in different electronic environments (one being *cis* to the oxygen atom and the other being *trans* to it), and therefore a chemical shift between them is expected. The situation is analogous to those in amides, differing only from the fact that a benzene ring has been introduced between the nitrogen atom and the aldehydic carbon atom. The ortho protons in p-aminobenzaldehydes could be compared with the N-CH_3 groups of *N*,*N*-dimethylacetamide and other substituted amides. Unfortunately, a similar study for restricted rotation about the C_{ar}-N bond is not possible due to symmetry of the molecule around this bond. The present work was undertaken to study the behaviour of the N.M.R. spectra of the ortho protons of p-aminobenzaldehydes, and to determine the energy barrier towards rotation about the C_{ald}-C_{ar} bond.

p-*N*,*N*-dimethylaminobenzaldehyde appeared to be a suitable compound for this purpose. The spectrum of this

compound has been reported (104), the ortho protons yield a doublet at a lower field than the doublet for the meta protons. The doublets are caused by mutual coupling between the single resonance lines of the ortho and the meta protons. In order to simplify the spectrum expected at low temperature for the ortho protons (i.e. to remove coupling with the meta protons), substitution of the meta protons by deuterium appeared desirable. The meta protons of p-*N*,*N*-dimethylaminobenzaldehyde underwent smooth exchange with deuterium in the presence of deuterium oxide (D_2O) and hydrochloric acid. This was expected from the ortho- and para-directing influence, as well as the activating influence of the $N(CH_3)_2$ group, in electrophilic substitution reactions of benzenoid compounds.

The N.M.R. spectrum of 4,*N*,*N*-dimethylamino-3,3'-d_2-benzaldehyde in methylene chloride exhibited a single peak in the aromatic region, the chemical shift being the same as the low field doublet of the undeuterated compound. The high field doublet was missing, and this confirmed the absence of any hydrogen atom at the 3,3'-positions of the deuterated compound. The single peak for the ortho protons of 4,*N*,*N*-dimethylamino-3,3'-d_2-benzaldehyde was fairly broad due to coupling with the deuterium atoms. The peak got quite sharp when a second rf field of the correct frequency was employed to remove the coupling effect due to deuterium nuclei. In

order to remove the interference of the coupling effects of deuterium atoms, all spectra needed for this investigation were measured with deuterium decoupling. The chemical shifts of the different protons of the compound at room temperature is given in Table IX; the assignments of the bands were straightforward. The single peak for the ortho protons at room temperature suggested the equivalence of the ortho protons, and that the rotation about the C_{ald}-C_{ar} bond was fast enough to average the different magnetic fields experienced by these protons. A low temperature investigation was therefore carried out.

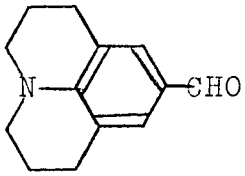
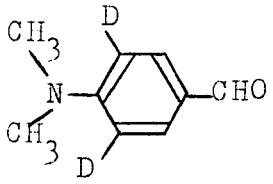
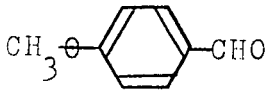
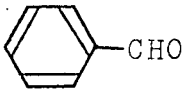
The single peak for the ortho protons at room temperature underwent changes (Fig. 9) with the lowering of temperature, and at -86° yielded a quartet. The ortho protons obviously constituted an AB system; the values of the chemical shift between the ortho protons and their coupling constant are given in Table X. The low field doublet of the quartet can probably be assigned to the proton cis to the oxygen atom, as the close proximity of this proton to the oxygen atom is expected (105) to shift its resonance towards a lower field. The mean position of the quartet (Table IX) was almost the same as the position of the singlet at room temperature; the rest of the protons of the molecule exhibited only small changes in their chemical shifts (Table IX).

The coalescence temperature for the transition between the singlet and the quartet for the ortho protons was determined to be about -71°. The relation $\frac{1}{2k} = \tau_c = \frac{\sqrt{2}}{2\pi \nu_{AB}}$ was used to calculate the rate constant for reorientation around the $C_{ald}-C_{ar}$ bond at the coalescence temperature; ν_{AB} being the measured chemical shift between the ortho protons. The expression is not strictly applicable in the case of an AB system, as it is derived for averaging between two single uncoupled lines. However, the comparatively large chemical shift compared to the coupling constant ($\nu_{AB}/J \approx 4$) in the present case, is unlikely to cause much error in the rate constant. The value for $\Delta F^{\neq}$, the free energy of activation, required for reorientation about the $C_{ald}-C_{ar}$ bond at the coalescence temperature was calculated from Eyring's equation. The transmission coefficient was assumed to be unity; the values for $\Delta F^{\neq}$ and the rate constant ($k = \frac{1}{2\tau_c}$) are shown in Table XIX.

9-Julolidinecarboxaldehyde was subjected to a similar type of investigation. The compound in methylone chloride solution exhibited a single peak for the ortho protons at room temperature. The spectrum of this compound at room temperature is shown in Figure 10 and parameters derived from it are given in Table IX. The assignment of the bands followed from the expected chemical shift values of the protons as well as from the multiplet pattern of the individual bands of the spectrum.

Table XIX

Kinetic Data for Hindered Rotation of some Aromatic Aldehydes

Compound	Solvent	Coalescence Temp. ^{o}C	Rate constant (k) $sec.^{-1}$ at coalescence temp.	$\Delta F^{\neq}$ Kcal./mole at coalescence temp.
	CH_2Cl_2	-61	29	10.9
	CH_2Cl_2	-71	19	10.5
	Vinyl chloride	-99	16	9.0
	Vinyl chloride	-123	19	7.7

On lowering the temperature, the signal for the ortho protons underwent changes (Figure 11), in the same way as observed with the signal of the ortho protons of 4-N,N-dimethylamino-3-3'-d_2-benzaldehyde; small changes in the chemical shifts of all the protons of the molecule were also observed (Table IX). The coalescence temperature was determined to be about -61°; the rate constant and $\Delta F^{\neq}$ (Table XIX) at the coalescence temperature were calculated as before.

The above observations indicated the presence of appreciable double bond character in the C_{ald}-C_{ar} bond of p-aminobenzaldehydes. This is in accordance with the resonance structures of these compounds (Fig. 22). In order to examine the role of the carbonyl group in such rotational isomerism a preliminary study on benzaldehyde was undertaken. The spectra of the aromatic protons of benzaldehyde in vinyl chloride solution at several low temperatures are shown in Fig. 12. No change in the spectrum was observed from room temperature down to -90°, but below -95°, the bands of the spectrum underwent broadening; at still lower temperature the appearance of new peaks was evident (Fig. 12). These changes indicated that a rate process identical to that observed with p-aminobenzaldehydes was involved. The spectrum of benzaldehyde was complex and no attempt was made to assign the bands. The "coalescence temperature" was estimated to be around -123°. The chemical

shift between the ortho protons of benzaldehyde at low temperature, is expected to be of the same order of magnitude as found for the ortho protons of 4-*N*-*N*-dimethylamino-3,3'-d_2-benzaldehyde (8.4 c.p.s.). The rate constant for the rate of reorientation around the C_{ald}-C_{ar} bond of benzaldehyde was calculated at the coalescence temperature in the same way as before (with ν_{AB} = 8.4 c.p.s.). The errors encountered in the rate constant and in $\Delta F^{\neq}$ (Table XIX) due to uncertainty in ν_{AB} should not be high. An uncertainty of a factor of 1.5 in ν_{AB} was calculated to change the $\Delta F^{\neq}$ value by about $\pm$ 0.2 kcal./mole. More accurate values for the coalescence temperature, and hence for the rate constant and the free energy of activation would be obtained by N.M.R. study on suitably deuterated benzaldehyde.

The problem was obviously extendable to any suitably *p*-substituted benzaldehyde. This led us to examine the N.M.R. spectrum of *p*-anisaldehyde which would be expected (see below) to have a coalescence temperature, as well as $\Delta F^{\neq}$ value, intermediate between those obtained for benzaldehyde and 4-*N*-*N*-dimethylamino-3,3'-d_2-benzaldehyde. The signals for the ortho protons underwent changes (Fig. 13) with lowering of temperature and ultimately yielded a triplet (actually two overlapping doublets). It indicated that rotational isomerism similar to that observed in *p*-aminobenzaldehydes was also

involved in p-anisaldehyde. The "coalescence temperature" was estimated to be around -99° and the chemical shift between the ortho protons was calculated to be 7.2 c.p.s. The rate constant and $\Delta F^{\neq}$ (Table XIX) at the coalescence temperature were evaluated in the usual way. The values for the rate constant and $\Delta F^{\neq}$ should be reasonably accurate. Any error involved in determining the coalescence temperature and the chemical shift would be avoided by using 4-methoxy-3,3'-d_2-benzaldehyde instead of p-anisaldehyde as the former would simplify the spectrum for the ortho protons at low temperature (cf. 4-N,N-dimethylamino-3,3'-d_2-benzaldehyde).

The data on the coalescence temperatures and $\Delta F^{\neq}$ values (Table XIX) indicate the importance of the p-substituent in the restricted rotation about the C_{ald}-C_{ar} bond. In benzaldehyde, only the resonance interaction of the carbonyl group with the benzene ring is present, and therefore, a freer rotation around the C_{ald}-C_{ar} bond than that in the p-substituted benzaldehydes is expected. The much lower coalescence temperature, as well as a low value of $\Delta F^{\neq}$ for benzaldehyde, compared to those of the p-substituted benzaldehydes are in agreement with this expectation. The presence of only small differences between the coalescence temperatures and $\Delta F^{\neq}$ values of 4-N,N-dimethylaminobenzaldehyde and 9-julolidine carboxaldehyde are not unexpected from the similar structure of the two compounds. The N< group of 9-julolidinecarboxaldehyde

is held in the same plane as the benzene ring; the resonance interaction of such a $N<$ group with the aldehyde group through the benzene ring, is greater than the one where the $N<$ group and the benzene ring are not in the same plane. The slightly higher value of $\Delta F^{\neq}$ for 9-julolidinecarboxaldehyde compared to that of p-N-N-dimethylaminobenzaldehyde is not therefore surprising. The small difference in the $\Delta F^{\neq}$ values of these two compounds indicate that the $N<^{CH_3}_{CH_3}$ group in p-N-N-dimethylaminobenzaldehyde is almost in the same plane as the benzene ring. In compounds with substituent, of appreciable size, ortho to the $N<^{CH_3}_{CH_3}$ group of p-N,N-dimethylaminobenzaldehyde, the bulk of the substituent is expected to hinder the $N<^{CH_3}_{CH_3}$ group from lying in the same plane as the benzene ring. The resonance interaction between the $N<^{CH_3}_{CH_3}$ group and the benzene ring in these compounds will therefore be decreased to a considerable extent and on this basis, it can be predicted that these compounds will have a lower $\Delta F^{\neq}$ value than p,N,N-dimethylaminobenzaldehyde.

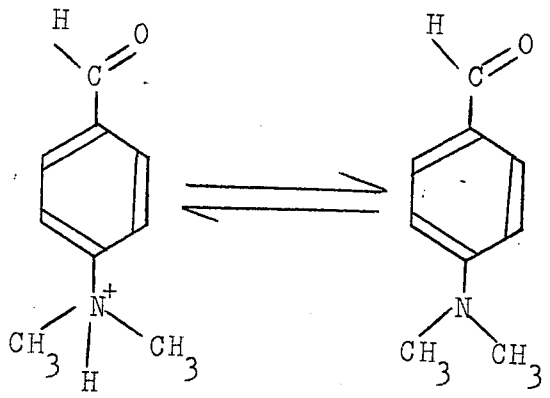
p-Anisaldehyde can be represented by the same number of resonance structures as met with in p-aminobenzaldehydes. However, resonance structures of p-anisaldehyde with a positive charge on the oxygen atom are less favourable than the resonance structures of p-dimethylaminobenzaldehyde with a positive

charge on the nitrogen atom. Therefore, the resonance interaction between the $N<$ group and the aldehyde group of p-dimethylaminobenzaldehyde should be greater than the resonance interaction between the OCH_3 group and the aldehyde group of p-anisaldehyde. This would explain the higher coalescence temperature and higher $\Delta F^{\neq}$ value for 4-N,N-dimethylamino-3,3'-d_2-benzaldehyde, with respect to the corresponding values for p-anisaldehyde.

The difference (10.5 - 7.7) = 2.8 kcal./mole in the $\Delta F^{\neq}$ values of p-N,N-dimethylaminobenzaldehyde and benzaldehyde must be due to interaction between the $-N(CH_3)_2$ group and the -CHO group, because of the following reasons. In benzaldehyde, only the resonance interaction between the -CHO group and the benzene ring operates towards establishing a partial double bond in the C_{ald}-C_{ar} bond. However, in p-N,N-dimethylaminobenzaldehyde, in addition to the resonance interaction between the -CHO group and the benzene ring, the resonance interaction between the -CHO group and the $-N(CH_3)_2$ group contributes to the double bond character in the C_{ald}-C_{ar} bond.

The effect due to resonance interaction between the $-N(CH_3)_2$ group and the -CHO group in p-N,N-dimethylaminobenzaldehyde can be estimated from the difference in the pKa values of this compound and its meta counterpart. This is possible for the following reasons. The pKa of p-N,N-dimethyl-

aminobenzaldehyde is given by the following equilibrium.



In the nonprotonated species, the resonance interaction of the aldehyde group with the benzene ring and the resonance interaction of the $-N(CH_3)_2$ group with the benzene ring, as well as with the aldehyde group are operative. However, in the protonated form only the resonance interaction of the aldehyde group with the benzene ring is present and therefore the pKa value of p-N,N-dimethylaminobenzaldehyde reflects the resonance interactions of the $-N(CH_3)_2$ group with the benzene ring and also with the aldehyde group. On the other hand, in a similar equilibrium of the meta compound the resonance interaction of the $-N(CH_3)_2$ group with the aldehyde group is absent even in the nonprotonated species and therefore the pKa of m-N,N-dimethylaminobenzaldehyde provides the resonance interaction of the $-N(CH_3)_2$ group with the benzene

ring alone. The inductive effects of the aldehyde group are expected to be of the same order of magnitude in both m- and p-compounds (106).

The pKa values of p-N,N-dimethylaminomethylbenzoate (107) and its meta analogue (108) are 2.52 and 3.86 pKa units respectively; the resonance interaction between the $-N(CH_3)(CH_3)$ group and the $-COOCH_3$ group is therefore 1.34 pKa units. On relating the pKa values with free energy changes (i.e. $\Delta F = -RT \ln K = 2.303\ RT\ pKa$), the resonance interaction of 1.34 pKa units amounts to 1.8 kcal./mole. This value is expected to be a rough approximation for the resonance interaction between the $-N(CH_3)(CH_3)$ group and the -CHO group of p-N,N-dimethylaminobenzaldehyde. The unavailability of the pKa value of m-N,N-dimethylaminobenzaldehyde barred us from estimating a more appropriate value for the resonance interaction between the $-N(CH_3)(CH_3)$ group and the -CHO group. In the ester a resonance interaction between the carbonyl group and the $-OCH_3$ group is also operative and this is likely to decrease the resonance interaction of the ester group with the benzene ring and hence with the $-N(CH_3)(CH_3)$ group. This is not the case with the aldehyde and therefore a greater value than 1.8 kcal./mole for the resonance interaction between the $-N(CH_3)(CH_3)$ and the -CHO group is probable.

An estimate of the maximum resonance interaction between the $-N(CH_3)_2$ group and the -CHO group of p-N,N-dimethylaminobenzaldehyde can be obtained from the difference in the pKa values of dimethylaniline, 5.1 (109), and p-N,N-dimethylaminobenzaldehyde, 1.57 (110). The difference, when translated into free energy changes, amounts to 4.8 kcal./mole. This is the maximum value for resonance interaction between the $-N(CH_3)_2$ group and the -CHO group of p-N,N-dimethylaminobenzaldehyde as no corrections for the inductive effect of the -CHO group, which affects the pKa of p-N,N-dimethylaminobenzaldehyde, have been considered.

The value obtained for resonance interaction between the $-N(CH_3)_2$ group and the -CHO group of p-N,N-dimethylaminobenzaldehyde (2.8 kcal./mole) by N.M.R. studies is thus in agreement with that obtained from pKa data (between 4.8 and 1.8 kcal./mole). A better agreement than this cannot be expected in view of the fact that the solvent effects have been ignored in these calculations.

The above discussion indicates that the barrier to rotation about the C_{ald}-C_{ar} bond of aromatic aldehydes is mostly due to interaction between the -CHO group and the benzene ring. This observation is consistent with the results obtained by acoustic absorption studies (111) on acrolein,

crotonaldehyde, cinnamaldehyde, methacrolein and furacrolein. It has been shown (111) that a barrier of about 5 kcal./mole for C-C bond adjacent to the carbonyl group exists in these compounds. Our finding of a $\Delta F^{\neq}$ value of 7.7 kcal./mole for benzaldehyde is not therefore unexpected. This is also consistent with the recent work of Bramley and Le Fèvre (112) which indicates that in benzaldehyde, the aldehyde group and the benzene ring are coplanar.

Our finding of restricted rotation about the C_{ald}-C_{ar} bond of aromatic aldehydes is the first of its kind in this field. The present work also reveals the role of a p-substituent in the restricted rotation about the C_{ald}-C_{ar} bond of p-substituted benzaldehydes. Our results indicate that in p-substituted benzaldehydes, where the p-substituent is a strong electron attracting group (e.g. NO_2 group), a smaller barrier to rotation about the C_{ald}-C_{ar} bond than that in benzaldehyde may exist. It will be interesting to investigate this aspect of the problem. It is obvious that the present work is extendable to any m- or p-substituted-benzaldehydes.

N.M.R. Studies on Cyclohexenes

The "half-chair" conformations of cyclohexane and its derivatives are expected to undergo rapid interconversion like the chair forms of cyclohexane unless suitably locked into one conformation. But no quantitative studies on the

conformational equilibria of any cyclohexene compounds have yet been published.

The bonds of C-4 and C-5 in the "half-chair" conformations of cyclohexene compounds are almost normal equatorial and axial and they are expected to possess properties similar to the corresponding bonds in the cyclohexanes. The bonds on C-3 and C-6, which are 'quasi-axial' and 'quasi-equatorial' are also likely to behave somewhat like the axial and equatorial bonds of cyclohexane respectively. The variation in the widths at half-height of the C-6 proton resonance of a number of 6-substituted-1-phenyl (and methyl) cyclohexenes have been used by Garbisch (65) to determine the preferred conformations of the C-6 substituents. His method is based on the assumption that the signal for a 'quasi-axial' proton on C-6 will have a larger width at half-height than the one arising from a 'quasi-equatorial' proton, as the width is mostly dependent on the coupling between the C-6 proton and the C-5 protons, and it is known from studies on cyclohexane compounds that $J_{a,a\ \text{vicinal}} > J_{e,a\text{vicinal}} \approx J_{e,e\text{vicinal}}$.

The geminal coupling constant in cyclohexene compounds, as well as the vicinal coupling constants in them, are expected to be almost of the same order of magnitude as the corresponding values observed in the cyclohexane system. We proposed to verify these expectations, and also to attempt to determine the

conformational equilibria of a few monosubstituted cyclohexene derivatives.

The 1-H protons (the proton attached to the carbon bearing the substituent) of Δ^3-tetrahydrobenzaldehyde, Δ^3-tetrahydrobenzoic acid, Δ^3-tetrahydroacetophenone, and Δ^3-tetrahydrobenzonitrile were chemically shifted from the rest of the protons, and their spectra were complex, due to coupling with the neighboring protons. The high field spectrum of the rest of the protons on the tetrahedral carbon atoms was still more complex, as the chemical shifts of the allylic and the homoallylic protons were almost the same. A much more simple spectrum for all these compounds was essential for our investigation, and this led us to synthesize, Δ^3-tetrahydrobenzaldehyde-2,2,3,4,5,5-d_6, Δ^3-tetrahydrobenzoacetophenone-2,2,3,4,5,5-d_6, Δ^3-tetrahydrobenzonitrile-2,2,3,4,5,5-d_6, and Δ^3-tetrahydrobenzoic acid-2,2,3,4,5,5-d_6. The first three of these compounds were prepared by the Diels-Alder condensation of butadiene-d_6 with the appropriate dienophile (see experimental). The fourth one, the acid, was prepared by the oxidation of the corresponding aldehyde with silver oxide. The purities of the compounds were ascertained by V.P.C. analysis, the impurities present in the ketone did not interfere with the analysis of the N.M.R. spectrum.

All these hexadeuterated cyclohexene compounds

contained three protons in the ring; one on C-4, and the other two on C-5. The protons constituted an ABX system, and analysis of the spectra of these compounds was carried out in the usual way (97); the results have been presented in an earlier section.

The variations in J_{BX} and the relatively constant value for J_{AX} (for three of these compounds), cannot be explained on the basis of deformation of the "half-chair" form for the cyclohexene ring. The quite large variation in J_{BX} (Table XII), from 10.2 to 12.9 c.p.s., need a fairly large distortion of the "half-chair" form which is expected to cause a similar variation in J_{AX}. The electronegativities of the substituents cannot explain the variations in J_{BX} either. Williamson (113) has observed during his studies on the hexachlorobicyclo [2.2.1] heptenes, that the values of J_{BX} and J_{AX} decrease with increase in the electronegativities of the substituents. If this was true in our case, then we would expect both J_{BX} and J_{AX} to decrease in the order nitrile > acid > aldehyde, as the electronegativities of these groups (114) are in the reverse order. No such uniformity in the changes in J_{BX} and J_{AX} is observed in our case.

It appears to us that the variations in J_{BX} and the relatively constant values for J_{AX} in three of these compounds (excluding the nitrile), can be explained on the basis of "half-chair" - "half-chair" interconversion of these compounds. At room temperature, when the interconversion is very rapid, the

vicinal coupling constants are a weighted average of the equilibrium forms and therefore their magnitudes depend on the population of the two conformers. Under these conditions, J_{cis} $(=J_{AX})$ = n $(J_{a,e})$ + (1 - n)$(J_{e,a})$, and J_{trans} $(=J_{BX})$ = n (J_{aa}) + (1 - n) J_{ee}, where n is the fraction of the molecules with the substituent group in the equatorial orientation. It is known (91) from the studies on cyclohexane derivatives, that the vicinal coupling constants decrease in the order $J_{aa} > J_{ea} \simeq J_{ae} \simeq J_{ee}$; therefore a higher value of J_{BX} would suggest a higher proportion of the equatorial conformer and vice versa, and in any case J_{AX} should undergo little change. These considerations indicate that the preference for the equatorial conformation in these three compounds decreases in the order $COCH_3 > COOH > CHO$.

The above conclusions are in agreement with the expectation from the conformational concept based on nonbonded interactions. On examining a model for the "half-chair" conformation of cyclohexene, it is seen that there is strong 1,3 interaction between the axial bond on C-4 and the quasi-axial bond on C-6; a similar interaction exists between the axial bond on C-5 and the quasi-axial bond on C-3. As such, a bulky group on C-4 (in these compounds C-1 from nomenclature used), is expected to favour an equatorial orientation, and the degree of this preference depends on the bulk of the substituent.

The bulk of the three substituents under consideration decreases in the order $COCH_3$ > COOH > CHO, and therefore, the preference for an equatorial orientation of these groups is expected to decrease in the same order.

However, the values of J_{BX} and J_{AX} for the nitrile cannot be explained in the same way. This linear group has been shown (115,116) to have only a slight preference for the equatorial conformation in the cyclohexane system. If this is also true in the case of the cyclohexene system, then a lower value for J_{BX} than (< 10.2 c.p.s.) would be expected. The low value for J_{AX} (1.7 c.p.s.) is also surprising, and no explanation can be given on the basis of present knowledge.

In an effort to determine the conformational equilibrium of the nitrile a preliminary low temperature study on the nitrile was carried out. No evidence for separate axial and equatorial 1-H (X proton) was obtained from room temperature down to -100°. However, a recent study in this laboratory has indicated the appearance of two sets of bands in the X-part of the spectrum of the nitrile at ~ -145°.

In the cyclohexene derivatives, the chemical shift of the X proton from the A proton as well as from the B proton is not large, and it may be that an ABC, rather than an ABX analysis on the spectra of these compounds, is more appropriate. The anomalous vicinal coupling constants of the nitrile with respect to those of other cyclohexene derivatives,

may be due to the inappropriateness of the ABX analysis employed to evaluate these coupling constants. Therefore ABC analysis of these spectra to evaluate the coupling constants seems desirable. This aspect of the work is now being pursued.

The chemical shifts of X, A, and B protons are influenced, amongst other things, by the electronegativity and the diamagnetic anisotropy of the substituents, as well as by the ratio of the population of the conformers. No simple explanation for the small differences in the chemical shift values of the cyclohexene compounds appears to be available.

N.M.R. Study on Cyclohexyl Acetate

2,2,3,3,4,4,5,5-Octadeuteriocyclohexyl acetate was prepared to determine the vicinal coupling constants, and to compare them with those obtained by Anet (55) from his studies on 3,3,4,4,5,5-hexadeuteriocyclohexyl acetate. The calculation of the coupling constants has been presented in an earlier section. Table XX shows that the vicinal coupling constant values obtained in this present investigation are in good agreement with those reported by Anet.

The equilibrium constant K reflects the ratio of the equatorial to the axial acetate, and has been calculated in the present case by correlating the $|J_{AX} + J_{BX}|$ value at room temperature, with those of the axial and equatorial

Table XX

Compound		J_{large} c.p.s.	J_{small} c.p.s.	K	Reference
cyclohexyl acetate	I*	9.26	3.89	3.0	Anet's work(55)
at room temp.	II*	9.28	4.07	3.3	Present work
		J_{aa} c.p.s.	J_{ae} c.p.s.	J_{ee} c.p.s.	
Equatorial acetate					
at -110°	I	11.43	4.24	-	Anet's work(55)
at -118°	II	11.66	4.03	-	Present work
Axial acetate					
at -110°	I	-	2.71	2.71	Anet's work(55)
at -118°	II	-	2.77	2.77	Present work

* I and II refer to 3,3,4,4,5,5-hexadeuterio- and 2,2,3,3,4,4,5,5-octadeuterio- cyclohexyl acetate respectively.

acetates obtained from the low temperature spectrum (see page 162). Our value for K is in good agreement with that obtained by Anet (Table XX).

Recently Reeves and his co-workers (59) have determined the conformational equilibrium of cyclohexyl acetate, from N.M.R. studies on 2,6-tetradeuteriocyclohexyl acetate;

the percentage of the equatorial acetate (76%) at room temperature agrees well with the K value obtained by us, as well as by Anet. Their method is based on interrelating the chemical shift of 1-H at room temperature with that of the axial 1-H, and equatorial 1-H, obtained from the low temperature spectrum. However, when this method is applied to our system as well as to Anet's system (117), contradictory results are obtained. This arises from the differences in chemical shift values as can be seen in Table XXI.

The differences in the chemical shift values are unexpected and quite puzzling. The relative chemical shift between the axial and the equatorial proton signals obtained by Reeves et al., is only 18.5 c.p.s., compared to 24.7 c.p.s. obtained by us. Our value of $\nu_a - \nu_e$ is in good agreement with that of Anet. The low value for $\nu_a - \nu_e$ obtained by Reeves and his co-workers may be due to incomplete separation of the axial and the equatorial proton signals at -96°. This is supported by our observation, that above -100° the peaks of the X-parts of the spectrum (one X for the axial proton and the other X for the equatorial proton), were fairly broad, even when the spectra were measured with deuterium decoupling.

Our chemical shift values are closer to those obtained by Anet. Comparison of our ν_a and ν_e values with those of Anet

Table XXI

Chemical Shift Values of 1-H of Cyclohexyl Acetate

Authors	$\nu_{a,e}$ av. c.p.s.	ν_a c.p.s.	ν_e c.p.s.	$\nu_a - \nu_e$ c.p.s.	K^a (= $\frac{\text{eq.acetate}}{\text{ax.acetate}}$)	K^{*b}
Reeves et al.*(59) (30% in CS_2)	273.6	269.1(-96°)	287.6(-96°)	18.5	3.1	-
Anet (117) (ca 25% in CS_2)	276.0	264.2(-110°)	289.1(-110°)	24.9	1.1	10:1 at-110°
Present work (ca 20% in CS_2)	275.2	261.5(-118°)	286.2(-118°)	24.7	0.8	4.5:1 at-106°

* Chemical shift values reported at 40 Mc have been corrected to 60 Mc.

a K from chemical shift data.

b K^* from peak areas.

shows that in our case both axial and equatorial proton signals have suffered shifts to high field to the same extent. The differences in ν_a and ν_e values as found between these two studies might have arisen from the difference in viscosities of the solutions, since the concentrations of the solutions, as well as the temperatures of investigation in the two cases were different. Any effect due to difference in deuterium substitution of the acetates, studied in the two cases, is expected to be small.

Use of chemical shift data obtained by Anet exhibits only a slight preference for the equatorial acetate (K = 1.1), and in our case, the chemical shift values show a slight preference for the axial acetate (K = 0.8). These values are in contrast to those obtained by measurement of the peak areas of the axial and equatorial proton signals (Table XXI) at low temperature. In our case, the relative areas of the two X-patterns were measured with the help of a Varian V3521 Integrator, whereas Anet determined the peak areas directly; the different methods employed in these two studies probably caused the difference observed in the K^* values.

Obviously the interrelationship of the chemical shift data yield an absurd K value. No definite explanation for this behaviour is available at the present moment. Variation in chemical shift between the axial and the equatorial proton signals

with temperature may be one of the reasons for it; a further study in this field at different temperatures is desirable to check this point. Furthermore, the acetate group itself, unlike the halogens, may exist in different conformations and its effect on the chemical shift of 1-H proton may depend on the population of the different conformers of the acetate group. The population of the different conformers of the acetate group will be temperature dependent, and therefore, its effect on the chemical shift of 1-H will be also temperature dependent. If this is true, then the interrelationship of chemical shift data for calculating the equilibrium constant will not be appropriate in the present case. However, before anything definite can be said, it appears to us that a reexamination of this investigation is essential.

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CLAIMS OF ORIGINAL RESEARCH

1. The structure and stereochemistry of lycofoline, an alkaloid of Lycopodium annotinum L., have been established by relating the alkaloid to acrifoline, another Lycopodium alkaloid, whose structure and stereochemistry are known. The stereochemistry of dihydrolycofoline, the hydrogenated product of lycofoline, has also been deduced.

2. Annofoline, and alkaloid of Lycopodium annotinum L., has been shown to be resistant towards dehydration and enol-acetylation. Baeyer-Villiger oxidation of annofoline does not give rise to the expected lactones.

3. Dihydroacrifoline, the hydrogenated product of acrifoline, does not undergo epimerization in the presence of a strong base. However, under vigorous treatment with strong base, it yields a dehydro-product which has been shown to be an α,β-unsaturated ketone.

4. Anhydrodehydrodeacetylfawcettiine remains mostly unchanged under epimerizing conditions.

5. The N.M.R. spectra of cyclohexane-d_{11} have been studied over a wide range of temperatures, -32 to -94°, in order to follow the kinetics of the ring inversion of cyclohexane. The enthalpy of activation, $\Delta H^{\neq}$, for the

ring inversion process has been found to be 10.87 ± 0.6 kcal./mole, the free energy of activation, $\Delta F^{\neq}$, 10.26 kcal./mole, and the entropy of activation, $\Delta S^{\neq}$, + 2.9 ± 2.3 e.u. The parameters obtained in this investigation should be more reliable than the values reported in the literature as the use of cyclohexane-d_{11} has enabled us to follow the ring inversion process over a wide range of temperature.

6. Low temperature N.M.R. studies on several aromatic aldehydes have revealed the presence of appreciable barrier to rotation about the C_{ald}-C_{ar} bond of these compounds. The free energy of activation, $\Delta F^{\neq}$, for the rotation about the C_{ald}-C_{ar} bond of these compounds has been determined and has been found to be appreciably dependent on the nature of the p-substituent.

7. Δ^3-Tetrahydrobenzaldehyde-2,2,3,4,5,5-d_6, Δ^3-tetrahydrobenzonitrile-2,2,3,4,5,5-d_6, Δ^3-tetrahydroacetophenone-2,2,3,4,5,5-d_6, and Δ^3-tetrahydrobenzoic acid-2,2,3,4,5,5-d_6 have been synthesized. The N.M.R. spectra of these compounds consist of easily analyzable ABX patterns; the geminal and vicinal coupling constants in these systems have been determined.

8. 2,2,3,3,4,4,5,5--Octadeuteriocyclohexyl acetate has been synthesized and has been used to determine the conformational equilibrium between the axial- and equatorial-acetate conformers.