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C O N F O R M A T I O N A L E F F E C T S
ON THE PROTON MAGNETIC RESONANCE SPECTRA
OF SIX-MEMBERED RING COMPOUNDS
(PART ONE)

A STUDY OF THE EFFECT OF A 3-METHOXY GROUP ON THE STEREOCHEMICAL ROUTES AND THE REACTIVITIES OF A VARIETY OF 1,2-SUBSTITUTED CYCLOHEXANES
(PART TWO)

Thesis submitted by

R U D O L P H K . K U L L N I G

In partial fulfillment of the requirements for the

P h . D . D e g r e e

at the

U n i v e r s i t y o f O t t a w a

Ottawa, Ontario. April 15th, 1958.

Prof. Dr. R.U.Lemieux,
Supervisor.

Rudolph K. Kullnig,
Candidate.

"Felix, qui potuit
rerum cognoscere causas,..."
P. Virgilius Maro,
Georgica, lib. II, 490.

P R E F A C E

The fact that a highly promising tool, Nuclear Magnetic Resonance* spectroscopy, has hitherto not been applied to problems in carbohydrate chemistry prompted the interest of Prof. Dr.R.U. Lemieux who consequently stimulated the author to explore the possibility of differentiating acetylated carbohydrates by means of their NMR spectra. In pursuance of this task, conformational effects on NMR spectra have been discovered. The research focused thereafter on the problem of recognizing the true significance of these effects and establishing the scope and limitations of their application to conformational analysis.

An effect, which will be called the "cis-effect", has been observed in previous researches on acetates of aldohexoses by Lemieux and Brice (1). Further investigations in order either to establish or to disprove this effect on simpler molecules deemed desirable to Prof. Dr.R.U. Lemieux who recommended this study to me.

The isomers of 3-methoxy-1,2-cyclohexanediol occurred to be both particularly suitable and readily accessible. Both cis-glycols were previously characterized and identified by Christian, Gogek and Purves (2). The trans-isomers, it

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(*) From hereon abbreviated to "NMR".

was hoped, could be obtained from two unidentified isomers of 3-methoxycyclohexene oxide which were reported by McRae, Moir, Haynes and Ripley (3). The proof of the structures of the involved compounds entered therefore the problem as a prerequisite.

In view of the fact that the research in NMR spectroscopy is of a very different nature to that on the stereochemistry of the trisubstituted cyclohexanes, it was decided to present this thesis in two parts. The first part deals with the NMR spectroscopy and the second part with the organic chemistry of the cyclohexane derivatives.

Dr.R.Y. Moir's great readiness to exchange latest results and thoughts and his kind supply with samples, particularly of the then unidentified 3-methoxycyclohexene oxides, their methanolysis products and two isomers of 1-tosyloxy-2-acetoxy-3-methoxycyclohexane is gratefully acknowledged.

The author feels much obliged to Drs.H.J. Bernstein and W.G. Schneider at the National Research Council of Canada and wishes to express his gratitude for introducing him to the theory and practice of NMR spectroscopy, for their interest in this research, and for their kind permission to use their instrument.

I acknowledge gratefully the receipt of a series of anhydro sugars from Dr.N.K. Richtmyer, a series of hexachlorocyclohexanes from Winchester Limited, several rare sugars including α- and β-D-glucopyranose-1-d pentaacetates from my

colleague P. Chü and levo-inositol hexaacetate from Dr.E.C. Horswill.

I wish to express my particular thanks to Prof. Dr. R.U. Lemieux for his stimulating guidance of this research, for his valuable and versatile instructions and for the support he provided from his National Research Council of Canada grant-in-aid of research.

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A B S T R A C T

PART ONE:

The NMR spectra of six-membered ring compounds show an approximately three times larger spin coupling constant for 1,2-diaxial hydrogen atoms than for 1,2-hydrogen atoms in other conformational relationship. Signals for equatorial hydrogen atoms are generally found at lower field/s than those for the corresponding axial hydrogen atoms. The signals of equatorial acetoxy or methoxy groups, however, are usually observed at higher field/s than their axial equivalent. The observations are applied to several determinations of configuration and conformation with emphasis on the acetylated aldopyranoses and some theoretical implications of the results are discussed.

PART TWO:

It was found possible to assign the structures and configurations to two of the diastereoisomeric 1,3-dimethoxy-2-acetoxycyclohexanes on the basis of their NMR spectra and thereby assign configurations to the parent diastereoisomeric 3-methoxycyclohexene oxides. The conclusions thus reached were substantiated by chemical means.

Two new isomeric 3-methoxy-1,2-cyclohexanediols were isolated and their structures were established. The rates of the periodate oxidation of these compounds and of the

other two previously known isomers were examined. Furthermore, the relative electrophoretic mobilities of the four isomers, on borate buffered filter paper, were determined.

The structures and configurations of the epimeric 3-methoxy derivatives of trans-1-tosyloxy-2-acetoxycyclohexane were established and the rates of their acetolyses measured.

The results of the rate studies and electrophoretic migration measurements are discussed in terms of interactions between the 3-methoxy groups and the 1,2-cyclic ions formed as reaction intermediates.

C O N F O R M A T I O N A L E F F E C T S

ON THE PROTON MAGNETIC RESONANCE SPECTRA

OF SIX-MEMBERED RING COMPOUNDS

(PART ONE)

I. I N T R O D U C T I O N

The growing importance of NMR spectroscopy reflects itself in the great number of reviews (4 - 22) which the literature has received within the decade of the existence of this technique. There will be neither need nor space enough to cover all the phenomena of NMR. I shall confine myself therefore to outlining the fundamental principles of NMR and to discuss in a qualitative fashion the chemical shift, the indirect spin coupling, the effect of rapid chemical exchanges of protons, and the analysis of NMR spectra. These phenomena were chosen because of their bearing on the subject of this thesis.

1. Early History and Fundamental Principles of NMR.

In 1924, Pauli (23) postulated that some nuclei should have an angular momentum and a magnetic moment in the direction of the angular momentum vector in order to account for the observed hyperfine structure of the atomic spectra of some heavy elements. Stern and his group (24 - 27) succeeded in the experimental demonstration of the nuclear magnetic moment and its space quantization by deflection of a molecular or atomic beam in an inhomogeneous magnetic field which was arranged perpendicular to the direction of the propagation of the beam. The spinning nuclei are forced to precess about the field-lines of the applied field and their

magnetic moment has then a component μ_H in the direction of the field given by;

(1.1) $$\mu_H = \mu_I m_I / I,$$

wherein μ_I is the maximum observable component of the nuclear magnetic moment, expressed in nuclear magnetons, I is the nuclear spin quantum number (dimensionless), and m_I is the magnetic quantum number which assumes the (2 I + 1) values;

$$I,\ (\ I\text{-}1\ ).....-(\ I\text{-}2\ ),-(\ I\text{-}1),-I.$$

If the applied field were homogeneous, the only effect on the nuclei would have been these orientations. However the field is inhomogeneous and,hence, the nuclei suffer a lateral force in the direction of μ_H, which may be parallel or antiparallel to the direction of the applied field. Furthermore, this force will be proportional to the magnitude of μ_H. The displacements can be measured by impinging the molecular beam on a suitable screen. From these and the known dimensions of the equipment, the nuclear magnetic moments can be evaluated; the observation of their quantization is obvious.

In 1939, Rabi, Millman, Kush and Zacharias (28) improved Stern's method by the introduction of nuclear magnetic resonance. From equation (1.1) the interaction energy E_H of the nuclear magnetic moment μ_I with the field H_o can be calculated as:

$$E_H = m_I \mu_I H_o / I.$$

If a second magnetic field H_{rf} is applied, which is oscilla-

ting in the plane of the rotating component of the precessing nucleus (that is perpendicular to H_o) and its frequency satisfies the Bohr equation;

$$\Delta E = h\nu = \mu_I H_o / I,$$

or

(1.2) $$\nu = \mu_I H_o / Ih,$$

then the precessing nuclei can exchange energy with this field and undergo transition (that means reorientation of the nucleus) from one energy level to another one, provided the change of m_I in this transition is ± 1. Rabi and his coworkers arranged their molecular beam in such a way, that it passed a inhomogeneous field, A, which dispersed it, and then a field, B, of exactly opposite field gradient, which refocused it. Before entering the field, B, the beam passed a homogeneous field, C, which by itself did not effect the trajectories of the nuclei. Hence the refocusing was not impaired. However, there was an oscillating field, D, perpendicular to C, which caused reorientation of the nuclei. D prevented refocusing when it had the resonance frequency of equation (1.2). The event of resonance could be detected very readily and highly accurate nuclear magnetic moments were obtainable from the resonance frequency and the field strength of the field, C, by this method provided, of course, that their spin was known. Though, Rabi and his coworkers were the first, who succeeded to demonstrate NMR and to employ it for their purpose, Gorter (29) suggested its use

in 1936 but failed in both of his experimental attempts (29 - 30) primarily because of an unlucky choice of compounds. In 1946, two groups performed successful NMR experiments on bulk matter by independent and different approaches. Bloch, Hansen and Packard's (31) goal was to devise a method to measure magnetic moments with high accuracy, particularly of the neutron, proton, deuterium and other light nuclei, in order to gain information on their structures, Purcell, Torrey and Pound (32) based their research on nuclear relaxation on a paper by Waller (33), who dealt with the relaxation in electronic paramagnetism. Due to the different concepts, Bloch's group called the observed phenomenon " nuclear induction ", while Purcell's group called it " nuclear magnetic resonance absorption ". However, both of the experiments are based upon the same principle. A nuclear magnetic moment, which is performing a Larmor precession around a constant magnetic field H_o has a constant component μ_H [equation (1.1)] in the direction of the field and a rotating component of constant amplitude in a plane perpendicular to the field. As Bloch (34) emphasized, it should be feasible to observe the induced electromotive force in a coil, due to the rotating component of the " free precession". He calculated the amplitude of the rotating component, from which the electromotive force could be calculated, when the precession was forced by a radiofrequency field which was perpendicular to the field H_o and near to the resonance frequency. He derived

how this amplitude attained a maximum value when resonance was achieved. It is completely equivalent for this purpose to bring about the resonance condition [equation (1.2)] by sweeping the radiofrequency or the fieldstrength H_o. Most experimenters choose the latter.

So far, all considerations were concerned with an isolated nucleus. There arises no complication from the presence of other nuclei in the molecular beam experiments of Rabi (28), but in Purcell's (32) and Bloch's (31) experiments, this fact demands attention. When a sample, which contains the nuclei of interest is brought into a magnetic field, their magnetic moments at first will be oriented at random. The beginning of precession will draw each nucleus into the nearest of these energy levels, which are distinguished by space orientation and, therefore, the population, N_m, of all the levels must be equal. The resultant moment, μ_m, of all nuclei of the same Zeeman level is,

$$\mu_m = N_m \mu_H .$$

It follows from equation (1.1) that for each positive value of μ_H there exists a matching negative one. Hence, the resultant moment of all the nuclei of the sample must be zero. It is also obvious that the sample is not now at thermal equilibrium in which case the population of the lower energy level, $N_{(m = 1/2)}$, must exceed that of the higher one, $N_{(m = -1/2)}$, by the Boltzmann factor;

$$(1.3) \qquad \frac{N_{1/2}}{N_{-1/2}} = e^{2\mu_I H_o/kT} \simeq 1 + \frac{2\mu_I H_o}{kT},$$

wherein k is the Boltzmann constant and I is assumed equal to 1/2 as is the case for the proton. It follows that there are only two Zeeman-levels, corresponding to $m = 1/2$ and $m = -1/2$. Since μ_I is 1.4×10^{-23} erg per gauss (34) the Boltzmann constant is 1.38×10^{-13} erg per degree and assuming an applied field H_o of 10,000 gauss and room temperature, 293°K, we find an excessive population of the lower level from equation (1.3);

$$\frac{N_{1/2}}{N_{-1/2}} \simeq 1 + \frac{2 \times 1.4 \times 10^{-23}(\text{erg gauss}^{-1}) \times 10^{4}(\text{gauss})}{1.38 \times 10^{-13}(\text{erg deg.}^{-1}) \times 293(\text{deg.})} \simeq 1 + 6.9 \times 10^{-6}.$$

It is this small fraction of nuclei, about seven parts in one million, upon which the NMR signals depend. It should be mentioned that their paramagnetic effect has actually been measured on hydrogen at 1.76 - 4.22° K by Lasarew and Schubikow (35) using Gouy's magnetic susceptibility balance. This thermal equilibrium and the magnetization which is connected with it will be attained only gradually. According to Purcell (36), this process of relaxation satisfies the equation;

$$D_{ex} = 100 \left(1 - e^{-t/T_1} \right),$$

wherein D_{ex} represents the percentage of equilibrium magnetization, t is the time and T_1 is a constant called the " spin

lattice relaxation time ". Local fluctuations in the field are caused by the lattice vibrations and provide a necessary mechanism for transitions between the Zeeman levels and, hence, make a thermal equilibration possible. The theory of nuclear spin relaxation has been developed from Purcell's and Bloch's first publications and is today quite well understood. An intimate knowledge of details and rate processes in crystals can be obtained which are not accessible otherwise and which are quite important to chemists as well as to physicists. A few examples, chosen at random, may illustrate the point. Richards and Smith (37 - 38) and Kakiuchi, Shono, Komatsu and Kigoshi (39) could demonstrate the existence of the hydroxonium ion, H_3O^+, in the lattice of crystalline monohydrates of strong acids. Pake (40) and many others calculated proton distances and bond angles from the shape and dimensions of the resonance line. This is indeed a very valuable supplement to X-ray analysis. Gutowski and Pake (41) calculated the rotational barrier of the H_3C-C rotation in 1,1,1-trichloroethane and other compounds from NMR data.

2. The Chemical Shift

As already mentioned, physicists expected to measure nuclear magnetic moments with high accuracy by this new method. The accuracy of one part in a million of radiofrequency measurements is suitable for the purpose. It is, however, a formidable task to measure the magnetic field strength better than one part in a thousand.* This experimental discord is often avoided, by reporting values relative to the proton moment which can be obtained by measuring both the resonance frequencies of the different nuclei. For this purpose, the samples containing the different nuclear species are either substituted for the sample containing the protons or the sample containing the different nuclei and the sample containing the protons are mixed together in a single probe and consequently experience the same field. But there is another serious difficulty (that is from the physicist's point of view - chemists ought to be grateful).

As it is known from the theory of diamagnetism, the circulating electrons are influenced in their motions by the applied magnetic field and are the source of a magnetic

---

(*) It seems worthwhile to draw attention to the achievement of Sommer, Thomas and Hippe (42), who measured the proton resonance frequency of water in a magnetic field of a known accuracy of one part in forty thousand. This is a valuable standard because it provides now an easy means to measure magnetic fields accurately.

field which is opposed to the applied one. The nucleus is therefore not in the field which is applied and an appropriate correction, ($1-\sigma_N$)(where σ_N is the shielding constant of the nucleus N) has to be made to obtain the field experienced by the nucleus. The Lamb equation (43) provides a rather accurate means of calculating σ_N for atoms. Molecules, however, do not possess the required spherical symmetry of their nuclear electrical potential which Lamb assumed for his derivation. Hence, uncertainty is inflicted even upon relative moments except for isotopes in the same compound. Thus, Wimett (36) could obtain the μ_D/μ_H ratio from measurements on hydrogen deuteride. The full complexity of this problem took shape when Knight (44), closely following Dickinson (45) and Proctor and Yu (46) observed shifts in the resonance frequencies of phosphorus-31, lithium-7, lead-207, nitrogen-14 and fluorine-19, which depended on which chemical compound they had chosen as a source of the particular nucleus. The " chemical shift ", as this phenomenon is called, of the proton was first reported by Lindström (47) and Thomas (48). Arnold, Dharmatti and Packard (49) resolved three proton magnetic resonance signals of ethanol and its higher homologs and visualized possible applications of NMR to studies of chemical reactions and other chemical problems.

What are the main features of the chemical shift?

First, it is directly proportional to the applied field. This is rather obvious on ground of the model men-

tioned before. It is therefore customary to report chemical shifts as,

(1.4)* $$\delta = (H_c - H_r) / H_r,$$

where H_c is the resonant magnetic field of the nucleus in question and H_r is the resonant magnetic field of an arbitrary reference. It follows from equation (1.2) that the corresponding resonance frequencies can be used in equation (1.4). This is, of course, equivalent to reporting the difference between the resonance signals in either milligauss or cycles per second (hereon referred to as c.p.s.), if the employed field strength or radiofrequency is stated. Water and cyclohexane are often chosen as reference compounds for the proton signal particularly when an external standard is used. If solutions are studied, it is convenient to use the solvent as internal standard provided it has one single sharp signal. Chloroform, dioxane, 1,2-dichloroethane as well as cyclohexane are generally suitable solvents. Other solvents, like water, acetone and benzene, although having only one sharp signal, are not recommendable for reasons to be discussed later.

The second feature of the chemical shielding of the nucleus is its relation to the electronegativity of the atom

---

(*) It should be noted, however, that some authors (50) prefer:

$$\delta = (H_r - H_c) / H_r.$$

or group to which it is bonded. Qualitatively, this is readily understood. The more the electrons are withdrawn, the less they can contribute to the shielding. However, numerous attempts (51 - 56) to afford a quantitative explanation have met with exceptions. The absence of a rigid correlation clearly suggests the presence of other influencing factors. These will be the subject of the subsequent paragraphs. Wherever the influence of an electronegative substituent is observed, its effect attenuates with increasing bond number. Thus, Shoolery (54) examined a series of ethane derivatives and observed that the signal for the methylene group in ethyl acetate had the largest shift (3.1 parts per million) among these compounds, while the methyl group in the same compound is displaced only 0.1 parts per million, both of them relative to the ethane signal.

A third property of chemical shielding is actually the counterpart to the second. Let us consider a polar bond, A→B. It was stated in the second paragraph that A should be less shielded than it would be if the bond was not polar. The same train of thoughts would lead to the expectation that B would be shielded more strongly. Saika and Slichter (57) and Gutowsky and McCall (58) explained fluorine-19 and phosphorus-31 shifts, respectively, in such terms. It is also evident that shielding of an atom increases with its effective nuclear charge.

A fourth feature is indicated by the presence of aromatic ring systems. Pople (59) explained the observed

chemical shift of benzene (which was previously considered as anomalous on grounds of hybridization considerations) in the following manner. The applied field induces a current of the π- electrons along the carbon skeleton, which gives rise to a diamagnetic moment in the center of the aromatic ring. The secondary magnetic field due to this moment at the positions of the protons can be calculated and provides satisfactory explanation of the observed shift. Bernstein, Schneider and Pople (60) used the same approach to account for the spectra of a series of polycyclic aromatic hydrocarbons.

A fifth factor controls the chemical shifts. The magnetic field induces not only diamagnetic currents but causes also mixing of the ground state with excited electronic states and thus produces paramagnetic currents. According to Pople (61) an excited state will contribute to the paramagnetic current only if transitions from one p-orbital to another are involved. He points out that p-functions are not important in a " linear combination of atomic orbitals " treatment for hydrogen atoms and consequently such currents can be neglected. However, large paramagnetic currents on a neighbouring atom may effect strongly the proton shielding. Apparent anomalies of the proton-shifts of acetylene, ammonia, water and hydrogen fluoride are accounted for by calculations of the paramagnetic effects of the adjacent atoms upon the hydrogen atoms. It is well to note that such paramagnetic proton shielding and the diamagnetic shifts, as observed in

proton-resonance spectra of aromatic hydrocarbons, are both caused by electrons which are not bond electrons of the hydrogen atoms and hence, do not surround the latter. They are both " long range " effects, which are not communicated via the bonds, but directly through the magnetic fields of the induced moments and are therefore inversely proportional to the third power of the distance of the proton from the axis of the moment. Nevertheless, they play an important role in the proton shielding, because these moments can be quite large and the diamagnetic moments from the bond electrons of the hydrogen atoms are rather small. Of course, in all calculations of shielding effects the average over-all orientations have to be taken into consideration in view of the rapid movement of the molecules in liquids. It follows, as shown by Pople (61) that induced moments can contribute to a shift only if they are anisotropic.

The sixth peculiarity of the chemical shift follows logically. Any induced moment will act not only upon the nuclei in its own molecule but also upon the nuclei of other molecules which may or may not be of the same kind. The average over-all combinations of orientations of both the molecules involved can differ from zero and thus result in a chemical shift. McConnell (62) has specified that the necessary conditions for this kind of chemical shift are an anisotropy of the induced moment and unequally probable relative orientations for the molecules. Shifts of this nature must necessarily be concentration dependent. Indeed,

Bothner-By and Glick (63,64) have observed that the shifts of the para-hydrogen resonance signals of mono-substituted benzenes can be related to Hammett's (65) para-substituent constants only if the shifts are extrapolated to infinitely dilute solutions.

Finally, Tiers (66) and Reid (67) both interpreted certain shifts that they have observed in fluorine-19 and proton resonance spectra, respectively, in terms of steric pressure. They implied, that the electrons of the involved atoms repel each other and render the nuclei less shielded. Meanwhile, the shifts observed by Reid were satisfactorily explained by Bernstein, Schneider and Pople (60) without the consideration of steric pressure. The agreement between the calculated and observed transitions published by Bernstein, Schneider and Pople is quite good and suggests that the steric pressure factor is not important in these compounds. Tiers' communication is inconclusive, because he deduced the steric origin of the observed shifts mainly on the basis of the fact that the results could not be made to tally with considerations of the electronegativity of the substituents.

Ramsey (68,69,70) has produced a generalized approach to the theory of chemical shielding. He arrived at a two term expression for the shielding constants, σ , in which the first term can be approximated by Lamb's equation (43) and the second term requires knowledge of the wave functions for the excited states which are usually not known. A fur-

ther shortcoming of Ramsey's equation is that both of its terms (which largely cancel each other) are dependent upon the choice of the origin of the coordinates while their difference is, as must be, invariant. Therefore, subsequent efforts were directed to circumvent these difficulties at the expense, of course, of generality. Ramsey (69) himself showed how the paramagnetic term can be evaluated from data of molecular beam experiments for linear molecules. Saika and Slichter (57) successfully applied Ramsey's expression for the shielding constant, σ, to the fluorine shift between hydrogen fluoride and fluorine by the adoption of appropriate simplifications. Pople (71,61) used local coordinate systems each centered at the individual atoms of the molecule rather than a single coordinate system for the calculation of the induced moments and found calculations more convenient. McConnell (62) was chiefly concerned with " long range shielding effects " and derived an expression for these using Ramsey's generalized theory. Hornig and Hirschfelder (72) have applied a variational method to calculate the shielding constant and thus, avoided the need of wave functions for excited states. However, their execution of this task has been criticized as inadequate by McGarvey (73) and he proposed an amendment.

3. Indirect Coupling of Nuclear Spins

Proctor and Yu (74,75) have observed five lines* of equal spacing of about two gauss in the antimony-121 and antimony-123 spectra of sodium fluoantimonate(V). This was rather unexpected since the molecule contains only one atom of antimony. Similar multiplets were observed by Gutowsky and McCall (76) in the NMR spectra of compounds of phosphorus-31 and fluorine-19. Hahn and Maxwell (77) observed interaction of the spins of the two protons in dichloroacetaldehyde by means of spin-echo experiments.

It was recognized from the beginning (74,76) that the multiplet structures of the spectra originate from interactions of the nuclear spins. This was concluded from the fact that the ratio of the line spacings, $\delta\omega$, in the multiplet signals, for the X and Y atoms of a compound XY_n are inversely proportional to the ratio of the magnetic moments of the nuclei provided they have the same spin; that is,

$$\frac{\mu_Y}{\mu_X} = \frac{\delta\omega_X}{\delta\omega_Y}.$$

Furthermore, the number of lines in the observed multiplet patterns is equal to ($2nI_Y + 1$) where I is the nuclear spin

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(*) Gutowsky and McCall (76) pointed out that the published spectra (75) consist of seven lines the outer of rather low intensity in better agreement with their proposed explanation.

quantum number for the atom Y. Their relative intensities correspond to the binomial coefficients, $\binom{2nI_Y}{i}$, where i follows the sequence of integers from $i = 0$ to $i = 2nI_Y$ with both limiting values included. The binomial coefficients are the mathematical expressions for the statistical weights of the different spin states of the aggregate of the Y nuclei. Gutowsky, McCall and Slichter (78) expressed the interaction energy as $A\,\vec{\mu}_1 . \vec{\mu}_2$, where A is a constant which is independent of the temperature and the applied field and $\vec{\mu}$ is the magnetic moment vector. Several hypotheses have been postulated about the nature of this interaction. Calculations by Ramsey and Purcell (79) have demonstrated that only coupling by way of the exchange force of the bond electrons has an effect large enough to account for the magnitude of the observed coupling constants. The authors (79) predicted, using Heitler-London wave functions, a 70 c.p.s. splitting in the spectrum of the hydrogen deuteride molecule. Wimett (80), Carr and Purcell (81) and Smaller, Yasaitis, Avery and Hutchison (82) found from independent experiments this coupling constant to be 43 c.p.s. Ramsey (83) then refined his calculations using James-Coolidge wave functions including all excited states and not only the lowest triplet state as he did in his first attempt. Since he could not provide an appropriate mean value for all of the energies of excitation, he approached the problem by satisfying himself that the observed coupling constant led to a reasonable mean value for the energy of excitation. Although Ramsey calcu-

lated all possible contributing effects, he found in the case of hydrogen deuteride, by far the largest effect was due to electron spin coupling. Less than one c.p.s. of the observed 43 c.p.s. could be attributed to electron orbital coupling - a mechanism which was suggested by Gutowsky, McCall and Slichter (78) and Hahn and Maxwell (77). However, the possibility was indicated that such effects may be considerably larger in other molecules. McConnell (84) took up this problem in much the same way as did Ramsey (79). He distinguished between the possibilities that the coupling of nuclear spins results from a magnetic interaction between the spin of a nucleus with the spin of an electron or with the orbital momentum of an electron, or with both. These interactions cause perturbations of the electron which in turn are communicated either magnetically directly to another nucleus or electrostatically to another electron. These effects can in turn be transmitted by either the spin or orbital magnetic mechanisms to other nuclei. McConnell (84) derived, using molecular orbital theory, general relations between molecular electronic structure and the individual contributions from the above mechanisms. His conclusions regarding proton-proton coupling are essentially the same as those of Ramsey (79). His (84) " (two-electron) - (s-orbital) - (electron-spin) coupling " are said to contribute the main effect. " (One-and two-electron)-(p-orbital)-(electron-spin) contributions " were thought to be generally negligible. The author tested his expression by estimating the pro-

ton-proton coupling constant for methane. The value obtained, 0.5 c.p.s., was questioned by the author. Meanwhile, Karplus, Anderson, Farrar and Gutowsky (85) calculated this parameter as 12.4 ± 0.6 c.p.s. from the observed proton-deuterium coupling constant of methane-d, and Nair and Roberts (86) found the constant to be 10-11 c.p.s. for methyl 2,3-dibromo-2-methylpropanoate. Nevertheless, some of McConnell's results are interesting. First of all, he pointed out that nuclear spin coupling due to two electrons in p-orbitals should depend on the angle ϑ between the p-orbital axis. Thus, bond angles should be of importance, when p-orbitals are involved. Secondly, proton-proton coupling constants should always be positive.

Gutowsky, Meyer and McCall (88) generalized, from the coupling constants between the nuclei of the hydrogens and fluorine in fluoroethane, that the coupling attenuates by a factor of about one-third for an additional carbon-carbon single bond between the interacting nuclei. This conclusion is not reflected in the expression that McConnell (84) has derived for the coupling constant and this deficiency was criticized by Aihara (89). Aihara derived, using molecular orbital theory, an expression for the coupling of non-bonded protons which accounts for the fall-off in the magnitude of the coupling constants with increasing number of bonds between interacting protons. His results conform with the generally observed trend and there seems to be no reported exception regarding this trend for proton-proton coupling.

Therefore, Aihara's results, seem to clash with McConnell's (87) who explicitly concluded that, " some J may not vary monotonically with internuclear distance." Indeed, such " exceptions " have been reported by Baker (90) for $J_{HPb}{}^{207}$, by Saika and Gutowsky (91) for J_{FF} and by Sharts and Roberts (92) for J_{HF}. It might, however, well be that effects which override the monotonic relationship between the coupling constant and the internuclear bond number play little or no role in proton-proton coupling.

4. Effect of Rapid Proton Exchange

It was observed by Gutowsky and Saika (93) that the proton signal of the hydroxyl group of aqueous acetic acid is highly concentration dependent. No separate proton signal of water was detected. This was explained in terms of rapid exchange of the acid's protons with the protons of the water. The authors calculated by means of modified Bloch equations* the line shape as a function of τ_A and τ_B which is the mean time the proton spends in the vicinity of A or B, respectively. The exchange is considered slow if τ_A and τ_B are much larger than the inverse of the difference of the proton resonance frequencies of these two states, $1/\delta\omega$. On the other hand, the exchange is considered fast if the opposite is the case. As the calculations indicated two separate

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(*) Bloch (94) derived equations which permit the calculation of the shape of a resonance signal.

signals have to be expected in the case of slow exchange. Rapid exchange produces only a single signal and its position is the average of the positions of the signals of the two states, but weighted according to their concentrations. Similar calculations by Gutowsky, McCall and Slichter (95) have demonstrated that a fast exchange will result in the collapse of the multiplet structures. A broad signal without structure is observed when $\tau \simeq 1/\delta\omega$. Ogg (96) presented a rather interesting application of this phenomenon. The proton signal of carefully purified and dried liquid ammonia was observed to be a triplet with a spacing of 46 c.p.s. This splitting is due to the coupling of the protons with nitrogen-14 (spin = 1). In the presence of water, potassium amide, sodium amide, ammonium bromide or other suitable compounds, proton exchange reactions take place. For example, in the reaction,

$$NH_3 + NH_2^- \underset{k}{\overset{k}{\rightleftharpoons}} NH_2^- + NH_3,$$

the exchange is rapid enough to collapse the triplet of ammonia to a sharp single line even at low concentrations of sodium amide. Continued dilutions produced finally a concentration at which the exchange rate was sufficiently slow to result in the expected line broadening. This concentration was roughly estimated as being about 10^{-7} molar in the case of sodium amide. Since, on the average, every molecule will have undergone exchange in the meantime, τ, the rate of reaction is equal to $1/\tau = \delta\omega$. Therefore, the velocity constant

for the exchange can be calculated from the expression,

$$v = \delta\omega = k\ [\ NH_2^-\ ].$$

Thus,

$$k = 2\pi \times 46/10^{-7} = 2.9 \times 10^9\ sec^{-1}.$$

This is, of course, only a rough estimate because of the inaccuracy of the concentration measurement. Assuming a normal frequency factor of 10^{11} sec.$^{-1}$, the activation energy can be estimated by means of the Arrhenius law to be in the order of 2 kcal./mole. Bottini and Roberts (97) and Gutowsky and Holm (98) have shown that the forementioned changes in the appearance of a resonance signal can also be brought about by temperature variation. The latter investigators have illustrated how both the frequency factor and the activation energy of the reaction can be obtained from such data.

5. Analysis of Nuclear Magnetic Resonance Spectra

The organic chemist's interest in spectroscopy of any kind is twofold. Either he needs a tool for quantitative analysis or he hopes for an aid in the elucidation of molecular structure. Jarrett, Sadler and Shoolery (99) for instance have employed NMR spectroscopy to study the keto-enol tautomerism of acetylacetone. Such applications depend on instrumental stability and are of obvious importance. There are, of course, many other examples of such applications in the literature and their number increases steadily with in-

creasing number of spectrometers in use and with the constant improvement of the sensitivity and stability of the available instruments.

NMR spectroscopy can provide information on molecular structure. Firstly, the spectral region, that is the combined statement of the resonance frequency and the strength of the main magnetic field, characterizes the isotopic species, which is responsible for the magnetic transition. Walchli's tables (100) provide the best available nuclear magnetic data from which the resonance conditions can be calculated according to equation (1.2) (p.15). Secondly, within a particular range, the number of signals indicates how many different kinds of the nuclear species are present in the molecule. Thirdly, the fact, that the ratio of the areas under the signals can be made proportional (that is, under suitably chosen instrumental conditions) to the ratio of the number of nuclei present in equivalent environments, is of practical importance. For example, Gutowsky, McCall and Slichter (95) found two proton signals for ortho-phosphorous acid (H_3PO_3). This confirmed the earlier conclusion that ortho-phosphorous acid is a dibasic acid and the third proton is attached to the phosphorus atom. Fourthly, the available resolution of close to 0.01 parts per millions (0.4 c.p.s. on a 40 Mc.p.s. instrument) requires some modification of the foregoing statements. Most proton signals are not single lines but instead line groups. As was discussed above, the origin of this fine structure is

the spin coupling via the bond electrons. Thus, the fine structure can provide useful information about the bonds. In the case of ortho-phosphorous acid, the signal of intensity two was a single sharp line while the other signal was a doublet caused by the spin interaction of one of the protons with phosphorus-31. This provides further evidence that one hydrogen atom is bonded directly to the phosphorus atom.

Obviously, in order to gain any knowledge from a given spectrum, the signals must be assigned accurately to the nuclei in the molecule. Furthermore, the assignment must also agree with the fine structure of the signals. Both the assignments and the interpretations of the fine structures are simplest when the bands or groups of bands are far apart; that is, when the chemical shifts are large. In such cases, the fine structure can, in general, be approximated as perturbations in the manner described by Gutowsky, McCall and Slichter (95) (see the paragraph dealing with spin multiplets on p. 28). The center of the multiplet represents the position of the chemical shift and the line separation within the multiplet is equal to the spin coupling constant, J.

The observed pattern become increasingly complicated, however, when several coupling constants are involved and when the chemical shifts and the coupling constants are of comparable magnitudes. McConnell, McLean and Reilly (101) have discussed a general quantum mechanical method of calculating energies and transition intensities of nuclear spin transitions in a polynuclear molecule. Bernstein, Pople

and Schneider (102,103) follow the same approach but they introduce a classification which permits a far simpler and clearer presentation. Tables of transition energies and intensities are also provided and are suitable for routine application. There can be no doubt that this procedure is an asset from an organic chemist's point of view. Their presentation is adopted in the following paragraphs.

The authors (102) used the letters A,B,C etc. to designate a set of non-equivalent nuclei of the same species whose differences in the chemical shifts are comparable to their mutual spin coupling constants. The letters X,Y,... were introduced when nuclei of other atoms which possess magnetic moments were present or when the chemical shift for nuclei of the same element were about ten times greater then the spin coupling constant. Carbon-12, having no moment, requires no consideration. Oxygen-16 has a quadrupole moment which does not interfere and can be neglected. The authors bring 1,1-difluoroethylene and thiophene as examples to illustrate A_2X_2 and A_2B_2 molecules, respectively.

As mentioned previously, Pauli (23) postulated, that some nuclei should have a spin angular momentum and a magnetic moment in the direction of the angular momentum vector. This and their quantization in a magnetic field was verified experimentally. The state of a nuclear species which possesses a magnetic moment is therefore properly described by a set of wave functions, ψ_i, which are solutions of the Schroedinger equation. The Schroedinger equation is,

(5.1) $$\mathcal{H}\psi_i = E_i\psi_i,$$

where $\mathcal{H}$ is the appropriate Hamiltonian operator and E_i are the corresponding energy values to the solutions ψ_i. The Hamiltonian operator in equation (5.1) can be separated into two parts, $\mathcal{H}(0)$ and $\mathcal{H}(1)$. The first part accounts for the interaction of the nuclear magnetic moments with the applied field and is given by the expression,

$$\mathcal{H}(0) = \sum_i \eta_i \, H_i \, I_z(i),$$

where $2\pi\eta_i$ is the ratio of the nuclear magnetic moment, in nuclear magnetons, to the spin angular momentum, in units of $h/2\pi$, of the nucleus i, H_i is the magnetic field at this nucleus, and $I_z(i)$ is the spin angular momentum component in the z-direction, in units of $h/2\pi$. The field strength H_i can be expressed;

$$H_i = H_o(1-\sigma_i)$$

by the use of the screening constant σ_i. For nuclei of spin 1/2, $I_z(i)$ can be +1/2 or -1/2. The external field is in the negative z-direction so that nuclei with positive spins have the higher energy.

The second part of the Hamiltonian accounts for the spin coupling and is expressed;

$$\mathcal{H}(1) = \sum_{i,j} J_{ij} \, \vec{I}(i).\vec{I}(j),$$

where $\vec{I}(i)$ is the vector of the spin angular momentum, in

units of $h/2\pi$. J_{ij} is the coupling constant between the nuclei i and j and has the dimensions of energy.

Being concerned only with protons, I_z can be only $\pm 1/2$ and consequently there will be only two wave functions for each nucleus. The wave function for a molecule containing n hydrogen atoms is obtained as the product of n wave functions of the individual nuclei, for instance;

$$\psi = \alpha(1)\beta(2)\beta(3)\alpha(4)....\alpha(n),$$

or shortened to

$$\psi = \alpha\beta\beta\alpha.....\alpha.$$

There are 2^n such basic product functions possible. If the nuclei were all independent, those basic product functions themselves would be stationary wave functions. However, due to the spin coupling, the different nuclei are no longer independent and it is therefore necessary to find the actual stationary wave functions as linear combinations of the basic product functions. The correct set of stationary wave functions will diagonalize the matrix of the Hamiltonian of equation (5.1). The matrix elements $\mathcal{H}_{mn}$ are defined by the equation;

$$\mathcal{H}_{mn} = \phi(\psi_m \mathcal{H} \psi_n)d\tau,$$

where the integration is to be taken over all coordinates of all nuclei. Once the matrix elements are known, the energies, E_i, which correspond to the wave functions, ψ_i, can be

computed from the set of the secular equations;

$$\left| \mathcal{H}_{mn} - \delta_{mn} E \right| = 0,$$

where $\delta_{mn} = 1$ for $m = n$ and $\delta_{mn} = 0$ for $m \neq n$.

For the evaluation of the matrix elements, $\mathcal{H}_{mn}$, simple rules can be derived from the fact, that α and β are normalized and orthogonal functions, that is;

$$\oint \alpha^2 \, d\tau = 1,$$

$$\oint \beta^2 \, d\tau = 1,$$

$$\oint \alpha\beta \, d\tau = 0.$$

It follows for simple product functions;

$$\oint (\psi_m \mathcal{H} \psi_n) d\tau = \oint (\psi_m \mathcal{H}(0) \psi_n) d\tau + \oint (\psi_m \mathcal{H}(1) \psi_n) d\tau.$$

$$\oint (\psi_m \mathcal{H}(0) \psi_m) d\tau = 1/2 \eta H_o \sum_i (1 - \sigma_i) S_i,$$

where $S_i = +1$ if nucleus i has α-spin and $S_i = -1$ if nucleus i has β-spin.

$$\oint (\psi_m \mathcal{H}(0) \psi_n) d\tau = 0,$$

for $m \neq n$ and

$$\oint (\psi_m \mathcal{H}(1) \psi_m) d\tau = 1/4 \sum_{i<j} J_{ij} T_{ij},$$

where $T_{ij} = +1$ if the spins of the nuclei i and j are parallel and $T_{ij} = -1$ if the spins are antiparallel.

$$\oint (\psi_m \mathcal{H}(1) \psi_n) d\tau = 1/2 \; U \; J_{ij},$$

for $m \neq n$, where U is one if ψ_m differs from ψ_n only by an interchange of the spins i and j and is zero otherwise. If the stationary wave function is a linear combination of basic product functions, the corresponding matrix element is found by expansion. McConnell, McLean and Reilly (101) derived two selection rules for allowed transitions:

(1) The change of total spin, $\triangle F$, is ± 1.

(2) Only transitions between two states of the same symmetry are allowed.

The intensities are calculated with the aid of the magnetic moment operator, M_x,

$$M_x = \sum_i \eta_i \, I_x(i),$$

and are proportional to the square of the transition moment, M_{pq},

$$M_{pq} = \oint (\psi_p M_x \psi_q) d\tau.$$

For simple basic product functions this moment is,

$$M_{pq} = \eta_i / 2,$$

if ψ_p and ψ_q differ only in the spin of the nucleus i. All other matrix elements are zero. To illustrate the application of the above equations, the simplest case of two coupled non-equivalent nuclei, A and B, each of spin 1/2, should be discussed. Four basic product functions can be readily found;

$$\psi_1 = \alpha\alpha, \quad \psi_2 = \alpha\beta, \quad \psi_3 = \beta\alpha, \quad \psi_4 = \beta\beta.$$

Calculating the off-diagonal elements of the Hamiltonian matrix, one finds that $\mathcal{H}_{23} = 1/2\ J$ is the only non-vanishing element. Thus, there is only mixing between the functions, ψ_2 and ψ_3, and we define new stationary functions, ψ_2' and ψ_3' by the matrix equation,

$$\begin{pmatrix} \psi_2' \\ \psi_3' \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \begin{pmatrix} \psi_2 \\ \psi_3 \end{pmatrix} .$$

Normalization and the required orthogonality of the new functions make the four matrix coefficients subject to the following equations:

$$\begin{aligned} a^2 + b^2 &= 1 , \\ c^2 + d^2 &= 1 , \\ ac + bd &= 0 . \end{aligned}$$

There are two solutions, which satisfy these equations

$$(\ 5.2\ ) \qquad \begin{pmatrix} \cos\theta & \sin\theta \\ -\sin\theta & \cos\theta \end{pmatrix} \text{ and } \begin{pmatrix} \cos\theta & \sin\theta \\ \sin\theta & -\cos\theta \end{pmatrix} .$$

Fourteen further combinations, which meet the requirements, can be reduced to the above by adjustement of θ . It can be readily verified, that the transition energies and their intensities are not affected by the choice of either set of (5.2). Calculating the diagonal elements of the Hamiltonian matrix, we find;

$$\mathcal{H}_{22} = \cos\ 2\theta \left\{ 1/2 \eta H_o (\sigma_B - \sigma_A) \right\} + \sin\ 2\theta (\ 1/2J\ ) - 1/4J ,$$

$$\mathcal{H}_{33} = -\cos 2\theta\{1/2\eta H_o(\sigma_B - \sigma_A)\} - \sin 2\theta(1/2J) - 1/4J.$$

It is obviously convenient to define two quantities, C and θ, by ;

$$(5.3) \qquad C\cos 2\theta = 1/2\eta H_o(\sigma_B - \sigma_A),$$

$$(5.4) \qquad C\sin 2\theta = 1/2\ J.$$

$\mathcal{H}_{22}$ and $\mathcal{H}_{33}$ becomes then C-1/4 J and -C-1/4 J respectively. The stationary state wave functions and their corresponding energies are:

n	ψ_n'	E_n
1	$\alpha\alpha$	$\eta H_o(1-1/2\sigma_A-1/2\sigma_B)+1/4\ J$
2	$\cos\theta(\alpha\beta)+\sin\theta(\beta\alpha)$	$-1/4\ J+C$
3	$-\sin\theta(\alpha\beta)+\cos\theta(\beta\alpha)$	$-1/4\ J-C$
4	$\beta\beta$	$\eta H_o(-1+1/2\sigma_A+1/2\sigma_B)+1/4\ J.$

The allowed transitions, their energies relative to the mean $\eta H_o(1-1/2\sigma_A-1/2\sigma_B)$ and their relative intensities are given in Table I.

TABLE I

Transition Energies and Intensities for an AB-system

Transition	Energy	Relative Intensity
$3 \longrightarrow 1$	$+1/2\ J + C$	$1 - \sin 2\theta$
$4 \longrightarrow 2$	$-1/2\ J + C$	$1 + \sin 2\theta$
$2 \longrightarrow 1$	$+1/2\ J - C$	$1 + \sin 2\theta$
$4 \longrightarrow 3$	$-1/2\ J - C$	$1 - \sin 2\theta$

The appearance of this spectrum depends solely upon the magnitude of the ratio $J/\eta H_o(\sigma_B - \sigma_A)$. If $|J| \simeq |\eta H_o(\sigma_B - \sigma_A)|$ four lines are observed. The two outer lines are weaker than the inner lines. The separation of an outer line from the next inner one is equal to J. The distance of the two outer lines is $2C + J$. With the aid of the equations (5.3) and (5.4) $|\eta H_o(\sigma_B - \sigma_A)|$ can be computed. Both signs of $\eta H_o(\sigma_B - \sigma_A)$ have to be considered, because the spectrum can give no information about the sign. If J is positive, the sequence of the transitions is from lower to higher field strength: $3 \rightarrow 1$, $4 \rightarrow 2$, $2 \rightarrow 1$ and $4 \rightarrow 3$. If J takes the negative sign, the order becomes $4 \rightarrow 2$, $3 \rightarrow 1$, $4 \rightarrow 3$ and $2 \rightarrow 1$, however, the two outer transitions are still the weaker one and the appearance remains unaltered. For $|J| \ll |\eta H_o(\sigma_B - \sigma_A)|$ the spectrum changes to two doublets, which become the single

B and A line respectively in the limit $J=0$. For this reason, the high-field pair of lines are often called " the B-transitions " and the others the A-lines, though each of the four transitions involves both nuclei. For decreasing $\eta H_o(\sigma_B-\sigma_A)$, the center lines approach each other, while the outer lines become weaker. For $\eta H_o(\sigma_B-\sigma_A)=0$, the A_2 case, only one transition is observed, the outer lines become forbidden transitions. This illustrates how no coupling is apparent in the spectrum but is still existing for identical nuclei.

Bernstein, Pople and Schneider (102,103) continued to discuss the spectra of the AB_2, ABX and A_2B_2 cases. Where symmetry is encountered, advantage is taken from it in the fashion McConnell, McLean and Reilly (101) have used it for their A_2X_2case.

Wilson (104) demonstrated the use of group theory to factorize the secular equation and determined selection rules for symmetrical molecules. 1,3,5-Trifluorobenzene served as an example. Anderson and McConnell (105) defined " multiplets moments " by the equation

$$\langle(\omega^a)^\tau\rangle = \frac{\sum_{mn} (\omega_{mn}^a)^\tau \lfloor_{mn}^a}{\sum_{mn} \lfloor_{mn}^a};$$

where $\langle(\omega^a)^\tau\rangle$ is the moment of the group "a" (a multiplet for instance) of the τ^{th} order (τ being integers). ω_{mn}^a are the transitions in the group "a" corresponding to the quantum numbers m and n. $\lfloor_{mn}^a$ are the corresponding line

intensities. The authors derived equations by means of which the chemical shift between two multiplets can be calculated from their second order moment. Spin coupling constants can be computed from their fourth order moments. The method has doubtlessly some merits. For example, in the case of two sets of nuclei, neither resolution within a group nor a theoretical understanding of the spectral pattern which is to be expected is required. The significance for complex spectra or poorly resolved spectra is obvious. The procedure by which the moments are obtained, is simple. The spectrum is divided into different regions under considerations of the symmetry and the ratio of the areas which can be expected. In each group the areas of every band is measured and multiplied with the square of its transition energy relative to an arbitrary axis. Where the group is not sufficiently resolved, the signal is divided into narrow strips which are then treated the way resolved bands were. The sum of all products is then divided by the area of the entire group to yield the second order moment of this group. The chemical shift between this group, A, and another group, B, can be calculated from the following equation,

$$\left\{\eta H_o(\sigma_B-\sigma_A)\right\}^2 = \frac{(n_A+n_B)^2}{n_A\, n_B}\left\{\langle(\omega^A)^2\rangle + \langle(\omega^B)^2\rangle\right\},$$

where n_A and n_B are the number of nuclei in the respective groups, or subgroups.

The method is, of course, rather sensitive to irregular drifts of the magnetic field which can be encountered when

very slow sweeping is employed. Only a series of self reproducing spectra can eliminate this source of error. Further, highly accurate intensity measurements are desirable, particularly when higher order moments are employed.

6. Description of the Problem

The results of the research in the field of NMR spectroscopy during the past decade, which were in part briefly outlined in the preceding section, clearly demonstrate NMR spectroscopy as a potential tool in structure elucidations. It seemed, therefore, desirable to investigate a possible application to the problems of carbohydrate chemistry. The acetates of monosaccharides were chosen as a start because of their availability in pure form and of their known structure. Hinging on the reasonable expectation that the signals of hydrogen atoms adjacent to primary or secondary acetoxy groups and of hydrogen atoms of acetylated hemiacetal groups will be sufficiently resolvable, one could anticipate being able to distinguish ketoses from aldoses, pentafuranoses from pentapyranoses and to recognize branching.

Beyond expectations, this study revealed NMR spectra to be sensitive to conformational differences. It was therefore important to correlate the discovered effects to the proper conformation with the aid of simple compounds of unambiguous conformation. This is of particular interest, because the conformations of acetylated aldopyranoses were assumed on basis of rules (106,107) which were derived from

compounds of an entirely different nature. It is by no means obvious, that compounds with a comparably great number of polar substituents (such as are the acetoxy groups) will follow the same rules.

II. E X P E R I M E N T A L

The spectra were measured with a Varian V-4300 NMR spectrometer, equipped with a field stabilizer, at a fixed frequency of 40 Mc.p.s. The positions of the prominent signals in a spectrum were measured by the side band technique of Arnold and Packard (108). The positions of the remaining signals were measured by interpolation on the record chart. The sample, contained in a 5 mm. spinning tube, was usually a nearly saturated solution of the compound in chloroform which served as an internal standard. In several instances the inter signal separation was also measured in dioxane or carbon tetrachloride, or in the liquid state and found to be the same as in chloroform solution. Nearly all of the compounds used in these studies are reported in the literature. The published methods were used to prepare most of the samples described in Table II. The compounds provided by other workers were checked for purity and identity by comparison of their physical constants with those published. The few preparations made for the first time are described in the experimental portion of part two of this thesis except for the acetates of the 4-t-butylcyclohexanols which were acetylated in boiling acetic anhydride containing sodium acetate.

TABLE II

Melting Points or Refractive Indices of the Compounds Used in this Study

Compound	m.p. or n_D	Reference
ALDOPENTOSES:		
α-L-Arabopyranose tetraacetate	95-96.5°	(109)
β-L-Arabopyranose tetraacetate	85-85.5	(109)
α-D-Xylopyranose tetraacetate	56-57	(110)
β-D-Xylopyranose tetraacetate	127-127.5	(110)
α-D-Ribopyranose tetraacetate	75-78	(111)
	$[\alpha]_D^{20}$ 54.0	(112)
β-D-Ribopyranose tetraacetate	110-111	(113)
α-D-Lyxopyranose tetraacetate	95-96	(114)
ALDOHEXOSES:		
α-D-Glucopyranose pentaacetate	113.5-114	(115)
β-D-Glucopyranose pentaacetate	132.3-133	(116)
α-D-Mannopyranose pentaacetate	73-74	(117)
β-D-Mannopyranose pentaacetate	115-116.2	(118)
α-D-Galactopyranose pentaacetate	95-98	(119)
β-D-Galactopyranose pentaacetate	144.5-147	(120)
β-D-Allopyranose pentaacetate	97-100	(1)
α-D-Altropyranose pentaacetate	119.5-121	(121)

α-D-Gulopyranose pentaacetate	105-106°	(122)
Methyl α-D-glucopyranoside tetraacetate	102.5-103.5	(123)
Methyl β-D-glucopyranoside tetraacetate	104-105	(123)
α-D-Glucopyranosyl chloride tetraacetate	71-72	(124)
β-D-Glucopyranosyl chloride tetraacetate	95.5-97.5	(125)
β-D-Fructopyranose pentaacetate	105-108	(126)
D-Glucosan 〈1,5〉β〈1,6〉 triacetate	111.5-112	(127)
D-Mannosan 〈1,5〉β〈1,6〉 triacetate	89-90	(128)
D-Altrosan 〈1,5〉β〈1,6〉 triacetate	102.5-103.5	(121)
D-Idosan 〈1,5〉β〈1,6〉 triacetate	64-68	(129)
D-Gulosan 〈1,5〉β〈1,6〉 triacetate	114-115	(130)
D-Galactosan 〈1,4〉α〈1,6〉 triacetate	78.5-81	(131)

SUGAR ALCOHOLS and INOSITOLS:

Glycol diacetate	1.4162(20°)	(132)
Gycerol triacetate	1.4313(20.5°)	(133)
1-Methoxy-2-acetoxyethane	1.4000(25.1°)	(134)
Erythritol tetraacetate	85.5-86	(135)
D-Arabitol pentaacetate	74.5-75	(136)
Xylitol pentaacetate	syrup	(137)
D-Sorbitol hexaacetate	99-99.5	(138)
Dulcitol hexaacetate	170.5-171	(139)
D-Mannitol hexaacetate	125.5-126	(140), (141)
Pentaerythritol tetraacetate	80.5-81.5	(142)
myo - Inositol hexaacetate	219-220	(143)

Hexa-O-methyl-myo-inositol	1.4511(28°) b.p.112 /0.85mm	(144)
cis-Inositol hexaacetate	206-207°	(144a)

1,2,3,4,5,6-HEXACHLOROCYCLOHEXANES:

α-Isomer	160-160.5	(145,146)
β-Isomer	312-315*	(145,146)
γ-Isomer	114-115.5	(145,146)
δ-Isomer	140-140.5	(145,147)
ε-Isomer	222-223.5*	(145)

CYCLITOLS:

trans-4-t-Butylcyclohexanol	80.5-81	(148)
trans-4-t-Butylcyclohexyl acetate	1.4512(23.5°)	Part I, p.49
cis-4-t-Butylcyclohexanol	81.5-82.5	(148)
cis-4-t-Butylcyclohexyl acetate	1.4491(24.5°)	Part I, p.49
1α,3α-Dimethoxy-2β-acetoxy-cyclohexane**	65.5-66.5	Part II, p.103
1α,3β-Dimethoxy-2α-acetoxy-cyclohexane**	1.4485(24.5°)	Part II, p.106
1α,2β,3α-Trimethoxycyclohexane	1.4393(25.0°)	Part II, p.108

(*) Compound was melted in a sealed tube.

(**) For system of nomenclature see footnote on page 86.

III. D I S C U S S I O N O F R E S U L T S

Winstein and Holness (148) have pointed out the great usefulness of cis-and trans-4-t-butylcyclohexanols for investigations concerned with the conformations of monocyclic six-membered ring compounds. Application of the parameters established by Beckett, Pitzer and Spitzer (149) for the interactions encountered in substituted cyclohexanes indicates that these compounds exist virtually entirely in conformations which have the tertiary butyl group in equatorial orientation. The validity of this conclusion depends, of course, upon the nature of the 1-substituent and the temperature, but can safely be assumed for the 4-t-butylcyclohexanols and their acetates for temperatures up to 100°. The predictions for the conformations of the alcohols and several derivatives have found experimental justification through studies of the chemical properties of both the alcohols and several derivatives (148,150). The conformations and NMR spectra of the trans-and cis-4-t-butylcyclohexanols and their acetates are presented in Figs. 1 and 2. The signals are readily assigned to the various kinds of hydrogens on the basis of their relative intensities and structures. Thus, the strong sharp signals of appropriate intensities which occur at 262-274 c.p.s. and at 230 c.p.s. in the case of the acetates must be produced by the hydrogens of the t-butyl group and acetyl groups, respectively. In the case

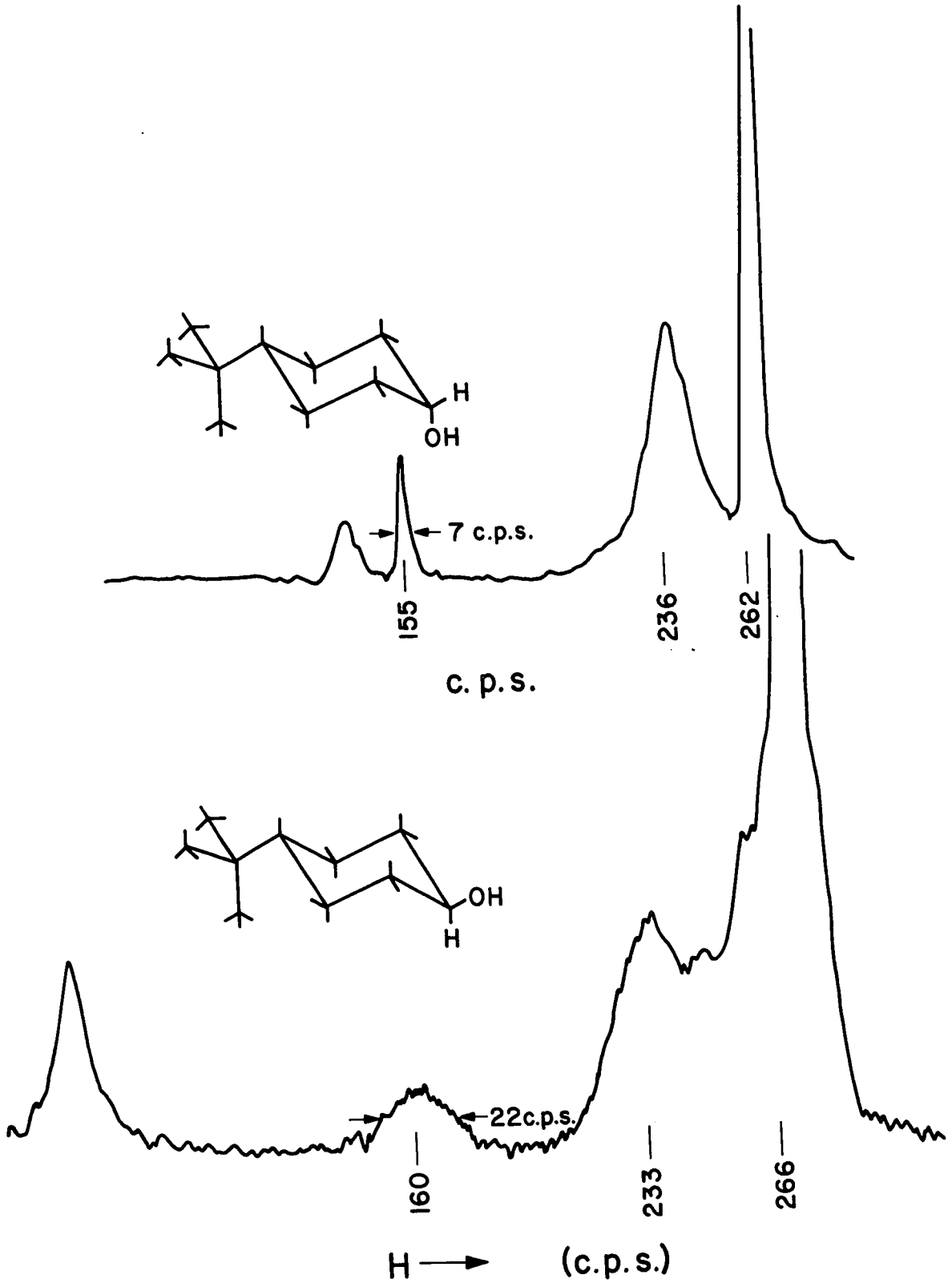


Fig. 1. - NMR spectra of <u>cis</u>- and <u>trans</u>-4-t-butylcyclohexanol.

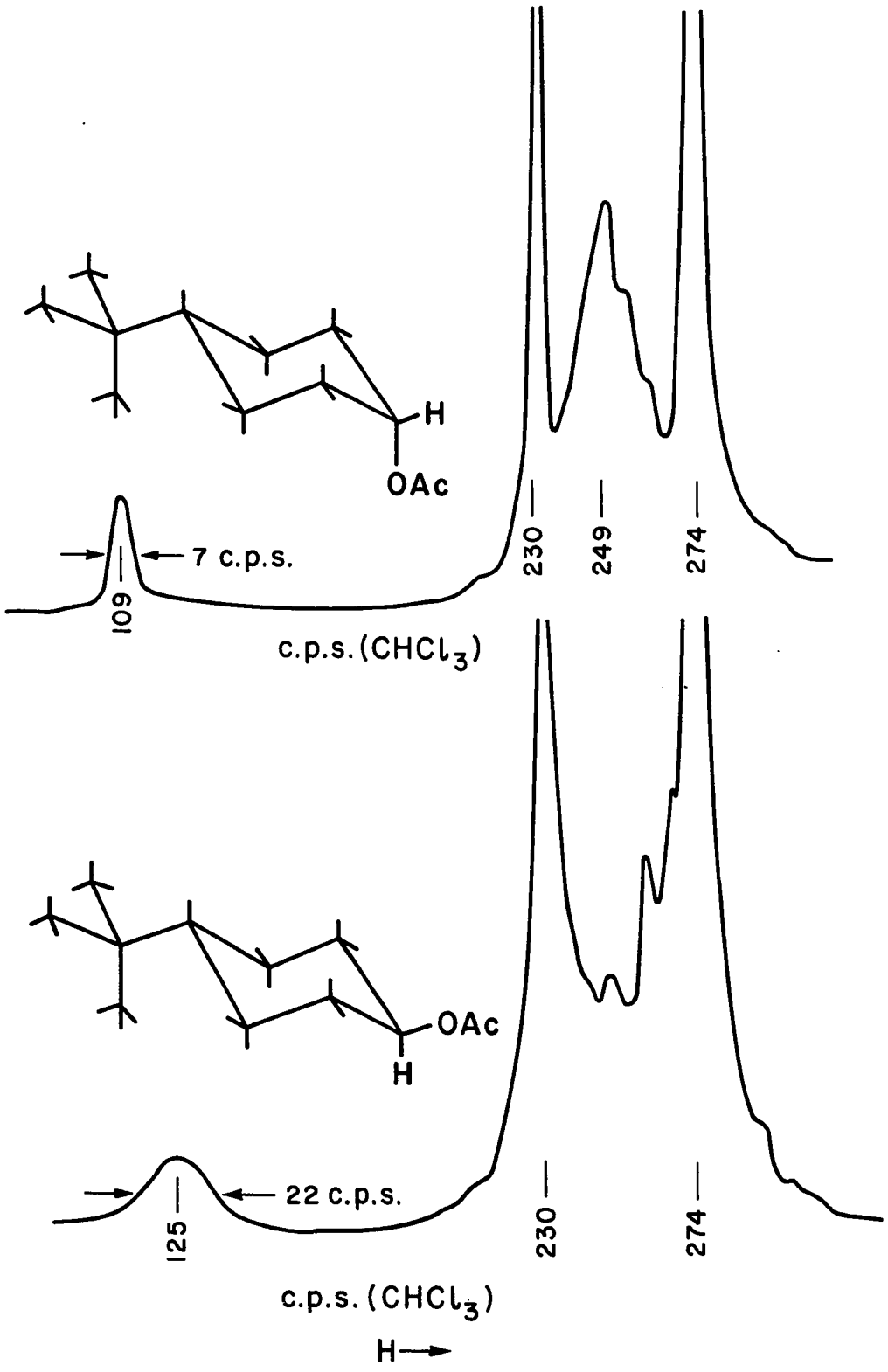


Fig. 2. - NMR spectra of <u>cis</u>- and <u>trans</u>-4-t-butylcyclohexyl acetate.

of the alcohols, the signal for the hydrogen of the hydroxyl group was readily recognized by its concentration dependence due to proton exchange when hydrochloric acid was admixed (93) (p.32). The signal of unit intensity in the region 109-160 c.p.s. must therefore belong to the 1-hydrogen and those in the 230-252 c.p.s. region to the other nine hydrogens on the ring. The points of interest in these spectra are the half-widths of the bands for the 1-hydrogens. It is seen the half-width of this band for both the cis-alcohol and the cis-acetate is 7 c.p.s. as compared to 22 c.p.s. for that of the trans-isomers. The only plausible interpretation for the line shape of these bands is that they represent an unresolved ensemble of transitions arising from spin coupling with the hydrogens on the neighboring carbons. The spread of such a pattern depends mainly on the stronger coupling constants. Further, the spin coupling of protons is so far known (p. 31) to attenuate rapidly with increasing number of bonds between the coupled nuclei. It will suffice, therefore, to consider only hydrogens no further than three bonds remote. On this basis, the pattern of the 1-hydrogen of the trans-compound is controlled by $J_{1a,2e}$, $J_{1a,2a}$, $J_{2a,2e}$ and ($\sigma_{2a}-\sigma_{2e}$), the corresponding pattern of the cis-compound by $J_{1e,2e}$, $J_{1e,2a}$, $J_{2a,2e}$ and ($\sigma_{2a}-\sigma_{2e}$) (102). Due to symmetry, $J_{1,6}$ must be identical with $J_{1,2}$ and needs no consideration. From the mutual character of spin coupling it follows directly that $J_{1e,2a}$ should be the same as $J_{1a,2e}$. Omitting equal parameters, the greater width of

the signal of the trans-compound is then caused by $J_{1a,2a}$ which should be at least 7.5 c.p.s. Furthermore, the sum of $J_{1e,2e}$ and $J_{1a,2e}$ should be less than 7 c.p.s. A further implication is, that the hydrogens in equatorial and axial orientations on carbons two and six should have a chemical shift relative to each other. This is a reasonable assumption in the light of the fact that the 1-hydrogen itself is shifted by 16 c.p.s. for the acetates and 5 c.p.s. for the alcohols to lower field when in equatorial position. Numerical values obtained from such unresolved bands can, of course, be accepted only with caution. There were obtained, however, spectra of other compounds which have their fine structure sufficiently well resolved to allow the determination of the coupling constants and chemical shifts more accurately.

The spectrum of 1α,3α-dimethoxy-2β-acetoxycyclohexane, Fig.3, provides a suitable example. The signal of the 2-hydrogen of this compound presents itself as three well resolved transitions at 107,116 and 125 c.p.s. This triplet structure arises from the spin coupling of the 2-hydrogen with the trans-1- and trans-3-hydrogens. In terms of Bernstein, Pople and Schneider's classification (102) (p.37), this is an AB_2 system in which the 2-hydrogen is the A-atom. This system is characterized by the ratio of the spin coupling constant, J_{AB}, to the chemical shift, $[\ \eta H_o(\sigma_B - \sigma_A)\ ]$. Since the latter is large, approximately 60 c.p.s. as compared to the inter proton spin coupling con-

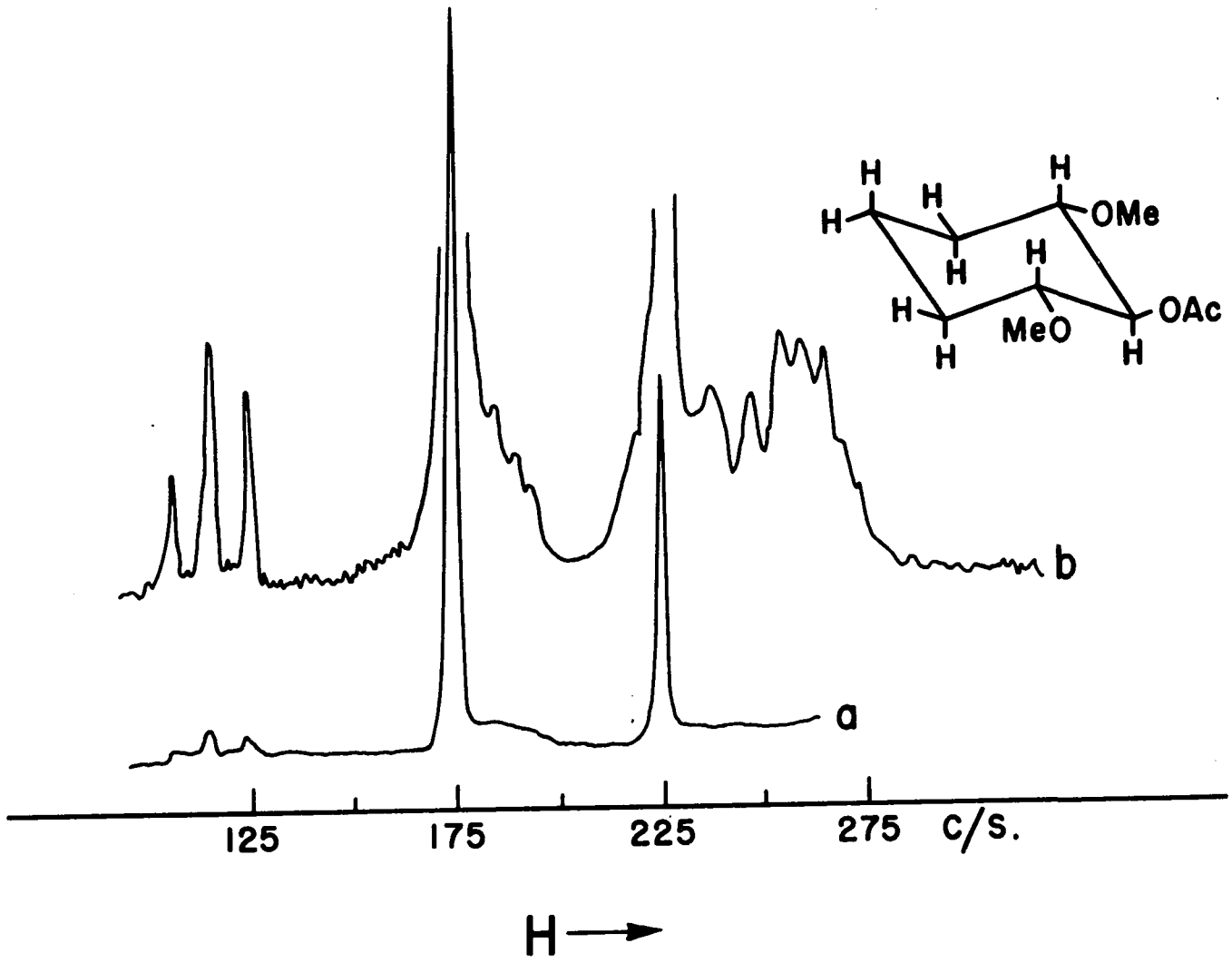


Fig. 3. - NMR spectrum of 1α,3α-dimethoxy-2β-acetoxycyclohexane. The trace (b) was recorded at high gain.

stants, which are normally encountered, the spacing of the triplet, 9 c.p.s., can be taken as the coupling constant. The theoretical pattern for the A-transitions can be calculated using these values for the chemical shift and the coupling constant and with the aid of the contents of the Tables IV and V provided by Bernstein, Pople and Schneider (102). The agreement between the calculated structure and that observed, shown in Table III, justifies the above interpretation. Comparison with the results obtained from trans-4-t-butylcyclohexanol verifies the estimate of the magnitude of $J_{1a,2a}$ and implies that 1α,3α-dimethoxy-2β-acetoxycyclohexane possesses the 1-,2-and 3-hydrogens in axial orientation, as would have been anticipated from rules of conformational analysis.

The signal of the 2-hydrogen of 1α,3β-dimethoxy-2α-acetoxycyclohexane occurred as a quartet of bands at 107.5, 110.0, 113.8 and 116.5 c.p.s. (see Fig. 4). In the terms proposed by Bernstein, Pople and Schneider (102), this signal represents the X-transitions of the spectrum of an ABX system where X represents the 2-hydrogen. Inspection of their (102) Table VII and equation (6.4) shows that for the system the outer lines of the X-transitions are separated by ($J_{AX} + J_{BX}$). Assuming J_{AB} is zero, (see p.31) the distance of the inner lines is equal to ($J_{AX} - J_{BX}$). Although this is certainly not strictly correct, both experience and theory show that it does serve as an acceptable approximation. The error thus introduced is unavoidable

TABLE III

The Calculated and Observed Signals for the 2-Hydrogen of 1α,3α-Dimethoxy-2β-acetoxycyclohexane

Line	Energy (c.p.s.*)		Relative Intensity
	Observed	Calculated	Calculated**
A1	107	107	0.85
A2	116	115.2	1.0
A3	116	116.7	1.0
A4	125	124.9	1.15

(*) The energies are measured in c.p.s. from the chloroform signal.

(**) Compare these values with those observed in Fig. 3.

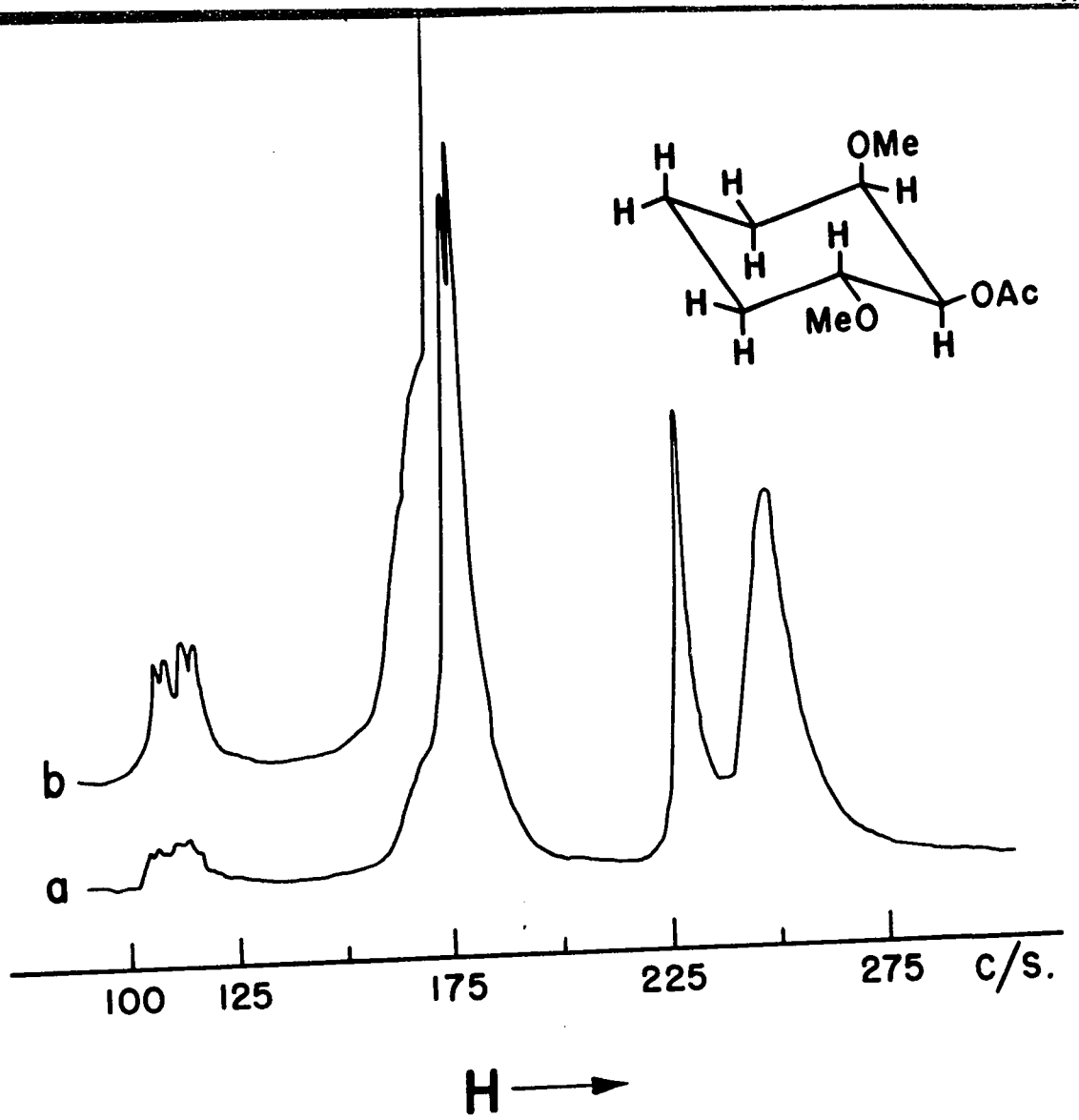


Fig. 4. - NMR spectrum of 1α,3β-dimethoxy-2α-acetoxycyclohexane. The trace (b) was recorded at high gain.

because of the lack of the A-and B-parts of the spectrum which are obscured by the large signal of the methoxy groups. Application of the above relations to the quartet under discussion yields values of 6.4 and 2.6 c.p.s. for J_{AX} and J_{BX}, respectively. This is consistent with the conclusions arrived at in the previous paragraphs if the conformation of 1α,3β-dimethoxy-2α-acetoxycyclohexane is assumed to be as shown in Fig. 4. Consequently J_{AX} and J_{BX} are assigned to $J_{2a,3a} = 6.4$ c.p.s. and $J_{2a,1e} = 2.6$ c.p.s., respectively.

These results clearly indicate that $J_{1a,2e}$ and $J_{1e,2e}$ are approximately equal and $J_{1a,2a}$ is 2-3 times larger. This conclusion should prove to be of great value to structural organic chemistry (see for example page 73).

Since our first communication (151), data have appeared which could well be interpreted as a manifestation of a dependence of the spin coupling constant on the bond angles. McConnell, Reilly and McLean (152) found the hydrogen-fluorine and the fluorine-fluorine coupling in a variety of ethylene derivatives to be consistently larger when the atoms were in trans- than when they were in cis-relationship. The same relationship was observed by Bernstein and Schneider (153) for the proton-proton coupling in spectra of styrenes. Sharts and Roberts (92) provided evidence that the proton-fluorine splitting in the spectra of cyclobutenes is considerably larger for coupling across the ring than for coupling of nuclei on adjacent sites. Bernstein, Pople and Schneider (103) have reported two different cou-

pling constants $J_{1,2}$ and $J'_{1,2}$ for the protons of 1-bromo-2-chloroethane.

It is noteworthy that McConnell's (84) theoretical treatment actually predicted that the spin coupling constant should depend on the angle ϑ between the p-orbital axes as ($1 - 3\cos^2\vartheta$). While the bond angle dependence of the fluorine-proton and fluorine-fluorine coupling constant had thus to be expected on theoretical ground, since p-orbital functions are recognized to make significant contributions to the spin coupling of fluorine nuclei (84), the above reported bond angle dependence of the proton-proton coupling constants come unexpectedly. For example, McConnell (84) has assumed: " It appears safe to say that nuclear spin couplings between protons, especially protons that are not directly bonded to one another, arise primarily through the mechanism of the (two-electron)-(s-orbital)-(electron-spin) coupling expressed in Eq. (38) for $J_{NN'}^{(3)}$. One- and two-electron (p-orbital)-(electron-spin) contributions ($J_{NN'}^{(2)}$) are probably generally negligible because (a) the " p-character " of atomic orbitals centered on protons in the LCAO MO approximation is generally considered to be small, and (b) hyperfine integrals involving $2p_H$ atomic orbitals are considerably smaller than hyperfine integrals involving $1s_H$ atomic orbitals. " However, since the spherical symmetry of s-orbital functions does not permit any bond angle dependence, p-orbital functions have to be included to an appropriate extent in the calculations of proton-proton

spin coupling. This conclusion seems to be further supported by the fact that the proton-proton coupling constant for methane, as calculated by McConnell (84) (see p. 31) using only terms dependent on s-orbital functions, was found (85, 86) to be seriously too small.

If p-orbital terms are to be included in the calculations of proton-proton coupling constants, the resulting values can be negative. It is important to be aware of this implication when interpreting NMR spectra, particularly when small constants are encountered, since it is customary to assume all proton-proton coupling constants to possess positive values (84,154).

The four groups of signals which normally are present in the NMR spectrum of an acetylated aldopyranose (Fig.5a-5d) can be assigned convincingly to the four different kinds of hydrogen atoms in the molecule simply through inspection of the intensities, positions and fine structure of these bands.

The anomeric hydrogen atom is attached to a carbon atom which is bonded to two oxygen atoms and from the point of electronegativity considerations the signal at lowest field, 45-75 c.p.s., should be assigned to it. The fact that this signal frequently occurred as a doublet confirms this conclusion because the anomeric hydrogen is the only hydrogen atom in the molecule which has only one other hydrogen atom within a distance of only three bonds. As was seen earlier, coupling with protons four and more bonds remote can be usefully neglected as a first approximation. That this is only

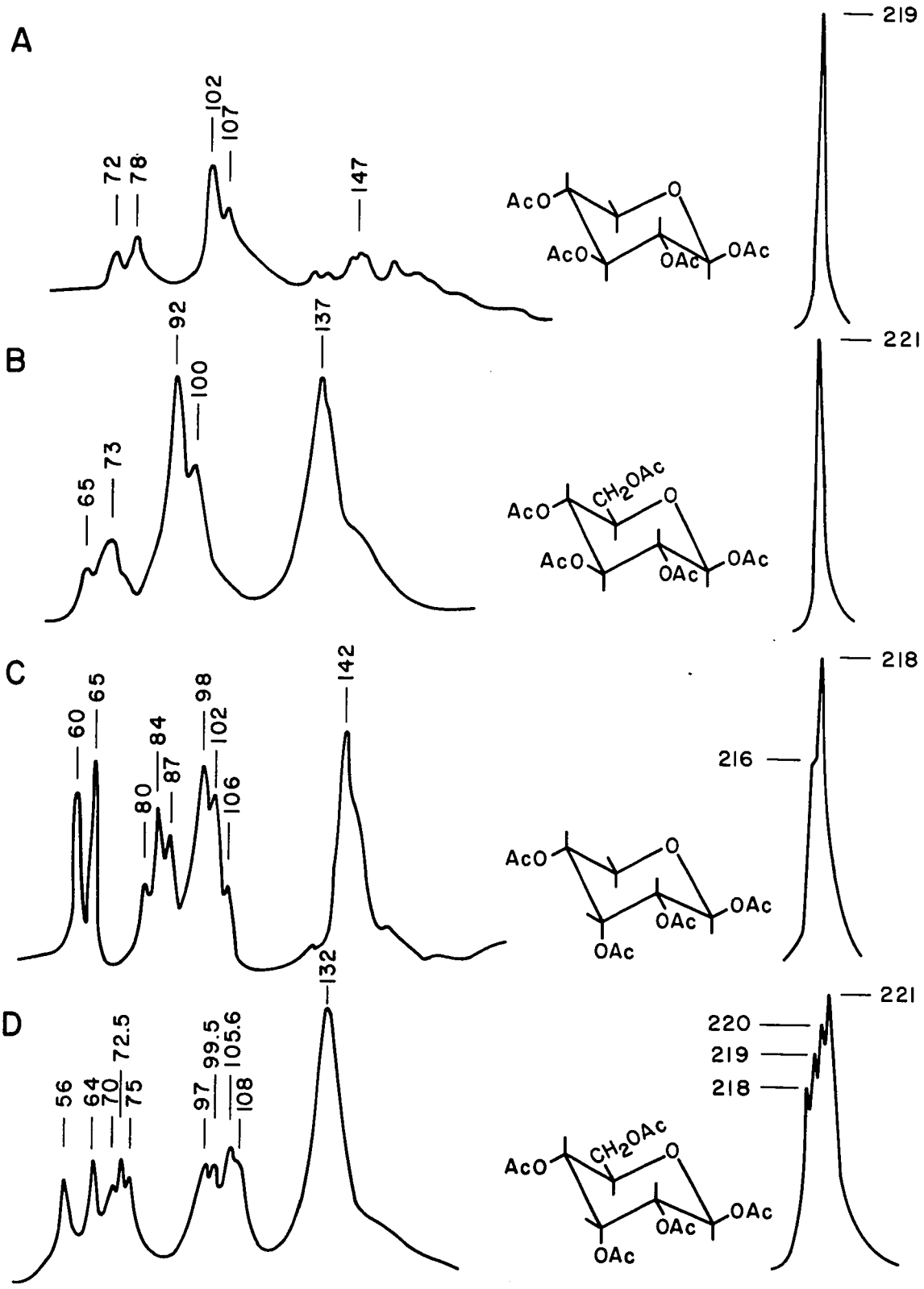


Fig. 5a. - NMR spectra of fully acetylated aldopyranoses: β-D-Xylose(A), β-D-glucose(B), β-D-ribose(C) and β-D-allose(D). For purposes of presentation, the signals for the acetyl-hydrogens were recorded on a different scale of intensity.

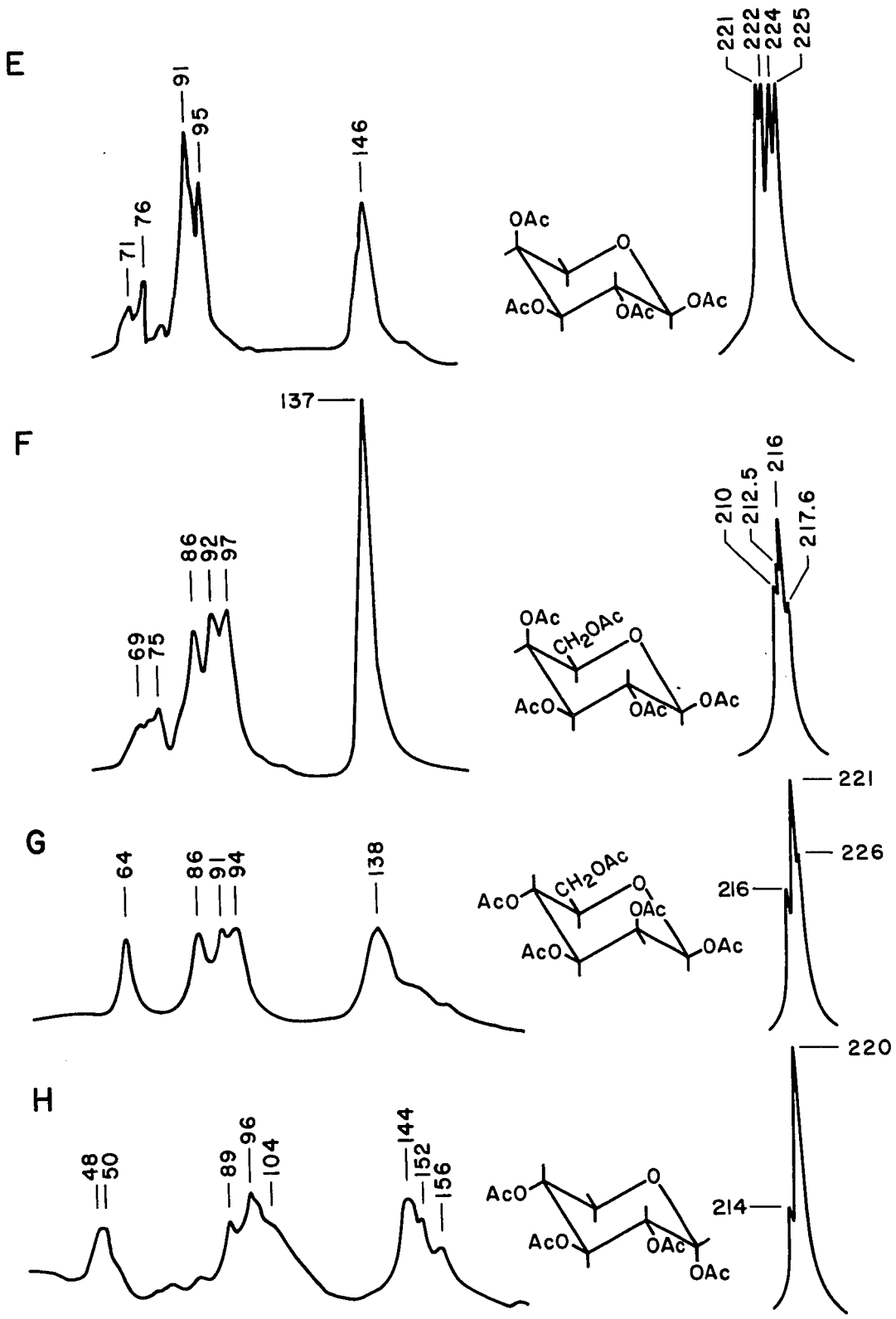


Fig. 5b. - NMR spectra of fully acetylated aldopyranoses: α-L-Arabinose(E), β-D-galactose(F), β-D-mannose(G) and α-D-xylose(H).

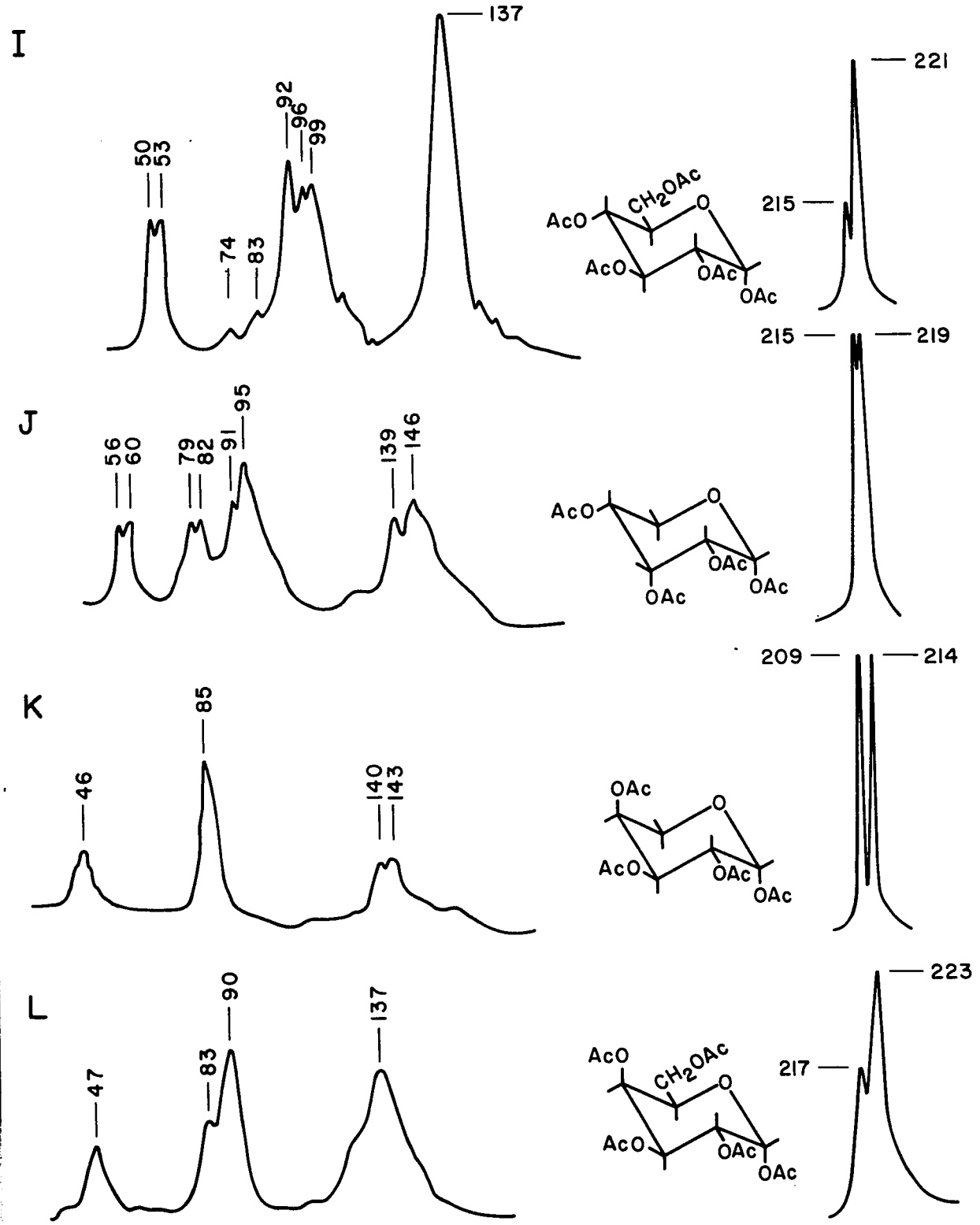


Fig. 5c. - NMR spectra of fully acetylated aldopyranoses: α-D-Glucose(I), α-D-ribose(J), β-L-arabinose(K) and α-D-galactose(L).

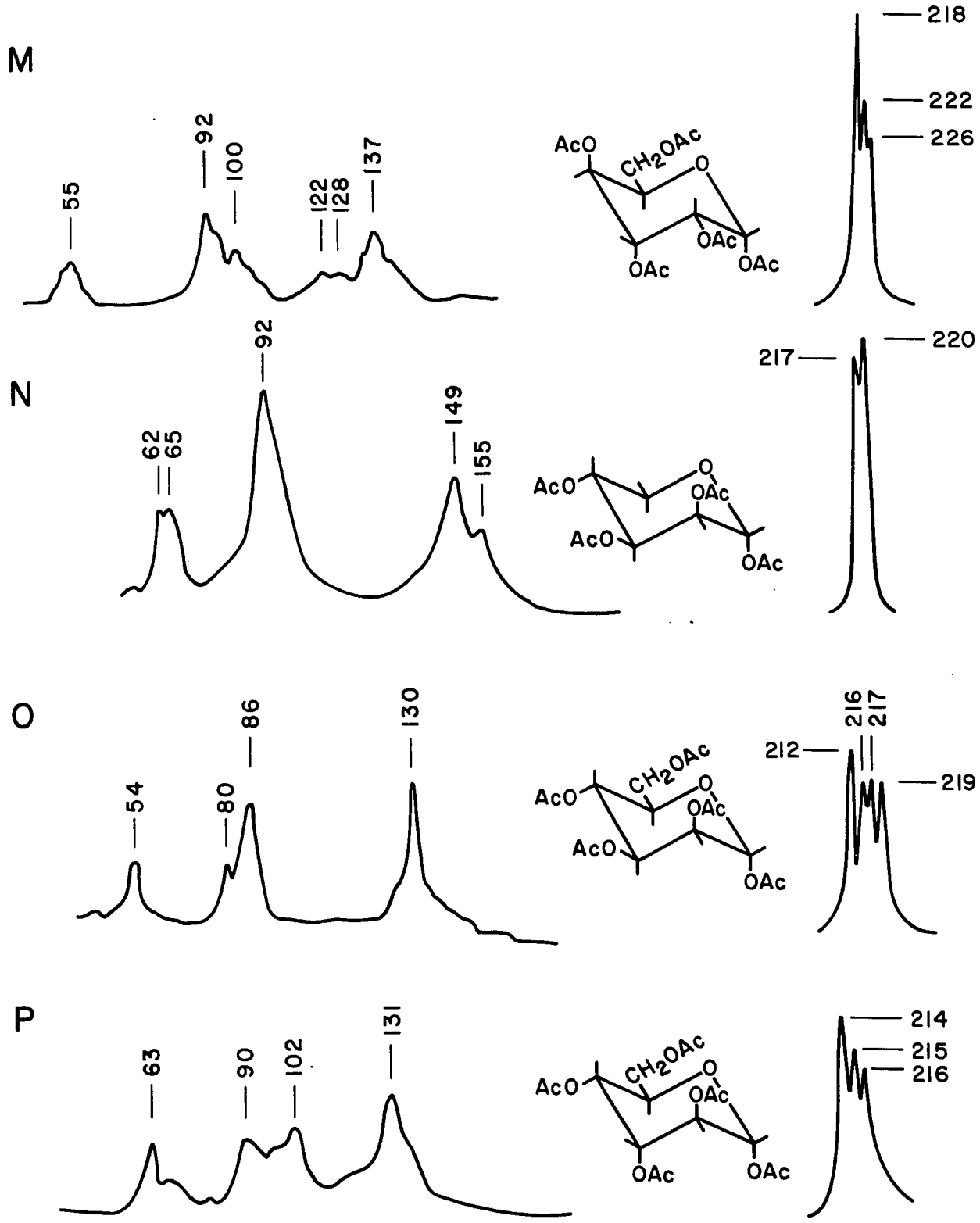


Fig. 5d. - NMR spectra of fully acetylated aldopyranoses: α-D-Gulose(M), α-D-lyxose(N), α-D-mannose(O) and α-D-altrose(P).

a rough approximation is clear from the shape of the signals for several of the anomeric hydrogens. The soundest verification for the assignment is doubtlessly the fact that there was no signal present in this region for either α- or β-D-glucopyranose-1-d pentaacetate.

The intensities of the bands in the NMR spectra of the aldose acetates in the region 85-105 c.p.s. clearly indicate that these signals arise from the three hydrogen atoms on the secondary carbon atoms. Additional evidence in support of this assignment is found in the spectra of polyol acetates. While ethylene glycol diacetate (or pentaerythritol tetraacetate) did not have a signal in this region, higher polyol acetates did and the intensity of the signal was indicative of the number of secondary acetoxyl groups present in the molecule. This fact bears out the expectation that chain branching should be detectable by means of NMR spectroscopy.

The signals of intensity two in the 130-150 c.p.s. region of the spectra A,C,E,H,J,K and N for the pentose acetates in Fig. 5 necessarily arise from the hydrogen atoms of the methylene groups. This is clear from the fact that the only other signal remaining to be identified is that for the acetyl group hydrogen atoms and the sharpness and high intensities of the signals in the 210-230 c.p.s. region definitely relates these signals to the twelve hydrogen atoms of the four acetoxy groups.

The gross features of the spectra of the aldohexo-

pyranose pentaacetates are essentially the same as those of the aldopentopyranose tetraacetates except that the intensity of the signals in the 130-150 c.p.s. region implies overlapping of the signals of the 5-hydrogen and 6-hydrogen atoms. This assignment is consistent with the fact that the methylene hydrogen atoms of acetylated sugar alcohols also produce their signal in this region.

It thus becomes apparent that the resolution is satisfactory for the anticipated applications such as the distinction of ketoses from aldoses [compare, for example, the spectrum of β-D-fructopyranose pentaacetate (Fig. 6) with those of the aldohexose pentaacetates (Fig. 5)]. The scope and the limitation of such usage is rather obvious and needs no further comment. However, the dependence of the spin coupling constant on the bond angles permits important information to be derived from observed fine structures. Thus, the coupling constant exhibited by the signal of the anomeric hydrogen atom yields information on the conformation of the pyranose ring because the 1- and 2-hydrogens should be in axial orientation whenever the coupling constant is as large as 6 to 8 c.p.s. Thus, the sugar acetates, A to F, in Table IV, should have the conformations shown in Fig. 5. Inspection of Table IV shows that the signal for the anomeric hydrogen atoms is in the 60 to 75 c.p.s. range for those sugar acetates which can be expected to have the 1-hydrogen in axial orientation. α-D-Gulopyranose pentaacetate is the only exception. The anomers of these compounds have the

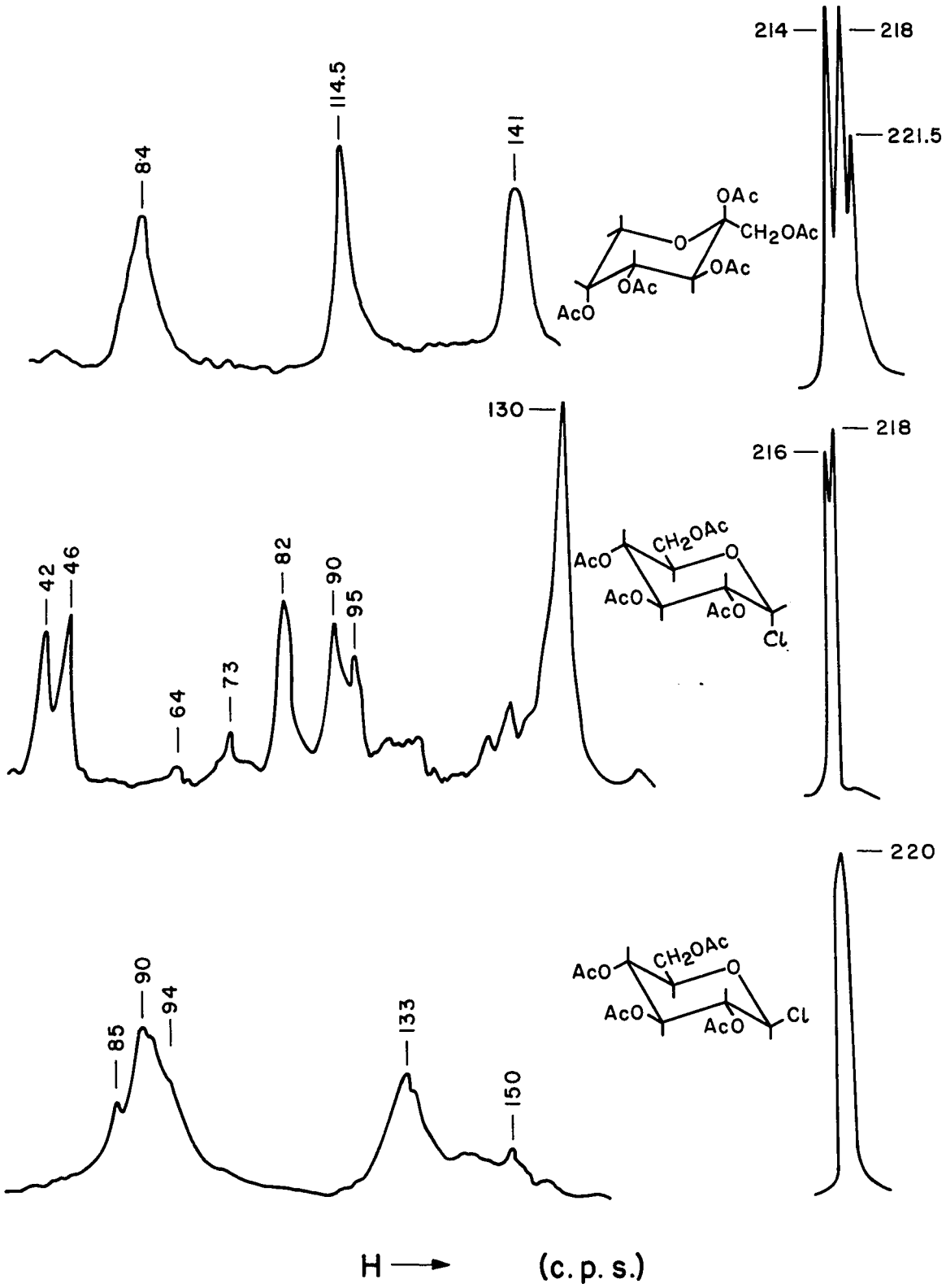


Fig. 6. - NMR spectra of β-D-fructopyranose pentaacetate and α- and β-D-glucopyranosyl chloride tetraacetates.

TABLE IV

Proton Magnetic Resonance Signals for the Anomeric Hydrogen of Acetylated Aldopyranoses

Desig-nation*	Fully Acetylated Aldopyranose	Energy (c.p.s.**)	Spin-Coupling Constant (c.p.s.)
1. Axial anomeric hydrogen			
	(a) Axial 2-hydrogen		
A	β-D-Xylose	75	6
B	β-D-Glucose	69	8
C	β-D-Ribose	62	5
D	β-D-Allose	60	8
E	α-L-Arabinose	73	8
F	β-D-Galactose	72	6
	(b) Equatorial 2-hydrogen		
G	β-D-Mannose	63.5	3
2. Equatorial anomeric hydrogen			
	(a) Axial 2-hydrogen		
H	α-D-Xylose	49.5	2
I	α-D-Glucose	51	3.2
J	α-D-Ribose	58	2.5
K	β-L-Arabinose	46	3***

Designation*	Fully Acetylated Aldopyranose	Energy (c.p.s.**)	Spin-Coupling Constant (c.p.s.)
L	α-D-Galactose	47	3
M	α-D-Gulose	55	6.2***
	(b) Equatorial 2-hydrogen		
N	α-D-Lyxose	63	4
O	α-D-Mannose	52	3
P.	α-D-Altrose	63	3***

(*) The designation of the compounds in this table is the same as was used for the spectra of these compounds in Fig. 5.

(**) Relative to the signal for the chloroform used as solvent and taking the mid-point between the two signals of the doublet.

(***) The width of the signal at half its height.

signal of the 1-hydrogen invariably in the 46-58 c.p.s. range and the coupling constants are not larger than 3 c.p.s. It seems safe, therefore, to conclude that the higher range is characteristic for an axial anomeric hydrogen atom and the lower region for an equatorial one. Thus, the conformations shown in Fig. 5 are, with only a few exceptions, consistent with the experimental data listed in Table IV.

The spin coupling constant, 6.2 c.p.s., for the anomeric hydrogen of α-D-gulopyranose pentaacetate suggests that the hydrogen atom is in axial orientation. However, the position, 55 c.p.s., of the signal is at rather low field for an axial anomeric hydrogen. The coupling constants for the anomeric hydrogen atoms of α-D-lyxopyranose tetraacetate and α-D-altropyranose pentaacetate suggests that these are in equatorial orientation. However, the positions of the signals at 63 c.p.s. is at exceptionally high field for equatorial hydrogens. These anomalies in the spectra of these compounds need not be surprising in view of the fact that, for each of these compounds, the two chair conformations probably differ little in stability and, therefore, both conformations should contribute to the spectrum of each compound. This situation could manifest itself by displaying either a signal for each conformation or only one signal in a weighted average position. This would depend on the height of the rotational barrier between both conformations. Assuming the signals for the 1-hydrogen in equatorial orientation to be 25 c.p.s. to lower field than when in axial

orientation, it can be calculated (93)(p.32) that the rotational barrier should be less than 16 kcal. to account for the presence of only one signal. It is unlikely that a barrier as high as 16 kcal. is present for any of the acetylated aldopyranoses. It is tempting therefore, to deduce the population of each conformation from the position at which the signal of the anomeric hydrogen atom occurs in the field. However, such a procedure is not sound since it would imply that the local magnetic fields at the position of the nuclei of an equatorial or axial 1-hydrogen atom are independent of the rest of the molecule. There exist both experimental and theoretical reasons for this not to be so. However, before these can be discussed, it has to be shown that a chemical shift for a proton in going from an equatorial to an axial orientation is a general feature of a six-membered ring system and is not restricted to the anomeric hydrogen atoms of sugar acetates.

As it can be seen in Fig.1, the signal of the 1-hydrogen of cis-4-t-butylcyclohexanol is 5 c.p.s. toward lower field than that of the trans-isomer. The positions of the corresponding signals of the acetyl derivatives differ by 16 c.p.s. (Fig.2). The signals of the ring hydrogen atoms of myo-inositol hexaacetate are separated by 8 c.p.s.(Fig.7). The spectra of β-D-ribopyranose tetraacetate and β-D-allopyranose pentaacetate are well enough resolved to permit detailed assignment (C and D of Fig.5) and shifts of 20-30 c.p.s. are observable between the signals of axial and equa-

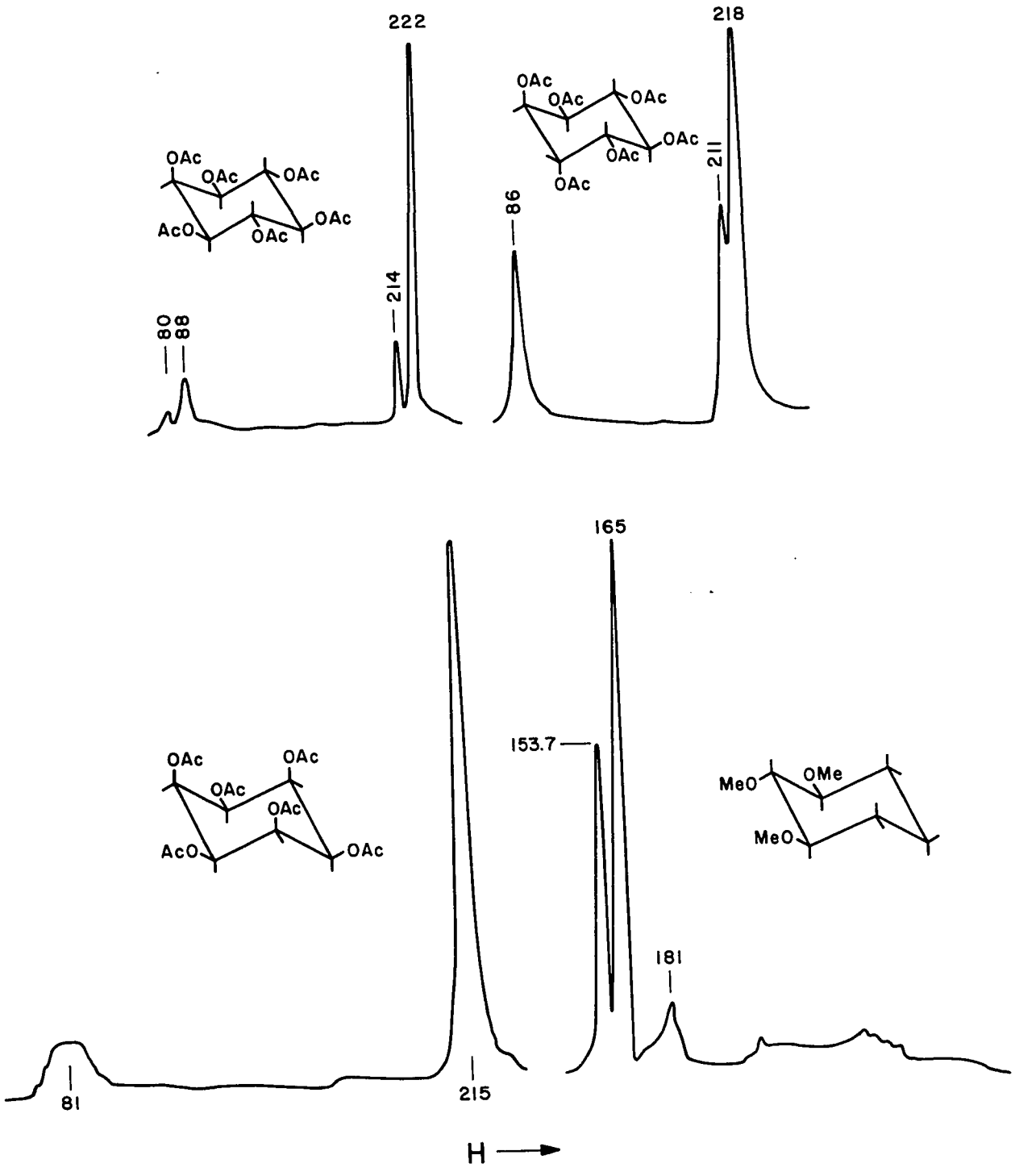


Fig. 7. - NMR spectra of the hexaacetates of myo- (upper left), levo- (upper right) and cis-inositol (lower left) and of 1α,2β,3α-trimethoxycyclohexane (lower right).

torial hydrogen atoms. The example of the 4-t-butylcyclohexanols and their acetates clearly illustrate the enhancement of the shift due to the acetylgroup, which might well give rise to an induced paramagnetic moment (61)(p.24). To find both signals of the ring hydrogen atoms of myo-inositol hexaacetate at much lower field (80 and 88 c.p.s.) than the signals of the 4-t-butylcyclohexyl acetates (109 and 125 c.p.s.) seems evidence in support of this interpretation. The magnitude such induced paramagnetic moments can attain (61) makes their effect on even remote protons quite obvious. Consequently, the signals of the anomeric hydrogen atoms of different aldopyranoses must be expected to scatter even if isolated conformational species could be observed.

Further examples of this phenomenon are found in the spectra of the α- and β-D-glucopyranosyl chloride tetraacetates (Fig. 6). Intensity measurements show the signal for the β-anomeric hydrogen atom to be in the same region as those for the hydrogens on the secondary carbons. The chemical shift is therefore approximately 40 c.p.s.

The spectrum of the methylene hydrogens at the 5-position of β-D-xylopyranose tetraacetate (Fig. 8) is of special interest since the signals are sufficiently well resolved to allow to assign these individually to the transitions of an ABX system (102). This analysis, the results of which are reported in Table V, yields the chemical shift (24 c.p.s.) and the spin coupling constant (12.0 c.p.s.)

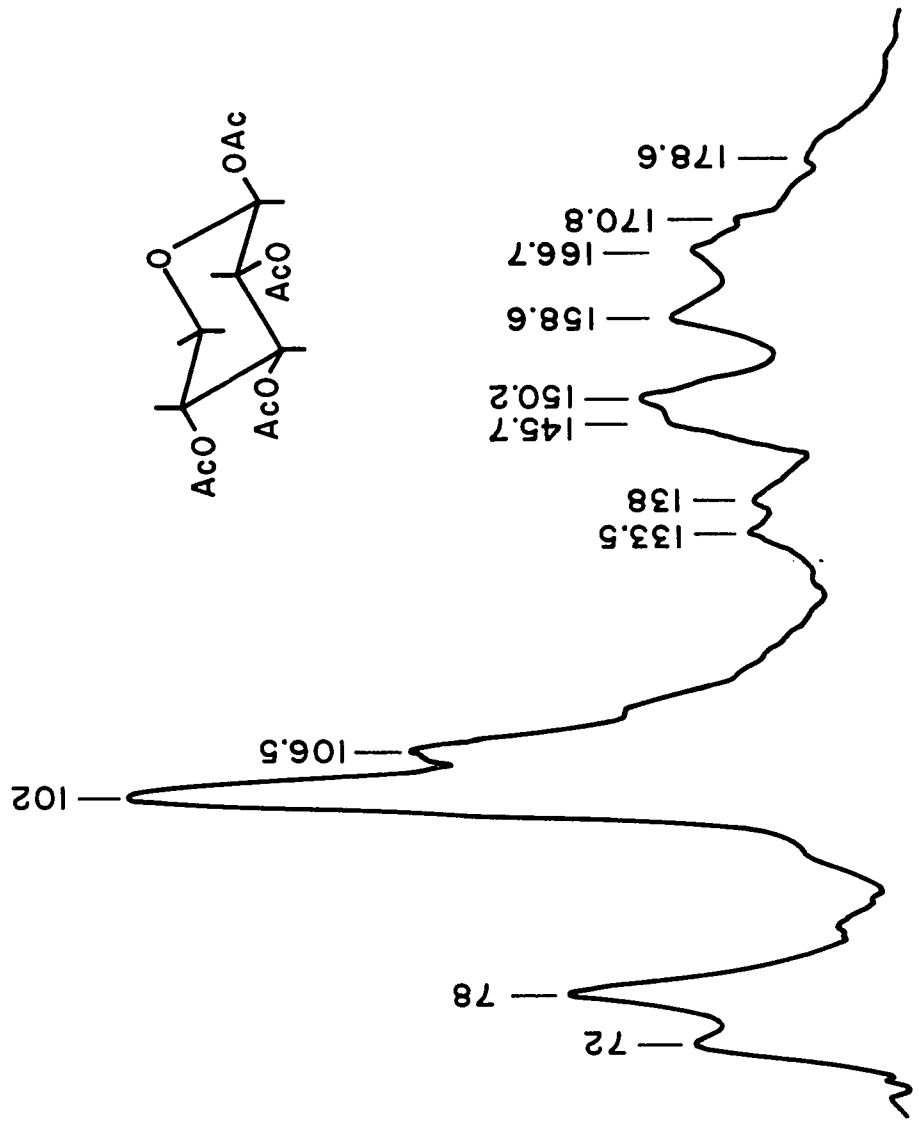


Fig. 8. - NMR spectrum of β-D-xylopyranose tetraacetate at high gain. The signal for the acetyl group hydrogens is omitted.

TABLE V

The Calculated and Observed Signals for the Methylene Hydrogens of β-D-Xylopyranose Tetraacetate

Line	Energy (c.p.s.*)		Relative Intensity
	Observed	Calculated	Calculated**
A1	178.6	178.3	0.58
A2	170.8	170.6	0.52
A3	166.7	166.4	1.42
A4	158.6	158.6	1.48
B1	150.2	149.8	1.42
B2	145.7	145.0	1.48
B3	138.0	137.8	0.58
B4	133.5	133.0	0.52

(*) The energies are measured in c.p.s. from the chloroform signal.

(**) Compare with observed intensities in Fig. 8.

between the two methylene hydrogens (A and B). The latter constant is in good agreement with the value (12.4 c.p.s.) obtained from the spectra of methane-d and 1,1,1-trichloroethane-d by Karplus, Anderson, Farrar and Gutowsky (85) and with the value of 10-11 c.p.s. found by Nair and Roberts (86) for methyl 2,3-dibromo-2-methylpropanoate.

The spectra of the α-, β-, γ-, δ- and ε-isomers of 1,2,3,4,5,6-hexachlorocyclohexane are shown in Fig. 9. The spectra of the β-, δ- and ε-isomers are obviously as expected. The single signal observed for the γ-isomer is also in agreement with expectation since the two chair conformations of this compound are identical and their interconversion is undoubtedly rapid enough to average the signals, as a rotational barrier of more than 16 kcal. is highly unlikely. The great number of transitions observed in the case of the α-isomer cannot be accounted for. It seems, however, safe to conclude from this appearance the preponderance of one conformation. It is of interest to note that the envelope of these transitions resembles the shape of the unresolved signal obtained from levo-inositol hexaacetate (Fig. 7) which possesses the same configuration. There is also a close similarity between the spectra of the δ-hexachloride and myo-inositol hexaacetate except for the magnitude of the shift.

Chemical shifts have also been observed to occur for the signals of the hydrogen atoms of acetoxy or methoxy groups when they were attached to six-membered ring

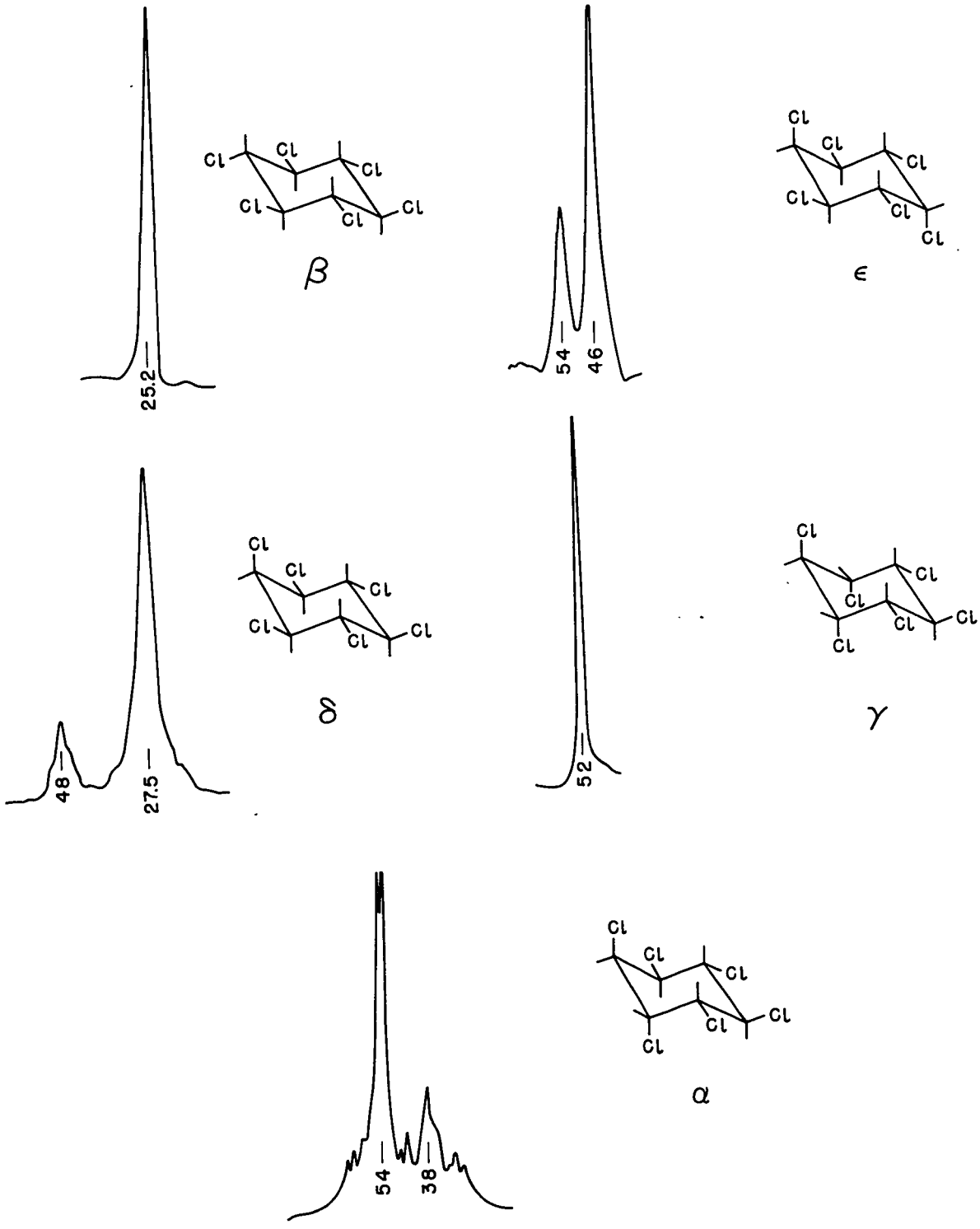


Fig. 9. - NMR spectra of α- ,β- ,γ- ,δ- and ε- 1,2,3,4,5,6-hexachlorocyclohexane.

compounds in different orientations. This is seen, for example, in the spectra of myo- and levo-inositol hexaacetates (Fig. 7). In both cases, the relative intensities of the two signals which were produced by the acetyl-hydrogen atoms show that the axial acetyl groups produce signals at lower field than did the equatorial acetoxy groups. This fact deserves attention, since just the opposite trend is displayed by the signals of the ring-hydrogen atoms. No explanation can yet be offered. This peculiarity of the signal of the acetoxy group can also be observed in the majority of the spectra for the sugar acetates (Fig. 5). For these compounds, none of the acetoxy groups are strictly equivalent and consequently it seems to be only a matter of resolution whether or not their signals can be observed individually. Nevertheless in most cases, the signals in this region of the spectra indicate clearly the ratio of equatorial to axial acetoxy groups in the molecule. The signals for the methoxy groups seem to be less sensitive to changes in orientation. In both spectra, for 1α,3β-dimethoxy-2α-acetoxycyclohexane (Fig. 4) and for a mixture of known concentrations of the α- and β-anomers of methyl D-glucopyranoside, the signals for the methoxy groups were separated by approximately 2 c.p.s. It is to be stressed, however, that substituents (groups or hydrogens) which are magnetically not strictly equivalent are to be expected to produce signals at different positions in the field regardless of whether or not their orientations on the six-membered ring are the same. For example,

1α, 2β, 3α-trimethoxycyclohexane, which undoubtedly has the three methoxy groups in equatorial orientations, possesses a spectrum (Fig. 7) with the signal for the 2-methoxy group 11 c.p.s. at lower field than that for the two others. Although the triacetates of the 1,6-anhydro-derivatives of D-glucopyranose, D-mannopyranose, D-idopyranose, D-gulopyranose, D-altropyranose and the 1,4-anhydro-D-galactofuranose gave spectra with signals for the acetoxy groups which followed apparently the discussed trend, yet the agreement was not sufficiently good to serve as a convincing standard for signals for axial and equatorial acetoxy groups. Post factum, this is quite understandable since some of these compounds must be strained due to the repulsion of large opposing groups and furthermore the magnetic anisotropy of the molecules must change greatly in such rigid and compact structures when the acetoxy groups alter their orientations.

A STUDY OF THE EFFECT OF A 3-METHOXY GROUP ON THE STEREOCHEMICAL ROUTES AND THE REACTIVITIES OF A VARIETY OF 1,2-SUBSTITUTED CYCLOHEXANES

(PART TWO)

IV. I N T R O D U C T I O N

7. Description of the Problem

Lemieux and Brice (1) studied the reactivity of a number of 1,2-trans-aldopyranose acetates in dissociation of the 1-acetoxy group. The reaction involved the formation of an intermediate cis-1,2-acetoxonium ion. An attempt was made to correlate the results with the combined influence exerted by the remaining substituents upon the stability of the acetoxonium ion. The substituent in the 3-position was found to have the greatest influence.

The authors pointed out that, although the pyranose ring in a boat conformation meets the steric requirements of the acetoxonium ion, their results are better rationalized by assuming the half-chair conformation for the six-membered ring. In this latter conformation, an acetoxy group in 3-position may be strongly eclipsed with the resonance stabilized cyclic ion when this group had originally a cis-relationship with the 2-acetoxy group. Consequently, steric and electrostatic interactions would be maximal and their combined effect could render the intermediate ion less stable and, therefore, less accessible. This postulated inhibiting effect will hereafter be termed the " cis-effect ".

The reactivities of several aldopyranoses, as observed by the authors, are consistently explainable in terms of this " cis-effect ". It must be borne in mind, however,

that the aldopyranoses are highly compact molecules and the interplay of so many functional groups within so limited dimensions must be judged with extreme care. The exchange of the substituents on a single carbon atom does not represent a single alteration under maintenance of the remaining molecule but is a drastic change for the entire molecule. From this point of view, it seems highly desirable to investigate whether or not the " cis-effect " can be found operative also in simpler molecules.

Inspection of the postulate of the " cis-effect " will make it evident that the presence of at least three functional groups is required, two of which ought to be engaged in the formation of a cyclic structure of some kind and the third is to interfere with this cyclic structure if they are in cis-relationship. Derivatives of 1,2,3-cyclohexanetriols are obviously a natural choice among the simple molecules which meet the specified requirements. Methylation of the 3-hydroxyl group should help generally to eliminate ambiguities which could arise if there is the possibility of active participation of this group in a reaction which normally would involve directly only the two other substituents.

Among the reactions which are believed to proceed through an intermediate cyclic species, the periodate oxidation, the electrophoretic migration on borate-buffered filter paper and the acetolysis of 1-tosyloxy-2-acetoxy-3-methoxycyclohexanes were chosen because of the important role which these reactions play in the chemistry of carbohydrates.

8. The Chemistry of the 3-Methoxy-1,2-cyclohexanediols.

Christian, Gogek and Purves (2) have studied the high pressure hydrogenation of pyrogallol using a variety of catalysts and were able to isolate all three isomers of 1,2,3-cyclohexanetriol from the reaction product. The 1α, 2α, 3α-isomer* was found to be the major product. The 3α-methoxy-1α, 2α- and the 3β-methoxy-1α, 2α-cyclohexanediols were obtained by preparation of the 1,2-O-isopropylidene derivatives of the corresponding triols, methylation of the remaining free hydroxy group and hydrolysis of the isopropylidene group. Gogek, Moir, McRae and Purves (156) obtained a mixture of 3α-methoxy-1α, 2β-cyclohexanediol and 3α-methoxy--1β, 2α-cyclohexanediol on reacting 3-methoxycyclohexene with peracetic acid and hydrolysis of the product. The presence of both isomers was established by demethylating the mixture with hydriodic acid and separation of the cyclohexanetriols in form of their tribenzoates by means of fractional recrystallization. Pure compounds were obtained only with considerable difficulty.

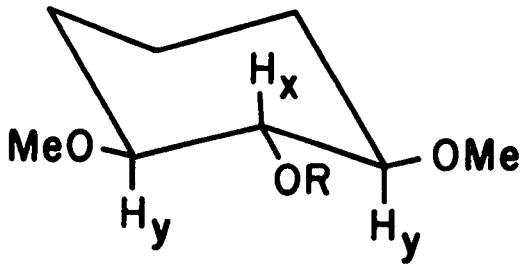
(*) The system of nomenclature used herein to describe the isomers of 1,2,3-cyclohexanetriol and some of their derivatives is adopted from the field of steroid chemistry and is similar to that proposed by Fieser (155) for carbohydrates. The names give no information on absolute configuration since the orientations of the molecules are not specified. The use of the symbol,α, is given preference over,β .

A more promising route to the isomeric methoxy-trans-diols was opened up by McRae, Moir, Haynes and Ripley's (3) success in isolating the two isomeric 3-methoxycyclohexene oxides. Methanolysis of the so-called α-oxide with sodium methoxide produced essentially only one product which on treatment with hydriodic acid gave 1α,2β,3α-cyclohexanetriol. Thus, the product of methanolysis appeared to be either Ia or IIa. Similar experiment with the so-called β-oxide produced 1α,2α,3β-cyclohexanetriol and led to the conclusion that the product of methanolysis was either IIIa or IVa. It could be hoped, therefore, that alkaline hydrolyses would give nearly pure isomers of 3-methoxy-trans-1,2-cyclohexanediol. It would be required, however, to establish their configurations.

9. Periodate Oxidation

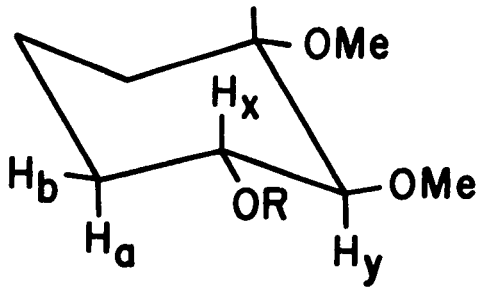
Recently, Bobbitt (157) has reviewed the literature on the periodate oxidation of carbohydrates. The mechanism of the reaction was discussed only briefly, apparently because this matter is still controversial and was believed of little consequence to the review.

It is generally agreed that the glycol and one of the anionic species of periodate which are present in aqueous solutions rapidly form a complex of some kind. This conclusion is based mainly on kinetic evidence (158-161). There is also observed (161) an immediate drop of the pH which indicates that the complex is a stronger acid than periodic



Ia, R = H

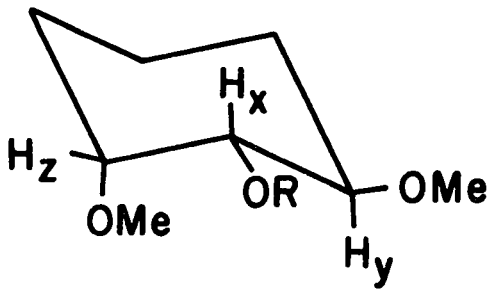
Ib, R = Ac



D,L–mixture

IIa, R = H

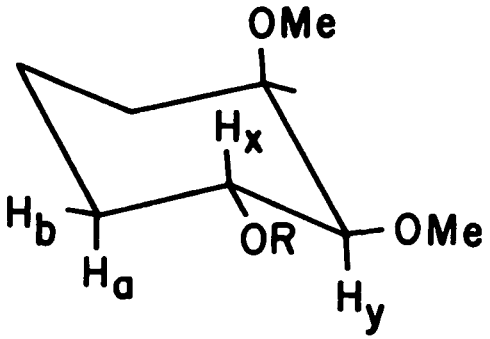
IIb, R = Ac



D,L–mixture

IIIa, R = H

IIIb, R = Ac



D,L–mixture

IVa, R = H

IVb, R = Ac

acid. Taylor (160) and Duke (159) have pointed out that their data do not permit differentiation between the following two reaction mechanisms;

(9.1) $$\text{periodate} + \text{glycol} \overset{K}{\rightleftharpoons} C \xrightarrow{k} \text{products},$$

or

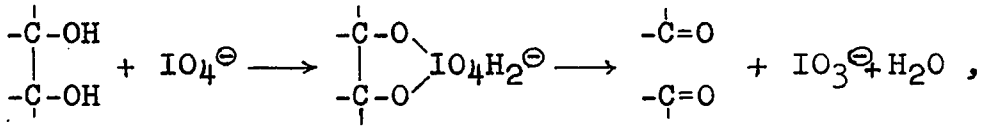
(9.2) $$\text{periodate} + \text{glycol} \overset{K}{\rightleftharpoons} C$$

$$\text{periodate} + \text{glycol} \xrightarrow{k} \text{products}.$$

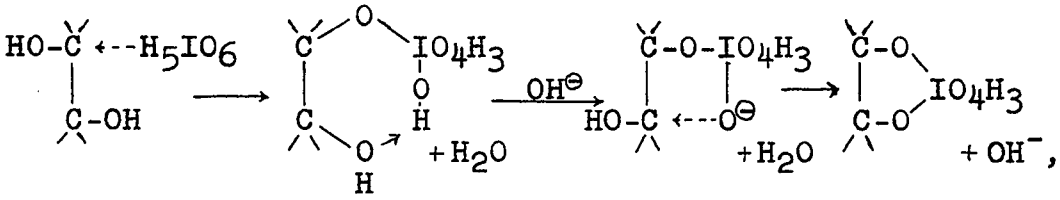
Whereas Duke (158,159) obviously favoured the first mechanism, 9.1, Taylor (160) seems inclined to favour the second mechanism, 9.2. Evidence was provided (158-161) that for ethylene glycol the equilibrium between the reactants and the complex, C, is rapidly established and strongly favours the complex. Also, it was found that the pH affects both the equilibrium constant, K, and the controlling rate constant, k. That both these constants are also strongly influenced by steric factors was demonstrated by Duke and Bulgrin (159) through a study of the periodate oxidation of a series of methyl-substituted ethylene glycols. Barker and Shaw (162) observed that in the case of D-ribopyranose the complex, C, is rapidly formed but releases the reactants only slowly when the equilibrium is forced to reverse by destroying the excess periodate. This peculiarity is believed to be a unique property of $1\alpha,2\alpha,3\alpha$-hydroxy groups situated on a six-membered ring.

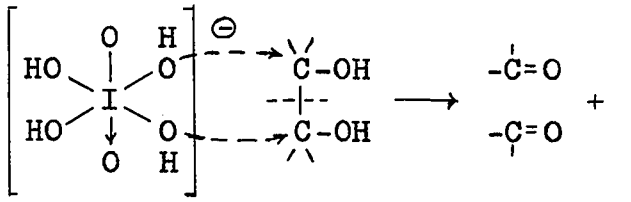
Three fundamentally different mechanisms have been postulated for the periodate oxidation of glycols which can

be approximately represented as follows;

(9.3) 

XXII

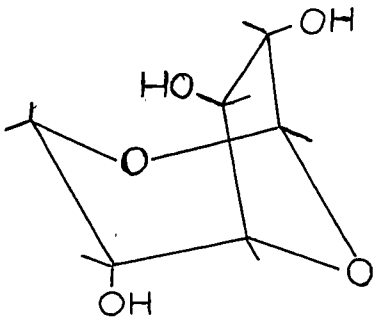
(9.4) 

(9.5) 

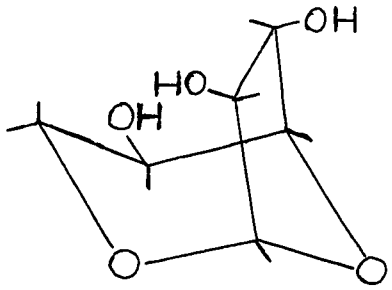
The reaction mechanism involving the disproportionation of a cyclic ester intermediate (XXII) in the rate-controlling stage was proposed by Criegee (163)(by analogy to the mechanism he proposed for the lead tetraacetate oxidation of glycols) and is widely accepted. The mechanism which would involve the scheme represented by equation 9.4 was introduced by Price and Knell (164) as pure speculation. The third mechanism which would involve a rearward attack on the glycol without the formation of any periodate ester intermediate is presently strongly supported by Taylor (165). The cyclic-ester intermediate was postulated by Criegee because of the different reactivities of the <u>cis</u>- and <u>trans</u>-1,2-cyclohexanediols. The <u>trans</u>-1,2-cyclohexanediol is oxidized about 30 times less rapidly than the <u>cis</u>-isomer. These

results were rationalized as due to the varying ease of closing the five-membered ring of the cyclic periodate ester.

It can be argued, however, that although it is possible to fuse a five-membered ring trans to a six-membered ring, two five-membered rings cannot be trans-fused. Indeed, D-glucosan ⟨1,4⟩β⟨1,6⟩(XXIII)(166) and D-galactosan ⟨1,4⟩∝⟨1,6⟩(XXIV)(167) were reported to resist period-



XXIII



XXIV

ate oxidation. However, other trans-glycols of five-membered rings have been reported to undergo oxidation completely within a few hours at room temperature; for example, trans-1,2-cyclopentanediol (168), L-threitan (48 hours at 5°) (169), D-glucosaccharo-1,4-lactone (48 hours at 5°)(169), 1,4-anhydro-D,L-xylitol (170), methyl α-D-arabinofuranoside (171) and ethyl 5,6-O-isopropylidene-β-D-galactofuranoside (172). It is to be noted, however, that the latter compounds do not have the five-membered ring fused to other ring structures and, consequently may undergo reaction because of their greater flexibility. The second mechanism,

9.4, is obviously argued against by the fact that the above mentioned glycosans resisted oxidation. The third mechanism presented by Taylor (165) is not applicable to any trans-1,2-glycol situated on five- or six-membered rings in any straight forward fashion.

Crouthamel, Hayes and Martin (173) established, by means of spectrophotometric and potentiometric measurements, the presence of three simultaneous equilibria of four different ionic species in an aqueous solution of periodic acid within the pH-range from zero to seven. Hydroxonium ions participate in two of the equilibria and affect the third indirectly. As Buist and Bunton (161) pointed out, each of these species can, in principle, coordinate with a glycol molecule and the various complexes can in turn be in equilibrium among themselves and with the hydroxonium ions. Furthermore, the possibility exists that either only one of the complexes has the ability to disproportionate or all of them are capable to do so but at different rates. This complicated system cannot be expected to respond uniformly with all the individual equilibria to changes in temperature, configuration of the glycols and hydroxonium ion concentrations. It seems therefore highly improbable that kinetic investigations alone can ever solve this problem.

10. Electrophoretic Migration of Polyalcohols on Borate-Buffered Filter Paper

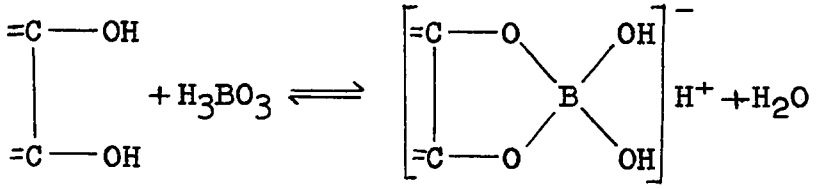
The migration of a charged particle in an electrostatic field is known (174) to be proportional to the charge and the field gradient and to be inversely proportional to the resistance to the migration provided by the medium. A variety of techniques [see (175,176)] have been developed which utilize this principle for the separation of ions. All of these techniques use some kind of a device to prevent mixing of the separated ions.

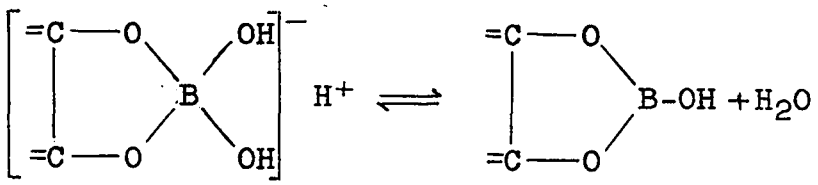
The technique which can be termed paper electrophoresis uses filter paper strips for this purpose. The strip is wetted with a salt solution and the ions to be separated are spotted usually near the middle of the length of the paper. The ends of the strip are then dipped into the electrode vessels containing salt solution and an appropriate potential is applied across the paper.

Under ideal experimental conditions, a compound should migrate equal distances in equal time intervals and this distance should be a linear function of the applied potential. Such conditions are rather difficult to establish but are a necessary prerequisite for mobility measurements. There are two inherent problems; the Joule's heat and the electroendosmosis. The heat will cause, when uncontrolled, increasing mobilities, diffusion and evaporation of the solvent from the paper. The evaporation will change the concentration of the electrolyte and consequently solvent will

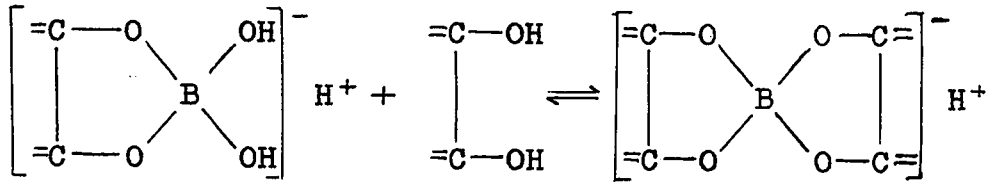
flow to restore the equilibrium. The electroendosmosis (177) produces a considerable flow of solvent in one direction because of the charges adhering to the material used to support the electrolyte. The ways in which the experimentalist has chosen to cope with these problems are responsible for the differences between the techniques now in use and which have been recently reviewed, among others, by Lederer (175) and McDonald (176). The technique which was used in this study is described in the experimental section (see p.122).

Alcohols in aqueous solutions are, of course, practically not dissociated and, consequently, cannot be expected to migrate under the influence of an electric field. However, Vignon (178) and Bouchardat (179) observed that mixtures of some polyalcohols and boric acid are highly acidic and the ions of these mixtures should therefore show electrophoretic mobility. Magnanini (180) and Böeseken (181) studied this phenomenon closely by means of conductivity measurements. Böeseken (181) postulated the following three equilibria to explain the interaction between polyols and boric acid. He wrote: " Equilibrium 1 is situated very much to the right; 3 is dependent upon the position of the two hydroxyl groups in the diol. Seeing that the bisdiol acid, at the dilution involved in this case, is entirely split into ions, the hydrogen ion concentration, under otherwise equal conditions, is a criterion of the more or less favorable position of the hydroxyl groups for the attachment

(1) 

(2) 

XXV

(3) 

of boric acid to form the spirane. " It is not readily understood why the steric requirements for the product formation in equations 1 and 3 should differ so greatly. Rippere and La Mer (182) have isolated boric acid esters of structure XXV in non-aqueous media. They could not detect the formation of any type of boric ester in aqueous solutions. Therefore, the highly acidic species may only be a complex but should have a cyclic- or a spirane-structure in order to explain Böeseken's (181) important observation that the constant of the equilibrium between the complex and the reactants seems to parallel the ability of the hydroxy groups of the glycol to approach coplanarity. Only 1,2-glycols were found to form strongly acidic complexes. Recently, Angyal

and McHugh (183,184) have provided evidence that 1α,3α,5α-cyclohexanetriol is also capable of complex formation with boric acid and postulated a tridentate structure in which all three oxygen atoms of the triol are bonded to the boron atom. This tridentate complex is implied (183,184) to be formed in preference to complexes which would involve cis-1,2-hydroxy groups.

The electrophoretic migration of these glycol-boric acid complexes has, indeed, been observed (185-190). Using this method, it was possible to detect weak complexing (infered from short migration) in cases, where conductivity measurements had failed; for example: myo-inositol and cis-1,2-cyclohexanediol (184).

Foster (191), who has studied the paper electrophoresis of carbohydrates extensively, has suggested the use of M_g-values to report the relative electrophoretic migrations of carbohydrates on borate-buffered filter paper. The M_g-value is defined as follows;

$$M_g = \frac{\text{True distance of migration of the substance}}{\text{True distance of migration of D-glucose}} .$$

The practice of reporting relative migration-values has, in principle, a distinct advantage because the experimental imperfections will then largely cancel. Angyal (184) has observed that the mobility of D-glucose decreased with a decrease in the borate buffer concentration. Since the effect was not similar for a number of cyclitols, the M_g-values were

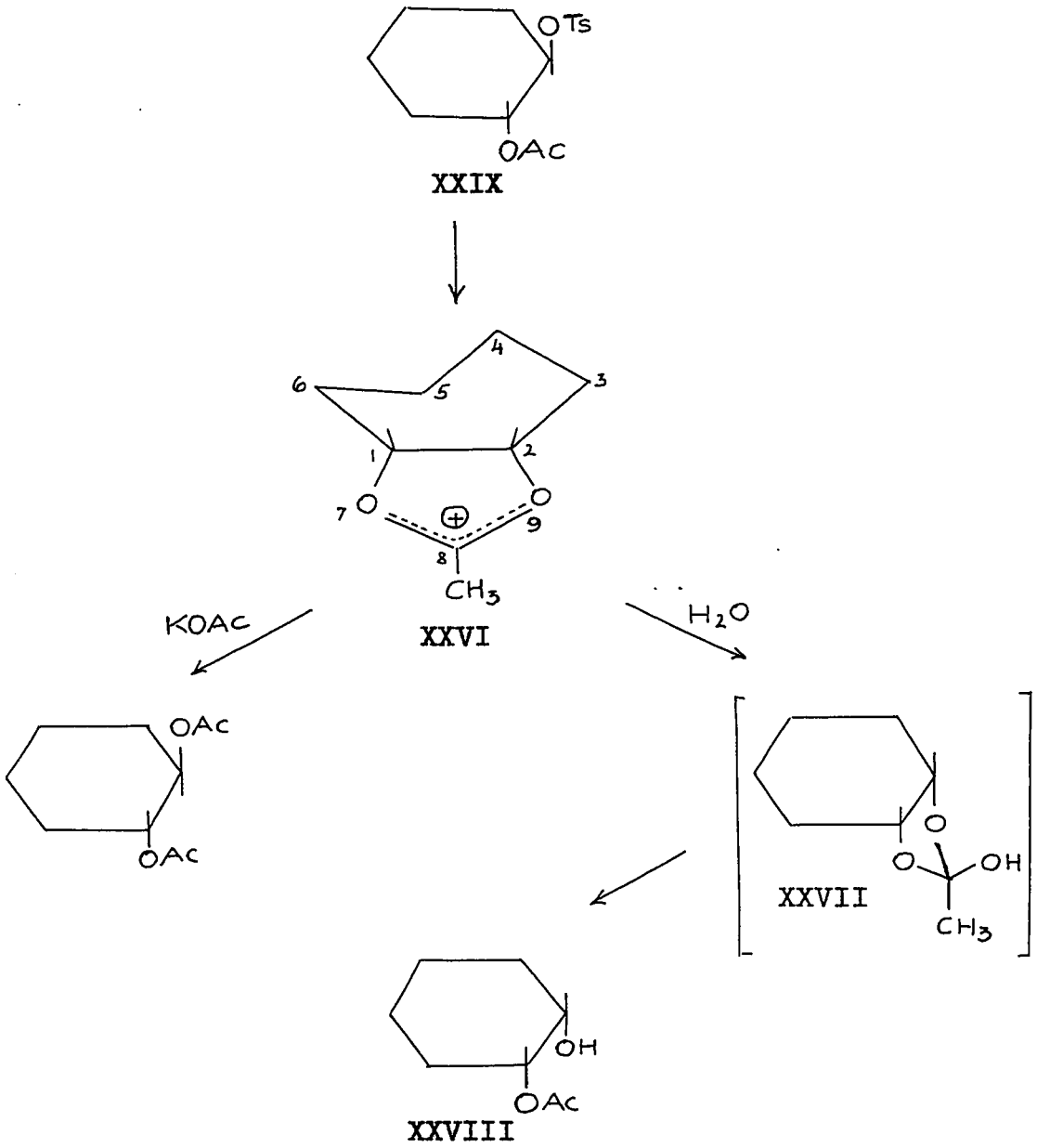
found dependent on the buffer concentration. In view of these complications, methyl orange was used as the reference compound in this work. This practice was of advantage in that the migration of a coloured compound of known acid strength permits visual inspection of the progress of the electropheris and renders the results somewhat more amenable to theoretical interpretation (192).

Foster (193) observed lower M_g-values for methyl β-D-lyxopyranoside, methyl β-D-mannopyranoside, methyl α-D-gulopyranoside and methyl β-D-rhamnopyranoside than for their corresponding anomers. The author (193) explained this fact in terms of Lemieux and Brice's (1) " cis-effect ". This evidence is seemingly confirmative for the existence of the " cis-effect " but has to be received with the same reservation as Lemieux and Brice's original observations (see p. 84).

11. The Acetolysis of trans-2-Acetoxycyclohexyl p-Toluenesulfonate

Winstein, together with numerous coworkers, has studied the role of neighbouring groups in replacement reactions. Several substituents, for example: carboxylate ions, iodo-, acetoxy-, bromo-, hydroxy-, chloro- and methoxy-groups (194) have been found capable to participate in replacement reactions if these groups were in, or could move into, a sterically suitable position. The acetoxy group is one of the most effective participating groups and is of particular interest in connection with the present study because the " cis-effect " was discovered (1) on reactions which proceeded with participation of an acetoxy group and, for this reason, the acetolyses of 1α-tosyloxy-2β-acetoxy-3α-methoxycyclohexane and the 1β,2α,3α-isomer were studied in the present investigation.

The acetolysis of trans-2-acetoxycyclohexyl tosylate was studied by Winstein and coworkers (195,196,197). Their results led to the conclusion that the rate-controlling step in the course of the reaction is the formation of the resonance stabilized acetoxonium ion (XXVI) due to the participation of the acetoxy group in the ionization of the molecule. This conclusion was based on the following facts. The ratio of the rate constants for the acetolysis of the tosylates of cyclohexanol, trans-2-acetoxycyclohexanol and cis-2-acetoxycyclohexanol was found to be 1 : 0.3 : 4.5×10^{-4}


OTs
OAc
XXIX
4
6
5
3
1
2
7
O
9
8
CH3
XXVI
KOAc
H2O
OAc
OAc
O
O
OH
CH3
XXVII
OH
OAc
XXVIII

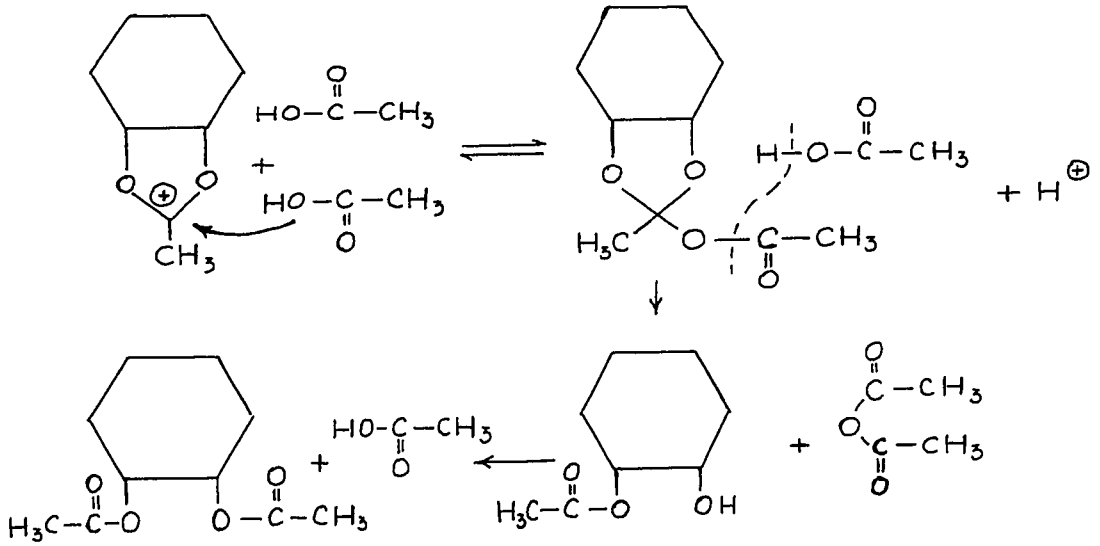
(198). The slow reaction rate of the cis-isomer reflects the resistance which the inductive effect of the acetoxy group exerts against the removal of the tosyloxy group. It must be concluded that the resonance energy of the cyclic ion, which is formed in the case of the trans-compound, compensates almost entirely for this inductive effect. The formation of the acetoxonium ion from the trans-compound was also inferred by the following observations. The cis-isomer yielded, on solvolysis in dry acetic acid and in the presence of potassium acetate, a diacetate which gave rise on hydrolysis to almost pure trans-glycol. This steric result indicates a simple Walden inversion. In contrast, the trans-isomer proceeded through the same reaction sequence with retention of configuration. This result implies a double Walden inversion during the course of the reaction (198). Furthermore, optically active trans-2-acetoxycyclohexyl tosylate gave completely racemized trans-product during the above mentioned reaction sequence (195). This fact implies that a symmetrical intermediate exists which gives both the oxygen carrying carbon atoms an equal chance to undergo the second Walden inversion. Also, cis-cyclohexene ethyl orthoacetate could be isolated in good yield from the products of the solvolysis of trans-2-acetoxycyclohexyl tosylate in dry ethanol (199). It was further demonstrated that the acetolyses of the orthoester gave the same products which were obtained from solvolyses of the trans-2-acetoxycyclohexyl tosylate under the same conditions (199). Finally, it was shown

(196) that compounds like water and acetate ions which are able to direct the steric results of the solvolyses (see below) do not affect the rate appreciably. An inspection of the proposed scheme of the reaction (see p.99) shows that the removal of the tosyloxy group with participation of the acetoxy group must be the rate determining step.

The formation of the products which were isolated from the solvolyses of trans-2-acetoxycyclohexyl tosylate in media of different composition was explained by the authors (195,196,199) on the basis of the assumption that the intermediate cyclic acetoxonium ion (XXVI) can be attacked at three different sites; that is, at the carbon atoms one, two or eight. An attack of a nucleophilic reagent, for example, acetate ion, at either of the carbon atoms one or two will produce trans-2-acetoxycyclohexyl acetate. The formation of a racemic product on acetolysis of the optically active trans-2-acetoxycyclohexyl tosylate may have been the result of racemization by way of an intermediate ion-pair formation (197) and internal return to the compound of opposite configuration. However, Winstein and Heck (197) have excluded this possibility by a comparison of the titrimetric and polarometric rates of the reaction. Consequently, the racemization must result from an equivalence of the reactive sites one and two of the acetoxonium ion. It is of interest to note that the extension of the Fürst - Plattner rule (200) for the formation and opening of 1,2-oxide rings to this situation would imply that the acetoxonium ion is

sufficiently stable to undergo conformational equilibration before reacting with the acetate ion.

On the other hand, if the attack by the acetate ion is at carbon atom eight, the product will be acetyl cis-cyclohexene orthoacetate which undoubtedly can rapidly revert to the acetoxonium ion. However, if the nucleophilic reagent is water, the product will be the orthoacid XXVII, a compound which is tautomeric to the monoacetate XXVIII. It was in fact observed that XXVIII was the product of the reaction when the solvolysis was performed in aqueous acetic acid (195). The solvolysis of the trans-acetoxy tosylate (XXIX) in dry acetic acid was observed (195) to produce appreciable amounts of acetylated cis-1,2-cyclohexanediol. This result could be rationalized by assuming that the acetoxonium ion can bring about the acetylation of acetic acid and that this route of reaction becomes favorable in the absence of potassium acetate.



V. E X P E R I M E N T A L

Melting points were determined on a Kofler micro hot stage and are uncorrected. Kofler's mixed fusion technique (201) was used to identify compounds.

1α,3α-Dimethoxy-2β-acetoxycyclohexane (Ib).- The product [now known to be 1α,3α-dimethoxy-2β-cyclohexanol (Ia)], n_D^{20} 1.4590, of the methanolysis of the so-called α-oxide (3) (now known to be D,L-2-exo-methoxy-7-oxa-bicyclo [4.1.0] heptane (V) and referred to hereon as the exo-oxide) was acetylated in boiling acetic anhydride containing sodium acetate. The acetate, isolated in the usual way, was completely crystalline. Recrystallization from ligroin gave pure material, m.p. 65.5-66.5°, which possessed the saponification equivalent, 202, expected for the compound Ib.

3α-Methoxy-1α,2β-cyclohexanediol (IX).- The exo-oxide (V), approximately 100 mg., was treated at 100° for 24 hours in a sealed tube with 0.2 ml. of 10% aqueous sodium hydroxide solution. The reaction mixture was absorbed on 1.2 parts by weight of dry Celite and the resulting powder, packed as a column, was extracted with chloroform (202). Evaporation of the chloroform left a sirupy residue which was examined by paper chromatography using the xylene-methyl ethyl ketone-water (1:1:1:) system and the ammoniacal silver nitrate spray described by Henbest and Wilson (203). It was observed that the sprayed chromatogram can be kept

for record purposes if it is washed with aqueous ammonium hydroxide immediately after the spots have appeared. The R_f-values obtained at room temperature for the variety of glycols prepared in this work are listed in Table VI. The chromatogram showed the presence of the 1α,2β,3α-compound (IX) contaminated with a small amount of the 1β,2α,3α-isomer (XIV). The same solvent system as was used in the paper chromatography was employed for quantitative separation of the compounds by partition chromatography on Celite (204). The amounts of the glycols in the zones were determined by titration using sodium metaperiodate (205). The method was established using known mixtures of the 1,2-cyclohexanediols and was found reliable to ±1%. It was necessary to completely remove the organic solvents prior to the periodate titration. It is noteworthy that considerable losses of the glycols occurred in the in vacuo evaporation of the solvents if a large excess of water (40 ml.) was not added. The purity of the compound in each fraction was tested by paper chromatography. These experiments indicated that the yield of 1α,2β,3α-compound (IX) was 80% and that of the 1β,2α,3α-isomer (XIV) was 7%.

A sample of the 1α,2β,3α-methoxydiol (IX), purified by chromatography, was converted to the di-O-p-nitrobenzoyl derivative. The derivative, purified by recrystallization from ethyl acetate, melted at 134.0-134.5°.

Anal. Calc. for $C_{21}H_{20}N_2O_9$: C,56.76; H, 4.54%. Found: C, 56.78; H, 4.56%.

TABLE VI

Paper Chromatography of Some 1,2-Glycols Using Xylene-Methyl Ethyl Ketone-Water (1:1:1)(203)

Compound	R_f
1α,2α-Cyclohexanediol	0.33
1α,2β-Cyclohexanediol	0.20
3β-Methoxy-1α,2α-cyclohexanediol (VIII)	0.28
3α-Methoxy-1β,2α-cyclohexanediol (XIV)	0.22
3α-Methoxy-1α,2α-cyclohexanediol (XIII)	0.18
3α-Methoxy-1α,2β-cyclohexanediol (IX)	0.15

1α,2β,3α-Trimethoxycyclohexane (X).- The 1α,3α-dimethoxy-2β-cyclohexanol (Ia), (purified by way of the crystalline acetate) was methylated with methyl iodide and silver oxide in the usual manner. The distilled product, n_D^{25} 1.4393, possessed no hydroxy group (infrared) and had the nuclear magnetic resonance spectrum expected for the trimethyl ether (X). The number of methoxy groups in the compound was clearly indicated by the presence in the NMR spectrum of two signals for methoxy group hydrogens of relative intensity 1 to 2 [see Fig.7 (p.75)]. A compound of identical infrared spectrum was obtained by methylation of 3α-methoxy-1α,2β-cyclohexanediol (XX) (purified by way of the dibenzoate, m.p. 121.5-122.5°).

Reduction of the exo-Oxide (V).- The exo-oxide (3), 1.5 g., was allowed to react with one gram of lithium aluminium hydride in etheral solution at the boiling point for about 16 hours. The mixture was acidified and extracted in the usual manner to yield a product which was distilled in vacuo. The yield, 400 mg., is not significant due to the accidental loss of about half the material during the isolation. The substance, n_D^{20} 1.4626, possessed an infrared spectrum which could be interpreted to mean that it was mainly 2β-methoxy-1α-cyclohexanol (XX). The material gave a 3,5-dinitrobenzoate derivative, m.p. 101.5-103°, which was identical (mixed m.p. and infrared spectra) with that (m.p. 102-104°) (206) prepared from authentic 2β-methoxy-1α-cyclohexanol.

Reduction of the 1α-Tosyloxy-2β-acetoxy-3α-methoxy-cyclohexane (VI).- The tosylate, 410 mg., which was obtained from the exo-oxide (V) (207) was dissolved in 20 ml. of 80% aqueous ethanol. Five grams of 5% sodium amalgam (208) was added in small portions to the solution kept at 0°. After standing overnight at about 4° and a further 24 hours at room temperature, the aqueous phase was neutralized with carbon dioxide and evaporated to near dryness. The residue was absorbed on Celite for extraction with chloroform (202). Evaporation of the chloroform and distillation of the residue at 0.08 mm. pressure gave 65 mg., 38% yield, of an oily substance which possessed an infrared spectrum identical to that of 3α-methoxy-1α,2β-cyclohexanediol (IX). The methoxy-diols (VIII, IX, XIII and XIV) were found to be clearly distinguishable by means of their infrared spectra.

3β-Methoxy-1α,2α-cyclohexanediol (VIII).- A solution of 6.55 g. of 3-methoxycyclohexene (XV) in 300 ml. of 66% aqueous ethanol containing 1 ml. of 10% aqueous sodium hydroxide solution was cooled to -60° and a solution of 18.5 g. of potassium permanganate in 300 ml. of water was added at once with stirring. After 90 seconds, an acidified solution of 60 g. of sodium bisulfite in 150 ml. of water was added and the resulting clear solution extracted continuously with ether. Solvent removal gave 4.0 g. of viscous oil (47% yield) which exhibited a positive dinitrophenylhydrazone test for ketones. It is probable that this was due to ketol impurities formed in the permanganate oxidation

(209). Acylation of the oil in pyridine with p-nitrobenzoyl chloride gave a 67% yield of the bis-p-nitrobenzoate of the 1α,2α,3β-methoxydiol (VIII), m.p. 164.4-165.3°, after three recrystallizations from ethanol. The compound was identical with the p-nitrobenzoate which was obtained from the tosylate (VI) by means of solvolysis in aqueous acetic acid (206), as shown by mixed melting point determination and infrared spectra. Saponification of the p-nitrobenzoate gave a substance with the type of physical properties (low melting, highly hygroscopic white needles) reported for the compound VIII by Christian, Gogek and Purves (2).

1α,3β-Dimethoxy-2α-acetoxycyclohexane (IIIb).- Acetylation as described above, of the product [now known to be 1α,3β-dimethoxy-2α-cyclohexanol (IIIa)], n_D^{20} 1.4588, obtained without special purification from the methanolysis of the so-called β-oxide [now known to be D,L-2-endo-methoxy-7-oxa-bicyclo[4.1.0]heptane (XI) and referred to hereon as the endo-oxide], gave a liquid, $n_D^{24.5}$ 1.4485, which resisted crystallization. The material gave a saponification equivalent, 199, in good agreement with that expected for IIIb. The NMR spectrum of this compound (IIIb), Fig.4, is a good criterion for assuming that it and the starting material (IIIa) were reasonably pure compounds, and this assumption was verified by identical infrared spectra which were obtained from this material (IIIb) and from a sample which was obtained from the alcohol (IIIa) which in turn was purified by recrystallization of the p-nitrobenzoate (207).

3α-Methoxy-1β,2α-cyclohexanediol (XIV).- The endo-oxide (XI), approximately 150 mg., was hydrolyzed with aqueous sodium hydroxide and the product was isolated in the same manner as described above for the exo-isomer. Partition chromatography on Celite with subsequent periodate titration of the isolated fractions showed the product to contain the 3α,1β,2α-methoxydiol (XIV), 60% yield, and the 3α,1α,2β-methoxydiol (IX), 15% yield. A sample of the 3α,1β,2α-methoxydiol (XIV) was isolated by preparative partition chromatography (204). On distillation, in vacuo, the compound crystallized, m.p. 50.5-52°. The substance possessed an infrared spectrum clearly different from those of its isomers (VIII,IX and XIII) and consumed the expected amount of sodium periodate. The bis-p-nitrobenzoate melted at 142.5-143.5°.

Anal. Calc. for $C_{21}H_{20}N_2O_9$: C, 56.76; H, 4.54%. Found: C, 56.53; H, 4.58%.

Reduction of the 1β-Tosyloxy-2α-acetoxy-3α-methoxycyclohexane (XII).- The tosylate, 368 mg., which was obtained from the endo-oxide (XI) (207), was converted using sodium amalgam, as described above for the reduction of the isomeric tosylate (VI), in 49% yield to a substance identical (infrared spectra) to the 3α,1β,2α-methoxydiol (XIV).

Periodate Oxidation of the 3-Methoxy-1,2-cyclohexanediol isomers (205).- A sample of about 0.25 mmole (36.6mg.) of the glycol was weighed accurately and dissolved together with one gram of disodium orthophosphate in 80 ml. of water in a 100 ml. volumetric flask. After this solution had attained 0° in an ice bath, 10 ml. of a standardized sodium metaperiodate solution at 0° was added from a pipette and the flask was filled to the mark with water of 0°, well shaken and restored to the ice bath. The zero time was taken as the time when half of the periodate solution had been added. At various times thereafter, 10 ml. aliquots were quenched by addition to mixtures of one gram of potassium iodide, one gram of sodium bicarbonate and exactly 5 ml. of a 0.0538 N sodium arsenite solution. Again, the moment of half-addition was recorded. After standing for at least 15 minutes, the excess arsenite was titrated with standardized 0.005 N iodine solution. The rates, given in Tables VIII - XIV and summarized in Table VII, were calculated as second order rate constants, k, from the following expression,

$$k = \frac{2.3}{t(a - b)} \log \frac{b(a - x)}{a(b - x)} ,$$

where t is the time in seconds, a and b are the initial concentrations in equivalents or moles per liter of the periodate ions and the glycol, respectively, and x is the concentration of the iodate ions at the time "t" in the same units. The latter concentration was calculated from the

analytical data. During a duplicate-run with trans-1,2-cyclohexanediol at 0°, the change of the pH was followed with a Beckman-potentiometer. The pH of the buffered glycol-solution was found to be 9.49. The addition of periodate caused an immediate drop to 7.80. The pH was 7.58 after 60 seconds. Thereafter, the pH increased slowly to a final reading of 7.72. For several other runs, only the reading at " infinite time " was taken and agreed within ±0.04 pH units.

TABLE VII

Half Life Times and Second Order Rate Constants of the Periodate Oxidations of the Isomers of 3-Methoxy-1,2-cyclohexanediol at 0° and pH 7.65

Compound	τ (sec.)	k^a (1/mole x sec.)	k^b (1/mole x sec.)
cis-1,2-Cyclohexanediol	(<10)[c]	(5.0)[c]	1.20
trans-1,2-Cyclohexanediol	375 380	0.138 0.130	
1,2-Ethanediol	1950	0.03	
3α-Methoxy-1α,2β-cyclohexanediol(IX)	1580 1580	0.031 0.029	0.016
3α-Methoxy-1β,2α-cyclohexanediol(XIV)	2960 3030 2790	0.018 0.016 0.020	
3β-Methoxy-1α,2α-cyclohexanediol(VIII)	245 285	0.186 0.161	
3α-Methoxy-1α,2α-cyclohexanediol(XIII)	(<10)[c]	(1.08)[c] (1.61)[c] (1.88)[c]	1.88 0.64 0.52

(a) less than 85% of the reaction was completed.

(b) more than 85% of the reaction was completed.

(c) at the time of the first measurement (120 sec.) more than 85% of the reaction was completed. The values in brackets were obtained by extrapolation (see Table XIV).

TABLE VIII

Periodate Oxidation of cis-1,2-Cyclohexanediol

The initial concentrations of sodium periodate (a) and glycol (b) were 0.01320 M and 0.01311 M, respectively. The concentration of the iodine solution was 0.00505 N.

Time (sec.)	I_2-sol. (ml.)	x (mmole/l)	$\frac{2.3}{a-b} \log \frac{b(a-x)}{a(b-x)}$ (l/mole)	k (l/mole x sec.)
0	1.04	0	0	
97	45.90	11.35	484	(5.0)
180	48.25	11.95	768	3.42
269	49.30	12.20	987	
386	49.18	12.18	970	0.98
562	50.12	12.32	1132	0.92
971	50.80	12.60	1720	1.44
			average*	1.69

(*) The values in brackets are not included in the average.

TABLE IX

Periodate Oxidation of trans-1,2-Cyclohexanediol

The initial concentrations of sodium periodate (a) and glycol (b) were 0.01320 M and 0.00764 M, respectively for the first run and 0.01317 M and 0.00582 M, respectively for the second run. The concentration of the iodine solution was 0.00505 N

Time (sec.)	I_2-sol. (ml.)	x (mmole/l)	$\frac{2.3}{a-b} \log \frac{b(a-x)}{a(b-x)}$ (l/mole)	k (l/mole x sec.)
First run:				
0	0.96	0	0	
133	9.40	2.135	27.4	(0.206)
215	12.63	2.95	42.4	0.183
357	15.92	3.78	62.2	0.139
888	22.25	5.38	131.8	0.131
1983	27.40	6.69	238.0	0.098
5800	31.10	7.62		
				average* 0.138
Second run:				
0	1.02	0	0	
129	7.15	1.55	25.4	(0.197)
238	9.90	2.25	41.4	0.147
368	12.21	2.83	60.5	0.147
774	17.20	4.09	114.3	0.132
1893	21.42	5.10	217.8	0.093
61/2 hrs.	24.24	5.82		
				average* 0.130

(*) The values in brackets are not included in the average.

TABLE X

Periodate Oxidation of 1,2-Ethanediol

The initial concentrations of sodium periodate (a) and glycol (b) were 0.01320 M and 0.00754 M, respectively. The concentration of the iodine solution was 0.00505 N.

Time (sec.)	I_2-sol. (ml.)	x (mmole/l)	$\frac{2.3}{a-b} \log \frac{b(a-x)}{a(b-x)}$ (l/mole)	k (l/mole x sec.)
0	1.03	0	0	
				(0.0615)
126	3.79	0.70	7.74	
				0.0216
219	4.52	0.88	9.75	
				0.0446
330	5.98	1.25	14.7	
				0.0371
591	8.70	1.94	24.4	
				0.0332
937	11.30	2.59	35.9	
				0.0302
1666	15.20	3.58	57.9	
				0.0280
4190	22.19	5.38	128.8	
				0.0278
6114	25.12	6.09	182.3	
				average* 0.0318

(*) The values in brackets are not included in the average.

TABLE XI

Periodate Oxidation of 3α-Methoxy-1α,2β-Cyclohexanediol

The initial concentrations of sodium periodate (a) and glycol (b) were 0.01320 M and 0.00246 M, respectively for the first run and 0.01322 M and 0.00287 M, respectively for the second run. The concentrations of the iodine solutions were 0.00505 N and 0.00513 N, respectively for the first and the second run.

Time (sec.)	I_2-sol. (ml.)	x (mmole/l)	$\frac{2.3}{a-b} \log \frac{b(a-x)}{a(b-x)}$ (l/mole)	k (l/mole x sec.)
First run:				
0	1.02	0	0	
				(0.074)
139	2.25	0.311	10.3	
				(0.020)
247	2.50	0.374	12.4	
				0.040
406	3.14	0.536	18.8	
				0.038
764	4.32	0.834	32.3	
				0.032
1213	5.35	1.09	46.7	
				0.023
1870	6.25	1.32	61.9	
				0.025
3911	8.28	1.84	113.8	
				average* 0.031
Second run:				
0	0.88	0	0	
				(0.062)
162	2.25	0.352	10.0	
				0.032
270	2.70	0.466	13.5	
				0.035
1195	5.68	1.255	45.8	
				0.026
1697	6.70	1.490	59.1	
				0.021
2429	7.60	1.722	74.8	
				average* 0.029

(*) The values in brackets are not included in the average.

TABLE XII

Periodate Oxidation of 3α-Methoxy-1β,2α-Cyclohexanediol

The initial concentrations of sodium periodate (a) and glycol (b) were 0.01321 M and 0.00228 M, respectively for the first run, 0.01322 M and 0.00204 M, respectively for the second run and 0.01320 M and 0.00236 M, respectively for the third run. The concentrations for the iodine solutions were 0.00512 N, 0.00505 N and 0.00509 N, respectively, for the three runs.

Time (sec.)	I_2-sol. (ml.)	x (mmole/l)	$\frac{2.3}{a-b} \log \frac{b(a-x)}{a(b-x)}$ (1/mole)	k (1/mole x sec.)
First run:				
0	0.92	0	0	
134	1.71	0.202	7.1	(0.053)
798	3.15	0.570	22.3	0.023
1590	4.22	0.845	36.1	0.017
2800	5.43	1.153	53.8	0.015
4866	6.90	1.530	90.5	0.018
				average* 0.018
Second run:				
0	0.96	0	0	
257	1.83	0.220	8.7	(0.034)
551	2.21	0.316	12.8	0.014
1092	3.05	0.528	23.4	0.019
1833	3.95	0.755	35.9	0.017
3312	5.21	1.075	59.4	0.016
				0.015

Time (sec.)	I_2-sol. (ml.)	x (mmole/l)	$\frac{2.3}{a-b} \log \frac{b(a-x)}{a(b-x)}$ (l/mole)	k (l/mole x sec.)
6010	6.65	1.440	99.0	0.015
8484	7.50	1.653	137	
				average* 0.016
Third run:				
0	1.00	0	0	(0.032)
152	1.50	0.127	4.8	0.026
402	2.23	0.314	11.2	0.024
703	2.95	0.496	18.5	0.018
1398	4.02	0.770	31.0	0.017
2301	5.11	1.048	46.7	0.015
4000	6.45	1.390	72.0	
24530	10.51	2.420		
				average* 0.020

(*) The values in brackets are not included in the average.

TABLE XIII

Periodate Oxidation of 3β-Methoxy-1α,2α-Cyclohexanediol

The initial concentrations of sodium periodate (a) and glycol (b) were 0.01320 M and 0.00229 M, respectively, for the first run and 0.01320 M and 0.00253 M, respectively for the second run. The concentrations of the iodine solutions were 0.00512 N and 0.00510 N, respectively for the first and the second run.

Time (sec.)	I_2-sol. (ml.)	x (mmole/l)	$\frac{2.3}{a-b} \log \frac{b(a-x)}{a(b-x)}$ (l/mole)	k (l/mole x sec.)
First run:				
0	0.99	0	0	
127	4.09	0.794	33.5	(0.264)
229	5.30	1.103	52.3	0.184
305	6.08	1.305	68.0	0.206
506	7.40	1.640	103.5	0.177
884	8.75	1.986	170.0	0.178
14014	9.90	2.280		
				average* 0.186
Second run:				
0	1.00	0	0	
108	4.09	0.787	29.4	(0.272
211	5.22	1.075	44.3	0.145
386	7.00	1.530	77.0	0.187
649	8.56	1.926	120.3	0.165
807	9.18	2.084	147	0.169
1200	9.95	2.280	201	0.137
				average* 0.161

(*) The values in brackets are not included in the average.

TABLE XIV

Periodate Oxidation of 3α-Methoxy-1α,2α-Cyclohexanediol

The initial concentrations of sodium periodate (a) and glycol (b) were 0.0133 M and 0.00210 M, respectively for the first run, 0.01331 M and 0.00262 M, respectively for the second run and 0.01312 M and 0.002158 M, respectively for the third run. The concentration of the iodine solution was 0.00503 N.

Time (sec.)	I_2-sol. (ml.)	x (mmole/l)	$\frac{2.3}{a-b} \log \frac{b(a-x)}{a(b-x)}$ (l/mole)	k* (l/mole x sec.)
First run:				
0	1.17	0	0	
161	8.30	1.79	173	(1.08)**
255	9.32	2.05	350	1.88
395	9.45	2.08	443	0.66
638	9.53	2.10		
8450	9.60	2.13		
Second run:				
0	1.17	0	0	
114	10.40	2.32	184	(1.61)**
176	10.25	2.28	173	negative
237	10.71	2.40	212	0.64
348	11.03	2.48	254	0.38
474	11.16	2.51	276	0.175
715	11.43	2.58	370	0.39

Time (sec.)	I_2-sol. (ml.)	x (mmole/l)	$\frac{2.3}{a-b} \log \frac{b(a-x)}{a(b-x)}$ (l/mole)	k* (l/mole x sec.)
Third run:				
0	1.30	0	0	
126	9.35	2.022	237	(1.88)**
191	9.32	2.018	234	negative
272	9.52	2.07	276	0.52
351	9.67	2.11	332	0.71
436	9.71	2.12	352	0.24
653	9.85	2.15	495	0.66

(*) These velocity constants could only be roughly approximated since the rate of the reaction was too great to be followed accurately with the adopted experimental technique.

(**) These values were obtained by extrapolation and are taken as a measure of the velocity constant during the main part of the reaction.

Electrophoretic Migration of the Isomers of 3-Methoxy-1,2-cyclohexanediol on Borate Buffered Filter Paper.- The technique employed for the following experiment is essentially the sandwich-technique introduced by Kunkel and Tiselius (210). The samples were applied in spots along a line across a sheet of filter paper (20 x 70 cm. Whatman No.1). This line was 13 cm. distant from the cathodic end of the sheet. After spraying with the buffer solution (0.1 molar in boric acid and 0.1 molar in borax) the wet strip was placed horizontally on a polyethylene sheet which in turn was cushioned by a layer of foam-rubber (1.5cm.). The filter paper was then covered by another polyethylene sheet in order to avoid the evaporation of water from the paper. Excessive buffer-solution was removed by rolling with rubber roller. Finally a glass plate was placed on top and the whole compressed by placing three 11.4 kg. lead bricks on the glass plate. After immersion of the ends of the filter paper into the buffer solution which was contained in the electrode vessels, a 400 volt potential was applied for fourteen to nineteen hours. In less than one hour a stationary direct current of 18-20 mAmp. was established in every case. After electrophoresis, the paper was dried and sprayed with ammoniacal silver nitrate solution as described on page 103.

The effect of the electroendosmosis (see page 94) was judged from the migration of trans-cyclohexanediol since this compound is reported by Foster (211) and Angyal and McHugh (184) to have no electrophoretic migration. Methyl

orange was used to follow the progress of the electrophoresis and the migration was found to be fairly uniform after an initial period of 45 to 50 minutes. The migration of methyl orange was arbitrarily taken as unity.

TABLE XV

Electrophoretic Migrations of Some 1,2-Glycols in 0.1 molar Boric Acid - 0.1 molar Borate Buffer

Compound	Migration Value*
cis-Cyclohexanediol	0.25
trans-Cyclohexanediol	0.0
3β-Methoxy-1α,2α-cyclohexanediol(VIII)	0.5
3α-Methoxy-1α,2α-cyclohexanediol(XIII)	0.08
3α-Methoxy-1α,2β-cyclohexanediol(IX)	0.0
3α-Methoxy-1β,2α-cyclohexanediol(XIV)	0.0

(*) The migration values are given relative to the migration of methyl orange =1. The experimental error is approximately 0.06.

Acetolyses of the Tosylates (VI) and (XII).- The method used to determine the rates of acetolysis is essentially that described by Winstein, Hanson and Grunwald (196). The reagents were prepared as follows. An anhydrous 0.1515 N standard solution of perchloric acid in acetic acid was prepared from exactly assayed commercial perchloric acid (60%) using commercial acetic anhydride and commercial acetic acid calculated to provide a slight excess of the anhydride. Anhydrous 0.3355 N sodium acetate solution was prepared from analytically pure sodium carbonate, acetic anhydride and acetic acid. A 0.2540 N solution of potassium acetate in acetic acid (containing 4% per volume acetic anhydride) was prepared. Titrations were performed with a calibrated syringe-type microburette which was provided with a micrometer.

Five ml. aliquots of the potassium acetate solution were added from a pipette to weighed samples of the tosylates, approximately 0.6 mole. The resulting solution was diluted to exactly 10 ml. using an acetic acid - acetic anhydride mixture (20:1). Six portions (one ml. each) of this solution were sealed in six glass tubes (10 x 75 mm.). The six vials were simultaniously submerged in a constant temperature bath. After an appropriate time interval, a vial was removed, quenched by chilling and quantitatively transferred to a flask containing one ml. of the standard perchloric acid solution. The excess perchloric acid was determined by titration using the standard sodium acetate solution and 0.1 % bromophenol blue in acetic acid as indicator.

The last sample of each run was hydrolized after the titration, in aqueous sodium hydroxide and the product examined by paper chromatography (203).

TABLE XVI

The Products of the Acetolyses
of Some Substituted Cyclohexyl Tosylates
in Anhydrous Acetic Acid Containing Potassium Acetate

Tosylate	Products
1α-Tosyloxy-2β-acetoxy-cyclohexane	trans-Cyclohexanediol(60%)*
	cis-Cyclohexanediol(40%)
1α-Tosyloxy-2β-acetoxy-3α-methoxycyclohexane(VI)	3α-Methoxy-1α,2β-cyclohexanediol(IX) (50%)
	3β-Methoxy-1α,2α-cyclohexanediol(VIII) (40%)
	3α-Methoxy-1β,2α-cyclohexanediol(XIV) (10%)
1β-Tosyloxy-2α-acetoxy-3α-methoxycyclohexane(XII)	3α-Methoxy-1β,2α-cyclohexanediol(XIV) (50%)
	3α-Methoxy-1α,2α-cyclohexanediol(XIII) (40%)
	3α-Methoxy-1α,2β-cyclohexanediol(IX) (10%)

(*) The quantities are rough estimates based on the sizes of the spots on the chromatograms.

TABLE XVII

Summary of the First Order Rate Constants of the Acetolyses of Some Substituted 2-Acetoxycyclohexyl Tosylates

Compound	Temperature	$k \times 10^5$ (sec^{-1})
1α-Tosyloxy-2β-acetoxycyclohexane	97.8°	17
1α-Tosyloxy-2α-acetoxycyclohexane	99.7	0.029*
1α-Tosyloxy-2β-acetoxy-3α-methoxy-cyclohexane (VI)	98.3 117.5	7.7 49
1β-Tosyloxy-2α-acetoxy-3α-methoxy-cyclohexane (XII)	97.8 117.2	8.1 51

(*) Measured by Winstein, Grunwald, Buckles and Hanson (198).

TABLE XVIII

Acetolysis of 1α-Tosyloxy-2β-acetoxycyclohexane* at 97.8°

The initial concentration of the above tosylate was 54.9 millimole per liter.

Time (min.)	x (mmole/l)	$\ln \frac{a}{a-x}$	$k \times 10^4$ (sec^{-1})
0	0.0	0.0	——
66	28.6	0.737	1.86
124	39.9	1.295	1.74
195	47.5	2.002	1.71
331	51.9	2.91	1.47
			average 1.7

(*) m.p. 76.5 - 78.5° (212).

TABLE XIX

Acetolysis of 1α-Tosyloxy-2β-acetoxy-3α-methoxycyclohexane (VI) (207) at 98.3°

The initial concentrations of the tosylate (VI) were 67.6 and 65.5 millimole per liter for the first and second run, respectively.

Time (min.)	x (mmole/l)	$\ln \frac{a}{a-x}$	k x 10^5 (sec^{-1})
First run:			
0	0.0	0.0	——
60	16.1	0.274	7.60
120	30.7	0.608	8.44
167	36.5	0.778	7.76
268	48.6	1.27	7.90
415	57.1	1.87	7.50
		average	7.7
Second run:			
0	0.0	0.0	——
45	12.45	0.192	7.1
92	22.03	0.410	7.45
160	35.6	0.784	8.16
315	50.0	1.44	7.62
450	57.2	2.06	7.63
		average	7.6

TABLE XX

Acetolysis of 1α-Tosyloxy-2β-acetoxy-3α-methoxycyclohexane (VI) (207) at 117.5°

The initial concentrations of the tosylate (VI) were 68.2 and 66.9 millimole per liter for the first and second run, respectively.

Time (min.)	x (mmole/l)	$\ln \frac{a}{a-x}$	k x 10^4 (sec^{-1})
First run:			
0	0.0	0.0	——
25	36.6	0.77	5.13
50	51.0	1.38	4.60
75	60.2	2.14	4.98
			average 4.9
Second run:			
0	0.0	0.0	——
20	29.2	0.57	4.78
40	45.8	1.15	4.80
60	58.6	2.08	5.78
90	61.3	2.48	4.59
			average 4.8

TABLE XXI

Acetolysis of 1β-Tosyloxy-2α-acetoxy-3α-methoxycyclohexane (XII) (207) at 97.8°

The initial concentrations of the tosylate (XII) were 57.2 and 68.0 millimole per liter for the first and second run, respectively.

Time (min.)	x (mmole/l)	$\ln \frac{a}{a-x}$	k x 10^5 (sec^{-1})
First run:			
0	0.0	0.0	——
75	18.7	0.396	8.80
190	36.0	0.991	8.70
280	41.8	1.31	7.80
436	50.0	2.07	7.90
735	54.4	3.02	6.85
			average 8.1
Second run:			
0	0.0	0.0	——
100	27.9	0.527	8.78
157	38.4	0.832	8.83
265	51.0	1.38	8.68
410	61.4	2.33	9.48
637	64.0	2.84	7.45
			average 8.4

TABLE XXII

Acetolysis of 1β-Tosyloxy-2α-acetoxy-3α-methoxycyclohexane (XII) (207) at 117.2°

The initial concentrations of the tosylate (XII) were 51.9 and 63.1 millimole per liter for the first and second run, respectively.

Time (min.)	x (mmole/l)	$\ln \frac{a}{a-x}$	$k \times 10^4$ (sec^{-1})
First run:			
0	0.0	0.0	——
20	25.1	0.660	5.5
41	36.8	1.232	5.0
61	43.5	1.820	5.0
91	48.0	2.59	4.8
			average 5.1
Second run:			
0	0.0	0.0	——
15	24.2	0.483	5.47
30	37.9	0.915	5.10
91	58.1	2.54	4.65
			average 5.1

VI. DISCUSSION OF RESULTS

12. Structure Proof of the 3-Methoxy-1,2-cyclohexanediols and Related Compounds

Inspection of the alternative structures Ia and IIa (p.88) for the product which was obtained on the methanolysis of the so-called α-oxide by McRae, Moir, Haynes and Ripley (3) (see page 87) led to the expectation that the correct structure could be assigned by application of the knowledge of the conformational effects on NMR spectra which were the subject of the first part of this thesis.

The hydrogen atom, H_X, of structure I is the A part of an AB_2 system [see Bernstein, Pople and Schneider's (102) system of classification on page 37] if the assumption is made that spin coupling with hydrogen atoms four and more bonds remote can be neglected*. Consequently, it follows from the calculations presented by the authors (102) that four A-transitions have to be anticipated in the NMR spectrum of such a compound. In the case of a small ratio, $J_{AB}/[\nu H_o(\sigma_B-\sigma_A)]$, the two central transitions merge to a single strong line with the result that the A-signal has the appearance of a triplet of intensities close to 1:2:1.

H_X in structure II is the A part of an AB_2C system. Although this system is not explicitly calculated in the

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(*) Experience generally justifies this assumption.

literature, the structure of the A signal can be approximated by application of perturbation theory (95). Each A transition of the AB_2 system becomes subsplit into two new transitions by the C nucleus and six to eight lines must therefore be expected.

The triplet in Fig.3 (107-125 c.p.s.) is obviously the A signal of an AB_2 system, clearly excluding the possibility of an AB_2C system [see p.57 and Table III (p.60)]. Consequently the compound for which this spectrum was obtained is Ib. Since the opening of an oxide ring by methoxide ion must invert the reacting carbon centre, the formation of Ia (the alcohol from which Ib was prepared) from the α-oxide requires this epoxide to be D,L-2-exo-methoxy-7-oxa-bicyclo [4.1.0] heptane (V).

Similarly, the NMR signal for H_X in III should consist of four lines [X-part of an ABX system (102)] and of eight lines in the case of structure IV [X part of ABCX (102)]. The quartet in Fig. 4 (107-117 c.p.s.) is clearly recognizable as the X-part of an ABX system (see p.59) and hence the compound from which this spectrum was obtained is IIIb. It follows, therefore, that the β-oxide must be the D,L-2-endo-methoxy-7-oxa-bicyclo [4.1.0] heptane (XI) and this result confirms the above assigned configuration for the diastereoisomer.

The above conclusions regarding the structures of the oxides (V and XI) have been fully substantiated by independent chemical means as outlined in Fig. 10.

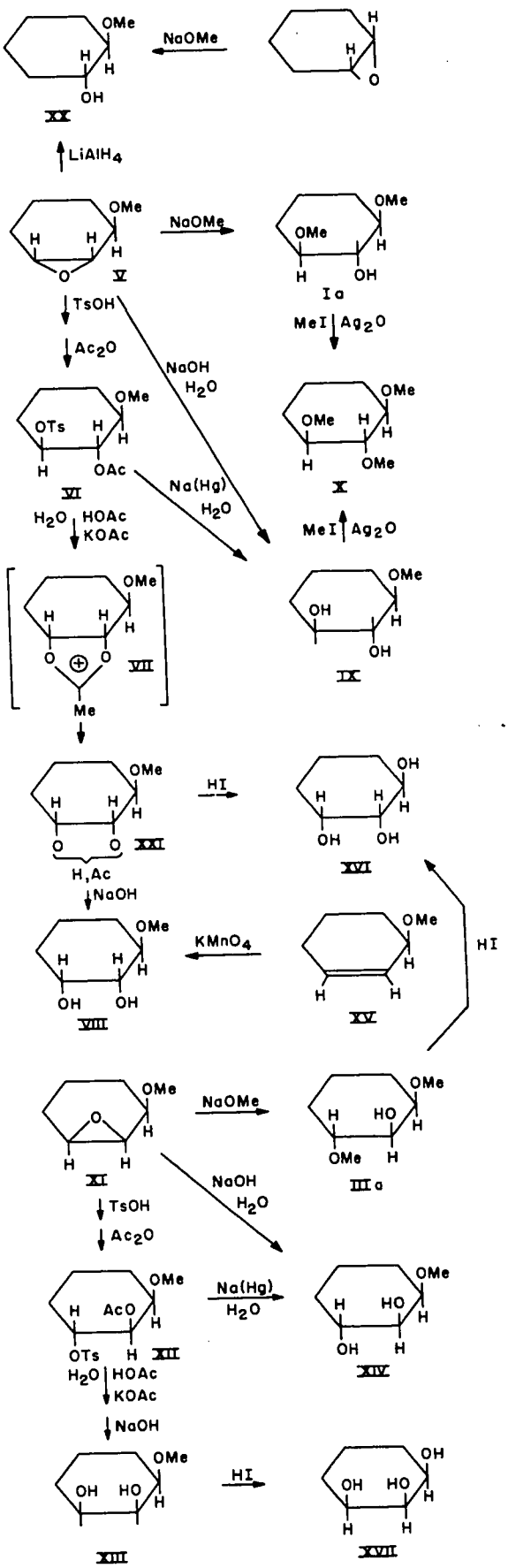


Fig. 10. - The chemical transformations used to establish the configurations of the isomeric 3-methoxy-1,2-cyclohexanediols and related compounds.

Reduction of the exo-oxide (see p.103) (V) with lithium aluminium hydride produced mainly 1β-methoxy-2α-cyclohexanol (XX) thus giving unambiguous chemical evidence for the exo-oxide structure.

The 3α-methoxy-1α,2α-cyclohexanediol (XIII) was prepared from pyrogallol as described by Christian, Gogek and Purves (2). The 3β-methoxy-1α,2α-cyclohexanediol (VIII) was obtained from permanganate oxidation of 3-methoxycyclohexene. The physical properties of the glycol (VIII) and its bis-p-nitrobenzoate were the same as reported in the literature (2).

By means of alkaline hydrolysis and subsequent chromatographic purification, a glycol was obtained as the main product from the exo-oxide. This glycol gave the same trimethoxycyclohexane (X) upon methylation with methyl iodide and silver oxide as was obtained from the 1α,3α-dimethoxy-2β-cyclohexanol (Ia). Consequently, this glycol was 3α-methoxy-1α,2β-cyclohexanediol (IX).

A fourth glycol was obtained as the main product from the alkaline hydrolysis of the endo-oxide (see p.108) (XI). Since all four glycols (VIII, XIII, IX and the last one) gave readily distinguishable infrared spectra and were reliably 1,2-glycols as was shown by periodate oxidation, structure XIV must be assigned to the last mentioned glycol.

Moir (207) took a different route to prove the structure of the epoxides (V and XI). By opening the 1,2-oxide rings with p-toluenesulfonic acid and acetylating

the product, he obtained from each epoxide a different crystalline acetoxy tosylate (VI and XII). The inversion which was to be expected in the opening of the oxide ring would render the acetoxy and tosyloxy groups in trans-relationship. Furthermore, the compounds should have the acetoxy groups on the same side of the cyclohexane ring as that formerly occupied by the oxide ring. On this basis, acetolysis of the tosylates (VI and XII) would proceed with participation of the acetoxy groups and lead in the presence of water subsequently to the cis-glycols (VIII and XIII). In view of the route of the reaction (see p.99) the hydroxy groups should be on the same side of the cyclohexane ring as was formerly occupied by the oxide ring. Moir's (207) conclusions regarding the structures of the epoxides (V and XI) proved to be in full agreement with the evidence presented above.

While the structures and configurations of the tosylates (VI and XII) were not required for Moir's evidence for the configurations of the epoxides, our plans to study the kinetics of the acetolyses of the tosylates (VI and XII) required an exact knowledge of these matters. The structures and configurations were established to be 1α-tosyloxy-2β-acetoxy-3α-methoxycyclohexane (VI) and 1β-tosyloxy-2α-acetoxy-3α-methoxycyclohexane (XII) by reduction with sodium amalgam to the trans-glycols (X and XIV respectively). Freudenberg and Brauns (208) have demonstrated that this reaction removes the tosyl group without Walden inversion

of the carbon center.

Both the 3-methoxycyclohexene oxides (V and XI) showed marked preference to undergo ring opening at position-1 when treated with either sodium methoxide or sodium hydroxide. The infrared spectrum from the product obtained on the lithium aluminium hydride reduction of the exo-oxide (V) showed that position-1 was also preferentially attacked by this reagent. Examination of the products formed on the alkaline hydrolyses of the epoxides (V and XI) by paper chromatography showed that both the trans-glycols (IX and XIV) were formed in each case. Quantitative analysis based on chromatographic separation of the glycols indicated that these were formed in about 87% yield from the exo-oxide (V) with the α,β,α-isomer (IX) being formed 10 to 12 times more rapidly than the β,α,α-isomer (XIV). The yield of the glycols was about 75% in the case of the endo-oxide (XI), with attack at position-1 to form the β,α,α-glycol (XIV) being preferred by a factor of four. The preference shown in these nucleophilic attacks is, in all probability, mainly an inductive effect due to the presence of the electronegative methoxy group on carbon atom-3.

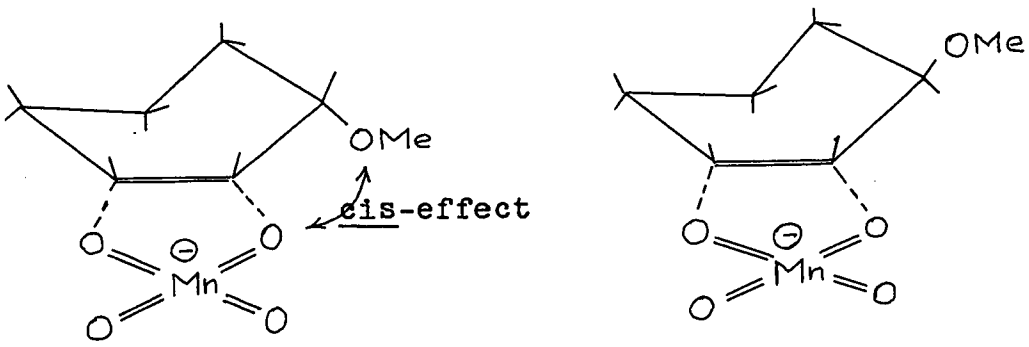
As discussed above, the exo-oxide (V) undergoes nucleophilic attack at position-1 to a greater extent than does the endo-oxide (XI). This result could well be explained by assuming that in the case of the exo-oxide the cis-effect is operative in addition to the inductive effect of the methoxyl group. That is, in order to open the oxide ring at

the carbon atom-2, the approaching methoxide or hydroxy ion has to overcome the repulsive influence of the methoxy group which will be in cis-relationship with the entering group in the transition state.

13. The " cis-Effect "

The periodate oxidations and electrophoretic migrations of the borate complexes of isomeric 3-methoxy-1,2-cyclohexanediols were examined in order to test whether or not the " cis-effect ", postulated by Lemieux and Brice (1), would manifest itself in these reactions. Furthermore, the permanganate oxidation of 3-methoxy-cyclohexene and the acetolyses of the 1α-tosyloxy-2β-acetoxy-3α-methoxy- and 1β-tosyloxy-2α-acetoxy-3α-methoxycyclohexanes were examined for this purpose.

The results of the permanganate oxidation appear to support the idea of the " cis-effect". The hydroxylation of 3-methoxycyclohexene (XV) with permanganate was found to yield the 3-β-methoxy-1α,2α-cyclohexanediol (VIII) almost exclusively since no evidence of the 3-epimer was obtained. In view of the now established mechanism for the permanganate oxidation of olefins (213), it is, thus, apparent that the transition state for the reaction which would have the permanganate ion approach on the same side of the cyclohexane ring as the methoxy group is less stable than that involving an approach from the other side of the double bond. It is of interest to note that the hydroxylation of acetylated



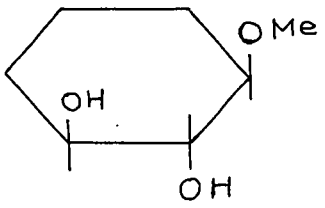
glycols with perbenzoic acid (214,215) or with osmium tetroxide (216) proceed by attack on the olefinic double bond from the side opposite to that of the 3-acetoxy group. Brunel (217) had provided some evidence that this was the preferred reaction in the hydroxylation of 3-ethoxycyclohexene with permanganate. It seems likely that the cis-glycol prepared by Mousseron, Winternitz and Combes (218) by the permanganate hydroxylation of 3-methylcyclohexene will prove to have the methyl group and the cis-hydroxy groups in trans-relationship. Recently, Henbest and Wilson (219) reported a similar steric preference in the epoxidation of 3-alkoxycyclohexenes with perbenzoic acid.

The results obtained from the electrophoretic experiments (Table XV) also appear to support the existence of the " cis-effect." Only the cis-glycols (VIII and XIII) were found to migrate. These results confirm the observations of Böeseken (181) and of Foster (211) that trans-glycols are incapable of forming complexes with borate ions. For the cis-glycols, the 1α,2α,3β-isomer (VIII) showed

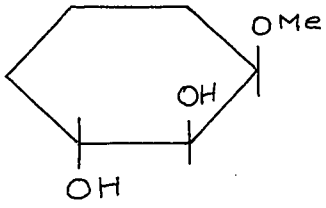
marked migration, whereas the migration of the 1α,2α,3α-isomer (XIII) was barely detectable. Since the migration of the 1α,2α,3α-methoxyglycol (XIII) was also considerably smaller than the migration of the 1α,2α-cyclohexanediol, it seems justified to explain the reduced ability of the 1α,2α,3α-isomer (XIII) to complex with borate ions as arising from the repulsion between the electronegative 3-methoxy group and the anionic cyclic borate-glycol complex as inferred above for the permanganate oxidation. The fact that the 3β,1α,2α-methoxyglycol (VIII) was found to migrate faster than the 1α,2α-cyclohexanediol cannot be rationalized with certainty.

Although the permanganate oxidation and electrophoretic studies seem to provide direct support for the existence of the " cis-effect " this was not the case for the periodate oxidation studies. This lack of support cannot be taken as evidence against the " cis-effect " since the mechanism of the periodate cleavage of 1,2-glycols is not known. It is of interest, nevertheless, to apply the current notions on the mechanism of the reaction to the results which were obtained.

The results obtained are listed in Table VII. It is seen that, as expected, the cis-glycols were oxidized more rapidly than the trans-isomers. No real significance can be attached to the fact that the 3α-methoxy-1α,2β-cyclohexanediol (IX) was oxidized nearly two times more rapidly than the 3α-methoxy-1β,2α-isomer (XIV). However, the fact that

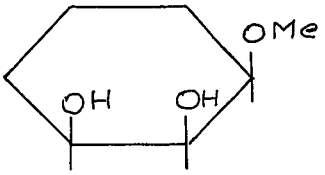


IX

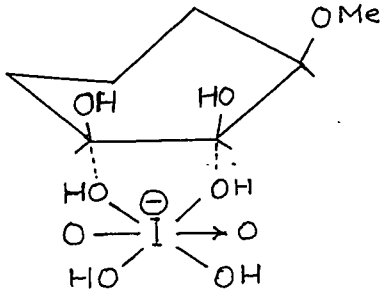


XIV

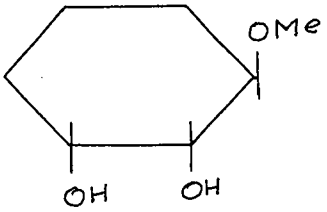
the 3α-methoxy-1α,2α-cyclohexanediol (XIII) was oxidized at least ten times more rapidly than the 3β-methoxy-1α,2α-isomer (VIII) is of interest. Assuming that the oxidation



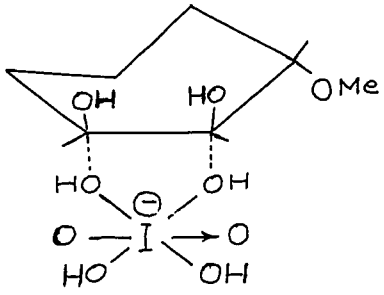
XIII



XXX



VIII



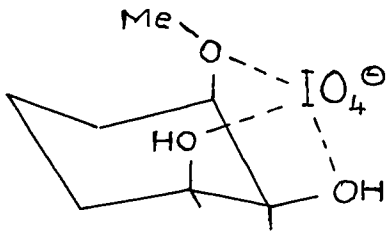
XXXI

proceeds by way of a cyclic ester intermediate as proposed by Criegee (163), it would be anticipated that VIII would be oxidized more rapidly than XIII in view of the hindrance

to ester formation which presumably would be provided by the cis-methoxyl group in the case of compound XIII. As seen above this was not the case. However, the results could be taken as evidence in favour of the " cis-effect " if the rate-controlling stage of the reaction involves a rearward attack as proposed most recently by Taylor (165). Thus, the greater rate of oxidation of XIII would be due to the easier formation of the transition state XXX over XXXI. The fact that cis-1,2-cyclohexanediol is oxidized at about the same rate (somewhat faster) than XIII would support this point of view since both compounds presumably are as readily approached by periodate for such an attack. However, the " cis-effect " is not considered to be sufficiently well established at present for these results to comprise evidence in support of the rearward attack.

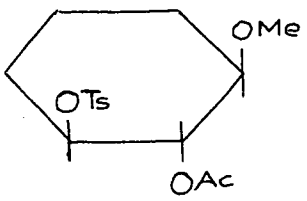
It is of interest to note that an experimental observation was made which suggests that the 1α,2α,3α-compound (XIII) may form a tridentate complex of the type suggested by Barker and Shaw (162) for 1α,2α,3α-triols situated on six-membered rings (see page 89). For example, during the kinetic study it was observed (see Table XIV) that the first titration indicated a greater consumption of periodate than a titration after a longer reaction time. Barker and Shaw have demonstrated their complexes to undergo hydrolysis only slowly at the pH of the titration. In the present experiments, the first sample was titrated sooner after the quenching than the later samples. Thus, the samples titrated

toward the end of the kinetic run had greater opportunity for the hydrolysis of any periodate-glycol complex. The unsatisfactory kinetic data obtained for this compound could in part be caused by this phenomenon. This matter warrants further investigation since the formation of a stable tridentate complex (XXXII) would imply that Barker and Shaw's periodate complex, which is believed to be specific for 1α,2α,3α-cyclohexanetriols, is formed even when one of the hydroxy groups is methylated.

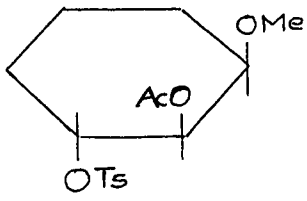


XXXII

The acetolysis of 1α-tosyloxy-2β-acetoxycyclohexane is a well studied reaction (195,196,197) (see p.98) and was shown to proceed with the participation of the acetoxy group. The tosylates VI and XII possess configurations



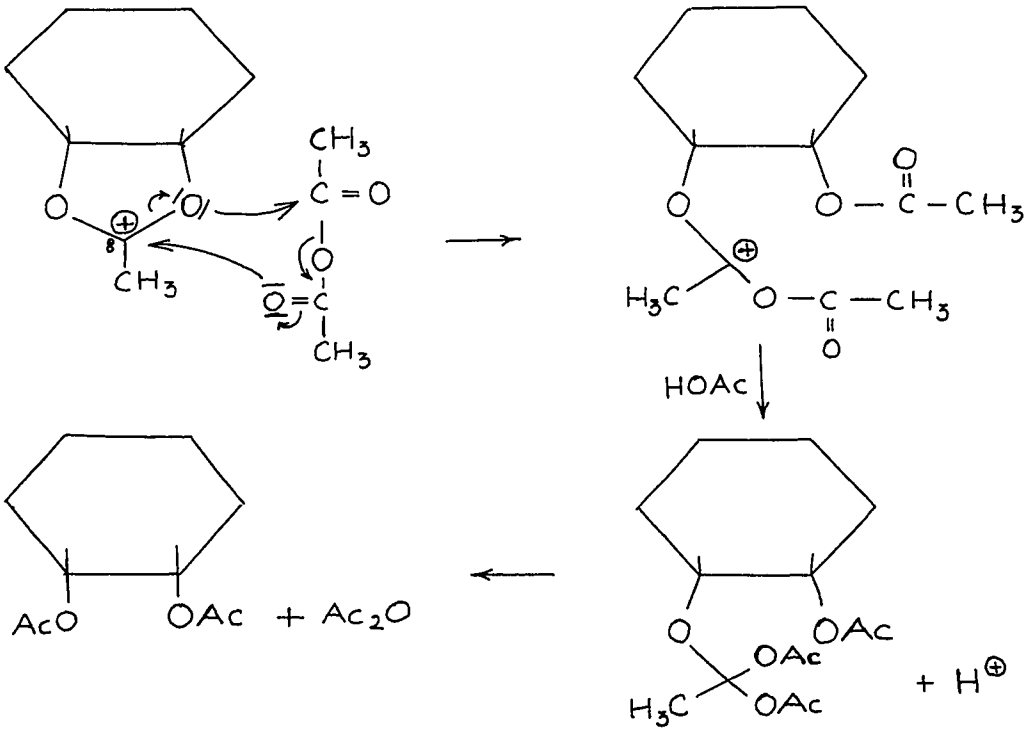
VI



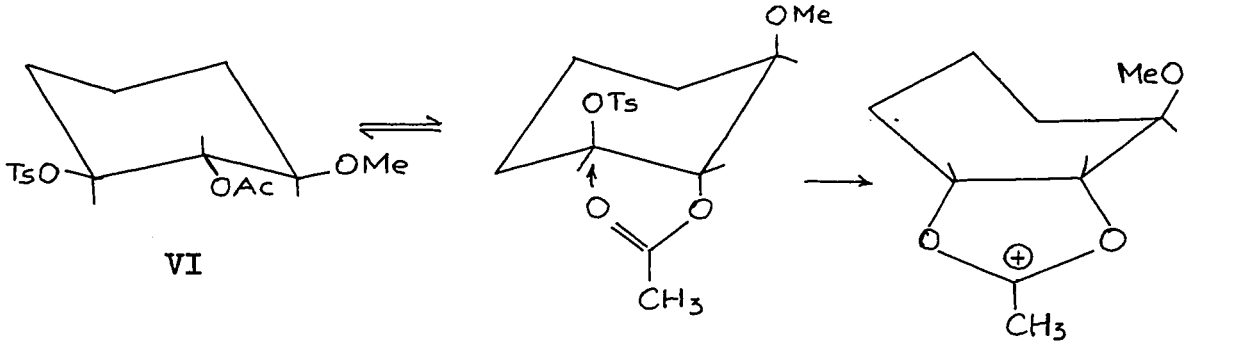
XII

which are suitable for neighbouring acetoxy group participation. The formation of substantial quantities of the cis-glycols (VIII and XIII) (see Table XVI) in the acetolyses

of the tosylates (VI and XII) in anhydrous media could be interpreted to mean that part of the reaction did not involve the participation of the acetoxy group. In view of the great resistance to acetolysis exhibited by cis-1-tosyloxy-2-acetoxycyclohexane (p.98 and Table XVII), the observed reaction rates for VI and XII are much too high to permit the assumption that the cis-products were formed without participation of the acetoxy group. The cis-products could have arisen from the presence of small amounts of water in the reaction mixture (see p.102). However, the reaction mixtures were shown to contain substantial amounts of acetic anhydride after completion of the solvolysis. This fact was established by the formation of acetanilide on the addition of aniline. It is therefore speculated that acetic anhydride also attacks at carbon atom-8 of the acetoxonium ion (XXVI) perhaps by way of a mechanism indicated below.



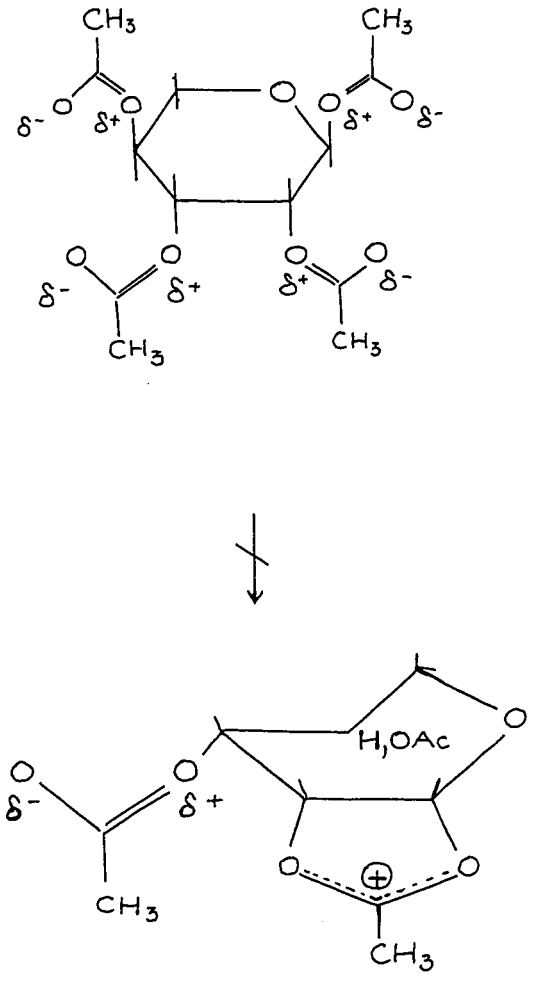
As seen in Table XVII, both the tosylates VI and XII underwent acetolysis at nearly the same rate with substantially identical temperature coefficients. This fact shows that the energies of activation are equal (27.5 kcal./ mole as calculated from the Arrhenius equation). Clearly, as pointed out by Winstein and Roberts (220), for the acetoxy group participation to provide a driving force for the dissociation of the tosylate, it must make an attack at the reacting center. Obviously, such an attack is only possible if both the acetoxy and tosyloxy groups are in axial orientation. Thus, the conformational changes indicated below must be expected to take place in the course of the reaction.



Presumably the steric interactions involved in these conformational changes will have some influence on the reactivities. On this basis alone, it would be quite surprising to find that the two compounds have the same reactivities and ener-

gies of activation. Application of the " cis-effect ", postulated by Lemieux and Brice (1), as the dominating effect would lead to the expectation that the compound VI would be more reactive than XII. This could be taken as evidence that the " cis-effect " is actually not important in this type of reaction. However, if the notion of the " cis-effect " is extended to include the consideration of electrostatic as well as steric repulsions, it is possible that any steric hindrance to reaction provided by the methoxy group in XII is counterbalanced by electrostatic attraction between the methoxyl group and the developing positive charge of the acetoxonium ion.

There remains to be explained the effect observed by Lemieux and Brice (1)(see p.84). Whereas, the above solvolytic reactions were base catalized (potassium acetate), these authors (1) used in their reactions one mole each of stannic tetrachloride and of stannic trichloride acetate. These Lewis acids must be expected to be rapidly transferred among all of the acetoxy groups in the sugar-acetate molecule. Thus, the acetoxy groups can be assumed to exist preferably in the polarized form. The positive charge on the oxygen atom on carbon atom-3 could now effectively inhibit the formation of the acetoxonium ion by way of the " cis-effect " in compounds with a 2,3-cis-configuration.


CH3
CH3
δ-
δ+
δ+
δ-
δ-
δ+
δ+
δ-
CH3
CH3
H,OAc
δ-
δ+
CH3
CH3

IV. C L A I M S T O O R I G I N A L R E S E A R C H

1. Discovery of an approximately three times larger spin coupling constant for 1,2-diaxial hydrogen atoms in six-membered ring compounds than for 1,2-hydrogen atoms in the other conformational relationships in the chair form.
2. Discovery of a different chemical shift for hydrogens in axial or equatorial position in rigid or stable conformations of six-membered ring compounds.
3. Discovery of a different chemical shift for acetoxy and methoxy groups in axial or equatorial position.
4. Application of the above observations:
   (a) to confirm prevailing assumptions about the conformation of acetylated monosaccharides.
   (b) to establish their usefulness in structure elucidation and conformational analysis, particularly for the identification of anomers.
5. Recognition of the necessity to employ to some extent p-orbital wave functions for the theoretical treatment of the proton-proton spin coupling.
6. Recognition of the important implication of the above conclusion that proton-proton spin coupling constants can assume negative values.
7. Proof of the structures and configurations of the following compounds:

(a) 1α,3α-dimethoxy-2β-acetoxycyclohexane,

(b) 1α,3β-dimethoxy-2α-acetoxycyclohexane,

(c) D,L-2-exo-methoxy-7-oxa-bicyclo[4.1.0]heptane,

(d) D,L-2-endo-methoxy-7-oxa-bicyclo[4.1.0]heptane,

(e) 3α-methoxy-1α,2β-cyclohexanediol,

(f) 3α-methoxy-1β,2α-cyclohexanediol,

(g) 1α-tosyloxy-2β-acetoxy-3α-methoxycyclohexane,

(h) 1β-tosyloxy-2α-acetoxy-3α-methoxycyclohexene.

8. Quantitative determination of the products of the alkaline hydrolyses of the isomeric 3-methoxycyclohexene oxides in order to establish the extent of the observed preference of these compounds to react at their carbon atom-1.

9. Measurements of the periodate oxidation rates of the four isomeric 3-methoxy-1,2-cyclohexanediols in order to study the effect of the 3-methoxy groups on the reactivity of these glycols.

10. Measurements of the electrophoretic relative migration of these glycols on borate buffered filter paper in order to study the effect of the 3-methoxy group on the ability of these glycols to form borate-glycol complexes.

11. Measurements of the acetolysis rates of two isomeric 1,2-trans-1-tosyloxy-2-acetoxy-3-methoxycyclohexanes in order to study the effect of the 3-methoxy group on the reactivity of these compounds.

12. Conclusions favourable to the existence of the " cis-effect " were derived from consistent interpretation of the experimental results.

13. Discovery of the formation of cis-glycols from trans-2-acetoxycyclohexyl tosylates on solvolyses in dry acetic acid containing potassium acetate and acetic anhydride; the latter being held responsible for the cis-glycol formation.

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