

The Structure of Molecules Containing Cyclohexane or Pyranose Rings

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The development of methods which make it possible to determine in some detail not only the molecular structures in crystals, but even the structure of free molecules in the vapour state, has revealed very interesting details throwing light on the forces acting between not directly linked atoms within the same molecule.

In 1943¹ one of the present authors, starting with the structure of ethane, discussed the structure of some of its derivatives and of a series of cyclic compounds drawing attention to the importance of the secondary intramolecular forces just mentioned. It was assumed that the stable form of ethane is the *trans* form in which the smallest distance between hydrogen atoms not belonging to the same methyl group is about 2.5 Å, a value corresponding to the smallest distance between hydrogen atoms belonging to different molecules in crystals. As a first approximation the simple conception of definite van der Waals' radii was adopted although the fundamental objections which may be raised were of course recognized.

In the case of the cyclohexane molecule² it is then obvious that the molecule must be considerably more stable in the symmetrical »staggered» form than in the so called »boat» form in which four pairs of hydrogen atoms would be in *cis* position and the distance between a fifth pair of hydrogen atoms would be 1.83 Å only (if normal valency angles are assumed). It was further pointed out³ that the model proposed by Mohr⁴ for the *cis* form of decalin containing two cyclohexane rings of the »boat» type would probably have to be rejected in favour of a new model based on two staggered rings. The correctness of this assumption has since been verified by electron diffraction investigations based on the sector method⁵. The discussion was extended to cycloparaffins with a number of carbon atoms smaller than six, and it was

pointed out that in cyclopropane and cyclobutane the *cis* position of hydrogen atoms resulting from a planar arrangement of the carbon atoms would not tend to increase the instability of the molecules. It was assumed, however, that in cyclobutane⁶ the very small distances between 1,3 carbon atoms of about 2.18 Å may explain the relatively great increase in heat of combustion per CH₂ group when the C-C-C-angle is decreased from 110° to 90° (in cyclobutane) compared with the figure corresponding to a further decrease to an angle of 60° (cyclopropane). In molecules like cyclopropane⁷ and phosphorus (P₄)⁸ the very small valency angle of 60° does not result in abnormally small distances between atoms which are not directly linked together.

The discussion of the structure of chlorinated hydrocarbons was based on the results obtained for ethane derivatives¹, in which the Cl-atoms introduced into one methyl group is never found in *cis* position relative to hydrogen atoms of the other methyl group, which would correspond to a H-Cl distance of 2.57 Å. The H-Cl distance of the equilibrium configuration is about 2.9 Å. This observation explains the fact, that the κ form of monochloro-cyclohexane is energetically more stable than the ϵ form⁹. If all valency angles were tetrahedral, the distances from the ϵ Cl atom to the two nearest H atoms would have values very little different from 2.57 Å calculated for the *cis* distance in chlorinated ethanes.

The designations κ ($\kappa\epsilon\acute{\iota}\mu\epsilon\nu\omicron\varsigma$ = lying), and ϵ ($\acute{\epsilon}\sigma\tau\eta\kappa\acute{\omega}\varsigma$ = erected), were introduced by one of us in 1943². To avoid confusion it should be mentioned that Beckett, Pitzer and Spitzer in 1947²⁵ introduced their own terms equatorial and polar for κ and ϵ respectively.

CYCLOHEXANE AND DERIVATIVES

In the case of 1,2 disubstituted cyclohexanes, one of the chemically separable forms, the κ,ϵ form, (or *cis* form according to the older conception) consists of a mixture of equal quantities of *d* and *l* molecules which are readily transformed into each other by a conversion of the ring. The separation of the *d* and *l* molecules is therefore impossible. The $\kappa,\kappa \rightleftharpoons \epsilon,\epsilon$ form (or *trans* form) on the other side will also consist of optically active molecules, but in this case the conversion process does not lead to racemisation and a separation of the optically active antipodes is always possible, at least in principle. It would be of great interest to determine the proportion of κ,κ and ϵ,ϵ molecules in the equilibrium mixture, but this is a difficult task, and only rough estimates have so far been possible.

The arguments which seem to explain the preponderance of κ molecules observed in the case of monosubstituted cyclohexanes, like cyclohexylchloride⁹

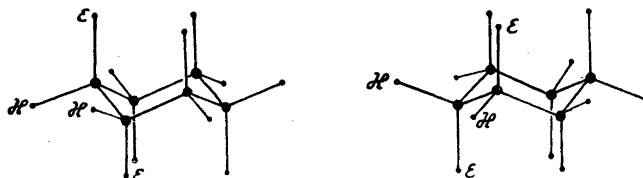


Fig. 1. The stepformed cyclohexane ring.

and cyclohexylmercaptan¹⁰, namely the small distance between an ϵ substituent and the nearest hydrogens might lead to the assumption that the $1\ \kappa, 2\ \kappa$ form would be energetically more stable than the $1\ \epsilon, 2\ \epsilon$ form. It must be born in mind, however, that the distance between two 1,2 substituents, both in κ positions, will in many cases be considerably smaller than the sum of their van der Waals radii if the valency angles retain their normal values. The interaction of the dipole moments of the two groups may also tend to increase the energy of the $1\ \kappa, 2\ \kappa$ form.

It is therefore not very surprising that the results obtained by electron diffraction methods indicate equilibria in the case of 1,2-dibromocyclohexane¹⁰ and cyclohexanediol-1,2¹¹ in which the concentration of the $1\ \epsilon, 2\ \epsilon$ form is somewhat greater than fifty per cent.

When considering 1,3-disubstituted cyclohexanes the *trans* form should theoretically correspond to the $1\ \kappa, 3\ \epsilon$ form, the *cis* form to $1\ \kappa, 3\ \kappa \rightleftharpoons 1\ \epsilon, 3\ \epsilon$ form. In the case of halogen derivatives it should be expected that the $1\ \kappa, 3\ \kappa$ configuration is considerably more stable than the $1\ \epsilon, 3\ \epsilon$ configuration. An electron diffraction investigation^{12,13} of the dibromide and diiodide carried out nearly ten years ago using the visual method confirms this view. In the latter case dipole measurements lead to the same result. It is also to be expected that the *cis* form (in the $1\ \kappa, 3\ \kappa$ configuration) has a smaller energy than the *trans* form ($1\ \kappa, 3\ \epsilon$ form).

In the case of 1,4-disubstituted cyclohexanes the $1\ \kappa, 4\ \kappa \rightleftharpoons 1\ \epsilon, 4\ \epsilon$ form should correspond to the *trans* compound, the $1\ \kappa, 4\ \epsilon$ form to the *cis* compound. X-ray crystallographic work [14, 15] indicates that the $1\ \kappa, 4\ \kappa$ configuration is the more stable. Here also the internal energy of the $1\ \kappa, 4\ \kappa$ configuration should in general be expected to be smaller than that of the κ, ϵ configuration.

So far we have omitted from our discussion the question of hydrogen (hydroxylic) bond formation. It must be admitted that such phenomena may render the use of a concept like that of van der Waals radii rather illusory. For example, the identity period of 2.5 Å only, reported for polyvinylalcohol seems to indicate that such bonds may bring the two oxygen atoms at a considerably smaller mutual distance than the distance permitted by the van

der Waals radii (about 2.9 Å). If this is so, there should be nothing to prevent the hydroxyl groups in cyclohexanediol-1,3 from having the ϵ, ϵ configuration. In the case of 1,2 hydroxyl groups, however, it seems less likely that hydrogen bonds should be formed (between 1 κ , 2 κ and 1 κ , 2 ϵ oxygens) because this should give C—O . . . O angles of about 60°.

Before discussing further structures containing alcoholic groups we should like to mention the studies of cyclohexane derivatives containing more than two halogen atoms. In these cases it seems reasonable to assume that configurations containing two halogen atoms in positions 1 ϵ , 3 ϵ will be relatively unstable because of the short distance of 2.52 Å between the atoms, if tetrahedral angles are conserved. We do not think, however, that molecules containing 1 ϵ , 3 ϵ halogen atoms are strictly forbidden, though in such cases considerable deformations of valency angles must be expected.

Turning to the benzene hexachlorides this would mean that more than four stereoisomeric forms may be expected. The possible configurations being:

Table 1. A survey of the eight possible isomers of benzenehexachloride. 1 ϵ — 3 ϵ = the number of 1 ϵ — 3 ϵ pairs of chlorine atoms. III and VI are optically active, conversion of the carbon ring, however, transposes the d-form of VI into the l-form and vice versa. The table presented by Kauer, DuVall and Alquist²⁴ shows that these authors are not familiar with the newer theory of cyclohexane isomerism².

	1 ϵ — 3 ϵ				1 ϵ — 3 ϵ	Dipole moment
I	0	$\kappa, \kappa, \kappa, \kappa, \kappa, \kappa$	\rightleftharpoons	$\epsilon, \epsilon, \epsilon, \epsilon, \epsilon, \epsilon$	6	zero
II	0	$\epsilon, \kappa, \kappa, \kappa, \kappa, \kappa$	\rightleftharpoons	$\kappa, \epsilon, \epsilon, \epsilon, \epsilon, \epsilon$	4	
III	0	$\epsilon, \epsilon, \kappa, \kappa, \kappa, \kappa$	\rightleftharpoons	$\kappa, \kappa, \epsilon, \epsilon, \epsilon, \epsilon$	2	
IV	0	$\epsilon, \kappa, \kappa, \epsilon, \kappa, \kappa$	\rightleftharpoons	$\kappa, \epsilon, \epsilon, \kappa, \epsilon, \epsilon$	2	zero
V	1	$\epsilon, \kappa, \epsilon, \kappa, \kappa, \kappa$	\rightleftharpoons	$\kappa, \epsilon, \kappa, \epsilon, \epsilon, \epsilon$	3	
VI	1	$\epsilon, \epsilon, \kappa, \epsilon, \kappa, \kappa$				
VII	3	$\epsilon, \kappa, \epsilon, \kappa, \epsilon, \kappa$				
VIII	1	$\epsilon, \epsilon, \epsilon, \kappa, \kappa, \kappa$				

Four different substances obtained by addition of chlorine to benzene have been known for a long time. One of these, the so-called β -benzenehexachloride, has been shown to have the structure I. Dipole measurements carried out in this laboratory has shown that of these four substances the β -compound only has zero dipole moment. This indicates that the structure IV does not correspond to any of the modifications α , γ or δ . It is interesting that one of the new hexachlorocyclohexanes (having the m. p. 145°) prepared in this laboratory by chlorination of cyclohexane or chlorocyclohexane has dipole moment zero. This can hardly be explained otherwise than by assuming this new

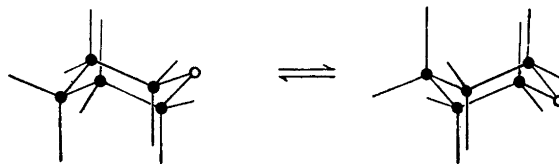


Fig. 2. The stepformed pyranose ring.

substance to be a benzenehexachloride corresponding to structure IV. It seems clear, however, when considering the electron diffraction curves of the α , β , γ and δ compounds, that slight deviations from tetrahedral angles occur, resulting in a flattening of the six-membered ring. This, of course, does not interfere with the designation of the individual bonds which we are using.

The only halogen derivatives containing four substituents so far thoroughly studied is the 1,2,4,5 tetrabromocyclohexane (m. p. 185°)¹⁶ which was found to have the configuration 1κ , 2κ , 4ε , 5ε . This substance contains optically active molecules like the 1κ , 2ε dihalogenides mentioned above, but here a conversion of the ring transforms d-molecules into d-molecules and vice versa, and a separation of the active forms is possible at least in principle.

THE PYRANOSE RING

All experimental evidence indicates that the six-membered pyranose ring found in many sugars will generally have the staggered form corresponding to the symmetrical cyclohexane ring discussed above. The discussion of these sugars, which were originally based on a plane ring, will therefore have to be revised to some degree. In addition to the well known configuration proofs of E. Fischer, the configuration at the first C-atom corresponding to the α and β forms respectively has been settled by the following convention: The compound, in which the two OH-groups linked to the C-atoms 1 and 2 are in *cis* position, is called the α form; the other compound in which these two groups occupy *trans* positions is the β form. Remembering what has been stated above concerning 1,2 disubstituted cyclohexanes, it is clear that the β compound may correspond to both of the configurations 1κ , 2κ and 1ε , 2ε . Which of these two configurations predominates in the equilibrium mixture will depend very much on the positions of the three other substituents attached to the pyranose ring. In the α form the OH groups will have either the configuration 1κ , 2ε or 1ε , 2κ . From these considerations it will be clear that each pyranose sugar will, at least theoretically, be able to occur in two different configurations. It will hardly ever be possible to separate the two forms

Table 2. The possible structures of the normal hexoses.

C-atom no. Substituend	1 OH	2 OH	3 OH	4 OH	5 CH ₂ OH	⇌	1 OH	2 OH	3 OH	4 OH	5 CH ₂ OH
α — <i>d</i> -allose	ϵ	κ	ϵ	κ	κ		κ	ϵ	κ	ϵ	ϵ
β — — —	κ		— — —				ϵ		— — —		
α — <i>d</i> -altrose	κ	ϵ	ϵ	κ	κ		ϵ	κ	κ	ϵ	ϵ
β — — —	ϵ		— — —				κ		— — —		
α — <i>d</i> -glucose	ϵ	κ	κ	κ	κ		κ	ϵ	ϵ	ϵ	ϵ
β — — —	κ		— — —				ϵ		— — —		
α — <i>d</i> -mannose	κ	ϵ	κ	κ	κ		ϵ	κ	ϵ	ϵ	ϵ
β — — —	ϵ		— — —				κ		— — —		
α — <i>d</i> -gulose	ϵ	κ	ϵ	ϵ	κ		κ	ϵ	κ	κ	ϵ
β — — —	κ		— — —				ϵ		— — —		
α — <i>d</i> -idose	κ	ϵ	ϵ	ϵ	κ		ϵ	κ	κ	κ	ϵ
β — — —	ϵ		— — —				κ		— — —		
α — <i>d</i> -galaktose	ϵ	κ	κ	ϵ	κ		κ	ϵ	ϵ	κ	ϵ
β — — —	κ		— — —				ϵ		— — —		
α — <i>d</i> -talose	κ	ϵ	κ	ϵ	κ		ϵ	κ	ϵ	κ	ϵ
β — — —	ϵ		— — —				κ		— — —		

because of the great velocity of conversion. Chemically one must expect the mixture to behave like a single compound, but it is evident that the conditions just mentioned may be of fundamental importance to the chemical reactivity and physical behaviour of the pyranose sugars.

Anomal optical activity in respect to the rules of Hudson may find an explanation in the different rotatory power of the two equilibrium forms of the pyranose sugars.

Table 2 shows the theoretically possible structures of the normal pyranose sugars. Before discussing which of the possible structures of Table 2 are realised, we will consider the behaviour of the step-formed six-membered ring in more detail.

During the transposing one or more of the angles of this ring must increase from 109.5° up to 120° . The structures of 1,2-epoxy-cyclohexane¹⁷ and the benzenehexachlorides show that the substituends may cause a more or less pronounced deformation of the tetrahedral angles in the six-membered ring. Between the atoms of the molecule forces of different types and strength are acting. Some of them produce a stabilising effect on the stepform of the six-membered ring, others tend to distort the tetrahedral angles. A quantitative

evaluation of all these forces is not possible, but experience from precision determinations of related molecular structures allows us to make the following general statements about these forces, in an empirical way¹⁸:

1. Deformation of the valency angles generally does not alter the length of the chemical bonds in question.
2. The four atoms attached to the same C-atom repel each other (compare methyl halides etc.).
3. The atoms attached to either of two C-atoms which are in turn linked to each other with a single bond will generally tend to occupy *trans*-positions (compare ethane and derivatives).

When we transfer these experiences to six-membered rings we must, of course, also take into consideration the forces between substituents linked to C-atoms further apart. Generally, only substituents in ϵ position on the same side of the six-membered ring need to be considered.

In the molecules all the forces producing these effects balance each other and the molecule oscillates about an equilibrium configuration. In the interferometric molecular structure determinations this equilibrium configuration only is observed. Deformation of the valency angles by introduction of new substituents means a shift of the equilibrium configuration. In the case of six-membered rings the oscillations are of special importance. Without any definite statements about the nature of the oscillations we must assume that they are able to cause considerable temporary deformations of the valency angles in the six-membered ring. Angular deformations corresponding to those, which when sufficiently great, cause the ring to be converted, should be more probable than deformations taking place in the opposite direction. In other words: The potential energy of the molecule taken as a function of the valency angles should be expected to display two minima corresponding to the equilibrium configurations in the two possible transposition forms of the six-membered ring. We must expect the potential curve to rise less steeply on the side where the conversion takes place. The energy difference between the two minima and the height of the barrier will of course depend on the nature of the substituents present.

It should be kept in mind that a beginning conversion will necessarily increase the mean value of the valency angles in the six-membered ring. It will be shown later that the picture just given makes it possible to explain certain chemical reactions taking place in molecules containing six-membered rings. Some caution is needed, however, when discussing the stability of local atomic arrangements in the molecule: An arrangement which is favourable in a certain molecule may be unfavourable in other molecules, due to the presence of other substituents within the molecule.

The structure of cyclohexanediol-1,2¹¹ indicate that the angle O—C—C is somewhat larger than the tetrahedral angle (about 112.5°). This is probably a manifestation of the effect mentioned under 2. If this deformation of the angle O—C—C is taken into consideration the following distances between the O-atoms in the hydroxyl groups are obtained:

$0_1\kappa - 0_2\kappa$	2.85 Å		
$0_1\kappa - 0_2\varepsilon$	2.96 »	$\angle C - 0_1\kappa$ $0_2\kappa \sim 60^\circ$
$0_1\varepsilon - 0_2\varepsilon$	3.73 »	$\angle C - 0_1\varepsilon$ $0_2\varepsilon \sim 60^\circ$
$0_1\varepsilon - 0_3\varepsilon$	2.78 »	$\angle C - 0_1\varepsilon$ $0_3\varepsilon \sim 84^\circ$

Remembering what has been said about the cyclohexanediols we think it probable that OH-groups linked to neighbouring C-atoms may occupy any combination of κ and ε positions in the pyranose ring and we even think it probable that the configuration $(OH)_{1\varepsilon}-(OH)_{3\varepsilon}$ is possible. Although allose is the only hexose based on a pyranose ring, which must necessarily contain 1 ε , 3 ε OH groups its existense is sufficient to demonstrate the possibility of such an arrangement, if we suppose that the ring has retained the staggered form. In pentoses containing pyranose rings it thus seems little reason to reject any one of the transposition forms. The relative stability of the configurations 1 κ , 3 κ and 1 ε , 3 ε of the hydroxyl groups might be determined by examining the structure of the *cis* 1,3-cyclohexanediol or the corresponding 1,3,5-cyclohexanetriol.

In the normal hexoses it seems reasonable to assume that configurations placing both the CH_2OH group and one OH group in ε positions on the same side of the ring are energetically unfavourable. If this argument holds, it settles the energetically preferred configuration of the following aldopyranoses:

β -allose, α -altrose, α - and β -glucose, α - and β -mannose, β -gulose, α -idose, α - and β -galactose, α - and β -talose. The configurations are printed in heavy types in Table 2. In the case of α -allose, β -altrose, α -gulose and β -idose this argument is without consequence.

In a few cases only experimental evidences are at hand, but then confirming the view just presented; compare x-ray analyses of substances like cellulose, sucrose and glucosamin.

POLYSACCHARIDES AND OTHER POLYMERS

In certain cases the determination of fiber-periods of polysaccharides may give valuable information concerning the configuration of the six-membered rings. If the chain is formed by 1,4-bonds the possible fiber periods are easily recognised: Each molecule may contribute with two κ -bonds, two ε -bonds or

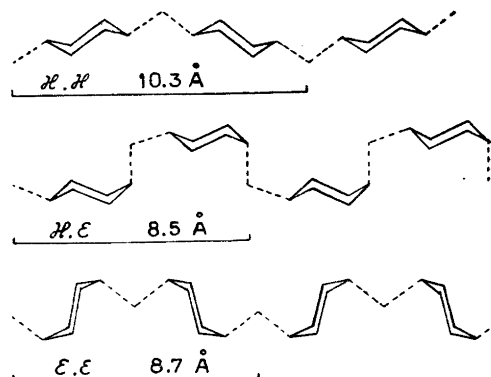


Fig. 3. Polysaccharide chains with 1,4-glycosidal linkages.

one κ - and one ε -bond. In the first case the computed fiber-period is about 10.3 \AA and in the two other cases nearly identical and about 8.7 \AA (the identity period comprises two rings). Well known examples of the 10.3 \AA period are those of cellulose and chitin¹⁹.

Astbury²⁰ has made a x-ray investigation of alginic acid. He finds an identity period of 8.7 \AA and favours the view that the alginic acid contains units of β -mannuronic acid molecules linked together in a way corresponding to the use of ε -bonds only (Fig. 3). The structure of β -mannuronic acid, however, excludes such a possibility. If the alginic acid is built up from β -mannuronic acid units the only alternative is a structure in which each mannuronic acid unit makes use of one κ - and one ε -bond. It may easily be shown, however, that an identity period of about 8.7 \AA may be obtained in this way also (Fig. 3). If 1 ε , 4 ε linkages are present in alginic acid, the chain unit must be α -mannuronic acid and not the β -acid. The chemical evidences, however, seem to indicate that the units are β -mannuronic acid rather than α -mannuronic acid.

Astbury, without knowledge of our work from 1943², points out that the alginic acid may change through a conversion of the six-membered ring into a structure with an identity period corresponding to that of cellulose. It is easily recognised, however, that a transposing of the six-membered ring will not alter the identity period if the units are β -mannuronic acid. In cellulose, however, a conversion of the ring will necessarily change the period, but it is difficult to foresee if this will be possible to carry out in practice. Probably a conversion will take place only by chemical changes in the substituents at the six-membered ring. The x-ray investigations of cellulose esters show that in these cases also the 1 κ , 4 κ configuration is the more stable.

In polymers containing open carbon chains fiber periods of 2.5 \AA or simple multipla of this distance have often been reported. In polymethylen chains

this is very easy to understand because it places H-atoms of adjacent methylene groups into *trans*-position and the 1.3 H-atoms at a distance of 2.5 Å. In the case of polyvinyl alcohol the short period of 2.5 Å is more surprising because a O—O-distance of 2.5 Å only seems somewhat small even when the possibility of hydrogen bond formation is taken into consideration. The period of about 5 Å in the case of polyvinyl chloride seems very probable considering the experiences so far obtained concerning van der Waals forces. The question in which way the different chains are linked together in the crystalline part of this chloride is much more involved. In each case the explanation given by Mark ²¹ assuming a real hydrogen bond formation between a methylene H-atom of one chain and a chlorine atom of a neighbouring chain has to be modified.

ORTHOESTERS OF SUGARS CONTAINING PYRANOSE RINGS

A very interesting survey of the recent advances in this field has been given by Pacsu ²². Experience has shown that under normal conditions only the α - or only the β -form of the acetylglucosyl halides in the d and l series are formed. Of these only one in each epimeric pair is able to give orthoesters by the reaction of Koenigs-Knorr. This has been experimentally verified in three of the four epimeric pairs. The studies of this reaction by Isbell and Frush ²³, were based on the modern conceptions of substitution reactions. On the basis of a plane six-membered ring they are able to give an explanation of the reaction. The normal Koenigs-Knorr reaction is a substitution reaction of the SN1 type, usually accompanied by a complete inversion at C-atom no. 1. When the acetyl glucosyl halide (Fig. 4, I) is heated with dry silver carbonate in anhydrous methyl alcohol at room temperature, usually the halogen atom is substituted by a methoxyl-group. If the inversion is incomplete a mixture of α - and β -glycosides is formed.

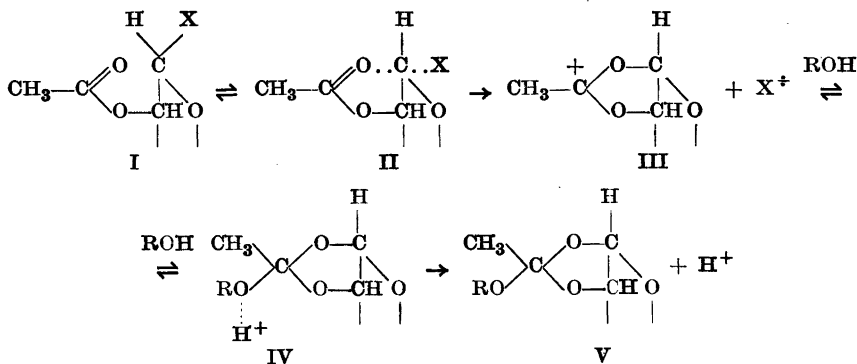


Fig. 4. Formation of the orthoester by the reaction of Koenigs-Knorr.

When, however, the acetoxy group at C-atom no. 2 is situated on the side of the ring opposite to the halogen atom at C_1 , the carbonyl oxygen of the acetyl group may take part in a substitution reaction at the SN2 type. This results in the formation of a intermediate carbonium ion (Fig. 4, III), which in turn may react with the solvent molecule under formation of a possible mixture of two diastereoisomeric ortoacetates (Fig. 4, V). Accordingly in this case the Konigs-Knorr reactions may result in a mixture of normal α - and β -glycosides and two diastereoisomeric ortoesters.

The investigations of these reactions have stated that orthoesters are only formed when the substituents in 1,2-positions are *trans*-situated, in the case of *cis*-position no orthoester is formed.

Taking into consideration that the six-membered ring is step-formed, the explanation of Isbell and Frush is not quite so evident. In an undeformed, step-formed ring (all angles being tetrahedral) the distances between two substituents in $1\kappa, 2\kappa$ and the same substituents in $1\kappa, 2\varepsilon$ positions are identical. If however, in the acetyl glycosyl halides the carboxylic oxygen in the acetyl group at C-atom no. 2 shall be able to substitute the chlorine atom at C atom no. 1 according to an SN2 reaction scheme with Walden inversion, the carboxylic oxygen must be brought into a favourable position by deformation of the six-membered ring. In the case of the $1\kappa, 2\kappa \rightleftharpoons 1\varepsilon, 2\varepsilon$ compound this deformation is consistent with a beginning conversion of the six-membered ring. In the case of an $1\kappa, 2\varepsilon \rightleftharpoons 1\varepsilon, 2\kappa$ compound the necessary deformation would mean a decrease of the valency-angles in the six-membered ring. The movement is thus opposite to that leading to a conversion of the ring. Accordingly the necessary activation energy of the deformation will be smaller in the case of an $1\kappa, 2\kappa$ compound. Accepting this view it is reasonable to assume that only the $1\kappa, 2\kappa \rightleftharpoons 1\varepsilon, 2\varepsilon$ acetyl glycosyl halides (*trans*-forms) are able to give ortho-esters.

The assumption of stepformed six-membered rings or plane rings thus leads to the same conclusion concerning the ability of the halogenoses in forming orthoesters (Fig. 4, V). The new point of view involves the readiness with which the ring is deformed in the process of conversion, thus bringing the carboxylic oxygen atom in a position favourable to the reaction in question. It also appears reasonable that a beginning conversion of the ring facilitates the inversion at the C_1 -atom, because it increases the angle $O-C_1-C_2$. Such an increase is necessary if the change of configuration at the C_1 -atom shall take place.

THE ACETYL GLYCOSYL HALIDES

Paesu points out that under normal conditions only one of the acetyl glycosyl halides in the hexose series, either the α or the β -form, is stable. In

many cases the unstable form may be obtained by taking special precautions, but it will always tend to mutarotate and give the stable form. Experience has further shown that in the cases where the normal stable halogenoses do not give ortho-esters by the Koenigs-Knorr reaction, orthoesters are obtained from the corresponding unstable forms. This has been used in order to determine the structure of the halogenoses. With regard to the stability of the halogenoses Pacsu points out that a satisfactory explanation of the experimental facts is still lacking. The experiences from the cyclohexane derivatives, however, draws the attention to the possibility of steric hindrance caused by substituents in ϵ -position on the same side of the six-membered ring.

The stable acetyl glycosyl halides are usually formed by the action of hydrogen halides on the completely acetylated sugars. This substitution of a »negative» group caused by a negative ion is normally accompanied by a Walden inversion. The transformation of the unstable form of the halogenoses into the stable form may also be interpreted as a substitution reaction with Walden's inversion.

To start the reaction the nucleophilic Cl^- ion must come in a favourable position to the C_1 -atom. This is the case if the molecule has the form shown in Fig. 5 a, with the H_1 -atom in α position. In the transition state (5 b) the

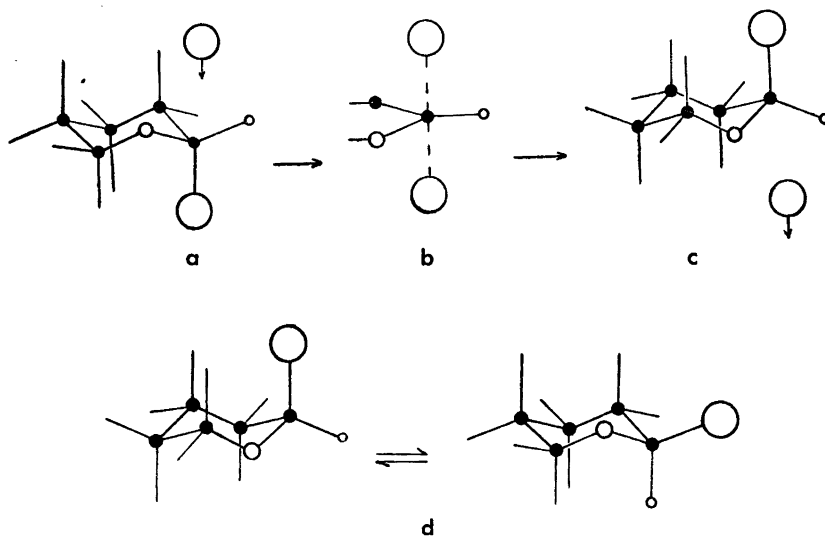


Fig. 5. Substitution reaction with Walden inversion at C-atom no. 1 of the stepformed pyranose ring.

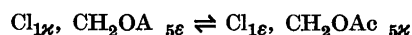
atoms H_1 , C_2 and the ring-oxygen must be brought into a plane with the central atom C_1 . This means a deformation of the six-membered ring which must nearly correspond to the transition state between the two possible forms of the six-membered ring. When the inversion is completed and the ring has retained the staggered form, it must have passed through a conversion, in order to give sufficient space for the escaping ion. The important result of this picture is that the new substituent in the first instance takes an ε -position in the new-formed molecule (5 c).

In the case of mutarotation the old and the new substituents are of the same sort. If one of the two possible endconfigurations with the new substituent in ε -position is energetically unfavourable, this will be the «unstable» one. If the old and the new substituent are different the formation of the unstable modification may be possible if the bond energy and space requirement of the two substituents favours this. If an unstable modification is produced in the 1 ε form, it will immediately transpose into the 1 \varkappa form (5 d).

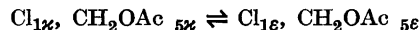
If the halogen atom in the unstable halogenoses shall take part in a new substitution reaction, it must first occupy the ε -position. Accordingly we may expect the activation energy of the so-called unstable modifications to be rather high if substitution reactions involving the C_1 -atom are considered.

THE HALOGENOSES OF THE HEXOSE, PENTOSE AND HEPTOSE SERIES

In the acetylated sugars of the hexose series the CH_2 -link of the CH_2OAc group at carbon atom 5 requires more space than the other substituents. Accordingly all the normal «stable» forms of the corresponding halogenoses have the configuration:



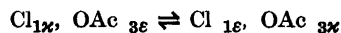
The unstable forms have the configuration:



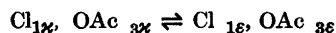
Since the formation of the unstable forms will usually pass through the energetically unfavourable 1 ε , 5 ε configuration these are not produced under normal conditions. Under special circumstances the unstable form may be obtained, for instance in the case of an SN_1 reaction with an unshielded carbonium ion or in cases where the nature of the old and new substituents are sufficiently different.

Such a case is that of the β -acetyl glucosyl halides which in conformity with the view just developed show little reactivity.

In the acetyl glycosyl halides of the pentose series based on a pyranose ring there is no steric hindrance at C-atom 5. In this case according to our theory the acetyl group at C-atom 3 must play the dominant role. Experimental evidences confirm this view. All the stable halogenoses of the pentose series have the configuration:



The unstable forms will have the configuration:



In the heptoses the stable forms of the halogenoses should correspond to the stable halogenoses of the hexose series, which have the same configuration at the pyranose ring.

We are of course aware of the complexity of the problems related to the rather complicated molecules which we have been discussing; so far our knowledge of the deformations from tetrahedral angles (which no doubt occur) is too limited. We hope, however, that the general ideas developed here may serve as a basis for further work dealing with the structure and chemical reactions of molecules containing the pyranose ring.

SUMMARY

The molecular structure of a series of organic substances containing single bonds only is discussed, and the importance of considering the interaction between atoms which are not directly linked together is pointed out. Starting with results previously obtained in the case of halogenated ethanes and some ring systems, chiefly sixmembered rings, the structure of cyclohexane derivatives and substances containing the pyranose ring are discussed in some detail. In the latter case the mechanism of chemical reactions not opening the six-membered ring has been dealt with, the special conditions arising from the non-planarity of the pyranose ring being taken into consideration.

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