741. *An Explanation of the Preferential Formation of Certain Rings in Acetals of the Polyhydric Alcohols.*

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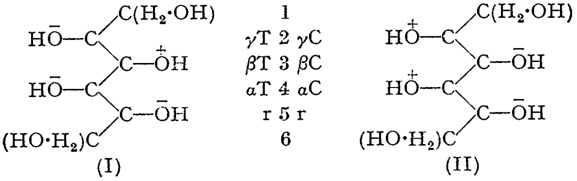
A detailed analysis is made of the stereochemical factors which govern the synthesis of cyclic acetals of the polyhydric alcohols; it relies on the basis that the most stable form of a polyhydric alcohol is that in which the carbon skeleton possesses a planar zig-zag structure. It is shown why certain types of cyclic acetals are possible while others are not, and why the different types are synthesised in the strict order of preference determined empirically by Barker and Bourne (*J.*, 1952, 905).

In a recent review of the condensation of polyhydric alcohols with acetaldehyde, benzaldehyde, and formaldehyde, Barker and Bourne (*J.*, 1952, 905) presented empirical rules which enabled the structures of the products to be predicted; these rules, which were an extension of the Hann–Hudson rules (*J. Amer. Chem. Soc.*, 1944, **66**, 1909; 1948, **70**, 765), were: (1) the first preference is for a βC-ring; (2) the second for a β-ring; (3) the third for an α-, αT-, βT-, or γT-ring; (4) in methylenation, a βT-ring takes precedence over an αT- or a γT-ring; (5) in benzylidenation and ethylidenation, an αT-ring takes precedence over a βT- or a γT-ring; (6) rules (4) and (5) may not apply when one (or both) of the carbon atoms carrying the hydroxyl groups concerned is already part of a ring system. Such an order of preference—at first sight rather arbitrary—might be expected to have an underlying unifying principle, and the purpose of this paper is to show that the marked tendency for a carbon chain to adopt the planar zig-zag form (see McCoubrey and Ubbelohde, *Quart. Reviews*, 1951, **5**, 364) is sufficient to explain the main features of the rules, since it appears that the most favoured rings involve the least energy for distortion of the planar chain. For brevity and clarity, all references to experimental data which were given by Barker and Bourne (*loc. cit.*) are omitted.

It will be recalled that the Greek letters, α, β, and γ, were used to signify the relative positions, along the carbon chain of the polyhydric alcohol, of the two hydroxyl groups engaged in the cyclisation, and that C and T indicated whether these two groups were disposed *cis* or *trans in the usual Fischer projection formula*; C and T were required only when *both* alcohol groups were secondary. Thus, a system in which an alkylidene residue spanned two secondary hydroxyl groups, located on adjacent carbon atoms and having a *trans*-orientation, was said to contain an αT-ring, whereas a β-ring was said to be present when one of the alcohol groups concerned was primary and the other was situated on the β-carbon atom. The same nomenclature is retained in the present paper, but is extended somewhat; in each case under discussion, the reference carbon atom is called C_r, and the others, C_α, C_β, etc., whilst the oxygen and hydrogen atoms are designated according to the carbon atoms to which they are united, *e.g.*, O_r and H_β are substituents on C_r and C_β, respectively. C_e refers to the external carbon atom belonging to the acetal addend.

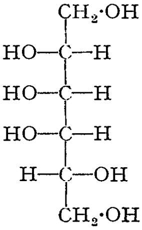
Before the relative merits of the various types of acetal rings can be assessed certain important factors must be considered, namely, the true spatial dispositions of the oxygen atoms in polyhydric alcohols (as distinct from the apparent dispositions seen in the usual Fischer projection formulæ), and the kinetics and energy changes involved in the formation of acetal rings. We take first the question of spatial dispositions. If it is accepted that the most stable arrangement in a polyhydric alcohol is that in which the carbon chain assumes a planar zig-zag form, then (I) and (II) represent the structures of talitol and allitol, respectively, viewed perpendicularly to the plane through the carbon atoms; for comparison, the Fischer projection formulæ for these hexitols are given in (I*a*) and (II*a*). It will be seen that, in (I) and (II), $O_{\alpha T}$, $O_{\beta C}$, and $O_{\gamma T}$ lie on the same side of the plane through the carbon atoms as does the reference oxygen atom, O_r, whilst $O_{\alpha C}$, $O_{\beta T}$, and $O_{\gamma C}$ lie on the opposite side. The distances between the various oxygen atoms shown in (I) and (II) are given in the Table; in calculating these distances, the bond angles at all carbon atoms were taken as the tetrahedral angle (109° 28′) and the bond lengths as C–C 1·54 and C–O 1·43 Å;

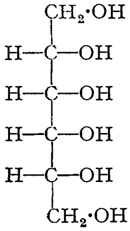
in subsequent calculations the length of the C–H bond will be taken as 1·09 Å. By using the same parameters, the O–O distance in an O–C_e–O group can be shown to be 2·34 Å, and so the oxygen atoms in a polyhydric alcohol which are already separated by a distance of this order are likely to participate most readily in acetal formation.

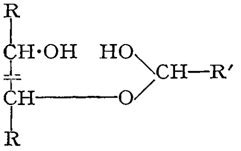


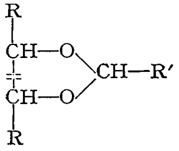
(I) (II)

$\overset{+}{O}$ represents an oxygen atom projecting towards the viewer.
$\bar{O}$ represents an oxygen atom projecting away from the viewer.
The hydrogen atoms at positions 2, 3, 4, and 5 are not shown.


(I*a*)


(II*a*)


(III)


(IV)

When a polyhydric alcohol is treated with an aldehyde (R′·CHO) and a condensing agent there are many plausible condensations possible and the product would be a mixture containing acetal rings of different types, were it not for some controlling influence, which could be either the relative rates of the various reactions or the relative stabilities of the products.

Distances (Å) *from* O_r.

	O_α	O_β	O_γ	O_δ
C	3·68	2·51	5·11	5·02
T	2·83	3·43	4·54	5·54

The synthesis of a cyclic acetal (IV) is a two-stage process (cf. Meldrum and Vad, *J. Indian Chem. Soc.*, 1936, **13**, 118), involving first the formation of a semiacetal (III) and then cyclisation, with accompanying dehydration; the differences in the activation energies necessary for syntheses of acetal rings of different types will be essentially the differences in the amounts of energy required to form the transition states of virtually the same geometrical configurations as the final products. It is precisely this energy needed to distort the zig-zag carbon chain which controls the energy differences in the products, and hence their relative stabilities. It is for this reason that those acetal rings which are most readily synthesised are those which are most resistant to acidic hydrolysis (cf. Barker and Bourne, *loc. cit.*). Moreover, the fact that the above rules apply under a wide variety of reaction conditions supports the idea that the most stable acetals are formed most quickly. In the light of these general observations, it is possible to consider in detail the formation of individual types of rings, and thus to furnish an explanation of the rules. The assumption is made, probably quite legitimately, that the alkyl group and the hydrogen atom carried by the carbonyl group of an aldehyde do not prevent the distribution of the valency bonds of C_e from being tetrahedral, either in the semiacetal or in the cyclic acetal; *i.e.*, the O–O distance in the O–C_e–O group of these compounds will still be 2·34 Å.

Rule (1).—βC-*Rings*. It can be seen from the Table that the shortest O–O distance in the undistorted planar form of a polyhydric alcohol is 2·51 Å, the value for O_r–$O_{\beta C}$. Acetal formation, in which this distance is reduced to 2·34 Å, will require less distortion in this case than in any other. Indeed, a rotation of only 8° in the appropriate sense about each of the bonds C_r–C_α and C_α–C_β will reduce the O_r–O_β distance to the required 2·34 Å without departure from tetrahedral angles at the carbon atoms.

Rule (2).—β-*Rings*. This rule deals with a terminal C_r, so that rotation about the C_r–C_α bond is possible without affecting the extended nature of the carbon chain. By such a rotation, O_r may be brought into the same position relative to O_β as is the normal one for $O_{\beta C}$, and acetal formation is possible with only the further, almost negligible, rotations of 8° mentioned under βC-rings. A β-ring is thus highly favoured, but further consideration of the rotation about C_r–C_α indicates why such a ring yields precedence to a βC-ring. It is unlikely that the most stable of the three configurations with a staggered arrangement about C_r–C_α (*i.e.*, with the deepest of the three potential minima) will be that corresponding to βC, since the O_r–O_β distance in this case would be 2·51 Å, which is less than the sum of the van der Waals radii for two oxygen atoms, namely 2·80 Å (see Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, 1948, p. 189). The consequent repulsion energy is absent in the other positions, which therefore will be more stable. The fact that such repulsion energy must be overcome in passing from the most stable to the final position makes a β-ring less favoured than a βC-ring where the repulsion energy is present in the initial, as well as the final, state. Alternatively, even if all three potential minima be of essentially equal depth, only one-third of the molecules are in the βC-configuration and an entropy term, $\boldsymbol{R}T \ln 3$, has to be subtracted from the free energy of reaction, so that β-rings are again less favoured than βC-rings.

α-, αC-, and αT-*Rings in General*.—The minimum O_r–O_α distance encountered during a 360° rotation about C_r–C_α is 2·49 Å; it is reached when the two oxygen atoms are in the eclipsed position. Thus, an acetal requiring O_r–O_α 2·34 Å cannot be formed without distortion of either the bond lengths or the tetrahedral bond angles. If the bond lengths are unchanged and the angles O_r–C_r–C_α and C_r–C_α–O_α are reduced by 2·5° to 107°, the O_r–O_α distance is 2·37 Å in the eclipsed structure, which is exactly the required distance if the O_r–C_e–O_α angle is increased by 2·5° to 112°. The energy required for this small degree of distortion, 2·5° at each carbon atom concerned, is not very large, and depends partly on the nature of the addend.

Rule (3).—(a) α-*Rings*. Here the situation is very similar to that obtaining in the case of β-rings, because again C_r is terminal; the requisite state for acetal formation can arise by rotation about the C_r–C_α bond with very slight adjustment of bond angles (see above); the carbon skeleton of the polyhydric alcohol can still retain its extended form. However, an α-ring is formed less readily than βC- or β-rings, because, in the former case, the product possesses the unfavoured eclipsed structure for the valencies about the C_r–C_α bond, whereas, in the latter cases, it has essentially the favoured staggered structure about all the C–C bonds. All other known types of acetal rings in derivatives of polyhydric alcohols (namely, αT-, βT-, and γT-rings) can be formed only when the planar zig-zag carbon chain is seriously distorted, and consequently, in accordance with rule (3), they too are less probable than β-rings. There is no experimental evidence which would enable them to be compared with α-rings as regards ease of formation or stability.

(b) αT-*Rings*. After $O_{\beta C}$ the next nearest oxygen atom to O_r is $O_{\alpha T}$, situated 2·83 Å away in the extended chain form. Rotation by 60° about C_r–C_α is required to reach the eclipsed form; this implies definite distortion of the carbon chain, which remains essentially extended, but loses its planar character.

(c) βT-*Rings*. Reference to the Table shows that in the planar chain form of a polyhydric alcohol $O_{\beta T}$ lies 3·43 Å from O_r, a distance too great to permit cyclic acetal formation directly. This distance can be reduced to the required 2·34 Å by rotations about the C_r–C_α and C_α–C_β bonds; of the many ways in which this may be done, the simplest requires a rotation of 30° in the proper sense about each of these bonds. Again there is distortion of the planar chain and βT-rings, though possible, will not be highly favoured.

(d) γT-*Rings*. A detailed analysis of the changes in the dispositions of the carbon atoms in a polyhydric alcohol which could result in a reduction of the O_r–$O_{\gamma T}$ distance from 4·54 Å (that in the zig-zag chain form) to 2·34 Å is complicated by the fact that rotations about the C_r–C_α, C_α–C_β, and C_β–C_γ bonds are all possible. Nevertheless, it is clear from models that the requisite transition state can arise, so that γT-rings are permissible. They are not favoured, even compared to α-, αT-, or βT-rings, since the reaction state requires the co-operation of several rotations and the 2·34-Å distance will be reached only rarely; in other words the entropy decrease is large.

Rules (4) *and* (5).—These rules concern the order of precedence in the formation of αT-, βT-, and γT-rings. Although it is clear from the foregoing that βC-, β-, and probably α-, rings are preferred to αT-, βT-, and γT-rings because serious distortion of the extended carbon chain is necessary in the latter group, but not the former, it is much more difficult to differentiate between the energies involved in the formation of members of the latter group. Consequently there is a much finer balance in the order of preference within this group, a balance which can be upset by minor changes in the structure of the carbonyl component. Thus, a change in the nature of the addend from methylene to benzylidene or ethylidene may easily change the order of preference for αT- and βT-rings and necessitate the inclusion of the alternative rules (4) and (5).

Rule (6).—*The influence of pre-formed rings.* In this section consideration will be given only to the polyhydroxy-compounds reviewed by Barker and Bourne (*loc. cit.*); cyclitols will not be dealt with as they were discussed fully by Angyal and Macdonald (*J.*, 1952, 686) in a paper which appeared when the present contribution was in draft. The compounds containing pre-formed rings which are most frequently subjected to acetal formation are cyclic acetals themselves, formed in an earlier stage of the reaction, and these must be the first consideration. All cases in which the new acetal ring does not overlap the ring already present can be dismissed, because there is no new factor which would interfere with the usual order of preference; these cases include the introduction of the second β-ring in the dulcitol, mannitol, and perseitol series, and of an α-ring into the 1 : 3-2 : 4-diacetals of sorbitol and talitol. Nor is detailed analysis necessary of those cases in which the parent compound carries an acetal ring of the βC- or β-type, together with a suitable configuration of the remaining hydroxyl groups to permit the formation of a new βC- or β-ring (even when the new ring will overlap the old), because, as has been demonstrated already, βC- and β-rings are formed with negligible distortion of the extended chain; these cases include the formation of β-rings with 2 : 4-acetals of ribitol, xylitol, sorbitol, talitol, and their derivatives, and of βC-rings with 2 : 4-acetals of allitol and iditol.

In another convenient group of reactions, cyclic acetals which overlap pre-formed acetal rings are synthesised from derivatives of polyhydric alcohols carrying only two free hydroxyl groups; among these are those involving the introduction of (*a*) βT-rings into 2 : 4-acetals of 1 : 6-disubstituted derivatives of mannitol, (*b*) βT-rings into analogous compounds in the sorbitol series, (*c*) γT-rings into 1 : 3-4 : 6-diacetals of mannitol, (*d*) a γT-ring (methylene) into 1 : 6-dibenzoyl 3 : 4-benzylidene mannitol, and (*e*) an αT-ring (benzylidene) into 1 : 6-dibenzoyl 2 : 5-methylene mannitol. In (*a*) the rotation of 30° about $C_{(3)}$–$C_{(4)}$ to form the first βT-ring in the 2 : 4-position is in the same sense as that required for the second (3 : 5-)βT-ring, which should be formed therefore rather more easily than is usual. In (*b*), where the 2 : 4-ring is βC, the locked configuration about $C_{(3)}$–$C_{(4)}$ is not ideal for accommodating a βT-ring in the 3 : 5-position, yet it is still possible to form such a ring by rotation about the $C_{(4)}$–$C_{(5)}$ bond to bring O_3–O_5 to 2·34 Å, even though the arrangement is not that postulated as the " simplest " in the discussion of βT-rings. In (*c*), rotation about $C_{(3)}$–$C_{(4)}$ can lead to γT-ring formation, as discussed later in more detail. In (*d*) and (*e*) the product is the same, 1 : 6-dibenzoyl 3 : 4-benzylidene 2 : 5-methylene mannitol; the required rotation about the $C_{(3)}$–$C_{(4)}$ bond is in the same sense for the formation of the αT- and γT-rings, and in the parent compound for (*d*) the O_2–O_5 distance is already reduced from 4·54 to 3·01 Å, even before rotations occur about the $C_{(2)}$–$C_{(3)}$ and $C_{(4)}$–$C_{(5)}$ bonds. When the latter rotations also become effective—and there is no reason why they should not—this distance is reduced further, so that only small distortions of the bond angles are then needed to bring it to 2·34 Å; thus it can be seen why the αT- and γT-rings can exist together.

These arguments explain why it was possible to restrict the application of rule (6) to those acetal syntheses in which the parent compound was a derivative of a polyhydric alcohol carrying a cyclic substituent and free hydroxyl groups of such a configuration that a choice between αT-, βT-, and γT-rings was necessary, one or more of these hydroxyl groups being attached to carbon atom(s) already forming part of the ring system. The only known reactions covered by rule (6) are (*a*) the methylenation of 1 : 3-methylene rhamnitol, and (*b*) the benzylidenation of 1 : 4-anhydrosorbitol and of its 6-chloro-6-deoxy- and 6-bromo-6-deoxy-derivatives. In (*a*) the usual order of preference for a βT-ring over a γT-ring is reversed, presumably because free rotation is no longer possible about $C_{(2)}$–$C_{(3}$ as is required for the "simplest" βT-case, so that the γT-ring is favoured relatively to the βT-ring; rotation remains possible about $C_{(3)}$–$C_{(4)}$, which is the most important requirement in the formation of a γT-ring. In (*b*), the reason why benzylidenation of 1 : 4-anhydrosorbitol leads to a βT-ring, rather than an αT-ring, is that $C_{(2)}$ and $C_{(3)}$ are part of the anhydro-ring system so that O_r and $O_{\alpha T}$ are fixed 3·68 Å apart, a limitation which does not apply to O_r and $O_{\beta T}$.

The Non-existence of Certain Types of Acetal.—α*C-Rings.* There seems to be no reason, on stereochemical grounds, why an αC-ring could not be formed from an acyclic polyhydric alcohol, just as it is in the cyclitol and sugar series. In the extended chain form of a polyhydric alcohol $O_{\alpha C}$ lies 3·68 Å from O_r; this distance can be reduced to that needed for acetal formation by a rotation of about 180° about C_r–C_α, followed by distortion of the angles by 2·5° as above, but this requires an eclipsed arrangement and also a considerable departure from the extended chain, making an αC-ring less probable than even an αT- or a βT-ring. It should be noted that when all the highly favoured βC- and β-configurations are satisfied in all unsubstituted tetritols, pentitols, and hexitols, and also in *gluco-gulo*-heptitol, and perseitol, then no αC-positions are available for acetal formation. There is no reported reaction in which an αC-ring fails to be formed after configurations suitable for all other rings have been satisfied.

γ*-Rings.* Since γT-rings have been proved experimentally to exist, the probable reason for a γ-ring not having been found is its lowly position in the order of preference; even if it were advanced in this order so that it followed βC- and β-rings, it could not possibly have been formed in any of the syntheses attempted to date, with the exception of the benzylidenation of arabitol and of the benzylidenation and methylenation of *gluco-gulo*-heptitol.

γ*C-Rings.* Since these rings are bound to rank very low in the order of preference, lower even than γT- or γ-rings, there is little point in attempting to unravel the complexities of their possible synthesis from an unsubstituted polyhydric alcohol; instead, attention will be confined to the one known case in which there is a possibility of γC-ring formation without competition from other types of rings, namely, the attempted conversion of 1 : 3-4 : 6-diacetals of dulcitol into the corresponding 1 : 3-2 : 5-4 : 6-triacetals. The failure of this reaction is interesting in view of the successful introduction of γT-rings into the isomeric 1 : 3-4 : 6-diacetals of mannitol. The only C–C bond in the carbohydrate moiety of a 1 : 3-4 : 6-diacetal of either hexitol about which free rotation is still possible is the $C_{(3)}$–$C_{(4)}$ bond, and in each case there are two angles of twist which would bring the relevant oxygen distance to 2·34 Å, as required for the formation of the third ring; these angles are ±133° in the dulcitol series, and 149·5° and 86·5° in the mannitol series. However, in each of the dulcitol cases there is a non-bonded O–H distance (O_r–H_γ or O_γ–H_r) of 1·73 Å, which is so much smaller than the sum (2·60 Å) of the van der Waal's radii of hydrogen (1·20 Å) and oxygen (1·40 Å) (see Pauling, *op. cit.*) that the repulsive forces between these two non-bonded atoms would not be surmounted. There is no such objection to the 86·5° rotation in the mannitol series because this brings the O_r–H_γ and the O_γ–H_r distance to 3·57 Å, which presents no hindrance to the synthesis of a γT-ring. The 149·5° case gives both these O–H distances as 1·98 Å and must be ruled out.

Higher Rings.—Rings of the δ- or ε-types are inherently unlikely, and, in particular, no amount of rotation about the terminal C–C bonds of 2 : 4-3 : 5-diacetals of allitol or iditol will produce an O_r–O_ϵ distance suitable for ε-ring formation.

Formation of Cyclic Ketals.—Although the above arguments provide a satisfactory explanation of the rules concerning favoured ring forms in acetals of the polyhydric alcohols, it is still necessary to show why ketals are not formed in accordance with the rules, *i.e.*, why ketones often give rise to α- and αT-rings when β- and βC-configurations also are available [cf. Hermans (*Z. physikal. Chem.*, 1924, **113**, 337), who found that the condensation of acetone with propane-1 : 2-diol to give an α-ring was more complete than in the case of β-ring formation from the isomeric 1 : 3-diol, the equilibrium constants being 0·44 and 0·026, respectively]. This discrepancy between aldehydes and ketones is probably due to a combination of factors, such as (*a*) the well-known reluctance of ketones to give semiketals with alcohols, and (*b*) the effect of two bulky alkyl groups on the O–C_e–O bond angle, and consequently on the O–O distance. It may well be, too, that ketones show a marked preference for addition to primary, rather than to secondary, hydroxyl groups of polyhydric alcohols and that, in the resulting semiketal, O_r and C_e will tend to continue the planar zig-zag carbon skeleton of the polyhydric alcohol. A partial explanation of the behaviour of ketones can be given on these lines, but it is not possible to make a detailed study until many more experimental data are available.

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