Cuprammonium–Glycoside Complexes. II.[2] The Angle Between Hydroxyl Groups on Adjacent Carbon Atoms

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During the examination of a large number of cuprammonium–glycoside complexes some relationships were observed which appeared to cast light on the subject of the shape (conformation) of glycoside molecules in solution. However, before the problem of conformation could be attacked it was necessary to secure a better understanding of the meaning of complex formation. In the present communication a theory applicable to complex formation is proposed and selected examples involving hydroxyl groups on adjacent carbon atoms are cited in its support. In forthcoming reports the theory will be tested by examining its application to a large number of carbohydrate derivatives.

Let it be assumed that there is a particular distance between hydroxyl groups most favorable for complex formation with cuprammonium, and a range of distances over which complex formation may occur more or less readily depending on the variation from the optimum distance. Thus, affinity for cuprammonium would be inversely related to the deviation of rigidly fixed hydroxyl groups from a particular position, or, for hydroxyl groups not rigidly fixed, to the energy required to move the groups to a complex-forming position.

In dealing with adjacent hydroxyl groups located on pyranose and furanose rings the relative position of the groups is determined by the configuration of the carbon atoms and shape of the rings. Regarding the latter the following first approximations have been assumed: (1) the shape of a pyranoside ring in solution may be represented, adequately for the present purpose, by a regular skew hexagon having the tetrahedral angle between sides, arranged in one of the eight Sachse strainless ring conformations; (2) the furanoside ring may be adequately represented by a flat structure having coplanar, or essentially coplanar, ring carbon atoms. In such ideal structures the angle between any pair of adjacent carbon–oxygen bonds projected onto a plane perpendicular to the carbon–carbon axis must be one of the following angles[3] for pyranoside boat forms,

$0°$, $\pm 60°$, $\pm 120°$, $180°$; for pyranoside chair forms, $\pm 60°$, $180°$; for furanosides, $0°$, $\pm 120°$. Note that the projection of the tetrahedral angle in this manner yields a projected angle of exactly $120°$. The sign of the projected angle is defined with the aid of three dimensional molecular models in the following manner. Sighting along a line through the centers of the two hydroxyl-bearing carbon atoms, the reference plane is defined as that passing through the centers of these two atoms and the center of the hydroxyl oxygen atom nearer the observer. The divergent plane passes through the centers of the same two carbon atoms and the center of the far oxygen atom. When the divergent plane makes a clockwise angle with the reference plane the angle will be designated negative; when the angle is counterclockwise, positive.

What Angle Is Capable of Complex Formation?

Having assumed that optimum conditions for complex formation occur when two hydroxyl groups are located at a particular distance from each other, it is apparent that for hydroxyl groups on adjacent carbon atoms this distance is a direct function of the projected angle between the carbon valences on which the hydroxyl groups are bound. There are cyclic substances in which this angle is fixed, for a particular conformation, more or less rigidly, by the spatial requirements of the whole molecule. A selected group of these substances will now be examined to see if there appears to be an optimum angle for complex formation.

Cellulose is the classical example of a complex-forming substance. In cellulose, the hydroxyl groups at positions 2 and 3 of each glucose unit react with cuprammonium to form a soluble complex.[4] Crystalline cellulose is composed of β-D-glucopyranoside units oriented in the particular chair form conformation in which the pyranoside oxygen and 6-carbon atom project on the same side of the plane of the 1,2,4,5-carbon atoms.[5,6,7] Cellulose is a very insoluble substance, and were it not for complex formation there is no reason to believe it would dissolve in cuprammonium. Furthermore, after regeneration from cuprammonium, cellulose exhibits the same unit cell length[8] and hence probably the same ring con-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) R. E. Reeves and J. R. Jung, Jr., THIS JOURNAL, **70**, 209 (1948).

(3) Admittedly in the actual molecules these angles are subject to small variations. In a rigorous determination of ring conformation exact knowledge of interatomic distances and valence angles would be required, and in studies dealing with the crystalline state these quantities would necessarily be emphasized. However, when the problem is one of conformation in solution, where shapes are undoubtedly more elastic than in the crystalline state, and where interchange of conformations is a possibility, it has not been attempted to interpret the results in terms of the exact angles and distances found for the crystalline state.

(4) R. E. Reeves, Science, **99**, 148 (1944).

(5) W. T. Astbury and M. M. Davies, Nature, **154**, 84 (1944).

(6) E. G. Cox, ibid., **154**, 84 (1944).

(7) F. T. Peirce, ibid., **154**, 398 (1944); Shirley Inst. Memoirs, **20**, 81-97 (1946). Peirce's contention that the X-ray data better fit a slightly modified chair conformation need not concern us here for the proposal retains the recognizable conformation.

(8) W. A. Sisson in "High Polymers," Vol. V, Emil Ott, Ed., Interscience Publishers, Inc., New York, N. Y., 1943, p. 212.

formation as native cellulose. Since cuprammonium undoubtedly reacts with cellulose as it exists in the crystalline state, it may be concluded that the angle between the hydroxyl groups on positions 2 and 3 of the glucose units of cellulose is capable of complex formation. Inspection of a D-glucopyranoside model oriented in the cellulose conformation discloses this angle to be −60°.

cis-2,3-Dihydroxytetrahydrofuran (erythritol anhydride) contains hydroxyl groups which according to assumption 2 must be situated at the true cis (0° projected angle) angle with respect to each other. That the groups are actually in the cis position has been confirmed by behavior of this substance toward cleavage by lead tetraacetate.[9] This substance, being optically inactive, can only show complex formation by the conductometric method, however, by this technique the evidence for complex formation was unmistakable.

A substance which must possess the true cis (0°) relationship for a pair of adjacent hydroxyl groups on a pyranoside ring is **methyl 2,6-anhydro-α-D-altroside** recently described by Rosenfeld, Richtmyer and Hudson (THIS JOURNAL, **70**, 2201 (1948)). The molecular model of this substance shows only one possible ring conformation, a boat form in which the hydroxyl groups at positions 3 and 4 are in the true cis position. A sample of this material was kindly furnished the writer by Dr. Richtmyer. The glycol group could be titrated directly with lead tetraacetate. An 0.01 molar concentration increased the specific resistance of cupra A from 324 to 564 ohm, cm. Its specific rotations (25°, 436 mμ) were +84° (c, 1.01, water) and +350° (c, 0.66, cupra B) corresponding to a rotational shift of +467°. The behavior with lead tetraacetate confirms the true cis relationship of the glycol and the behavior with cuprammonium indicates a strongly complex-forming group with an intermediate rotational shift.

Non-Complex-Forming Substances.—There are a number of substances which, though possessing hydroxyl groups on adjacent carbon atoms, fail to form cuprammonium complexes under the usual conditions. Among these is the newly discovered glucose anhydride, D-glucosan <1,4>β<1,6>. Examination of a molecular model representing this substance discloses that the groups are very rigidly held at the −120° angle. Dimler, Davis and Hilbert[10] have commented on the resistance of this substance against oxidation by the glycol cleavage reagents, and have attributed this property to the widely spaced trans orientation of the hydroxyl pair. It seems probable that its failure to form a cuprammonium complex is also due to this condition.

A second non-complex-forming substance was 2,5-anhydrosorbitol. The trans (+120°) orienta-

tion for the hydroxyl groups has been confirmed by the low rate of reaction of this substance with the glycol cleavage reagents.[11]

The two preceding substances illustrate non-complex-formation in trans spaced hydroxyl groups located on a furan ring. A pyranoside derivative, methyl 4,6-benzylidene-α-D-altroside, also failed to form a complex, and consideration of molecular models of this substance shows that the benzylidene ring limits the possibilities to three of the eight conformations, one chair and two boat forms. Since the theoretical arguments of Gorin, Kauzmann and Walter[12] and Scattergood and Pacsu[13] tend to exclude the two boat forms, it is most probable that methyl 4,6-benzylidene-α-D-altroside exists in the chair form in which the angle between hydroxyl groups would be 180°.

These examples have included substances having hydroxyl pairs oriented at 0°, 60°, 120°, and (probably) 180°, and of the four angles only the 60° and 0° angles have shown a marked reaction with cuprammonium. Considered in relation to the theory, it may be said either that the latter two angles are sufficiently close to the optimum angle to allow complex formation to occur, or that the substances which possessed these angles had sufficient elasticity to allow the hydroxyl groups to move to a position capable of complex formation; while neither of these possibilities apply to the non-complex-forming substances.

Experimental Results and Discussion

Conductivity measurements were made by the method described in the preceding communication.[2] The constant for the cell employed at the start of this work was 0.116. As the cell showed small changes with use all readings were recalculated to this value. Optical rotations were measured with the mercury blue line (436 mμ) or the sodium D line, as indicated. The cuprammonium solution used for optical rotations contained 15 g. of copper, 240 g. of ammonia and 1 g. of glycerol per liter. This solution is designated cupra B.

The results of conductivity measurements on the non-complex-forming substances in cuprammonium solution (cupra A)[2] are shown in Fig. 1, curve B. Observed resistances are plotted against molar glucide concentrations. Included for comparison is the curve representing methyl 4,6-benzylidene-α-D-glucoside, a typical complex-former. The results with this substance also show that the presence of a benzylidene ring does not inhibit complex formation provided the hydroxyl pair is properly oriented. In Table I are listed the specific rotations in water and

(9) R. E. Reeves, Anal. Chem., in press.

(10) R. J. Dimler, H. A. Davis and G. E. Hilbert, THIS JOURNAL, **68**, 1377–1380 (1946)

(11) R. C. Hockett, M. Zief and R. M. Goepp, Jr., ibid., **68**, 935–937 (1946).

(12) E. Gorin, W. Kauzmann and J. Walter, J. Chem. Phys, **7**, 327 (1939).

(13) A. Scattergood and E. Pacsu, THIS JOURNAL, **62**, 903–910 (1940).

TABLE I

OPTICAL BEHAVIOR OF VARIOUS SUBSTANCES IN WATER
AND CUPRAMMONIUM HYDROXIDE SOLUTION

	$[\alpha]^{25}_{436}$ Water	$[\alpha]^{25}_{436}$ Cupra B	Rotational shift[a]
D-Glucosan <1,4>β<1,6>	+ 78°	+ 69°	— 15°
2,5-Anhydrosorbitol	+ 48°	— 32°	— 132°
Methyl 4,6-benzylidene-α-D-glucoside[b]	+159°	—608°	—2163°
Methyl 4,6-benzylidene-α-D-altroside	+204°	+188°	— 45°

[a] [Sp. rot. (cupra B) — sp. rot. (water)] × Mol. wt./100.   [b] Reference 4.

cuprammonium, and the rotational shifts ([α] cupra B [α] water) × Mol. wt./100 for the substances considered in Fig. 1.
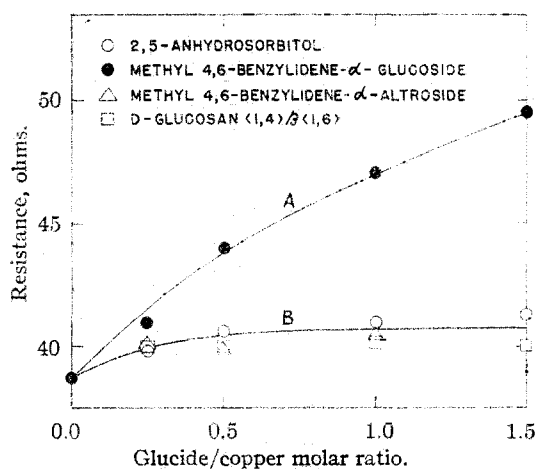

Fig. 1.—Resistance vs. concentration relationships for a complex-forming substance (curve A) and three non-complex-forming substances (curve B) in cupra A.

It is apparent that the non-complex-formers produced neither a marked change in conductance nor a pronounced shift in rotation (Table I) comparable with that caused by the complex-forming methyl 4,6-benzylidene-α-D-glucoside.

The complex-forming action of erythritol anhydride as measured conductometrically is shown in Fig. 2. For comparison the curve previously reported[2] for an active complex-forming substance, methyl α-D-gulopyranoside is reproduced in this figure.

The D-glucosan <1,4> β <1,6>, m. p. 110–11°, gave the following optical rotations: [α]$^{25}_{436}$ +78° (c, 0.94 water), and +69° (c, 0.81 cupra B).

The sirupy 2,5-anhydrosorbitol was prepared by debenzoylation of the crystalline 1,6-dibenzoate[11] in methanol solution with barium methylate. It was purified by distillation at 0.002 mm. pressure at a bath temperature of 170°. The colorless
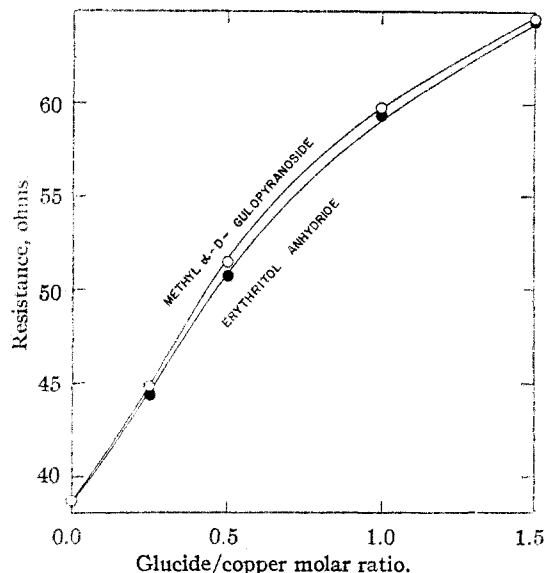

Fig. 2.—Resistance versus concentration relationships for erythritol anhydride and methyl α-D-glucoside in cupra A.

distillate gave the correct carbon–hydrogen analyses. Its optical rotations were [α] D^{25} + 21° (c, 0.95 water); [α]$^{25}_{436}$ + 48° (c, 0.95 water); —32° (c, 0.43 cupra B).

Methyl 4,6-benzylidene-α-D-altroside, m. p. 171–172°, was prepared from methyl benzylidene-α-D-glucoside by the method of Richtmyer and Hudson.[14] The optical rotations of the benzylidenealtroside were [α]^{25}D + 106° (c, 1 water), [α]$^{25}_{436}$ + 204° (c, 1 water) and + 188° (c, 1.16 cupra B).

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Summary

The position is taken that complex formation between cuprammonium and two hydroxyl groups occurs most readily when the hydroxyl groups are located at a particular distance apart. Examination of a number of substances having hydroxyl groups on adjacent carbon atoms held more or less rigidly at a number of angles (hence distances) has shown complex formation to occur readily at the true cis-position (0° angle) and the 60° angle, but not at the 120° or the 180° angle.

(14) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, 63, 1727–1731 (1941).