[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

Cuprammonium–Glycoside Complexes. III. The Conformation of the D-Glucopyranoside Ring in Solution

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In the preceding article of this series[2] a theory has been presented which defines some necessary conditions for complex formation between cuprammonium and two hydroxyl groups. According to this speculation the two complex-forming hydroxyl groups must be located at or near a particular optimum distance from each other. Distances capable of complex formation occur when hydroxyl groups on adjacent carbon atoms are oriented at the true *cis*-position (0° projected angle) or the ±60° projected angle positions. When the properties of numerous D-glucopyranoside derivatives were considered in the light of these findings it became possible to draw certain conclusions in regard to the ring conformation of glucopyranoside molecules in solution.

In an earlier communication[3] it was concluded on the basis of optical rotation measurements that glucopyranoside derivatives can form complexes at the 2–3 and 3–4 positions but the possibility of complex formation between other hydroxyl pairs was not rigorously excluded. Since that time it has been recognized that cuprammonium complexes can form without appreciable shift in optical rotation, hence the question of possible sites for complex formation has been reinvestigated by a conductometric technique. These results, given in the last column of Table II, indicate that only the above mentioned hydroxyl pairs are capable of complex formation, as far as the substituted ordinary D-glucopyranosides are concerned.

Proceeding on the assumption that the pyranoside ring can be adequately represented by a regular skew hexagon with tetrahedral angles between sides, oriented in one of the eight Sachse strainless ring conformations, it is possible by inspection of molecular models to evaluate, approximately, the angle between any pair of adjacent hydroxyl groups. These angles between the hydroxyl groups of positions 2–3 and 3–4 of D-glucopyranosides have been estimated and are shown in Table I. The conformations are those illustrated in Fig. 1 and the angles are those projected onto a plane perpendicular to the carbon–carbon bond as defined in the preceding article.[2] It is apparent by inspection of models that the hydroxyl pair at the 2–3 position can assume the complex-forming −60° angle, but not the 0° or the + 60° angles, while the hydroxyl pair at position 3–4 can form the + 60° angle but not the 0° or −60° angles. This situation is probably responsible for the strikingly different optical behavior of the first two groups of substances listed in Table II. Group I contains D-glucopyranosides substituted to allow complex formation only at position 2–3 while the second group is substituted to allow reaction only at posi-

TABLE I

THE ANGLE BETWEEN ADJACENT HYDROXYL GROUPS OF THE D-GLUCOPYRANOSE RING

Conformation	2–3 hydroxyls	3–4 hydroxyls
C1	− 60°	+ 60°
1C	180°	180°
B1	−120°	+ 60°
1B	−120°	180°
B2	− 60°	+120°
2B	180°	+120°
B3	180°	180°
3B	− 60°	+ 60°

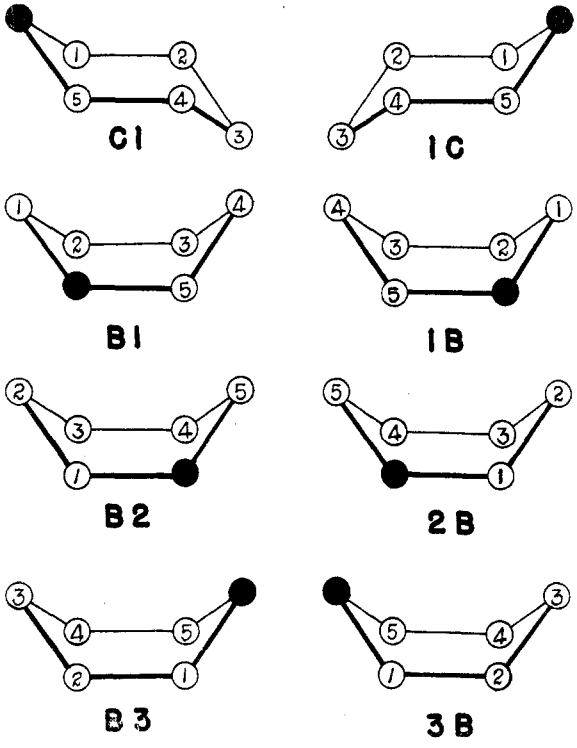

Fig. 1.—The eight pyranose strainless ring conformations and the corresponding symbols. By convention the heavy lines represent the sides of the three-dimensional figure nearer the observer. The dark circles represent ring oxygen atoms, and the numbered circles carbon atoms 1 to 5.

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(2) R. E. Reeves, Part II, THIS JOURNAL, **70**, 212 (1948).

(3) R. E. Reeves, *J. Biol. Chem.*, **154**, 49–55 (1944).

tion 3–4. It is apparent that strongly levorotatory complexes form at position 2–3 (−60° angle), while complexes of similar dextrorotation form at position 3–4 (+ 60° angle, Table II, Group II).

TABLE II

THE BEHAVIOR OF VARIOUS SUBSTANCES IN CUPRAMMONIUM SOLUTION

D-Glucopyranoside	Rotational shift[a] deg.	Increase in sp. res.[b] ohm., cm.	Proof of position of complex
(Group I, complex at 2-3 position)			
Methyl 4-methyl-β-	−2020[c]	..	.....
Methyl 4,6-dimethyl-β-	−1990	52	Levo at 2-3
Methyl 4,6-ethylidene-β-	−1970[d]	73	Levo at 2-3
Methyl 4,6-benzylidene-α-	−2160[d]	69	Levo at 2-3
Methyl 4,6-benzylidene-β-	−2230	82	Levo at 2-3
(Group II, complex at 3-4 position)			
Methyl 2-methyl-β-	+2190[e]	67	.....
Methyl 2,6-dimethyl-α-	+2110[e]	..	Dextro at 3-4
(Group III, compensating complexes)			
Methyl 6-methyl-β-	+ 435[c]	70	.....
Methyl α-	+ 244[d]	50	.....
Methyl β-	+ 250[d]	67	.....
Phenyl α-	+ 292	61	.....
Phenyl β-	− 74	85	.....
(Group IV, regarded as non-complex forming)			
Methyl 3-methyl-β-	− 83[c]	16	No complex at 2-4, 2-6, or 4-6
Phenyl 3-methyl-β-	+ 32	2	
Methyl 2,3-dimethyl-α-	+ 20	10	No complex at 4-6
Methyl 2,3-dimethyl-β-	− 9	14	No complex at 4-6
Methyl 2,4-dimethyl-α-	− 74[d]	7	No complex at 3-6
Secondary alcohols			
Isopropyl alcohol	....	18	.....
Butanol-2	....	20	.....

[a] Rotational shift equals ($[\alpha]_{436}$ Cupra B − $[\alpha]_{436}$ water) × mol. wt./100. For composition of Cupra B see Experimental part. [b] Increase in specific resistance of 0.01 molar glucoside or *s*-alcohol in Cupra A. For composition of Cupra A see Experimental part. [c] See footnote 3. [d] R. E. Reeves, *Science*, **99**, 148–9 (1944). [e] R. E. Reeves, THIS JOURNAL, **70**, 259–60 (1948). The rotational shift previously given did not include the mol. wt./100 factor.

The third group of substances listed in Table II have hydroxyl groups at positions 2, 3 and 4, unsubstituted (*i. e.*, with both the 2–3 and 3–4 glycol groups free). Complex formation in these substances produces a much smaller shift in optical rotation than it does in those compounds which can react at only one site. The affinities for cuprammonium of the substances in groups I–III (Table II) have been found to be approximately equal by the conductometric technique. Examples illustrating this similar affinity of the three complex-forming groups are given in Fig. 2. Since there is no reason to suspect a marked difference in the amount of cuprammonium complex formed by the three classes of substances under similar conditions, the reason for the relatively low shift in rotation for the third class may lie in simultaneous formation of dextro- and levorotatory complexes (compensating complexes). Table I shows that only the C1 and 3B conformations would allow the formation of compensating complexes in the glucopyranoside series.

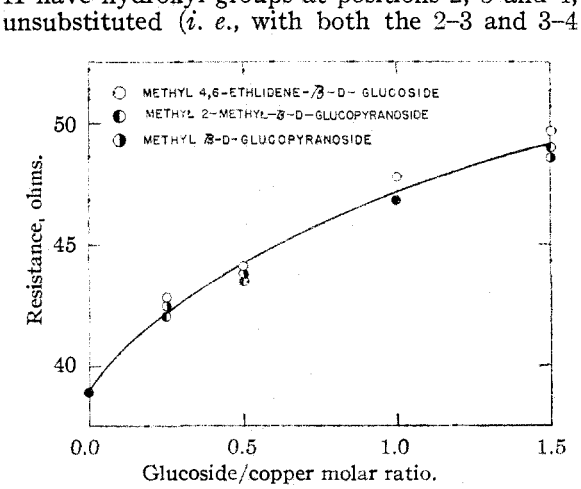

Fig. 2.—Resistance *versus* concentration relationships for some glucopyranosides in cupra A.

The group IV substances of Table II include simple alcohols and glucopyranoside derivatives regarded as non-complex forming because of their low rotatory shifts and the small changes in specific resistances. That these values are not zero is believed to be due to the formation of alcoholates between the basic cuprammonium and the secondary alcohol groups. Although they may be a particular form of bivalent alcoholate, complexes show a more pronounced increase in resistance and the effect increases more rapidly with increasing concentration than is the case in the reaction between cuprammonium and non-complex forming alcohols.

All the glucosides substituted to restrict complex formation to the 2–3 position showed marked evidence of reaction with cuprammonium. This behavior would be compatible with ring conformations C1, B2 and 3B. However, three of the sustances, the 4,6-ethylidene and 4,6-benzylidene compounds, could not exist in either the B2 or 3B conformations for steric reasons because of the spatial requirements of the second ring; hence, for these three substances a definite assignment of ring conformation can be made—they must exist in the C1 conformation.

Both of the glucosides substituted to allow complex formation only at the 3–4 position showed marked evidence of complex formation, behavior compatible with ring conformations C1, B1 or 3B.

It is noteworthy that a single conformation, C1, is compatible with the properties of all the complex forming D-glucopyranoside derivatives here examined. Furthermore this is the form which has been assigned to the D-glucopyranoside units of cellulose[4] and sucrose[5] which have been examined by physical methods in the crystalline state. Cox[6] has listed some reasons for believing

(4) W. T. Astbury and M. M. Davies, *Nature*, **154**, 84 (1944).
(5) C. A. Beevers and W. Cochran, *ibid.*, **157**, 872 (1946).
(6) E. G. Cox, T. H. Goodwin and A. I. Wagstaff, *J. Chem. Soc.* 1495–1504, (1935).

TABLE III

SPECIFIC ROTATION OF SOME D-GLUCOPYRANOSIDES IN WATER AND IN CUPRA B

D-Glucopyranoside	M. p., °C.	$[\alpha]^{25}D$ in H_2O c	deg.	$[\alpha]^{25}_{436}$ in H_2O c	deg.	$[\alpha]^{25}_{436}$ in Cupra B[a] c	deg.
Methyl 4,6-dimethyl-β-	67–68[b]	0.92	− 17	0.92	− 33	0.47	−920
Methyl 4,6-benzylidene-β-	202	0.3	− 71	0.3	−146	0.95	−938
Phenyl α-[c]	171–173	1.0	+175	1.0	+353	0.95	+467
Phenyl β-	174–175	1.1	− 65	1.1	−135	1.0	−164
Phenyl 3-methyl-β-	144–145	0.8	− 64	0.6	−124	0.8	−112
Methyl 2,3-dimethyl-α-	84–85	0.7	+154[d]	0.69	+290	0.69	+299
Methyl 2,3-dimethyl-β-	52–53	0.97	− 34	0.72	− 62	0.56	− 66

[a] A standard cuprammonium solution containing 15 g. copper, 240 g. ammonia and 1 g. glycerol per liter. [b] Bell and Synge give m. p. 50–52°. See ref. 9. [c] The rotations determined with the monohydrate were recalculated to the anhydrous basis. [d] In acetone.

that glycoside molecules do not readily change from one conformation to another in solution, or even in the change of state, crystalline⇄solution. While it does not seem that the arguments so far advanced against possible interchange of conformation can apply with equal validity to all glucosides and all permutations of conformation changes, nevertheless the data in the glucopyranoside series are consistent with a single conformation persisting in the crystalline state and, at ordinary temperatures, in solution.

Experimental

Resistance measurements were made by the procedure previously described.[7] The readings were plotted against molar concentration of glucoside and the values at 0.01 molar concentration were taken from the smooth curve through the experimental points. The resistances were divided by the cell constant (0.116) to give specific resistance at 25°. The cuprammonium solution used for conductivity measurements, cupra A, contained 0.01 mole copper, 3 moles ammonia and 10 ml. ethanol per liter. It had a specific resistance of 336 ohm, cm. at 25°.

Melting points were measured between crossed polaroids in a Fisher–Johns melting point apparatus drilled to allow the passage of a 1 mm. beam of light.

Optical rotations were measured in a Gaertner polarimeter with the mercury blue line (436 mμ) or the sodium D line, as indicated. The cuprammonium solution used for optical measurements, cupra B, contained 15 g. copper, 240 ± 5 g. ammonia and 1 g. glycerol per liter. Copper to glucoside ratios of approximately 7:1 were employed to ensure essentially complete reaction between cuprammonium and the complex forming glucosides. The blue line specific rotations not previously recorded are given in Table III together with melting points and D line rotations which identify the substances and establish the purity of the preparations employed.

Methyl 2,3-di-N-phenylcarbamyl-4,6-dimethyl-β-D-glucoside was prepared from four grams of the methyl 2,3-di-N-phenylcarbamyl-β-glucoside[8] by methylation with methyl iodide and silver oxide in the presence of anhydrous calcium sulfate and dry acetone. After several recrystallizations from alcohol the product melted at 222–225°, $[\alpha]^{25}D$ −12° (*c* 2.5, acetone). It was dried at 78° in vacuum over phosphoric anhydride for analysis.

Anal. Calcd. for $C_{23}H_{28}O_8N_2$ (460.47): C, 59.99; H, 6.13. Found: C, 59.98; H, 6.16.

Methyl 4,6-dimethyl-β-glucoside was prepared by hydrolyzing 377 mg. of the above substance with barium hydroxide for four hours in boiling dilute ethanol. Carbon dioxide was passed through the solution which was then filtered and evaporated to dryness *in vacuo*. The residue was taken up in warm acetone which left 171 mg. residue on evaporation of the solvent. This material was distilled at 0.2 mm. pressure at 100° and the distillate crystallized on the condenser. At first the product melted at 52–55°, but on standing a higher melting form, m. p. 65–67°, appeared, and on recrystallization from a mixture of ether and petroleum ether the substance melted sharply at 67–68°. The high melting form was not hygroscopic. Its optical rotation in chloroform was $[\alpha]^{25}D$ −27° (*c* 0.92). Bell and Synge[9] give m. p. 50–52°, $[\alpha]D$ −28.8° (chloroform) for this substance.

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Summary

Consideration of the properties of seventeen D-glucopyranoside derivatives has led to the conclusion that, in this series, complex formation between cuprammonium and two hydroxyl groups occurs only with the glycol on the second and third or third and fourth carbon atoms.

Consideration of the behavior of twelve complex-forming glucosides in the light of a previously presented theory reduces from eight to not more than three the number of conformations which need be considered to represent the shape of the pyranoside ring of each glucoside in solution; for three of the substances only one ring conformation appears to be possible. It is noted that a single ring conformation, the *trans* "chair form" in which the ring oxygen and 6-carbon atom project on the same side of the plane of the 1,2,4,5-carbon atoms, is sufficient to explain the behavior of all the complex forming glucosides in solution.

Methyl 2,3-di-N-phenylcarbamyl-4,6-dimethyl-β-D-glucoside has been prepared and a higher-melting form of methyl 4,6-dimethyl-β-D-glucoside has been described.

A symbol has been assigned to each of the eight pyranose strainless ring conformations.

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

(8) W. M. Hearon, G. D. Hiatt and C. R. Fordyce, *ibid.* **66**, 995 (1944).

(9) D. J. Bell and R. L. M. Synge, *J. Chem. Soc.*, 1711 (1937).