Rotatory Dispersion and Stereochemistry of Organic Compounds. IV. On the Optical Rotatory Contribution of Hydroxyl Groups in Glucose. (Preliminary Report)*

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The rotatory dispersion of hydroxy compounds usually shows plain curves, so that the configurational environments around the asymmetric center can not be revealed by the curves. Therefore, it would be desirable to convert the hydroxyl group to one which exhibits a Cotton effect in a convenient spectral region.

The chromophore C=S, one of the most suitable for this purpose, was introduced by Tschugaeff[1] in the form of xanthates and dithiourethans; it has already been experimentally demonstrated by Lowry[2] to produce anomalous rotatory dispersion, and later Fredga[3] and Djerassi et al.[4] successfully applied it to a number of hydroxy acids.

In the present investigation, the authors have prepared various derivatives of D-glucose containing such a chromophore, namely 1,2-5,6-*O*-diisopropylidene-D-glucofuranose-3-(*S*-methyl)-xanthate (II), μ-thioglucoxazoline (III),

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* I. This Bulletin, **11**, 586 (1936); II. *Sci. Pap. Inst. Phys. Chem. Res.* (*Tokyo*), No. 890, Vol. **35**, 425 (1939); III. ibid., No. 901, Vol. **36**, 31 (1939).

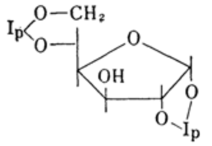
[1] L. Tschugaeff, *Ber.*, **42**, 2244 (1909); L. Tschugaeff and A. Ogorodnikoff, *Z. physik. Chem.*, **74**, 503 (1910) and later papers.

[2] T. M. Lowry and H. Hudson, *Phil. Trans. Roy. Soc. London*, **A232**, 117 (1933).

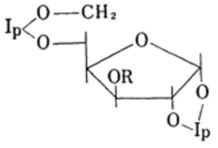
[3] A. Fredga, *Svensk. Kem. Tidskr.*, **53**, 221 (1941); **54**, 26 (1942).

[4] C. Djerassi, "Optical Rotatory Dispersion", McGraw-Hill Book Co., New York, N. Y. (1960), p. 203.

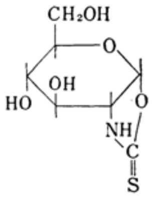
tetraacetyl-μ-thioglucoxazoline (IV), and methyl-2, 3, 4-*O*-triacetyl-α-D-glucopyranosyl-6-(*S*-benzyl)-xanthate (V); the rotatory dispersion was measured with a Rudolph spectropolarimeter at room temperature over the wavelength region of from 300 to 700 mμ, with a view of getting information on the rotatory contribution of the hydroxyl groups in sugars.



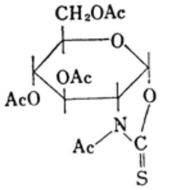
(I) Ip=-CH(CH$_3$)$_2$



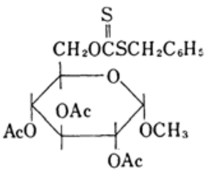
(II) $R=-\underset{\underset{S}{\|}}{C}-SCH_3$



(III)



(IV) Ac=-COCH$_3$



(V)

TABLE I. MEASUREMENT OF RD

Compound	Solvent	Concn. gr./100 cc.	Light source
I	Methanol	1.0304	Zr
II	Methanol	0.1244	Xe
III	Water	1.0132	Xe
IV	Chloroform	0.1240	Xe
V	Chloroform	0.1002	Xe

Results and Discussion

Compound I exhibits a negative, plain, rotatory dispersion curve, since in the measured wavelength region the compounds has no optically-active absorption band (Fig. 1).

C_3–OH, which is the only free hydroxyl group in this compound, has an L-configuration according to the Fischer-Tollens projection formula. The rotatory dispersion curve II of compound II, which was obtained by treating I with metallic sodium, carbon disulfide and methyl iodide in absolute ether, first exhibits a broad extreme (trough) near 500 mμ and then a sharp extreme (peak) near 375 mμ, thus producing an anomalous dispersion curve. The former trough (ca. 550 mμ) is of no special significance, but the latter sharp peak is related to the configuration, judging from its ultraviolet absorption spectrum, which does not exhibit a peak between 400 and 700 mμ.

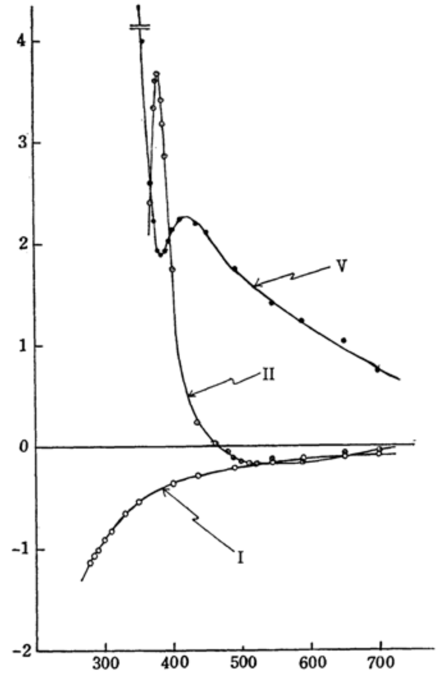


Fig. 1. RD of derivatives of glucose.
○ I, ⊙ II, ● V

The ultraviolet absorption maxima appear at 280 mμ ($\varepsilon=13000$) and at 358 mμ ($\varepsilon=49.21$); the peak at 280 mμ is attributed to the C=S moiety, and the maximum at 358 mμ, to the $-\overset{\overset{S}{\|}}{C}-S-$ group.

The anomalous rotatory dispersion curve is caused by the ultraviolet, optically-active absorption band near 375 mμ due to the $-\overset{\overset{S}{\|}}{C}-S-$ group.

Although no data are available below 370 mμ, because of the difficulty of measurement, the extrapolated curve intersects the abscissa at about 360 mμ, a point which is substantially identical with the wavelength of maximum ultraviolet absorption, 358 mμ.

The positive Cotton effect seen in curve II is considered to be due to the C_3– group of the L-configuration; this would, however, be expected to give a negative partial rotation[5].

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[5] One of the authors has inferred from an analysis of the rotatory dispersion and various experimental facts that the OH group of L-hydroxy acids should contribute to the negative rotation, and has therefore given a rational interpretation to the anomalous behavior of the optical rotation of some hydroxy carboxylic acids. Y. Tsuzuki, *Sci. Pap. Inst. Phys. Chem. Res.* (*Tokyo*), No. 890, Vol. **35**, 425 (1939); No. 901, Vol. **36**, 31 (1939); *J. Chem. Soc. Japan*, (*Nippon Kwagaku Kwaisi*), **64**, 282, 290 (1943); Y. Tsuzuki et al., *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **78**, 764 (1957).

On the contrary, the xanthate group on the hydroxyl of L-types of lactic, malic and mandelic acids is clearly responsible for the positive rotation which has been demonstrated by Tschugaeff[1], by Fredga[3], and particularly by Djerassi's rotatory dispersion studies[4].

The reason for this is not clear; however, the authors think that inversion of the sign of rotation may occur when the order of the magnitude of the substituents attached to the asymmetric center is inverted, such as:

$$\text{COOH} > \text{OH} \quad \text{(negative)}$$

$$\text{COOH} < \text{O–CSSR} \quad \text{(positive)}$$

Thus, the observed rotatory contribution of the C_3 of glucose becomes comprehensible, quite in harmony with the former views and observations.

The rotatory dispersion of III, both in a neutral and in an acidic solution, exhibits obviously single Cotton effect curves (Fig. 2).

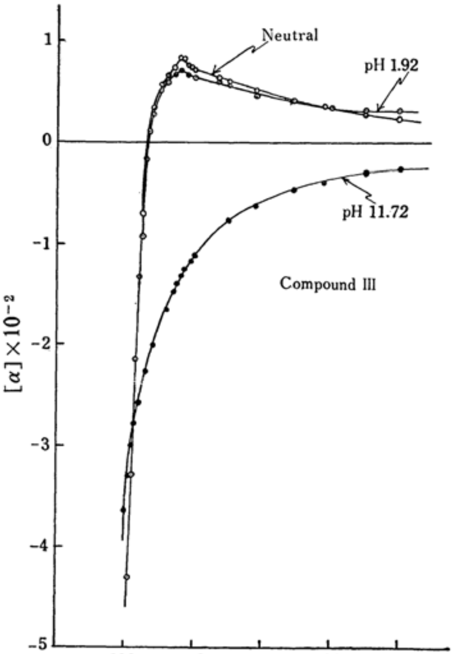
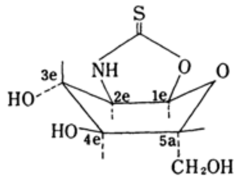


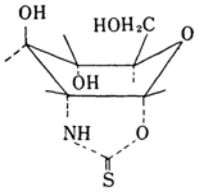
Fig. 2. RD of III.

○ Neutral, ⊙ pH=1.92, ● pH=11.72

However, compound III and its acetyl derivative IV present a complicated and difficult problem for the interpretation of the rotational behavior. Undoubtedly this anomalous dispersion originates in the partial contribution of C_1 and C_2, the possible form of which may be shown as follows (IIIa):



(IIIa)



(IIIb)

The hydrogen atoms directly attached to the ring carbon atoms are ommited for the sake of simplicity. The pyranose must be at the same time of both the α- and the boat forms; otherwise, a five-membered ring including 1- and 2-carbon atoms cannot be formed. All the hydrogen atoms except C_5–H are axial. The alternate boat form, IIIb, in which the oxazoline five-membered ring and the two OH groups are axial is clearly more unstable than IIIa and is therefore to be left out of consideration.

Acetyl derivative IV of compound III also exhibits a single positive Cotton effect, however, with a larger amplitude, as may be seen by a comparison of the RD-curves of III and IV. In compound IV the thion moiety is well preserved even by acetylation, giving a maximum absorption at 345 mμ (ε=35.6) and also a nearly corresponding Cotton effect (zero rotation point at about 385 mμ) (Fig. 3). Compound III shows no ultraviolet maxima, being transparent in this spectral region. This

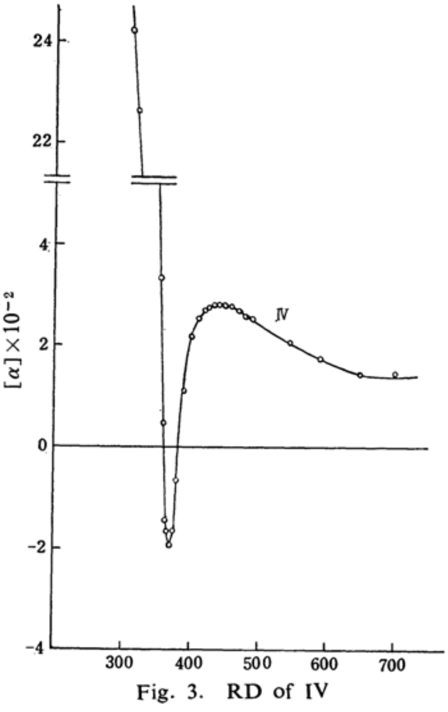


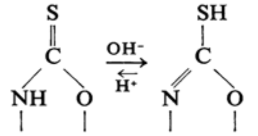
Fig. 3. RD of IV

TABLE II. DISPERSION CONSTANTS FOR GLUCOSE DERIVATIVES

$$[\mathrm{M}]=\frac{A}{\lambda^2-\lambda_0^2}+\frac{B}{\lambda^2}$$

Compound	A	B	λ_0 mμ	Peak		Trough		UV absorption 10^{-2} mol./l.	
				mμ	[M]	mμ	[M]	mμ	ε
II	4.54	−37.82	380	380	321.54	—	—	358	49.21
III neutral	−0.11	27.73	367	385	191.49	—	—	no absorption	
III pH 1.92			308	380	154.76	—	—	no absorption	
III pH 11.72	−25.62	0.893	243	—	—	—	—	240~245	
IV	−9.99	280.24	407	445	1104.3	370	−759.17	345	35.65
V	2.53	193.09	399	410	1078.9	385	918.4	358	77.73

compound is considered to be in the non-chromatic μ-thiol form of the following tautomerism:



thion-form thiol-form

In the hydrogen chloride solution (pH=1.92) the rotatory dispersion curve was almost identical with that observed in the neutral solution except that the rotation at the peak is lower. In the sodium hydroxide solution (pH =11.72), the RD curve is shown by a negative plain curve. Thus, it is revealed by these curves that the ⟩C=S moiety of compound III has no influence on the thion-thiol equilibrium when acidic, but in an alkaline solution the equilibrium is displaced so completely towards the enol form that the optically-active absorption band disappears and only a negative plain dispersion curve is obtained. This somewhat unexpected feature may be due to the basic rotation of the boat form.

Compound V, in which C_6 is benzylated, exhibits a rotatory dispersion curve with an obvious single positive Cotton effect near 400 mμ; however, the amplitude is small. This Cotton effect is responsible for the partial contribution of the C_5- carbon. The small amplitude implies that the effect of benzyl xanthate is lessened considerably by the intervention of the C_6-methylene group. The positive sign of this small Cotton effect is in harmony with the L-type of the C_5-$CH_2OCSCH_2C_6H_5$ group, namely, the inversion of the sign of rotation. The ultraviolet absorption maximum of compound V was found to be 358 mμ (ε=77.7), in chloroform, which absorption is responsible for the –C–S– group, perhaps being optically active. The basically strong positive rotation, the peak of which is presumably below 250 mμ, is no doubt related to the D-type of C_1-configuration (α-D-glucoside).

On the Two-term Drude Equation

It is to be expected that the dispersion data can be expressed by the two-term Drude equation:

$$[\mathrm{M}]=\frac{A_1}{\lambda^2-\lambda_1^2}+\frac{A_2}{\lambda^2-\lambda_2^2}$$

and that the physical meaning of the values of λ_1 and λ_2 can be interpreted with relation to the chromophores of the molecules; however, for the sake of simplicity the authors have attempted for the present to see whether the experimental data conform to the following abbreviated two-term expression:

$$[\mathrm{M}]=\frac{A}{\lambda^2-\lambda_0^2}+\frac{B}{\lambda^2}$$

The first term depends on a particular chromophore, while the second term is concerned with the sum of all the other chromophores or with the remainder of the molecule. The calculations were carrried out by means of the least square method with an electronic computer. The results are shown in Table II.

It may be seen in Table II that the optically-active absorption band in all cases shifted more or less towards wavelengths longer than the corresponding ultraviolet absorption maximum. The values of A, namely, the partial rotatory contribution of the particular chromophores, is negative in sign, in compounds III and IV, and positive in the others.

Experimental

The derivatives of glucose were prepared according to the methods of the literature.

1,2,5,6-*O*-Diisopropylidene-D-glucofuranose (compound I)⁶⁾; m. p., 108~110°C.

1,2,5,6-*O*-Diisopropylidene-D-glucofuranose-3-(*S*-methyl)-xanthate (compound II)⁷⁾; m. p., 59.8~60.5°C.

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6) E. Fischer and C. Rund, *Ber.*, **49**, 93 (1916).

7) K. Freudenberg and A. Wolf, ibid., **60**, 232 (1927).

μ-Thioglucoxazoline (compound III)[8]; m. p., 172°C.

Tetraacetyl-μ-thioglucoxazoline (compound IV)[8]; m. p., 119~120°C.

Methyl-2, 3, 4-*O*-triacetyl-α-D-glucopyranosyl-6-(*S*-benzyl)-xanthate (compound V)[9]; m. p., 106°C.

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[8] G. Zemlén, A. Grecs and M. Rados, ibid., **69**, 748 (1936).

[9] J. J. Willard and E. Pascu, *J. Am. Chem. Soc.*, **82**, 4347 (1960).