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Stereochemistry of Organic Compounds XXXI¹⁾

On the Optical Contribution and Solvent Effects of Sugar Nitrates Having Fused Rings

Koko SATSUMABAYASHI, Yoko NISHIDA and Kiyoshi TANEMURA

The Nippon Dental University, School of Dentistry at Niigata,
Hamaura-cho, Niigata 951-8580, JAPAN

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In earlier studies²⁻⁴⁾, optical contributions of nitrates of glycosides were reported. It was reported that the C₁-, C₂-, C₃-, C₄-, C₆-nitrates of glycosides show the different optical contributions. These optical contributions are effective for determining the configuration of asymmetric Carbons of glycoses.

In this study, we have investigated the optical contributions as related to solvent dependency of the nitrates of glycosides fused 1,3-dioxane rings. As to the glycosides having the fused rings, Frelek *et al.* made a study of the circular dichroism (CD) from a different aspect⁵⁾. This paper will report data pertaining to chiroptical measurements which have yet to be identified, as well as data obtained by using ethanol as a polar solvent, and tetrahydrofuran (THF) and 1,4-dioxane as non-polar solvents.

For this purpose, measurements were made with these compounds on their rotatory dispersion (RD), the circular dichroism (CD), and the ultraviolet absorption (UV) spectra. In addition, the proton nuclear magnetic resonance (¹H-NMR) spectra were measured in chloroform-*d*.

The following compounds were examined, as listed in **Figure 1** :

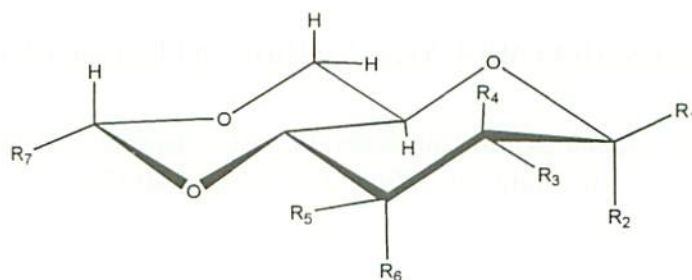
Methyl 4,6-*O*-ethylidene- α -D-mannopyranoside 2,3-dinitrate (Compound **I**),

Methyl 4,6-*O*-ethylidene- α -D-glucopyranoside 2,3-dinitrate (Compound **II**),

Methyl 4,6-*O*-ethylidene- β -D-glucopyranoside 2,3-dinitrate (Compound **III**),

Methyl 4,6-*O*-ethylidene- β -D-glucopyranoside 2-nitrate (Compound **IV**),

Methyl 4,6-*O*-ethylidene- β -D-glucopyranoside 3-nitrate (Compound V),
 Methyl 4,6-*O*-benzylidene- β -D-glucopyranoside 2,3-dinitrate (Compound VI),
 Methyl 4,6-*O*-benzylidene- α -D-glucopyranoside 3-nitrate (Compound VII),
 Methyl 4,6-*O*-benzylidene- α -D-altropyranoside 3-nitrate (Compound VIII),



Compound	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇
I	H	OCH ₃	H	ONO ₂	ONO ₂	H	CH ₃
II	H	OCH ₃	ONO ₂	H	ONO ₂	H	CH ₃
III	OCH ₃	H	ONO ₂	H	ONO ₂	H	CH ₃
IV	OCH ₃	H	ONO ₂	H	OH	H	CH ₃
V	OCH ₃	H	OH	H	ONO ₂	H	CH ₃
VI	OCH ₃	H	ONO ₂	H	ONO ₂	H	C ₆ H ₅
VII	H	OCH ₃	OH	H	ONO ₂	H	C ₆ H ₅
VIII	H	OCH ₃	H	OH	H	ONO ₂	C ₆ H ₅

Figure 1. Compounds I~VIII examined.

Results and Discussion

The RD, CD and UV curves of Compounds I~VIII are shown in Figures 2~9 in ethanol, THF, and dioxane respectively. The data of RD, CD and UV are summarized in Table 1. Figures 10~13 show the CD curves of all the compounds compared with three typical solvents by reference to several compounds.

As may be seen in Figures 2 and 3, the first Cotton Effects on Compound I are positive around 260 nm, while its Effects on Compound II are negative. In the cases of α -anomer, the Cotton Effect of C₃-ONO₂ with equatorial configuration attributes to the positive sign (Compound VII), and its Effect of C₃-ONO₂ with axial configuration attributes to the negative sign (Compound VIII). The C₂-configuration of Compound

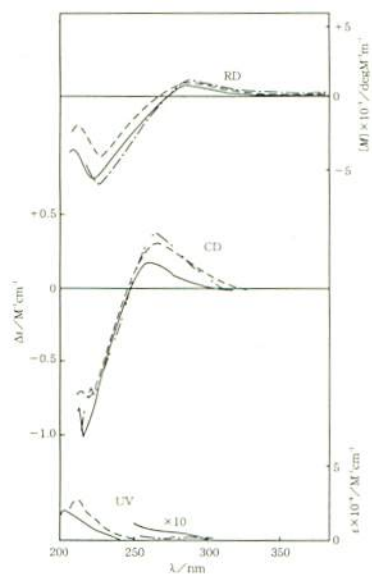


Figure 2. RD, CD and UV of I (— in ethanol, in THF, --- in dioxane).

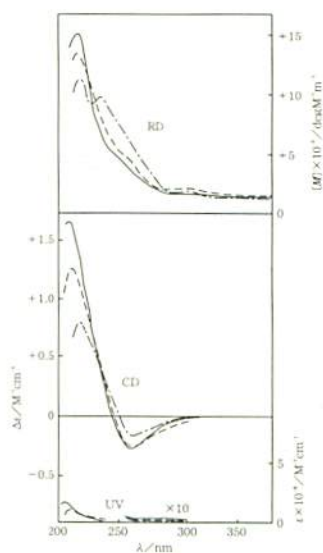


Figure 3. RD, CD and UV of II (— in ethanol, in THF, --- in dioxane).

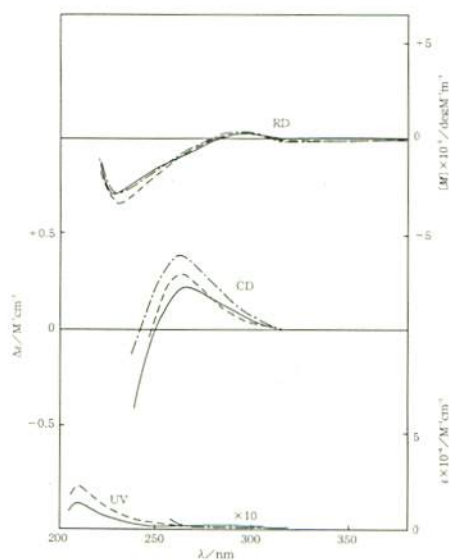


Figure 4. RD, CD and UV of III (— in ethanol, in THF, --- in dioxane).

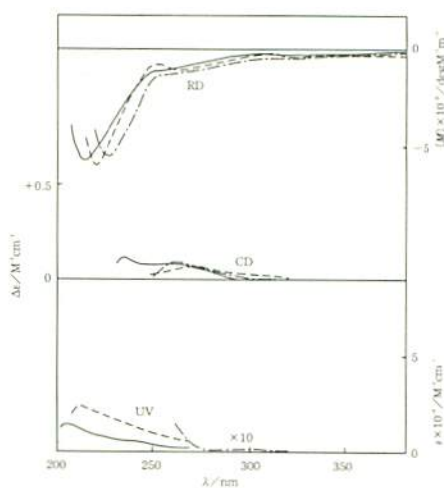


Figure 5. RD, CD and UV of IV (— in ethanol, in THF, --- in dioxane).

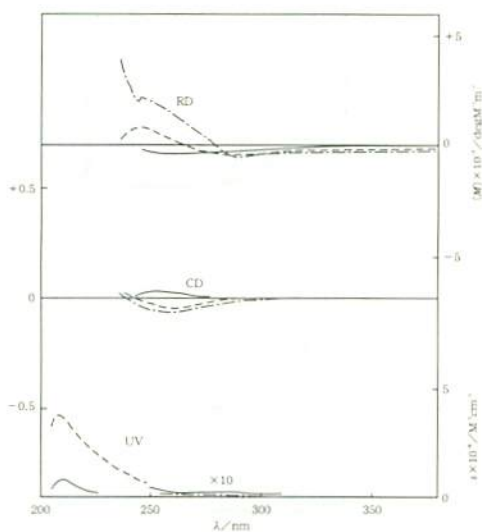


Figure 6. RD, CD and UV of V (— in ethanol, in THF, --- in dioxane).

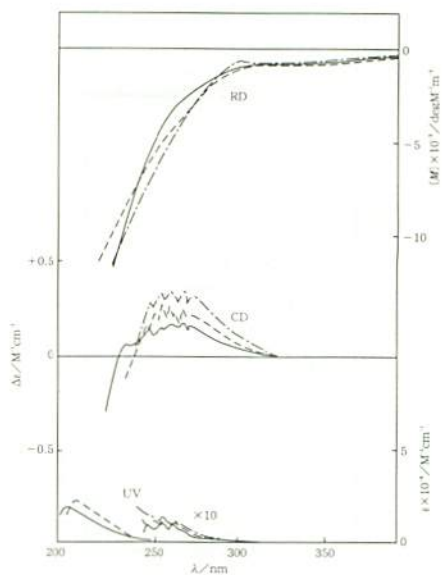


Figure 7. RD, CD and UV of VI (— in ethanol, in THF, --- in dioxane).

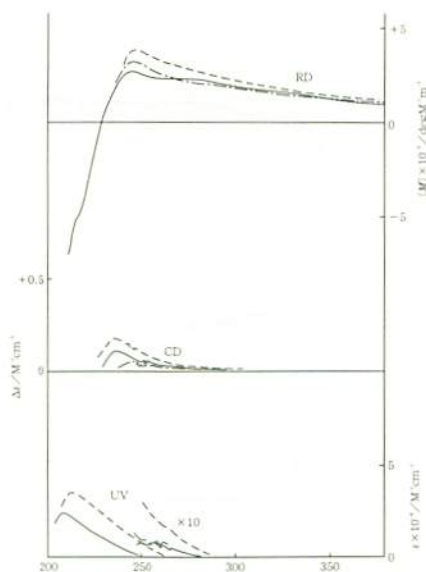


Figure 8. RD, CD and UV of VII (— in ethanol, in THF, --- in dioxane).

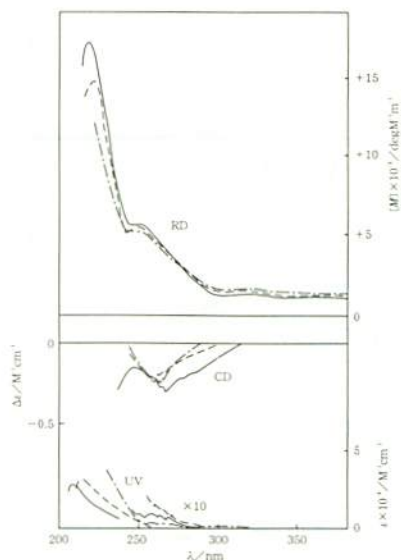


Figure 9. RD, CD and UV of VIII (— in ethanol, in THF, --- in dioxane).

Table 1 Data of CD, RD and UV spectra

Compound	spectrum	solvent	$\lambda_{\max}/\text{nm}(\Delta\epsilon/\text{M}^{-1}\text{cm}^{-1}; [\text{M}]/\text{deg M}^{-1}\text{m}^{-1}; \epsilon/\text{M}^{-1}\text{cm}^{-1})$
I	CD	ethanol	260(+0.197), 216(-1.04)
		THF* ¹	264(+0.328), 220(-0.761)
		dioxane	264(+0.384), 223(-0.742)
	RD	ethanol	286(+800), 224(-5720)
		THF	287(+1140), 228(-4050), 212(-1930)
		dioxane	287(+1150), 226(-6030)
	UV	ethanol	292-260(306-689, shoulder), 202(18100)
		THF	212(26900)
		dioxane	290(29.3), 282(31.6), 274-264(39.3-49.1, shoulder)
II	CD	ethanol	260(-0.288), 206(+1.69)
		THF	260(-0.272), 210(+1.28)
		dioxane	262(-0.167), 218(+0.827)
	RD	ethanol	310(+1680, I* ²), 240(+7350, I), 214(+15500)
		THF	310(+1990, I), 260(+4260, I), 214(+13800)
		dioxane	310(+1770, I), 234(+10100), 218(+11700)
	UV	ethanol	300-256(23.8-131, shoulder), 202(17900)
		THF	288-268(15.2-31.5, shoulder), 208(10100)
		dioxane	296-278(12.4-19.5, shoulder)
III	CD	ethanol	265(+0.211)
		THF	263(+0.293)
		dioxane	262(+0.391)
	RD	ethanol	297(+252), 228(-3090)
		THF	295(+485), 232(-3460)
		dioxane	294(+487), 230(-2990)
	UV	ethanol	300-260(41.8-93.0, shoulder), 208(13200)
		THF	210(22200)
		dioxane	296-278(12.3-27.4, shoulder)
IV	CD	ethanol	262(+0.0788), 232(+0.113)
		THF	265(+0.0545)
		dioxane	260(+0.0808)
	RD	ethanol	335(-351), 300(-220), 248(-1060), 214(-5940)
		THF	320(-510), 310(-106), 258(-1060), 250(-792), 220(-6070)
		dioxane	322(-412), 305(-330), 250(-1370), 226(-5600)
	UV	ethanol	204(14200)
		THF	210(23900)
		dioxane	300-276(8.15-20.6, shoulder)
V	CD	ethanol	250(+0.0280)
		THF	260(-0.0533)
		dioxane	258(-0.0663)
	RD	i-PrOH	264(+0.0355)
		ethanol	256(-354)

		THF	292(-470), 230(+710)
		dioxane	288(-504), 245(+2160)
		i-PrOH	328(-221), 298(-194)
	UV	ethanol	308-260(85.8-257, shoulder), 210(7820)
		THF	210(37300)
		dioxane	312-270(85.2-104, shoulder),
		i-PrOH	280-265(15.7-28.3, shoulder), 204(12500)
VI	CD	ethanol	268(+0.162), 264(+0.180), 258(+0.170), 253(+0.155), 246(+0.132), 234(+0.0767)
		THF	268(+0.228), 265(+0.256), 258(+0.256), 254(+0.289), 250(+0.236), 245(+0.164)
		dioxane	270(+0.327), 266(+0.348), 259(+0.348), 254(+0.331), 248(+0.273)
	RD	ethanol	320(-840), 307(-807)
		THF	318(-926), 304(-878)
		dioxane	320(-777), 294(-651)
	UV	ethanol	266(625), 262(852), 256(938), 248(873), 204(17300)
		THF	266(812), 262(1060), 256(1160), 250(1110), 210(21700)
		dioxane	266(796), 260(1150), 256(1370), 250(1450)
VII	CD	ethanol	236(+0.105)
		THF	236(+0.171)
		dioxane	244(+0.0487)
	RD	ethanol	274(+2130, I), 242(+2600), 216(-5080, I)
		THF	282(+2690, I), 244(+3890)
		dioxane	280(+2090, I), 244(+3270)
	UV	ethanol	268(368), 262(596), 258(710), 250(608), 208(22100)
		THF	262(1650), 258(2070), 212(35000)
		dioxane	268(450), 262(729), 258(804), 250(879)
VIII	CD	ethanol	282(-0.191), 276(-0.225), 266(-0.309), 262(-0.291), 256(-0.236)
		THF	258(-0.226)
		dioxane	262(-0.252)
	RD	ethanol	324(+1310, I), 250(+5660), 216(+18100)
		THF	318(+1470, I), 250(+5460), 220(+14900)
		dioxane	315(+1550, I), 250(+5130, I)
	UV	ethanol	322-302(17.8-28.8, shoulder), 292-276(155-238, shoul- der), 268(606), 262(868), 258(975), 250(904), 208(28200)
		THF	268(861), 263(1230), 258(1510), 212(32400)
		dioxane	296-278(31.6-46.2, shoulder), 268(266), 264(355), 258(354), 252(477)

*¹Tetrahydrofuran, *²Inflection point. *³isopropyl alcohol(2-propanol).

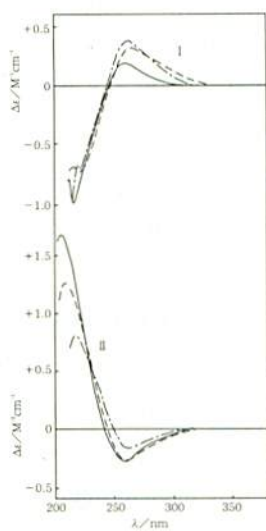


Figure 10. CD of I and II in ethanol, THF and dioxane (— in ethanol, in THF, --- in dioxane).

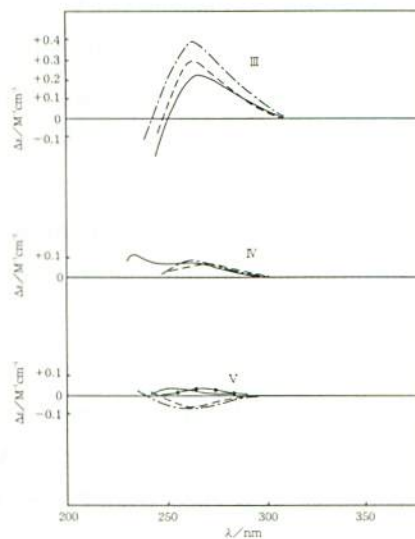


Figure 11. CD of III and IV in ethanol, THF and dioxane; V in ethanol, 2-propanol, THF, and dioxane (— in ethanol, ••• in 2-propanol, in THF, --- in dioxane).

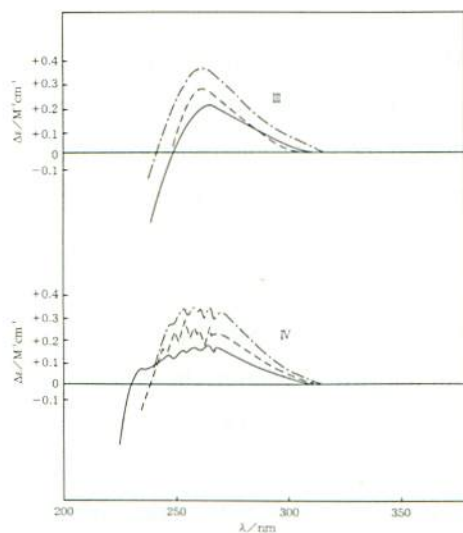


Figure 12. CD of III and VI in ethanol, THF and dioxane (— in ethanol, in THF, --- in dioxane).

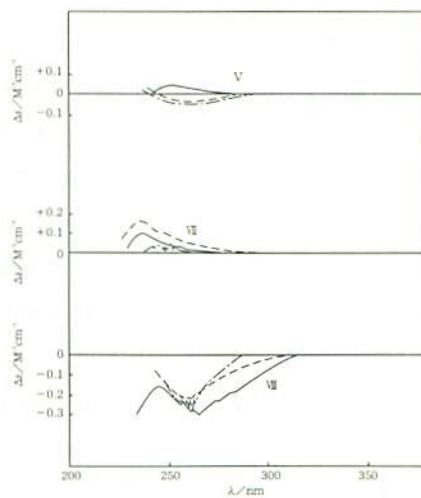


Figure 13. CD of V, VII and VIII in ethanol, THF and dioxane (— in ethanol, in THF, --- in dioxane).

I is axial, while Compound **II**'s C₂-configuration is equatorial. As a result, in the case of α -anomer, the C₂-ONO₂ with axial configuration assigns to the positive.

As to Compound **V**, the strong positive Cotton Effect at 213 nm and shoulder on CD curve around 280 nm in ethanol were reported in a previous communication²⁾. In the present study, the shoulder was confirmed as the weak positive Cotton Effect at 250 nm in ethanol by a detailed CD measurement. As seen in **Figure 6** and **Table 1**, in tetrahydrofuran and dioxane, the first Cotton Effects show negative whose signs reverse in ethanol. Therefore, to confirm the reverse sign of CD bands, 2-propanol, which has a stronger polarity than ethanol, was employed in addition to the three typical solvents. All data is given in **Table 1** together with the other data. As a result, the first weak CD bands of Compound **V** are strongly affected by the different polarity of the solvent as is clear from **Figure 6** and **Table 1**. It is clearly indicated that $\Delta\epsilon$ -values of CD_{max} shifted to the positive by the increase of polarity of solvent, and the sign of the Cotton Effects changed in ethanol and 2-propanol.

As evident in **Figures 8** and **9**, the first Cotton Effects on Compound **VII** show positive sign, while Compound **VIII** shows negative sign. That is, C₃-ONO₂ with equatorial configuration causes a positive Cotton Effect, while an axial configuration causes a negative Cotton Effect.

In **Figure 12**, the CD curves of Compound **III**, which has a methyl group at the fused 1,3-dioxane ring, were compared with Compound **VI**, which has a phenyl group at the fused 1,3-dioxane ring. The CD curve of **VI** indicated the vibrational and broad pattern that result from the benzene ring attached to the asymmetric carbon in the 1,3-dioxane ring. However, the sign and strength of Cotton Effect are almost equal. This is supported by the 1,3-dioxane ring introduced C-nitroalcohols⁶⁾.

The optical contribution and rotatory strength of the asymmetric carbons in pyranose decrease with increasing distance from the ring oxygen in the order of C₁ > C₂ > C₃ > C₄. It follows that the $\Delta\epsilon$ -values of CD_{max} of Compound **IV** is larger than that of Compound **V**. As a whole, however, the optical contribution of Compounds **IV**, **V** and **VII** are smaller than the other compounds. It is obvious that $\Delta\epsilon$ -values of CD_{max} are quite different in magnitude; that is, the values for Compounds **IV**, **V** and **VII** are less than a third of each of the other compounds. In the cases of pyranosides fused six membered rings, when a nitrate group was arranged at C₂- or C₃-equatorial position,

it is considered that the asymmetry effect decreases by the increasing of symmetry in the molecule.

In order to investigate the conformation of Compounds **IV** and **V**, geometry optimizations were carried out using the MM2 and the MOPAC calculations. Almost the same structures were introduced by both calculations on the minimized energy. The structures in **Figure 14** represent the lowest energy conformations. It is clear that C_2 -ONO₂ group of **IV** and C_3 -ONO₂ group of **V** are situated in positions which orient the opposite direction against condensed rings.

According to the above results and the previous communications^{2,3)}, the optical contributions to the first Cotton Effects of C_2 -ONO₂ and C_3 -ONO₂ in the non-polar solvents are summarized in **Table 2**.

On the basis of **Table 2**, we discuss Cotton Effects of the 2,3-dinitrates on Compounds **I**, **II**, **III** and **VI**.

First of all, α -anomers are examined according to the results of **Table 2**. Compound

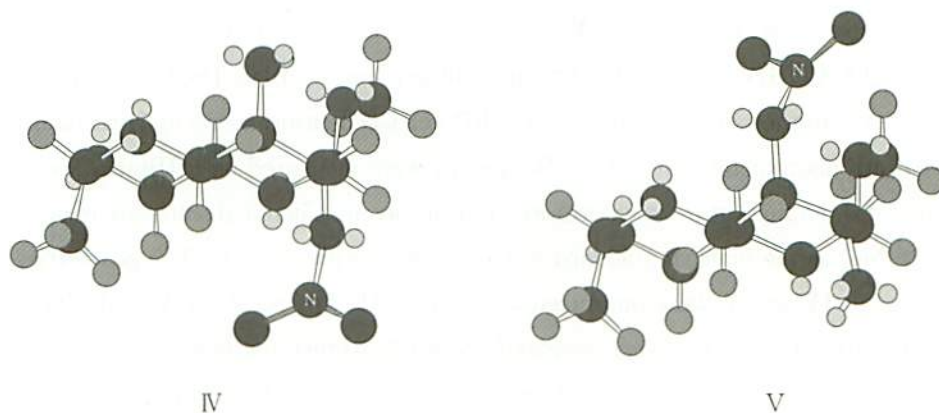


Figure 14. Optimized geometries of **IV** and **V**.

Table 2 The sign of first Cotton Effect at C_2 and C_3 .

Chiral Center Configuration	C_2		C_3	
	axial	equatorial	axial	equatorial
α -Glycoside	+	-	-	+
β -Glycoside	-	+	+	-

I has axial-configuration of C_2 -ONO₂ and equatorial-configuration of C_3 -ONO₂. Therefore, the positive Cotton Effect of Compound **I** is greater than the positive Cotton Effects of the mononitrates. In the case of Compound **II**, C_2 - and C_3 -ONO₂ are equatorial but with opposite signs. Since the optical contribution of C_2 is greater than C_3 , the overall Cotton Effect of **II** is negative.

Next, β -anomers are examined according to the results of **Table 2**. In the cases of Compounds **III** and **VI**, C_2 - and C_3 -ONO₂ are equatorial but with opposite signs. As a result, Compounds **III** and **VI** are positive because the optical contribution of C_2 is greater than C_3 .

This statement is consistent with the results of the experimental data.

Experimental

Measurements. The RD and CD were measured in ethanol, tetrahydrofuran and dioxane (with Compounds **I**~**IV** and **VI**~**VIII**), and ethanol, tetrahydrofuran, dioxane and 2-propanol (with Compound **V**) at 25°C, in the wavelength region from 200 to 600 nm with JASCO/UV-5 type optical rotatory dispersion recorder. The UV spectra were measured with the same conditions as the RD and CD measurements by Hitachi Model 320 Spectrophotometer. The ¹H-NMR spectra were measured on a Hitachi Model R-24B at room temperature in chloroform-*d* as a solvent. Chemical shifts are in ppm (δ) from SiMe₄ as the internal standard and *J*-values are given in Hz. The geometries of Compounds **IV** and **V** were optimized using the MM2 and the MOPAC calculations.

Materials. The samples were prepared according to then methods of literature⁷⁻¹⁰.

Methyl 4,6-*O*-ethylidene- α -D-mannopyranoside 2,3-Dinitrate (Compound **I**)⁷. White crystals, mp 72-73°C; ¹H-NMR δ =1.26-1.34 (3H, d, *J*=5.2Hz), 3.40 (3H, s), 3.56-4.16 (4H, m), 4.59-4.82 (2H, m), 5.38-5.62 (2H, br s).

Methyl 4,6-*O*-ethylidene- α -D-glucopyranoside 2,3-Dinitrate (Compound **II**)⁷. Colorless needles, mp 100-101°C; ¹H-NMR δ =1.27-1.35 (3H, d, *J*=5.2Hz), 3.39 (3H, s), 3.62-4.24 (4H, m), 4.54-4.80 (1H, q, *J*=5.1Hz), 4.84-5.10 (2H, m), 5.40-5.74 (1H, br s).

Methyl 4,6-*O*-ethylidene- β -D-glucopyranoside 2,3-Dinitrate (Compound **III**)⁷. Colorless needles, mp 88-89°C; ¹H-NMR δ =1.31-1.39 (3H, d, *J*=5.6Hz), 2.92-3.02 (1H, d, *J*=3.6Hz), 3.16-3.86 (3H, m), 3.46 (3H, s), 4.08-5.12 (4H, m).

Methyl 4,6-*O*-ethylidene- β -D-glucopyranoside 2-Nitrate (Compound **IV**)⁸⁾. Colorless needles, mp 143-144°C; ¹H-NMR δ = 1.26-1.34 (3H, d, J = 5.8Hz), 3.34-3.74 (4H, m), 3.48 (3H, s), 4.08-5.48 (5H, m).

Methyl 4,6-*O*-ethylidene- β -D-glucopyranoside 3-Nitrate (Compound **V**)⁸⁾. Colorless needles, mp 145-146°C; ¹H-NMR δ = 1.24-1.32 (3H, d, J = 5.6Hz), 2.61-2.68 (1H, d, J = 3.8Hz), 3.26-3.70 (3H, m), 3.49 (3H, s), 4.12-4.38 (3H, m), 4.50-4.74 (1H, q, J = 5.1Hz), 4.90-5.54 (2H, m), 5.08-5.90 (1H, br s).

Methyl 4,6-*O*-benzylidene- β -D-glucopyranoside 2,3-Dinitrate (Compound **VI**)⁹⁾. Colorless prisms, mp 163°C; ¹H-NMR δ = 3.48 (3H, s), 3.60-3.94 (3H, m), 4.28-4.54 (2H, m), 5.46 (1H, s), 7.30 (5H, s).

Methyl 4,6-*O*-benzylidene- α -D-glucopyranoside 3-Nitrate (Compound **VII**)⁷⁾. Colorless crystals, mp 168-169°C; ¹H-NMR δ = 2.18-2.36 (1H, br s), 3.44 (3H, s), 3.78-4.36 (5H, m), 4.77-4.83 (1H, d, J = 4.2Hz), 5.30-5.60 (1H, m), 5.46 (1H, s), 7.34 (5H, s).

Methyl 4,6-*O*-benzylidene- α -D-altropyranoside 3-Nitrate (Compound **VIII**)¹⁰⁾. Colorless prisms, mp 165°C; ¹H-NMR δ = 2.26-2.37 (1H, d, J = 6.4Hz), 3.38 (3H, s), 3.71-4.39 (6H, br s), 4.59-4.62 (1H, d, J = 2.0Hz), 5.38 (1H, br s), 5.56 (1H, s), 7.35 (5H, s).

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