$C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.66. Found: C, 56.74; H, 7.08; N, 17.05.

In another similar run, the oil obtained after washing the initial ether solution of the product with water was recrystallized from ether at −70 °C to give 4.7 g of white crystals, mp 63–75 °C. Fractional crystallization of this from ether gave **13**, mp 62–63 °C (impure, see below), and **14**, mp 119–119.5 °C, as the more and less soluble components, respectively (see Table I). **14**: Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.66. Found: C, 56.4; H, 7.1; N, 16.5. **13**: NMR, mass, and IR spectra suggested that the sample contained (about 20%) **14** as an impurity.

1,2-Dichlorocyclobutane-1,2-dicarbonitrile. A solution of 7.1 g (0.1 mol) of chlorine in 150 mL of carbon tetrachloride was stirred at room temperature while 10.4 g of **1** was added slowly. After 16 h, reaction was only ca. 50% complete (VPC); another 10 g of chlorine was added. After another 18 h (VPC showed that reaction was 91% complete), the reaction solution was evaporated. The residual colorless oil, 20 g, was recrystallized from ethanol at −70 °C to give *trans*-1,2-dichlorocyclobutane-1,2-dicarbonitrile, mp 73–75 °C.[19]

Addition of Hydrogen Chloride to Cyclobutene-1,2-dicarbonitrile. A solution of 50 g of **1** in 250 mL of chloroform was stirred under nitrogen with water-bath cooling while hydrogen chloride was introduced slowly. Monitoring by VPC and NMR showed that the reaction was complete in a few hours. After a short time, a white solid began appearing. After 45 h, the mixture was filtered under nitrogen, and the solid was washed well with chloroform and ether (yield 16.7 g): IR (KBr) 3320 (NH), 2670 (~N·HCl?), 1785, 1700 (C=O), 1590 cm^{-1} (C=N). A small sample was recrystallized from a mixture of chloroform and ether at −70 °C (under nitrogen) to give white crystals: mp 200–205 °C; IR (KBr) 2800–3300 (broad, strong, acid?), 1785 and 1700 (imide or anhydride C=O?), ca. 1640, 1168 cm^{-1}. Anal. Found: C, 36.12; H, 3.69; Cl, 35.9; N, 4.13.[21] A small sample of the (unrecrystallized) solid, 2.9 g, dissolved immediately in 3 mL of water, accompanied by a copious evolution of hydrogen chloride and a strong exotherm. After heating for 1 h at 100 °C, cooling gave 0.13 g of ammonium chloride; another 0.60 g of the salt was recovered by addition of isopropyl alcohol and ether to the aqueous filtrate.

After removal of the solid reaction product, the chloroform solution was washed four times with water, dried ($MgSO_4$), and distilled in vacuo through a Claisen head to give 42 g of 1-chlorocyclobutane-1,2-dicarbonitrile, bp 100 °C (0.7 mm).[22]

Registry No.—**1**, 3716-97-0; **2**, 23335-15-1; **3**, 1128-10-5; **4**, 16508-05-7; **5**, 61812-58-6; **6**, 61812-59-7; **7**, 61812-60-0; **9**, 61812-61-1; **9** HCl, 61812-62-2; **10**, 18329-03-8; **11**, 6652-02-4; **12**, 52903-54-5; **13**, 61812-63-3; **14**, 61812-64-4; **15**, 61812-65-5; **16**, 61812-66-6; piperidine, 110-89-4; dimethylamine, 124-40-3; glutaric acid, 110-94-1; methanol, 67-56-1; *trans*-1,2-dichlorocyclobutane-1,2-dicarbonitrile, 52477-39-1; chlorine, 22537-15-1; HCl, 7647-01-0; *cis*-1-chlorocyclobutane-1,2-dicarbonitrile, 61812-67-7; *trans*-1-chlorocyclobutane-1,2-dicarbonitrile, 61812-68-8; *cis*-1,2-dichlorocyclobutane-1,2-dicarbonitrile, 52477-38-0.

References and Notes

(1) J. L. Greene, N. W. Standish, and N. R. Gray, U.S. Patent 3 275 676 (1966).
(2) D. Belluš, K. von Bredow, H. Sauter, and C. D. Weis, *Helv. Chim. Acta*, **56**, 3004 (1973).
(3) R. L. Cobb and J. E. Mahan, unpublished.
(4) (a) D. Belluš and C. D. Weis, *Tetrahedron Lett.*, **12**, 999 (1973); (b) D. Belluš and G. Rist, *Helv. Chim. Acta*, **57**, 194 (1974); (c) D. Belluš, H.-C. Mez, G. Rihs, and H. Sauter, *J. Am. Chem. Soc.*, **96**, 5007 (1974); (d) D. Belluš, H.-C. Mez, and G. Rihs, *J. Chem. Soc., Perkin Trans. 2*, 884 (1974).
(5) F. B. Kipping and J. J. Wren, *J. Chem. Soc.*, 1628 (1933).
(6) R. C. Fuson and W. E. Lundquist, *J. Am. Chem. Soc.*, **60**, 1889 (1938).
(7) (a) T. Mukaiyama, S. Aizawa, and T. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **40**, 2641 (1967); (b) R. Gompper, W. Elser, and H. J. Mueller, *Angew. Chem., Int. Ed. Engl.*, **6**, 453 (1967).
(8) F. W. Starks, U.S. Patent 3 254 091 (1966).
(9) The product was not investigated, but the presence of strong "cyano enamine" absorption in the infrared region (at 2180 and 1630 cm^{-1}) supported the formation of 2-(1-piperidino)acrylonitrile.
(10) J. Ficini and A. M. Tonzin, *Bull. Soc. Chim. Fr.*, 2385 (1972), and subsequent papers.
(11) M. E. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959); cf. ref 10.
(12) Ammonia itself, under mild conditions, was essentially unreactive toward **1**; ammonia with **3** reportedly gave diamide **2** with no addition to the double bond.[13]
(13) H. Prinzbach and H.-D. Martin, *Chimia*, **23**, 37 (1969).
(14) G. A. R. Kon and B. L. Nandi, *J. Chem. Soc.*, 1628 (1933).
(15) Previous workers isolated only the trans product from the reaction of the diester with bromine.[5]
(16) Melting points (uncorrected) were determined on a Mel-Temp apparatus; IR spectra were recorded on a Perkin-Elmer Model 137 Infracord; NMR spectra were determined (vs. Me_4Si) on Varian T60 and XL 100 instruments.
(17) While elemental analyses were not entirely satisfactory, these with supporting spectral data clearly established the assigned structure.
(18) Elemental analyses agreed as well as would be expected for the dihydrate of such a moisture-sensitive material. Anal. Calcd for $C_{10}H_{14}N_2 \cdot HCl \cdot 2H_2O$; C, 51.17; H, 8.16; N, 11.93; Cl, 15.10. Found: C, 51.6; H, 7.0; N, 13.7; Cl, 16.2.
(19) This material was identical with authentic *trans*-1,2-cyclobutane-1,2-dicarbonitrile prepared by chlorination of cyclobutane-1,2-dicarbonitrile.[2,3,20]
(20) J. L. Greene, J. D. Idol, and N. W. Standish, U.S. Patent 3 454 618 (1969).
(21) These results correspond to an empirical formula of $C_6H_7Cl_2N_{0.5}O_{2.5}$. Anal. Calcd: C, 36.58; H, 3.58; Cl, 35.99; N, 3.55. Partial hydrolysis of the moisture-sensitive salt, perhaps **17** or **18**, introduced oxygen-containing derivatives as impurities.
(22) Identical (by VPC) with material prepared by chlorination of cyclobutane-1,2-dicarbonitrile.[2,3,20]

A Rationalization on the Relative Thermodynamic Stabilities of Fused Five-Membered Tetrahydrofurans with Epimerizable Substitutents. An Anomeric Effect in Furanoses

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A rationalization on the fact that the thermodynamically more stable isomers of fused five-membered tetrahydrofuran derivatives with epimerizable substituents are generally not the expected exo isomers but the endo isomers is proposed. The fact that 2,3-*O*-isopropylidene or benzylidene furanoses exist mainly in the trans-C_1,C_2 configuration should not be explained based on the generally accepted concept that the bicyclo[3.3.0]octane system tends to exist with the fewest possible large endo substituents but should be explained in terms of the anomeric effect.

In this paper, we would like to propose a rationalization on the unexpected fact that the thermodynamically more stable isomers of the fused five-membered tetrahydrofuran derivatives with epimerizable substituents are generally not the exo isomers but the endo isomers.[1] Although the fact was first observed by Ohrui et al.[1] in the field of carbohydrate chemistry, the fact and the rationalization proposed in this paper are believed to be general in organic chemistry.

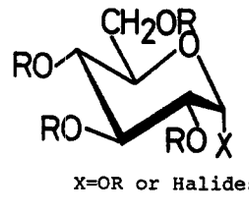

Figure 1.

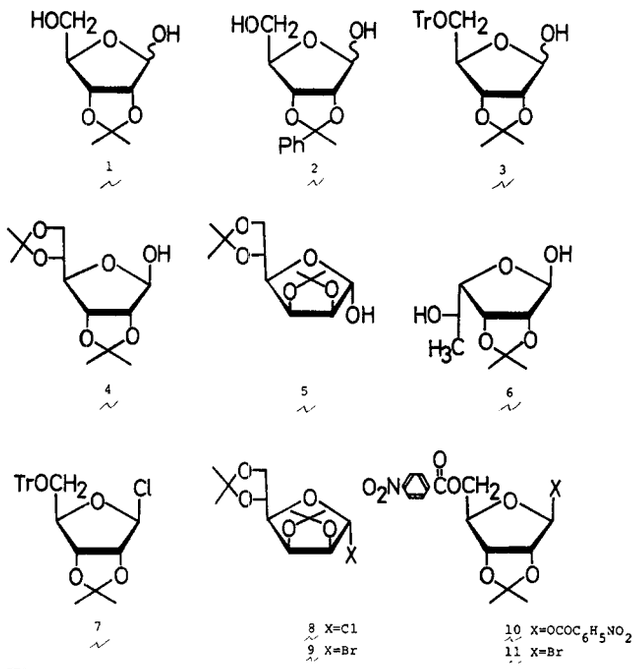

Figure 2.

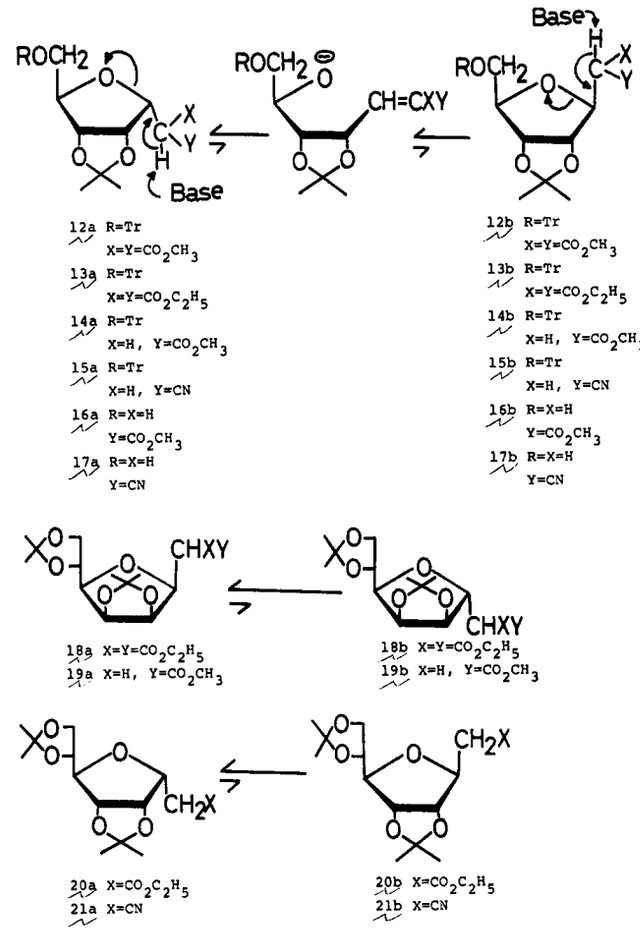

Figure 3.

The anomeric effect[2,3] is a generally recognized phenomenon in the field of conformational analysis of heterocyclic compounds. In carbohydrate chemistry, it is well rationalized by the anomeric effect that such large groups as OR and halides take the axial orientation at the anomeric position of pyranoses. In furanoses, too, several examples of anomeric effect have been reported in the literature.[4-6] However, it is considered that the anomer with a trans-C_1,C_2 relationship is a more favorable configuration in furanoses.[7]

It seems that the trans-C_1,C_2 relationship is the case especially in furanoses of which vicinal 2,3-glycols are protected by forming a 1,3-dioxolane ring. Ample evidences are found in the literature, for example, 2,3-*O*-isopropylidene-D-ribofuranose (1)[8], 2,3-*O*-benzylidene-D-ribofuranose (**2**),[8] 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose (**3**),[1,9a] and 2,3:5,6-di-*O*-isopropylidene-D-allofuranose (**4**)[10] exist primarily in the β form, while 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**5**)[11] and 2,3-*O*-isopropylidene-L-rhamnofuranose (**6**)[11] have the α configuration. The furanosyl chlorides, such as 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl chloride (**7**)[1,9] and 2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl chloride (**8**),[12] have been shown to possess the β and α configurations, respectively, in spite of the fact that they are both prepared using reactions that normally proceed with inversion.[13] It is known[14,15] that the treatment of **5** with *N*-bromosuccimide and triphenylphosphine gives the corresponding α bromide (**9**) and the treatment of 2,3-*O*-isopropylidene-1,5-di-*O*-*p*-nitrobenzoyl-D-ribofuranose (**10**, β:α = 8:1) with hydrogen bromide affords the corresponding β bromide (**11**).

The above trans-C_1,C_2 relationship has been explained by many chemists based on the generally accepted concept that *the bicyclo[3.3.0]octane system tends to exist with the fewest possible large endo substituents.*[16,17]

Very recently, however, Ohrui et al.[1] showed that the base-catalyzed equilibrium of epimerizable 2,3-*O*-isopropylidene-D-furanosyl-*C*-glycosides led to the thermodynamically more stable isomers in which C_1 substituent and the isopropylidene function are in the cis disposition. For example, the base-catalyzed equilibrium of methyl 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl malonate (**12**)[1,9b] gives a 9:1 mixture of methyl 3,6-anhydro-2-deoxy-2-methoxycarbonyl-4,5-*O*-isopropylidene-7-*O*-trityl-D-*altro*-heptonate (**12a**) and -D-*allo*-heptonate (**12b**), through the elimination and recyclization mechanism shown in Figure 3. Many other examples are to be shown; the endo isomers of D-ribofuranosyl *C*-glycosides **13, 14, 15, 16,** and **17,** D-mannofuranosyl *C*-glycosides **18** and **19,** and D-allofuranosyl *C*-glycosides **20** and **21** are thermodynamically more stable than the corresponding exo isomers.

It is clear, therefore, that the generally accepted concept in organic chemistry that *cis fusion of two five-membered rings in the bicyclo[3.3.0]octane system favors the fewest endo substituents is not always the case.*

The factors that makes the endo isomers thermodynamically more stable than the exo isomers in these *C*-glycosyl compounds attracted our attention.

In order to search the forces that stabilize the endo isomers, the conformational analyses of these *C*-glycosyl compounds were undertaken. The chemical shifts and the coupling constants of these *C*-glycosyl compounds are listed in Tables I and II. The ^{1}H NMR spectra of compounds **15a** and **15b** are shown in Figure 4. As can be seen in Table II, the coupling constants of the tetrahydrofuran ring protons of α-D-ribofuranosyl

Table I. 100-MHz Proton Magnetic Resonance Spectra [a]

Compd	Solvent	C_2H	C_2H'	C_3H	C_4H	C_5H	C_6H	C_7H	C_7H'
12a	C_6D_6	4.34 (d)		5.28 (dd)	5.09 (dd)	4.46 (d)	4.27 (m)	3.21 (dd)	3.01 (dd)
12b	C_6D_6	3.85 (d)		4.82 (dd)	4.98 (dd)	4.69 (dd)	4.21 (dt)	3.29 (m)	
13a	C_6D_6	4.29 (d)		5.27 (dd)	5.08 (dd)	4.43 (d)	4.25 (dd)	3.20 (dd)	3.01 (dd)
13b	C_6D_6	ca. 4.0		4.84 (dd)	4.98 (dd)	4.68 (dd)	4.23 (m)	3.32 (m)	
14a	$CDCl_3$	2.75 (d)		4.61 (dt)	4.82 (dd)	4.68 (d)	4.19 (t)	3.27 (dd)	3.09 (dd)
14b	$CDCl_3$	2.62 (dd)	2.78 (dd)	4.31 (dd)	4.63 (dd)	4.55 (dd)	4.13 (ddd)	3.26 (dd)	3.12 (dd)
15a	$CDCl_3$	2.67 (d)		4.50 (dt)	4.79 (dd)	4.71 (d)	4.22 (dd)	3.33 (dd)	3.11 (dd)
15b	$CDCl_3$	2.58 (dd)	2.77 (dd)	4.12 (m)	4.50 (dd)	4.65 (dd)	4.18 (m)	3.33 (dd)	3.21 (dd)
16a	$CDCl_3$	2.72 (d)		4.38 (dt)	4.78 (dd)	4.68 (d)	4.10 (t)	3.60 (d)	
16b	$CDCl_3$	2.56 (dd)	2.74 (dd)	4.24 (ddd)	4.48 (dd)	4.70 (dd)	4.03 (ddd)	3.60 (dd)	3.76 (dd)
17a	$CDCl_3$	2.68 (d)		4.36 (dt)	4.77 (dd)	4.79 (d)	4.16 (dd)	3.65 (m)	
17b	$CDCl_3$	2.67 (dd)[b]	2.85 (dd)[b]	4.10 (m)	4.49 (dd)	4.73 (dd)	4.10 (m)	3.63 (dd)[b]	3.80 (dd)[b]
18a	$CDCl_3$	3.77 (d)		~4.3 (m)	4.90 (dd)	4.74 (dd)	3.51 (dd)	ca. 4.0 (m)	
18b	$CDCl_3$	3.52 (d)		4.60 (d)	4.76 (m)	4.76 (m)		3.8–4.5 (m)	
19a	$CDCl_3$	2.65 (dd)	2.83 (dd)	3.93 (m)	4.76 (m)	4.76 (m)	3.50 (m)	4.38 (ddd)	

[a] Chemical shifts in parts per million from Me_4Si (0), by first-order analysis. [b] After addition of D_2O.

Table II. Coupling Constants (Hz)

Compd	$J_{2,2'}$	$J_{2,3}$	$J_{2',3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{6,7'}$	$J_{7,7'}$
12a		10.5		3.5	6	0	3.5	5	10
12b		7.5		4	6.5	4.5	5	5	
13a		10.5		3.5	6	0	3.5	5	10
13b		7.5		3.5	6.5	5			
14a	0	6.5	6.5	4	6	0	4.5	4.5	10
14b	16	6	6	4	6	3.5	4	4.5	10
15a	0	6.5		3.5	6	0	4	4	10.5
15b	16	5.5	7	4.5	6.5	3.5	4	4	10
16	0	7	7	4	6	0	4.5	4.5	
16b	16	5	6.5	4.5	7	4	3.5	3.5	12
17a	0	7	7	4	6	0	4.5	4.5	
17b	16	5	6	5	6.5	3.5	3.5	4.5	12
18a		10		3.5	6	3	7		
18b		9.5		0		3.5	6		
19a	16	6.5					7		
19b	16	7.5		0	6	3.5	7.5		
22a	0	6.5	6.5						0
22b	16	4.5	5	4.5	6	4	4	4	4

Table IIIA. Dihedral Angles Calculated Based on the Karplus Equations. Endo Isomers of D-Ribofuranosyl Derivative

	Hz	Dihedral angle, deg
$J_{3,4}$	3.5–4	45–48 or 129–132
$J_{4,5}$	6	31 or 144
$J_{5,6}$	0	79 or 100

Table IIIB. Dihedral Angles Calculated Based on the Karplus Equations. Exo Isomers of D-Ribofuranosyl Derivative

	Hz	Dihedral angle, deg
$J_{3,4}$	3.5–4	38–48 or 129–138
$J_{4,5}$	6–6.5	27–31 or 144–147
$J_{5,6}$	3.5–4	38–48 or 129–138

C-glycosides (endo isomers) are $J_{3,4}$ = 3.5–4, $J_{4,5}$ = 6, $J_{5,6}$ = 0 Hz (the $J_{3,4}$ corresponds to the $J_{1,2}$ of the furanose ring and so does the $J_{4,5}$ to the $J_{2,3}$ and the $J_{5,6}$ to the $J_{3,4}$) and those of β-D-ribofuranosyl *C*-glycosides (exo isomers) are $J_{3,4}$ = 3.5–5, $J_{4,5}$ = 6–6.5, and $J_{5,6}$ = 3.5–5 Hz. These data indicate that the endo isomers of D-ribofuranosyl *C*-glycosides all exist in very closely related conformations and the same is the case with the exo isomers. The x-ray structure of the endo isomer **22a** is shown in Figure 5. As can be seen in Figure 5, the tetrahydrofuran ring is not the plane but the oxygen atom down envelope form (*Eo*).[7] It seems that the oxygen atom in the tetrahydrofuran ring makes the conformation of the ring fairly flexible and plays the important role in the relative stabilities between the endo and exo isomers. The distances between H_2 and O_2 and between $H_{2'}$ and O_2 in Figure 5 are 2.586 and 2.907 Å, respectively. Therefore, the hydrogen bonding between these atoms is ruled out even in the crystal form.[18] In Figure 5, the cyanomethylene group takes the quasi-equatorial orientation and the interaction by this group is minimized; on the other hand the *p*-bromobenzoyloxy methylene group takes the quasi-axial orientation and there is 1,3-diaxial interaction between this group and H_3. There is almost no change in the ^1H NMR spectra of the endo isomer **15a** in the range of temperature from −50 to 70 °C and this indicates that the conformation of the endo isomer is very rigid and the conformation of compound **22a** shown in Figure 5 will be the same in solution.

Although it is known that the application of the Karplus equations[19] to the five-membered ring might not be appropriate, the conformational analysis of these *C*-glycosyl compounds based on the Karplus equations was next undertaken. The dihedral angles calculated by the Karplus equations

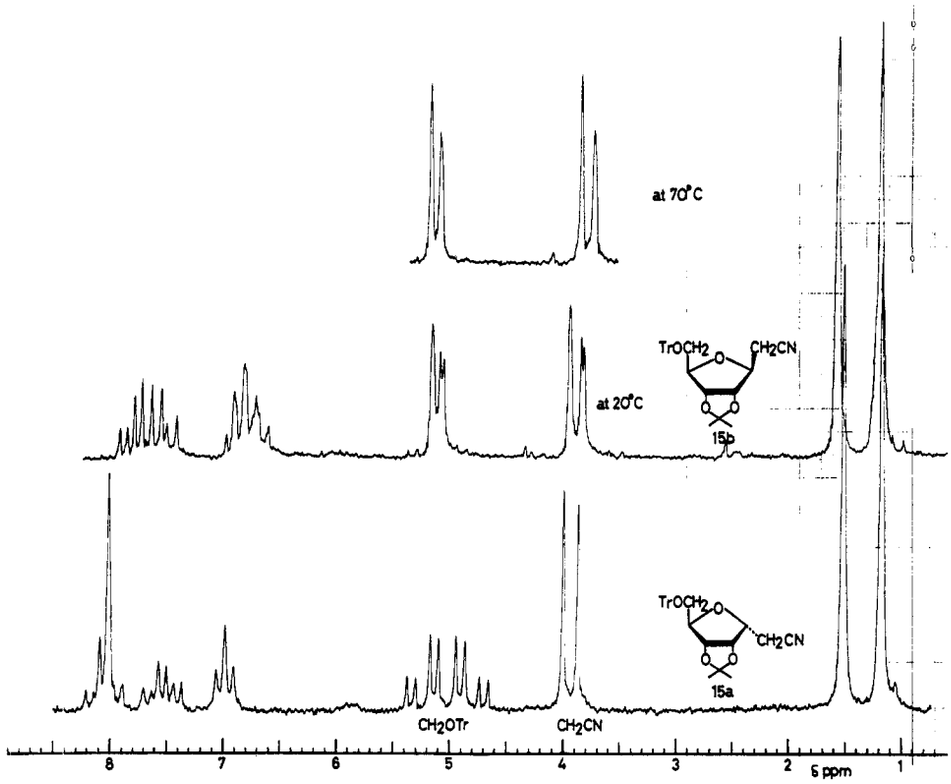

Figure 4. ^1H NMR spectra of compounds **15a** and **15b** at 100 MHz in $CDCl_3$.

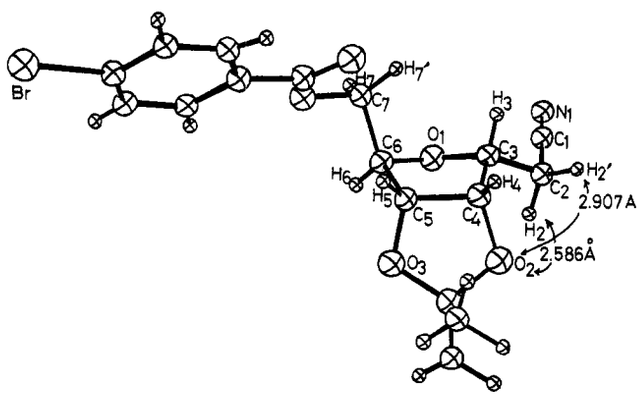

Figure 5. X-ray structure of compound **22a** (endo isomer).

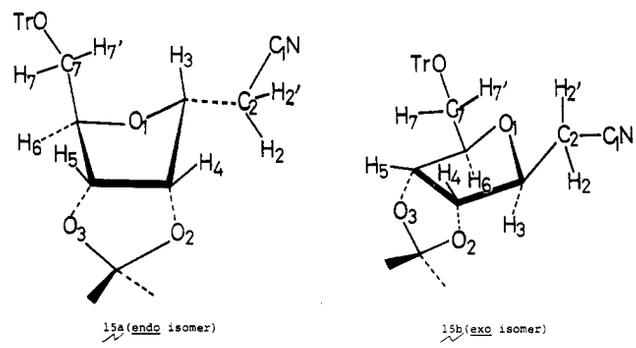

Figure 6.

based on the coupling constants are listed in Tables IIIA and IIIB.

With the help of the Dreiding models and the consideration of steric interactions, the most preferred conformations of both the endo and the exo isomers of D-ribofuranosyl *C*-glycosides are shown using compounds **15a** and **15b,** respectively, in Figure 6. It can been seen that the two conformations of the endo isomers, one based on the x-ray crystallographic method in Figure 5 and another based on the Karplus equations in Figure 6, are both the oxygen atom down envelope form (*Eo*) and resemble each other very well. This indicates that the discussions based on these conformations are very reliable.

In the conformation of the endo isomer **15a** in Figure 6, the cyanomethylene group takes a quasi-equatorial orientation and the cis 1,2- and 1,3-interactions between this group and other atoms are almost relieved. This is consistent with the equivalency (free rotation of C_2–C_3 single bond) of the cyanomethylene protons in the ^1H NMR spectrum. Further, in this conformation the cis 1,2-interaction between O_3 and H_6 and the 1,3-interaction between O_2 and H_6 are decreased, since the H_6 takes a quasi-equatorial orientation. On the other hand, the trityloxy methylene group (C_7) takes a quasi-axial orientation. Therefore, there exists the 1,3-diaxial interaction between this group and H_3. This is also consistent with the ABX splitting of the trityloxy methylene protons (H_7 and $H_{7'}$) in the ^1H NMR spectrum. In the case of the exo isomers, the conformation is a little twisted oxygen atom up envelope form (°*E*). In this conformation, both the cyanomethylene and the trityloxy methylene group tend to take the quasi-equatorial orientation to decrease the large 1,3-interaction between these groups. Consequently, the H_3 and H_6 are forced to take the quasi-axial orientation and come inside the fused ring system. Therefore, the cis 1,2- and the 1,3-interactions between these protons and the oxygen atoms in the dioxolane ring increase. As the result, the two methylene group cannot take the complete quasi-equatorial orientation and there remain some 1,2- or 1,3-interactions by these methylene groups and the rotation of the C_2–C_3 and C_6–C_7 single bonds is restricted. This is consistent with the ^1H NMR spectrum which shows that the two methylene protons are not equivalent at room temperature.

When the instability factors of these two conformations in Figure 6 are compared, there are two O/H cis 1,2-interactions, two O/H 1,3-interactions, and the interaction between the two

Table IV. Final Positional Parameters

Name	G (SD)	X (SD)	Y (SD)	Z (SD)	B (SD)
Br-1	1.00 (0)	0.01904 (27)	0.16811 (9)	0.22336 (4)	
C-15	1.00 (0)	−0.07513 (196)	0.05703 (68)	0.27454 (40)	
C-16	1.00 (0)	−0.27918 (200)	0.00178 (83)	0.26673 (38)	
C-17	1.00 (0)	−0.35097 (210)	−0.07442 (78)	0.30583 (39)	
C-12	1.00 (0)	−0.21709 (171)	−0.09455 (71)	0.35062 (36)	
C-13	1.00 (0)	−0.00316 (245)	−0.03956 (78)	0.35568 (39)	
C-14	1.00 (0)	0.06249 (197)	0.03678 (87)	0.31790 (44)	
C-11	1.00 (0)	−0.29245 (206)	−0.17323 (85)	0.39380 (40)	
O-5	1.00 (0)	−0.16820 (134)	−0.19689 (58)	0.43088 (28)	
O-4	1.00 (0)	−0.51020 (142)	−0.20882 (44)	0.38769 (21)	
C-7	1.00 (0)	−0.59843 (206)	−0.27937 (92)	0.43016 (47)	
C-6	1.00 (0)	−0.63239 (201)	−0.39942 (81)	0.40656 (41)	
C-5	1.00 (0)	−0.40655 (175)	−0.45994 (82)	0.39666 (39)	
C-4	1.00 (0)	−0.37178 (196)	−0.53855 (88)	0.44471 (38)	
C-3	1.00 (0)	−0.57619 (181)	−0.51540 (84)	0.47942 (41)	
O-1	1.00 (0)	−0.75039 (117)	−0.46647 (52)	0.44571 (24)	
O-3	1.00 (0)	−0.43124 (131)	−0.53324 (49)	0.35188 (23)	
C-8	1.00 (0)	−0.33174 (174)	−0.63854 (81)	0.36561 (34)	
O-2	1.00 (0)	−0.37866 (116)	−0.64832 (47)	0.42149 (23)	
C-9	1.00 (0)	−0.46147 (282)	−0.73163 (115)	0.33828 (54)	
C-10	1.00 (0)	−0.07384 (211)	−0.63976 (118)	0.35546 (47)	
C-2	1.00 (0)	−0.67483 (246)	−0.61614 (100)	0.50921)45)	
C-1	1.00 (0)	−0.88965 (271)	−0.58807 (100)	0.53753 (41)	
N-1	1.00 (0)	−1.05160 (221)	−0.56664 (92)	0.56040 (34)	
H-17	1.00 (0)	−0.36907 (1655)	0.01044 (780)	0.23906 (320)	4.00 (0)
H-18	1.00 (0)	−0.47755 (1864)	−0.10890 (744)	0.29829 (314)	4.00 (0)
H-15	1.00 (0)	0.08449 (1739)	−0.06337 (802)	0.38266 (328)	4.00 (0)
H-16	1.00 (0)	0.21583 (1760)	0.07836 (731)	0.32420 (326)	4.00 (0)
H-7	1.00 (0)	−0.49895 (1887)	−0.28116 (654)	0.46399 (296)	4.00 (0)
H-8	1.00 (0)	−0.72373 (1950)	−0.26022 (923)	0.43244 (417)	4.00 (0)
H-6	1.00 (0)	−0.68801 (1725)	−0.40403 (858)	0.37771 (334)	4.00 (0)
H-5	1.00 (0)	−0.28432 (1816)	−0.39881 (852)	0.38843 (349)	4.00 (0)
H-4	1.00 (0)	−0.21437 (1782)	−0.52127 (800)	0.45698 (327)	4.00 (0)
H-3	1.00 (0)	−0.55170 (1824)	−0.46740 (657)	0.50792 (322)	4.00 (0)
H-9	1.00 (0)	−0.38680 (1639)	−0.80607 (752)	0.35062 (305)	4.00 (0)
H-10	1.00 (0)	−0.63316 (2065)	−0.71728 (916)	0.38586 (392)	4.00 (0)
H-11	1.00 (0)	−0.45152 (2062)	−0.71538 (790)	0.30787 (324)	4.00 (0)
H-12	1.00 (0)	−0.03602 (1988)	−0.59870 (724)	0.38143 (313)	4.00 (0)
H-13	1.00 (0)	−0.00246 (2130)	−0.71837 (721)	0.36799 (311)	4.00 (0)
H-14	1.00 (0)	−0.04224 (1899)	−0.62724 (751)	0.32310 (315)	4.00 (0)
H-1	1.00 (0)	−0.56108 (1745)	−0.64192 (721)	0.52979 (313)	4.00 (0)
H-2	1.00 (0)	−0.74587 (1707)	−0.66393 (767)	0.48018 (359)	4.00 (0)

Table V. Final Thermal Parameters

Name	B11 (SD)	B22 (SD)	B33 (SD)	B12 (SD)	B13 (SD)	B23 (SD)
Br-1	7.95 (9)	4.64 (5)	4.50 (5)	−1.89 (7)	1.81 (7)	0.31 (5)
C-15	5.66 (73)	1.95 (38)	3.27 (41)	−0.89 (45)	1.32 (52)	−0.94 (40)
C-16	4.33 (64)	2.53 (41)	3.54 (54)	−1.02 (47)	−0.63 (45)	0.00 (45)
C-17	3.65 (60)	2.34 (48)	3.62 (47)	−0.19 (43)	−0.11 (49)	−1.26 (39)
C-12	1.98 (50)	2.09 (42)	3.40 (46)	−0.02 (40)	−0.17 (41)	−0.21 (38)
C-13	3.46 (61)	2.95 (43)	4.08 (50)	0.29 (60)	0.13 (58)	0.77 (42)
C-14	3.04 (66)	3.95 (53)	4.76 (53)	−0.30 (50)	−0.19 (50)	−0.88 (48)
C-11	4.16 (63)	2.00 (42)	3.84 (51)	0.48 (52)	0.15 (45)	−0.83 (47)
O-5	4.63 (41)	4.33 (40)	4.66 (36)	−0.30 (33)	−0.96 (35)	0.62 (32)
O-4	2.41 (33)	2.72 (28)	4.15 (30)	−0.16 (35)	−0.03 (33)	0.65 (22)
C-7	2.96 (58)	2.89 (46)	4.08 (50)	0.00 (46)	0.87 (49)	0.12 (43)
C-6	3.23 (61)	2.06 (45)	3.03 (46)	−0.44 (43)	0.90 (45)	0.73 (41)
C-5	2.20 (55)	2.41 (44)	3.52 (49)	−0.13 (44)	−0.05 (42)	0.66 (42)
C-4	2.90 (50)	3.42 (49)	3.30 (46)	0.08 (46)	−0.50 (45)	−0.67 (41)
C-3	3.01 (58)	3.47 (49)	3.52 (47)	1.29 (46)	0.49 (47)	−0.47 (41)
O-1	2.88 (31)	3.13 (32)	3.53 (31)	−0.19 (32)	0.20 (30)	0.30 (27)
O-3	5.63 (51)	2.73 (28)	3.64 (29)	0.59 (33)	−0.71 (32)	−0.30 (24)
C-8	3.05 (53)	2.90 (48)	2.97 (43)	0.51 (43)	0.48 (41)	0.23 (37)
O-2	4.77 (37)	2.57 (30)	4.00 (30)	0.43 (30)	1.08 (29)	0.48 (26)
C-9	3.73 (77)	4.04 (57)	5.39 (57)	−0.11 (63)	0.36 (67)	−0.88 (53)
C-10	3.21 (70)	6.08 (68)	4.32 (56)	−0.40 (54)	0.42 (53)	−1.52 (58)
C-2	5.00 (83)	4.33 (65)	4.02 (56)	0.77 (56)	1.05 (54)	1.08 (47)
C-1	6.26 (82)	3.75 (57)	3.04 (55)	0.78 (61)	−0.26 (53)	0.55 (46)
N-1	6.32 (76)	5.16 (51)	4.42 (50)	0.93 (57)	1.15 (56)	1.33 (43)

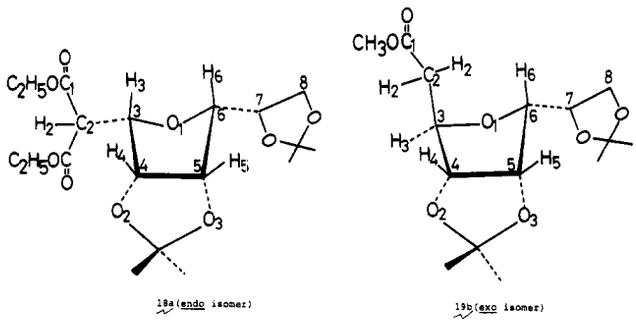

Figure 7.

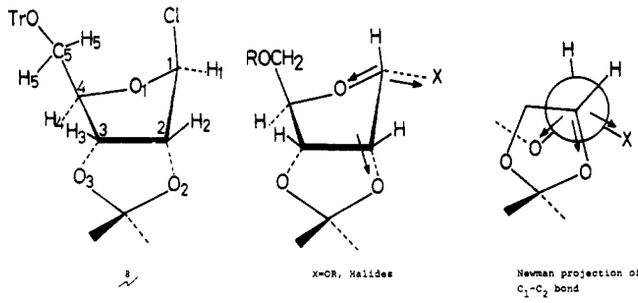

Figure 8.

methylene groups in the exo isomer **15b**. On the other hand, there is only one 1,3-diaxial interaction between the trityloxy methylene group and H_3 in the endo isomer **15a**. The sum of the former interactions apparently exceeds that of the latter one. Thus, the endo isomers are thermodynamically more stable than the exo isomers.

The relative stabilities of D-allofuranosyl derivatives can be rationalized by the same discussions used for D-ribofuranosyl derivatives if the trityloxy methylene group is replaced by the 1,3-dioxolane substituent.

When the coupling constants of the tetrahydrofuran ring protons of α-D-mannofuranosyl *C*-glycosides (exo isomer) and those of α-D-ribofuranosyl *C*-glycosides (endo isomer) are compared, it is easily recognized that the conformation of the tetrahydrofuran ring of the α-D-mannofuranosyl *C*-glycosides (exo isomers) is the same as that of α-D-ribofuranosyl *C*-glycosides (endo isomers) but the mirror image as shown in Figure 7 using compound **19b**. On the other hand, the coupling constants of β-D-mannofuranosyl *C*-glycosides **18a** (endo isomer) are $J_{3,4} = 3.5$, $J_{4,5} = 6$, and $J_{5,6} = 3$ Hz. The $J_{3,4}$ and the $J_{4,5}$ of **18a** are the same as those of α-D-ribofuranosyl *C*-glycoside (endo isomer). The fact that the endo isomer **18a** has very similar $J_{3,4}$ and $J_{5,6}$ indicates that the conformation of the tetrahydrofuran ring of **18a** will be symmetrical. Thus, the conformation of **18a** is the oxygen atom down envelope form (*Eo*) which is very similar to **15a** in Figure 5 but more C_6 up as shown in Figure 7. It is very reasonable that the endo substituent at C_6 of **18a** takes a more quasi-equatorial orientation than the H_6 of **15a** (more C_6 up conformation of **18a** than **15a**).

In the conformation of **18a** in Figure 7, the interactions caused by the two methylene group at C_3 and C_6 are minimized, because they take the quasi-equatorial orientation. The instability factors that should be taken into consideration in this conformation are the interactions caused by the ring protons, because they sit on the same side of the tetrahydrofuran ring. It is apparent that the sum of the interactions of compounds **18a** is smaller than that of compound **19b**. Therefore, the endo isomer is thermodynamically more stable than the exo isomer.

Thus, the order of the relative thermodynamic stability of

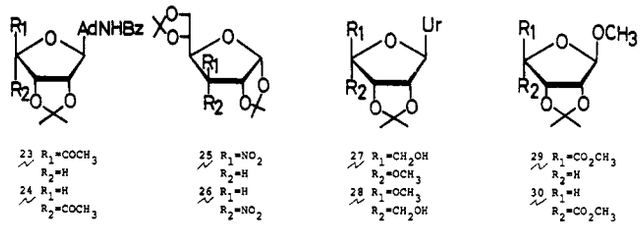

Figure 9.

these *C*-glycosyl compound is **18a** > **19b** or **15a** > **15b**. It is very interesting that the order is completely reverse of that which would be expected based on the generally accepted concept, in spite of the fact that there are two endo substituents in the most stable structure, there is one endo substituent in the next stable structure, and there is no endo substituent in the most unstable structure.

Very recently Wertz and Allinger[20] have proposed a very challenging rationalization on the conformational analysis of organic compounds that *the H/H gauche interactions are not negligible, and in fact may be the most important contributors to the gauche effect.* However, it seems that the gauche effects such as O/H and H/CH_2OR are playing a more important role than H/H gauche interactions in these *C*-glycosyl compounds.

As described in the beginning of this paper, aglycons such as OR and halides exist primarily in the trans C_1, C_2 configuration in these fused five-membered ring systems. In order to clarify the factors that make the exo isomers thermodynamically more stable than the endo isomers in the case of *O*-glycosides and halogeno sugars in this system, the conformational analysis of compound **7** was next undertaken. The coupling constants of the tetrahydrofuran ring protons of **7** are $J_{1,2} = 0$, $J_{2,3} = 5.8$, and $J_{3,4} = 1.8$ Hz. These coupling constants indicate that the conformation of **7** is very similar to that of **15a** but a little C_4 down envelope form. It is very reasonable that compound **7** has more C_4 down conformation than **15a** to decrease the 1,3-interaction between the chlorine atom and the trityloxy methylene group. The difference between halogeno sugars or *O*-glycosides and *C*-glycosides is the presence of a dipole between C_1 and the polar aglycons in the former case. If halides or OR take the endo configuration (quasi-equatorial orientation), the dipole between C_1 and the polar aglycon becomes parallel to other dipoles caused by the oxygen atoms in the molecule as shown in Figure 8. The dipole interactions destabilize the endo configuration. Therefore, the electronegative groups exist mainly in the quasi-axial orientation (trans C_1,C_2 relation) in this system.

Several other examples of isopropylidene sugars that prefer to exist in an endo (cis to the *O*-isopropylidene group) configuration are found in the literature. Moffatt et al.[21] showed that 5′-keto nucleoside **23** rapidly epimerized at $C_{4'}$ giving **24** upon chromatography on silicic acid; Kovar and Baer[22] reported the base-catalyzed epimerization of nitro sugar **25** to the more stable **26**. The acid-catalyzed equilibration of 4′-methoxyuridine (**27**) gave the more stable α-L-lyxo nucleoside (**28**).[23] A recent observation on the base-catalyzed epimerization of methyl (methyl 2,3-*O*-isopropylidene-β-D-ribofuranosyl)uronate (**29**) to the more stable α-L-lyxofuranosyluronate (**30**) was reported.[24] All of these facts can be explained based on the rationalization proposed above.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained using a Varian HA-100 spectrometer.

X-Ray Crystallography. Unit cell parameters and intensity data were obtained with a Syntex $P2_1$ diffractometer using monochromatized Mo Kα radiation. Calculations were performed using the

Syntex XTL system, and the solution of the structure was served by the conventional heavy-atom method. The position of the bromine atom of **22a** was determined from a Patterson function, and subsequent Fourier synthesis, based on the phase angles due to the bromine atom, located other atoms. The refinement was concluded by eight cycles of full matrix least squares in which positional parameters of all atoms and anisotropic temperature factors of all atoms other than hydrogens were included. Atomic scattering factors are those of Cromer and Waber,[25] and anisotropic temperature factors fell in normally encountered ranges. For structure of **22a**, the crystals were orthohombic, $a = 5.775$ (5), $b = 11.878$ (6), $c = 25.007$ (6), and were in space group $P2_12_12_1$; $Z = 4$, $F(000) = 808$. The calculated density was 1.53 cm^{-1}, and the linear absorption coefficient was 25.7 cm^{-1} for Mo Kα. Of the 1347 reflections in the range $0 < 2\tau < 45$ that were measured using the scan technique, 1074 had an intensity greater than 1.96 times the standard deviation and were recorded as observed. The final R value for the crystal during data collection was suggested by a somewhat larger value of B_{11} for the bromine atom.

The final positional and thermal parameters are in Tables IV and V.

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Registry No.—**12a**, 56703-38-9; **12b**, 56703-37-8; **13a**, 56781-38-5; **13b**, 56781-37-4; **14a**, 56703-39-0; **14b**, 56752-57-9; **15a**, 56779-60-3; **15b**, 56703-40-3; **16a**, 56703-41-4; **16b**, 55036-19-6; **17a**, 56703-43-6; **17b**, 56703-42-5; **18a**, 52921-56-9; **18b**, 52921-55-8; **19a**, 56703-46-9; **19b**, 56703-45-8; **22a**, 56703-44-7; **22b**, 57078-06-5.

References and Notes

(1) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, **97**, 4602 (1975).
(2) R. U. Lemieux, A. A. Pavia, J. C. Martin, and K. A. Watanabe, *Can. J. Chem.*, **47**, 4427 (1969).
(3) W. D. Ollis and J. H. Ridd, *Annu. Rep. Chem. Soc.*, **63**, 240 (1966).
(4) S. J. Angyal, *Angew. Chem., Int. Ed. Engl.*, **8**, 157 (1969).
(5) R. U. Lemieux and R. Nagarajan, *Can. J. Chem.*, **42**, 1270(1964).
(6) J. F. Stoddart, *MTP Int. Rev. Sci. Ser.*, **7**, 1 (1973).
(7) (a) J. F. Stoddart, "Stereochemistry of Carbohydrates", Wiley-Interscience, New York, N.Y., 1971, p 101. (i) An example which does not obey the rule has been reported by S. J. Angyal; see ref 4.
(8) T. B. Grindley and W. A. Szarek, *Carbohydr. Res.*, **25**, 187 (1972).
(9) (a) H. Ohrui and J. J. Fox, *Tetrahedron Lett.*, **22**, 1951 (1973). (b) Systematically this compound should be referred to as **12a** and **12b** but, for ease of comparison with furanoses, the more immediate obvious trivial name and numbering will be used for compound **12**.
(10) J. M. Ballard and B. E. Stacey, *Carbohydr. Res.*, **12**, 37 (1970).
(11) S. J. Angyal, V. A. Pickles and R. Ahlualia, *Carbohydr. Res.*, **3**, 300 (1967).
(12) L. M. Lerner and P. Kohn, *J. Org. Chem.*, **31**, 339 (1966).
(13) J. B. Lee and T. J. Nolan, *Tetrahedron*, **23**, 2789 (1967).
(14) M. M. Ponpipon and S. Hanessian, *Carbohydr. Res.*, **18**, 342 (1971).
(15) S. D. Bernardo and M. Weigele, *J. Org. Chem.*, **41**, 287 (1976).
(16) J. A. Mills, *Adv. Carbohydr. Chem.*, **10**, 1 (1955).
(17) R. J. Ferrier and W. G. Overend, *Q. Rev., Chem. Soc.*, **13**, 265 (1959).
(18) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond", W. H. Freeman, San Francisco, Calif., 1960, p 197.
(19) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(20) D. H. Wertz and N. L. Allinger, *Tetrahedron*, **30**, 1979 (1974).
(21) R. S. Ranganathan, G. H. Jones, and J. G. Moffatt, *J. Org. Chem.*, **39**, 290 (1974).
(22) J. Kovar and H. H. Baer, *Can. J. Chem.*, **49**, 3203 (1971).
(23) J. P. Verheyden and J. G. Moffatt, *J. Am. Chem. Soc.*, **97**, 4386 (1975).
(24) M. P. Kotik and D. L. Leland, *Carbohydr. Res.*, **46**, 299 (1976).
(25) D. Cromer and J. Waber, "International Tables for X-Ray Crystallography", Vol. IV, Kynoch Press, Birmingham, England, 1974.

Proton Magnetic Resonance Spectra of Cubane Derivatives. 3. Transmission of Substituent Effects in 4-Substituted 1-Bromohomocubane Derivatives

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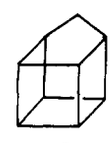
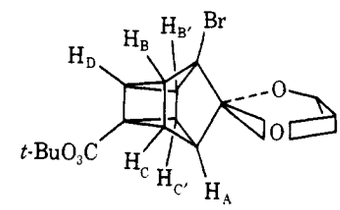
An analysis of the NMR spectra of some homocubane derivatives is reported and shown to be in accord with a previous study of cubane NMR spectra. The results obtained have been interpreted in terms of a through-space mechanism for both cross-ring coupling and the transmission of substituent effects in these systems.

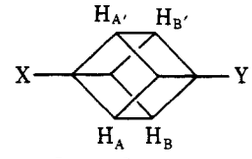
In the first paper[1] of this series we reported our analyses of the NMR spectra of cubane and various mono- and 1,4-disubstituted cubanes, and examined the effects of substituents upon the observed chemical shifts and coupling constants. Such information should assist in the subsequent analysis of the spectra and structures of related cage compounds. Analyses for systems related to cubanes may then be compared with that for cubanes to examine the effects of ring expansion, relative substituent geometries, strain, etc., as subtle differences arising from such effects should be reflected in the observed NMR spectra.[2] In the present paper such a comparison is made for some derivatives of homocubane (I), data from the previous study being used to assist in the detailed analysis of the spectrum of 1-bromohomocuban-9-one-4-carboxylic acid ethylene ketal *tert*-butyl perester (II).



I



II

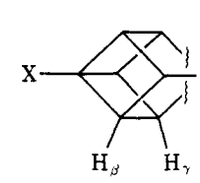


$J_{AB} = J_{ortho}$

$J_{AA'}, J_{BB'} = J_{meta}$

$J_{A'B} = J_{para}$

III



IV

Experimental Section and Results

The syntheses of the compounds studied have all been described elsewhere.[1,3-6]