129. *Modification of Hudson's Rules of Isorotation for Sugar Derivatives containing Highly Polarisable Aglycones.*

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Hudson's rotational correlations of glycosyl halides have been critically examined. New A_{Cl} and B_{Cl} values have been calculated from anomeric glycosyl chlorides now available. The presence of a highly polarisable group attached to the reducing centre may cause a change in both A and B values, but constant A values and regular changes in B values have been observed for closely related structures. For $(1' \rightarrow 4)$- and $(1' \rightarrow 6)$-linked disaccharides the modification of the B value is apparently confined to the reducing-sugar component, and the modified B value may be evaluated by a simple procedure. Specific rotations calculated for numerous derivatives of disaccharides agree well with reported values; the derivatives include acetylated phenyl glycosides and thioglycosides, and *O*-acetylglycosyl chlorides, bromides, and iodides. The procedure is also applicable to derivatives of monosaccharides. Consideration of structural similarities around the anomeric centres and of the polarisabilities of aglycones allows Hudson's rules of isorotation and the present modifications of them to be rationalised, and their applicability is more closely defined.

PREPARATION of a series of authentic pairs of poly-*O*-acetyl glycosyl chlorides[1] has permitted a precise test to be made of Hudson's rules of isorotation for the first time in this series. This was impossible in 1924, as only the more stable of the anomeric chlorides derivable from each sugar was then known, and Hudson[2] had to assume the validity of his second rule for the numerous halides he examined. Using the B values (°) (rotational contribution from the ring portion other than the anomeric centre) derived from acetylated sugars, Hudson calculated A values (°) (contribution from the anomeric centre and its substituent) for the different halogens. The A values so obtained showed a reasonable uniformity and Hudson was able to assign configurations (usually α-D) to the known halides. These have been confirmed by subsequent work.[3] He was also able to detect at least one error in published work, revealed by an abnormal A value in his list.[2,4] One further correction may now be made. Hudson[1] observed an abnormal A value (52,200) for tetra-*O*-acetyl-α-D-galactopyranosyl chloride, but it is now known[1] that the value[5] for the specific rotation (212·5°) used by him and accepted for 56 years, is wrong, and the corrected rotation (177·5°) gives an A value (39,700) near to Hudson's average for A_{Cl} (37,800). The only seriously discordant A_{Cl} value left in Hudson's list is therefore that for tetra-*O*-acetyl-α-D-mannopyranosyl chloride, and by 1930[6] it was apparent that the original rules of isorotation do not hold accurately for compounds with inverted configuration at $C_{(2)}$.

Table 1 gives optical parameters (A and B values) for seven pairs of anomeric glycosyl chlorides, which were determined independently of Hudson's assumption that $B_{Cl} = B_{Ac}$ (the subscripts show the substituent at $C_{(1)}$ in the acetylated sugar to which the B values refer). The new values have been compared with those of fully acetylated sugars. All optical rotations ($[\alpha]_D$ at about 20°) of these and other acetylated derivatives discussed in this paper refer to chloroform solutions, and the unacetylated ones to water solutions, as suggested by Hudson.[2] In all cases the B_{Cl} values differ appreciably from B_{Ac} values, and the A_{Cl} value is similar in only the first four pairs. It is suggested that the A and B values

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[1] Korytnyk and Mills, *J.*, preceding paper.
[2] Hudson, *J. Amer. Chem. Soc.*, 1924, **46**, 462.
[3] Haynes and Newth, *Adv. Carbohydrate Chem.*, 1955, **10**, 207.
[4] Hudson and Kunz, *J. Amer. Chem. Soc.*, 1925, **47**, 2052.
[5] Skraup and Kremann, *Monatsh.*, 1901, **22**, 375.
[6] Haworth and Hirst, *J.*, 1930, 2615.

derived from Hudson's procedure should be designated A'_{Cl} and B'_{Cl} to distinguish them from true values derived from anomers.

Phenyl glycosides are known to differ from alkyl glycosides in not conforming accurately to the original isorotation rules,[7] and Table 2 shows a situation closely resembling that for the chlorides in Table 1.

TABLE 1. *Optical data for anomeric fully acetylated pyranose sugars and corresponding poly-*O*-acetyl glycosyl chlorides (in chloroform)* (°).

(1) *Molecular rotations,* $[M]_D$, *of anomers* [a]

	Acetylated sugar		Acetylated chloride	
Parent sugar	α-form	β-form	α-form	β-form
D-Glucopyranose	39,700	1,480	60,900	−4,770
Methyl D-glucopyranuronate	36,900 [b]	3,270 [b]	59,700 [c]	−5,900 [b]
D-Galactopyranose	41,650	9,760	65,100 [d]	5,450 [d]
Maltose	83,330	42,500	104,500	37,600 [d]
D-Mannopyranose	21,470	−9,840	32,970	−12,500 [d]
D-*glycero*-D-*gulo*Heptopyranose	40,230	2,220	41,690	4,830
D-Xylopyranose	28,400	−7,860	50,450	−41,600 [d]

(2) *Optical parameters for acetylated derivatives*

Parent sugar	A_{Ac}	B_{Ac}	A_{Cl}	B_{Cl}	A_{Ac}/A_{Cl}	B_{Ac}/B_{Cl}
D-Glucopyranose	19,110	20,590	32,840	28,060	0·58	0·74
Methyl D-glucopyranuronate	16,820	20,080	32,800	26,900	0·51	0·75
D-Galactopyranose	15,950	25,700	29,830	35,280	0·53	0·73
Maltose	20,420	62,920	33,450	71,050	0·61	0·89
D-Mannopyranose	15,660	5,820	22,740	10,240	0·69	0·57
D-*glycero*-D-*gulo*Heptopyranose	19,010	21,230	18,430	23,260	1·0	0·91
D-Xylopyranose	18,130	10,270	46,030	4,430	0·39	2·3

[a] Calculated from the data of ref. 8, unless specified. [b] Goebel and Babers, *J. Biol. Chem.*, 1934, **106**, 63. [c] Ref. 15. [d] Ref. 1.

TABLE 2. *Optical parameters of some fully acetylated phenyl glycosides (in chloroform)* (°).

Acetate of		$[M]_D$	A_{OPh}	B_{OPh}	A_{Ac}/A_{OPh}	B_{Ac}/B_{OPh}
Phenyl D-glucopyranoside	α	71,500 [a]	40,520	30,980	0·47	0·66
	β	−9,540 [a]				
Phenyl D-galactopyranoside	α	74,400 [b]	37,350	37,050	0·43	0·69
	β	−300 [c]				
Phenyl maltoside	α	117,000 [d]	43,500	73,400	0·47	0·86
	β	29,900 [d]				
Phenyl cellobioside	α	59,200 [c]	42,400	16,700	0·45	0·53
	β	−25,700 [e]				
Phenyl D-xylopyranoside	α	47,600 [a]	32,700	14,900	0·55	0·69
	β	−17,800 [a]				

[a] Montgomery, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 690. [b] Helferich and Bredereck, *Annalen*, 1928, **465**, 166. [c] Helferich and Schmitz-Hillebrecht, *Ber.*, 1933, **66**, 378. [d] Asp and Lindberg, *Acta Chem. Scand.*, 1952, **6**, 941. [e] Ref. 10.

It is evident from both Tables that constant A values are only observed in sugar derivatives that have a similar configuration round positions 1, 2, 3, and 5. A modification of either configuration or structure at positions 4 and 6 appears not to have a marked effect on the A value. Poly-*O*-acetylglycosyl chlorides and phenyl glycosides with a *xylo*- or *gulo*-configuration show discrepancies of their A values, although acetates and methyl glycosides of gulose and xylose seem to conform well to the isorotation rules. It is shown below that the variations in A and B values are due to interactions between polarisable groups at position 1 and the closer portions of the rest of the molecule.

The ratios A_{Ac}/A_{Cl} and B_{Ac}/B_{Cl} are fairly constant for the first three pairs in Table 1, and the corresponding ratios are also similar for the first two pairs of phenyl glycosides in Table 2. The different B_{Ac}/B_{Cl} ratio for maltosyl chlorides in Table 1, and the variable

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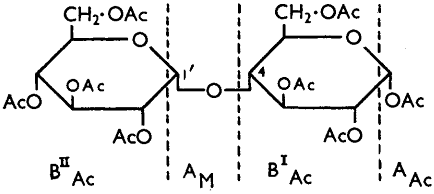
[7] Bonner, Kubitshek, and Drisco, *J. Amer. Chem. Soc.*, 1952, **74**, 5082.

B_{Ac}/B_{OPh} ratios for phenyl glycosides of disaccharides in Table 2, are due to the fact that B values of these derivatives are composite values for two D-glucopyranose rings, and probably only one ring is close enough to the 1-substituent to suffer modification of its partial B value. For the purpose of evaluating the influence of the phenoxy-group or chlorine atom on the B value of the reducing D-glucopyranose ring, it is proposed to dissect the disaccharide molecule as shown for maltose in (I) and evaluate the contribution of the non-reducing ring, $B^{II}_{Ac} + A_M$, by subtracting the molecular rotation of α-D-glucopyranose penta-acetate from that of α-maltose octa-acetate. Subtracting this value (43,630) from B_{Ac} and B_{Cl} for maltose then gives the partial B values for the reducing ring; they are $B^I_{Ac} = 19{,}330$, $B^I_{Cl} = 26{,}420$, whence $B^I_{Ac}/B^I_{Cl} = 0{\cdot}73$ in good agreement with the simple sugars. When this method is applied to the acetylated phenyl glycosides of disaccharides in Table 2, B^I_{Ac}/B^I_{OPh} is found to be 0·65 for maltose and 0·73 for cellobiose.



(I)

As would be expected if the method is sound, the contribution $B^{II}_{Ac} + A_M$ is practically constant when calculated in all possible ways: the values obtained from the β-acetates, α-chlorides, and β-chlorides of maltose and D-glucose are 41,020, 43,600, and 42,370, respectively. The above numerical analysis is equivalent to stating that the difference, $B_{Cl} - B_{Ac} = \Delta B$, is constant for related anomeric pairs of mono- and di-saccharides; for maltose and D-glucose the actual values of ΔB are 8130 and 7470 respectively. If this relation is true in general, it provides a means of calculating the specific rotation of both chlorides of derivatives of D-glucose, provided the substitution is confined to points beyond the modifying influence of the chlorine atom. In particular, the method may be applied to (1′ ⟶ 4)- and (1′ ⟶ 6)-linked disaccharides with D-glucose as the reducing component. The exact relation:

$$[M_{Cl}]^{di} = B_{Cl}^{di} \pm A_{Cl}^{di}$$

becomes, on these assumptions:

$$[M_{Cl}]^{di} = B_{Ac}^{di} + B_{Cl}^{mono} - B_{Ac}^{mono} \pm A_{Cl}^{mono} \quad . \quad . \quad . \quad . \quad (1)$$

$[M_{Cl}]$ indicates the molecular rotation of the chloride, the superscripts indicate mono- or di-saccharide, and the + or − sign is appropriate to the α- or β-anomer, respectively. The success of this method as applied to poly-*O*-acetyldisaccharide chlorides is shown in Table 3. Thus the specific rotation of hepta-*O*-acetyl-β-maltosyl chloride was predicted by Hudson[2] to be 38°; the present method gives 57°, which is in perfect agreement with the found value. An exactly similar method should hold for acetylated phenyl glycosides of these disaccharides, and the appropriate relation is obtained from equation (1) on substituting B_{OPh} and A_{OPh} for D-glucose (Table 2) for B_{Cl}^{mono} and A_{Cl}^{mono}. The results of calculations are also shown in Table 3. The agreement with the known value is as good as could be expected.

If the extent of modification of the B value of the reducing monosaccharide unit is known, it is generally possible to predict rotations of anomeric forms of oligosaccharides, provided the modifying influence of the aglycone does not reach carbon atoms to which the other sugar units are attached.

Thus it should be possible to evaluate the specific rotations (in water) of unacetylated phenyl glycosides by using the parameters derived from methyl glycosides of mono- and di-saccharides and the phenyl glycosides of the monosaccharide. Unfortunately, the requisite data [8] are scanty and of doubtful quality; the A value for the methyl cellobiosides (20,650) is significantly different from the A values for the methyl gentiobiosides (18,070) and methyl D-glucopyranosides (18,750). By use of the data for these glycosides and the phenyl D-glucopyranosides,[8] the following rotations were calculated, the reported values being shown in parentheses: phenyl α-cellobioside,[9] 115° (122°); phenyl β-cellobioside,[10] —40° (—59·5°); and phenyl β-gentiobioside,[11] —60° (—67°). Further study of this series is necessary, to find whether the rather less satisfactory agreement is due to inaccurate parameters, or to the possibly greater anomalies in water as solvent.

TABLE 3. *Calculated and reported rotations (in chloroform) for poly-*O*-acetyl glycosyl chlorides and acetylated phenyl glycosides of some disaccharides.*

		Maltose	Melibiose	Lactose	Gentiobiose	Cellobiose
		$[\alpha]_D$	$[\alpha]_D$	$[\alpha]_D$	$[\alpha]_D$	$[\alpha]_D$
α-Chloride	calc.	157°	197°	87°	86°	75°
	found [a]	159	192·5	84	80·5	72
β-Chloride	calc.	57	97	—13	—14	—25
	found	57 [b]	*g*	*g*	*g*	*g*
Phenyl α-glycoside	calc.	160	196	95	94	84
	found	164 [c]	*g*	*g*	*g*	83 [e]
Phenyl β-glycoside	calc.	46	82	—19	—20	—30
	found	42 [c]	*g*	—23 [d]	—29 [e]	—36 [f]
Parameters used						
B_{Ac} (known) [h]		62,960	88,670	16,600	16,000	8,900
B_{Cl} (calc.)		70,430	96,140	24,070	23,470	16,370
B_{OPh} (calc.)		73,350	99,080	26,990	26,390	19,290

[a] Unless specified, reported rotations are from ref. 8. [b] Ref. 1. [c] Asp and Lindberg, *Acta Chem. Scand.*, 1952, **6**, 941. [d] Helferich and Griebel, *Annalen*, 1940, **544**, 191. [e] Ref. 11. [f] Ref. 10. [g] Compound not known. [h] Calc. from data in ref. 8.

If equation (1) is expressed in general terms, for an aglycone X, it may be reduced to:

$$[M_X]^{di} - B_{Ac}^{di} = [M_X]^{mono} - B_{Ac}^{mono} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and have the same validity, provided A_X is constant and the molecular rotations refer to derivatives of the *same* anomeric configuration. This implies that if one α-anomer containing X is known, and the appropriate B_{Ac} values are available, it is possible to calculate the rotations of other α-anomers with substituent X in the series without having any β-anomers available, and conversely for a series of β-anomers. Equation (2) may be used for the foregoing calculations made from equation (1), and gives identical results. The validity of equation (2) was checked for the following series, in which only one anomeric form of the derivative is known for each sugar; the calculated specific rotations are shown, with reported values in parentheses.

(*a*) Acetylated phenyl thioglycosides (β-forms):[12,13] cellobiose, —27° (—28·5°); lactose, —16° (—19·6°); maltose, 48° (49·0°). Specific rotations of acetylated 2′-naphthyl-1-thio-β-D-glucopyranosides [14] can also be predicted with a similar degree of accuracy.

(*b*) Poly-*O*-acetylglycosyl bromides (α-forms):[8] cellobiose 100° (95·8°); gentiobiose, 110° (101·1°); lactose 111° (108·7°); maltose 177° (180·1°); melibiose 214° (209·9°).

(*c*) Poly-*O*-acetylglycosyl iodides (α-forms):[8] cellobiose, 130° (125·7°); gentiobiose, 140° (126·1°); lactose, 141° (136·9°).

[8] Bates and associates, " Polarimetry, Saccharimetry and the Sugars," U.S. Government Printing Office, Washington, 1942, Tables, pp. 704 *et seq.*

[9] Stanek and Kocourek, *Chem. Listy*, 1953, **47**, 697 (*Chem. Abs.*, 1955, **49**, 190).

[10] Montgomery, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 1848.

[11] Helferich and Schmitz-Hillebrecht, *Ber.*, 1933, **66**, 383.

[12] Purves, *J. Amer. Chem. Soc.*, 1929, **51**, 3619.

[13] *Idem, ibid.*, p. 3631.

[14] Haskins, Hann, and Hudson, *ibid.*, 1947, **69**, 1668.

The fair success achieved by Hudson in his analysis of the rotation of *O*-acetylglycosyl halides and other derivatives which are known (or would be expected) not to conform to his rule of isorotation, is now explicable. His A'_{Cl} values are in fact $[M_{Cl}] - B_{Ac}$, and his assumption that A'_{Cl} is constant was fully justified for all derivatives of D-glucose for which the relation (2) is now shown to hold with numerical accuracy, and also for sugars such as D-galactose in which changes are made outside the range of the vicinal action of the chlorine atom. For the same sugars, the ratio B_{Ac}/B_{Cl} is nearly constant; therefore, although Hudson's A_{Cl} and B_{Cl} values were wrong, they were wrong in a constant ratio for the majority of sugars he examined, and therefore self-consistent. Calculation of A'_X values for Goebel and Babers's methyl 2 : 3 : 4-tri-*O*-acetyl-1-chloro-1-deoxy-α-D-glucopyranuronate[15] ($A'_{Cl} = 39,600$) and the corresponding 1-bromo-derivative[15] ($A'_{Br} = 58,500$) gives results very close to the mean values for A'_{Cl} (37,800) and A'_{Br} (59,300) as determined by Hudson[2] for structurally similar α-D-halides, and this strongly confirms the α-D-configuration of these derivatives. The more serious discrepancies are found in his data for such sugars as D-mannose, in which changes are made close to the anomeric centre.

Hudson's method could not lead to accurate predicted rotations for the unknown β-chlorides, because the modification of the B value by the chlorine requires at least one β-chloride as a starting point for the β-series. Hudson's predicted rotation[2] of $[\alpha]_D$ —42° for tetra-*O*-acetyl-β-D-glucopyranosyl chloride differed from that found[16] for " β-acetochloroglucose " shortly after, and the discrepancy has been used as an argument for the reassignment of structure to the latter compound.[17]

The present analysis can also be successfully applied to some derivatives of D-mannose. Knowledge of rotational parameters of tetra-*O*-acetyl-D-mannopyranosyl chlorides (Table 1) allows the calculation of specific rotations of hepta-*O*-acetyl-4-*O*-(β-D-glucopyranosyl)-D-mannopyranosyl chlorides by equation (1); the calculated values are 53·5° for the α-anomer (Brauns[18] found 51·2°) and —16° for the β-anomer (not known). By means of equation (2) the following values have been calculated for the other acetylated α-halides of this disaccharide (found values[8,18] in parentheses): fluoride, 15° (13·6°); bromide, 80° (77·9°); and iodide, 119° (111·5°).

The calculations may be simplified without serious error when the 4- and the 6-substituent do not contain an asymmetric centre, as B_{Ac} values are not then required. To get the B_{Cl} value for the derivative, the B_{Cl} value for the parent acetylated sugar is multiplied by the factor required to compensate for the change of molecular weight caused by substitution. For example, the molecular weight of the " basal chain " or ring in tetra-*O*-acetyl-D-glucopyranosyl chloride is 331, and in the corresponding tri-*O*-acetyl-6-*O*-tosyl derivative is 443. The B_{Cl} value for the parent compound is 28,060, therefore this is multiplied by 443/331 to get the B_{Cl} value (37,600) for the 6-*O*-tosyl derivative. Combined with the A_{Cl} value of D-glucose (32,840) this gives a calculated specific rotation of 10° for 2 : 3 : 4-tri-*O*-acetyl-6-*O*-tosyl-β-D-glucopyranosyl chloride; the measured value[1] is 9°.

Useful information may sometimes be obtained even when anomeric pairs of acetates and glycosyl halides are not available, as is shown in the following calculation of the specific rotation of 2 : 3-di-*O*-acetyl-4 : 6-*O*-benzylidene-β-D-glucopyranosyl chloride. Only one form of 4 : 6-*O*-benzylidene-D-glucose triacetate is known, for which a β-configuration is indicated by the method of preparation and its conversion into a glycosyl chloride by aluminium chloride under mild conditions.[1] The modification of the D-glucose molecule in the benzylidene derivative is confined to $C_{(4)}$ and $C_{(6)}$; therefore A_{Ac} for the benzylidene triacetate and A_{Cl} for the benzylidene chloride should be very similar to A_{Ac} and A_{Cl} for D-glucopyranose itself; therefore, $A_{Cl} = 32,840$ is adopted for calculations on the

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[15] Goebel and Babers, *J. Biol. Chem.*, 1935, **111**, 347.

[16] Schlubach, *Ber.*, 1926, **59**, 840.

[17] Zemplen, Mester, and Eckhart, *Acta Chim. Acad. Sci. Hung.*, 1954, **4**, 73.

[18] Brauns, *J. Amer. Chem. Soc.*, 1926, **48**, 2770.

benzylidene chloride. Calculation of the B_{Ac} value for the benzylidene derivatives from the molecular rotation (—20,400) of 4 : 6-*O*-benzylidene-β-D-glucopyranose triacetate and A_{Ac} for D-glucopyranose gives $B_{Ac} = -1290$. A check is available in a calculation of the B value from the known anomeric forms[19] of methyl 2 : 3-di-*O*-acetyl-4 : 6-*O*-benzylidene-D-glucopyranoside; for these, $B_{OMe} = -2800$, and this should be very close to the true B_{Ac} value. The factor by which B_{Ac} has to be modified to get B_{Cl} for the benzylidene derivative is unknown, but fortunately the postulated B_{Ac} value is very small compared with the postulated A_{Cl} value (32,840), and it may be assumed that $B_{Cl} = B_{Ac} = -1290$ without risk of serious error. The specific rotation of 2 : 3-di-*O*-acetyl-4 : 6-*O*-benzylidene-β-D-glucopyranosyl chloride calculated from the A_{Cl} and B_{Cl} values obtained by this series of approximations is —92°, which agrees closely with the measured value (—89·2°) for the known compound.[1] Good agreement is also obtained in analogous calculations for the corresponding 4 : 6-*O*-ethylidene derivatives;[1] for these, the calculated $B_{Ac} = 9540$, giving a calculated specific rotation for 2 : 3-di-*O*-acetyl-4 : 6-*O*-ethylidene-β-D-glucopyranosyl chloride of —76·5°, comparable with a reported value[1] of —70·5°. If A_{Cl} for glucose applies accurately for these compounds the ratio B_{Ac}/B_{Cl} seems to be about 0·85, and the assumption that $B_{Cl} = B_{Ac}$ was quite safe. A usable correlation would have been obtained even if the ratio had departed much further from unity. The optical correlations confirm the β-configurations assigned on chemical grounds[1] to these 4 : 6-acetals of D-glucose.

The above results show that surprisingly accurate predictions of optical rotations may be made, by using equation (1) or (2), for several classes of carbohydrate derivative to which Hudson's rules of isorotation were formerly thought not to apply with numerical accuracy. For $(1' \longrightarrow 4)$- and $(1' \longrightarrow 6)$-linked oligosaccharides derived from D-glucose and D-mannose the predicted specific rotations of the acetylated derivatives should be in error by not more than 10°, and often by not more than 5°. Disaccharides have been chosen as illustrations, but the method should apply to other derivatives of (say) D-glucopyranose modified at position 6 or 4 by replacement of an acetoxy-group by alkoxyl or another acyl group, or, probably, by halogen. Specific rotations calculated for 2 : 3 : 4-tri-*O*-acetyl-6-bromo-6-deoxy-α-D-glucopyranosyl bromide and 2 : 3 : 4-tri-*O*-acetyl-6-chloro-6-deoxy-α-D-glucopyranosyl chloride are 199° and 187°, the reported values being 191·4° and 196·8°, respectively.[20, 21]

TABLE 4. *Constancy of* B-*values on interchange of " aglycones " of moderate polarisability in acetylated and unacetylated* D-*glucopyranose rings.*

		Acetylated derivative[a, c]			Unacetylated derivative[b]		
Substituent		$[M]_D$	A	B	$[M]_D$	A	B
1-*O*-Methyl	α	47,280	26,930	20,340	30,860	18,750	12,110
	β	−6,590			−6,640		
1-*O*-Ethyl	α	49,700[d]	29,120	20,580	31,600[d]	19,620	11,980
	β	−8,540[d]			−7,640[d]		
1-*O*-*cyclo*Hexyl	α	52,330[e]	31,270	21,050	34,900[e]	22,870	12,070
	β	−10,230[e]			−10,850[f]		
1-*O*-Acetyl	α	39,700	19,110	20,590			
	β	1,480					
1-*O*-Benzoyl	α	51,300[g]	32,650	19,650			
	β	−12,000					

[a] In chloroform. [b] In water. [c] Unless specified, data are from ref. 8. [d] Ferguson, *J. Amer. Chem. Soc.*, 1932, **54**, 4086. [e] Pascu, *ibid.*, 1930, **52**, 2568. [f] Fischer and Helferich, *Annalen*, 1911, **383**, 68. [g] Fischer and Bergmann, *Ber.*, 1918, **51**, 1760.

These regularities may be rationalised by considering the basis of the rules of isorotation. For the rules to be strictly accurate in the original form, and applicable to a series of

[19] Mathers and Robertson, *J.*, 1933, 696.
[20] Karrer and Smirnoff, *Helv. Chim. Acta*, 1922, **5**, 124.
[21] Helferich and Bredereck, *Ber.*, 1927, **60**, 1995.

anomeric pairs of carbohydrates, two alternative conditions must be satisfied: (*a*) There should be no interaction between the anomeric centre and its substituent, $C_{(1)}$–X, and the rest of the molecule. In this case van't Hoff's principle of optical superposition would hold exactly. (*b*) There should be a strictly comparable interaction between $C_{(1)}$–X and the rest of the molecule if the structural environment around $C_{(1)}$ is similar and X is either the same group or has similar electronic properties. It is the latter condition which is applicable in carbohydrates, and to which regularities in steroids and terpenoids[22] have been ascribed. A departure from condition (*b*) leads to irregular A and B values. The most probable source of electronic interactions between the anomeric substituent and the rest of the molecule is the polarisability of the $C_{(1)}$–X bond. Interchange of aglycones, which may show considerable variations in the A value, leaves the B value unaltered, as required by the second isorotation rule, only when the " aglycone " is of low or moderate polarisability. This is illustrated by the data for various acetylated and free alkyl D-glucopyranosides in Table 4, which should be compared with the data for glucose in Tables 1 and 2. The polarisability of the C–F bond is fairly low,[23] and it is not surprising to find for two known pairs of anomeric acetylated glycosyl fluorides that the B value is not greatly altered by the presence of the fluorine atom: for α- and β-tetra-*O*-acetyl-D-glucopyranosyl fluorides,[24] $B_F = 19,640$, and for the D-glucose penta-acetates (Table 1), $B_{Ac} = 20,590$; and for the corresponding anomeric derivatives of 6-bromo-6-deoxy-D-glucose, $B_F = 25,900$ for the fluorides,[25] and $B_{Ac} = 25,190$ for the acetates.[26]

If the aglycone is of low or moderate polarisability, its A value remains fairly constant, as required by the first isorotation rule, even if marked changes occur at positions 3 and 5. Only changes at position 2 appear to have an effect on the A values of all aglycones; therefore the vicinal action of the $C_{(1)}$–X group always extends at least as far as $C_{(2)}$.

The vicinal action of the more readily polarisable groups at position 1, such as chlorine, phenoxy, phenylthio, and probably bromine and iodine, but not fluorine, extends further, embracing at least position 5 and probably position 3, so that an exact correspondence of structure is required over this part of the molecule to obtain concordant optical parameters. The interaction causes a modification of A and B values, the extent of which is determined by the nature of the aglycone. Considerable latitude is still permissible in structural changes at the most distant parts, positions 4 and 6, without causing further changes in A values or irregularities in B values. Close correspondence of conformation will also be required over the whole molecule, and in fact in all compounds discussed the pyranose rings have stable C1 conformations. The same considerations would apply for mannopyranose derivatives, for which conformational differences have been postulated to cause irregularities of optical rotations.[27]

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