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LINEAR RELATIONSHIP BETWEEN MOLECULAR ROTATION AND BOND REFRACTION IN CARBOHYDRATES

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ABSTRACT

The molecular rotations ($[M]_D$) of derivatives of α-D-glucopyranose, α-D-galactopyranose, and α-D-xylopyranose having different substituents at the anomeric carbon atom are shown to be linearly related to the bond refractions ΣR_D in the form of the empirical equation $[M]_D = m\Sigma R_D + I$, where m and I are constants.

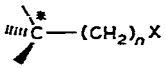
INTRODUCTION

The search for a relationship between the optical rotation and the configuration of a compound has long occupied the attention of chemists. Currently, theoretical approaches[1–4] have had only limited success in the quantitative prediction of optical rotation, but empirical approaches[5–12] seem to be more promising in this aspect.

We have shown[12] that, with a different treatment of the term ΣR_D, the empirical equation *1*[11],

$$[M]_D = m\Sigma R_D + I \qquad (1)$$

(where $[M]_D$ is the molecular rotation, ΣR_D is the sum of bond refractions, and m and I are constants for a given series of compounds; the subscript D denotes the sodium D-line), gives good correlations for several series of aliphatic and cyclic compounds having one chiral centre (**1**). Each series was formed by varying either the substituent X[12] or the carbon chain-length *n*[13]. Poorer plots were obtained when X and *n* were varied together[13].



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Since equation *1* is simple (the R_D values for the individual bonds are known[14]) and has potential for predicting the molecular rotations of other compounds in the same series, it was of interest to extend its use to carbohydrates. Hitherto, there

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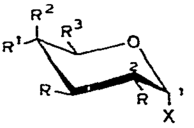
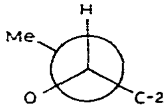
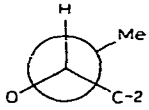
has been no satisfactory quantitative treatment of the vast amount of literature data on the molecular rotations of carbohydrates. Derivatives of α-D-glucopyranose (**2–5**), α-D-galactopyranose (**6** and **7**), and α-D-xylopyranose (**8** and **9**) having different substituents at the anomeric carbon atom were chosen for the first part of the investigation, in order to avoid dealing with a mixture of conformers. Compounds **2–9** are expected to exist practically in the $^4C_1$ conformation only[15,16]. For substituents that can form an asymmetric conformational unit (*e.g.*, X = OMe), the orientation shown in **10a** is favoured because of both the exo-anomeric effect and steric factors[10]; **10a–10c** are Newman projections viewed from C-1 along the C-1–OMe bond axis. It is now reported that equation *1* can be applied to these carbohydrates.



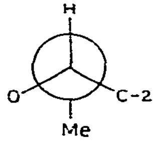
2 $R = R^1 = OAc$, $R^2 = H$, $R^3 = CH_2OAc$
3 $R = R^1 = OH$, $R^2 = H$, $R^3 = CH_2OH$
4 $R = R^1 = OBz$ $R^2 = H$, $R^3 = CH_2OBz$
5 $R = R^1 = OCH_2Ph$, $R^2 = H$, $R^3 = CH_2OCH_2Ph$
6 $R = R^2 = OAc$, $R^1 = H$, $R^3 = CH_2OAc$
7 $R = R^2 = OH$, $R^1 = H$, $R^3 = CH_2OH$
8 $R = R^1 = OAc$, $R^2 = R^3 = H$
9 $R = R^1 = OH$, $R^2 = R^3 = H$



10a



10b



10c

METHOD AND RESULTS

For a monovalent substituent (*e.g.*, X = Br), the term ΣR_D is equal to the bond refraction of the C–X bond. For substituents that are polyatomic and form asymmetric conformational units (X = YZ, where Y = N, O, or S), there are two cases to be considered. When Z contains an acetyl group attached to Y (*e.g.*, $X = OCOCH_3$), the term ΣR_D is equal to the sum of the bond refraction of the C–Y bond and the projection of the bond refraction of the Y–Z bond on the C-1–Y bond axis. When Z does not contain an acetyl group attached to Y (*e.g.*, $X = OCH_3$), the term ΣR_D is equal to the sum of the bond refraction of the C–Y bond and the projection of the bond refraction of the Y–Z bond on the C-1–C-2 bond axis. For the latter case, the conformer **10a** was used for the calculations of ΣR_D. There are also two cases to be considered when Z contains a substituted phenyl ring. When the ring-substituent X_1 is strongly electron-withdrawing (*e.g.*, NO_2, CN, and $COCH_3$), its contribution to the bond refraction of the parent ring is the bond refraction of the C-X_1 bond (*para* position) or half of it (*ortho* or *meta* position; the C_{Ar}–X_1 bond is at 60° to the Y–C_{Ar} bond in these two positions; the subscript Ar connotes aryl). When X_1 is not strongly electron-withdrawing (*e.g.*, OH, NH_2, OR, and the halogen atoms), the contribution of X_1 to the bond refraction of the parent ring is obtained

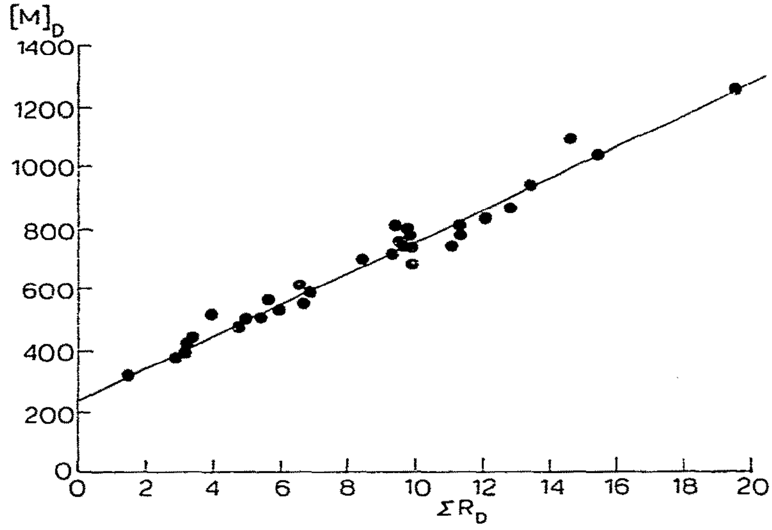


Fig. 1. Relationship between molecular rotation and bond refraction in α-D-glucopyranose tetra-acetate derivatives **2**.

TABLE I

BOND REFRACTIONS (ΣR_D)[a] FOR VARIOUS SUBSTITUENTS

X	*C-X*	*X*	*C-X*[b]	*X*	*C-X*[b]
H	0[c]	OEt	4.95	$OC_6H_4NO_2$(*o*)	11.3
F	1.44	OPr^i	5.62	$OC_6H_4NO_2$(*m*)	11.3
Cl	6.51	OBu	5.38	$OC_6H_4NO_2$(*p*)	13.4
Br	9.39	OHex	5.41	OC_6H_4Me(*o*)	9.87
I	14.6	OC_6H_{11}	5.92	OC_6H_4Me(*m*)	9.50
OAc	3.14	OCH_2CHCH_2	5.75	OC_6H_4Me(*p*)	9.32
$OCOCH_2F$	2.91	OPh	9.23	OC_6H_4COPh(*p*)	9.55
$OCOCH_2Cl$	3.20	OC_6H_4Cl(*m*)	9.94	SMe	10.9
$OCOCH_2Br$	3.36	OC_6H_4Cl(*p*)	9.54	SEt	11.1
OBz	3.91	OC_6H_4Br(*p*)	9.72	SC_6H_{11}	12.1
$OCOC_6H_4NO_2$(*p*)	3.96	OC_6H_4OH(*p*)	9.26	SBu^t	8.40[d]
SAc	6.62	$OC_6H_4NH_2$(*p*)	9.31	SPh	15.4
NHAc	3.73	OC_6H_4OMe(*o*)	9.79	$SC_6H_4NO_2$(*p*)	19.5
ONO_2	6.86[b]	OC_6H_4COMe(*p*)	13.7	SCH_2Ph	12.8
OH	3.20[b]	$O(CH_2)_2NHCO(CH_2)_8CH_3$	5.40	$S(CH_2)_6NH_2$	11.6
OMe	4.76[b]	$O(CH_2)_3NHCO(CH_2)_8CH_3$	5.41		

[a] Calculated from individual bond refractions given in ref. 14. Angle CSC = 105° (*Handbook of Chemistry and Physics*, 4th edn., Chemical Rubber Co., Cleveland, Ohio, 1968, p. F-157). All other angles are given in the previous work[12]. [b] Calculated for conformer **10a**. [c] See text. [d] Calculated for the eclipsed conformer (see text).

TABLE II

MOLECULAR ROTATIONS OF COMPOUNDS 2–9

X	$[M]_D$	*Ref.*	*X*	$[M]_D$	*Ref.*	*X*	$[M]_D$	*Ref.*
Compounds 2^a								
F	315	17	OAc	397	21	SPh	1030	25
Cl	609	17	OBz	513	21	$OC_6H_4Br(p)$	803	19
Br	813	17	$OCOCH_2F$	378	17	$OC_6H_4Cl(m)$	737	19
I	1087	17	$OCOCH_2Cl$	428	17	$OC_6H_4Cl(p)$	760	19
						$OC_6H_4NO_2(o)$	783	19
OMe	471	18	$OCOCH_2Br$	445	17	$OC_6H_4NO_2(m)$	811	19
OPh	715	19	$SC_6H_4NO_2(p)$	1242	22	$OC_6H_4NO_2(p)$	938	19
ONO_2	586	20	SAc	548	23	$OC_6H_4Me(o)$	679	19
OHex	505	21	SEt	745	24	$OC_6H_4Me(p)$	718	19
OC_6H_{11}	525	21	SC_6H_{11}	834	24	$OC_6H_4COPh(p)$	749	19
OPr^i	566	21	SBu^t	697	24	$OC_6H_4OMe(o)$	774	19
OEt	497	21	SCH_2Ph	863	24			
Compounds 3^b								
OMe	309	26	SMe	386	24	$OC_6H_4NO_2(o)$	620	19
OH	203	27	OPh	463	19	$OC_6H_4NO_2(m)$	569	19
$S(CH_2)_6NH_2$	646	28	$O(CH_2)_2NHCO(CH_2)_3CH_3$	256	30	$OC_6H_4NO_2(p)$	650	19
OEt	316	21	$O(CH_2)_3NHCO(CH_2)_3CH_3$	274	30	$OC_6H_4Me(o)$	421	19
OC_6H_{11}	349	21	$OC_6H_4NH_2(p)$	526^c	19	$OC_6H_4Me(p)$	480	19
OCH_2CHCH_2	332	29	$OC_6H_4OH(p)$	486	19	OBu	320	31
H	70	25	$OC_6H_4OMe(o)$	447	19	F	176	32
Compounds 4^a								
F	658^d	33	Br	811	33	H	244	34
Cl	670	33	I	981	33			
Compounds 5^a								
SPh	973	35	Cl	384	36	$OCOC_6H_4NO_2(p)$	503	37
OBz	403	36	OH	117	37			
Compounds 6^a								
OAc	416	21	Br	862	38	$OC_6H_4OMe(o)$	794^e	43
Cl	651	21	NHAc	457	39	$OC_6H_4COMe(p)$	974	43
OPh	744	21	$OC_6H_4Me(o)$	758	19			
ONO_2	625	21	$OC_6H_4Me(m)$	780	19			
Compounds 7^b								
OPh	556	19	$OC_6H_4Me(o)$	508	19	$OC_6H_4COMe(p)$	674	19
OMe	380	40	$OC_6H_4Me(m)$	559	19	OCH_2CHCH_2	398	29
NHAc	431	39	$OC_6H_4OMe(o)$	605	19	$S(CH_2)_6NH_2$	590	28
OH	272	41						
Compounds 8^a								
F	187	17	Br	718	17	OMe	347	42
Cl	504	17	OAc	283	20	OPh	476	42
Compounds 9^b								
OH	141	41	OMe	253	41	F	115	32

[a] Sodium D-line, chloroform. [b] Sodium D-line, water. [c] Methanol. [d] Pyridine. [e] There was a calculation error in the original source.

TABLE III

CORRELATIONS OF MOLECULAR ROTATIONS WITH BOND REFRACTIONS IN COMPOUNDS **2–9** BY USE OF EQUATION *1*

Compounds	*n*[a]	*r*[b]	*Slope (m)*	*Intercept (I)*	*Average deviation*[c] *(%)*
2	33	0.984	50.8	251	4
3	21	0.947	41.5	84	10
4	4	0.985[d]	51.0	288	9
5	5	0.903	55.3	110	44 (19)[g]
6	10	0.976	53.5	269	3
7	9	0.967[e]	36.9	187	6
8	5	0.993[f]	67.3	68	5
9	3	0.929	41.0	41	14

[a] Number of points used in the correlations. [b] Correlation coefficient. [c] Average deviation of calculated molecular rotations from the corresponding observed values. [d] X = F is excluded in the plot because it was measured in pyridine. [e] X = NHAc is excluded; if included, r = 0.937, m = 32.8, I = 232. [f] X = OPh is excluded. [g] If X = OH is excluded.

by successive projections[12] of the bond refraction of the C–X_1 bond on the Y–C_{Ar} bond axis. Using the literature R_D values[14], the relevant ΣR_D values shown in Table I were calculated.

Equation *1* was used to correlate the reported molecular rotations (Table II) of compounds **2–9**. The results are given in Table III, and the plot for the α-D-glucopyranose tetra-acetates (**2**) is shown in Fig. 1.

DISCUSSION

Some deviations from the correlation lines are expected because (*a*) the assumption of perfect chair conformation used in our calculations of ΣR_D may not be fully correct[10]; (*b*) there could be some contribution from conformer **10b**[10]; and (*c*) the molecular rotations for the same compound reported by different workers often vary significantly. In view of these factors, the plots of $[M]_D$ against ΣR_D are good (Table III). The average deviation from the correlation line is only 6% for the four series (**2**, **3**, **6**, and **7**) that have more data for their plots. The larger deviations for series **5** and **9** probably do not give a true picture, because few data are available for the plots. The average m value for the three polyacetate series (**2**, **6**, and **8**) is 57 ±6, and that for the three parent series (**3**, **7**, and **9**) is 40 ±3. The m values for the tetrabenzoate (**4**) and the tetrabenzyloxy (**5**) series are also within the range of the polyacetate series. Therefore, it may be inferred that the effects of varying the α-substituents at the anomeric carbon atom on the molecular rotations for the α-D-glucopyranose, α-D-galactopyranose, and α-D-xylopyranose series are about the same if the parameter m is interpreted as a measurement of such effects.

It must be emphasised that the above approach is empirical, and no explanation can be offered for the two different ways of calculating the ΣR_D values for X = YZ (Y = N, O, or S) as well as for the substituents on a phenyl ring. However, in both cases, one way involves the strong electron-withdrawers and the other way involves the weak electron-withdrawers and electron donors.

Examination of Dreiding models shows that, for steric reasons, the three conformations **10a–10c** are not favoured when X = SBu^t. The conformation with the *tert*-butyl group and H-1 eclipsed is favoured sterically. Indeed, the ΣR_D value calculated for this conformation gives a good fit in Fig. 1 (the point for $\Sigma R_D = 8.40$), whereas that calculated for **10a** ($\Sigma R_D = 12.2$) deviates considerably from the correlation line.

The case where X = H is unique, in the sense that there are no α and β anomers. Since, in principle, the plots for the α and β series have the same intercept, in order for the point X = H to lie on both plots it must occur at $\Sigma R_D = 0$. For this reason, $\Sigma R_D = 0$ is assigned for X = H, instead of using the value of 1.676 for a C–H bond. Our value gives a better fit for X = H in series 3.

The α-D-mannopyranose and the β-D-glycopyranose series are more complicated to deal with, because of the presence of the two chair conformations[15,16] and the increase in importance of the conformer **10b**[10]. As expected, no linear plots were obtained with the present approach. This problem is being investigated further.

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