Application of Coupled Oscillator Theory to Conformational Analysis of Glycosides with Aromatic Groups

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To confirm the range of application of the dipole–dipole interaction approximation in the coupled oscillator theory, the rotational strength of several *p*-nitrophenylglycosides (glucopyranoside, galactopyranoside, mannopyranoside, xylopyranoside, and fucopyranoside) and phenylglycoside (glucopyranoside) have been calculated with the Kirkwood–Tinoco equation. The orientations of the aromatic groups estimated by the above equation turn out to be in good agreement with those obtained from the semiempirical molecular orbital calculation (MNDO method) and molecular mechanics calculation (CHARMm). It is confirmed, therefore, that the Kirkwood–Tinoco equation is sufficiently applicable even when a chromophore is located relatively near a saturated group.

The rotational strength of a molecule or a complex composed of a chromophore and chiral saturated vicinal groups can be calculated according to the Kirkwood's coupled oscillator theory. For example, the orientations of chromophores included in the cavities of α- and β-cyclodextrins were determined by the Kirkwood–Tinoco equation, where a dipole–dipole interaction approximation is assumed.[1–4] In general, however, the method with monopole interaction is more correct than the method with dipole interaction approximation, although the monopole interaction is more difficult to calculate. The dipole interaction approximation is expected to give good results when the chromophore is located far from the saturated group, but the approximation will be worse as the chromophore approaches it. To avoid this problem, Moffitt applied the monopole interaction to the nearest moiety and the dipole interaction to others situated farther away.[5] Here the question arises how far the chromophore can approach the saturated group under the dipole approximation. In the present work, therefore, the author has estimated the limitation of application of the Kirkwood–Tinoco expression in chiral organic compounds, by using simple structure glycosides where aromatic groups are covalently and closely bound to sugar moieties.

Experimental

All the glycosides used were commercially available. Circular dichroism (CD) and absorption spectra were measured at room temperature with a Jasco J-20 spectropolarimeter and a Shimadzu UV-265FS spectrophotometer, respectively.

The experimental dipole strength (*D*) was calculated according to equation (1), where ε_{max} is the maximum value of

$$D = 0.92 \times 10^{-38}\,\pi^{\frac{1}{2}}\,\varepsilon_{max}\,\frac{\Delta}{\lambda_{max}} \qquad (1)$$

the molar extinction coefficient, λ_{max} is the wavelength at absorption maximum, and Δ is the half-band width at 1/e of maximum absorption. On the other hand, the experimental values of the rotational strength (*R*) were obtained by using equation (2),[6] where $[\theta]_{max}$ is the maximum value of the molar

$$R = 0.696 \times 10^{-42}\,\pi^{\frac{1}{2}}\,[\theta]_{max}\,\frac{\Delta}{\lambda_{max}} \qquad (2)$$

ellipticity and Δ is the half-band width at 1/e of maximum ellipticity.

Table 1. Frequency of electronic transitions (ν_{0j}) and polarizability (α_{33}, α_{11}) of bonds.

Bond	$\nu_{0j}/10^{15}\ s^{-1}$	$\alpha_{33}/Å^3$	$\alpha_{11}/Å^3$
C–O	1.67	0.89	0.46
C–C	2.00	0.98	0.27

Theoretical.—The theoretical rotational strength of the transition from the ground state (0) to the excited state (a), R_{0a}, was calculated by using equations (3) and (4) developed by Kirkwood and Tinoco.[1] Here $\boldsymbol{e}_j$ is the unit vector in the

$$R_{0a} = \pi\nu_a\mu_{0a}{}^2 \sum_j \frac{\nu_{0j}{}^2(\alpha_{33}-\alpha_{11})_j(GF)_j}{c(\nu_{0j}{}^2 - \nu_a{}^2)} \qquad (3)$$

$$(GF)_j = \frac{1}{r_{j3}}\left[\boldsymbol{e}_{0a}\cdot\boldsymbol{e}_j - \frac{3(\boldsymbol{e}_{0a}\cdot\boldsymbol{r}_j)(\boldsymbol{e}_j\cdot\boldsymbol{r}_j)}{r_j{}^2}\right]\boldsymbol{e}_{0a} \times \boldsymbol{e}_j\cdot\boldsymbol{r}_j \qquad (4)$$

direction of the symmetry axis of the bond *j* in the glycone (sugar moiety); $\boldsymbol{r}_j$ is the vector directed from the centre of the chromophore (*p*-nitrophenyl or phenyl group) to the bond *j*; ν_{0j} is the frequency of the electronic transitions of the bond *j*; $\boldsymbol{e}_{0a}$ is the unit vector in the direction of the electric dipole moment (μ_{0a}) of the transition from the ground state (0) to the excited state (a) in the chromophore, and ν_a is its frequency; α_{33} and α_{11} are parallel and perpendicular bond polarizabilities, respectively, to the symmetry axis of the bond *j*; *c* is the velocity of light.

The values of α_{33}, α_{11},[7,8] and $\nu_{0j}{}^2$ are shown in Table 1. The assignment of each electronic transition of the aromatic groups in the glycosides was undertaken in view of the calculation by Shimizu *et al.*[3] The electric transition moment was put at the centre of the aromatic ring. The co-ordinates of the glycones were obtained from the data of X-ray analysis.[9–15] All the C(6)–O(6) and O–H bonds were neglected owing to their flexibility. Moreover, since all the C–H bonds may have isotropic polarizability,[16] their effects were also neglected.

In the calculation of the rotational strength, only three typical conformers were taken into consideration concerning

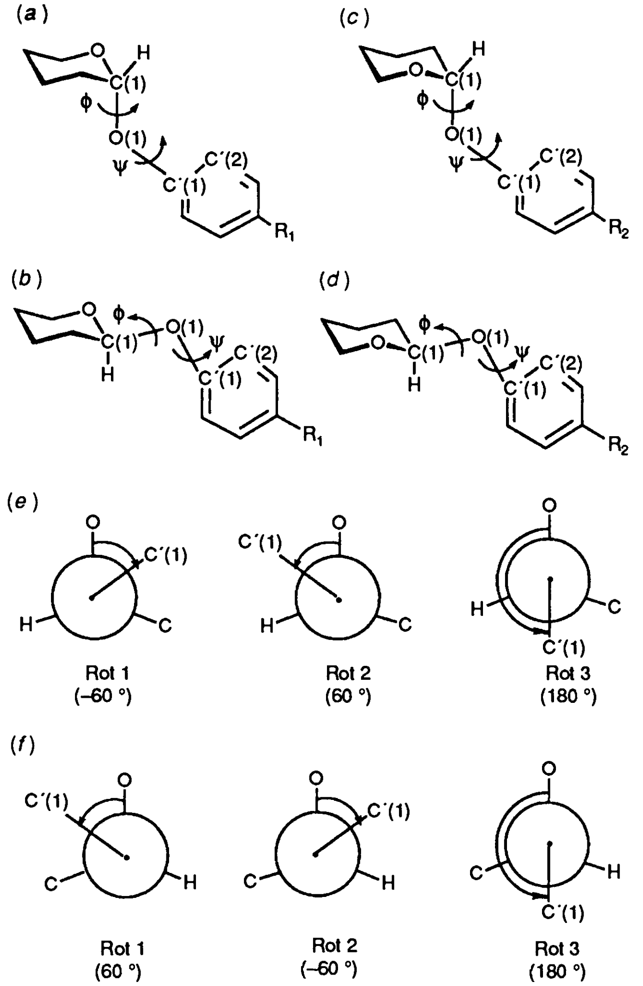

Figure 1. Schematic structures of (*a*) α-D-type, (*b*) β-D-type, (*c*) α-L-type, and (*d*) β-L-type glycosides. φ and ψ are dihedral angles for O–C(1)–O(1)–C′(1) and C(1)–O(1)–C′(1)–C′(2), respectively; φ is defined as shown in (*e*) for α-D-type and β-L-type glycosides and in (*f*) for β-D-type and α-L-type glycosides.

the orientations of the phenyl and the *p*-nitrophenyl rings; namely, the dihedral angle φ was fixed to 60°, −60° or 180° (Figure 1). On the other hand, the dihedral angle ψ was assumed to change continuously.

The stable orientations of the aromatic groups were also estimated by semiempirical molecular orbital calculation, MNDO method,[17] and by molecular mechanics calculation using the program 'CHARMm'.[18] The calculations were carried out on a CRAY X-MP/216 computer.

Results and Discussion

p-Nitrophenyl-α-D-glucopyranoside (PNPADGLU) showed two positive CD bands at 304 and 219 nm, while *p*-nitrophenyl-β-D-glucopyranoside (PNPBDGLU) gave two negative CD bands at 314 and 220 nm. The CD bands at *ca.* 220 and *ca.* 310 nm correspond respectively to the $^1B_2 \longleftarrow {}^1A_1$ and $^1A_1 \longleftarrow {}^1A_1$ transitions of the *p*-nitrophenoxy group.[3] Other α-D-type *p*-nitrophenylglycosides[galactopyranoside (PNPADGAL), mannopyranoside (PNPADMAN), xylopyranoside (PNPADXYL)] and *p*-nitrophenyl-β-L-fucopyranoside (PNPBLFUC) show CD spectra similar to those of PNPADGLU, and other β-D-type *p*-nitrophenylglycosides[galactopyranoside (PNPBDGAL), mannopyranoside (PNPBDMAN), xylopyranoside (PNPBDXYL)] and *p*-nitrophenyl-α-L-fucopyranoside (PNPALFUC) give the CD spectra analogous to those of PNPBDGLU. On the other hand, phenyl-α-D-glucopyranoside (PADGLU) shows two positive CD bands at 261 and 213 nm, whereas phenyl-β-D-glucopyranoside (PBDGLU) has two negative CD bands at 262 and 214 nm. The CD bands at *ca.* 210 and *ca.* 260 nm correspond to the $^1A_1 \longleftarrow {}^1A_1$ and $^1B_2 \longleftarrow {}^1A_1$ transitions of the phenoxy group, respectively.[3]

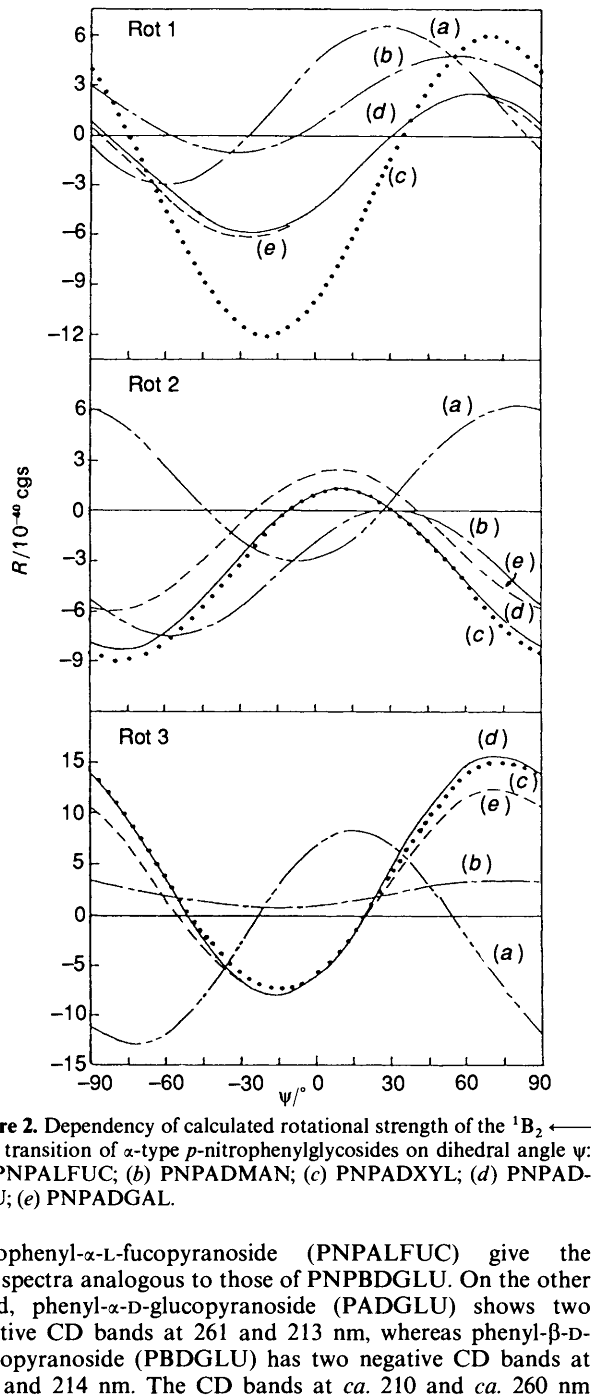

Figure 2. Dependency of calculated rotational strength of the $^1B_2 \longleftarrow {}^1A_1$ transition of α-type *p*-nitrophenylglycosides on dihedral angle ψ: (*a*) PNPALFUC; (*b*) PNPADMAN; (*c*) PNPADXYL; (*d*) PNPADGLU; (*e*) PNPADGAL.

Since the $^1A_1 \longleftarrow {}^1A_1$ transition is parallel to the long axes of the phenoxy and *p*-nitrophenoxy groups, the rotational strength of this transition does not depend on the rotation angle ψ of the aromatic rings (Figure 1). On the other hand, the $^1B_2 \longleftarrow {}^1A_1$ transition is short-axis polarized in both groups, and consequently the rotational strength should depend on the ψ value.

Table 2 shows the comparison between the calculated and the experimental rotational strength, while the calculated values are illustrated only for the $^1A_1 \longleftarrow {}^1A_1$ transition. It should be noticed here that concerning the $^1A_1 \longleftarrow {}^1A_1$ transition the calculated values for the rotamer 1 (Rot 1) and rotamer 2 (Rot 2) are in relatively good agreement with the experimental data.

As for the $^1B_2 \longleftarrow {}^1A_1$ transition, Figures 2 and 3 illustrate the dependency of the calculated rotational strength on the rotation angle ψ for the α- and β-types of *p*-nitrophenylglycosides, respectively, and Figure 4 shows that for α- and β-types of phenylglucosides. As a whole, the dependence curves for PNPADGLU, PNPADGAL, PNPADXYL, and PNPADMAN all show similar tendencies, while those for PNPBDGLU, PNPBDGAL, PNPBDXYL, and PNPBDMAN resemble each other.

The dihedral angles φ and ψ, which bring about the rotational strength compatible with the experimental values, are summarized in Table 3, together with the dihedral angles optimized by molecular orbital (MNDO) and molecular mechanics (CHARMm) methods. Although, qualitatively, the values obtained by the coupled oscillator theory agree well with the optimized values by MNDO and CHARMm, it is recognized that generally the absolute values of calculated rotational strength do not agree strictly with experimental values. In the calculation of CD, the sign of the rotational strength is more important than the absolute values. That is to say, the requirement for the good agreement is the

Table 2. Calculated and experimental rotational strength (R).[a]

	$R/10^{-40}$ cgs				
	Calculation $^1A_1 \longleftarrow {}^1A_1$			Experimental $^1A_1 \longleftarrow {}^1A_1$	$^1B_2 \longleftarrow {}^1A_1$
Glycoside	Rot 1	Rot 2	Rot 3		
PADGLU	1.6	3.3	−3.6	5.4	1.3
PBDGLU	−1.3	−0.6	1.0	−3.5	−1.0
PNPADGLU	3.1	7.7	−10.9	6.8	3.0
PNPBDGLU	−1.1	−2.9	2.5	−5.5	−2.5
PNPADGAL	2.8	4.0	−7.3	6.1	3.3
PNPBDGAL	−1.8	−3.3	2.9	−5.4	−2.9
PNPADMAN	−5.1	8.0	−6.8	6.0	2.0
PNPBDMAN	1.6	−3.6	4.4	−5.1	−1.5
PNPADXYL	7.9	8.7	−11.0	7.5	1.9
PNPBDXYL	−5.4	2.3	0.9	−1.7	−1.8
PNPALFUC	−2.9	−3.7	7.2	−6.4	−3.7
PNPBLFUC	1.5	4.2	−3.4	4.1	2.2

[a] Calculation data are shown only for $^1A_1 \longleftarrow {}^1A_1$. As for the $^1B_2 \longleftarrow {}^1A_1$ transition, calculation data are illustrated in Figures 2–4.

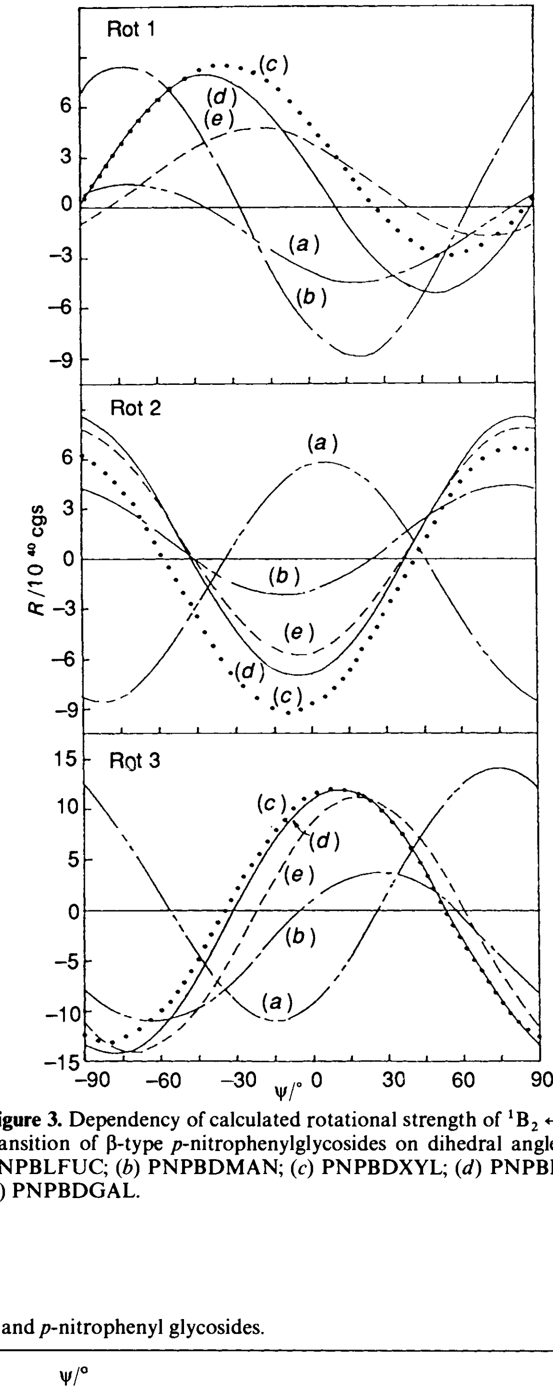

Figure 3. Dependency of calculated rotational strength of $^1B_2 \longleftarrow {}^1A_1$ transition of β-type *p*-nitrophenylglycosides on dihedral angle ψ: (*a*) PNPBLFUC; (*b*) PNPBDMAN; (*c*) PNPBDXYL; (*d*) PNPBDGLU; (*e*) PNPBDGAL.

Table 3. Geometric parameters (φ, ψ) obtained by various methods for phenyl and *p*-nitrophenyl glycosides.

	φ/°			ψ/°		
Glycoside	CHARMm	MNDO	CD[a]	CHARMm	MNDO	CD[a]
PADGLU	61.0	83.7	60	−5.2	10.1	−17–31
PBDGLU	−63.4	−75.9	−60	6.1	−5.8	−47–35
PNPADGLU		89.9	60		−6.1	−10–30
PNPBDGLU		−77.2	−60		−5.3	−47–37
PNPADGAL		85.0	60		8.7	−25–40
PNPBDGAL		−67.9	−60		−11.7	−46–37
PNPADMAN		87.0	60		−10.6	30
PNPBDMAN		−62.7	−60		−11.6	−46–25
PNPADXYL		87.7	60		−5.7	−10–30
PNPBDXYL		−74.9	−60		−4.2	−58–41
PNPALFUC		−82.0	−60		−12.4	−43–27
PNPBLFUC		79.7	60		−8.1	−34–46

[a] Dihedral angles φ and ψ which give the rotational strength which is qualitatively compatible with the experimental rotational strength shown in Table 2; the ψ values shown are the range where the sign of the rotational strength is the same as that of the experimental data.

Table 4. Calculated and experimental rotational strength (R).[a]

	$R/10^{-40}$ cgs			
	Calculation		Experimental	
Glycoside	$^1A_1 \longleftarrow {}^1A_1$	$^1B_2 \longleftarrow {}^1A_1$	$^1A_1 \longleftarrow {}^1A_1$	$^1B_2 \longleftarrow {}^1A_1$
PADGLU	2.1	0.04	5.4	1.3
PBDGLU	−0.4	−0.3	−3.5	−1.0
PNPADGLU	3.2	0.8	6.8	3.0
PNPBDGLU	−2.0	−5.0	−5.5	−2.5
PNPADGAL	1.8	1.2	6.1	3.3
PNPBDGAL	−2.9	−4.6	−4.5	−2.9
PNPADMAN	5.0	−2.2	6.0	2.0
PNPBDMAN	−3.4	−1.9	−5.1	−1.5
PNPADXYL	3.7	1.1	7.5	1.9
PNPBDXYL	2.8	−7.8	−1.7	−1.8
PNPALFUC	−2.0	−1.5	−6.4	−3.7
PNPBLFUC	2.8	4.1	4.1	2.2

[a] The angles φ and ψ are those of the most stable conformation calculated from MNDO method.

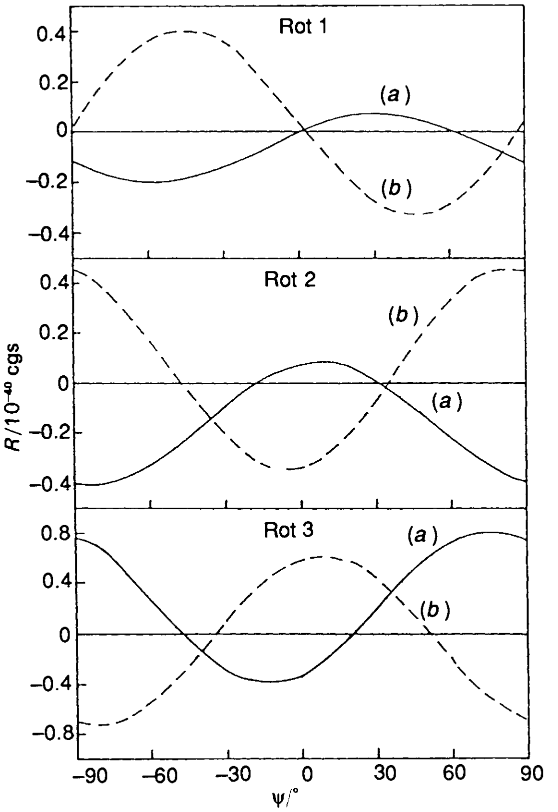

Figure 4. Dependency of calculated rotational strength of $^1B_2 \longleftarrow {}^1A_1$ transition of α- and β-type phenylglycosides on dihedral angle ψ: (*a*) PADGLU; (*b*) PBDGLU.

coincidence of the sign and the order of the rotational strength, especially the sign.[2,3,19] In view of such limitation of the calculation of rotational strength, it can be said that as a whole the calculated values in Tables 2 and 3 are compatible with the observed values. Here, it should be noted that strictly speaking, the stable conformations obtained from MNDO and molecular mechanics calculations are considered as those *in vacuo*, whereas the conformations determined experimentally are those in solution. In many cases, however, this difference is neglected. Moreover, the φ and ψ values (Table 3) from molecular mechanics method (CHARMm) do not agree well with those of MNDO. The molecular mechanics program used in this study 'CHARMm' is that generally used for biopolymers such as protein and DNA, and therefore its force field is a little coarse. Accordingly, the results from MNDO method seem to be more reliable. As for the ψ values estimated from CD in Table 3, only the angle range is shown, because of the difficulty in determining the ψ value unequivocally from Figures 2–4.

Then, in order to confirm further the validity of the Kirkwood–Tinoco equation, the rotational strength was calculated for the orientations of the aromatic rings determined from MNDO method, and it was compared with the observed values (Table 4). The stable rotamers, which correspond to Rot 1, Rot 2, and Rot 3, were found in the MNDO calculation. By calculating the populations of these rotamers assuming the Boltzmann distribution, it was revealed that Rot 2 predominates (more than 76%), specially (more than 94%) for PNPADMAN, PNPADGLU, PNPBDGLU, PNPBDGAL, PNPBDMAN, and PNPBDXYL. Therefore, only Rot 2 was taken into account in this calculation. As shown in Table 4, relatively good coincidence was obtained between the calculated and observed rotational strength. Although only qualitative, this suggests that the coupled oscillator theory is sufficiently applicable to the determination of the chromophore orientation even when it is located relatively near to the chiral saturated groups.

As for the dihedral angle φ, it is worth mentioning the experimental and calculated results of methyl glucosides. For example, the calculation by the PCILO semiempirical method indicates that for methyl-α-D-glucopyranoside (MADGLU) the global minimum occurs at φ = 65.8°, while in methyl-β-D-glucopyranoside (MBDGLU) the most advantageous is the conformer with φ = −57.8°.[20] X-Ray data give similar results: φ = 63.0° for MADGLU and −73.2° for MBDGLU.[10,21]

In conclusion, it has been confirmed in this work that the Kirkwood–Tinoco equation based on the dipole–dipole interaction approximation is generally applicable to the estimation of an aromatic group orientation bound covalently near to chiral saturated groups.

Acknowledgements

The author wishes to thank Dr. Toshio Fukaya, National Chemical Laboratory for Industry, for kindly supplying the MNDO program.

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Paper 9/04222I
Received 4th *October* 1989
Accepted 6th *February* 1990