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Note

Calculation of the optical rotation of some anhydro sugars in aqueous solution

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1,6-Anhydro-D-pyranoses and methyl 3,6-anhydro-D-pyranosides (Fig. 1) take up crystal structures[1–4] in which the ring form approximates $^1C_4$. We have applied a recently developed calculational model of saccharide optical activity to a series of anhydro sugars with the aim of interpreting observed solution rotations in terms of conformation.

The calculational method, previously described in detail[5,6], has its origins in Kirkwood's polarizability theory of optical activity[7]. It is less empirical than the group additivity models of Whiffen[8], Brewster[9], and others, and has previously been applied to a number of monosaccharides and disaccharides[5,6,10–12]. The method is based on a coupled-oscillator model which requires the solution of the secular equations:

$$\sum_{i=1}^{N} C_{ik}(V_{ij} - E_k\delta_{ij}) = 0 \quad j = 1, 2, \ldots, N$$

where V_{ij} is the coulombic interaction energy of bond localized transition dipole moments. The solution yields eigenvalues, E_k, specifying molecular transition energies, and eigencoefficients, C_{ik}, which describe the molecular transition-moments as linear combinations of the unperturbed-bond transition-moments. Circular dichroic rotational strengths are obtained directly, from which the optical rotation is calculated via a Kronig–Kramers transform. We report results as the molar rotation [M] at 589 nm. The estimated uncertainty in the calculational method[6] is $\pm 24°$ cm^2 dmol^{-1}. A FORTRAN algorithm MOLROT is available from the author upon request.

Atomic coordinates for 1,6-anhydro-β-D-glucopyranose were taken from the X-ray structure determination of Lindberg[2]; they were adapted appropriately for the corresponding galactopyranose, mannopyranose, and talopyranose. Atomic coordinates for methyl 3,6-anhydro-α-D-galactopyranoside were taken from the X-ray structure determination of Campbell and Harding[3]; coordinates for the corresponding glucopyranoside and mannopyranoside, and for the β anomers,

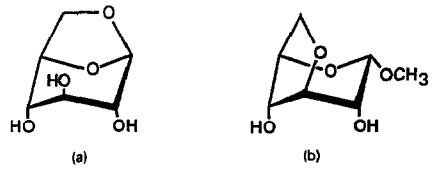

Fig. 1. $^1C_4$ conformations of (a) 1,6-anhydro-β-D-glucopyranose and (b) methyl 3,6-anhydro-α-D-glucopyranoside.

were generated by appropriate interchange of coordinates. In 1,6-anhydropyranoses, the chromophoric C-5–O-5–C-1–O-1–C-6 acetal moiety is part of the strained anhydro bridge (Fig. 1a); e.g., the C-5–O-5–C-1 bond angle is only 102°. This structural feature resulted in the three corresponding bond-interaction matrix elements being unrealistically large. An ad hoc reduction of these three V_{ij} by 20% brought the low-energy eigenvalue into agreement with earlier results on unstrained sugars[6]; the procedure resulted in only a 10% change in calculated rotation. The uncertainty in the calculational method for this class of sugars is thus estimated as $\pm 30°$ cm^2 dmol^{-1}.

Table I shows a comparison of the calculated and observed optical rotations. For 1,6-anhydro-β-D-pyranoses the calculated rotations, significantly, display the same dependence on chemical structure as the observed rotations, with the magnitude of negative rotation increasing in the order *galacto* < *gluco* < *talo* < *manno*. The calculated values are less negative than the observed values, but the difference is close to the estimated uncertainty in the model. Only small changes in geometry would be required to bring the calculated rotations into quantitative agreement with the observed values; the resulting ring forms would be very close to the crystal structure. The results for 1,6-anhydro-β-D-pyranoses, therefore, support

TABLE I

Calculated and observed Na_D molar rotations (deg cm^2 dmol^{-1}) for a series of anhydro sugars

Compound	$[M]_D^{calcd}$		$[M]_D^{obsd}$	Reference
	$^1C_4$			
1,6-Anhydro-β-D-galactopyranose	−17		−35	13–17
1,6-Anhydro-β-D-glucopyranose	−79		−107	16,18–21
1,6-Anhydro-β-D-talopyranose	−96		−130	22
1,6-Anhydro-β-D-mannopyranose	−156		−205	19,23
	$^1C_4$	E_4		
Methyl 3,6-anhydro-α-D-glucopyranoside	−46 (*gt*)	118 (*gt*)	96	24–27
Methyl 3,6-anhydro-α-D-galactopyranoside	−44 (*gt*)	129 (*gt*)	145	28–31
Methyl 3,6-anhydro-α-D-mannopyranoside	38 (*gt*)	188 (*gt*)	170	25,32–34
Methyl 3,6-anhydro-β-D-glucopyranoside	−418 (*gt*)	−327 (*gt*)	−243	24
	−199 (*tg*)	−206 (*tg*)		
Methyl 3,6-anhydro-β-D-galactopyranoside	−422 (*gt*)	−329 (*gt*)	−202	30,35
	−175 (*tg*)	−172 (*tg*)		
Methyl 3,6-anhydro-β-D-mannopyranoside	−382 (*gt*)	−261 (*gt*)	−169	34
	−167 (*gt*)	−86 (*tg*)		

a picture of nearly equivalent solution and crystal structures. This is in agreement with a substantial amount of ^{1}H NMR data, which has been reviewed by Černý and Staněk[36]. Of particular significance are the $J_{2,3}$ and $J_{3,4}$ coupling constants which reflect the slight pyranose ring flattening in the structure, relative to a canonical $^1C_4$ ring form; e.g., in the equatorial–equatorial arrangement, the coupling constant does not exceed 2.5 Hz. Previous analyses of the optical rotation of 1,6-anhydro-β-D-pyranoses based on empirical group additivity models, by Černý et al.[37] and by Horton and Wander[38,39], also indicated that a $^1C_4$ pyranose ring form satisfactorily accounts for the observed optical rotations.

Although the boat conformation B_{30} is not energetically competitive with $^1C_4$ (Fig. 1a), we examined the question of whether optical rotation would be sensitive to small populations of B_{30} in an equilibrium mixture. Coordinates of an MM3 energy-minimized B_{30} conformer of 1,6-anhydro-β-D-glucopyranose were kindly provided by T.B. Grindley, Dalhousie University. We calculate a molar rotation of $-94°$ cm^2 dmol^{-1}, similar to the observed value and that calculated using the crystal structure geometry (Table I). There is apparently a fortuitous cancellation of the optical rotation changes that occur in the $^1C_4 \rightarrow B_{30}$ conversion, indicating that optical rotation would not be sensitive to the presence of small amounts of B_{30}.

For methyl 3,6-anhydro-α-D-pyranosides and methyl 3,6-anhydro-β-D-pyranosides the present results indicate substantial departure from crystal structure geometries in solution. For methyl 3,6-anhydro-α-D-pyranosides (Fig. 1b) the crystal structure $^1C_4$ (*gt*) geometry consistently gives calculated rotations which are 150–173° cm^2 dmol^{-1} more negative than the observed values, which is well outside the range of estimated uncertainty in the model. Therefore, we examined the possibility that the extent of pyranose ring flattening is greater in solution than in crystals. We find that the rotation is very sensitive to ring conformation, with additional ring flattening sharply increasing the rotation. Calculated rotations for the E_4 conformation agree with the observed rotations (Table I). Given the uncertainty in the calculational model, the appropriate conclusion to be drawn from the present results is that the solution conformation more closely approximates E_4 than $^1C_4$. NMR evidence that the ring is in fact not fully flattened is the ^{1}H $J_{1,2}$ value of 2.8 Hz[40–42].

For methyl 3,6-anhydro-β-D-pyranosides the crystal structure $^1C_4$ (*gt*) geometry also gives calculated rotations which are more negative than the observed values, by 175–220° cm^2 dmol^{-1}. The effect of additional ring flattening on calculated rotation was again examined and, because of the presence of the *syn*-axial OMe in β anomers, both *gt* and *tg* methoxy conformers were considered. Both types of modification give significantly more positive rotations (Table I); interpretation of the results is thereby complicated. The presence of the *syn*-axial OMe argues for more extensive flattening in the β anomers than in the α anomers, however, and the E_4 ring geometries account for the observed rotations if *tg* methoxy forms are present as a minor, yet significant, conformer. It should also be pointed out that

the calculations reproduce the observed smaller magnitude of the mannopyranoside rotation. An E_4 solution conformation for methyl 3,6-anhydro-β-D-pyranosides is also consistent with the ^{1}H NMR $J_{1,2}$ value of 0 Hz observed in methyl 3,6-anhydro-β-D-glucopyranoside[43].

Although the solution conformation of methyl 3,6-anhydro-α-D-pyranosides and methyl 3,6-anhydro-β-D-pyranosides have in the past been discussed solely in terms of $^1C_4$ or "distorted" $^1C_4$ ring conformations, the present interpretation of their optical rotations indicates that the ring flattening that occurs in solution is so substantial that qan envelope form more closely approximates the actual conformation. Molecular modeling has become useful in the conformational analysis of carbohydrates[44], but no studies of anhydro sugars have yet been reported. In unstrained pyranose rings, all ring forms other than $^4C_1$ are "high energy" ring forms, but French[45] has shown that the energy differences among these high energy ring forms are not great. Detailed molecular modeling calculations on anhydro sugars may shed additional light on this matter.

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