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Note

The exo-anomeric effect: experimental evidence from crystal structures

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The exo-anomeric effect is of importance in the conformational analysis of polysaccharides as it implies an interaction, in addition to those considered thus far, in preparing isoenergy conformational contour-maps. This additional interaction involves a bias on the dihedral angles (ϕ, ψ) governing rotation about the glycosidic linkage. By using the (ϕ, ψ) information available from single-crystal, X-ray structure-determinations for glycopyranosides and oligosaccharides, it is shown that glycopyranosides fall into two main conformational classes. Within narrow limits, α- and β-glycopyranosides correspond to the *gauche–gauche* and *trans–gauche* classes, respectively, in relation to dimethoxymethane. Among the compounds studied, the distribution of ϕ values is more restricted for the β-pyranosides. Rotations about the glycosidic linkages (C-1–O-1 and O-1–C-x) are subject to different restrictions, thus ϕ values cover a range of 30°, whereas ψ values are spread over a range of 100°. This information offers strong experimental evidence that a conformational bias restricts rotation about the C-1–O-1 bond. The same type of evidence emerges from a comparison of the range of glycosidic dihedral-angles (ϕ, ψ) for cellobiose and methyl cellobioside as compared with cellobiose acetates. It is found that the angle ϕ varies but little, whereas the range of ψ is considerably greater.

Background. — Molecules whose skeletal structure involves atomic sequences of alternating polarity and atoms having free electron-pairs favor the *gauche–gauche* orientation[1–3]. In sugars, this phenomenon is described as the "generalized anomeric effect"[4] or the "Edward–Lemieux effect"[5]. Although studies based on molecular-orbital and semi-empirical calculations have confirmed the experimental observations[6–9], explanations for this phenomenon still invite debate[3,9,10]. Among the different manifestations of the "generalized anomeric effect", that influencing the rotameric states about the anomeric bond in carbohydrates (angle Φ in Fig. 1) has been referred to as the exo-anomeric effect[11,12]. Lemieux and Koto[13] have concluded that the exo-anomeric effect substantially influences the conformations of glycopyranosides.

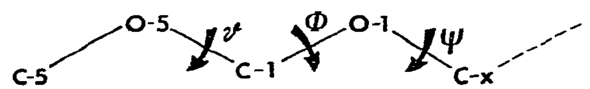


Fig. 1. Schematic representation of carbon–oxygen alternation, and definition of dihedral angles.

As experimental data for polysaccharides do not define short-range conformation adequately, the elucidation of the three-dimensional, crystalline structure of polysaccharides begins with the determination of the allowed conformational space of contiguous residues rotating about the glycosidic linkages (angles Φ, ψ in Fig. 1). The existence of a conformational bias, resulting from the "generalized anomeric effect" would provide a new insight for the investigation of allowed conformations. The aim of this communication is to use the information available from single-crystal, X-ray structure-determinations of glycopyranosides and oligosaccharides, to show that a conformational *bias* does indeed exist in the solid state. This information constitutes the most direct experimental manifestation of what is referred to as the exo-anomeric effect.

Fig. 1. is a schematic depiction of carbon–oxygen alternation characteristic of glycopyranosides and oligosaccharides. For the α and β configuration of the ${}^4C_1$(D) and ${}^1C_4$(D) conformers: $\theta = 60°$ denotes the α configuration for the ${}^4C_1$(D) ring; $\theta = 180°$ denotes the β configuration for the ${}^4C_1$(D) ring; $\theta = 180°$ denotes the α configuration for the ${}^1C_4$(D) ring; and $\theta = -60°$ denotes the β configuration for the ${}^1C_4$(D) ring.

When the conformation of a crystalline glycopyranoside or oligosaccharide corresponded to the ${}^1C_4$(D) ring-form, the data were transposed into the mirror-image conformation [${}^4C_1$(L)] to restrict the comparison to only two classes of rotamers involving angle θ, namely "*gauche*" and "*trans*".

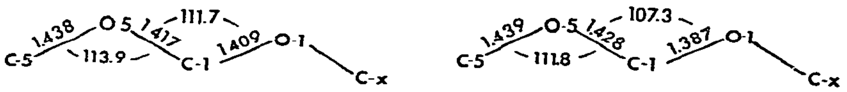
The exo-anomeric effect, itself, is expressed by the value of angle Φ. When Φ is referred to O-5, it is labelled $\Phi^{\text{O-5}}$, where $\Phi^{\text{O-5}} = 0$ corresponds to the *cis* arrangement of O-5–C-1–O-1–C-x.

For oligosaccharides, a second torsional angle (ψ) is required to define the relative arrangement of the contiguous sugars. This angle is referred to the adjacent oxygen or carbon atoms (following the Cahn–Ingold–Prelog priority[14]). For cellobiose, $\psi^{\text{C-(x+1)}} = 0$ corresponds to the *cis* arrangement of C-1–O-1–C′-4–C′-5. The sign of the torsional angles is defined according to the IUPAC–IUB convention[15].

Crystal data for free sugars, or the free reducing-end of oligosaccharides, are not included in this survey as the directional influence of intermolecular hydrogen-bonding of the terminal hydroxyl group could override the "exo-anomeric effect".

Molecular geometry. — The mean geometry of the bond distances and angles of the carbon–oxygen alternation in Fig. 1 is depicted in Fig. 2. The data were derived by averaging 27 and 24 equivalent sets of bond distances and bond angles in *gauche* and *trans* carbohydrate structures, respectively. These structures are listed in Table I. The characteristic features of the "generalized anomeric effect" appear clearly. Carbohydrates in the *gauche* disposition display shorter than normal (1.428 Å)

C-1–O-1 and C-1–O-5 bonds. The deviation from normality is even more pronounced in the *trans* structures, where C-1–O-1 averages 1.387 Å. A relation between the C–O bond lengths and the torsional conformation has been demonstrated by Jeffrey *et al.*[6,7].



2a

2b

Fig. 2. Molecular geometry of the carbon–oxygen alternation: 2a, *gauche* disposition ($\theta = 60°$); 2b, *trans* disposition ($\theta = 180°$).

TABLE I

LIST OF GLYCOPYRANOSIDE AND OLIGOSACCHARIDE X-RAY CRYSTAL-STRUCTURES ANALYZED

Compounds (and references)
Aldotriouronic acid trihydrate[16], methyl α-D-altropyranoside[17], methyl β-cellobioside·MeOH[18], β-cellobiose[19], cellobiose octaacetate[20], cellotriose undecaacetate[21], chondrosine monohydrate[22] Methyl α-D-galactopyranoside[23], methyl 3,4-*O*-ethylidene-β-D-galactopyranoside[24], methyl 3,6-anhydro-α-D-galactopyranoside[25], methyl 6-*O*-acetyl-β-D-galactopyranoside[26], methyl tri-*O*-acetyl-6-deoxy-6-[methylsufinyl(*S*)]-α-D-glucopyranose[27], methyl α-D-glucopyranoside[28], methyl 6-*O*-acetyl-β-D-glucopyranoside[29], (3,6-anhydro-α-D-glucopyranosyl)-1,4:3,6-dianhydro-β-D-fructoside[30], methyl-β-D-hamameloside[31], isomaltulose[32], 1-kestose[33], α-lactose monohydrate[34], β-lactose[35], lactose–calcium chloride heptahydrate[36], lactose·calcium heptahydrate[37], β-laminarabiose[38], methyl 2,3,4,6,2′,4′,6′-hepta-*O*-acetyl-β-laminarabioside[39], methyl β-maltoside[40], β-maltose monohydrate[41], phenyl α-maltoside[42], methyl α-D-mannopyranoside[43], melezitose monohydrate[44], α-melibiose monohydrate[45], planteose[46], raffinose[47], stachyose[48], sucrose[49], 4,6-dideoxy-4-(dimethylamino)-α-D-talopyranoside methiodide[50], α,α-trehalose·$2H_2O$[51], α,α-trehalose·calcium bromide·H_2O[52], methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-2-ulose[53], methyl β-D-xylopyranoside[54], and xylobiose hexaacetate[55].

A coupling of bond angles to torsion angle is also observed: the C-5–O-1–C-1 bond-angle differs by ±1° from the normal value of 112.6° for *gauche* and *trans* structures, respectively. Another such difference between the two structural classes is to be found on comparing the O-5–C-1–O-1 bond-angle, which is about 2 degrees larger than tetrahedral for *gauche* structures and 2° smaller for *trans* structures. Such differences were first noted by Sundaralingam[56]. The significance of this bond-angle distortion with respect to conformation has been demonstrated through *ab initio* calculations by Gorenstein and Kar[9]. For dimethoxymethane, they showed that variations of the type just noted are coupled to the rotameric state; thus the O–C–O bond-angle was 112° for the *gauche–gauche* conformation whereas it was 107° for the *trans–gauche* disposition.

Conformation and the exo-anomeric effect. — The analogy between dimethoxymethane and glycopyranosides has often been invoked to explain the *gauche* conformation favored by the latter. Classification of the carbohydrate conformations as *gauche* and *trans* aids greatly in deriving the maximum enlightenment from this analogy. As the observed values of θ fall into two classes, namely 52–67° (av. 60°) and 171–193° (av. 178°), the classification is more than justified. However until sufficient data were at hand, it was difficult to determine whether or not the $\Phi^{O\text{-}5}$ values were consistently *gauche*.

The crystal-data surveys for the two classes of methyl pyranosides are shown in Figs. 3a and 3b. The individual values of $\Phi^{O\text{-}5}$ range from 61 to 74° and from -68 to $-87°$. Thus the "*gauche*" label for angle $\Phi^{O\text{-}5}$ is reasonable, and pyranosides may be labelled "*gauche–gauche*" and "*trans–gauche*" for α and β, respectively, which makes the analogy to such small molecules as dimethoxymethane more evident.

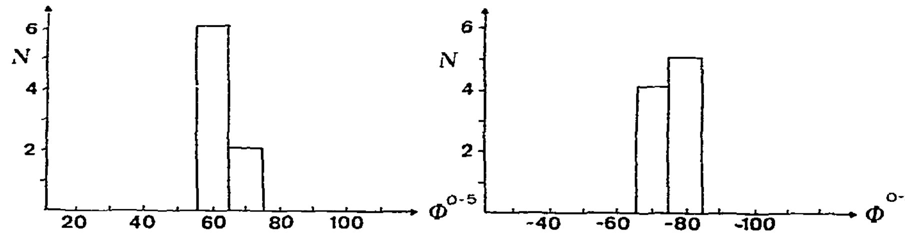


Fig. 3. Histograms of the distribution of $\Phi^{O\text{-}5}$ in methyl pyranosides: left (3a), *gauche* disposition ($\theta = 60°$); right (3b), *trans* disposition ($\theta = 180°$).

Histograms showing the distribution of values of $\Phi^{O\text{-}5}$ angles in structures of *gauche–gauche* and *trans–gauche* oligosaccharides are depicted in Figs. 4a and 4b, respectively. Despite the fact that a wide variety of linkage-types between different sugars are compared for the *gauche–gauche* structures, the range of variation is restricted (ranging from 75 to 121°). It should be noted also that C–O–C–O–C (5-atom) and C–O–C–O–C–O–C (7 atom) sequences[7] are similarly distributed. The

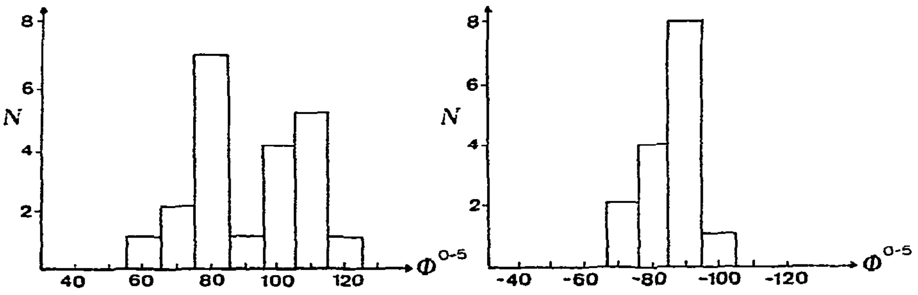


Fig. 4. Histograms of the distribution of $\Phi^{O\text{-}5}$ in oligosaccharides: left (4a) *gauche* disposition ($\theta = 60°$); right (4b), *trans* disposition ($\theta = 180°$).

trend in $\Phi^{O\text{-}5}$ values (Fig. 4b) is even more noteworthy, as the observed range for the angle is only about 30° (range from −71 to −105°). This range clearly indicates the existence of a favored conformation about the C-1–O-1 bond, although the average position is significantly shifted from perfect staggering.

The orientational tendency about this bond is illustrated again by the general feature displayed by the bivariate (Φ, ψ)* distribution shown in Fig. 5. It appears that rotations around the glycosidic linkages C-1–O-1 and O-1–C-x are non equivalent; the variation in Φ covers a range of 30° whereas values of ψ are spread over a range of 100°. *We consider that this fact provides the strongest evidence thus far accumulated in favor of the existence of a conformational bias that restricts rotation about the anomeric carbon atom to the glycosidic-oxygen bond in the solid state.*

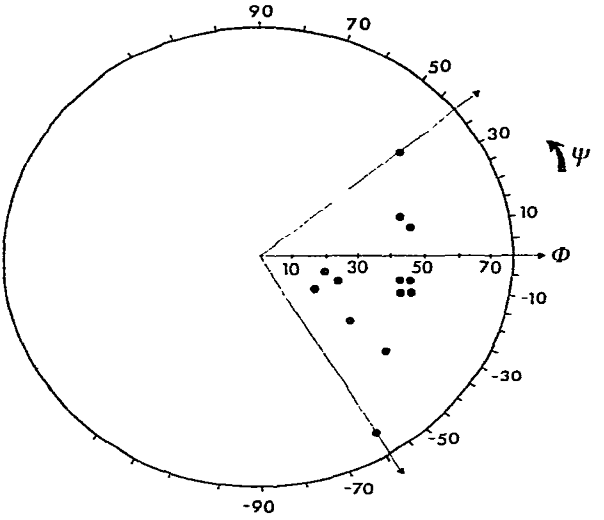


Fig. 5. The bivariate (Φ, ψ) distribution in *trans–gauche* oligosaccharides. Each point corresponds to an observed combination of Φ, ψ for a given glycosidic linkage.

To illustrate this principle, (Φ, ψ) values are compared in Table II for compounds having two contiguous, (1→4)-linked, β-D-glucose residues: β-cellobiose[19], methyl β-cellobioside[18], cellobiose octaacetate[20], and the two cellobiose peracetate entities within the cellotriose peracetate molecule[21]. Angle Φ varies but little, whereas ψ extends over a wider range. This relative invariance of ϕ is found despite removal of intramolecular hydrogen-bonds [O-3′–O-5 in β-cellobiose, O-3′–O-5 and O-3′–O-6 in methyl β-cellobioside] by peracetylation. Similarly, with the acetylated derivatives, a different disposition displayed by the primary acetate group at C-6

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*The relative orientation of contiguous residues is described by the torsion angles around the glycosidic bond C-1–O-1 and O-1–C-x, which are denoted as the conformational angles: $\phi = [\text{H-1–C-1–O-1–C-x}]$ and $\psi = [\text{C-1–O-1–C-x–H-x}]$. In these calculations, the hydrogen positions used were computed on the basis of a perfect tetrahedral coordination according to the convention of Sundararajan and Rao[57].

results in a greater conformational adjustment of the angle ψ, whereas Φ is only slightly modified.

TABLE II

COMPARISON OF (Φ, ψ) VALUES FOR OLIGOSACCHARIDES

Compounds	Φ	ψ	*Disposition*[a] *at C-6–O-6*	*Interactions*
β-Cellobiose	45	−14	gt/gt	O-3′–O-5 hydrogen bond
Methyl β-cellobioside	31	−38	gg/gt	O-3′–O-5 hydrogen bond O-3′–O-6 hydrogen bond
Cellotriose octaacetate	44	16	gt/gg	Van der Waals
Cellotriose octaacetate (reducing entity)	46	12	gt/gg	Van der Waals
Cellotriose undecaacetate (non-reducing entity)	24	−20	gg/gg	Van der Waals

[a] This terminology refers to the dihedral angles O-5–C-5–C-6–O-6 and C-4–C-5–C-6–O-6, with the "aglycon" entity stated first.

Conclusions. — These results must indicate that forces energetically comparable to those involved in hydrogen-bond and van der Waals interactions govern the disposition about the anomeric carbon atom–"aglycon" bond. By combining results from *ab initio* studies on dimethoxymethane with semi-empirical calculations, suitable potential-functions for these forces should be obtainable, These functions may, in turn, be added to the various potential functions already known to be important for defining the conformations of polysaccharides.

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