Tetrahedron. Vol. 30, pp. 1933 to 1944. Pergamon Press 1974. Printed in Great Britain

THE CONFORMATIONAL PROPERTIES OF GLYCOSIDIC LINKAGES

R. U. LEMIEUX and S. KOTO[a]

Department of Chemistry, The University of Alberta, Edmonton, Alberta, Canada

(*Received in the UK* 14 *February* 1974)

Abstract—The developments in stereochemistry which have made possible our present appreciation of the preferred orientation of the aglycon for a glycopyranoside are briefly reviewed. Recent studies in this laboratory are presented wherein, for model compounds, measurements were made of the coupling constant between the ^{13}C-aglyconic carbons and anomeric hydrogens as an estimate of the torsion angles, of ^{13}C-chemical shifts as a measure of relative steric compressions at the anomeric centers, and of contributions to the molecular rotations by units of conformational asymmetry defined by atoms about the glycosidic bond. These measurements are compared to the results of hard-sphere calculations. It is concluded that the *exo*-anomeric effect offers an important resistance to rotation about the anomeric carbon to glycosidic bond (ϕ angles) and that the preferred conformation for a glycopyranoside arise mainly from rotation about the aglyconic carbon to glycosidic oxygen bond (ψ angles).

INTRODUCTORY REMARKS

Glycosidic structures, ranging from simple glycosides through oligo- and polysaccharides, encompass most aspects of biological phenomena. Although this review will be restricted to a consideration of O-glycopyranosides, similar considerations apply to glycofuranosides especially the N-glycofuranosides related to the nucleic acids and their nucleoside and nucleotide components; the glycosyl phosphates and the wide variety of their biologically crucial derivatives. The classical O-glycopyranosides of carbohydrate chemistry such as cellulose, hemicelluloses, starch, pectins, gums, carrageenan and sucrose are of great economic importance because of their high natural abundance in plants, some arising among the first products of photosynthesis. However, the more recent advances[1] in the chemistry of natural products display an ever increasing number of naturally occurring glycosidic structures which possess important pharmacological and antimicrobial activities. Likely of even greater importance is the constantly deepening appreciation of the wide varieties of complex polysaccharides which occur in bacteria, fungi, algae and the higher animals where these play key roles both for the maintenance of structure (cell wall structure and protection) and biological activity (cell recognition, enzyme activity). These considerations include the glycolipids such as those which occur in brain and nerve tissue (cerebrosides) and on red-blood cells (certain blood-group antigenic determinants) and the importance of the glycosidic components of an ever increasing list of glycoproteins, for example, those found in blood and tissue fluids (including the blood-group substances), milk and many enzymes. Thus, it is clearly evident that the chemistry and detailed conformational properties of O-glycosidic bonds is of basic importance to both industry and biology. This brief review is concerned with the progress made in the understanding of the O-glycosidic bond from a stereochemical standpoint, a subject which has its origin in van't Hoff–Le Bel theory for optical isomerism.

The concept of optical isomerism to which this issue is dedicated had an immediate and profound influence on the development of carbohydrate chemistry. As pointed out by Hudson,[2] Emil Fischer's cyanohydrin synthesis[3] of higher-carbon sugars played a major role in the establishment of the van't Hoff–Le Bel theory of the asymmetric carbon atom. Emil Fischer applied the theory to the sugars and thereby established the configurations of many of the individual sugars in a brilliant series of researches published in 1891.[4] Although Emil Fischer prepared methyl α-D-glucopyranoside in 1893[5] in an effort to synthesize the dimethyl acetal by treatment of D-glucose with methanolic hydrogen chloride, Michael[6] presented in 1879 the first successful synthesis of a glycoside (*p*-methoxyphenyl β-D-glucopyranoside) using conditions chemically similar to those later developed by Koenigs and Knorr.[7] The size of the pyranoid ring became firmly established in the 1920's beginning with the structure of methyl α-D-xylopyranoside.[8] The configurations assigned to C-1 of glycosides were initially not assigned.[9] The term "α" was assigned to methyl α-D-glycopyranoside then

[a] University of Alberta Postdoctoral Fellow, 1972–74.

named "α-methyl-*d*-glucoside," in the first instance simply because it was the first to be discovered.[5] Classification of these diastereoisomers, which differ only in the configuration of C-1, using Hudson's rules of isorotation[10] and the Fischer–Rosanoff system[9] of naming the two enantiomorphous series in the carbohydrate group is now universally adopted. Riiber and Sørensen,[11] in 1933, introduced the term "anomeric" as a class name for the α- and β-forms of sugars and their glycosides. Acceptance of this terminology has led to the specification of the asymmetric center formed through the cyclization of a sugar as the anomeric center. The sugar residue of an alkyl glycoside is referred to as the glycosyl group and the alkyl group as the aglycon group. The oxygen atom linking the glycosyl and the aglycon groups (O-1) is designated the glycosidic oxygen atom and the carbon of the aglycon group to which it is attached is termed the aglyconic carbon.

The configurations of the anomeric centers in sugars and glycosides were not beyond dispute until relatively recent times. Ballou *et al.*[12] reviewed the basis for the allocation of anomeric configurations in 1951 and presented evidence for the configuration of benzyl aldopyranosides. Chemical evidence for the anomeric configurations of acetylated sugars was presented in 1951.[13] X-ray crystallographic analysis[14] starting with the structure of α-D-glucosamine by Cox and Jeffrey in 1939[15] and proton magnetic resonance spectroscopic studies[16] initiated in 1957[17] have thoroughly confirmed the earlier conclusions as to anomeric configuration.

The advent of conformational analysis in the early 1950's[18] initiated a new age for carbohydrate chemistry. The earlier notion that the only generalization about carbohydrate chemistry was that there was no generalization was soon to be abandoned. Indeed, within the following twenty years, carbohydrate chemistry became as fully coherent and systematized area of chemistry as any other field of organic chemistry.[19-22]

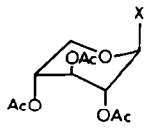
The anomeric effect

A basic tenet of conformational analysis predicts that the equatorial orientation is the energetically more favored orientation for a large substituent on a 6-membered ring. However, from the beginnings of conformational analysis, this principle did not appear to apply to polar substituents (alkoxy, acyloxy and halogens) at an anomeric center. An anomaly existed either in chemical bonding or conformational preferences or the configurations assigned to anomeric centers were in error. This was apparent, for example, for the relative rates of acid-catalyzed hydrolysis of anomeric glycopyranosides,[23] which could be expected to maintain the Reeves Cl-conformation.[24] In the absence of detailed knowledge of the mechanisms of these reactions, it could be imagined that the differences in rate of reaction were more related to differences in the energies of the transition states than in differences of the ground states, but this seemed improbable. Pacsu's[25] classical β to α anomerization of acetylated alkyl glycopyranosides using either stannic chloride or titanium tetrachloride in chloroform appeared definitely to require a greater thermodynamic stability for the axial orientation of the alkoxy group at the anomeric center. That the driving force was not related to complexing reactions involving the Lewis acid catalysts (including boron trifluoride[26]) became evident with the observations[27,28] that extensive β to α anomerization of several acetylated methyl glycopyranosides occurred in the course of sulphuric acid-catalyzed acetolyses. A detailed kinetic investigation of the acetolysis of the anomeric methyl tetra-O-acetyl-D-glucopyranosides was reported in 1955.[29] Anomerization of ^{14}C-methyl tetra-O-acetyl-β-D-glucopyranoside in the presence of its unlabelled L-enantiomer showed these reactions to follow an intramolecular mechanism.[30] Thus, there could be no doubt that for acetylated alkyl glycopyranosides, the α-anomer was the thermodynamically favored form.

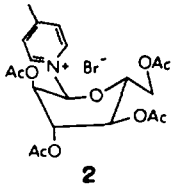
In 1928, Schlubach, Stadler and Wolf[31] demonstrated the instability of tetra-O-acetyl-β-D-glucopyranosyl chloride by finding that it anomerized to the α-anomer in a number of solvents. The conformations of such compounds were not known in 1947 when Hassel and Ottar[32] offered an explanation based on non-bonded interaction between the *syn*-axial halogen and the acetoxymethyl group. A detailed study of this anomerization has shown the reaction to be halide-ion catalyzed and to proceed by way of an ion-triplet transition state.[33] The point of equilibrium was estimated to be near 16 in favor of the α-anomer indicating a driving force of about 2 kcal/mole for the so-called anomeric effect.

The term anomeric effect was introduced[34] as the result of a detailed study of the anomerization of the acetylated pento- and hexopyranoses.[35] It was shown that this anomerization, beginning with a study of the D-glucopyranose pentaacetates by Jungius in 1905,[36] could only be explained on the basis of a special driving force for the 1-acetoxy group to achieve a *syn*-clinal orientation relative to C-5 of the pyranose ring. Details of this study are reported in a review.[19] The driving force was estimated to be about 1·5 kcal/mole depending on the sugar involved. It was possible to draw these conclusions since the advent of proton magnetic resonance spectroscopy had enabled unequivocal establishment of the conformations of these and related compounds in solution.[37,38] It was pointed out[19,35] that the conclusions reached were in accord with the *syn*-clinal–*syn*-clinal conformation established for methylal by Kubo[39] in 1936. The conformation of this most simple model for a glycoside

has been confirmed by electron diffraction studies.[40,41] The polymeric analogue of methylal, polyoxymethylene, has the analogous *syn*-clinal helical conformation.[42] As was to be expected from the properties of the acetylated glycosyl halides, the methyl group and the chlorine atom of methoxychloromethane are in *syn*-clinal orientation.[43,44] It is interesting to note in this regard that the conformational properties of the complex carbohydrate group of substances can be quite surprising. For example, both tri-O-acetyl-β-D-xylopyranosyl chloride[45] and fluoride[46] exist extensively in the all axial conformer 1, and N - (tetra - O - acetyl - α - D - glucopyranosyl)4 - methylpyridinium bromide in the boat conformation 2.[47,48]



1



2

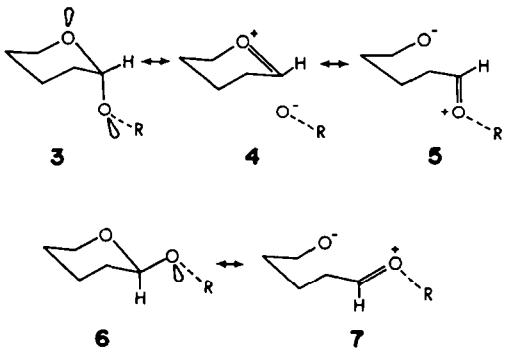
The anomeric effect is displayed in a wide variety of non-carbohydrate compounds. Thus, in 1959, Altona, Romers and Havinga[49] showed the *trans*-2,5-dichloro- and *trans*-2,3-dibromodioxanes to exist essentially entirely in the chair conformation with both halogens in axial orientation. Such findings are too numerous to mention within the confines of this review. Many examples are documented in the recent chapter by Romers *et al.*[50] which reviews the geometry and conformational properties of many relevant compounds. Indeed, the term generalized anomeric effect has been proposed.[51]

It is not within the scope of this review to critically examine the various explanations which have been proposed to account for the physical origin of the anomeric effect, a subject of much debate in recent years.[52-55] The first rationalization was proposed by Edward[56] and was based on the idea that there exists a greater repulsion between an electro-negative C-1 substituent and the unshared electron pairs of the ring oxygen atom when the substituent is in equatorial orientation. This explanation was further elaborated by Kabayama and Patterson[57] to what became termed the "rabbit-ear effect".[58] Lemieux and Chü[34,35] offered no explanation but pointed out that the simple consideration of the effect on charge distribution arising from a change of the polar bonds from the *anti*-periplanar to the *syn*-clinal orientation provided a change in energy near that experimentally found for anomeric effect. Wolfe *et al.*[52] carried out an *ab initio* quantum mechanical calculation for the model compound fluoromethanol and concluded that the anomeric effect "can be understood, principally, in terms of interactions of bonded electron pairs." Romers *et al.*,[50] primarily in view of experimental results obtained in X-ray crystallographic examinations of halogenated 1,4-dioxanes, suggested that the non-bonding electrons on the oxygen of an α-halogenoether are delocalized by quantum mechanical mixing with a suitably oriented antibonding σ*-orbital of the carbon to halogen bond. These conclusions were reinforced by *ab initio* molecular orbital calculations on methanediol by Radom *et al.*[53] The results were applied to the anomeric effect and a comparison of the theoretical predictions and the experimental data from X-ray crystal-structure determinations were made.[54] Of special interest to this contribution is the prediction that the torsion angle defined by the methyl group of a methyl D-glycopyranoside and the ring oxygen atom (O-5) is + 60° for the α-anomers and somewhat numerically larger for the β-form (close to − 70°). The most recent interpretation of the anomeric effect[55] utilizes the suggestion by Altona[50,59] that interaction of the oxygen lone pairs with low-lying σ*-orbital of the ligand bond stabilizes the axial orientation for the ligand. However, account is made for the different energies of the two oxygen lone pairs which requires oxygen atoms *to be* sp^2 *rather than* sp^3 *hybridized.* This interpretation then places a premium on conformations which have the *p*-type lone pair in *peri*-planar relationship to the C to ligand bond and, as a consequence, the conformations expected to be stereoelectronically most favorable for α and β methyl glycopyranosides would have torsion angles of 90° defined by the methyl group and O-5. This theory may be compatible with the early result[19,35] that increasing the electronegativity of the C-6-substituent of D-glucopyranose pentaacetate reinforces the anomeric effect. Following the rule that induced charges alternate[60] the substitution of a more electronegative group renders the C-6 carbon more electronegative but the C-5 carbon more electropositive. This substitutional effect was substantiated by Edward, Morand and Puskas.[61]

Lemieux and Morgan[47] postulated the reverse anomeric effect in order to rationalize the strong driving force possessed by quaternary nitrogen to adopt the equatorial orientation. Evidence in support of this contention was achieved by a study of N-(α-D-hexopyranosyl) imidazoles.[62,63] The PMR spectra for the free bases of the *gluco* and *manno* configurations were in good accord with expectation for the chair conformation with the imidazole in axial orientation. However, either protonation or methylation of the imidazole so as to quaternize the glycosidic nitrogen caused extensive conformational change toward the imidazole group adopting the equatorial orientation, presumably the pyranose ring adopting a boat-like conformation as was found for the pyridinium glycoside 2. David *et al.*[55] pointed out that if the positively charged imidazole ring is less electronegative than hydrogen, their

theory would provide some rationalization for the reverse anomeric effect.

That there should exist an orientation effect on an aglycon arising from the special properties of the acetal group was first suggested in a lecture presented in 1959 primarily with reference to cellulose.[64] The term *exo*-anomeric effect was later introduced[65] for this presumed orientation effect on the aglyconic portion of a glycopyranoside. The remainder of this paper is concerned with recent attempts made in this laboratory to better identify the existence of the effect and to assess its contribution to glycoside conformation. For the purposes of this discussion, the anomeric effect can be presented in terms of the canonical structures **3** to **5** for α-pyranosides and **6** and **7** for the β-anomers. The structures **3** and **4** are those originally proposed by Altona.[59] Structures **5** and **7** are to display the origin of the *exo*-anomeric effect.

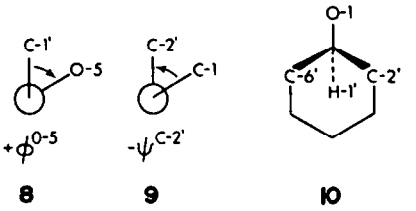


3 **4** **5**

6 **7**

Conformations about the glycopyranosidic bond

(a) *Definitions.* The determination of the conformational preferences about glycopyranosidic linkages has received considerable attention in recent years but mainly with reference to disaccharide and polysaccharide structures. These studies have been based, for the compounds in the dissolved state, on empirical rules for the interpretation of optical rotation[66–68] and on predictions[69–71,73,74] by so-called hard-sphere calculations to indicate conformers in which non-bonded interactions of steric origin are minimum. However, as already mentioned the *exo*-anomeric effect may have an important influence on the conformational preferences of glycosides, particularly in solution where its influence on conformation may be affected by solvation[63,65] but not by crystal field forces. Therefore, it was apparent that a first stage in any consideration of the conformational properties of glycopyranosides would require information on torsion angle defined by the aglyconic carbon and the oxygen atom of the pyranose ring. This torsion angle has been termed a ϕ angle (**8**) and this designation will be used in this review except the involvement of the ring oxygen atom will be specified, thus, $\phi^{O\text{-}5}$.



8 **9** **10**

The description of the conformation of a glycosidic linkage with an aglycon more complex than the methyl group requires the specification of a second torsion angle, namely, that which involves one of the atoms attached to the aglyconic carbon (e.g., C-2′ in **9**) and the anomeric carbon (C-1). This torsion angle has been referred to as a ψ angle and this designation is retained for the purposes of this review but specifying the carbon of aglycon which is involved, e.g., $\psi^{C\text{-}2'}$.

The discussion will refer mainly to glucopyranosides which possess secondary aglyconic carbons and, therefore, a simple device will be needed to differentiate the two carbons attached to the aglyconic carbon. Very considerable complications in presentation arise if this differentiation is not made especially with reference to the cyclohexyl D-glucopyranosides which form the basic model compounds for the studies to be reported. The nomenclature device is adopted whereby the carbon atoms of the cyclohexyl ring are numbered clockwise as in the projection shown for partial formula **10** and this numbering is maintained regardless of substitutional changes on the cyclohexane ring. A second matter which complicates simple presentation arises if the Cahn–Ingold–Prelog Sequence Rule[75] is employed to describe the absolute configurations of compounds arising from substitutional changes at the prochiral carbon atoms C-2′ and C-6′. That is, C-1′ has the R configuration when the substitution is at C-2′ but the S configuration when the substitution is at C-6′, although the order of the substitution of O-1′, C-2′ and C-6′ about C-1′ has not changed. Although these matters do not cause insurmountable complications, standard nomenclature will not be used. Instead, the absolute configurations will be presented simply by indicating whether the substitution was at 2′ or 6′ following the procedure presented with reference to **10**.

(b) *The* exo *anomeric effect, vicinal* ^{13}C *to* ^{1}H *coupling constants.* The discovery that the coupling constant for vicinal protons was torsion angle dependent and particularly the now well established tendency for this coupling to follow the Karplus relationship[76] together with the accumulated evidence[16] for similar relationships for the coupling of protons with other vicinal atoms with nuclear spins of 1/2 suggested that information on the magnitude of ϕ angles in glycosides could be achieved through studies of ^{13}C-1′ to H-1 (anomeric hydrogen) coupling.[77] Such studies seemed mandatory as back-

ground information in any attempt to appreciate the conformational preferences of glycopyranosides with aglycons more complex than the methyl group. For example, as seen from Table 1, the introduction of methyl groups into the methyl group of methyl D-glucopyranosides causes substantial change in optical rotation although the introductions do not introduce new chiral carbon atoms. These changes in rotation could be expected to arise, at least in part, from the introduction of new screw patterns of asymmetry involving C-methyl groups in the aglycon.[68] However, an appreciation of the ψ torsion angles thus introduced would be dependent on a knowledge of the ϕ angles which may or may not have undergone important change from those existing in the methyl glucopyranosides.

Table 1. Some properties of anomeric D-hexopyranosides in aqueous solution[80]

Configuration	Aglycon	$[M]_D^{25}$	$^3J_{C\text{-}1',H\text{-}1'}$ Hz	N.O.E. (H-1) %[a]
α-Anomers				
Gluco	Methyl	309°	3·8	0
Gluco	Ethyl	314	3·8	—
Gluco	Isopropyl	324	3·8	—
6-Deoxy-*gluco*	Methyl	—	—	8
Manno	Methyl	—	3·8	8
6-Deoxy-*manno*	Methyl	—	—	1
2-Deoxy-*arabino*	Methyl	—	3·2	—
β-Anomers				
Gluco	Methyl	−66	4·6	12
Gluco	Ethyl	−76	4·6	—
Gluco	Isopropyl	−84	4·6	—
Gluco	*t*-Butyl	−45	4·2	—
6-Deoxy-*gluco*	Methyl	—	—	17
Manno	Methyl	—	4·3	—
6-Deoxy-*manno*	Methyl	—	—	14
2-Deoxy-*arabino*	Methyl	—	4·2	—

[a] Considered meaningful to ± 5% in total enhancement.

That $^3J_{C,H}$ follows a Karplus-type relationship was established by the examination of the coupling between vicinal ^{13}C and H atoms in a number of compounds specifically enriched in carbon-13.[77] $^3J_{H,H}$ coupling is well established to be dependent on several molecular parameters other than torsion angle and this necessarily has to be the case of $^3J_{C,H}$ coupling constants as well.[78] Indeed, this was well demonstrated in a recent publication from this laboratory.[79] However, that a useful relationship can exist for closely related structures is well established for vicinal proton to proton coupling and therefore expected for vicinal carbon-13 to proton coupling. An examination of $^{13}CH_3$ to anomeric hydrogen coupling in simple alkyl glycopyranosides was therefore undertaken by the synthesis of the compounds enriched (60–90%) with carbon-13 at aglyconic carbon position.[80]

The data in Table 1 show that the coupling constants for β-glycopyranosides is consistently greater than that for the α-anomer. Assuming that this difference arises from a smaller torsion angle ($\phi^{H\text{-}1}$) for the β-glycopyranosides, then the results would be in accord with conclusions suggested both by X-ray structures of crystalline methyl glycopyranosides and theoretical calculations.[54] If so, the methyl group of the β-glycopyranosides would compress the anomeric hydrogen more than that of the α-anomer and, therefore, a greater nuclear Overhauser enhancement of the PMR signal for the anomeric hydrogen on double irradiation of the methyl group of these β-glycosides would be expected than for the α-anomers. Coxon[81] has shown nuclear Overhauser enhancement of the proton signal of certain cyclic methyl orthoformates on irradiation of the methyl group. Indeed, it was observed,[80] as seen from Table 1, that definite enhancement occurred for the β-glycopyranosides studied, whereas for the α-anomers the enhancement was so weak as to be barely detectable. These results require that the $\phi^{O\text{-}5}$ torsion angle be somewhat greater for the methyl β-glycopyranosides but the difference need not be more than a few degrees. The enhancement increases very rapidly as compression is introduced and vicinal coupling must be expected to change rapidly with change in torsion angles in the region of 60°.[76]

It is not presently possible to assign torsion angles on the basis of the $^3J_{C,H}$ coupling constants reported in Table 1. All that can be concluded is that the magnitude of the coupling constants indicate $\phi^{H\text{-}1}$ torsion angles of 60° or less. This conclusion was supported by the observation that ^{13}C in the methoxy group of 1-methoxy-*cis*- and of 1-methoxy-*trans*-4-*t*-butylcyclohexane were coupled to H-1 by 3·8 and 3·9 Hz, respectively.[80] Also, the average coupling of ^{13}C in the methyl groups of methylal with the methylenic hydrogens was found to be 6·6 Hz.[80] Therefore, $J_{60°} + J_{180°} = 13{\cdot}2$ Hz for this compound which bears a structural relationship to methyl glycopyranosides. The effect of substituting methyl groups for the hydrogen atoms in the methoxy group on $^3J_{C,H}$ coupling was not established. It would be surprising however if this effect was such as to cause changes in $^3J_{C\text{-}1',H\text{-}1}$ for the methyl, ethyl and isopropyl D-glucopyranosides which would be cancelled out to within ± 0·1 Hz by appropriate changes in the $\phi^{H\text{-}1}$ angles. It seems more probable that the coupling constants reflect that little change in the ϕ angles occurred as a result of the substitutions. A change in ϕ angles is to be expected on going from isopropyl to *t*-butyl β-D-glucopyranoside since unfavorable nonbonded interactions in the latter compound cannot be relieved through a simple change in the ψ angles. This presumably is the major reason for the coupling constant being slightly smaller for the *t*-butyl compound (Table 1).

The molecular rotations for the methyl, ethyl and isopropyl D-glucopyranosides are listed in Table 1 since these suggest a change in ψ angles because the coupling constants provide evidence that the ϕ angles remained nearly constant for both the α- and β-anomers. The directions of rotational change (positive for the α-anomers and negative for the β-anomers) are in accord with expectations based on conformational analysis.

The first indication that the ϕ torsion angles for anomeric methyl glycopyranosides are nearly the same in magnitude was provided by the Whiffen's interpretation of the optical rotations for such compounds that could be expected to exist in a given chair conformation.[82] That is, a contribution of $\pm$ 113° (J parameter) was assigned to contributions arising from the presence of the methyl group in the molecule. The origin of this conclusion is readily appreciated from the content of Table 2 where it is

Table 2. The difference in molecular rotation between a D-hexopyranose and its methyl glycoside[82,83]

Configuration	$[M]_D$ (H_2O)		Difference
	Glycoside °C	Sugar °C	°C
α-Anomers			
Gluco	309°	202°	107°
Galacto	380	272	108
Manno	157	53	104
β-Anomers			
Gluco	− 66	34	− 100
Galacto	0	95	− 95
Manno	− 135	− 31	− 104

seen that the difference in rotation between a glycopyranose and its methyl glycopyranoside is near constant, positive for the α-D (or β-L) configuration and negative for the β-D (or α-L) configuration. The signs of the rotation were interpreted to indicate a positive $\phi^{O\text{-}5}$ angle for the α-glycopyranosides and a negative but numerically nearly equal $\phi^{O\text{-}5}$ angle for their β-anomers. Brewster[83,84] further elaborated and justified these empirical rules to account for optical rotation and pointed out that the inferred conformational preference corresponds with the orientation for the methoxy group that should be least incumbered by non-bonded interactions of steric origin.

It is to be noted however that, although the above described $^3J_{C\text{-}1',H\text{-}1}$ and molecular rotations strongly infer near equal $\phi^{O\text{-}5}$ angles for anomeric methyl hexopyranosides, only the X-ray data for the compounds in the crystalline state indicate $\phi^{O\text{-}5}$ angles near $\pm$ 60°.[54] As readily seen from appropriate projection formulas, the *exo*-anomeric effect would demand an angle of $\pm$ 60° if the glycosidic oxygen is tetrahedral. However, the more recent evidence that such oxygen atoms are sp^2 hybridized[55] could require the *exo*-anomeric effect to be best expressed with $\phi^{O\text{-}5} = \pm 90°$. This would render $\phi^{H\text{-}1} \simeq \pm 30°$ and, indeed, the values for $^3J_{C\text{-}1',H\text{-}1}$ presented in Table 1 could be judged to be in as good accord with this value as for $\phi^{H\text{-}1} \simeq \pm 60°$.

(c) *Molecular models through hard-sphere calculations.* Discussion of the preferred conformations for the orientation of an aglycon about the anomeric center of a glycoside appears best initiated by consideration of suitable molecular models. Perhaps the most useful models presently available are those provided by relatively simple computer calculations[42] using the hard-sphere procedure.[85] The utility arises in that having chosen a model (bond lengths, bond angles and atomic sizes); the *relative* stabilities of different conformers arising from rotations about given chemical bonds are assessed and presented in the computer read-out.[42]

Ramachandran *et al.*[70] introduced hard-sphere calculations to estimate the relative stabilities of conformations about glycosidic bonds and their calculations for maltose and amylose have now been extended to several disaccharides and polysaccharides.[66,68,71,73,74] The results are sometimes expressed in the form of "conformational contact maps" which show the influence of the torsion angles ϕ and ψ on conformation as expressed through the non-bonded interactions between atoms considered as hard spheres. The maps show areas where given conformations are "allowed," that is, in these conformations no contacts between non-bonded atoms exist as the result of the angles ϕ and ψ chosen for the spheres.[66,70] The procedure used in our calculations to obtain relative non-bonded interaction energies is that described by Rao *et al.*[70] The potential energy of a given conformer is calculated using the Kitaygorodsky formula[86] and the equilibrium distances, r_0 (presented as K_1 by Venkatachalam and Ramachandran[72]) where r_0 is estimated by requiring that the potential energy be zero at a distance of separation equal to the sum of the van der Waals radii of the two atoms.

The 3-dimensional model used for our calculations was derived from the X-ray crystallographic structure for (1S,2S)-*threo*-methylcyclohexyl β-D-glucopyranoside determined by Delbaere and James.[87] The structural features found for the methylcyclohexyl residue were used in establishing the model for the α-anomer and those for the anomeric D-glucopyranosides derived from (1R,2R)-*threo*-methylcyclohexanol, cyclohexanol and the *xylo*-2,6-dimethylcyclohexanol.[88] In the case of the α-D-glucopyranosides, the structure of the α-D-glucopyranosyl residue reported for methyl β-maltoside by Chu and Jeffrey[89] was used. In order to simplify the hard-sphere calculations, the models employed the 6-deoxy-D-glucopyranosides. This approximation was also used by Rees and Skerrett[71] in their conformational

Table 3. Molecular rotations of model α- and β-D-glucopyranosides[88]

Aglycon	α-Anomers		β-Anomers	
	$[M]_D^{25}$ (H_2O)	$\Delta[M]_D^{25}$[a]	$[M]_D^{25}$ (H_2O)	$\Delta[M]_D^{25}$[a]
Cyclohexyl	+349°	+33°	−105°	+32°
2′-Methylcyclohexyl	+260	+33	−200	+33
2′-Chlorocyclohexyl	+253	—	−199	—
2′-Hydroxycyclohexyl	+259	—	−170	—
6′-Methylcyclohexyl	+476	+33	+28	+33
6′-Chlorocyclohexyl	+477	—	+29	—
6′-Hydroxycyclohexyl	+477	—	+26	—
2′,6′-Dimethylcyclohexyl	+347	—	−52	—

[a] The molecular rotation of the compound listed minus that of its 6-deoxy derivative.

analysis of cellobiose and cellulose. The approximation is well justified by a consideration of molecular models and the optical rotations listed in Table 3 where it is seen that the conversion of the hydroxymethyl group to methyl group has a constant effect on the molecular rotation regardless of the structure of the aglycon.[88] These data thus require that there exists no appreciable non-bonded interaction between the aglycon and the C-6 hydroxyl group. The hydroxyl group was treated as a sphere following the approximation in this regard used by Rao *et al.*[70] Although there can be little doubt that crystal field effects have an influence on the overall conformational properties of crystalline compounds as compared to when the compounds are in aqueous solution, it is assumed that the changes are negligible except for those immediately about the glycosidic bond. The calculations assumed both the bond lengths and valence angles about both the anomeric and aglyconic carbon atoms to be those found in the crystalline state and to remain constant for all conformers. It seemed, however, necessary to anticipate that substantial change in the bond angle defined by C-1, O-1 and C-1′ (the τ angle) can occur. The τ angles found for (1S,2S)-*threo*-methylcyclohexyl β-D-glycopyranoside[87] (hereon referred to as 6′-methylcyclohexyl β-D-glucopyranoside) and the intersugar bond of methyl β-maltoside[89] were 114·9° and 117·6°, respectively. In contrast, the τ-angles for methyl α-D-glucopyranoside[90] and methyl β-maltoside[89] were found to be 113·0° and 113·2°, respectively. A τ value of 113° was chosen for the present calculations both because the values found for the methyl glycopyranosides are those found in crystal structures wherein the aglycons (methoxy groups) are not involved in important intermolecular bonding[54,91] and because calculations using τ values ranging from 109·5° to 116·4°[91] provided no basis for employing angles greater than 113°. That is, the same conclusions would be reached as to the more favorable conformers using angles larger than 113° except that as the τ-angle becomes larger the flatter and broader becomes the bottom of the potential-energy curve. In determining the potential-energy curves for a given glucoside, computer calculations were normally made using 5° increments for the torsion angles.

The preferred conformations for α- and β-D-glucopyranosides, as estimated by hard-sphere calculations only and using $\tau = 113°$, are given in Table 4. The calculations were based on the above-described approximations and assumptions and, therefore, the conformations differ only in the torsion angles of the vicinal atoms about the glycosidic bonds, namely, the ϕ-type ($\phi^{H\text{-}1}$, $\phi^{O\text{-}5}$ and $\phi^{C\text{-}2}$) and ψ-type ($\psi^{H\text{-}1}$, $\psi^{C\text{-}2}$ and $\psi^{C\text{-}6}$) angles. As expected, the substitution of methyl groups for the hydrogen atoms *trans* to the aglyconic oxygen atom tended to change both the ϕ and ψ angles.

Consider, for example, the potential energy plot for cyclohexyl α-D-glucopyranoside presented in Fig 1. It is seen that setting $\phi^{O\text{-}5} = +60°$ and varying the $\psi^{H\text{-}1}$ angle over 360° produces a minimum non-bonded interaction energy at $\psi^{H\text{-}1} = -20°$, i.e., the C-1–O-1 and C-1′–H-1′ bonds are nearly eclipsed. The eclipsed conformer is indicated as conformer α-b. The conformations in which all neighboring groups are in *syn*-clinal (gauche or staggered) orientation are relatively much less stable. The main origins of the destablizing interactions can be conveniently analyzed using Lemieux's proposals[19] for indicating *syn*-axial-like relationships between atoms separated by four bonds and these are indicated in both Figs 1 and 2. Although no real significance can be attached to the absolute values of these non-bonded interaction energies, as pointed out by Rees,[68] the energies of the conformers are ordered well as to the relative stabilities that would be anticipated on the basis of the known quantitative aspects of conformational analysis.[20]

Examination of Fig 2 shows that for cyclohexyl β-D-glucopyranoside the differences in energy for the various conformers also well follow expectations based in quantitative conformational analysis. The model provides the eclipsed conformer (β-b)

Table 4. Estimated molecular rotations[a] for α- and β-D-glucopyranosides

Aglycon[b]	Calculated conformations and molecular rotations						Observed
	Variable ϕ and ψ[c]			ϕ Fixed[d]		$[M]_D$ and ϕ Fixed[e]	$[M]_D$
	ϕ^{O-5}	$\psi^{C-2'}$	$[M]_D$	$\psi^{C-2'}$	$[M]_D$	$\psi^{C-2'}$	
α-Anomers							
Cyclohexyl	60°	100°	352°	100°	352°	100°	349°
2'-Methylcyclohexyl	65	120	249	120	254	120	260
6'-Methylcyclohexyl	80	90	399	80	444	70	476
2',6'-Dimethylcyclohexyl	90	110	286	100	352	100	347
β-Anomers							
Cyclohexyl	−55	120	−78	130	−89	140	−105
2'-Methylcyclohexyl	−60	140	−171	140	−165	160	−200
6'-Methylcyclohexyl	−55	110	2	110	9	100	28
2',6'-Dimethylcyclohexyl	−60	95	−95	125	−78	115	−52

[a] Using the expression 1 in the text. [b] The methyl groups and O-1 are in *trans* relationship. [c] Hard-sphere calculation only. [d] Hard-sphere calculation of $\psi^{C-2'}$ with $\phi^{O-5} = +60°$ for the α-anomers and −65° for the β-anomers. [e] $\psi^{C-2'}$ calculated from the observed molecular rotation using the expressions of footnote *a* and ϕ^{O-5} fixed as in footnote *d*.

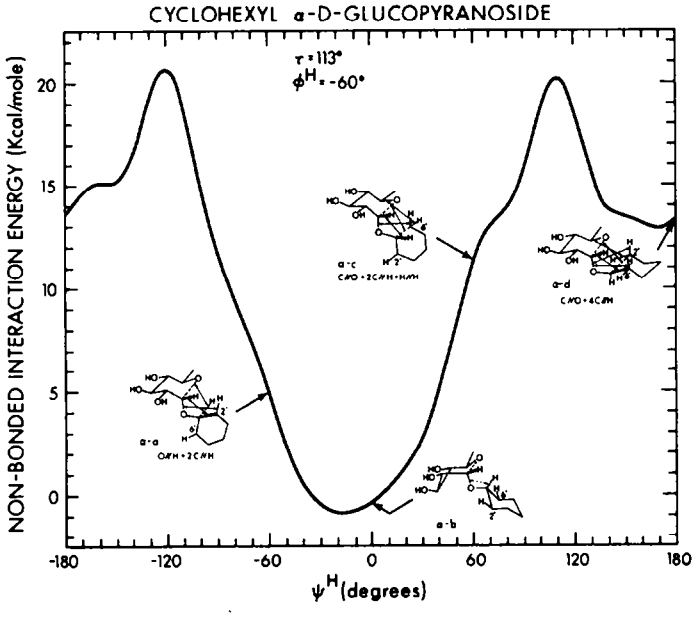


Fig 1. Potential energy plot derived by hard-sphere calculation of the relative energies of conformers of cyclohexyl α-D-glucopyranoside which arise from rotation about the O-1 to C-1' bond and plotted as the angle projected by H-1' and C-1 when viewed along the O-1 to C-1' bond (ψ^H torsion angle). The main non-bonded interactions in the staggered conformations (α-a, α-c and α-d) are indicated by double-headed arrows and described[19] below the formulas. The α-b conformation has the C-1 to O-1 and C-1' to H-1' bonds eclipsed.

as a most favorable form and about 4·5 kcal more stable than the most favorable staggered conformer (β-a). It is of interest to note at this point that the potential energy "trough" has a much broader and flatter "bottom" for the β- than the α-anomer. Fig 3 illustrates the effect of further substitution on the carbons geminal to the aglyconic carbon.

(d) *Molecular rotation.* The molecular rotations were calculated on the following basis. Following Brewster[83] and as adopted by Rees,[67] the contribu-

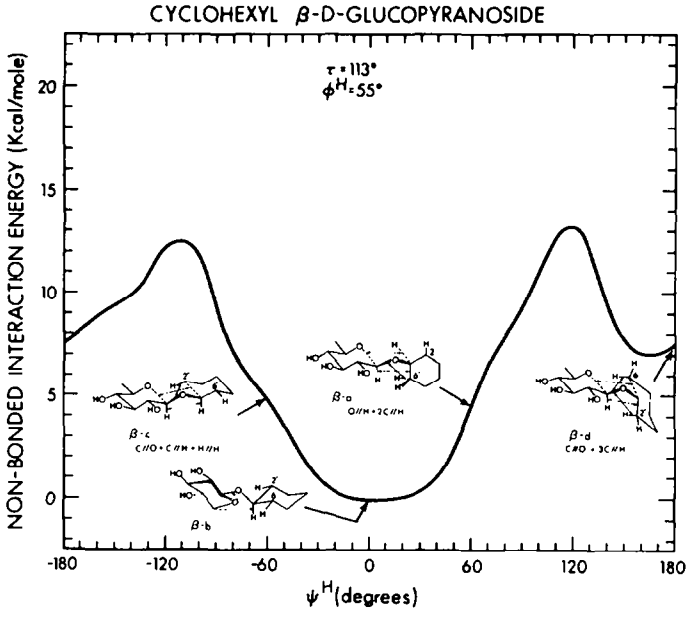


Fig 2. Potential energy plot for conformers of cyclohexyl β-D-glucopyranoside derived and described as indicated in Fig 1 for the α-anomer.

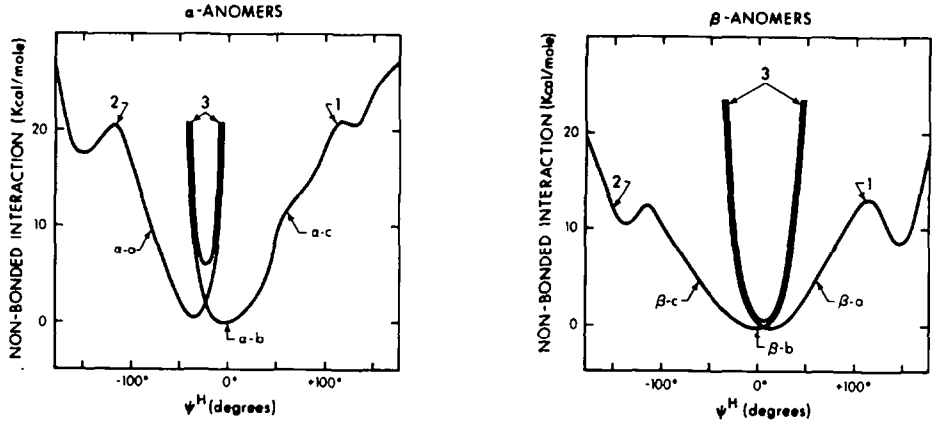


Fig 3. Hard-sphere calculations of the conformational preferences for the cyclohexyl α- and β-D-glucopyranosides. The positions of the conformers described in Figs 1 and 2 are indicated. Plots 1 refer to the 2'-*trans*-methylcyclohexyl glucosides, plots 2 refer to the 6'-*trans*-methylcyclohexyl glucosides and plots 3 to the 2',6'-dimethylcyclohexyl glucosides. The plots are to illustrate the constraints on conformation imposed by the successive introduction of equatorial methyl groups on the carbons geminal to the aglyconic carbon.

tion to rotation $[\Delta M]_D$ by a unit of conformational asymmetry was taken as proportional to the sine of the torsion angle θ,

$$[\Delta M]_D = k \sin \theta.$$

The differences in rotation, between the α- and β-methyl D-glucopyranosides and the α- and β-D-glucopyranoses, respectively, (Table 2) were used to calculate values of k using $\psi^{O\text{-}5}$ angles in the range + 60° to + 90° for the α-anomers and − 60° to − 90° for the β-anomers. These k values were then used to calculate the molecular rotations in the various conformations described in Table 4 employing the following expression,

$$[M]_D = [M]_D \text{ (}\alpha\text{- or }\beta\text{-D-glucopyranose)} + k \sin \phi^{O\text{-}5} + k \sin \phi^{C\text{-}2} + k \sin \psi^{C\text{-}2'} + k \sin \psi^{C\text{-}6'} + [M]_D \text{ (aglycon). (expression 1)}$$

and the following approximations (a) the projected angles for geminal atoms are all 120°, and (b) the *trans*-2-methylcyclohexyloxy groups make a contribution to molecular rotation of ± 55°. This latter assumption is based on the value of ± 55° for vicinal oxygens separated by two carbons[92] and the rotations listed in Table 3. It is noteworthy at this point that these data (Table 3) indicate the optimum space requirements for methyl, chlorine and hydroxy groups to be remarkably the same unless the contributions to rotation by the C/O, Cl/O and O/O units of the cyclohexyl residues vary substantially but this effect on rotation is near exactly cancelled by a change in conformation. This coincidence is considered highly improbable. The only marked difference in rotation is between the 2'-methylcyclohexyl and 2'-hydroxycyclohexyl β-D-glucopyranosides and the difference of 30° molecular rotation is not unexpected in view of the close proximity of the 2'-hydroxyl group to O-5 in the latter compound. Indeed, hydrogen bonding is normally invoked for such β-D-glucopyranosides.[68]

As a result of the above-mentioned calculations, it became evident that the k values calculated for the methyl α- and β-D-glucopyranosides with $\phi^{O\text{-}5}$ angles of + 60° and − 65°, respectively, provided molecular rotations in best accord with the observed rotations. However, as seen from Table 4, the agreement was not as good as when $\phi^{O\text{-}5}$ was fixed at + 60° for the α-glucosides and at − 65° for the β-anomers and the $\psi^{C\text{-}2'}$ angle then assessed by the hard-sphere calculation. This is seen to be the case especially for the α-glucosides. The same procedure was used to establish the best fit between calculated and observed molecular rotation assuming fixed $\phi^{O\text{-}5}$ angles in the ranges + 60° to 90° (α-anomers) and − 60° to − 90° (β-anomers) and again the best fit was for values near ± 60°. For reasons stated above with reference to Table 1, it seems necessary to give the $\phi^{O\text{-}5}$ value for β-anomers a slightly greater numerical value than that for the α-anomers. It is on this basis that the values of + 60° and − 65° were chosen as near optimum $\phi^{O\text{-}5}$ angles for the α- and β-D-anomers, respectively. Using these angles and the observed rotation, the $\psi^{C\text{-}2'}$ angles that would be required for a near exact fit are listed in Table 4. On this basis, for the α-glucosides, it would appear that the hard-sphere calculation overestimated the $\psi^{C\text{-}2'}$ angle by about 10° in the case of the 6'-methylcyclohexyl aglycon. Otherwise, the agreement is as good as can be expected. In the case of the β-glucosides, the hard-sphere calculations would appear to underestimate the $\psi^{C\text{-}2'}$ angles for the cyclohexyl and 2'-methylcyclohexyl β-glucosides by 10° and 20°, respectively, and to overestimate the 6'-methylcyclohexyl and 2',6'-dimethylcyclohexyl β-glucosides each by 10°. A consideration of molecular models shows that these discrepancies are all in the directions compatible with expectations based in conformational analysis. It is therefore tentatively concluded that the *exo*-anomeric effect plays an important role in establishing conformational preferences for glycopyranosides. Syntheses of further model compounds, especially the model glucosides listed in Table 4 with C-1' enriched in ^{13}C, are planned to better establish this conclusion which as will be seen below is strongly supported by ^{13}C-1 chemical shift data.

It is of interest first of all to examine the ^{13}C-chemical shift data reported in Table 5. It would be predicted[93] that the smaller the $\psi^{C\text{-}2'}$ angle for the α-glucosides and the greater the $\psi^{C\text{-}2'}$ angle for the β-glucosides, the more compressed the anomeric hydrogen and therefore the more shielded would be the anomeric carbon (C-1). The results are seen to

Table 5. Carbon-13 chemical shifts ppm (TMS external) for atoms about the glycosidic linkage of α- and β-D-glucopyranosides

Aglycon	Chemical shifts and torsion angles[a]							
	C-1, ppm	$\psi^{C\text{-}2'}$[b]	C-1', ppm	$\psi^{H\text{-}1'}$	H_2C-2' ppm	$\psi^{C\text{-}2'}$	H_2C-6' ppm	$\psi^{C\text{-}6'}$
α-Anomers								
Methyl	100·0	—	57·7	—	—	—	—	—
Cyclohexyl	96·9	100°	77·1	—	31·6	100°	33·4	140°
2'-Methylcyclohexyl	100·6	120	85·9	0°	—	—	33·7	120
6'-Methylcyclohexyl	94·5	80	80·8	− 40	30·1	80	—	—
2',6'-Dimethylcyclohexyl	99·1	100	91·0	—	—	—	—	—
β-Anomers								
Methyl	104·1	—	57·9	—	—	—	—	—
Cyclohexyl	100·9	130	79·1	—	33·6	130	32·0	110
2'-Methylcyclohexyl	100·1	140	83·9	20	—	—	31·3	100
6'-Methylcyclohexyl	104·0	110	87·2	− 10	33·8	110	—	—
2',6'-Dimethylcyclohexyl	102·7	125	91·2	—	—	—	—	—

[a] For the α-anomers, $\phi^{O\text{-}5} = +60°$, for the β-anomers, $\phi^{O\text{-}5} = -65°$.
[b] Column 4 of Table 4.

be in good agreement with this expectation. Similarly, for the aglyconic carbon (C-1'), the smaller numerically the $\psi^{H-1'}$ angle, the less the compression of H-1' with O-5 of the glucosyl residue and, therefore, the less shielded should be C-1' as was indeed the case for the 2'- and 6'-methylcyclohexyl glucosides where substitutional effects on the chemical shift of C-1' can be expected to be constant. These kinds of considerations can be applied to the relative chemical shifts of the 2' and 6' methylene groups of the cyclohexyl glucosides and of those of the 2'- and 6'-methylcyclohexyl glucosides. It is seen (Table 5) that there is a good overall agreement between the assigned $\psi^{C-2'}$ and $\psi^{C-6'}$ torsion angles and the chemical shifts. Finally, the chemical shift difference for the C-1 atoms of the α- and β-cyclohexyl glucosides is 3 ppm for a difference of 30° in $\psi^{C-2'}$ angles. For the dimethylcyclohexyl glucosides, the difference is 3·6 ppm for a change, *in the same direction*, of 25° for the $\psi^{C-2'}$ angle. Thus, the ^{13}C-chemical shift data are in good general agreement with expectations based on the assigned conformations.

We consider that the strongest evidence accumulated in this research in favor of constant ϕ angles for the glucosides listed in Tables 3, 4 and 5 was found in the chemical shifts of the anomeric carbons. Table 6 lists ρ torsion angles which were calculated from the models used for the hard-sphere calculations. It is at once seen that there is no correlation between the ρ torsion angles estimated by the hard-sphere calculations only. However, good correlation exists when the values for the ϕ^{O-5} angles were fixed and $\psi^{C-2'}$ determined by hard-sphere calculation. A somewhat better correlation was found with ϕ^{O-5} fixed and the $\psi^{C-2'}$ angles estimated from the molecular rotations. Thus, it has become apparent that ^{13}C- NMR may become the method of choice for estimating the conformations of glycosides and efforts are underway to properly calibrate the method. If successful, the fact that the signal for anomeric carbons is normally readily observed would be of great value especially for complex oligosaccharide units such as are found in glycolipids and glycoproteins. The method would of course depend on a predictable constancy for the ϕ angles as expected from the *exo*-anomeric effect. Rees and Scott[68] have recently suggested that the *exo*-anomeric effect may override steric considerations for α-linked disaccharides.

Table 6. Correlations between ^{13}C-chemical shifts for anomeric carbons and a torsion angle by projecting C-1 to C-1'[a]

Aglycon	C-1 ppm	ρ^b	ρ^c	ρ^d
α-Anomers			$\phi^{O-5} = +60°$	
6'-Methylcyclohexyl	94·5	51°	24°	16°
Cyclohexyl	96·9	39	40	40
2',6'-Dimethylcyclohexyl	99·1	83	46	46
2'-Methylcyclohexyl	100·6	68	64	64
β-Anomers			$\phi^{O-5} = -65°$	
2'-Methylcyclohexyl	100·1	−31	−35	−19
Cyclohexyl	100·9	−44	−44	−35
2',6'-Dimethylcyclohexyl	102·7	−45	−59	−63
6'-Methylcyclohexyl	104·0	−60	−69	−79

[a]The C-2' to H-1 torsion angle for the α-anomers and the C-6' to H-1 torsion angle for the β-anomers.

[b]Calculated using the ϕ^{O-5} and $\psi^{C-2'}$ angles obtained by hard-sphere calculations only (columns 1 and 2, Table 4).

[c]Calculated setting ϕ^{O-5} constant and estimating the $\psi^{C-2'}$ angle by hard-sphere calculation (column 4, Table 4).

[d]Calculated setting ϕ^{O-5} constant and estimating the $\psi^{C-2'}$ angle from the molecular rotation (column 6, Table 4).

Acknowledgements—The authors are indebted to Mr. A. Adams, computer analyst for the Department of Chemistry and Dr. L. T. J. Delbaere of the Department of Biochemistry for guidance for the hard-sphere calculations and to Dr. J. Hudec for valuable discussion. The work was supported by NRC-T172 Grant in Air of Research to R.U.L.

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