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CONFORMATIONAL ANALYSIS OF THE GLYCOSAMINOGLYCANS

II. BOND-ANGLE STUDIES, TORSIONAL POTENTIAL, AND STERIC MAP FOR THE β-D-(1→3) LINKAGE

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ABSTRACT

The geometry of the glycosidic valence-bond angle for both the β-D-(1→4) and β-D-(1→3) linkages has been investigated by using CNDO and PCILO molecular-orbital techniques on model compounds. In each case, the glycosidic valence-bond angle of minimum energy was about 111°, corresponding to the value observed in ether analogs. A secondary energy-minimum was found near 116°, which is the value experimentally observed for saccharides. It was concluded that long-range intra- and/or inter-molecular interactions are responsible for overall preference for the 116° value of the valence-bond angle. The force constants predicted from the shapes of the 116° bond-angle minima gave poor agreement with the experimental values found for ethers and employed in normal coordinate analyses of saccharides. The results did suggest that the β-D-(1→3) bond angle should be 115.6°, which is smaller than the corresponding β-D-(1→4) bond angle. An intrinsic torsional potential-function and general steric map were also determined for the torsion-angle rotations of the β-D-(1→3) linkage.

INTRODUCTION

This is the second report from a continuing investigation of the theoretical conformational analysis of six glycosaminoglycans: hyaluronic acid, chondroitin, chondroitin- 6-sulfate, chondroitin 4-sulfate, dermatan sulfate, and keratan sulfate. Previously we have reported charge distributions over these molecules as well as the torsional-potential steric map for the β-D-(1→4) glycosidic linkage[1]. In this report we focus upon the conformational properties associated with the β-D-(1→3) glycosidic linkage.

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GEOMETRY OF THE GLYCOSIDIC VALENCE-BOND ANGLE

Arnott and Scott[2] have reviewed crystal structures of 27 pyranose sugars and have compiled standard bond-lengths, bond angles, and torsion angles. These serve as starting points in refinement of new crystal structures for saccharides. For the glycosidic bond-angle, they report an average value of 116.5°, varying from 115.7 to 117.6°. These were determined from data of compounds having β-D-(1→4) glycosidic linkages. The β-D-(1→3) linkage has not been studied in detail. Because of the lack of structural data on the β-D-(1→3) valence-bond angle and the necessity for such data in the conformational analysis of glycosaminoglycans, we chose to study this bond angle using two molecular-orbital techniques: CNDO/2 (ref. 3) and PCILO (refs. 4 and 5). The reasonableness of such a study can, at least in part, be ascertained by comparison of experimental values with a similiar study on the β-D-(1→4) linkage.

Our technique was to use a model structure which approximates, with appropriate coordinates, either the β-D-(1→4) or β-D-(1→3) linkage (see Fig. 1). The total molecular energy was computed as a function of the glycosidic bond-angle. Three different conformations were used, having ϕ, ψ values of [0°,0°], [60°,330°], and [90°,330°]. (See ref. 1 for the definition of the angle–conformation convention.) These correspond to energetically favorable conformations. The total molecular energy was evaluated by allowing the bond angle to vary from 110 to 120° while maintaining

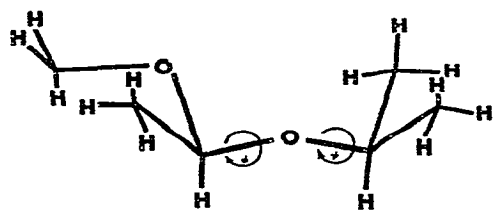

Fig. 1. Structure used to evaluate bond-angle geometry and torsional potential.

each torsional conformation constant. These results for the β-D-(1→4) and β-D-(1→3) linkages are shown in Fig. 2. Except for the [0°,0°] conformation for the β-D-(1→3) linkage, which is erratic because of the close contacts between atoms, the global minima for the valence-bond angle are found between 110 and 112°. The energy increases smoothly as the bond angle increases, except for a point of inflection, mainly for the β-D-(1→3) linkage, or a discrete local minimum, mainly for the β-D-(1→4) linkage at 116°. The minimum at the lower bond-angles agrees with a valence-bond angle of 111 ±3°, for an sp^2-hybridized oxygen atom and found in simple ethers[6]. The valence-bond angle at 116° corresponds to a secondary energy-minimum for the model compound used in this analysis. The model compound, in turn, is a first nearest-neighbor interaction representation of polysaccharide structure. Thus the narrow Arnott and Scott range, about 116° for sugars, suggests that long-range intra- and/or inter-molecular packing forces are involved in deforming the

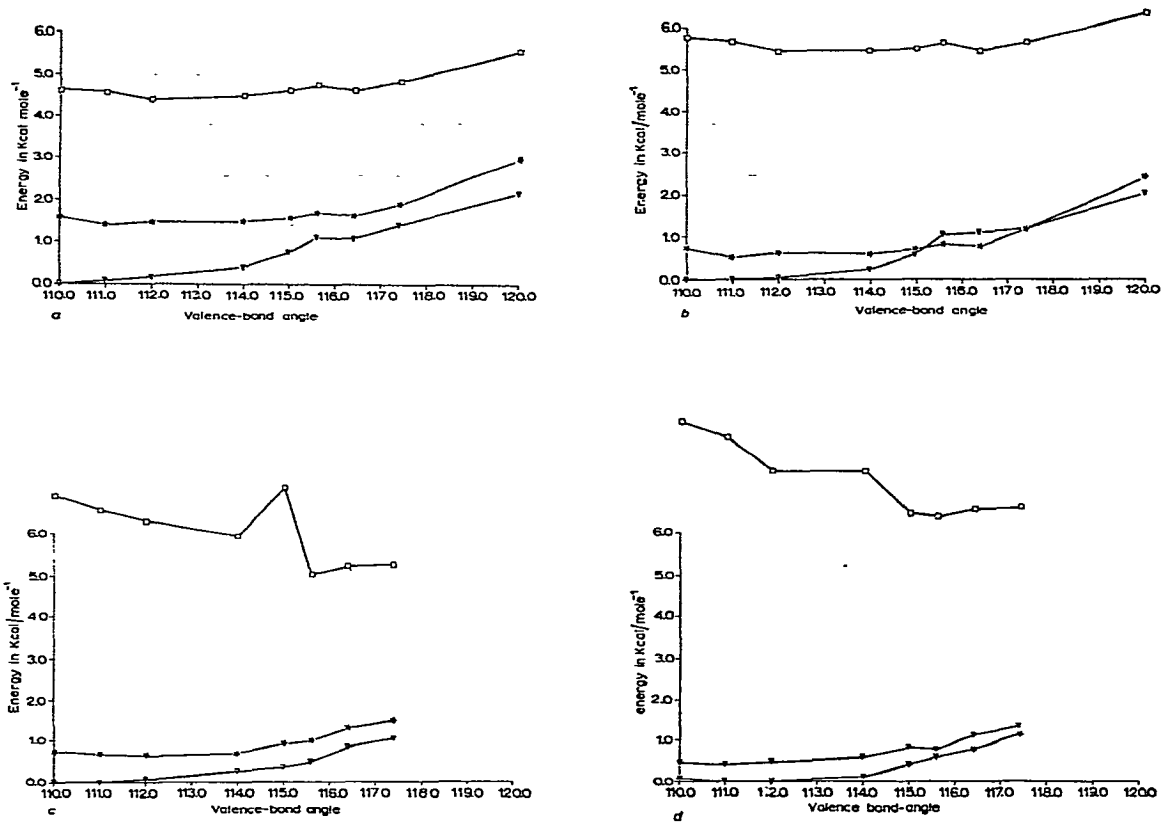

Fig. 2. Total energy (kcal mol^{-1}) *vs.* bond angle (degrees), with □ for conformation [0°, 0°], ▽ [60°, 300°], and ☆ for [90°, 330°], and: (*a*) the (1→4) linkage using CNDO; (*b*) the (1→4) linkage using PCILO; (*c*) the (1→3) linkage using CNDO, and (*d*) the (1→3) linkage using PCILO.

valence angle from that observed in small molecules and stabilizing to the large value. It is tempting to speculate that the 116° valence angle may not always be maintained in dilute solutions where intermolecular packing-forces are absent.

A parabola has been fitted to the secondary energy-minimum found in the region of the 116° valence-bond angle, and it has been used to describe the potential energy for an idealized Hookean deformation of the C–O–C bond angle, the second derivative being the force constant. The predicted force-constants are listed in Table I. In only one instance, for both the β-D-(1→4) and β-D-(1→3) linkage, is the predicted force-constant in reasonable agreement with that found for dimethyl ether, namely, 1.313 mdyne.Å.rad^{-2} (ref. 8), and successfully used in the normal coordinate analysis of saccharides[9–13]. The [60°,330°] β-D-(1→4) conformation found by using PCILO yields a force constant of 0.990 mydne.Å.rad^{-2} and the [90°,330°] conformation of the β-D-(1→3) conformation possesses a force constant of 3.205 mydne.Å.rad^2. Interestingly, these correspond to the torsional conformational states of lowest

TABLE I

FORCE CONSTANTS CALCULATED FROM TOTAL ENERGY

Conformation	*Force constant in mdyne. Å. rad*$^{-2}$			
	β-D-(*1*→*4*)		*β*-D-(*1*→*3*)	
	CNDO	*PCILO*	*CNDO*	*PCILO*
[0°,0°]	9.367	11.927	−4.967	−4.617
[60°,330°]	9.078	0.990	−6.326	−4.833
[90°,330°]	9.147	11.439	−6.185	3.205

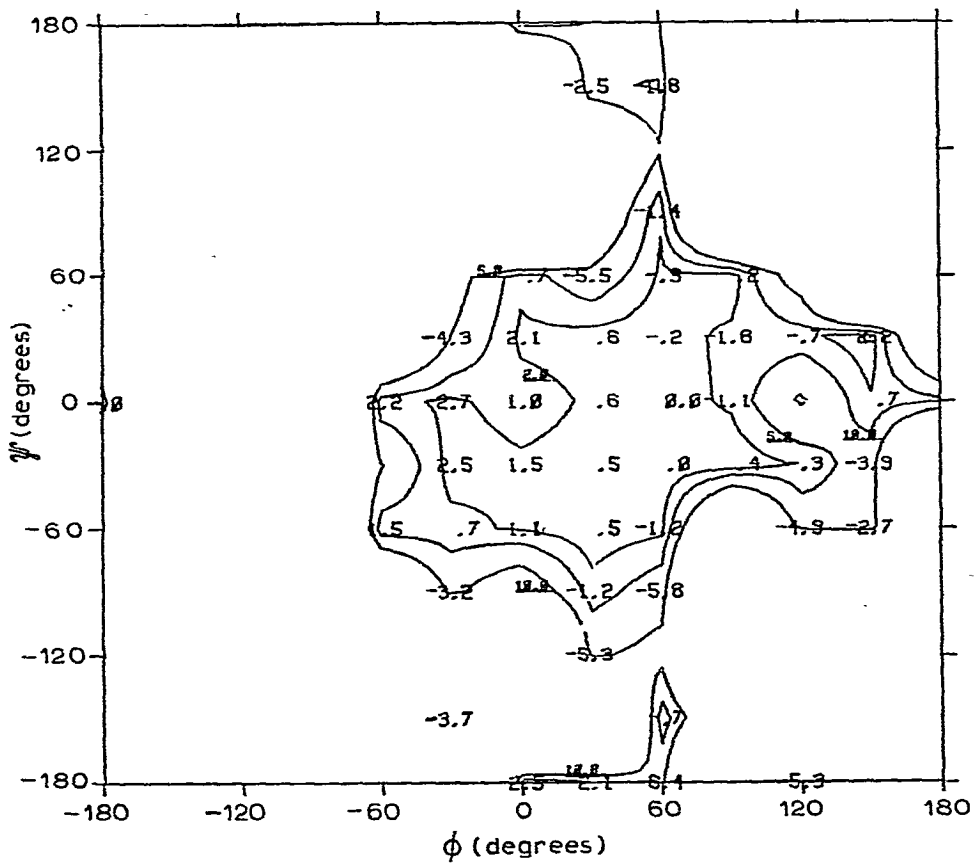

Fig. 3. Iso-energy contour-map for the molecule in Fig. 1, approximating the *β*-D-(1→3) glycosidic linkage. The levels are 2.0, 5.0, and 10.0 kcal. mol^{-1} above the minimum at (150°, 30°). Superimposed are torsional-energy values in kcal mol.$^{-1}$.

energy. The calculations indicate that the favored β-D-(1→3) valence-bond angle is 115.6° rather than 116.5° as used for the β-D-(1→4) valence-bond angle. This slightly smaller value has been adopted in the subsequent calculations reported here.

β-D-(1→3) TORSIONAL POTENTIAL AND STERIC MAP

The torsional potential and steric map of the β-D-(1→3) linkage were computed by using the same procedures as applied to the β-D-(1→4) linkage and reported in ref. 1. Fig. 3 displays the torsional potential. The torsional potential makes it possible to estimate the conformationally sensitive orbital interactions, mainly between the electrons of the ring oxygen and the glycosidic oxygen atoms. The torsional barrier height is 9.2 kcal.mole^{-1}. This is 4.4 kcal.mole^{-1} above the experimental value[14] for dimethyl ether and 2.06 kcal.mole^{-1} above that found for the β-D-(1→4) linkage[1]. This latter difference is due, in part, to the smaller valence-bond angle (115.6°), which decreases the distance between the ring and glycosidic oxygen atoms. The torsional-energy surface is very similar in shape, however, to the β-D-(1→4) surface. Fig. 4 illustrates the disaccharide used to evaluate the steric map. The steric map, which

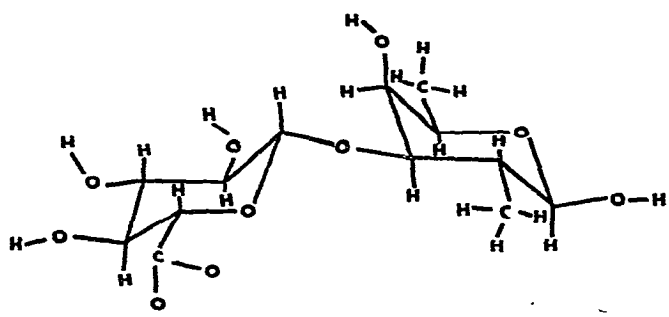

Fig. 4. Disaccharide used to evaluate the steric restrictions for the β-D-(1→3) linkage.

allows a straightforward reduction of the conformational hyperspace that needs to be considered in an analysis, is again similar to the β-D-(1→4) map, being even more restricted. Superimposed, as indicated, are the locations of two possible β-D-(1→3)-linked X-ray structures for xylan, as predicted by Atkins *et al.*[14,15]. This comparison indicates the stereochemical reasonableness of the calculations. The minimum in the remote corner is a point at which the bulky group at C-2 is at a most favorable position. This map is similar in shape to other maps for β-D-(1→3)-linked disaccharides[16,17]. Differences in the minimum and specific topography result from the group at C-2, which is added to approximate the acetamido group in the glycosaminoglycans.

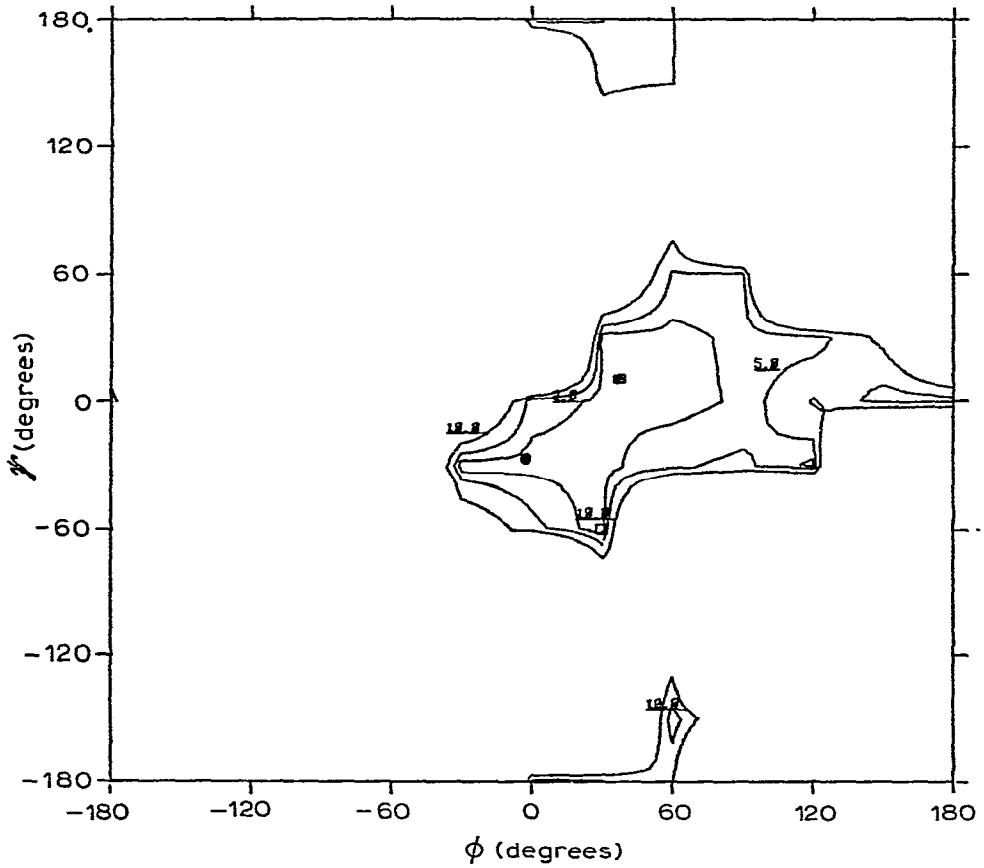

Fig. 5. Steric map for the β-D-(1→3)-linked disaccharide in Fig. 4. Iso-energy levels are plotted at 2.0, 5.0, and 10.0 kcal. mole^{-1} above them inimum at (30,–60). Superimposed are crystal structure of three-stranded (1→3)-β-D-xylan at ● for lefthanded and ■ for righthanded strands[14,15].

CONCLUSIONS

The results of this study on the β-D-(1→3) linkage of sugars have shown that this structure has a similar bond angle, torsional potential, and general steric map as the β-D-(1→4) glycosidic linkage. Certain differences are noted, however, with the β-D-(1→3) geometry that give rise, overall, to a compound that is conformationally more restricted. These results, together with those in our preceding paper, provide the basis from which a complete, theoretical conformational analysis can be conducted.

An investigation of the glycosidic valence-bond angle has not been particularly rewarding. The main conclusion is that the valence angle of about 116.5° is a secondary energy-minimum based upon a nearest-neighbor energy calculation. Intra- and/or inter-molecular packing interactions are responsible for the overall energetic preference of this bond-angle geometry over the bond angle near 111° observed in simple

compounds. Along the same lines, little success was achieved in the prediction of reasonable force constants owing, most probably, to the same reasons. It was concluded, nevertheless, that the bond angle of the β-D-(1→3) linkage should be slightly smaller than the β-D-(1→4) linkage.

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