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CONFORMATIONAL DIFFERENCES AND STERIC ENERGIES FOR COMPOUNDS CONTAINING α-D-GLUCOPYRANOSE CHAIRS HAVING A RANGE OF O-4–O-1 DISTANCES

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ABSTRACT

Conformations corresponding to minimal energies are predicted with molecular mechanics for a series of compounds containing α-D-glucopyranose rings. These model rings, in the $^4C_1$ conformation, were constrained to have O-4–O-1 distances ranging from 360 to 500 pm. The predicted conformation of lowest energy has an O-4–O-1 distance of 426 pm, close to the midpoint of the observed 400–460-pm range. The predicted monomers with O-4–O-1 distances of 400 and 460 pm have energies ~2.51 kJ.mol^{-1} (~0.6 kcal.mol^{-1}) above the minimum. Systematic relationships of valence and torsion angles to the O-4–O-1 distance were examined with these molecular models, and the predicted relationships were compared to changes observed by single-crystal diffraction-studies. All of the ring torsion-angles, except C-1–C-2–C-3–C-4, several ring-valence angles, and the virtual angles involving O-1, C-1, C-4, and O-4, showed systematic changes with change in O-4–O-1 distance. Discrepancies between the observed and predicted rings include the values for the virtual angle C-1–C-4–O-4, values for the C-1–C-4 distance (10 pm) and its rate of change, and values for C–O bond-lengths.

INTRODUCTION

The conformations of the α-D-glucopyranose ring in crystalline compounds thereof (see Fig. 1) vary somewhat from the perfect, $^4C_1$ shape. In part, this is caused by packing forces and, for cyclic oligomers and polymers, by the number of monomers per cycle or helix pitch, and by the helical rise per monomer[1]. These conclusions follow from single-crystal studies of cycloamyloses and maltoses[2]. In particular, packing forces often induce variations in the individual monomers of the cycloamylose

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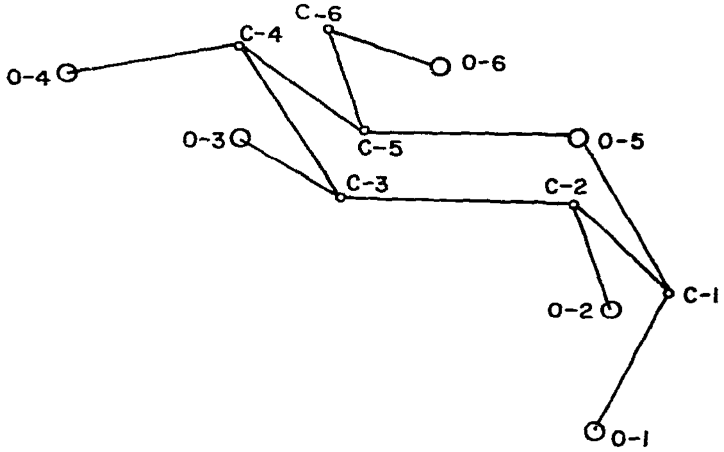

Fig. 1. The α-D-glucopyranose molecule, showing the conventional numbering of the atoms

rings[3]. Despite the chemical identity of each D-glucosyl residue in the ring of a cycloamylose, deviations from structural identity are often substantial.

The distance between O-4 and O-1 is a simple, but useful, indicator of monomeric shape in studies of amylose [the α-D-(1→4)-linked D-glucan] and cycloamyloses[1]. Distance ranges from 400 to 460 pm are found in published, single-crystal studies. We wished to learn the energy involved in that particular deformation, and to obtain a better conception of the nature of individual changes in the pyranoid ring as it undergoes changes in its O-4–O-1 distance. The technique of molecular mechanics offers approximate energies and idealized molecular geometries, and has previously been used to predict conformations having minimal energy for D-glucose[4], maltose[5], cellobiose[6], gentiobiose[7], and anhydroaldohexopyranoses[8] and an anhydroheptulopyranose[8]. The present paper explores systematic changes in molecular geometry that occur when the pyranose ring takes on different O-4–O-1 distances. This is a more rigorous test of the assumptions of molecular mechanics. Our modeling is expected to reproduce the nature of inherent flexibility in a complicated structure, rather than reproducing the conformational details of an individual, or averaged, sugar structure.

The concept of systematic change is important in the construction of accurate models of polysaccharides. Such models are used, for example, in structure determinations, in order to supplement the limited amount of diffraction data that can be obtained from polysaccharides.

When using molecular mechanics, the force field selected affects the exact conformation resulting from energy minimization. However, results are generally similar, despite a variety of force fields. Herein, we describe our testing of the applicability of a readily available, general-purpose, computer program for performing molecular-mechanics calculations.

METHODS

The minimal, molecular energies for conformations having fixed O-4–O-1 distances, and the conformation having the global minimum, were determined by use of program TRIBBLE[9]. This interactive program incorporates the MMI molecular mechanics program[10], and has been described in another report[9]. Briefly, the force-field constants are those of the current version of MMI, and minimization involving all atoms was accomplished by a Davidon–Fletcher–Powell[11] technique. Instead of an extra-large force-constant to drive the O-4–O-1 distance to a given value, better results were obtained when that distance was rigidly fixed. All energy calculations were performed on the DEC-VAX 11/780 computer system* at the Experimental Station in Wilmington.

Conformational parameters for D-glucose rings, the coordinates of which are in the literature, were calculated on a CDC 1700 computer at the Southern Regional Research Center. The program, written by V. G. Murphy, has been modified to graph, and perform, linear, least-squares, regression analyses on the collection of calculated parameters.

For comparisons of the predicted, conformational changes with those of real structures, 47 sets of coordinates of D-glucose rings from the single-crystal literature were surveyed[3,12–36]. Most cycloamylose studies were excluded, because of possible distortions of molecular parameters arising from the closed, cyclic structure. Results for so many D-glucosyl residues are available from data for cycloamyloses that they could possibly overwhelm results for noncyclic molecules. Additionally, none of the determinations of cycloheptaamylose[37–40] were considered to be sufficiently accurate for our purposes. (The criterion arbitrarily selected for accuracy was whether any C–O bond-length exceeded 146.0 pm.) Four cyclohexaamylose structures that met this criterion were included, because they provided monomers that have O-4–O-1 distances in a range sparsely populated by other structures. The residues excluded were also analyzed, and the results supported those reported herein; the standard deviations were, however, higher.

Also surveyed were the rings derived by Rasmussen *et al.* for α-D-glucose[4] and β-maltose[5]. This separate analysis of theoretical rings also included the widely used, averaged monomer derived by Arnott and Scott[41] and a D-glucose ring from a study of V amylose by Zugenmaier and Sarko[42].

RESULTS AND DISCUSSION

Shown in Fig. 2 are the calculated energies and resulting Boltzmann distribution for the populations of predicted D-glucose structures having O-4–O-1 distances

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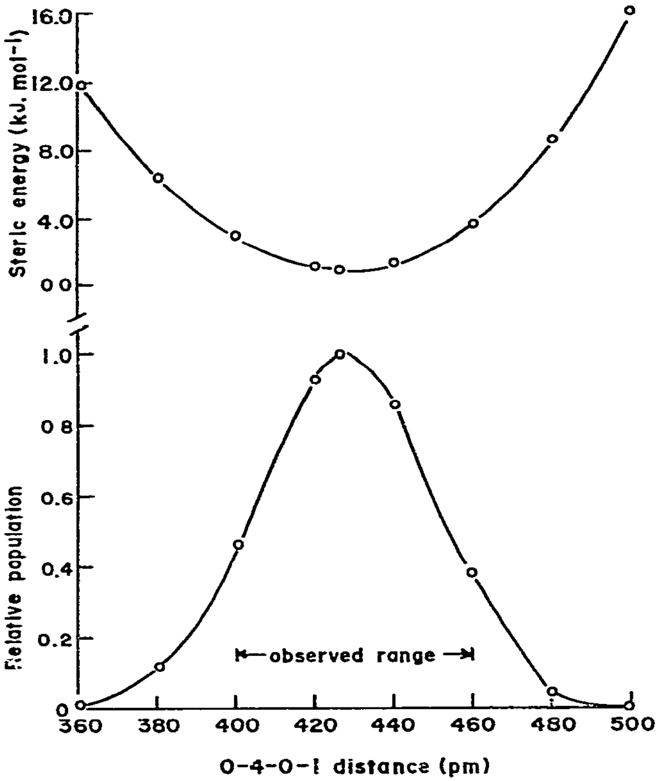

Fig 2 Calculated steric energy (upper curve), and resulting Boltzmann distribution, for predicted D-glucose rings having the lowest energy for different O-4–O-1 distances.

ranging from 360 to 500 pm. The predicted structure having the lowest energy has an O-4–O-1 distances of 426 pm, which is 4 pm from the center of the observed range, a good agreement. The population-distribution curve suggests that roughly 80 percent of the shapes possible for isolated molecules have O-4–O-1 distances that are observed in single crystals. Were the observed range corrected for thermal motion, an even larger number of predictable molecules would fall in the observed range.

Our calculations show that the energy needed to deform the molecule to the limits of the observed range (see Fig. 2) is ~2.51 kJ.mol^{-1} (~0.6 kcal.mol^{-1}). This rather small value illustrates the possibility of error in assuming any particular conformation for D-glucose. Many different shapes are accessible at little cost in energy.

Table I presents the rates of change for a number of conformational parameters that might be expected to correlate with change in the O-4–O-1 distance. As predicted earlier[43]. strong correlation is found for the torsion index, a contrived sum of ring torsion-angles (see Table I and Fig. 3). The slope of the torsion index against the O-4–O-1 distance that was reported earlier[43], namely, 75° per 100 pm, is somewhat larger than the present values. Although the slope of the torsion index for our predicted rings is close to that for the actual structures (see Fig. 3), there is a difference

TABLE I

SLOPES AND INTERCEPTS[a] FOR CHANGES OF MOLECULAR PARAMETERS WITH CHANGE IN O-4–O-1 DISTANCE

	Predicted rings (present work)		Observed rings (47 geometries)		Survey of 8 theoretical rings		Distances and angles	
	Slope	Intercept	Slope	Intercept	Slope	Intercept	Least-energetic structure, 426.19 pm (present work)	Calculated from slopes, intercepts of observed rings at 426.19 pm
Distance[b]								
C-1–C-4	0.107(3)	234.0(2)	0.030(20)	270(10)	0.062(2)	260(10)	279.5	287.5
Angles[c]								
O-5–C-1–C-2	26(2)	102.1(6)	21(11)	100(5)	66(22)	80(9)	112.9	109.6
C-1–C-2–C-3	75(2)	78.1(6)	50(9)	89(4)	56(21)	86(9)	110.0	110.0
C-2–C-3–C-4	−2(2)	109.7(6)	−36(14)	126(6)	6(12)	107(5)	108.6	110.3
C-3–C-4–C-5	−71(3)	143.0(10)	−77(11)	144(5)	42(18)	130(8)	112.7	111.5
C-4–C-5–O-5	−15(1)	117.6(6)	−29(11)	123(5)	4(30)	109(13)	111.1	110.1
C-5–O-5–C-1	40(1)	94.5(3)	2(9)	113(4)	−5(20)	115(9)	111.7	113.9
O-1–C-1–C-4	270(10)	−15.0(4)	240(10)	−2(4)	250(30)	11(14)	99.3	98.6
C-1–O-1–O-4	−283(6)	192.0(30)	−270(1)	189(3)	−280(20)	192(9)	71.8	74.2
C-1–C-4–O-4	184(6)	71.0(20)	250(10)	34(6)	200(40)	57(18)	149.5	143.1
C-4–O-4–O-1	−170(1)	111.9(6)	−220(10)	139(4)	−180(30)	120(12)	39.4	44.0
I O-5–C-1–C-2–C-3	−230(8)	155.0(30)	−160(20)	127(8)	−200(70)	147(32)	57.5	58.5
II C-1–C-2–C-3–C-4	50(10)	−72.0(50)	0(30)	−53(14)	90(40)	−94(17)	−50.2	−53.7
III C-2–C-3–C-4–C-5	110(10)	4.0(50)	170(30)	−23(12)	70(60)	21(27)	50.0	51.0
IV C-3–C-4–C-5–O-5	−180(8)	22.0(40)	−250(20)	53(10)	−160(70)	16(29)	−54.3	−52.0
V C-4–C-5–O-5–C-1	59(7)	34.0(30)	100(30)	16(11)	40(40)	44(18)	58.9	58.8
VI C-5–O-5–C-1–C-2	180(6)	−138.0(20)	130(20)	−116(7)	160(50)	−131(20)	−61.9	−62.3
Torsion index[d]	−690(10)	417.0(6)	−600(40)	389(17)	−650(230)	411(100)	124.0	130.0

[a] Numbers in parentheses are standard deviations for the digit reported last. [b] The slope of the distance change has no dimensions; the intercepts and distances are in pm. [c] The slopes of the angles are in degrees of angular change per nm of change in O-4–O-1 distance. [d] The torsion index equals the sum of the torsion angles, *i.e.*, |I| + |II| + |III| + |IV| + |V| + |VI|.

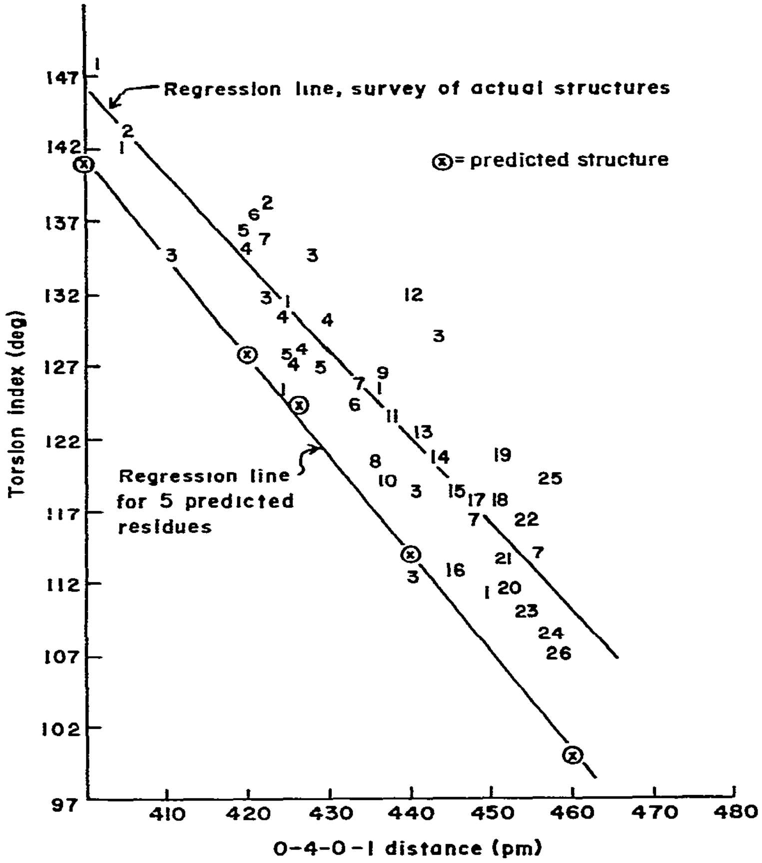

Fig 3. Least-squares regression-lines, and data for torsion index (defined in Table I), against O-4–O-1 distance Circles represent torsion indices of the rings now predicted, and the numbers refer to the following α-D-glucose molecules or residues (data from single-crystal studies): 1, cyclohexaamylose–p-nitrophenol[11]. 2, α-maltose[12]; 3, cyclohexaamylose–H_2O[13]; 4, cyclohexaamylose–1-propanol[14]; 5, cyclohexaamylose–KOAc[15]; 6, α,α-trehalose[16]; 7, phenyl α-maltoside[17]; 8, decyl α-D-glucopyranoside[18]; 9, planteose[19]; 10, isomaltulose[20], 11, methyl α-D-glucopyranoside[21]; 12, α,α-trehalose · $CaBr_2$[22]; 13, β-maltose[23]; 14, raffinose[24]; 15, lactose · H_2O[25]; 16, methyl α-D-glucopyranoside cyclic 4,6-phosphate[26]; 17, α-D-glucopyranose–urea[27]; 18, α-D-glucopyranose[28]; 19, lactose · $CaBr_2$[29]; 20, α-D-glucopyranose H_2O[30]; 21, lactose · $CaCl_2$[31]; 22, melibiose[32]; 23, sucrose[33]; 24, methyl β-maltoside[34]; 25, melibiose[35]; and 26, 1-kestose[36].

of ~6° in the torsion index for given O-4–O-1 distances in the observed range. This discrepancy, which is a sum of the discrepancies in the six individual, ring-torsion angles, must result from the standard, MMI force-field.

Large rates of change were also shown by the virtual bond-angles involving O-1, C-1, C-4, and O-4. The standard, MMI force-field predicts the flexibility at C-1 in a satisfactory manner, but the discrepancy in the calculated and observed slopes for the angle C-1–C-4–O-4 is significant. All of the ring torsion-angles, except II, have significant slopes for both our predicted monomers and the actual residues. A

TABLE II

ATOMIC COORDINATES FOR LEAST-ENERGETIC RING

Atom	x *(pm)*	y *(pm)*	z *(pm)*
C-1	43.435	−153.411	−22.162
C-2	154.849	−55.393	−53.143
C-3	128.177	76.891	15.972
C-4	−13.768	120.051	−15.431
C-5	−115.488	9.801	9.632
C-6	−255.756	48.488	−35.208
O-1	40.825	−180.094	113.240
O-2	275.275	−110.372	−12.813
O-3	217.337	173.114	−28.389
O-4	−44.781	233.645	57.278
O-5	−81.606	−106.469	−59.266
O-6	−344.848	−51.556	0.366
H-C-1	52.651	−251.378	−70.888
H-C-2	168.956	−41.166	−161.049
H-C-3	146.846	70.695	123.962
H-C-4	−19.253	155.958	−118.949
H-C-5	−120.451	−18.187	115.796
H-C-6	−263.865	56.213	−144.387
H-C-6′	−294.885	136.974	16.560
H-O-1	−36.616	−230.086	132.732
H-O-2	268.361	−133.147	78.410
H-O-3	183.402	238.472	−6.853
H-O-4	−55.262	211.507	148.212
H-O-6	−317.726	−132.532	−40.124

slowly changing, curvilinear relationship is predicted between torsion angle II and the O-4–O-1 distance; no significant rate of change is observed in actual crystals. Of the valence bond-angles, the ring bonds about C-2 and C-4 seem to undergo the largest, systematic changes. Although the ranges of observed angles about C-3 and C-5 are comparable to those of other ring-atoms, they do not exhibit highly systematic changes resulting from changes in the O-4–O-1 distance. The predicted, angular range about C-3 is small, and nonlinear within the 400 to 460-pm range. The predicted change about C-5 is small, and, outside the observed range, deviates strongly from a straight line.

The observed variations in bond length do not correlate with the O-4–O-1 distance. The predicted slopes range from 0.001 to 0.10, rates that are too small to observe by present diffraction studies. The predicted slope for the C-1–C-4, virtual bond-length is much higher than the insignificant rate observed.

Also shown in Table I are the parameters for the predicted ring having the lowest energy, and the parameters representing an actual structure having the same O-4–O-1 distance, namely, 426.19 pm. The values representing actual structures were calculated from the slope, and the intercept values from the regression analyses. Close agreement characterizes all of the ring torsion-angles and the virtual angles O-1–C-1–C-4. A discrepancy is found for the observed and calculated C-1–C-4 distances, in addition to a predicted, systematic change larger than is observed for this parameter. That deficiency may result partly from the use of 138.15 pm for the length of the standard, C–O bond; this value is based on experience with ether and alcohol bonds, but does not take into account any effects that might result from ring closure. The C–O distances predicted are all 3 to 5 pm too short.

Table II presents the atomic coordinates of atoms of the predicted monomer of lowest energy.

From the present survey of actual molecules, the ranges of the various types of torsion angles reported by Jeffrey and French[2] need to be expanded. The observed angles C–O–C–C (V and VI) range from 54° to 67°, angles C–C–C–O (I and IV) range from 44° to 63°, and angles C–C–C–C (II and III) range from 42° to 61°.

The standard deviations for the rates of change predicted by the survey of the other, theoretically derived rings are large compared to both the present calculations and the present survey of actual structures. This shows the incompatibility of several force fields and modeling assumptions that are at present current.

The use of modified force-fields by other workers has resulted in least-energetic rings having O-4–O-1 distances of 442 (ref. 4) and 451 pm (ref. 7). The latter figure seems unlikely, because of its position close to the extreme, upper limit of the observed range. The value of 442 pm may not be a significantly poorer indicator of the conformation of lowest energy than the 426-pm distance predicted herein. We consider that it will be important to avoid circular arguments in future attempts to ascertain the O-4–O-1 distance that represents the ring having the lowest energy.

Shortly before this manuscript was submitted, a report was published by Joshi and Rao describing the flexibility of α- and β-glucose rings[44]. They related the changes in ring-torsion and valence-bond angles to rotational changes about three virtual bonds across the glucose ring. The known, residue geometries fell within ~2.08 kJ (0.5 kcal) of the minimum, based on their methods, and the ranges of all individual torsion angles and bond angles were ~10° and ~3°, respectively. For the specific system of flexibility that we studied, some changes were larger, and some, smaller; however, we view the two studies as complementary.

CONCLUSIONS

The application of standard, molecular-mechanics modeling to D-glucose rings has produced excellent correlations of the O-4–O-1 distance with some molecular parameters. In other cases, it has indicated that no strong relationship is likely to exist. A new survey of single-crystal studies was able to confirm, at least qualitatively, the predicted strong relationships, with the exception of the C-1–C-4 distance.

Without using a force field adjusted to reproduce a particular, pyranose geometry, we were able to predict a least-energetic conformation having an O-4–O-1 distance only 4 pm from the center of the observed 400 to 460-pm range. Although the standard force-field did introduce some significant discrepancies, use of modified force-fields by other workers has resulted in least-energetic rings farther from the center of the observed range

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