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## Note

# Application of molecular-mechanics calculations to D-glucal and its acetate; a comparison of X-ray and n.m.r. results

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1,2-Unsaturated glycopyranoses have served both as versatile intermediates in syntheses[1] and as transition-state inhibitors of glycosidases[2]. In both of these aspects, the conformation of these molecules is of importance. A detailed knowledge of the conformations of these versatile molecules is essential for understanding their chemical and biochemical properties. $^1$H-N.m.r. investigations of 3,4,6-tri-*O*-acetyl-D-glucal (3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol, **1**) have been interpreted in terms of a distorted half-chair form[3], but more recently an equilibrium mixture of two half-chair forms, namely $^4H_5$ and $^5H_4$, has been proposed[4]. The orientation about the C-5–C-6 bond has also been studied for **1** and other glycals by the n.m.r. technique, and was found to depend on the ring conformation[4]. Only recently has the structure of **1** been determined by X-ray crystallography, and the ring conformation was found[5] to be $^4H_5$(D).

Molecular-mechanics (empirical force–field) calculations have provided a satisfactory description of conformations and other properties of a number of molecules[6] and have been utilized in computer-assisted drug design. Nevertheless, some limitations of the technique have been noted[7]. An earlier version of a molecular-mechanics program (MM1), developed by Allinger and coworkers[6], has been applied by Jeffrey and coworkers[8] with considerable success to several types of carbohydrate derivative. We have applied the newest version (MM2) of this program[9] to D-glucal (**2**) and its triacetate (**1**) to answer the following questions:

(*1*) Does the molecular-mechanics method predict the conformation as determined by X-ray crystallography or n.m.r. spectroscopy?

(*2*) How close is the calculated conformation for the isolated molecule to that observed in the crystalline state?

(*3*) Does the molecular-mechanics calculation predict other important conformations and how are they related to each other?

(*4*) To what extent does the nature of the side groups affect the ring conformation and conformational energies?

Crystal coordinates[5a] of **1** were used directly for input into the MM2 program, and the lone-pair coordinates were calculated by the same program (see Ex-

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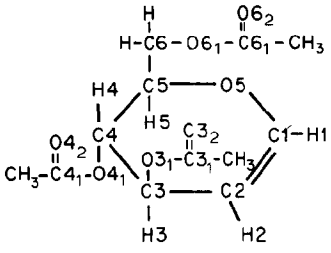

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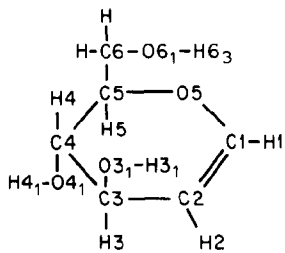

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perimental section for details). As the program is not capable of providing a "global" minimum, we concentrated initially on comparing the calculated ring-conformation with that obtained from X-ray crystallography, leaving the conformations of the side groups for separate treatment. This comparison was performed with the

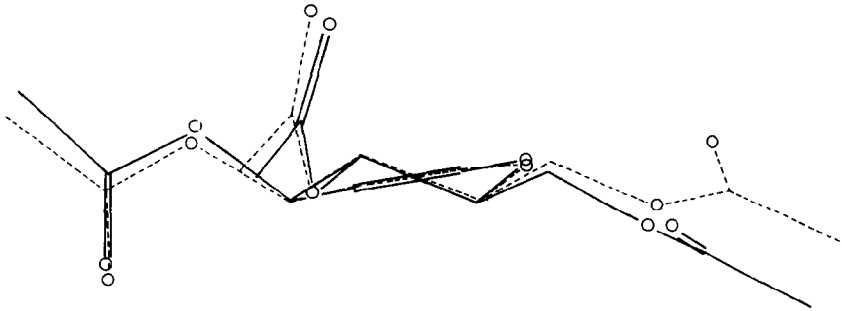

Fig. 1. Comparison of the conformation of **1** as determined by X-ray crystallography (——) with the conformation as calculated by the MM2 program (------).

TABLE I

OBSERVED AND CALCULATED SELECTED BOND-LENGTHS IN 3,4,6-TRI-*O*-ACETYL-D-GLUCAL (**1**)

| *Bond lengths* | *X-Ray* | *MM2* | $\Delta^a$ |
|---|---|---|---|
| C-1–C-2 | 1.314(4) | 1.340 | −0.026 |
| C-1–H-1 | 0.95(2) | 1.105 | −0.155 |
| C-2–C-3 | 1.502(4) | 1.506 | −0.004 |
| C-2–H-2 | 0.98(3) | 1.103 | −0.123 |
| C-3–C-4 | 1.509(3) | 1.544 | −0.035 |
| C-3–O-$3_1$ | 1.455(3) | 1.424 | 0.031 |
| C-4–C-5 | 1.529(3) | 1.544 | −0.015 |
| C-4–O-$4_1$ | 1.443(3) | 1.425 | 0.018 |
| C-5–O-5 | 1.438(3) | 1.425 | 0.013 |
| C-5–C-6 | 1.508(4) | 1.542 | 0.034 |
| C-6–O-$6_1$ | 1.444(3) | 1.421 | 0.023 |
| O-5–C-1 | 1.368(3) | 1.364 | 0.004 |

[a]X-Ray − MM2.

TABLE II

OBSERVED AND CALCULATED SELECTED BOND-ANGLES IN 3,4,6-TRI-*O*-ACETYL-D-GLUCAL (**1**)

| *Bond angles* | *X-Ray* | *MM2* | $\Delta^a$ |
|---|---|---|---|
| O-5–C-1–H-1 | 112 (1) | 115.5 | −3.5 |
| O-5–C-1–C-2 | 125.6(2) | 125.7 | −0.1 |
| H-1–C-1–C-2 | 122 (1) | 118.8 | 3.2 |
| C-1–C-2–C-3 | 121.7(2) | 121.4 | 0.3 |
| C-1–C-2–H-2 | 123 (2) | 120.0 | 3.0 |
| H-2–C-2–C-3 | 116 (2) | 118.6 | −2.6 |
| C-2–C-3–C-4 | 109.4(2) | 108.5 | 0.9 |
| C-2–C-3–O-$3_1$ | 110.1(2) | 111.9 | −1.8 |
| O-$3_1$–C-3–C-4 | 106.5(2) | 108.3 | −1.8 |
| C-3–C-4–C-5 | 108.5(2) | 109.2 | −0.7 |
| C-3–C-4–O-$4_1$ | 107.5(2) | 108.3 | −0.8 |
| O-$4_1$–C-4–C-5 | 108.8(2) | 110.2 | −1.4 |
| C-4–C-5–O-5 | 109.5(2) | 110.8 | −1.3 |
| C-4–C-5–C-6 | 112.0(2) | 112.7 | −0.7 |
| C-6–C-5–O-5 | 107.4(2) | 107.9 | −0.5 |
| C-5–O-5–C-1 | 113.5(2) | 116.1 | −2.6 |

[a]X-Ray − MM2.

TABLE III

OBSERVED AND CALCULATED SELECTED TORSION-ANGLES IN 3,4,6-TRI-*O*-ACETYL-D-GLUCAL (**1**)

| *Torsion angles* | *X-Ray* | *MM2* | $\Delta^a$ |
|---|---|---|---|
| O-5–C-1–C-2–C-3 | −2.2 | −2.1 | −0.1 |
| C-1–C-2–C-3–C-4 | −15.0 | −18.6 | 3.6 |
| C-2–C-3–C-4–C-5 | 46.2 | 47.8 | −1.6 |
| C-3–C-4–C-5–O-5 | −65.0 | −61.3 | −3.7 |
| C-4–C-5–O-5–C-1 | 48.3 | 41.3 | 7.0 |
| C-5–O-5–C-1–C-2 | −15.4 | −9.8 | −5.6 |
| H-1–C-1–C-2–H-2 | −3.8 | −0.7 | −3.1 |
| H-2–C-2–C-3–H-3 | −73.1 | −80.5 | 7.4 |
| H-2–C-2–C-3–O-$3_1$ | 49.7 | 40.8 | 8.9 |
| H-3–C-3–C-4–H-4 | 158.3 | 170.4 | −12.1 |
| H-3–C-3–C-4–O-$4_1$ | 38.4 | 49.0 | 10.6 |
| O-$3_1$–C-3–C-4–H-4 | 42.6 | 50.8 | −8.2 |
| O-$3_1$–C-3–C-4–O-$4_1$ | −77.3 | −70.6 | −6.7 |
| H-4–C-4–C-5–H-5 | 170.9 | 175.6 | −4.7 |
| H-4–C-4–C-5–C-6 | −65.3 | −63.6 | −1.7 |
| O-$4_1$–C-4–C-5–H-5 | −64.6 | −61.9 | −2.7 |
| O-$4_1$–C-4–C-5–C-6 | 59.2 | 58.9 | 0.3 |

[a]X-Ray − MM2.

software developed for the PROPHET system*, which provided both graphic (Fig. 1) and numerical (Tables I–III) comparison of the fit. These comparisons show that the molecular-mechanics program predicts the ring to be the $^4H_5$(D) conformer (the same as that found by X-ray crystallography[5]), which has also been shown by n.m.r. spectroscopy[4] to be the low-energy conformation. The ring had an asymmetry parameter[10] [$\Delta C_2(1 - 2)$] of 2.1° for both the crystal and the calculated structure, indicating relatively minor distortion from the ideal symmetry (0°) of the half-chair ring. As is evident from the bond-length data (Table I), the program systematically overestimates the length of the C–C and C–H bonds and underestimates the length of the C–O bonds. The much greater deviations for the hydrogen atoms is expected, as the precision in X-ray structure determination for these "light" atoms is rather low, and hence we concentrated on comparing heavier atoms. The correspondence of the bond angles (Table II) is also satisfactory, but the slight overestimation of the bond angles involving the ring oxygen atom is noteworthy. A similar problem exists in comparing the torsion angles (Table III); those involving the ring oxygen atom exhibit the largest deviations (one in the 7° range). Thus the MM2 program reproduces with reasonable accuracy the atomic parameters of the ring atoms and hence the favored ring-conformation.

The orientation about the C-5–C-6 bond has received considerable attention in the carbohydrate literature[11]. The three possible rotamers are shown in Fig. 2. Based on the analysis of $^1$H-n.m.r. spectra, Rico and Santoro[4a] concluded that for **1** the *gg* conformer preponderates in its $^4H_5$(D)-conformation, whereas X-ray structural analysis shows the presence of the *gt* conformer. The C-5–C-6 bond has been rotated using the "driver option" of the MM2 program. This resulted in an energy profile (Fig. 3) having three minima (Table IV) corresponding to the three conformations (Fig. 2). The "steric energy" calculated by this program is the thermally averaged energy relative to a hypothetical molecule having the same constitution, but with the bond lengths and bond and torsion angles at their "strainless" values[6]. These, in turn, are more closely related to enthalpy differences than to free-energy differences. As the latter determines the relative percentage of the conformers at a given temperature, steric energy cannot be used in such determinations[12]. Nevertheless, steric energy as a measure of the stability of the system provides insight into the relative ease of interconversion of one conformer into another. Thus consideration of the energy profile of **1** in Fig. 3 and values in Table IV shows that the three conformers are readily interconvertible, and that *gg* and *gt* conformers are the most stable, which is indeed found to be the case from n.m.r. spectroscopy and X-ray crystallography.

Rotation around the C–O bonds of the 3- and 4-acetoxyl groups also produced three minima. For the 3-*O*-acetyl group, rotation about the C-2–C-3–O-3$_1$–C-3$_1$ dihedral angle produced the lowest minimum at 50°, as compared with −82°

*PROPHET is an NIH sponsored, biomedical computer-network based on the molecular-modeling approach.

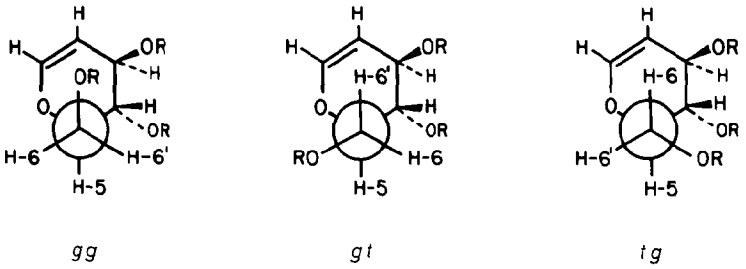


Fig. 2. Newman projections of the three favored rotamers of the C-5–C-6 fragment.

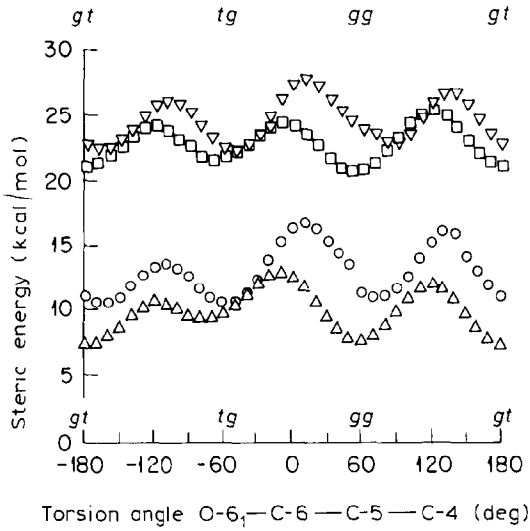


Fig. 3. Steric-energy profile of rotation about the C-5–C-6 bond for **1** $^4H_5$ (□) and $^5H_4$ (▽) and for **2** $^4H_5$ (△) and $^5H_4$ (○).

found in the X-ray structure. Similarly, rotation around the C-3–C-4–O-$4_1$–C-$4_1$ dihedral angle for the 4-*O*-acetyl group gave a minimum at 100°, as compared with 134° for X-ray. The minimal conformations computed for the side chains were shown to be independent of each other, and the rotation of the side-chain groups has very little effect on ring conformation.

As the conformation of the nonacetylated D-glucal (**2**) is also of importance, its conformation was likewise calculated. Its ring conformation was found identical with that of the acetylated derivative, namely, $^4H_5$(D). This is demonstrated by the almost perfect fit of the crystal coordinates of the ring atoms for **1** with those calculated for **2**. The minimum-energy conformation of the C-5–C-6 bond (Fig. 3 and Table IV) was determined by rotation and found to be *gt* (−177°). Rotations of the ring OH groups involved comparatively smaller changes in energy and gave essentially one minimum: for the C-2–C-3–O-$3_1$-H-$3_1$ angle it was −62° and for C-3–C-

TABLE IV

STERIC ENERGIES OF THE C-5–C-6 ROTAMERS[a]

| *Compound* | *Conformer* | | *O-6$_I$–C-6–C-5–C-4 (deg.)* | *E (kcal/mole)*[b] |
|---|---|---|---|---|
| **1** | ($^5H_4$) | *gt* | −167 | 22.28 |
| | | *tg* | −49 | 22.07 |
| | | *gg* | 89 | 22.90 |
| **1** | ($^4H_5$) | *gt* | 180 | 21.12 |
| | | *tg* | −66 | 21.60 |
| | | *gg* | 58 | 20.85 |
| **2** | ($^5H_4$) | *gt* | −164 | 10.48 |
| | | *tg* | −58 | 10.54 |
| | | *gg* | 71 | 10.98 |
| **2** | ($^4H_5$) | *gt* | −177 | 7.38 |
| | | *tg* | −78 | 9.38 |
| | | *gg* | 58 | 7.65 |

[a]See Fig. 3 for graphical representation. [b]Steric energy obtained from MM2.

4–O-4$_I$–H-4$_1$ angle, 61°. Thus molecular mechanics provided significant information on the effects of side-groups on the conformation of the molecule.

In order to find other conformational-energy minima for the ring, we rotated the C-4–C-5 bond of both acetylated and deacetylated D-glucal. The resulting strain-energy profiles are shown in Fig. 4. The graph shows a smooth conversion between two conformers representing the two minima. It was shown that the second minimum corresponds to the $^5H_4$(D) conformer. The steric-energy difference between the two minima representing the two conformations in acetylated D-glucal was 0.85 kcal/mol, whereas for the deacetylated derivative it was 3.0 kcal/mole (Table V). The minimum conformations about the C-5–C-6 bond in the $^5H_4$ conformers were again found by rotation of the C-5–C-6 bond (Fig. 3) and were *gt* for both molecules. The same preponderant conformation was indicated from analysis of n.m.r. data for the acetylated derivative[4a]. The similarity of the steric energies for the three primary-alcohol orientation of **2** in the $^5H_4$ conformation (Table IV) is expected, as the C-4 and C-5 groups are both axially disposed and hence no interaction between them is expected.

The conformation corresponding to the energy maximum for the acetylated derivative (**1**) was determined to be a slightly distorted boat ($B_{3,0}$) (Fig. 4).

In these calculations, we used the default value for the bulk dielectric-constant (1.5 D) corresponding to the gas phase. In a series of experiments, this value was replaced by the bulk dielectric-constant of several common solvents. The steric energy of the minimum ($^4H_5$) conformation of **1** (21.4 kcal/mol) decreases to 14.3 kcal/mol in chloroform (D = 4.8), in acetone (D = 20.7) to 11.7 kcal/mol, and in water (D = 78.25) to 11.2 kcal/mol. These changes may be understood by the decrease of electrostatic interactions on increasing the dielectric constant[6]. Changes in ring conformation because of different dielectric constants were found to be slight, never exceeding 1° in torsional angles.

TABLE V

STERIC ENERGIES OF THE RING CONFORMERS[a]

| *Compound* | *Conformer* | *C-3–C-4–C-5–O-5 (deg.)* | *E (kcal/mole)*[b] |
|---|---|---|---|
| **1** | $^4H_5$ | −61 | 21.45 |
| | $^5H_4$ | 58 | 22.30 |
| **2** | $^4H_5$ | −61 | 7.45 |
| | $^5H_4$ | 56 | 10.48 |

[a]See Fig. 4 for graphical representation. [b]Steric energy obtained from MM2.

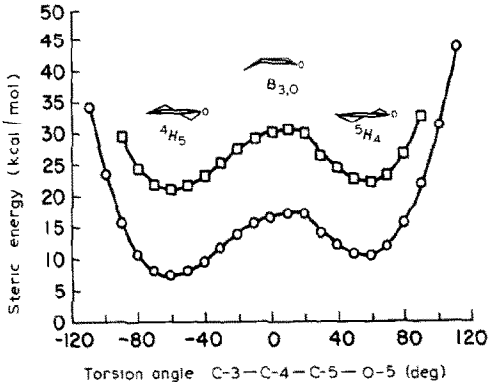


Fig. 4. Steric-energy profile of ring inversion for **2** (-○-) and **1** (-□-). Ring conformations corresponding to the minima and the maximum are indicated.

In conclusion, it may be stated that the new version of the molecular-mechanics program (MM2), in addition to predicting conformations of D-glucal and its acetate, also provides insight into the interconversion of conformations and the influence of side chains on conformational stabilities. It strengthens the interpretation of the n.m.r. data of **1** as an equilibrium mixture of two regular half-chair forms[4]. Thus a combination of X-ray, n.m.r. spectroscopy, and molecular-mechanics calculations are seen to complement each other in providing a more complete description of the conformational interconversions.

## EXPERIMENTAL

*Coordinates.* — For **1** the crystal coordinates given[4a] were used as initial input coordinates. They were converted to Cartesian coordinates by the "crystal conversion option" of the MM2 program and were subsequently refined. In a second calculation, the coordinates for lone pairs on ether-type oxygen atoms were calculated by using the "coordinate calculation option".

Refined coordinates of **1** were used as the starting point for **2**. The acetate groups in **1** were replaced by hydrogen atoms by using the carbonyl carbon coordi-

nates as an approximation for positions of the hydrogen atoms of the hydroxyl group.

*Calculations.* — For all calculations, the names and weights of atoms as defined in MM2 were used without modification. No restricted-motion data or symmetry restrictions were necessary. The heat of formation was calculated simply from the default values for partition function. The dipole-interaction energy was calculated by using the default value for dielectric constant and excluding interactions between dipoles with a common atom. With one exception, all of the constants for torsional, stretching, van der Waals interactions, bending, and stretch–bend parameters were unchanged. It was necessary to provide a parameter for a torsion angle not included in the program's data, namely, $Csp^2$–$Csp^3$–O–C carbonyl. The values listed in the program documentation for a "$Csp^3$–$Csp^3$–O–C carbonyl" torsion angle were used as a suitable approximation.

The driver option was used to invert the initial ring-conformation by driving C-3–C-4–C-5–O-5 from $-61$ (the initial value) to $-111°$ and from $-61$ to $+119°$ in 10° increments. It was necessary to change the coordinates for these 4 atoms by hand to drive the angle through 0° (from $-1°$ to $+9°$). These coordinates were estimated by graphing atom movement *vs* angle.

The driver option was also used to rotate the C-4–C-5–C-6–O-$6_1$ angles from $-180$ to $+180°$ in 10° increments to determine energy minima for the conformation of the primary alcohol. The program handles side-chain driving differently and it is not necessary to manually change coordinates to pass through 0°.

Refined coordinates for all energy minima were determined by using, as initial coordinates for a new calculation, the values from the driver experiment closest to the minima. In every instance, the molecule stayed in the (local) minimum and energy was minimized in a few iterations.

ACKNOWLEDGMENTS

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