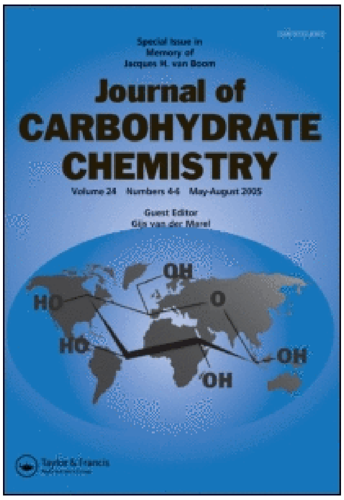

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SEMIEMPIRICAL PM3 QUANTUM MECHANICS CALCULATIONS OF CARBOHYDRATE CRYSTALS[1]

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ABSTRACT

Miniature crystal models of six small carbohydrates were examined using the PM3 semiempirical quantum mechanics method. The minicrystal structures, consisting of 27 sugar residues, were optimized by the combined procedure of partial optimization and reconstruction of the model, while maintaining the original crystal symmetries. All of the minicrystals were successfully optimized without exhibiting a great increase in an energy at any reconstruction step. Some minicrystals showed a prolonged behavior of optimization cycles. A major source of structure change appeared to arise from hydroxyl group rotations wherein the largest movements mostly occurred in an early optimization stage. No significant deformations in geometry of either residues or hydrogen bonds were observed in the final minicrystal structures. The thermodynamic values calculated for the optimized minicrystals were in reasonably good agreement with the literature data. The present study indicated that the PM3 semiempirical method successfully predicted the basic features of intermolecular hydrogen bonding involved in a condensed system.

INTRODUCTION

Owing to continuous improvement of computer hardware, molecular modeling techniques, that were originally only applicable to isolated small molecules, can be readily applied to calculations of larger systems including molecular assemblies. French and

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coworkers have reported extensive studies on models of various small carbohydrate crystals.[2-6] The small model crystal, called a miniature crystal or minicrystal, consisting of no more than 30 sugar residues was examined using the MM3[7,8] molecular mechanics method. The minicrystal method was used to predict lattice energies,[2,3,6] to reproduce hydrogen bond geometries,[4] and to estimate the optimal dielectric constant.[2,3] This method has also been applied to testing some polysaccharide crystal structures determined by fiber diffraction studies, such as cellulose allomorphs,[2,9,10] anhydrous chitosan,[11] and anhydrous mannan.[12]

In the present article, we have attempted to assess similar carbohydrate miniature crystals with quantum mechanical models. Instead of using *ab initio* quantum mechanics which is based on more rigorous theory but is prohibitively time-consuming, we have adopted the PM3[13] semiempirical quantum mechanics method as a realistic choice. Among the semiempirical methods, the PM3 method is most recently developed and it has been used for a wide variety of organic molecules. Jurema and Shields reported from the PM3 calculations of 32 hydrogen bonding dimers that the PM3 method can successfully predict intermolecular hydrogen bond geometries but tends to underestimate their energies by 1-2 kcal/mol.[14] Thus, the ability of the PM3 method to replicate hydrogen bonding features in a condensed system of a model crystal is our prime interest. The carbohydrate crystals studied herein are α-D-glucose,[15] β-D-glucose,[16] α-L-xylose,[17] β-L-arabinose,[17] methyl-α-D-glucopyranoside,[18] and methyl-α-D-mannopyranoside.[18] Because of necessity of comparing hydrogen bond geometries, and therefore knowing the hydrogen atom positions, these crystal data have been obtained from the neutron diffraction studies except those for β-D-glucose. For comparison, MM3 calculations of the same minicrystals have been carried out and the α-D-glucose minicrystal has been examined with the AM1 method,[19] another semiempirical formality.

CALCULATIONAL METHODS

All of the modeled sugar crystals have an orthorhombic unit cell with $P2_12_12_1$ symmetry. The model miniature crystals were constructed by assembling 27 sugar residues; three sugar layers were stacked on each other so as to place a central residue in the cage of the remaining 26 residues. These residues were generated in the three dimensional space based on the published atomic coordinates, unit cell dimensions and space group.[15-18] As a result, the central molecules was embedded in crystal-like environments, at least in terms of short range forces. The structures were checked by a visual inspection of the minicrystals using interactive graphics software. When two or more candidates were suggested for a minicrystal, the one exhibiting the lowest lattice energy, as discussed below, was selected.

The present semiempirical calculations adopted an iterative procedure involving a partial optimization of a minicrystal with the molecular orbital program package MOPAC. First, a central residue was fully geometry optimized, while geometries of surrounding residues were fixed. A new minicrystal was then constructed using the central residue with the optimized geometry. The optimization-reconstruction step was repeated until no further geometry change occurred in the central residue. The criterion for termination of each optimization run was defined by a gradient norm, or GNORM; the RMS of derivatives of energy with respect to the geometry variables.[20] The value 10.0 was first adopted and, after completing the optimization-reconstruction runs, it was then decreased to 5.0 in the following runs. Unfortunately, a further calculation with a smaller GNORM resulted in prolonged fluctuations of geometries. The restricted Hartree-Fock option was used throughout the calculations. In the case of MM3 calculations, a whole system of a minicrystal was optimized at various dielectric constants. The fit between initial and final models was represented by the RMS deviations of the structural parameters of interest. In the case of estimating atomic movements in Cartesian coordinate system, the RMS deviations were minimized by a least squares procedure,[21] based on the heavy atom coordinates.

The lattice energy of the optimized minicrystal was defined to be the difference between the total energy of the minicrystal and the sum of the energies of the central residue and of the outer shell. A stabilizing interaction is inferred on calculation of a negative value for the lattice energy. The energies used herein are the heat of formation from MOPAC or the steric energy from MM3. A thermodynamic quantity that was compared with an experimental value was the heat of formation of the sugar in a solid state. The corresponding calculated value was derived by adding the lattice energy and the calculated heat of formation of the sugar molecule in the gas phase. The latter value was averaged over possible conformers with respect to exocyclic hydroxyl group rotations using the Boltzman distribution function at 298K.

The program versions used in the present study were MOPAC 93 (ver.6.0) and MM3 (92). All calculations were performed with a Fujitsu SUN compatible computer S4-20H.

RESULTS AND DISCUSSION

Figure 1 shows variations of the total PM3 energy and the GNORM value for α-D-glucose minicrystal during the course of structure optimization. The energy drops

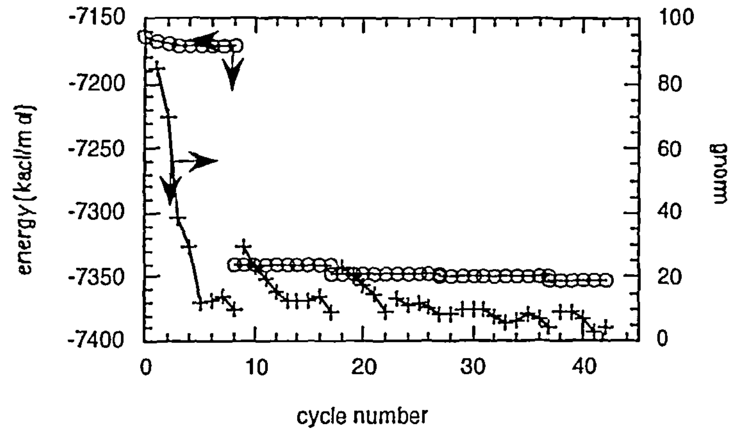

Figure 1. Courses of energy (○) and GNORM (+) of α-D-glucose. A cycle number that minicrystal reconstruction has taken place is indicated by discontinuous change in energies.

substantially at the first reconstruction step and gradually decreases in the following steps. Similar behavior during optimization was observed for all of the other minicrystal calculations; no significant increase in total energy occurred at any reconstruction step. In Figure 1, the GNORM decreased quickly as the optimization cycles proceeded. Under these conditions, the cycle numbers never exceeded 10 at the minicrystal run. On the other hand, in the other minicrystal calculations, the GNORM was sometimes observed to fluctuate, resulting in a considerable number of optimization cycles. Changes in lattice energy among the various minicrystal calculations are compared in Figure 2. The AM1 energies, tested only for the α-D-glucose model, show the large positive value of 289 kcal/mol at the initial model which corresponds to the literature structure. The energy quickly fell into a negative range in the second minicrystal. This obviously suggests that AM1 Hamiltonian overestimates nonbonding interactions involved in the condensed carbohydrate system. On the contrary, the PM3 energies exhibit more moderate variations. During a few initial runs, the energies either increase or decrease by several kilocalories per mol as a result of structure relaxation. The values then become virtually stationary in the following runs. When rotations of hydroxyl groups were monitored, the largest rotations were observed mostly during the first run for each minicrystal. In the case of the β-D-glucose calculation that required the most reconstruction runs 16, the first run involved a significant amount of rotations, ranging about 10-30°, for the O3-H, O4-H, and O6-H groups. Especially, the O3-H group fluctuated with about 10° during the first several runs.

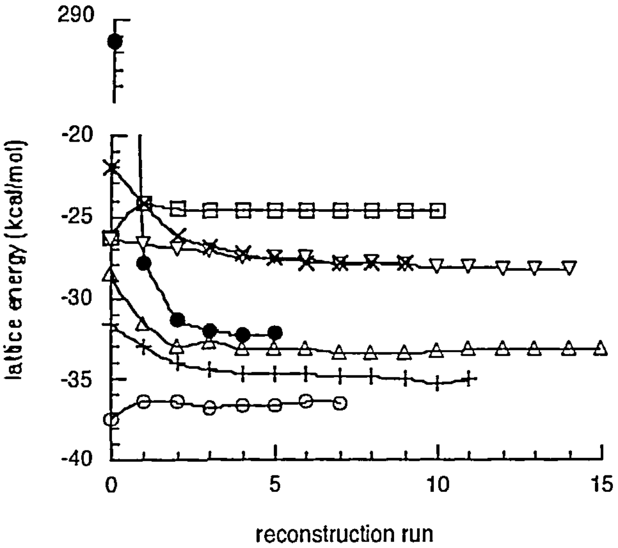

Figure 2. Course of a lattice energy for α-D-glucoe (○), AM1 of α-D-glucoe (●), β-D-glucose (△), α-L-xylose (□), β-L-arabinose (▽), methyl-α-D-glucopyranoside (+), and methyl-α-D-mannopyranoside (×). The plot shows the PM3 energy unless noted.

The calculation of the methyl α-D-mannopyranoside minicrystal required the longest CPU time, being about 3-10 times as much as that required for the other minicrystals. Although its number of reconstruction runs was moderate, nine, a large number of optimization cycles was involved during a single run. Therefore, in this case, a larger GNORM should have been introduced at the early stage of optimization in order to encourage minicrystal reconstruction to arise more frequently. The use of the two GNORM values, 10 and 5, in the present calculations was rather arbitrarily defined and we did not attempt a systematic search for optimization conditions. There may have been a more appropriate way to define the values by which more effective optimization could be achieved for individual minicrystal models.

The RMS atomic movement between the initial and final structures of each minicrystal was of a range of 0.3-2.6 pm. The values are considerably small even compared with the mean atomic movement reported for the MM3 calculations, ranging about 10-20 pm.[2] Obviously, this is because of more constrained conditions, *i.e.*, imposition of crystal symmetries, adopted in the present PM3 calculations. Moreover, PM3 minicrystals replicated the observed bond lengths and angles slightly better than the

PM3-optimized isolated molecules. Thus, the deviations of hydroxyl groups from their initial rotational positions appear to be a major source of atomic movements. As was suggested above, such rotations of the hydroxyl groups changed the amount of the lattice energy, as a sum of intermolecular hydrogen bond interactions, at each reconstruction run. Table 1 compares the RMS deviations of the hydrogen bond parameters of the final minicrystal structures obtained from the PM3 calculations and the MM3 calculations with various dielectric constants. The MM3 results have been derived from the same minicrystal systems as the PM3 calculations. The results of the β-D-glucose minicrystal have not been included in the table because there was less precision in the hydrogen atom locations in the X-ray diffraction based, literature data.[16] It should also be noted that the RMS values of the MM3 minicrystals were estimated from the hydrogen bonds involving the central residue, while excluding those between the residues in an outer cluster. As obvious from the table, the RMS errors in the PM3 minicrystals are close to those in the MM3 minicrystals with the dielectric constant of either 2 (r_{OH}), or of 3 (r_{OO} and τ), depending on a parameter type. When an individual hydrogen bond was inspected for the final PM3 minicrystals, significant deviations in r_{OO} were mostly observed for the initial bond lengths of medium distance, around 0.29 nm. In the final structures, their bond lengths shortened into the optimum distance of near 0.28 nm. Similar behavior was observed for r_{OH} with the medium distances. This suggested that the minicrystal structures were optimized so as to further stabilize a moderate hydrogen bond, probably by a slight reorientation of some hydroxyl groups from their initial positions. In fact, neither disappearance of the original bond nor formation of a new bond occurred in any of the final minicrystals. The internal parameters of the carbohydrate structures can be featured most typically by the anomeric parameters; the bond lengths and angles, and the torsion angles involved in the anomeric centers.

Table 2 lists the RMS deviations of the anomeric parameters obtained from the MM3- and PM3-optimized molecules in isolation and minicrystals. The RMS values for the minicrystals have been calculated based on the optimized parameters of the central molecule. The MM3 molecules used to calculate their RMS values are those optimized with the dielectric constant 3. The use of the optimized models with the dielectric constant 4 gave similar RMS values and, with the values 2 and 5, increased the RMS values. As the general features found in the table, the RMS values of the minicrystal molecules are smaller than those of the isolated molecules in both the MM3 and PM3 calculations. When the two optimization formalities are compared, it is clearly shown that the MM3 calculations have reproduced better most of the anomeric parameters except the bond length C1-O1 and the glycosidic bridge angle C1-O1-H or C1-O1-C7. French suggested that MM3 tended to predict longer C1-O1 lengths than those of the crystal data.[6] On the other hand, the PM3

Table 1. RMS deviations of hydrogen bond parameters of PM3 and MM3 minicrystals

Parameter[a]	PM3	MM3		
		Dielectric constant		
		2	3	4
r_{OH} (pm)	7.7	6.3	10.5	18.6
r_{OO} (pm)	6.3	5.7	6.1	11.1
τ (degree)	9.5	7.5	10.2	13.2

a. r_{OH}, nonbonding O---H distance; r_{OO}, nonbonding O---O distance; and τ, angle between O-H and O---O.

Table 2. RMS deviations of anomeric parameters for isolated and minicrystal molecules optimized by MM3 and PM3 methods

	PM3		MM3[a]	
Anomeric parameter	Isolated	Minicrystal	Isolated	Minicrystal
Bond length (pm)				
C1-O1	1.6	0.6	5.1	4.8
C1-O5	1.2	1.0	0.7	0.8
C5-O5	1.4	1.3	0.8	0.6
total	1.4	1.0	3.0	2.9
Bond angle (degree)				
C5-O5-C1	2.4	2.3	1.2	0.7
O1-C1-O5	5.0	6.5	3.8	3.9
C1-O1-H (C1-O1-C7[b])	2.9	2.7	5.0	4.7
total	3.6	4.3	3.7	3.5
Dihedral angle (degree)				
C5-O5-C1-O1	7.4	5.7	4.1	2.0
H-O1-C1-O5 (C7-O1-C1-O5[b])	20.1	10.3	16.2	9.9
H-O1-C1-H1 (C7-O1-C1-H1[b])	21.4	13.7	16.4	8.9
total	17.5	10.5	13.5	7.8

b. Based on the optimized models with dielectric constant 3.
a. Parameters for methyl-*O*-pyranoside residue.

Table 3. Comparison of calculated and observed energies (kcal/mol) for six carbohydrate crystals

Carbohydrate crystal	Lattice energy	Heat of formation	
	calcd	calcd	obsd
α-D-Glucose	-36.4	-306.6	-304.6[a]
α-D-Glucose (AM1)	-32.2	-336.0	
β-D-Glucose	-33.1	-303.4	
α–L-Xylose	-24.6	-250.6	-250.3[b]
β–L-Arabinose	-28.2	-255.2	-251.9[b]
Methyl-α-D-glucopyranoside	-35.0	-299.5	
Methyl-α-D-mannopyranoside	-27.8	-292.7	

a. Ref 22.
b. Calculated from the heat of combustion given in ref 23.

calculations exhibited fairly good agreement in all of the bond lengths listed, including the C1-O1 lengths, between the original crystals and the minicrystals. In the case of the bond angles, the large RMS values of the O1-C1-O5, 6.5° in the minicrystals and 5.0° in the isolated molecules, were caused mainly by the deformations involved in the PM3-optimized β-D-glucose molecules, where smaller O1-C1-O5 angles, 96.3°and 102.6°, were found in the minicrystal and isolated molecules, respectively, than the observed value 107.0°. The PM3 calculations for the minicrystal molecules otherwise could have reproduced the anomeric geometries of the original crystals reasonably well.

Table 3 compares the heat of formation and the lattice energies calculated for the final minicrystal models along with the literature values for some of the sugar crystals.[22,23] The calculated values are reasonably close to the corresponding literature values. The largest difference is found in the result for the α-L-arabinose minicrystal, being 3.3 kcal/mol lower than the observed value; the difference is comparable to a single hydrogen bond energy. The MM3 lattice energy reported for α-D-glucose was -37.4 kcal/mol at the dielectric constant of 4 and that for β-D-glucose was -37.6 kcal/mol and -38.2 kcal/mol at the dielectric constants of 4 and 3.5, respectively.[2,4] In the table, our results for these PM3 model crystals show an appreciable stability with about 3 kcal/mol in both a lattice energy and a heat of formation for α-D-glucose over β-D-glucose. It should be also noted that the literature value of the heat of formation for α-D-glucose is found between the PM3 values calculated for the α-D-glucose and β-D-glucose minicrystals. When the AM1 and PM3 energies of the α-D-glucose minicrystals are compared, the former is 4.2 kcal/mol higher in the lattice energy but about 30 kcal/mol lower in the heat of formation, which seems to arise from a failure of AM1 Hamiltonian to balance intra- and intermolecular interactions. Generally, a minicrystal with a lower lattice energy also exhibits a lower heat of formation. While the lattice energies of β-L-arabinose and methyl-α-D-mannopyranoside are similar, the latter is suggested to be more stable because of its lower heat of formation. When the lattice energy was divided by the number of hydrogen bonds, the resulting values, as a crude estimation of hydrogen bond energy, ranged 3.0-3.5 kcal/mol in absolute magnitude. Similar PM3 hydrogen bond energies calculated for the various dimer complexes have been reported to be 2.6-4.5 kcal/mol;[14] this value spans the above energy range of the minicrystals. Such a similarity in the calculated energies between the gas phase and our condensed, crystal systems seems to indicate that hydrogen bond interactions are still overwhelming in the latter system.

CONCLUSION

The present calculations studied the miniature crystal models of six small carbohydrates mainly using the semiempirical PM3 method. The calculated heats of formation of the minicrystals were found to be in reasonably good agreement with the literature values and the fundamental features of the crystal structures, especially the hydrogen bond geometries, were replicated in the final minicrystals. These results suggest that the PM3 method can provide a fairly reliable prediction of carbohydrate crystal systems. What has most concerned us in the present study is that the optimization should not reach a stationary point in a strict sense, although lattice energy and hydroxyl group rotations became virtually invariant in the final stage. However, unless one wants to discuss, for example, vibrational frequencies, the present calculations seem to have achieved sufficient accuracy to satisfy our primary objectives. Of course, semiempirical calculations still require much more computational time and, for carbohydrate molecules, may result in less accurate predictions than the molecular mechanics methods. With a quantum mechanics basis, semiempirical minicrystal model can be readily applied to carbohydrate systems involving coordinate or ionic bonds. The method will be also extended to an investigation of polysaccharide crystal structures to complement the fiber diffraction technique, as has been first suggested for MM3 minicrystal calculations.[2]

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