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Proper Balance of Solvent-Solute and Solute-Solute Interactions in the Treatment of the Diffusion of Glucose using the Drude Polarizable Force Field

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Abstract

Motivated by underestimation of the diffusion constant of glucose in aqueous solution at high glucose concentrations we performed additional optimization of the Drude polarizable hexopyranose monosaccharide force field. This indicated aggregation of the glucose at higher concentrations, which is a concern for studies of complex glycan systems such as the HIV Envelope where high effective concentrations of sugars are present. High-level quantum mechanical calculations were undertaken on water monohydrate-glucose interactions, on water cluster-glucose interactions and on glucose-glucose dimers in stacked (parallel) and perpendicular orientations. Optimization of the nonbond and dihedral parameters targeting these data yielded a revised model that showed improved agreement with experimental aqueous diffusion data. However, limitations in the diffusion constants were still present. These were due to the SWM4-NDP inherently overestimating the diffusion constant of water, a problem that was validated by calculation of the aqueous diffusion constants using the SWM6-NDP water model. In addition, results show the water diffusion constant to be significantly overestimated at high glucose concentrations though the glucose diffusion is in satisfactory agreement with experiment. These results indicate the subtle balance of water-sugar, water-water and sugar-sugar interactions that needs to be properly modeled to account for the full range of aqueous behavior of sugars in aqueous solution.

Graphical Abstract

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Keywords

CHARMM; MD simulations; carbohydrates; monosaccharides; molecular mechanics

Introduction

Empirical force field based theoretical studies of biological macromolecules, including carbohydrates,[1–4] is a growing field associated with increases in computer hardware as well as improvements on algorithms and in the force fields central to the accuracy of such methods. Towards this end work in our laboratory in collaboration with Roux and coworkers has focused on the development of a comprehensive biomolecular force field that explicitly treats electronic polarizability based on the classical Drude oscillator model.[5, 6] The Drude force field is now available for proteins,[7] DNA,[8–10] lipids,[11, 12] monoatomic ions,[5] and a range of small model compounds[13–17] as well as for acyclic carbohydrates, hexopyranose and furanose monosaccharides.[18–21] These models have now been utilized in a number application studies from which novel insights into the role of polarization in conformational transitions have been obtained.[22–25] In addition, these studies are also identifying limitations in the Drude model, motivating additional improvements in the model.

During development of the hexopyranose monosaccharides comparison of experimental and simulated self-diffusion constants for D-glucose showed good agreement with experiment at a glucose concentration of 1 M. [20] However, there was a trend for the self-diffusion constant to be underestimated at higher concentrations (2 and 5 M). Such a trend is indicative of aggregation of the monosaccharides, a problem that could be due to overestimation of monosaccharide-monosaccharide interactions, an underestimation of water-monosaccharide interactions or a combination of both. While many simulation studies of saccharides are on dilute solutions or glycans in the context of glycolipids and glycoproteins that are relatively isolated, there are many systems in which complex glycans are undergoing extensive glycan-glycan interactions such that they are essentially present at a high concentration. Such systems are now accessible to simulations, such as the glycosylated HIV Envelope,[26–28] where the proper balance of the aforementioned interactions is quite important. In addition, improvements in our optimization protocols and associated parameters from the development of the Drude furanose monosaccharide parameters required adjustment of the hexopyranose monosaccharides to maintain

consistency.[19] Accordingly, we undertook additional optimization of the Drude hexopyranose model focused on maintaining the overall quality of the model while improving its properties in aqueous solution, including improving the balance of the monosaccharide-water (eg. solute-solvent) and monosaccharide-monosaccharide (eg. solute-solute) interactions.

Methods

Empirical force fields calculations were performed with the program CHARMM.[29] The initial parameters were the published Drude hexopyranose[20] and furanose monosaccharide parameters[19] along with the SWM4-NDP[30] and SWM6-NDP[31] water models. Quantum mechanical (QM) calculations used the Gaussian03 program[32] for energy minimizations to default tolerances with single point calculations performed using Psi4 and Q-Chem.[33, 34] The specific QM model chemistries are described below.

Empirical energy minimization were performed using the steepest descent minimizer followed by the adapted-basis Newton-Raphson (ABNR) minimizer to a gradient of 10^{-5} kcal/mol/Å. Gas phase calculation did not use atom truncation. All Drude and QM interaction energies were calculated based on the total energy of the dimer (or multimers) minus the individual monomer energies as required to account for the electronic degrees of freedom in the model. This involved use of the gas phase optimized monomer geometries for both the dimers and monomers with the Drude energies calculated by restraining the real atoms with a harmonic force constant of 10^7 kcal/mol/Å and allowing the Drude oscillators to relax using the ABNR optimizer.

For molecular dynamics (MD) simulations the nonbonded Lennard-Jones interactions were computed within a cutoff of 12 Å, with a smoothing switch function over the range from 10 to 12 Å and a isotropic long-range correction term.[35] The electrostatic interactions were treated by the particle mesh Ewald method with a real space cutoff of 12 Å, a charge grid of 1 Å, and the 6-th order spline function for mesh interpolation.[36] The covalent bonds involving hydrogen atoms were constrained with the SHAKE algorithm and a time step of 1 fs was used to integrate the equations of motion.[37] The hard-wall constraint was applied to prevent the Drude particles moving more than 0.2 Å from their parent nuclei.[11] The Nose-Hoover thermostat was used to maintain the temperature of the real atoms at 298 K and the Drude particles at 1 K, respectively.[38]

Results and Discussion

The partial atomic charges for the Drude hexopyranose monosaccharides were transferred from the furanose force field to maintain the same charges on chemical groups with similar bonded environments. The atomic polarizabilities and Thole screening factors were then refitted against the QM dipole moments of 215 hexopyranose conformations using the Monte Carlo simulated annealing algorithm (MCSA).[39] These include target QM dipole moments computed at the RIMP2/cc-pVQZ//MP2/6-31G(d) model chemistry for different conformations of the 16 hexopyranose isomers (Table 1). During MCSA optimization, the range that the parameters could vary was set to $[-1.3$ to $-0.5]$ and $[-2.1$ to $-1.0]$ for the

atomic polarizabilities of oxygen atoms and the remaining non-hydrogen atoms, respectively, and [0.2 to 2.5] for all Thole scale factors. The MCSA was initialized at a temperature of 500 K and gradually reduced by a factor of 0.75 after every 200 steps for each parameter until it approached 0 K.[19] The final parameters were derived from averaging the last 20 MCSA steps of the optimization. Upon MCSA optimization, the root-mean-square difference (RMSD) between the MM and QM total dipole moments was reduced from 0.21 to 0.16 while the original Drude force field had a RMSD value of 0.19. Figure 1 presents the comparison of the MM and QM results for both total and component dipole moments.

To further validate the new electrostatic parameters, we examined the molecular polarizability of the glucose monosaccharide (Table 2). The result from the new Drude force field accounts for 70% of the QM polarizability, which is comparable to the original Drude alcohol force field[17] and the general trend with the Drude force field in which the gas phase molecular polarizabilities are scaled relative to the QM values.[40]

Additional optimization focused on selected dihedral parameters targeting the conformational energies of the monosaccharides. For dihedral fitting, the QM target energies were computed at the RIMP2/cc-pVQZ//MP2/6-31G(d) model chemistry for different monosaccharide conformations (Table 3). For each monosaccharide, the relative energies of both anomers were all offset to the global minimum energy conformation. A relative energy cutoff of 20 kcal/mol was used to include more non-chair conformations that have a higher relative energy in the target data versus the previous cutoff value of 12 kcal/mol.[20] Figure 2 shows the ϕ/θ distribution according to Cremer-Pople definition of the ring conformers.[41] The majority of the ring conformations are in the 1C_4 states though alternate puckers are included in the target data.

A total of 2004 conformational energies were used as target data in the fitting of all possible dihedrals including 4 non-hydrogen atoms or 3 non-hydrogen atoms and 1 hydroxyl hydrogen (Table 3). The multiplicity for intra-ring dihedrals is set to 1, 2, 3 and 4, and 1, 2 and 3 for the other dihedrals. The same energy offset was used for all 2004 conformations in the fitting, i.e. the previously reported non-group fitting was adopted in which all conformations were fit simultaneously. The *lsfitpar* program was used for dihedral fitting.[42] The RMSD for the updated parameters (Drude new), the original Drude force field and additive force field are shown in Table 3.[20, 43] Figure 3 plots the relative conformational energies of the target data from QM, the new Drude force field and the original Drude force field. In addition to the 2004 conformations used in dihedral fitting, we also prepared 148 new conformations for validation of the force field, which shows a substantial improvement with the new parameters versus the original Drude and additive force field (Table 4).

Refitting the van der Waals (vdW) parameters of the hexapyranose monosaccharide C1/C2/C3/C4 atoms

As mentioned above and shown in the original Drude force field publication,[20] the diffusion constant was substantially underestimated at high glucose concentrations. Such overestimation is associated with aggregation of the monomers. Such aggregation could be

associated with the interactions between the monosaccharides being too favorable or the interactions of the monosaccharides with water not being adequately favorable.

From solution simulations under different glucose concentration, the relative position and orientation between monosaccharide pairs were analyzed with the aid of a local coordinate frame associated with the ring plane of each monosaccharide (Figure 4a). The relative orientation is represented by three Euler angles defined with the two local coordinate frames associated with the two monosaccharide ring planes and the relative position is denoted as the spherical coordinate of one monosaccharide in the local coordinate frame of the other monosaccharide. These variables were computed from the trajectories for any pair of monosaccharides within a distance cutoff of 12.0 Å. The potential of mean force was computed along any combination of two variables to show the most populated relative orientation and position. The results indicate a flat distribution ϕ and α throughout the available range $[0^\circ, 180^\circ]$. The distance (defined as d in figure 4) between the two monosaccharides can be as close as 4.0 Å with the ring surfaces arranged parallel (stacked, $\Theta=180^\circ$ or 0° and $\beta=180^\circ$ or 0°) to each other (Figure 4b). Another typical interaction orientation between glucose monomers also appeared frequently with the ring surfaces perpendicular to each other ($\Theta=90^\circ$ and $\beta=90^\circ$) (Figure 4b and 5). These two types of interaction pattern are not only observed in solution simulations under different glucose concentrations but are also adopted in many packing patterns of monosaccharide crystal structures but with a distance longer than 4.0 Å between the ring planes. We thus used these two interaction modes to examine and correct the original Drude force field. To this end, a number of glucose dimers with the two interaction modes were extracted from the solution simulation of glucose at 5M and the QM interaction energy between the pairs was calculated using single-point calculations at the MP2/cc-pVQZ model chemistry with correction for basis set superposition error.[44] As compared to QM result, the original Drude force field systematically overestimates the interaction energy of the dimers with two ring surfaces arranged in parallel orientation. Further examination revealed that the Lennard-Jones (LJ) parameters ($\epsilon=-0.12$ kcal/mol and $R_{\min}/2=2.15\text{Å}$) of the C1, C2, C3 and C4 ring carbons are the dominant contribution to the overestimated interaction energies. We thus refitted the LJ parameters of the 4 carbon atoms targeting the glucose interaction energies. The new parameters ($\epsilon=-0.06$ kcal/mol and $R_{\min}/2=1.90\text{Å}$) produce better agreement with QM interaction energies, with the RMSD value reduced from 1.58 kcal/mol for the original Drude parameters to 0.92 kcal/mol for the new parameters (Figure 5b). The simulated diffusion coefficients are also substantially improved with the new LJ parameters as presented below.

Hexopyranose monosaccharide-water interactions

With the updated parameters, the hexopyranose monosaccharide-water interaction energies were validated using the constructed interaction dimers from the original paper[20] as well as new glucose-water cluster calculations. A small but overall improvement in the monosaccharide-water interaction energies was obtained with the new Drude force field compared to the original one (Table 5). Additional water-saccharide analysis was performed on water-glucose clusters. From the solution simulations of glucose at 1M used for the diffusion calculations (see below), three water clusters were extracted that included all

waters with the oxygen within a radius of 3.5 Å from the glucose non-hydrogen atoms. From the comparison of the QM and MM results, better agreement was also obtained with the new Drude force field compared to the original Drude and additive force field (Table 6). The results show the original Drude model to yield slightly more favorable interactions with water over the new model. This result and the above change in the glucose dimer interaction energies show that the overestimation of the glucose diffusion constants was primarily due to the interactions between the glucose monomers being too favorable, leading to their increased aggregation in solution.

Normal mode analysis

To check if the above changes in the nonbond and dihedral parameters altered the intrinsic flexibility of the pyranose ring in the new Drude force field, normal mode analysis was performed using both QM (MP2/6-31G(d)) and MM potentials for the glucose monosaccharide. The frequency distribution derived from QM and the new Drude force field agrees very well with each other (Figure 6). Symbolic PED analysis was also carried out to examine the decomposition of the 5 lowest normal modes into internal degrees of freedom of the molecule.[45] An overall very good agreement of the main components was observed upon comparing results from QM and MM (Table 7).

Aqueous glucose diffusion and viscosity analysis

Simulations of glucose in aqueous solution were performed to verify that the revised parameters did improve the diffusion and viscosity problems present with the original Drude model. The ratio of α-D-glucose and β-D-glucose contained in the simulation systems was 1:2 to reflect the anomeric equilibrium distribution at room temperature.[49] A total of 1167 water molecules were included in the simulation system of a cubic box, corresponding to 21, 42, 63 and 105 glucose molecules yielding concentrations of 1M, 2M, 3M and 5M, respectively. The initial size of the box is determined according to the experimental density measured for each concentration.[50] A 100 ps equilibration was then carried out for each system under the NPT ensemble and then the size of the simulation system was fixed for the production runs under the NVT ensemble. For the computation of the diffusion constants, three independent NVT simulations, each of 20 ns, were performed under each glucose concentration. The diffusion constant (D_{pbc}) for the glucose and water molecules was computed from the mean-squared displacement of the respective molecules and corrected for the periodic boundary condition artifacts with the following equation,[51]

$$D_0 = D_{pbc} + \frac{k_B T \xi}{6\pi\eta L} \quad (1)$$

where k_B is the Boltzmann constant, T the simulation temperature, $\xi=2.837297$, L the cubic box length, and η the viscosity of the solution. The viscosity η was computed using the off-diagonal elements of the instantaneous pressure tensor from 9×5 ns NVT simulations for each system.[52]

Table 8 shows the comparison of the simulated and experimental diffusion constants of both glucose and water with the system viscosities shown in Table 9. Without the system size correction, the agreement of D_{pbc} for glucose molecules in the SWM4 water is very good with respect to the experimental measurements at all four concentrations. However, after the correction using equation 1 and the calculated viscosity (Table 9), the computed diffusion constant D_0 is overestimated from 32% for the 1M solution to 26% for the 5M solution. Consistent with this the water diffusion constant is overestimated under all four glucose concentrations and the viscosity of the solution is systematically underestimated (Table 9). As previously reported the sugar diffusion constant has almost a linear relationship with water diffusion constant, as studied using the additive CHARMM36 carbohydrate force field with the CHARMM TIP3P water model.[52] The diffusion constant of the SWM4-NDP water model is overestimated by 22% when the system-size correction is applied[51] (corrected simulated value $2.8 \times 10^{-5} \text{cm}^2/\text{s}$ vs experimental value $2.3 \times 10^{-5} \text{cm}^2/\text{s}$) due to the SWM4 model being developed prior to knowledge of the need for the correction. Accordingly, the SWM4 sugar and water D_0 diffusion constants were scaled by 0.82 and are included in Table 8. Comparison with experiment shows the agreement to be substantially improved, though the $^{\text{sug}}D_0$ values are still systematically overestimated and the $^{\text{wat}}D_0$ values overestimated. With respect to the original Drude model with a $^{\text{sug}}D_0$ of $0.14 \times 10^{-5} \text{cm}^2/\text{s}$ at 5M, the new model represents a significant improvement.

To further investigate the impact of the water model diffusion constant on the calculated glucose and water diffusion rates at different glucose concentrations, simulations using the SWM6-NDP water model were undertaken. This water model, which includes 2 particles representative of lone pairs in addition to the 4 particles in the SWM4 model reproduces the experimental diffusion constant of water and has improved orientational behavior with respect water clusters and other properties.[31] Analysis of the ability of the SWM6 water model to reproduce QM water-sugar dimer interactions showed the of agreement to be similar to that of the SWM4 model (Table 5). For the sugar-water cluster interaction energies, the SWM6 water model shows a better agreement to the QM result, which is systematically less favorable than the SWM4 water model for all 3 clusters (Table 6). The resulting diffusion constants shown in Table 8 show good agreement for the sugar with the values being slightly underestimated with respect to experiment. Correspondingly, the water diffusion constant is slightly overestimated at 1M glucose with that overestimation becoming significantly larger at 3 and 5M glucose. The improved agreement for the SWM6 water model supports that assertion that the limited agreement with experiment for the SWM4 model is indeed due to the overestimation of the diffusion constant of that water model.

While agreement with experiment with the SWM6 model is significantly improved, the water diffusion at the higher concentrations is significantly overestimated (328% at 5 M) though $^{\text{sug}}D_0$ is in satisfactory agreement (14% underestimated at 5M). Consistent with this is the significant underestimation of the system viscosity at 5M (Table 9). This discrepancy was observed for both SWM4 and SWM6 water models at high glucose concentration. Figure S1 of the supporting information shows the ratio for $\eta_{\text{exp}}/\eta_{\text{simu}}$ and $^{\text{wat}}D_{\text{simu}}/^{\text{wat}}D_{\text{exp}}$, suggesting a strong correlation between the deviation of the water diffusion constant and the viscosity of the solution at high glucose concentration. Such a result is intriguing as it

indicates that perturbation of the water structure due to the higher glucose concentration is not being properly modeled by the force field. Future studies will be required to better understand this observation.

Crystal simulations

Crystal simulations were carried out to examine the performance of the new parameters on solid structures. A total of 11 crystal structures were selected from the Cambridge Structural Database[53] for the hexopyranose isomers. For each system, a supercell was constructed with $2 \times 2 \times 2$ primary units. The simulation was then performed with each supercell with the additive C36 and two Drude force fields under the NPT ensemble for 10 ns. The results show the Drude force fields to systematically produce smaller deviations of the crystal lattice parameters compared to the additive force field for all 11 systems (Table 10), consistent with previous results for the original Drude force field. Comparison between the two Drude fields shows the new Drude force field to produce better agreement with experimental values for 4 systems (adgala03, adtalo01, bdglos01 and civvag), comparable performance for 3 systems (adman, glucose02 and glucmh11), and worse performance than the original Drude force field for 4 systems (cokbin, efuwei, cokbin01 and glucsa03). Overall the two Drude force fields have comparable performance in description of the solid structures.

Summary

Presented is a revised Drude polarizable force field for hexopyranose monosaccharides, which included parametrization of methyl-hexopyranose as described in the supporting information. Motivation for the additional optimization was the poor agreement between calculated and experimental diffusion constants using the original Drude force field.[20] In that model the sugar diffusion was significantly too low at higher concentrations indicating aggregation of the sugar. To address this issue QM calculations on glucose monosaccharide-water interactions and monosaccharide-monosaccharide dimer interactions were performed and used as additional target data for parameter optimization. This allowed for correction of the overestimation (too favorable) of the monosaccharide dimer interaction energies via the introduction of modified LJ parameters on select pyran ring carbons. The resulting model was shown to yield significant improvements in the diffusion constants while maintaining the quality of the model in the treatment of crystals.

While significant improvements in the diffusion constant of glucose in solution were obtained, problems are still present. In the case of the SWM4 water model the overestimation of the intrinsic diffusion constant of that model, due to it being optimized prior to awareness of the need to correct diffusion for system size effects, lead to systematic overestimation of the sugar and water diffusion constants. While these differences may be partially corrected by scaling associated with the ratio of the calculated and experimental D_0 values, that diffusion of water at high glucose (both 3 and 5M) is even more significantly overestimated. This indicates that perturbation of water structure by glucose is not being properly modeled by the force field, an issue that warrants further investigation.

The final parameters are available in the CHARMM force field release at (http://mackerell.umaryland.edu/charmm_ff.shtml).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Empirical force field parameters with explicit treatment of polarization offer the potential to more accurately model carbohydrates.

Overestimation of glucose-glucose interactions and underestimation of glucose-water interactions can lead to aggregation at high glucose concentrations leading to inaccurate modeling of diffusion.

Improvements in the treatment of glucose-glucose interactions in the Drude polarizable force field leads to more accurate modeling of aqueous diffusion of glucose.

Overestimation of water diffusion at high glucose concentrations indicates the need for further force field improvements.

Figure 1. Comparison of the QM and MM total (D_{total} in Debye) dipole moments and dipole moment X, Y and Z components (D_X , D_Y , D_Z in Debye) for different hexopyranose monosaccharide conformations listed in Table 1.

Figure 2.

Cremer-Pople diagram for the hexopyranose monosaccharide ring conformations. The ring conformations included in the target data are at 1C_4 ($\theta=180^\circ$), ${}^O S_2$ ($\theta=90^\circ/\varphi=330^\circ$), ${}^1 S_5$ ($\theta=90^\circ/\varphi=270^\circ$), ${}^3 S_1$ ($\theta=90^\circ/\varphi=30^\circ$), ${}^5 S_1$ ($\theta=90^\circ/\varphi=90^\circ$), ${}^1 S_3$ ($\theta=90^\circ/\varphi=210^\circ$), $B_{2,5}$ ($\theta=90^\circ/\varphi=300^\circ$), ${}^1,4 B$ ($\theta=90^\circ/\varphi=240^\circ$), $B_{3,O}$ ($\theta=90^\circ/\varphi=180^\circ$), and $B_{1,4}$ ($\theta=90^\circ/\varphi=60^\circ$) states.

Figure 3.
Comparison of the relative conformational energies of the hexapyranose monosaccharides between QM RIMP2/cc-pVQZ//MP2/6-31G(d) and MM models.

Figure 4.

The relative orientation and position of two monosaccharides in aqueous solution. (a) The local coordinate frame is defined to associate the ring plane of the 1C_4 and 4C_1 chair conformations of the pyranose monosaccharide, where X axis is along the line connecting the C2 and C5 atoms, the origin is located at the middle of the line C2–C5, the Z axis is perpendicular to the ring plane composed of C2, C3, C5 and O5, and the Y axis is in the ring plane. The relative orientation of the two monosaccharides is defined with 3 Euler angles using the local coordinate frame associated with each monosaccharide ring. The relative position of the two monosaccharides is represented using the spherical coordinate of the second monosaccharide in the local coordinate frame of the first monosaccharide. (b) The potential of mean force (PMF, kcal/mol) computed along the variables defining the relative position and orientation of two monosaccharides from the 5 M aqueous solution simulation. The interaction pairs in the green-boxed regions are extracted for QM calculation to fit the vdW parameters. Similar results were obtained in the simulations under 1, 2, and 3 M, respectively.

Figure 5.

Pyranose-pyranose interactions with glucose as the monosaccharide. (a) and (b) Two typical interaction modes between two pyranose molecules, one with two rings in a parallel arrangement (a) and the other with two rings in a perpendicular arrangement (b). (c) Comparison of QM and MM interaction energies between two hexopyranose molecules. The interaction energy was computed at RIMP2/cc-pVQZ with BSSE for each dimer. The first 32 interaction pairs (index 1–33) are in parallel mode and the remaining ones in perpendicular mode.

Figure 6. Frequency distribution for (a) α -D-glucose and (b) β -D-glucose computed from normal mode analysis using QM (MP2/6-31G(d)) (black) and new Drude force field (red).

Table 1

Number of conformations used for the dipole moment calculation for each hexopyranose isomer. QM calculations were performed at the RIMP2/cc-pVQZ//MP2/6-31G(d) model chemistry unless noted.

Monosaccharide	no. of conformations
α -D-allose	11
β -D-allose	15
α -D-altrose	12
β -D-altrose	13
α -D-glucose	13
β -D-glucose	16
α -D-galactose	13
β -D-galactose	13
α -D-talose	16
β -D-talose	12
α -D-gulose	14
β -D-gulose	16
α -D-mannose	14
β -D-mannose	14
α -D-idose	14
β -D-idose	9
Total	215

Table 2
Molecular polarizability tensor computed from the QM (MP2/6-31G(d)) and MM models.

Monosaccharide		XX	YX	YY	ZX	ZY	ZZ	Total
α -D-glucose	QM	16.6	-0.1	14.9	0.0	0.1	12.6	44.1
	Drude New	11.2	-0.2	10.3	0.1	0.1	8.1	29.5 (66.9%) ^a
	Drude Orig	11.4	-0.0	10.3	0.2	-0.1	8.8	30.4 (69.0%) ^a
β -D-glucose	QM	16.4	0.2	15.3	-0.3	0.0	12.8	44.5
	Drude New	11.1	0.4	10.9	-0.4	0.1	7.8	29.8 (66.6%) ^a
	Drude Orig	11.3	0.1	10.7	-0.2	0.1	8.5	30.5 (68.6%) ^a

^aThe ratio computed from total MM polarizability divided by total QM polarizability

Table 3

Details of the target data used in the hexopyranose monosaccharide dihedral fitting and resulting RMSD between MM and QM relative conformational energies in kcal/mol.

monosaccharide	type of conformational scan ^a	no. of conformations	RMSD/Drude new	RMSD/Drude orig	RMSD/additive
α -D-altrose	exocyclic + ring + C1, C2, C3, C4, C6 hydroxyl	449	0.66	2.15	1.21
β -D-altrose	exocyclic + ring + C1, C2, C3, C4, C6 hydroxyl	449	0.66	1.65	1.52
α -D-glucose	exocyclic + ring + C1, C2, C3, C4, C6 hydroxyl	353	0.56	1.75	1.60
β -D-glucose	exocyclic + ring + C1, C2, C3, C4, C6 hydroxyl	327	0.59	1.84	2.01
α -D-galactose	exocyclic + ring	138	0.83	1.85	1.90
β -D-galactose	exocyclic + ring	88	0.87	1.88	1.32
α -D-talose	C3, C4 hydroxyl	48	0.64	2.14	2.41
β -D-gulose	exocyclic + C4 hydroxyl	48	0.85	2.72	1.11
β -D-mannose	C2, C3 hydroxyl	48	0.69	1.90	1.10
β -D-idose	C3 hydroxyl	24	0.39	3.12	1.49
all pyranose	1 boat and 1 skew conformation for each pyranose	32	1.64	3.13	2.68
Total		2004	0.68	1.94	1.62

^a exocyclic = O5-C5-C6-O6 torsion, ring = O1-C1-O5-C5, O2-C2-C1-O5, and O4-C4-C5-O5 torsions, hydroxyl = the torsion of hydroxyl group connected to a given carbon atom.

Table 4

RMSD of the hexopyranose monosaccharide relative conformational energies for conformations that were **not** included in the dihedral fitting. Energies in kcal/mol.

Monosaccharide	no. of conf.	Drude new	Drude orig	Additive
α -D-allose	11	1.13	2.49	1.58
β -D-allose	15	1.21	2.36	1.95
β -D-galactose	13	1.65	4.66	1.94
α -D-talose	16	1.51	1.85	1.70
β -D-talose	12	0.72	3.71	1.72
α -D-gulose	14	1.82	4.63	1.49
β -D-gulose	16	0.66	3.41	1.42
α -D-manose	14	1.58	2.66	2.04
β -D-manose	14	0.62	4.09	1.29
α -D-idose	14	1.17	3.60	1.97
β -D-idose	9	0.92	1.83	1.64
Total	148	1.26	3.38	1.72

Table 5

Difference of glucose monosaccharide-water interaction energies computed from QM (MP2/cc-pVQZ with BSSE) and MM models. The energies are in kcal/mol.^a

Monosaccharide	Ener. Diff.	Drude new	Drude orig
α -D-glucose	Ave. diff.	0.23(0.27)	0.09(0.16)
	RMS diff.	0.47(0.42)	0.58(0.48)
	Ave. abs. error	0.43(0.41)	0.46(0.40)
β -D-glucose	Ave. diff.	-0.10(-0.03)	-0.22(-0.15)
	RMS diff.	0.44(0.52)	0.47(0.44)
	Ave. abs. error	0.33(0.33)	0.43(0.34)

^aBoth SWM4-NDP and SWM6-NDP (values in parenthesis) water models were used for sugar-water interaction energy calculation.

Table 6

Glucose-water cluster interaction energies from QM (MP2/cc-pVQZ with BSSE corrections) and MM models. The energy is in kcal/mol.

Monosaccharide	QM	Drude new ^a	Drude orig	Additive
1 α -D-glucose molecule with				
29 water molecules or	−46.97	−47.75 (−44.40)	−49.27	−44.82
31 water molecules	−36.67	−42.61 (−39.94)	−44.26	−43.56
1 β -D-glucose molecule with				
29 water molecules	−38.53	−43.71 (−40.59)	−44.49	−42.01

^aThe values inside and outside the parenthesis are from SWM6-NDP and SWM4-NDP water models, respectively.

Table 7

Symbolic PED analysis of the 5 lowest normal modes from QM and MM for α - and β -D-glucose.^a

Mode	Frequency/cm ⁻¹					
QM1	68.9(72.5)	ta6RNG1 57% (68%)	torC6-C5 17%	ta6RNG1a 1% (11%)		
MM1	69.5(69.8)	ta6RNG1 65% (78%)	torC6-C5 15% (1%)			
QM2	108.4(95.0)	ta6RNG1a 78% (43%)	torC6-C5 12% (35%)			
MM2	102.2(91.9)	ta6RNG1a 69% (54%)	tp6RNG1 10%	torC6-C5 10% (33%)		
QM3	127.9(122.2)	torC6-C5 34% (21%)	ta6RNG1 32% (13%)	tp6RNG1 23% (30%)	ta6RNG1a 1% (18%)	
MM3	118.7(113.3)	torC6-C5 50% (32%)	ta6RNG1 21% (8%)	tp6RNG1 20% (27%)	ta6RNG1a (1%)	
QM4	175.5(140.8)	torC6-C5 28% (14%)	tp6RNG1 23% (19%)	rC5H2 4% (15%)	ta6RNG1a 4% (14%)	
MM4	185.7(141.6)	tp6RNG1 30% (21%)	torC6-C5 21% (18%)	ta6RNG1a 12% (13%)	rC1H2 10% (5%)	rC5H2 8% (16%)
QM5	200.1(214.7)	iC5H2 29%	wC5H2 20%	iC3H2 7% (21%)	wC3H2 5% (18%)	iC2H2 (14%)
MM5	221.8(226.8)	iC5H2 34% (1%)	wC5H2 21% (1%)	dC6CO 14% (14%)	tp6RNG1 (12%)	

^aThe components contributing larger than 10% for either α -D-glucose or β -D-glucose (values in parenthesis) were listed in the table.

Comparison of simulated and experimental diffusion constant with SWM4-NDP and SWM6-NDP water models for both glucose (sugD) and water (watD) under different sugar concentrations^a

Sugar	sugD_{phc}			sugD_0			sugD_{exp}
	Conc	SWM4	SWM6	SWM4	SWM6	SWM6	
Sugar	1M	0.52(0.07)	0.38(0.01)	0.70(0.07)	0.57	0.52(0.01)	0.53
	2M	0.43(0.02)	0.29(0.01)	0.56(0.01)	0.46	0.39(0.02)	0.43
	3M	0.34(0.01)	0.23(0.01)	0.44(0.01)	0.36	0.30(0.01)	0.34
	5M	0.23(0.00)	0.15(0.01)	0.29(0.00)	0.24	0.20(0.00)	0.23
<hr/>							
Water	watD_{phc}			watD_0			watD_{exp}
	Conc	SWM4	SWM6	SWM4	SWM6	SWM6	
Water	1M	2.04(0.01)	1.53(0.03)	2.22(0.00)	1.82	1.67(0.02)	1.59
	2M	1.71(0.02)	1.29(0.02)	1.84(0.02)	1.51	1.39(0.02)	
	3M	1.47(0.01)	1.18(0.01)	1.58(0.00)	1.30	1.25(0.01)	0.68
	5M	1.12(0.01)	0.90(0.01)	1.18(0.01)	0.97	0.95(0.01)	0.29

The unit of diffusion constant is in $10^{-5}\text{cm}^2/\text{s}$, and the numbers in the parenthesis are standard errors from 3 independent simulations. As a comparison, the corrected sugar diffusion constants, sugD_0 , from the original Drude force field are 0.53 at 1M, 0.32 at 2M and 0.14 at 5M computed in the SWM4 water model. For the SWM4 D0 results the values after the slash are corrected for the overestimation of the water diffusion constant by the SWM4 water model as discussed in the text. The experimental results for sugD_{exp} and watD_{exp} are derived from references ([46]) and ([47]), respectively.

Table 9

Comparison of simulated (η_{calc}) and experimental (η_{exp}) viscosity in both SWM4-NDP and SWM6-NDP water models under different sugar concentrations

Conc	$\eta_{\text{calc}}/\text{SWM4}$	$\eta_{\text{calc}}/\text{SWM6}$	$\eta_{\text{exp}}/\text{cP}$
1M	1.03(0.16)	1.31(0.12)	1.59
2M	1.34(0.14)	1.81(0.27)	2.54
3M	1.67(0.14)	2.27(0.32)	4.02
5M	2.72(0.26)	3.36(0.29)	9.60

The unit of viscosity is cP. The numbers in the parenthesis are standard errors from 9 independent simulations. The experimental viscosity value is interpolated from reference ([48]).

Table 10Lattice parameter deviation between simulated and experimental values.^a

Refcode	Crystal system	a/Å	b/Å	c/Å	$\alpha/^\circ$	$\beta/^\circ$	$\gamma/^\circ$	V/Å ³
adgala03	orthorhombic	5.9	7.84	15.69	90	90	90	725.8
	Drude new	0.003	0.017	-0.004	0	0	0	0.016
	Drude orig.	-0.007	0.011	0.025	0	0	0	0.029
	Additive	0.04	0.028	-0.002	0	0	0	0.068
Adman	orthorhombic	23.45	9.46	6.89	90	90	90	1528.5
	Drude new	0.033	0.003	0.003	0	0	0	0.039
	Drude orig.	0.068	0.031	-0.056	0	0	0	0.039
	Additive	0.054	0.019	-0.007	0	0	0	0.067
adtalo01	orthorhombic	8.1	12.13	7.66	90	90	90	752
	Drude new	0.038	0.017	-0.029	0	0	0	0.025
	Drude orig.	0.045	0.049	-0.054	0	0	0	0.036
	Additive	0.031	0.032	-0.015	0	0	0	0.047
bdglos01	orthorhombic	12.65	7.77	7.7	90	90	90	757.3
	Drude new	-0.143	0.063	0.111	0	0	0	0.011
	Drude orig.	-0.131	0.043	0.13	0	0	0	0.025
	Additive	-0.064	0.058	0.044	0	0	0	0.034
Civvag	orthorhombic	7.08	9.86	10.62	90	90	90	741.4
	Drude new	-0.001	-0.018	0.042	0	0	0	0.021
	Drude orig.	0	0.007	0.019	0	0	0	0.026
	Additive	-0.016	0.031	0.037	0	0	0	0.052
Cokbin	Orthorhombic	4.92	11.93	12.8	90	90	90	751
	Drude new	0.043	0.036	-0.033	0	0	0	0.045
	Drude orig.	0.003	0.023	0.016	0	0	0	0.042
	Additive	0.06	0.017	-0.013	0	0	0	0.065
cokbin01	Hexagonal	16.6	16.6	4.86	90	90	120	1158.6
	Drude new	0.01	0.01	0.006	0	0	0	0.027

Refcode	Crystal system	a/Å	b/Å	c/Å	$\alpha/^\circ$	$\beta/^\circ$	$\gamma/^\circ$	$V/\text{\AA}^3$
Efluwei	Drude orig.	0.005	0.005	0	0	0	0	0.010
	Additive	0.017	0.017	0.049	0	0	0	0.084
	Hexagonal	7.17	7.17	12.74	90	90	120	568
	Drude new	-0.011	-0.011	0.091	0	0	0	0.066
glucsa03	Drude orig.	0.022	0.022	0.011	0	0	0	0.056
	Additive	0.028	0.028	0.028	0	0	0	0.086
	orthorhombic	4.95	10.34	14.85	90	90	90	759.7
	Drude new	0.018	0.017	0	0	0	0	0.035
glucose02	Drude orig.	-0.052	0.037	0.02	0	0	0	0.003
	Additive	0.1	-0.019	-0.025	0	0	0	0.051
	orthorhombic	6.59	9.01	12.72	90	90	90	756.2
	Drude new	0.056	-0.042	-0.016	0	0	0	-0.005
glucmh11	Drude orig.	0.038	-0.036	-0.004	0	0	0	-0.004
	Additive	0	0.021	0.018	0	0	0	0.039
	Monoclinic	8.8	5.08	9.71	90	97.7	90	430.7
	Drude new	-0.002	0.05	-0.006	0	0.002	0	0.041
	Drude orig.	-0.002	0.048	-0.008	0	-0.019	0	0.041
	Additive	0.001	0.056	0.012	0	0.011	0	0.067

For each system, the experimental lattice parameters are given in the first row and the deviation of simulated lattice parameters were presented in the 2nd to 4th rows for new Drude, original Drude and additive C36 force fields, respectively. The deviation was computed as $(L_{\text{simu}} - L_{\text{exp}})/L_{\text{exp}}$, where L_{simu} and L_{exp} are the simulated and experimental lattice parameters or volumes.