CHARMM Drude Polarizable Force Field for Furanoses

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ABSTRACT

An empirical all-atom CHARMM polarizable force filed for aldopentofuranoses and methyl-aldopentofuranosides based on the classical Drude oscillator is presented [1]. A single electrostatic model is developed for eight different diastereoisomers of aldopentofuranoses by optimizing the existing electrostatic and bonded parameters as transferred from ethers, alcohols, and hexopyranoses to reproduce quantum mechanical (QM) dipole moments, furanose–water interaction energies and conformational energies. Optimization of selected electrostatic and dihedral parameters was performed to generate a model for methyl-aldopentofuranosides. Accuracy of the model was tested by reproducing experimental data for crystal intramolecular geometries and lattice unit cell parameters, aqueous phase densities, and ring pucker and exocyclic rotamer populations as obtained from NMR experiments. In most cases the model is found to reproduce both QM data and experimental observables in an excellent manner, whereas for the remainder the level of agreement is in the satisfactory regimen. In aqueous phase simulations the monosaccharides have significantly enhanced dipoles as compared to the gas phase. The final model from this study is transferrable for future studies on carbohydrates and can be used with the existing CHARMM Drude polarizable force field for biomolecules.

THEORETICAL BACKGROUND

- The extra nonbonded energy term added to the CHARMM potential energy function by the introduction of the Drude particles

$$E_{Drude} = \frac{1}{4\pi D}\left(\sum_{i<j}\frac{q_{D,i}q_j}{\|\mathbf{r}_{D,i}-\mathbf{r}_j\|}+\sum_{i<j}\frac{q_{D,i}q_{D,j}}{\|\mathbf{r}_{D,i}-\mathbf{r}_{D,j}\|}\right) + \frac{1}{2}\sum_{\substack{polarizable\\ atoms\,i}} k_D\|\mathbf{r}_{D,i}-\mathbf{r}_i\|^2.$$

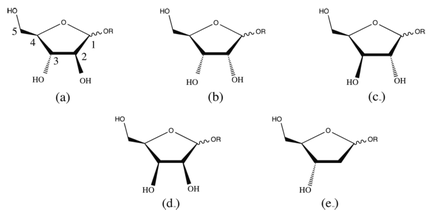
- Thole-like screening function used in the CHARMM Drude model

$$S_{ij}(r_{ij}) = 1-\left(1+\frac{(a_i+a_j)r_{ij}}{2(\alpha_i\alpha_j)^{1/6}}\right)e^{-\frac{(a_i+a_j)r_{ij}}{(\alpha_i\alpha_j)^{1/6}}}$$

Ref: K. Vanommeslaeghe, A.D.MacKerell ; Biochim. Biophys. Acta (2014)

FURANOSES

- A class of carbohydrates
  - Five membered rings exist in many biological and natural products including DNA, RNA, and bacterial cell walls.
  - Contains anomeric carbon that undergoes mutarotation in solution



Schematic representation of (a) arabinofuranose, (b) ribofuranose, (c) lyxofuranose, (d) xylofuranose and (e) deoxyribofuranose where R = H/CH3.

COMPUTATIONAL DETAILS

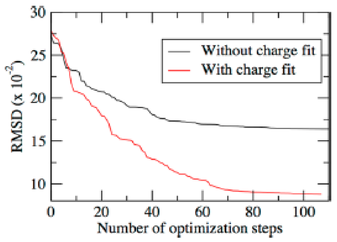
- QM optimization of the geometries, dipole moments, and potential energy scans (PES) for model compounds were performed using the MP2/6-31G(d) model chemistry.
- Final energy surfaces were obtained by single point calculations at the RIMP2/cc-pVQZ level.
- Gas phase molecular polarizabilities were carried out at the B3LYP/ aug-cc-pVDZ//MP2/6-31G(d) model chemistry.
- QM interaction energies for furanoses and water were obtained at the RIMP2/cc-pVQZ//MP2/6-31G(d) model chemistry with correction made for the basis set superimposition error (BSSE).
- Empirical force field calculations were carried out using the CHARMM program. The water model used in this study is the four-site SWM4-NDP model.
- Thole scale factors were optimized targeting QM dipole moments by using a Monte Carlo simulated annealing (MCSA) approach.

RESULTS AND DISCUSSIONS

Development of Drude polarizable parameters for furanoses involved a hierarchical process. Initially, electrostatic, bonded, and nonbonded parameters were transferred from the existing tetrahydrofuran (THF), ethanol, glycerol and hexopyranose. Initial analyses indicated the need for optimization of electrostatic parameters along with several dihedral angles, whereas the other bonded parameters, including the bond and valence angle terms and the Lennard-Jones parameters were found to be completely transferrable

Electrostatic parameters

compound	no of configs	RMSD Isomerfit	Anomerfit	Globalfit	direct	additive
arib	15	0.036	0.074	0.120	0.358	1.269
brib	15	0.023	0.057	0.089	0.308	0.832
aarb	15	0.015	0.031	0.083	0.195	0.743
barb	15	0.020	0.044	0.068	0.277	0.712

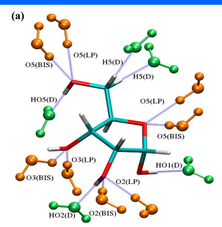


Convergence of the RMSD between MM and QM total dipole moments for Globalfit MCSA approach with (a) only the α and Thole terms optimized (without charge fit) and with the (b) α, Thole, and charge terms optimized (with charge fit).

Validation: Polarizability tensors

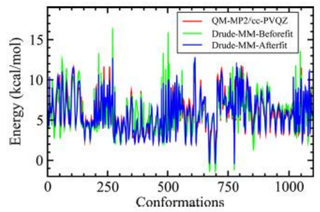
compound	component	QM	QM*0.75	Drude
AARB	XX	11.89	8.92	9.78
	YY	12.13	9.10	9.95
	ZZ	12.33	9.25	8.98
	total	36.36	27.27	28.71
BARB	XX	12.50	9.38	9.52
	YY	13.11	9.83	11.07
	ZZ	11.18	8.38	8.15
	total	36.79	27.59	28.75

Validation: Water interactions



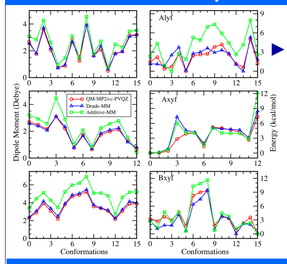
compound	energy	Isomerfit	Anomerfit	Globalfit	direct	additive
arib	avg difference	−0.105	−0.040	−0.157	−0.324	−0.483
	RMSD	1.152	0.768	0.789	1.210	1.040
	avg abs difference	0.900	0.587	0.580	1.013	0.937
brib	avg difference	−0.149	−0.060	−0.163	−0.243	−0.391
	RMSD	0.830	0.570	0.559	0.961	0.753
	avg abs difference	0.725	0.515	0.546	0.803	0.587

Dihedral parameters



- The RMSD calculated from the direct transfer model was 1.97 kcal/mol, which is improved over the RMSD of 2.18 kcal/mol obtained with the additive force field. When the Globalfit electrostatic parameters are used with the directly transferred dihedral parameters, the RMSD becomes 1.31 kcal/mol, indicating the importance of the polarizable electrostaticmodel in improving the treatment of the conformational energies. Least square fitting of the dihedral parameters yields an RMSD value of 0.59 kcal/mol.

Validation: Gas phase Dipole moment and Energy



- Transferability and validation of the final set of parameters optimized targeting arabinofuranose and ribofuranose were carried out by reproducing QM conformational energies and dipole moments for selected conformations of xylofuranose and lyxofuranose.

Validation: Crystal simulations

Crystal Lattice Parameters and Volumes As Obtained from Crystal Simulations

compound	CSD ID	method	a (Å)	% diff	b (Å)	% diff	c (Å)	% diff	vol (Å³)	% diff
methyl-α-arabinofuranoside	JUQSET	expt	12.26		6.83		4.60		378.17	
		Drude	12.31	0.41	6.91	0.43	4.66	0.42	383.04	1.29
		add.[a]	12.92	5.41	6.79	−0.62	4.60	−0.08	390.62	3.29
methyl-β-arabinofuranoside	QIBTIE	expt	5.90		10.79		12.15		773.75	
		Drude	5.88	−0.38	10.75	−0.37	12.11	−0.37	765.09	−1.12
		add.[a]	6.71	13.68	9.41	−12.78	12.42	2.23	783.66	1.28
methyl-α-lyxofuranoside	JUQSOD	expt	10.34		15.50		4.63		741.18	
		Drude	10.35	0.10	15.50	0.05	4.63	0.16	743.54	0.32
		add.[a]	10.49	1.45	15.83	2.10	4.59	−0.78	762.54	2.88
methyl-β-ribofuranoside	ZOWJAW	expt	4.86		24.16		12.88		1511.84	
		Drude	4.93	1.52	24.53	1.50	13.07	1.54	1582.16	4.65
		add.[a]	4.78	−1.59	25.82	6.88	12.99	0.88	1603.90	6.09
methyl-α-xylofuranoside	JUQSUJ	expt	6.22		8.14		7.42		369.11	
		Drude	6.32	1.48	8.27	1.53	7.54	1.56	386.25	4.64
		add.[a]	6.50	4.53	8.20	0.72	7.49	1.00	389.82	5.61
VG % diff		Drude	0.63		0.63		0.66		1.96	
avg % diff		add.[a]	4.70		−0.74		0.65		3.83	

Experimental and Calculated Average Pseudorotation Angles and Amplitudes As Obtained from Crystal Simulations

compound	P_{expt}	P_{calc}	Φ_{expt}	Φ_{calc}
Me-aarb	61	57	41	45
Me-barb	322	332	40	42
Me-alyf	28	31	44	45
Me-brib	350	343	38	37
Me-axyf	156	157	40	40

Conformational flexibilities of Furanoses in Aqueous solution

Population of N and S Conformers of Furanoses As Obtained from the Aqueous Phase Simulations

compound		North state expt	North state calc		South state expt	South state calc	(Φ_m)
Me-aarb	P_N	44/70	72	P_S	123/238	156	37
	% N	39/67	47	% S	61/33	53	
Me-barb	P_N	353/352	331	P_S	162/187	230	38
	% N	86/87	63	% S	14/13	37	
Me-arib	P_N	119/37	55	P_S	125/278	209	42
	% N	4/29	47	% S	96/71	53	
Me-brib	P_N	338/28	231	P_S	85/219	220	40
	% N	86/73	70	% S	14/27	30	
Me-alyf	P_N	24/20	65	P_S	145/219	136	41
	% N	71/65	55	% S	29/35	45	
Me-blyf	P_N	36/349/345	336	P_S	139/305/95	239	39
	% N	60/77/74	56	% S	40/23/26	44	
Me-axyf	P_N	114/309/324	49	P_S	122/188/124	137	43
	% N	11/39/8	48	% S	89/61/92	52	
Me-bxyf	P_N	348/27	154	P_S	265/267	174	38
	% N	66/45	78	% S	34/55	22	

Experimental and Computed Population of Exocyclic Rotamer

compound	method	% gg	% gt	% tg
Me-aarb	expt	48	38	14
	calc	50	45	5
Me-barb	expt	35	57	8
	calc	21	67	12

CONCLUSIONS

The reported Drude polarizable model for furanoses may be used to study their structural, dynamical, and thermodynamical properties as well as be part of more complex polysaccharides and more heterogeneous systems in conjunction with the Drude polarizable parameters for hexapyranoses, polyols, lipids, DNA, and proteins. The pameters may be obtained from the MacKerell Web site at http://mackerell.umaryland.edu/ and via the Drude Prepper utility in the CHARMM-Gui.

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References: Madhurima Jana, and Alexander D. MacKerell, Jr., J. Phys. Chem. B 2015, 119, 7846−7859