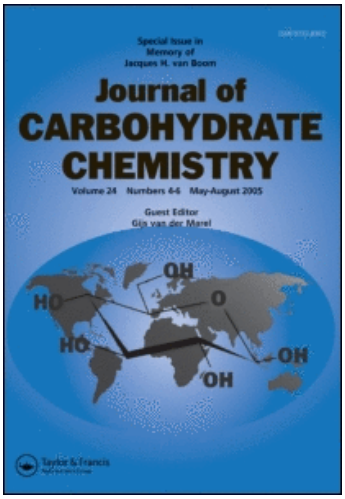

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Gregurick, Susan K. and Kafafi, Sherif A.(1999) 'Computation of the Electronic and Spectroscopic Properties of Carbohydrates Using Novel Density Functional and Vibrational Self-Consistent Field Methods', Journal of Carbohydrate Chemistry, 18: 8, 867 — 890
To link to this Article: DOI: 10.1080/07328309908544041
URL: http://dx.doi.org/10.1080/07328309908544041

J. CARBOHYDRATE CHEMISTRY, 18(8), 867–890 (1999)

COMPUTATION OF THE ELECTRONIC AND SPECTROSCOPIC PROPERTIES OF CARBOHYDRATES USING NOVEL DENSITY FUNCTIONAL AND VIBRATIONAL SELF-CONSISTENT FIELD METHODS

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Received October 22, 1998 - Final Form July 19, 1999

ABSTRACT

A novel density functional method is presented for the calculation of electronic and thermodynamical properties of oligosaccharides. This method, termed K2-BVWN, offers two advantages; it scales as N^3, where N is the number of basis functions, and there are only two adjustable parameters. The current density functional method is tested in terms of reproducing high level gas phase *ab initio* calculations in eleven low energy conformers of D-glucopyranose including exo-anomeric and different hydroxymethyl orientations (G^-,G^+, and T). The K2-BVWN method is also tested in terms of reproducing the spectroscopic features of D-glucopyranose and D-mannopyranose (α/β) as compared with both a vibrational self-consistent field calculation (VSCF) as well as experimental infrared spectroscopy. The VSCF calculations offer the advantage that it is possible to include higher order mode coupling and anharmonic effects directly into the calculation of the vibrational frequencies. In general, the K2-BVWN method reproduces the *ab initio* energetic trends of the different conformers of D-glucose. While the absolute energies are not the same between the *ab initio* and the K2-BVWN method, both methods do predict a preference for the α-anomer in the gas phase (0.4 kcal/mol *ab initio*, 0.0 – 0.5 kcal/mol K2-BVWN). The K2-BVWN method was able to reproduce the experimental and VSCF calculated spectrum of both D-glucopyranose and D-mannopyranose in the frequency range between 1500 – 800 cm^{-1}. Because the current density functional method is both relatively quick and accurate, it represents a significant advancement in the development of oligosaccharide force fields.

INTRODUCTION

Carbohydrates play a critical role in many biological processes from energy metabolism, glycolipid recognition, glycoprotein interaction to structural polysaccharides. They are the most ubiquitous of all biological molecules and yet some of the least understood. Even monosaccharides pose quite a theoretical challenge in terms of understanding the enormous conformational potential energy surface. This is due in part to the many torsional degrees of freedom, that is the rotation of the exocyclic hydroxyl and hydroxymethyl groups. Furthermore, at the anomeric carbon (C_1) the hydroxyl group can take an equatorial or axial orientation. This leads to an anomeric equilibrium which can be determined experimentally by ^{13}CNMR spectroscopy[1-4] and by optical rotation.[5,6] The problem of studying all of conformational space is further complicated when aqueous effects are included into the calculation. It is known for example that the anomeric equilibrium between β- and α-D-glucopyranose favors the β anomer by 0.3 kcal/mol,[7] while in the gas phase, the anomeric effect is reversed to favor α-D-glucopyranose by 0.4 kcal/mol.[8,9] Ideally, one may be interested in examining the relative energies of the anomers as well as the intramolecular rotational relationship of the hydroxyl and hydroxymethyl groups for D-glucopyranose and each of its epimers. Recently, Barrows and co-workers have investigated the hydroxyl/hydroxymethyl rotational and anomeric conformers of D-glucopyranose in the gas phase as well as in solution.[9] In this study, the authors used the MM3(96) program and found 107 unique low energy $^4C_1$ conformers of α-glucopyranose and 113 conformers of the corresponding β-glucopyranose by an exhaustive minimization procedure. From the MM3 calculations, eleven lowest energy structures were further studied by high level *ab initio* methods to deduce the relative energies between the conformers.[9] In a related study, Damm et al. also studied conformers of D-glucopyranose using both *ab initio* and density functional methods.[10] These studies are to date the most comprehensive *ab initio* investigations of glucopyranose.

A full quantum mechanical *ab initio* calculation is one of the most reliable theoretical methods in the study of atomic and molecular electronic and thermodynamical properties. In terms of the application of *ab initio* methods to the study of carbohydrates and carbohydrate model compounds, there is an ever increasing body of literature.[8,9,11-20] In fact *ab initio* calculations have been essential in the development of a variety of molec-

ular mechanical carbohydrate force fields.[10,21-26] While *ab initio* methods are extremely accurate, the price in computational cost make such methodology, to date, prohibitively expensive for all but mono and perhaps disaccharides. This is due primarily to scaling difficulties in *ab initio* methods. It is noted that methods such as Hartree Fock (HF) and MP2 offer reasonable scaling properties (N^3 and N^5 respectively); however, higher correlated and hence higher accuracy treatments (QCI and CC) scale roughly at N^7. A promising alternative to *ab initio* methods, with less stringent scaling properties, are density functional based (DFT) methods.[27-31] Recently, density functional methods have also been employed in the study of carbohydrates.[11,12,16,17,19]

The success of DFT methods in predicting electronic properties relies on the choice of the exchange-correlation energy functional used in the computation. A major advance of DFT methods came in the late 80's with the development of the hybrid-exchange functionals of Becke and the formulation of the generalized gradient approximations.[32] Today, one of the most popular semi-empirical DFT methods for predicting structures, energies and thermochemical properties is Becke's three-parameter procedure, B3LYP.[32,33] Becke introduced this hybrid HF-DFT method in which the exact nonlocal HF exchange is semi-empirically mixed with the local slater exchange through the adiabatic connection formula.[33] The accuracy of such methods for predicting atomization energies is within 3 to 5 kcal/mol, however the scaling of such methods is still rather large ($\sim N^4$ to $\sim N^5$).[27-31] Recently Kafafi and co-workers have developed a semi-empirical HF-DFT based method which mixes the HF and gradient corrected local spin density exchange using the adiabatic connection formula[33] together with the Pade approximated Vosko, Wilk, and Nusair (VWN) correlation functional.[34] This method (K2-BVWN) offers two very attractive new features to DFT based methods; the scaling has been improved to $\sim N^3$,[35,36] and there are only two adjustable parameters.[36] Using this method, Kafafi and co-workers were able to reproduce (within $\pm$ 2 kcal/mol) the heats of formation for over 300 molecular systems as well as the binding energies of noble gas dimers and hydrogen bonded complexes.[35,36] It is also noted that current developments in DFT approaches with linear scaling is an active area of research.[31]

The aim of the present work is to apply this novel density functional method to the calculation of the energetics and spectroscopy for α,β-D-glucopyranoses and α,β-D-

mannopyranose. In the study of D-glucopyranose, we investigated the relative energies of 11 different gas phase conformers as in the work of Barrows et al.[9] The resulting energy optimized spectrum for two of the conformers will be compared to both previous experimental spectroscopy[37–39] as well as vibrational frequencies obtained from a vibrational self consistent study(VSCF). Previously, Gregurick and co-workers refined parameters for an Amber-based carbohydrate force field utilizing the VSCF method and the experimental spectrum of α-D-glucopyranose.[40] The VSCF method is quite unique in that anharmonic as well as mode coupling terms are included directly in the calculation of the vibrational frequencies. Using this spectroscopically refined force field, the authors then calculated the anomeric free energy difference between α and β glycopyranosein solution. Based on six molecular dynamics simulations they found an average $\bar{G}_{\alpha\rightarrow\beta} \sim -0.1$ kcal/mol. However, the ΔG ranged from 0.23 to -0.34 kcal/mol. Moreover, while this force field reproduced the spectroscopic features of D-mannopyranose it could not reproduce the experimental free energy difference. The authors attributed this large variation in ΔG values to be due in part to a difficulty in physically capturing the intermolecular hydrogen bonding between pyranose sugars and the surrounding solvent. It is therefore the future goal of the authors to develop and further improve oligosaccharide force fields by combining theoretical efforts in both DFT and VSCF based approaches.

METHODS

A. K2-BVWN Density Functional Method

All of the density functional theory (DFT) computations reported in this work were done using the K2-BVWN methodology of Kafafi and coworkers.[35,36] In the K2-BVWN scheme, the total exchange-correlation energy functional, Exc, was approximated by a sum of two terms. Namely, an exchange component, Ex, and a correlation term, Ec. The Ex term consisted of a hybrid mixture of 37.5% exact exchange and the appropriate local spin density exchange using the adiabatic connection formula.[35] On the other hand, the Ec component was a linear combination of the Vosko, Wilk and Nusair (VWN) correlation energy functional of the free electron gas, Ec(VWN),[34] and a generalized gradient approximation (GGA) term containing one adjustable parameter, as described in detail elsewhere.[35,36]

The K2BVWN method has previously been applied to the calculation of room temperature heats of formation, ionization potentials, electron and proton affinities of 350

molecular systems, including the G2 database of Curtiss et al.[41] The overall performance of the K2-BVWN methodology was comparable to the accurate G2 *ab initio* theory,[41] with a total average error in computed electronic and thermodynamic properties of 1.4 kcal/mol.[35,36] The main advantage of the K2-BVWN methodology over G2-theory is in its N^3 scaling, where N is the number of basis functions, compared to N^7 for G2-theory. Therefore, the K2-BVWN approach may be applicable to larger chemical systems than corresponding *ab initio* methods. The K2-BVWN methodology has been implemented into the Gaussian 94 computer code by Kafafi and coworkers.[35,36,42]

It is well known that the majority of reported DFT-based methods have a common difficulty in handling Van der Waals and charge-transfer interactions.[28,30,27,35] In general, DFT approaches normally underestimate the binding energies of these systems. In particular, Van der Waals complexes, such as dimers of noble gases, were predicted by various DFT methods to have either no, or strongly repulsive interactions. The K2-BVWN scheme has been shown to approximately overcome this difficulty that is inherent to other DFT methods.[35] The K2-BVWN method predicted the binding energies of 9 noble gas dimers (helium through Xenon) and a variety of charge-transfer complexes with remarkable accuracy.[35] This was shown to be due to the long-range behavior of the correlation potential, V_c, used in the formulation of this method. That is, V_c had a $\sim \frac{1}{r^6}$ dependence as $r \to \infty$, which mimics the Van der Waals interactions. Therefore, the K2-BVWN methodology accounts for both electrostatic and Van der Waals non-bonded interactions reasonably well.

For all of the molecules investigated in this work, full geometry optimizations with analytical gradients using K2-BVWN/6-311g(d) level of theory were performed. These were followed by a single point computation using the K2-BVWN/6-311+g(3df,p) method. Geometry optimizations were generally terminated when the largest component of the gradient was smaller than 0.0001 Hartree/Bohr. Vibrational frequencies of all of the species of interest and corresponding thermal corrections were also computed using the K2-BVWN/6-311g(d) method. All of the optimization, diagonalization, numerical integration routines, and DFT exchange-correlation functionals used in connection with the K2-BVWN methodology were obtained from the Gaussian 94 computer code.[35,36,43]

B. VSCF Method

In the Vibrational Self-Consistent Field (VSCF) calculations, we utilize an all atom force field as implemented in the molecular dynamics program MOIL.[44] A complete de-

scription of this force field may be found in the work of Gregurick et al.[40] The parameters which describe the dihedral torsional barriers and atomic partial charges were determined by fitting our VSCF vibrational frequencies to the experimental IR and Raman frequencies (α-D-glucopyranose only) of Dauchez and co-workers,[45] Korolevich and co-workers,[37,38] and Atalla and Wells.[39] This reparameterized force field yielded excellent agreement not only in reproducing the vibrational spectrum of both α and β-glucopyranose (errors are $\pm$ 3.3 cm^{-1} for α-glucopyranose, and $\pm$ 5.1 cm^{-1} for β-glucopyranose) but also reproduced a reasonable estimate of the anomeric free energy difference (D-glucopyranose only) between these two anomers in solution.[40]

In the VSCF method, the N-dimensional Schrödinger equation is solved by making the approximation that the wavefunction representing each normal mode is near separable. Furthermore the normal quadratic equilibrium expansion of the potential (harmonic case) is extended to fourth order. This expansion is valid about a single minimum. In principle, the spectroscopy depends on the specific conformer, and a previous study of the peptide di-L-serine illustrated that different minima had different spectroscopic frequencies.[46] Thus for a complete spectroscopic study of all conformations, a separate expansion for each unique conformer will be required.

In the VSCF method, each degree of freedom, or normal mode, is solved separately for by integrating over all the other degrees of freedom. This then leads to N single mode VSCF equations. In the present calculation we solved each VSCF Hamiltonian using the collocation method of Yang and Peet.[47] For an adjustable grid, sensitive to each mode, we choose to work in the dimensionless variable, $\bar{q}_k$, where

$$\bar{q}_k = \frac{Q_k}{(\lambda_k)^{\frac{1}{4}}}.$$

Here, λ_k is the k^{th} eigenvalue of the Hessian. Convergence was determined when $\Delta\sum_k \varepsilon_k \leq$ 0.0001 kcal/mol from one iteration to the next. The calculations were carried out on a Silicon Graphics Indigo workstation. A complete description of the VSCF methodology and application may be found in references 40, 46, and 48-50.

RESULTS AND DISCUSSION

A. Structures and Energetics

In the present work, we compare the eleven lowest energy conformers of both α-

and β-D-glucopyranose as in the work of Barrows et al. (Figure 1).[9] In our present DFT method, a full optimization with analytic gradients was performed at the K2-BVWN/6-311g(d) level of theory. These were then followed by a single point calculation at the K2-BVWN/6-311+g(3df,p) level. Table 1 summarizes the calculated relative energies in kcal/mol for the conformers of D-glucopyranose in the gas phase. Using a high level of theory (MP2/cc-pVDZ) Barrows and co-workers were able to illustrate that in the gas phase the α anomer is stabilized over the β by 0.4 to 0.6 kcal/mol.[9] In the present calculations we find that the conformer number 7 (G^+) is the lowest energy structure, which is not in complete agreement with the *ab initio* results. From table I, the lowest *ab initio* energy conformer is the G^- conformer number 8. However, we do find that the G^+ and G^- conformers are lower in energy than the T conformers as in the *ab initio* calculations.

In the study of the effect of the hydroxyl orientation, two conformers had a completely clockwise orientation of intramolecular hydrogen bonding (numbers 1 and 10). Conformer number 1 represents the clockwise β anomer while conformer number 10 is the clockwise α anomer. In this case, the α anomer is stabilized over the β by 1.98 kcal/mol. Although the absolute energies are different between the *ab initio* and K2-BVWN calculation, the stabilization of the α anomer over β is the same for both calculations. This stabilization may be due to a better intramolecular hydrogen bond between the hydroxyls at positions C_1 and C_2 for the α anomer. As in the *ab initio* calculations, we also find evidence for the C_1 hydroxyl orientation to take advantage of the exo-anomeric effect. In this case, the clockwise conformers number 2 (β) and 11 (α) have an energy difference of roughly 0.5 kcal/mol in favor of the α conformer. In general the energy difference between the α/β pairs in the present calculation is roughly $\sim$ 0.8 kcal/mol, which is only slightly less than for the *ab initio* calculations (1 kcal/mol). An estimation of the K2-BVWN free energy difference between α and β, using the rovibrational contribution to the free energy from the work of Barrows and co-workers yields an estimate of $\Delta G_{\alpha\rightarrow\beta}$ of $\sim$ 0.0 to 0.5 kcal/mol. The *ab initio* calculated free energy difference of the $\alpha \rightarrow \beta$ anomerization was 0.4 kcal/mol in the gas phase.

B. Calculation of Spectroscopic Frequencies and a Comparison with VSCF Frequencies and Experimental Frequencies

One of the main aims of the present study is to present a methodology which can not only accurately predict energetics of carbohydrate compounds but also predict vibra-

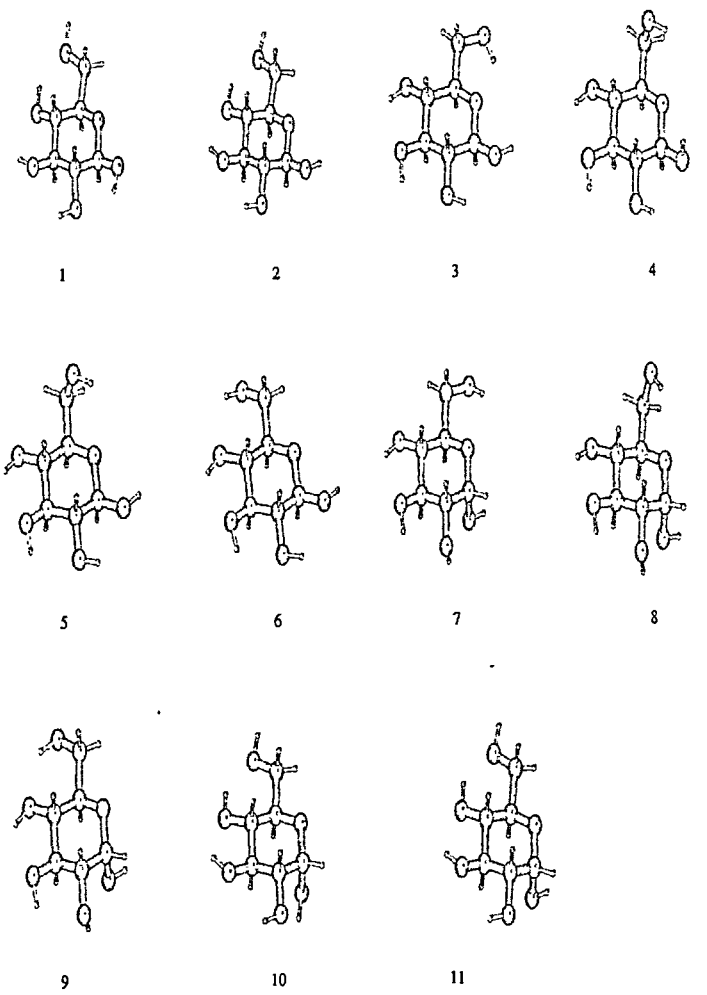

Figure 1. The eleven conformers of D-glucopyranose calculated at the K2-BVWN/6-311g(d) level. These are the same conformations as in the original work of Barrows et al.[9]

tional frequencies as well as thermodynamic properties. In this section, we illustrate that the present density functional method (K2-BVWN) will reproduce the vibrational spectrum of not only D-glucopyranose but also D-mannopyranose. We have selected two conformers of D-glucopyranose, conformer number one and ten (Figure 1) to represent β- and α-D-glucopyranose, respectively. These conformers were selected based on the previous work of Gregurick et al.[40] However, they are not the lowest K2-BVWN energy structures and in any complete discussion of the spectroscopy, all of lowest energy conformers should be

Table 1. Calculated relative energies(kcal/mol) of D-glucopyranose conformers in the gas phase

Theory	1	2	3	4	5	6	7	8[a]	9	10	11
MP2/cc-pVTZ//MP2/cc-pVDZ[b]	4.3	4.7	1.7	2.4	1.4	1.8	0.3	0.0	0.3	1.4	3.3
HF/cc-pVZ//MP2/cc-pVDZ[b]	2.9	3.1	-0.2	1.2	-0.1	0.2	-0.3	0.0	0.1	1.2	2.7
HF/cc-p^{T}VQZ//MP2/cc-pVDZ[b]	2.6	2.8	-0.6	0.9	-0.4	-0.1	-0.4	0.0	0.1	1.1	2.6
MP2/6-31G*, *b*	5.3	5.9	3.0	3.5	2.4	2.5	0.5	0.0	-0.0	1.3	2.6
CCSD/6-31G*//MP2/6-31G*, *b*	5.2	5.6	2.7	3.2	2.1	2.3	0.5	0.0	0.0	0.25	1.3
K2-BVWN/6-311 + g(3df,p)	3.2	3.5	0.5	1.4	0.5	0.7	-0.08	0.0	0.04	1.3	3.0

a. Absolute Energies for this column are: -686.50324,-683.60583,-683.64949, -685.18081, -685.25213, -685.027197172 hartrees.
b. Reproduced from Table 1 of Barrows et al.[9]

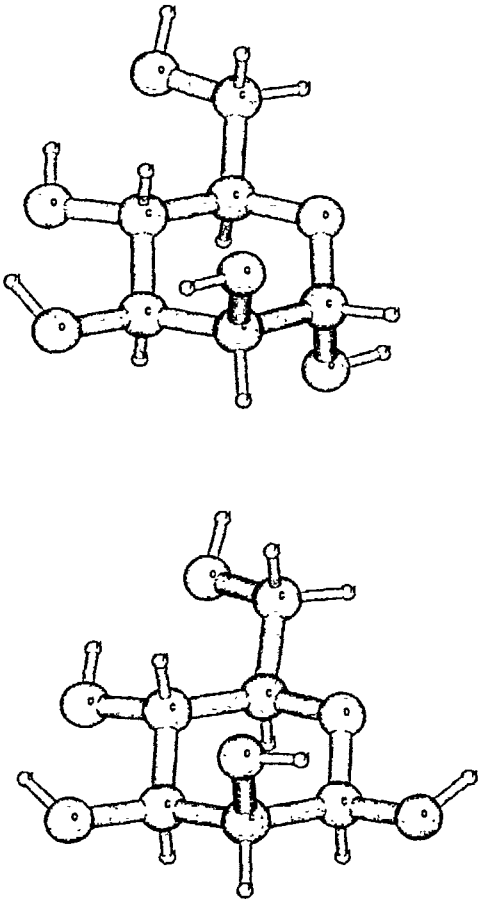

Figure 2. The conformers of α (upper) and β-D-mannopyranose (lower) calculated at the K2-BVWN/6-311g(d) level.

included. These conformers were chosen so as to make a comparison with the VSCF calculations more meaningful. The α- and β- conformers of D-mannopyranose were generated from the corresponding α and β conformers of D-glucopyranose by switching the H and OH groups at the C_2 position and then optimizing at the K2-BVWN/6-311 g(d) level. The two anomers of D-mannopyranose are illustrated in Figure 2.

We have calculated the K2-BVWN vibrational frequencies and IR intensities for the anomers of D-glucopyranose and D-mannopyranose by a diagonalization of the energy optimized Hessian. We have also calculated the VSCF frequencies. The frequencies obtained from this method will include both anharmonic and mode coupling effects which are not

yet possible to capture directly from the density functional method. In the future we would like to refine the existing molecular mechanics force field, which the VSCF calculations are based on, using this density functional method. Thus an underlying comparison between the two methods, as well as the experimental spectrum, is imperative. For the comparison of the results for D-glucopyranose we choose the room temperature experimental infrared spectrum of Korolevich and co-workers in part because these authors have made an accompanying valence force field calculation of the frequencies.[37,38] For the D-mannopyranose spectrum, we used the crystalline IR frequencies (100 K) of Wells and Atalla.[39] Tables 2 and 3 list a comparison of the vibrational spectrum for D-glucopyranose (α and β) while Tables 4 and 5 is a comparison of the vibrational spectrum for D-mannopyranose (α and β). Table 6 list the average errors in the calculated frequencies for both α/β glucopyranose and α/β mannopyranose. In calculating the averages we did not include the $(OH)_s$ frequencies, as these are overestimated in the K2-BVWN method due to an unavoidable shortening of the OH bond. In this case, the OH stretching frequencies should be rescaled by $\sim 8\%$ in order to compare well with the experimental and VSCF frequencies.

In general both the K2-BVWN and VSCF methods compare well in terms of reproducing the vibrational spectrum for mannopyranose and glucopyranose in the region between 1500 and 900 cm^{-1}. However, both methods have difficulty in reproducing the lower frequency vibrations (< 800 cm^{-1}), particularly for α/β mannopyranose. In the case of the mannopyranose spectrum the comparison between the experimental and calculated frequencies became extremely difficult below 500 cm^{-1}, and in general, the assignment to the experimental frequencies in this region is suggestive at best.

In all four spectra, we calculate two bands at roughly 1530 and 1500 cm^{-1} which have no corresponding experimental frequency. Previously Gregurick, et al.[40] speculated that the change in the dipole moment associated with these two modes may be rather small, which may explain why they do not show up in the experimental or Valence Force Field spectrum.[40] Based on an eigenvector analysis, these modes were assigned to a COH distortion and to a distortion of the ring. In general the COH and CCH distortion modes occur in the region from 1490 to 1300 cm^{-1}. It was previously illustrated that the COH distortion will strongly couple to the methylene and methine modes,[45,40] which will shift the VSCF frequencies to the blue relative to the K2-BVWN frequencies. In this region of the spectrum, the VSCF frequencies agree slightly better than those of the K2-BVWN

Table 2. Comparison of calculated and experimental vibrational frequencies of α-D-glucopyranose (cm^{-1}).

Expt.[37]	Valence FF[37]	K2-BVWN	VSCF calc.	assignment
3415	3412	3811	3414	$(OH)_s$
3350	3320	3768	3404	$(OH)_s$
3310	3312	3761	3402	$(OH)_s$
	3324	3718	3400	$(OH)_s$
3200	3203	3697	3399	$(OH)_s$
	2975	3050	2948	$(CH)_s$
2944	2947	3032	2921	$(CH)_s$
	2930	3030	2918	$(CH)_s$
	2928	3009	2916	$(CH)_s$
2912	2911	2993	2913	$(CH)_s$
2889	2882	2992	2953	$(C_6H_2)_{as}$
2875	2851	2953	2880	$(C_6H_2)_{ss}$
		1531	1532	$(C_3C_4C_5)_d$,$(C_4OH)_d$
	1488	1481	1508	$(C_1C_2C_3)_d$,$(C_2OH)_d$
1458	1450	1464	1490	$(CC_1H)_d$,$(C_2OH)_d$
1442	1435	1440	1474	$(HC_6H)_d$,$(C_3OH)_d$
1425	1415	1436	1468	$(HC_6H)_d$
1405		1419	1452	$(CC_4H)_d$,$(C_3OH)_d$
		1412	1393	$(CC_1H)_{ipb}$,$(C_3OH)_d$
1380	1389	1384	1359	$(CC_4H)_{ipb}$,$(C_3OH)_d$
1370	1381	1373	1350	$(CC_4H)_{ipb}$,$(C_2OH)_d$
				$(CC_5H)_{ipb}$,$(HC_4)_d$,$(C_1OH)_d$
1347	1360	1369	1345	$(CC_2H)_{ipb}$,$(C_4OH)_d$
				$(C_1OH)_d$
	1344	1341	1333	$(CC_3H)_{ipb}$,$(C_4OH)_d$
				$(C_2OH)_d$,$(HC_1O)_d$
1339	1331	1316	1331	$(CC_6H)_{ipb}$,$(C_4OH)_d$
				$(HC_1O)_d$,$(HC_2O)_d$
				$(HC_3O)_d$
1328	1317			$(HC_3O)_d$,$(O_5C_1H)_d$
				$(HC_2O)_d$
	1307			$(CC_3H)_d$,$(HC_3O)_d$
				$(HC_2O)_d$,$(HC_6O)_d$
1295	1300	1298	1288	$(C_6C_5H)_{opb}$,$(C_3OH)_d$
				$(HC_4O)_d$

Table 2. Continued

Expt.[37]	Valence FF[37]	K2-BVWN	VSCF calc.	assignment
1280	1276			$(CC_6H)_d$,$(HC_6O)_d$ $(O_5C_5H)_d$
1270	1276	1275	1267	$(CC_5H)_{opb}$,$(CC_2H)_{opb}$ $(HC_4O)_d$,$(HC_3O)_d$,$(CH_2)_b$
	1258			$(HC_6O)_d$,$(HC_4O)_d$ $(HC_5O)_d$
	1250	1263		$(HC_4O)_d$,$(HC_3O)_d$
1223	1226	1257	1234	$(CC_2H)_{opb}$,$(CC_4H)_{opb}$ $(HC_3O)_d$
	1241			$(CC_2H)_{opb}$,$(CC_2H)_{opb}$ $(HC_3O)_d$
1202	1205	1214	1219	$(CC_1H)_{opb}$,$(CC_2H)_{opb}$ $(HC_3O)_d$,$(HC_4O)_d$
1147	1145	1156	1177	$(CC_3H)_d$,$(CC_4H)_d$ $(CC_5H)_d$,$(CH_2)_{sc}$
	1140	1147		$(CC_1H)_d$,$(CC_2H)_d$ $(CC_3H)_d$
1130	1130	1132		$(C_2OH)_t$,$(C_3OH)_t$,$(CC)_d$
		1124		$(C_2OH)_t$,$(C_3OH)_t$ $(C_4OH)_t$,$(C_3C_4)_d$
1112	1116	1119	1111	$(O_5C_5H)_d$,$(O_5C_1H)_d$
1078	1084	1098,1094	1089	$(O_5C_5H)_d$,$(O_5C_1H)_d$ $(HC_3O)_d$
	1056	1068	1073	$(C_2C_3)_t$,$(C_3C_4)_t$,$(C_4C_5)_t$
1050		1049	1042	$(C_6H_2)_{sc}$,$(C_4O)_t$ $(HC_2O)_d$,$(HC_3O)_d$
1025	1033		1035	$(C_5C_6)_t$,$(HC_2O)_d$
1015	992	1019	1013	$(HC_1C_2)_t$,$(C_3C_4)_t$
	992	998	1003	all CCH_t, $(HC_2O)_d$ $(HC_1O)_d$
997	986		987	all CCH_t, $(C_3C_4)_t$
	934		966	$(C_5C_6)_t$,$(CC_1H)_t$,$(CC_2H)_t$
		919	946	$(C_2O)_t$, $(C_6H_2)_{tw}$ $(C_3C_4O)_t$
917	913	910	923, 912	$(C_1C_2)_t$,$(C_6O)_t$ $(O_5C_1)_{asring}$
840	860		843	$(C_6H_2)_{sc}$,$(C_1O)_t$,$(C_3O)_t$
775	757	782	827	$(O_5C_1C_2)_t$,$(C_3O)_t$

(continued)

Table 2. Continued

Expt.[37]	Valence FF[37]	K2-BVWN	VSCF calc.	assignment
670	670			$(CC_6O)_t$
645	664	646	610	$(O_5C_1)_{ssring}$
	625			$(CC_3O)_t$,$(CC_4O)_t$
	607	579	574	$(O_1H)_{opd}$,$(O_2H)_{opd}$
557	552	556	549	$(O_4H)_{opd}$,$(O_6H)_{opd}$
537	531	553	547	ring distortion
		518	535	$(O_1H)_{opd}$,$(O_2H)_{opd}$ $(O_3H)_{opd}$,$(O_4H)_{opd}$
517	517		505	ring distortions
	485	486,470	489,472	ring distortions,$(O_3H)_{opd}$ $(O_4H)_{opd}$
	430	443,430	452	ring distortion
408	418	422	378	ring distortion

s = stretch, as = asymmetric stretch, ss = symmetric stretch, d = distortion, ipb = in plane bend, opb = out of plane bend, tw = twist, t = torsion, sc = scissors, opd = out of plane distortion

calculation, however the VSCF calculation could not account for all of the COH distortions in β-glucopyranose (Table III). This represents a weakness in the present molecular mechanics force field.

It is well known that all sugars have characteristic C-O, C-C vibrations and CH_2 distortions in the region from 1200-950 cm^{-1}.[38] The region from 1288 to 1100 cm^{-1} was previously identified as the CCH out-of-plane bend as well as distortion of the HCO angles.[40] Modes in this region are coupled somewhat to the COH distortions. While both methods agree with the experimental frequencies, the VSCF calculation tends to underestimate the number of the CCH distortions in the range of 1130 cm^{-1}. However, the IR spectrum of both α and β glucopyranose from Dauchez and co-workers significantly reduces the number of CCH distortions in this region in agreement with the VSCF results.[45,40] We also find two frequencies [1111, 1089 (α) and 1109, 1084 (β-glucopyranose,); 1116, 1094 (α) and 1112, 1081 (β-mannopyranose)] which correspond to distortions of the $O_5 - C_1$ bond, coupled to the COH distortions. This is in excellent agreement with the experimental evidence (D-glucose) that these frequencies are indeed $O_5 - C_1$ distortions.[45,38] The region from 1070-1000 cm^{-1} is mainly dominated by torsions of the C-C bond along the

Table 3. Comparison of calculated and experimental vibrational frequencies of β-D-glucopyranose (cm^{-1}).

Expt.[38]	Valence FF[38]	K2-BVWN	VSCF calc.	assignment
3340	3355	3812	3411	$(OH)_s$
	3355	3773	3403	$(OH)_s$
	3355	3770	3401	$(OH)_s$
	3355	3753	3399	$(OH)_s$
	3355	3702	3399	$(OH)_s$
2975	2965	3045,2999	2948,2922	$(CH)_s$
2950	2951,2942	2997	2917	$(CH)_s$
2915	2915	2977	2915	$(CH)_s$
	2906	2957	2911	$(C_6H_2)_{as}$
2895	2888	2912	2880	$(C_6H_2)_{ss}$
		1531	1535	$(C_3C_4C_5)_d$,$(C_4OH)_d$
	1519	1484	1514	$(C_1C_2C_3)_d$,$(C_2OH)_d$
1480	1484	1465	1488	$(CC_1H)_d$,$(C_2OH)_d$
		1457	1474	$(HC_6H)_d$,$(C_1OH)_d$ $(C_2OH)_d$
1465	1462	1438	1467	$(HC_6H)_d$
1448	1446	1430	1452	$(CC_4H)_d$,$(CC_5H)_{ipb}$ $(C_2OH)_d$
	1426			$(C_2OH)_d$,$(C_1OH)_d$ $(CC_3H)_d$
1410	1408	1408	1410	$(CC_1H)_{ipb}$,$(C_3OH)_d$ $(C_4OH)_d$
1392	1390	1389		$(C_4OH)_d$,$(C_2OH)_d$ $(C_1OH)_d$
1380	1381	1373	1363	$(C_4OH)_d$,$(C_3OH)_d$ $(C_5OH)_d$
1365	1361	1360	1359	$(CC_3H)_{ipb}$,$(C_3OH)_d$ $(HC_1O)_d$
1353	1352	1349	1344	$(CC_2H)_{ipb}$,$(C_1OH)_d$ $(C_5OH)_d$
				$(CC_5H)_{ipb}$,$(C_4OH)_d$
1340	1338		1333	$(CC_3H)_{ipb}$,$(C_4OH)_d$ $(C_2OH)_d$,$(HC_1O)_d$
		1321	1331	$(CC_6H)_{ipb}$,$(C_4OH)_d$ $(HC_1O)_d$,$(HC_2O)_d$ $(HC_3O)_d$
1308	1330	1296	1284	$(C_6C_5H)_{opb}$,$(C_3OH)_d$ $(HC_4O)_d$
1270	1289,1282	1276	1277	$(CC_5H)_{opb}$,$(CC_2H)_{opb}$ $(HC_4O)_d$,$(HC_3O)_d$
1250	1264,1260	1259,1239	1244	$(CC_2H)_{opb}$,$(CC_4H)_{opb}$ $(HC_3O)_d$,$(HC_6O)_d$

(continued)

Table 3. Continued

Expt.[38]	Valence FF[38]	K2-BVWN	VSCF calc.	assignment
1223		1210		$(CC_1H)_{opb}$,$(CC_2H)_{opb}$ $(CC_3H)_{opb}$ $(CC_4H)_{opb}$
1200	1183	1184	1207	$(CC_1H)_{opb}$,$(CC_2H)_{opb}$ $(HC_3O)_d$,$(HC_4O)_d$
1152	1157	1155		$(HC_1O)_d$,$(HC_4O)_d$,$(C_5O_5)_d$
1128	1139	1142	1147	(CC_1H),$(CC_2H)_d$,$(CC_3H)_d$
	1121	1129,1121		$(HC_2O)_d$,$(HC_4O)_d$
1108	1106	1110	1109	$(C_6H_2)_{sc}$,$(O_5C_1H)_d$ $(CC_1H)_d$,$(CC_3H)_d$
	1093	1105	1084	$(C_6H_2)_{sc}$,$(O_5C_1H)_d$ $(C_2C_3)_t$,$(C_3C_4)_t$
1080	1079	1073	1073	$(HC_1O)_d$,$(C_6H_2)_{sc}$,$(C_5C_6)_t$
1065	1069	1045	1051	$(C_6H_2)_{sc}$,$(C_4O)_t$ $(HC_2O)_d$,$(HC_3O)_d$
1034	1038	1035	1038	$(C_5O)_t$,$(HC_3O)_d$
		1018	1027	$(C_4C_5O)_d$,$(HC_2O)_d$
1012	1001	1009	1004	$(C_2C_3)_t$, $(HC_2O)_d$
980	981		977	all CCH_t, $(C_3C_4)_t$
960	961		961	$(CC_1H)_t$,$(CC_2H)_t$ $(CC_4H)_t$
			959	$(C_2O)_t$,$(C_6H_2)_{tw}$ $(C_5C_6)_t$
913	920	918	932, 924	$(C_6O)_t$, $(O_5C_1)_{asring}$,
900	886		908	$(O_5C_1)_{asring}$,$(CC_1H)_t$
735	743	670	843	$(O_5C_1C_2)_t$,$(C_6H_2)_{sc}$
636	637,611	623	647	$(O_6H)_{opd}$,$(O_5H)_{opd}$ $(O_3H)_{opd}$
592	593	597	599	$(CCO_1)_{opd}$,$(CCO_2)_{opd}$ $(CCO_3)_{opd}$
580	580	567	570	$(CCO_1)_{opd}$,$(CCO_4)_{opd}$
550	541	553	563	$(CCO_1)_{opd}$,$(CCO_2)_{opd}$ $(CCO_4)_{opd}$
			533	ring distortion
517	517		506	ring distortions
		479	490,476	ring distortions,$(O_3H)_{opd}$ $(O_4H)_{opd}$
457	450	441,430	464	ring distortions
425	427	422	394	ring distortions

s = stretch, as = asymmetric stretch, ss = symmetric stretch, d = distortion, ipb = in plane bend, opb = out of plane bend, tw = twist, t = torsion, sc = scissors, opd = out of plane distortion

Table 4. Comparison of calculated and experimental vibrational frequencies of α-D-mannopyranose (cm^{-1}).

Expt.[39]	K2-BVWN	VSCF calculations	assignment
3500	3809	3412	$(OH)_s$
	3778	3403	$(OH)_s$
	3760	3401	$(OH)_s$
	3738	3399	$(OH)_s$
3200	3699	3398	$(OH)_s$
3000	3050,3040	2948,2920	$(CH)_s$
	3022	2917	$(CH)_s$
	3011,3004	2916,2915	$(CH)_s$
	2994	2910	$(C_6H_2)_{as}$
2800	2979	2880	$(C_6H_2)_{ss}$
	1529	1531	$(C_3C_4C_5)_d$,$(C_4OH)_d$
	1483	1503	$(C_1C_2C_3)_d$,$(C_2OH)_d$
1486	1473	1481	$(CC_1H)_d$,$(C_2OH)_d$
1460	1455	1474	$(HC_6H)_d$,$(C_3OH)_d$,$(C_1OH)_d$
1448	1445	1464	$(HC_6H)_d$,$(CC_4H)_d$,$(C_3OH)_d$
1443	1428	1431	$(CC_4H)_d$,$(C_3OH)_d$
1425	1408	1430	$(CC_1H)_{ipb}$,$(C_3OH)_d$
1395	1395	1372	$(CC_1H)_{ipb}$,$(C_2OH)_d$
1386	1381		$(CC_2H)_{ipb}$, $(CC_3H)_{ipb}$ $(CC_5H)_{ipb}$,$(HC_4)_d$
1373	1366	1361	$(CC_2H)_{ipb}$,$(C_3OH)_d$,$(C_4OH)_d$
1343,1327	1348	1347	$(CC_3H)_{ipb}$,$(C_4OH)_d$ $(C_2OH)_d$,$(HC_1O)_d$
1313	1319	1332	$(CC_6H)_{ipb}$,$(C_4OH)_d$ $(HC_1O)_d$, $(CC_1H)_{ipb}$,$(HC_2O)_d$ $(HC_3O)_d$
1299	1287	1295	$(C_6C_5H)_{opb}$,$(C_3OH)_d$,$(HC_4O)_d$
1282	1271	1275	$(C_1OH)_d$,$(HC_2O)_d$,$(C_3OH)_d$
1272	1258	1270	$(CC_5H)_{opb}$,$(CC_2H)_{opb}$ $(HC_4O)_d$,$(HC_3O)_d$
1254	1253	1256	$(CC_2H)_{opb}$,$(CC_4H)_{opb}$,$(HC_3O)_d$
1237	1233		$(CC_1H)_{opb}$,$(CC_3H)_{opb}$,$(HC_1O)_d$
1222	1222	1224	$(CC_1H)_{opb}$,$(CC_2H)_{opb}$ $(HC_3O)_d$,$(HC_4O)_d$
1216, 1205 1193		1203	$(CC_2H)_{opb}$,$(HC_3O)_d$,$(HC_4O)_d$
1169	1155		$(HC_3O)_d$,$(CC_4H)_{opb}$,$(CC_5H)_{opb}$
1138	1147		$(CC_1H)_d$,$(CC_2H)_d$,$(CC_3H)_d$
1130	1129		$(CC_5H)_d$

(continued)

Table 4. Continued

Expt.[39]	K2-BVWN	VSCF calculations	assignment
1112	1122	1116	$(O_5C_5H)_d$,$(O_5C_1H)_d$
1105	1107		$(O_5C_5H)_d$,$(O_5C_1H)_d$,$(HC_3O)_d$ $(HC_4O)_d$
1085	1097	1094	$(O_5C_5H)_d$,$(O_5C_1H)_d$,$(HC_3O)_d$
1072,1066	1072,66	1064	$(C_2C_3)_t$,$(C_3C_4)_t$,$(C_4C_5)_t$,$(HC_3O)_d$
1040	1042	1042	$(C_6H_2)_{sc}$,$(C_4O)_t$ $(HC_2O)_d$,$(HC_3O)_d$
1022		1036	$(C_5C_6)_t$,$(HC_2O)_d$
1015	1012	1021,1001	$(HC_1C_2)_t$,$(C_3C_4)_t$,all CCH_t
971		984,975	all CCH_t, $(C_3C_4)_t$
959	954	954	$(C_5C_6)_t$,$(CC_1H)_t$,$(CC_2H)_t$
912	918	918	$(C_6O)_t$, $(O_5C_1)_{asring}$,$(C_6H_2)_{tw}$
883	873	885	$(C_6H_2)_{sc}$,$(C_1O)_t$,$(C_3O)_t$
844		843	$(C_6H_2)_{sc}$,$(C_2O)_t$,$(C_3O)_t$
813,807	815	801	$(O_5C_1C_2)_t$,all $(CO)_t$
698	692		$(O_5C_5)_{asring}$,all $(CO)_t$
667	600	636	$(O_5C_1)_{asring}$
626	563	628	$(O_4H)_{opb}$, $(O_6H)_{opb}$
602	527	565	$(O_1H)_{opb}$, $(O_3H)_{opb}$, $(O_4H)_{opb}$
565	520	562	$(O_2H)_{opb}$, $(O_3H)_{opb}$,$(O_4H)_{opb}$
523	490,484	550	$(O_2H)_{opb}$, $(O_3H)_{opb}$
500	455	546,520	$(O_3H)_{opb}$,$(O_2H)_{opb}$,ring distortions
466	446	516	$(O_2H)_{opb}$

s = stretch, as = asymmetric stretch, ss = symmetric stretch, d = distortion, ipb = in plane bend, opb = out of plane bend, tw = twist, t = torsion, sc = scissors, opd = out of plane distortion

ring. In our calculations, we do see a very characteristic CH_2 twisting motion at 946 (α), 959 cm^{-1} (β-glucopyranose) and 918 α, β-mannopyranose. Experimentally, Korolevich et al.[38] calculated this twist to lie at 934 cm^{-1} for α-glucopyranose. While the density functional method (K2-BVWN) was not able to reproduce the frequency of the CH_2 twist for β-D-glucopyranose, it was in reasonable agreement with the VSCF and experimental frequencies for the other sugars studied.

The molecular skeleton deformations involving the $(C_2C_1)_t$ occur around 775 (α), 735 (β-glucopryanose) to 800 cm^{-1}(α,β-mannopyranose).[37] In the case of glucopyranose, the VSCF method overestimates this mode by 100 cm^{-1}, while the K2-BVWN method underestimates it by as much as 65 cm^{-1}. However, in the case of D-mannopyranose,

Table 5. Comparison of calculated and experimental vibrational frequencies of β-D-mannopyranose (cm^{-1}).

Expt.[39]	K2-BVWN	VSCF calculations	assignment
3500	3810	3412	$(OH)_s$
	3779	3401	$(OH)_s$
	3753	3399	$(OH)_s$
	3742	3399	$(OH)_s$
3200	3712	3396	$(OH)_s$
3000	3037,3015	2949,2921	$(CH)_s$
	2993	2917	$(CH)_s$
	2985,2966	2916,2915	$(CH)_s$
	2938	2910	$(C_6H_2)_{as}$
2800	2924	2880	$(C_6H_2)_{ss}$
	1529	1528	$(C_3C_4C_5)_d$,$(C_4OH)_d$
	1483	1506	$(C_1C_2C_3)_d$,$(C_2OH)_d$
1486	1476	1476	$(HC_6H)_d$,$(CC_1H)_d$,$(C_2OH)_d$
1467	1462	1469	$(C_1OH)_d$,$(C_2OH)_d$,$(C_3OH)_d$
1440	1443	1459	$(HC_6H)_d$,$(CC_4H)_d$,$(C_3OH)_d$
1435	1418	1423	$(CC_5H)_d$,$(C_2OH)_d$
1422	1408	1411	$(CC_5H)_{ipb}$,$(C_3OH)_d$,$(C_4OH)_d$
~1400	1397	1366	$(CC_1H)_{ipb}$,$(C_2OH)_d$
1380	1383		$(CC_2H)_{ipb}$, $(CC_3H)_{ipb}$,$(C_4OH)_d$
			$(CC_5H)_{ipb}$,$(HC_4)_d$
1372	1360	1362	$(CC_2H)_{ipb}$,$(C_3OH)_d$,$(C_4OH)_d$
1338,1322	1347	1341,1334	$(CC_4H)_{ipb}$,$(CC_1H)_{ipb}$,$(HC_1O)_d$
1309	1311	1334	$(CC_6H)_{ipb}$,$(C_4OH)_d$
			$(CC_4H)_{ipb}$,$(HC_3O)_d$
1292	1293	1293	$(C_2OH)_d$,$(C_3OH)_d$,$(HC_4O)_d$
1282	1277	1288	$(C_1OH)_d$,$(HC_2O)_d$,$(C_3OH)_d$
1261	1260		$(CC_5H)_{opb}$,$(CC_2H)_{opb}$
			$(HC_6O)_d$,$(HC_3O)_d$
1253	1246	1252	$(CH_2)_t$,$(CC_2H)_{opb}$,$(CC_1H)_{opb}$
			$(HC_3O)_d$
1239,1233	1244		$(CC_1H)_{opb}$,$(CC_3H)_{opb}$,$(HC_1O)_d$
1212	1214	1201	$(CC_1H)_{opb}$,$(CC_2H)_{opb}$
			$(HC_3O)_d$,$(HC_4O)_d$
1171	1181	1195	$(CC_1H)_{opb}$, $(CC_4H)_{opb}$
1147	1150		$(HC_3O)_d$,$(HC_2O)_d$,$(CC_1H)_{opb}$
			$(CC_5H)_{opb}$
1127,1121	1141		$(CC_1H)_d$,$(CC_2H)_d$,$(CC_3H)_d$
1116	1132		$(CC_1H)_d$,$(CC_4H)_d$
1111	1110	1112	$(C_6H_2)_{sc}$,$(O_5C_1H)_d$,$(CC_4H)_d$

(continued)

Table 5. Continued

Expt.[39]	K2-BVWN	VSCF calculations	assignment
1103	1104		$(C_6H_2)_{sc}$,$(O_5C_1H)_d$,$(HC_4O)_d$
1088	1087	1081	$(C_6H_2)_{sc}$,$(O_5C_1H)_d$,$(C_1C_2)_t$ $(C_4C_5)_t$
1072	1074	1071	$(C_6H_2)_{sc}$,$(C_3C_4)_t$,$(C_4C_5)_t$ $(HC_3O)_d$
1059	1046	1058	$(HC_1O)_d$,$(HC_2O)_d$,$(HC_4O)_d$ $(HC_6O)_d$
1044			
1035	1023	1036	$(C_5O_5)_t$,$(HC_1O)_d$
1010		1013,1015	$(C_3C_4)_t$, $(C_2C_3)_t$,all CCH_t
998		993	all CCH_t, $(C_2C_3)_t$
973		974	$(C_2C_3C_4)_d$
942	939	959	$(C_5C_6)_t$,$(CC_1H)_t$,$(CC_2H)_t$
934	910	918	$(C_6O)_t$, $(O_5C_1)_{asring}$,$(C_6H_2)_{tw}$
899,892	877	891	$(HC_1O)_t$,$(HC_2O)_t$
862,855		843	$(C_6H_2)_{sc}$,$(O_5C_1C_2)_t$
809	795	802	$(O_5C_1C_2)_t$, all $(CO)_t$
771	692		$(O_5C_5)_{asring}$,$(O_2H)_{opb}$
735			
688	646	638	$(O_5C_1)_{ssring}$,$(O_1H)_{opb}$, $(O_2H)_{opb}$
624	551,540	610	$(O_4H)_{opb}$
603		592,555	ring distortion
556		541	$(O_1H)_{opb}$, $(O_2H)_{opb}$
513	494	518	$(O_6H)_{opb}$, $(O_1H)_{opb}$,$(O_2H)_{opb}$
496	461	498,462	$(O_2H)_{opb}$,$(O_1H)_{opb}$
449	448	455	$(O_3H)_{opb}$
430	418	447	$(O_1H)_{opb}$, $(O_2H)_{opb}$
400	408		$(O_3H)_{opb}$

s = stretch, as = asymmetric stretch, ss = symmetric stretch, d = distortion, ipb = in plane bend, opb = out of plane bend, tw = twist, t = torsion, sc = scissors, opd = out of plane distortion

Table 6. Estimation of the error in the vibrational frequency calculations (cm^{-1}).[a]

Sugar	K2-BVWN	VSCF calculations
α-D-glucopyranose	6.7	4.4
β-D-glucopyranose	4.1	3.9
α-D-mannopyranose	5.9	4.1
β-D-mannopyranose	4.7	3.8

a. The estimation of the error for both methods does not include the $(OH)_s$ frequencies.

this mode poses no difficulty for either method. Below 700 cm^{-1}, the hydroxyl out-of-plane modes and the ring distortions begin to dominate. In this region of the spectrum (650 – 400 cm^{-1}), the K2-BVWN frequencies are somewhat lower than the corresponding VSCF and experimental frequencies. This could be due to the anharmonic nature of these low frequencies. Such effects are not yet accounted for in DFT-based methods. We did not attempt to assign the region below 400 cm^{-1}, and in fact the experimental assignment of D-mannopyranose below 800 cm^{-1} is quite subjective. We find however, that in general the K2-BVWN frequencies compare well to both the VSCF frequencies and experimental spectrum. Although the average errors for the K2-BVWN method are always slightly higher than those of the VSCF calculation, the general agreement of frequencies in the range between 1500 and 900 cm^{-1} is quite good. The average errors for the K2-BVWN method are highest for α-D-glucopyranose due in part to the large overestimation of the CH stretch. Below 800 cm^{-1}, the agreement between both the K2-BVWN and VSCF calculations to the experimental frequencies falls off, and is in fact poor for the $(O_5C_1C_2)_t$ modes (750 – 800 cm^{-1}). We did not attempt to assign the modes below 400 cm^{-1}.

CONCLUSION

In this paper, we begin with a study of a novel density functional method (K2-BVWN) to the calculation of the energetics and spectroscopy for both α, β-D-glucopyranose and α, β-D-mannopyranose. The K2-BVWN method signifies an advancement in density functional methods in that it mixes the HF and gradient corrected local spin density exchange using the adiabatic connection formula[33] together with the Pade-approximated Vosko, Wilk and Nusair (VWN) correlation functional.[34] This new method has two attractive features, the scaling is roughly N^3, where N is the number of basis functions, and there are only two adjustable parameters. The calculation of the vibrational frequencies in the K2-BVWN method are compared to both the VSCF calculated and experimentally measured IR frequencies. In the case of the VSCF calculation, we begin with the assumption that for many of the modes in condensed systems, we can use the near separability of the normal mode degrees of freedom to reduce the fully N-dimensional coupled Hamiltonian into N-single mode equations. We further restrict the coupling between the modes to occur in a pair-wise manner, such that a quartic expansion of the potential is realized. In previous work we have illustrated that for many modes in biological systems, this approximation is

valid.[46] This leads to N-single mode VSCF equations which are solved in a self-consistent manner.

A comparison between previous high level *ab initio* calculations and the density functional method K2-BVWN is made in order to illustrate that the present method will compare well with higher level *ab initio* methods. The advantage of the present method is that the scaling is drastically reduced making such a method attractive for larger oligosaccharide systems. In the present study, 11 low energy conformers were chosen from the previous work of Barrows et al.[9] We find that in general the relative energies of the 11 conformers do follow the same trends (Table I). As in the *ab initio* calculations, the clockwise conformers are higher in energy relative to the corresponding counterclockwise conformers. Furthermore, the relative energy difference between α/β pairs (either clockwise or counterclockwise) is roughly 0.8 kcal/mol (counterclockwise) and 1.98 kcal/mol (clockwise). This is in agreement with the *ab initio* results at the MP2/cc-pVDZ level of theory. The only difference between the two results, the K2-BVWN method would predict the G^+ conformer number 7 to be the lowest energy conformer as opposed to the G^- conformer number 8 low energy *ab initio* structure. Finally, a very rough estimation of the gas phase free energy difference between α and β-D-glucopyranose is made using the rovibrational contributions to the free energy of Barrows and co-workers.[9] We estimate the free energy of $\alpha \rightarrow \beta$ anomerization at 298 K to be roughly between 0.0 to 0.5 kcal/mol in favor of the α anomer. This would be within the *ab initio* calculated range of 0.4 kcal/mol.

We also find that in general a comparison between the VSCF and K2-BVWN frequencies is quite good in the region between 1500 and 900 cm^{-1}. The average error of the calculations compared to the experimental frequencies are slightly larger for the K2-BVWN method compared with the VSCF method. This is due in part to an overestimation of the CH stretching frequency, and an underestimation of the hydroxyl out-of-plane modes in the K2-BVWN calculation. In general we also find that the VSCF frequencies are blue shifted somewhat compared to the K2-BVWN frequencies due to the inclusion of the anharmonic and mode coupling effects in the VSCF method. At present it is not possible to include these effects into the K2-BVWN calculation.

ACKNOWLEDGMENTS

This work was supported by grants from the Department of Defense Supercomputing Center under Contracts number ARONC-1538 and ARONC-1700 to SAK. SKG would

like to gratefully acknowledge support for this work from the Sloan Foundation and the U.S. Department of Energy in the form of a postdoctoral fellowship.

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