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Calculation of NMR Chemical Shifts in Carbohydrates with ONIOM: A Study of the Conformers of *β*-D-Glucopyranose

Gail A. Rickard and Peter B. Karadakov*

Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.

Graham A. Webb

The Royal Society of Chemistry, Burlington House, Piccadily, London W1J 0BA, U.K.

Keiji Morokuma

Cherry L. Emerson Center for Scientific Computation and Department of Chemistry,
Emory University, Atlanta, Georgia 30322

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The two-layer ONIOM2(MP2-GIAO:HF-GIAO) (our own *n*-layer integrated molecular orbital and molecular mechanics approach, in which a small model system containing the nuclei of interest is described at the MP2-GIAO level of theory, and the rest of the molecule—using the HF-GIAO method) ansatz is applied to the calculation of ^{13}C, ^{1}H, and ^{17}O NMR chemical shifts in the $^4C_1$ G^+, $^4C_1$ G^-, $^4C_1$ T, $^1C_4$ G^+, and $^1C_4$ G^- conformers of β-D-glucopyranose. It is shown that with an appropriate choice of the model system this construction yields chemical shifts that represent close approximations to the corresponding MP2-GIAO values for the entire molecule, which makes it suitable for post-HF NMR chemical shift calculations on higher carbohydrates. The best correlations between experimental and theoretical ^{13}C chemical shifts are achieved using the results of the calculations on the $^4C_1$ G^+ and $^4C_1$ G^- conformers, which is in agreement with the experimental evidence about the predominance of these two forms in aqueous solution.

1. Introduction

NMR is one of the most important experimental tools for the study of carbohydrates. These molecules can assume a large variety of possible conformations, most of which incorporate extensive hydrogen bonding and are influenced by various long-range interactions. Much of this structural information is available within their ^{13}C, ^{1}H, and ^{17}O NMR spectra, but its extraction can prove to be far from straightforward. The assignment of the usually complicated NMR spectra of carbohydrates can be facilitated considerably by the establishment of structure−spectrum relationships through the use of theoretical approaches allowing the accurate calculation of NMR chemical shifts.

In most cases, the ^{13}C and proton chemical shieldings can be calculated with sufficient accuracy using the standard Hartree−Fock approach with gauge-including atomic orbitals (HF-GIAO) in combination with carefully chosen atomic basis sets. As a rule, the ^{17}O chemical shieldings require a higher level of theory. For example, Gauss and Stanton have demonstrated,[1] through a series of calculations on an isolated H_2O molecule using the HF-GIAO, MP2-GIAO, MP3-GIAO, MP4(SDQ)-GIAO (second-, third- and fourth-order Møller−Plesset perturbation theory using GIAOs in the MP4 case with the inclusion of single, double and quadruple substitutions only), CCSD-GIAO, and CCDS(T)-GIAO (coupled-cluster with singles and doubles or singles, doubles, and perturbative treatment of the triple excitations) approaches, in combination with a large basis set, that the correlation corrections to the ^{17}O HF-GIAO isotropic shielding are nonnegligible and range between about 9 and 18 ppm. Because of their high computational requirements, most of the post-HF approaches included in this list, with the exception of MP2-GIAO, are not applicable to carbohydrates. Even with the most efficient current MP2-GIAO implementation, in TURBOMOLE,[2] calculations making use of basis sets of a reasonable quality on carbohydrates larger than monosaccharides can prove to be prohibitively expensive. However, since the NMR shielding constants are predominantly local properties, it can be expected that a high-level post-HF description should be required only within the close neighborhood of a nucleus of interest whereas the remaining, normally much larger part of the molecule could be described using a simpler and more efficient technique. A recently formulated systematic treatment of this type,[3] which is based on the ONIOM (our own *n*-layer integrated molecular orbital and molecular mechanics) approach,[4] is capable of achieving sufficiently high accuracy and significant computational savings by subdividing a molecule into several layers, each of which can be described at a different level of theory. The corresponding NMR shielding tensor represents a combination of the NMR shielding tensors for the different layers.

The present paper reports the results of the first “pilot” applications of the ONIOM method to the calculation of NMR chemical shieldings in carbohydrates. We have chosen to study β-D-glucopyranose, which has become the focus of a number of recent computational studies.[5−8] This monosaccharide is sufficiently small to allow an MP2-GIAO calculation on the whole molecule within a good-quality atomic basis set and yet contains pertinent examples of the structural elements that should

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* Corresponding author. E-mail: pbk1@york.ac.uk.

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be identifiable through interpretation of the NMR spectra of carbohydrates, namely, several low-energy conformations, the differences between some of which are relatively minor, and intramolecular hydrogen bonding. We perform detailed analyses and comparisons of the results of HF-GIAO, MP2-GIAO, and ONIOM2(MP2-GIAO:HF-GIAO) NMR chemical-shielding calculations for the $^4C_1$ G^+, $^4C_1$ G^-, $^4C_1$ T, $^1C_4$ G^+, and $^1C_4$ G^- conformers of β-D-glucopyranose and provide simple guidelines about the selection of suitable model systems that should allow the reliable application of the ONIOM2(MP2-GIAO:HF-GIAO) construction to higher carbohydrates.

2. Methods

The ONIOM scheme used in the calculation of NMR parameters for β-D-glucopyranose conformers in the present paper involves two layers described at two different levels of theory, MP2-GIAO and HF-GIAO, respectively. The expression for the isotropic NMR chemical shielding of nucleus N within this two-layer approach is given by

$$\sigma_{\mathrm{iso}}^{\mathrm{N}}[\mathrm{ONIOM2(MP2\text{-}GIAO{:}HF\text{-}GIAO)}] = \sigma_{\mathrm{iso}}^{\mathrm{N}}(\mathrm{MP2\text{-}GIAO, model}) + \sigma_{\mathrm{iso}}^{\mathrm{N}}(\mathrm{HF\text{-}GIAO, real}) - \sigma_{\mathrm{iso}}^{\mathrm{N}}(\mathrm{HF\text{-}GIAO, model}) \quad (1)$$

where the “model” system corresponds to the inner, usually much smaller layer surrounding the nucleus of interest and the “real” system represents the entire molecule.

The computational work reported in this paper was performed using the ab initio packages Gaussian 98[9] and TURBOMOLE.[2] Following Cramer et al.,[5] the geometries of the five β-D-glucopyranose conformers were optimized at the MP2/cc-pVDZ level of theory within the Gaussian 98 default “frozen-core” approximation [MP2(FC)], subject to the “tight” convergence criteria. The NMR chemical-shielding calculations were carried out at the HF-GIAO/6-311++G(2d,2p) and MP2(full)-GIAO/6-311++G(2d,2p) levels of theory.

The theoretical NMR shieldings were converted to chemical shifts to enable comparison with experimental data using the expression

$$\delta^{\mathrm{N,\,theor}} = \sigma_{\mathrm{iso}}^{\mathrm{N,\,theor}}(\mathrm{ref}) - \sigma_{\mathrm{iso}}^{\mathrm{N,\,theor}} \quad (2)$$

where $\sigma_{\mathrm{iso}}^{\mathrm{N,theor}}(\mathrm{ref})$ and $\sigma_{\mathrm{iso}}^{\mathrm{N,theor}}$ stand for the calculated isotropic NMR chemical shieldings of nucleus N in a reference compound and in the molecule of interest, respectively. The reported proton and carbon chemical shifts were expressed relative to TMS, and the corresponding oxygen shifts were referenced against water. Just as in the case of the β-D-glucopyranose conformers, the chemical shieldings for the reference molecules were calculated at the MP2(full)-GIAO/6-311++G(2d,2p) and HF-GIAO/6-311++G(2d,2p) levels of theory at MP2(FC)/cc-pVDZ-optimized geometries (tight convergence criteria). The values of the ^{13}C, ^{17}O, and ^{1}H nuclear shieldings obtained for the reference compounds (in ppm) are as follows:

^{13}C: 191.43 (HF-GIAO); 195.31 (MP2-GIAO)
^{17}O: 324.00 (HF-GIAO); 342.53 (MP2-GIAO)
^{1}H: 31.65 (HF-GIAO); 31.31 (MP2-GIAO)

It should be noted that the ^{17}O MP2-GIAO value is in excellent agreement with the gas-phase absolute experimental value of 344 ± 17.2 ppm.[10]

3. Results and Discussion

The MP2/cc-pVDZ-optimized geometries of the $^4C_1$ G^+, $^4C_1$ G^-, $^4C_1$ T, $^1C_4$ G^+, and $^1C_4$ G^- conformers of β-D-glucopyranose studied in this paper are shown in Figure 1. A detailed discussion of the features of these geometries can be found in the papers by Cramer et al.[5]

To evaluate the isotropic NMR shieldings for all nuclei within the five conformers at the ONIOM2(MP2-GIAO:HF-GIAO) level of theory, it was necessary to define suitable model systems. Following the general guidelines established in ref 3, these model systems have to include the nuclei for which higher accuracy is desired, plus their immediate neighbors. To balance the computational resources needed for the calculation with the degree of accuracy required, initially we decided to restrict the sizes of the model systems to a maximum of seven heavy atoms. The six model systems chosen for the $^4C_1$ G^+ β-D-glucopyranose conformer are shown in Figure 2. Each model system represents a fragment taken out of the whole molecule without changing its geometry. Severed C−C bonds were replaced, as usual in the ONIOM approach, by C−H bonds of 1.085 Å involving “link hydrogens”. In cases where the ring oxygen turned out to be a terminal atom (see model systems M1 and M3), it was also necessary to cut through a carbon−oxygen bond and replace it with an O−H bond. This O−H bond was given a bond length of 0.963 Å, the experimental O−H bond length for methanol.[11] The replacement bonds to link hydrogens retain the directions of the original C−C and O−C bonds. The highlighted nuclei are those for which the isotropic NMR shieldings were evaluated using a particular model system.

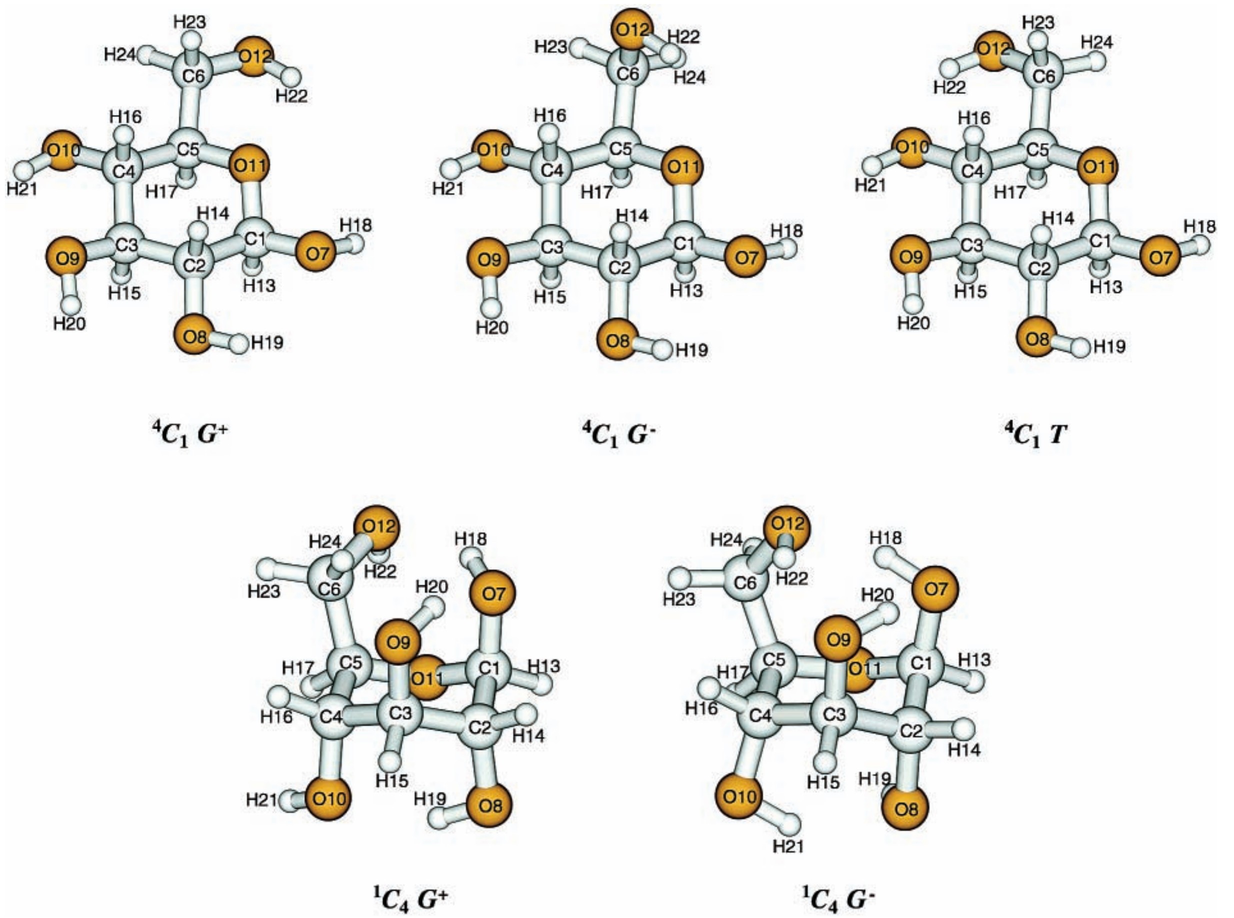
For each of the remaining four β-D-glucopyranose conformers ($^4C_1$ G^-, $^4C_1$ T, $^1C_4$ G^+, and $^1C_4$ G^-), we used six model systems, the topologies of which are identical to those of M1−M6 (see Figure 2).

3.1. Isotropic Chemical Shieldings for β-D-Glucopyranose.

3.1.1. $^4C_1$ Conformers of β-D-Glucopyranose. The geometries of the three $^4C_1$ conformers G^+, G^-, and T are very similar, with the orientation of the hydroxymethyl group the only significant variation in their structures. The atoms are numbered as in Figure 1. The absolute isotropic NMR chemical shieldings for all nuclei within these conformers calculated at the HF-GIAO/6-311++G(2d,2p) and MP2-GIAO/6-311++G(2d,2p) levels of theory for the entire molecules and using the ONIOM2(MP2-GIAO:HF-GIAO) approach are reported in Table 1.

The differences between the HF-GIAO and MP2-GIAO nuclear shieldings for all nuclei are much greater than those between the ONIOM2(MP2-GIAO:HF-GIAO) and MP2-GIAO shieldings. The largest discrepancies between the HF-GIAO and MP2-GIAO shieldings occur for the C1 nucleus (the anomeric carbon) and the ring oxygen (O11). The average MP2-level correlation effects are approximately −11 ppm for the C1 nucleus and about −15 to −14 ppm for the O11 nucleus.

The largest MP2-GIAO/ONIOM2(MP2-GIAO:HF-GIAO) separation for the carbon nuclei does not exceed 2 ppm and occurs for the C5 nucleus in each conformer. These results indicate that the ONIOM2(MP2-GIAO:HF-GIAO) approach using model systems incorporating three carbon atoms (see M1−M6 in Figure 2) provides reasonable approximations to the full MP2-GIAO shieldings for the carbon atoms in the $^4C_1$ conformers.



$^4C_1$ G^+ $^4C_1$ G^- $^4C_1$ T

$^1C_4$ G^+ $^1C_4$ G^-

Figure 1. MP2/cc-pVDZ-optimized geometries of the $^4C_1$ G^+, $^4C_1$ G^-, $^4C_1$ T, $^1C_4$ G^+, and $^1C_4$ G^- conformers of β-D-glucopyranose.

The ONIOM2(MP2-GIAO:HF-GIAO) shieldings for all protons are in good agreement with the MP2-GIAO values. The largest discrepancies of 0.09 ppm are observed for H21 in the $^4C_1$ G^+ and $^4C_1$ T conformers. This is not surprising, given the relatively small magnitudes of the correlation corrections to proton shieldings.

The situation regarding the oxygen atoms is more complicated. The nuclear shieldings obtained for the hydroxyl oxygens using the ONIOM2(MP2-GIAO:HF-GIAO) approach are close to the corresponding MP2-GIAO values. The largest observed difference amounts to 2.21 ppm and occurs for O12 within the $^4C_1$ G^- conformer. The model systems used for the ONIOM2(MP2-GIAO:HF-GIAO) calculations therefore appear to describe the chemical environments of these oxygens within the three $^4C_1$ conformers reasonably well.

The difficulty with the oxygen atoms becomes apparent upon examination of the ONIOM2(MP2-GIAO:HF-GIAO) shieldings for the O11 ring oxygen atom. The differences between the MP2-GIAO and ONIOM2(MP2-GIAO:HF-GIAO) shieldings are in the range of 8.19−8.41 ppm for all three conformers, with the ONIOM2(MP2-GIAO:HF-GIAO) results coming approximately halfway between their MP2-GIAO and HF-GIAO counterparts. This is an indication that model system M5 (see Figure 2) does not reproduce the chemical environment of the ring oxygen within the entire molecule sufficiently well. A careful comparison of model systems M1−M6 reveals that, whereas in model systems M1−M4 and M6 the bonds severed in order to obtain the model system are two or three bonds away from the oxygens described by each of these model systems, in model system M5 the ring oxygen is just one bond away from the severed bonds C1−C2 and C4−C5. Thus, the disruption of the environment of O11 upon separation of M5 from the whole molecule is more pronounced than the corresponding disruptions of the environments of the hydroxyl oxygens surrounded by model systems M1−M4 and M6. As one of the aims of the current investigation of the NMR properties of β-D-glucopyranose is to test the efficiency of the ONIOM2(MP2-GIAO:HF-GIAO) approach for calculating nuclear shieldings in general carbohydrate structures, it is obviously important to determine the size of the model system required to describe the environment of the ring oxygen atom with reasonable accuracy.

The two larger model systems selected to enhance the representation of the chemical environment of O11 are shown in Figure 3 (for the case of the $^4C_1$ T conformer). The improvement in the ONIOM2(MP2-GIAO:HF-GIAO) shielding following from the inclusion of the C4−O10 fragment in the model system (see model system M7) is just under 3 ppm whereas the addition of the C2−O8 fragment provides about another 4 ppm and brings the O11 ONIOM2(MP2-GIAO:HF-GIAO) shielding for model system M8 to within 1.40 ppm of the MP2-GIAO value. M7 still retains one severed bond (C1−C2) that is one bond away from the ring oxygen whereas in M8 both severed bonds (C2−C3 and C3−C4) are two bonds away from O11. Another possibility that cannot be discarded is that, despite the three-bond separations, both O8 and O10 make significant contributions to the environment of the ring oxygen (say, by polarizing bonds C4−C5 and C1−C2), which necessitates their inclusion in the model system. The size of model system M8 does not allow the ONIOM model to achieve very significant computational savings in the calculation of the isotropic shielding for the ring oxygen in β-D-glucopyranose and possibly in other monosaccharides. However, if we consider

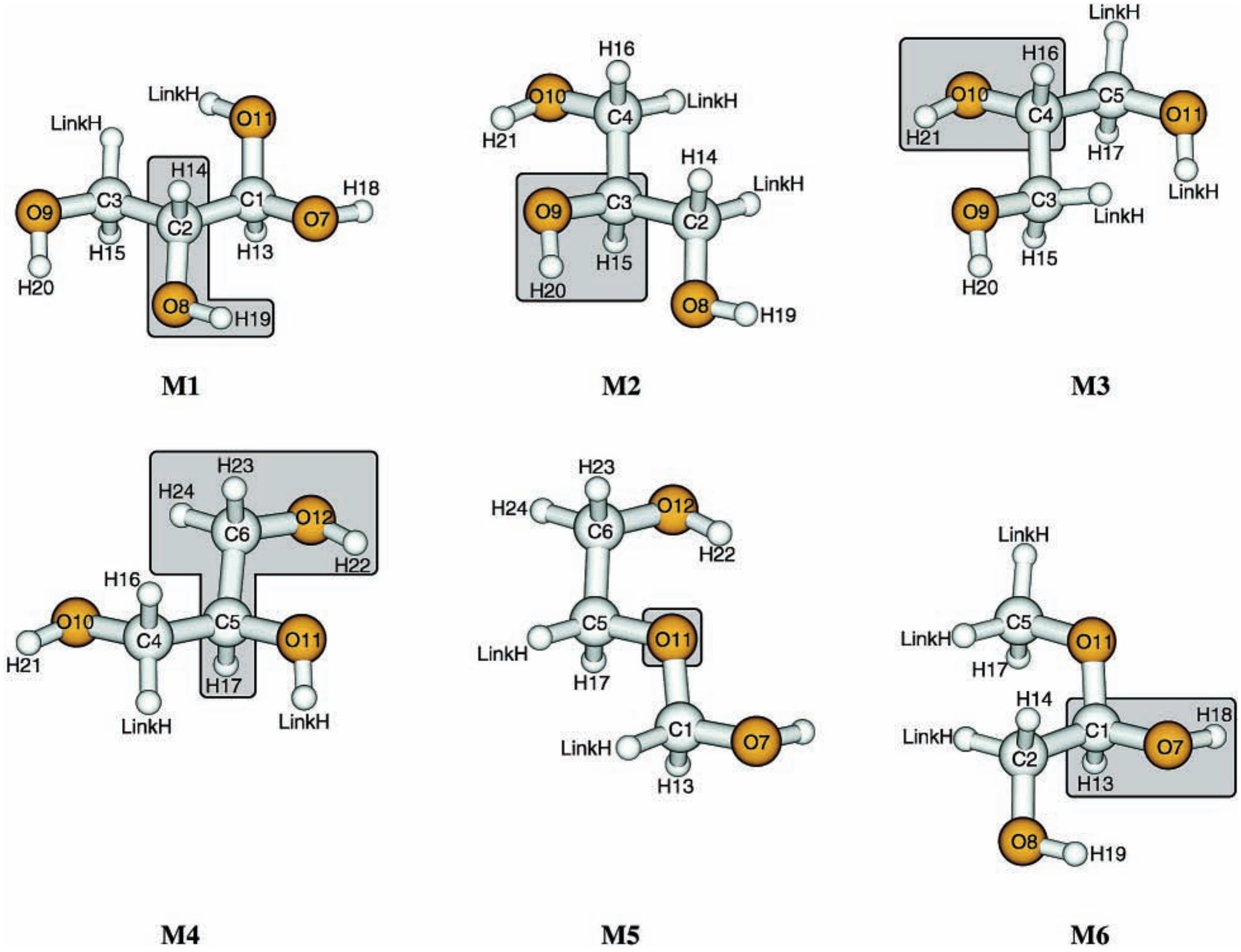


Figure 2. Six model systems used in the ONIOM2(MP2-GIAO:HF-GIAO) calculations for the $^4C_1$ G^+ β-D-glucopyranose conformer. The shaded regions highlight the nuclei for which the chemical shieldings were obtained using each model system.

TABLE 1: Isotropic NMR Chemical Shieldings (ppm) for the Nuclei within the $^4C_1$ Conformers of β-D-Glucopyranose[a]

	$^4C_1$ G^+			$^4C_1$ G^-			$^4C_1$ T		
atom	HF	MP2:HF	MP2	HF	MP2:HF	MP2	HF	MP2:HF	MP2
C1	102.89	92.38	91.97	103.06	92.70	92.19	102.93	92.43	92.03
C2	122.81	116.13	116.00	123.01	116.36	116.22	122.69	115.94	115.84
C3	121.27	115.16	114.13	121.35	115.22	114.16	121.71	115.66	114.75
C4	126.54	120.48	120.02	129.99	124.06	124.46	120.78	114.72	113.42
C5	120.42	115.03	113.30	120.74	115.71	113.68	123.87	118.76	117.07
C6	132.55	128.43	128.44	135.80	132.48	132.17	129.82	124.94	124.81
O7	267.61	270.29	269.74	267.34	270.13	269.39	267.09	269.67	268.99
O8	311.74	315.12	314.20	311.65	315.06	314.16	311.90	315.37	314.49
O9	310.17	314.39	313.68	310.09	314.36	313.56	310.76	314.99	314.68
O10	310.69	315.22	314.55	310.28	315.25	314.12	311.09	315.63	314.97
O11	261.54	254.99	246.54	263.28	256.94	248.75	261.95	256.47	248.06
O12	320.60	328.00	327.49	329.60	340.41	338.20	318.98	324.88	323.82
H13	27.64	26.85	26.81	27.62	26.81	26.75	27.65	26.86	26.82
H14	28.70	28.19	28.15	28.72	28.21	28.18	28.73	28.21	28.18
H15	28.60	27.93	27.93	28.63	27.96	27.94	28.54	27.87	27.86
H16	28.80	28.12	28.12	28.11	27.44	27.39	28.53	27.84	27.82
H17	28.63	27.98	27.98	28.89	28.20	28.17	28.69	28.01	28.01
H18	29.29	28.96	28.95	29.32	29.00	29.00	29.35	29.04	29.04
H19	29.59	29.36	29.37	29.61	29.38	29.38	29.60	29.38	29.39
H20	29.32	28.96	29.01	29.32	28.97	29.00	29.31	28.95	29.01
H21	29.45	29.11	29.20	29.45	29.15	29.17	29.04	28.68	28.77
H22	29.91	29.71	29.71	30.11	30.02	29.99	28.60	28.60	28.59
H23	28.55	27.91	27.87	28.06	27.44	27.40	28.30	27.57	27.52
H24	28.05	27.40	27.37	28.35	27.64	27.61	28.30	27.66	27.63

[a] HF, MP2:HF, and MP2 stand for HF-GIAO, ONIOM2(MP2-GIAO:HF-GIAO), and MP2-GIAO, respectively.

di-, tri-, and polysaccharides, the analogues to model system M8 would form decreasingly smaller parts of the entire molecule, making the computational requirements of the ONIOM2(MP2-GIAO:HF-GIAO) construction an insignificant fraction of those of an MP2-GIAO calculation for the whole molecule. One additional observation is that the MP2-GIAO

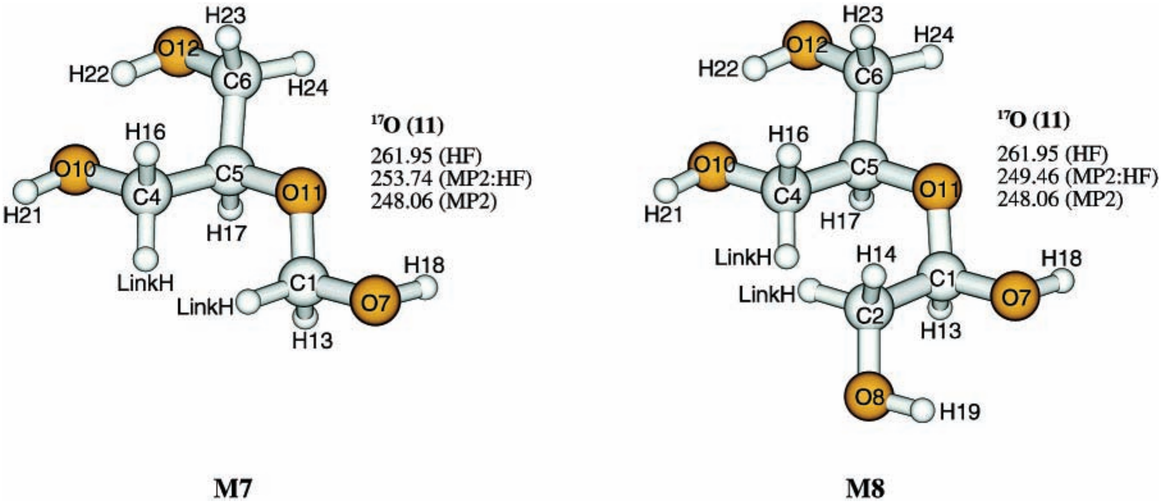


Figure 3. Two larger model systems used to provide a better approximation to the chemical environment of O11 (shown for the case of the $^4C_1$ *T* conformer).

and ONIOM2(MP2-GIAO:HF-GIAO) shieldings for O11 as well as the differences between the values obtained within the two approaches are similar for all three $^4C_1$ conformers. This suggests that it should be sufficient to perform ONIOM2(MP2-GIAO:HF-GIAO) calculations targeting the ring oxygen and using the larger model systems for one of these conformers only (we selected the $^4C_1$ *T* conformer). It is important to emphasize that, whereas it is safe to use model systems such as M8 in fixed-geometry ONIOM applications (e.g., when calculating various molecular properties), model systems of this type are very likely to prove inappropriate for ONIOM-based geometry optimizations as a consequence of the steric repulsion between the link hydrogens.

3.1.2. $^1C_4$ Conformers of *β*-D-Glucopyranose. The differences between the geometries of the $^1C_4$ G^+ and $^1C_4$ G^- conformers are much more pronounced than those observed between their $^4C_1$ counterparts. The orientations of the hydroxyl groups attached to C2 and C4 differ considerably between the two conformers, and the hydroxymethyl group rotates noticeably about the C5−C6 bond (see Figure 1, which provides the atom numbering schemes for both conformers). The absolute isotropic NMR shieldings for the nuclei within these conformers calculated at the HF-GIAO/6-311++G(2d,2p) and MP2-GIAO/6-311++G(2d,2p) levels of theory for the entire molecules as well as using ONIOM2(MP2-GIAO:HF-GIAO) constructions are reported in Table 2.

Just as in the case of the $^4C_1$ conformers, the differences between the HF-GIAO and MP2-GIAO nuclear shieldings for carbon and hydrogen nuclei are much greater than those between the corresponding ONIOM2(MP2-GIAO:HF-GIAO) and MP2-GIAO values. The largest discrepancy between HF-GIAO and MP2-GIAO carbon shieldings occurs for the C1 nucleus in both conformers, with correlation corrections of −10.69 and −10.17 ppm for the $^1C_4$ G^+ and $^1C_4$ G^- conformers, respectively. The differences between MP2-GIAO and HF-GIAO proton shieldings range from −0.86 to 0.15 ppm over the two species, with the largest variation occurring for the H13 nucleus in both conformers.

TABLE 2: Isotropic NMR Chemical Shieldings (ppm) for the Nuclei within the $^1C_4$ Conformers of *β*-D-Glucopyranose[a]

	$^1C_4$ G^+			$^1C_4$ G^-		
atom	HF	MP2:HF	MP2	HF	MP2:HF	MP2
C1	102.72	92.57	92.03	107.42	96.95	97.25
C2	130.08	124.65	124.54	129.74	124.46	124.88
C3	129.35	123.59	123.13	129.55	123.74	123.76
C4	126.78	121.20	120.97	125.93	120.37	119.22
C5	121.09	113.79	113.19	115.37	107.79	107.04
C6	134.12	130.22	129.65	130.09	125.58	126.37
O7	271.61	274.02	266.81	264.33	267.30	254.82
O8	303.65	307.74	302.48	302.19	303.33	301.41
O9	298.05	304.62	295.85	300.23	307.03	297.78
O10	283.00	288.57	285.27	282.20	288.37	279.37
O11	296.13	289.59	288.38	284.29	273.05	274.12
O12	305.16	313.39	308.34	301.13	311.35	300.35
H13	26.91	26.17	26.08	27.14	26.37	26.28
H14	28.38	27.76	27.72	28.21	27.57	27.58
H15	28.03	27.48	27.33	27.93	27.34	27.22
H16	28.30	27.61	27.53	28.42	27.81	27.76
H17	28.42	27.81	27.67	27.89	27.29	27.12
H18	26.16	26.09	25.99	24.45	24.31	24.60
H19	27.76	27.58	27.60	29.60	29.55	29.41
H20	30.98	30.76	30.78	27.35	27.14	27.10
H21	27.02	26.86	26.91	27.65	27.30	27.32
H22	30.42	30.46	30.36	27.58	27.49	27.54
H23	28.36	27.64	27.67	28.36	27.58	27.67
H24	27.75	27.23	27.07	28.22	27.72	27.74

[a] For further details, see Table 1.

In contrast to the $^4C_1$ conformers in which the pattern of MP2-GIAO correlation corrections to the HF-GIAO ^{17}O nuclear shieldings was the same for all three conformers, there are differences in the patterns exhibited by the two $^1C_4$ conformers. For the $^1C_4$ G^+ conformer, these corrections range from −7.75 to 3.18 ppm, and the nuclei that are more shielded at the MP2-GIAO level of theory are O10 and O12. In the case of the $^1C_4$ G^- conformer, the MP2-GIAO correlation corrections range from −0.78 to −10.17 ppm, and all ^{17}O nuclei are less shielded at the MP2-GIAO level of theory. Both $^1C_4$ patterns are different from that observed for the $^4C_1$ conformers, in all of which the only ^{17}O nucleus that becomes deshielded as a result of the MP2-GIAO correlation correction is O11. These variations in the ^{17}O nuclear shieldings reflect the fact that all members of the $^4C_1$ series contain just a single hydroxyl group (O12−H22), the orientation of which changes noticeably between conformers, whereas the differences between the orientations of the hydroxyl groups within the two $^1C_4$ conformers are more pronounced. It is hardly surprising to observe that the ^{17}O shieldings in the $^4C_1$ and $^1C_4$ series have very little, if anything, in common: all C−O bonds connecting hydroxyl groups to the ring are equatorially oriented in the $^4C_1$ conformers and axially oriented in the $^1C_4$ conformers, which creates very different chemical environments for the ^{17}O nuclei.

TABLE 3: NMR Chemical Shifts (ppm) for the $^4C_1$ Conformers of β-D-Glucopyranose ^{13}C and ^1H Chemical Shifts Calculated Relative to TMS and ^{17}O Chemical Shifts Relative to Water[a]

		$^4C_1$ G^+			$^4C_1$ G^-			$^4C_1$ T		
atom	exptl[12]	HF	MP2:HF	MP2	HF	MP2:HF	MP2	HF	MP2:HF	MP2
C1	96.65	88.54	102.93	103.35	88.37	102.6l	103.12	88.51	102.88	103.28
C2	74.87	68.63	79.18	79.31	68.42	78.95	79.09	68.75	79.37	79.47
C3	76.49	70.16	80.15	81.19	70.08	80.09	81.15	69.73	79.65	80.57
C4	70.33	64.89	74.83	75.29	61.45	71.25	70.85	70.66	80.59	81.90
C5	76.69	71.02	80.28	82.02	70.70	79.60	81.63	67.57	76.55	78.24
C6		58.89	66.88	66.88	55.63	62.84	63.14	61.61	70.37	70.51
O7	47.5	56.39	72.24	72.79	56.66	72.41	73.14	56.91	72.86	73.54
O8	4.3	12.25	27.41	28.33	12.35	27.47	28.37	12.10	27.16	28.04
O9	4.3	13.83	28.14	28.85	13.91	28.18	28.98	13.23	27.54	27.85
O10	4.3	13.31	27.31	27.98	13.71	27.29	28.41	12.91	26.90	27.57
O11	56.2	62.46	87.54	95.99	60.71	85.60	93.78	62.04	86.06	94.47
O12	−14.3	3.40	14.53	15.04	−5.60	2.12	4.33	5.02	17.65	18.71
H13	4.51	4.01	4.46	4.50	4.04	4.50	4.56	4.00	4.45	4.49
H14	3.11	2.96	3.12	3.16	2.93	3.10	3.13	2.93	3.10	3.13
H15	3.34	3.05	3.38	3.38	3.03	3.35	3.37	3.12	3.44	3.45
H16	3.27	2.85	3.19	3.20	3.54	3.87	3.92	3.13	3.47	3.49
H17	3.32	3.02	3.33	3.33	2.76	3.12	3.14	2.96	3.30	3.30
H18		2.37	2.35	2.37	2.34	2.31	2.31	2.30	2.27	2.27
H19		2.07	1.95	1.94	2.05	1.93	1.93	2.05	1.93	1.92
H20		2.34	2.35	2.30	2.34	2.34	2.31	2.35	2.36	2.31
H21		2.20	2.20	2.11	2.20	2.16	2.14	2.62	2.63	2.55
H22		1.75	1.60	1.60	1.55	1.29	1.32	3.06	2.71	2.72
H23		3.10	3.40	3.45	3.59	3.88	3.91	3.36	3.74	3.79
H24		3.60	3.91	3.94	3.30	3.67	3.70	3.35	3.65	3.68

[a] For further details, see Table 1.

The largest deviation of an ONIOM2(MP2-GIAO:HF-GIAO) ^{13}C shielding from the corresponding MP2-GIAO value over the two $^1C_4$ conformers amounts to 1.15 ppm. This shows that for both $^1C_4$ conformers, just as in the case of the $^4C_1$ conformers, the ONIOM2(MP2-GIAO:HF-GIAO) approach using model systems involving three carbon atoms provides very reasonable approximations to the whole-molecule MP2-GIAO results for the ^{13}C nuclei.

The ONIOM2(MP2-GIAO:HF-GIAO) shieldings for all $^1C_4$ protons are also in good agreement with the MP2-GIAO values; the largest discrepancy of 0.29 ppm is observed for H18 in the $^1C_4$ G^- conformer.

The discrepancies between the ONIOM2(MP2-GIAO:HF-GIAO) and MP2-GIAO ^{17}O shieldings for the $^1C_4$ G^+ and G^- conformers are different from those observed in the case of the $^4C_1$ conformers. All ^{17}O ONIOM2(MP2-GIAO:HF-GIAO) nuclear shieldings for the $^4C_1$ conformers are in good agreement with the MP2-GIAO values except for the ring oxygens. In contrast to this, in both $^1C_4$ conformers the ONIOM2(MP2-GIAO:HF-GIAO) ^{17}O nuclear shieldings for the O11 nucleus are in reasonable agreement with the corresponding MP2-GIAO values, but the shieldings for oxygens within the hydroxyl groups show larger deviations. This suggests that within the $^1C_4$ conformers the effect that O8 and O10 have on the chemical environment of the ring oxygen is weaker than within the representatives of the alternative chair form, $^4C_1$. In the case of the $^4C_1$ conformers, the three-carbon model systems used in the calculations of the ONIOM2(MP2-GIAO:HF-GIAO) nuclear shieldings for O7, O8, and O9 (see Figure 2) preserve the hydrogen bonds in which these atoms are engaged: all of these are hydrogen bonds involving oxygens and hydrogens from hydroxyl groups attached to neighboring carbons (O7...H19, O8....H20, O9...H21). However, the hydrogen bonds in the $^1C_4$ conformers—O7...H20, O12...H18, O10...H19 (in $^1C_4$ G^+), and O8...H21 (in $^1C_4$ G^-)—connect atoms coming from hydroxyl groups attached to non-neighboring carbons. These hydrogen bonds are not retained within the $^4C_1$ model systems with topologies identical to M1−M6 in Figure 2, which explains the relatively poor performance of the corresponding ONIOM2(MP2-GIAO:HF-GIAO) constructions in the calculation of shieldings for O7−O10 and O12.

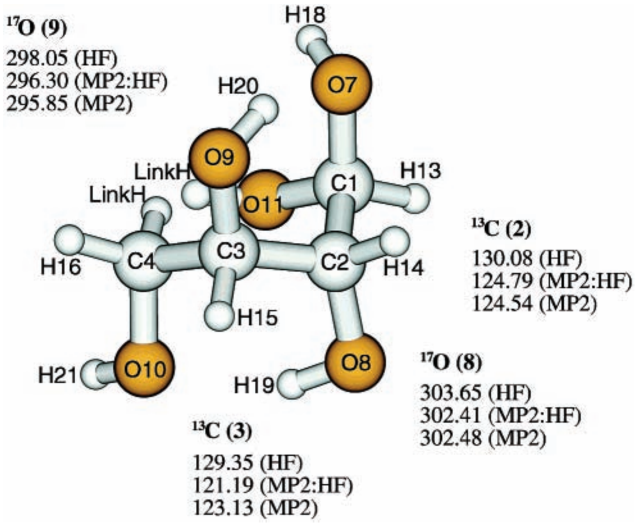


Figure 4. Enlarged model system allowing improved representations of the chemical environments of O8 and O9 in the $^1C_4$ G^+ conformer.

The quality of the ONIOM2(MP2-GIAO:HF-GIAO) results for the exocyclic oxygens in the $^1C_4$ conformers can be improved through the use of larger model systems. An example is provided by the M9 model system for the $^1C_4$ G^+ conformer displayed in Figure 4. As shown in this Figure, the use of the larger M9 model system decreases the differences between the MP2-GIAO and ONIOM2(MP2-GIAO:HF-GIAO) shieldings for O8 and O9 from 5.26 to just 0.07 ppm and from 8.77 to 0.45 ppm, respectively.

3.2. Chemical Shifts for β-D-Glucopyranose Conformers.

The theoretical chemical shifts calculated for the β-D-glucopyranose conformers are compared with the available experimental data in Tables 3 and 4. The chemical shifts for carbon nuclei predicted by the HF-GIAO method are consistently lower

TABLE 4: NMR Chemical Shifts (ppm) for the $^1C_4$ Conformers of β-D-Glucopyranose[a]

atom	exptl[12]	$^1C_4$ G^+			$^1C_4$ G^-		
		HF	MP2:HF	MP2	HF	MP2:HF	MP2
C1	96.65	88.71	102.74	103.28	84.02	98.37	98.06
C2	74.87	61.35	70.66	70.78	61.69	70.85	70.44
C3	76.49	62.09	71.72	72.19	61.88	71.57	71.55
C4	70.33	64.66	74.11	74.34	65.51	74.94	76.09
C5	76.69	70.35	81.52	82.13	76.06	87.52	88.28
C6		57.31	65.09	65.66	61.34	69.73	68.94
O7	47.5	52.38	68.51	75.72	59.67	75.23	87.71
O8	4.3	20.35	34.79	40.05	21.80	39.20	41.12
O9	4.3	25.94	37.91	46.69	23.77	35.50	44.76
O10	4.3	41.00	53.96	57.26	41.79	54.16	63.17
O11	56.2	27.87	52.94	54.15	39.71	69.48	68.41
O12	−14.3	18.83	29.14	34.19	22.86	31.18	42.19
H13	4.51	4.74	5.14	5.24	4.51	4.94	5.03
H14	3.11	3.28	3.55	3.59	3.44	3.74	3.73
H15	3.34	3.62	3.83	3.98	3.73	3.97	4.09
H16	3.27	3.36	3.70	3.78	3.23	3.50	3.55
H17	3.32	3.23	3.50	3.64	3.76	4.02	4.19
H18		5.49	5.22	5.32	7.20	7.00	6.72
H19		3.89	3.73	3.71	2.05	1.76	1.90
H20		0.67	0.55	0.53	4.31	4.17	4.21
H21		4.64	4.45	4.40	4.00	4.01	3.99
H22		1.24	0.85	0.95	4.07	3.82	3.77
H23		3.30	3.67	3.64	3.30	3.73	3.65
H24		3.91	4.08	4.24	3.44	3.59	3.57

[a] For further details, see Tables 1 and 3.

TABLE 5: Linear Regression ($y = ax + b$) Analysis of the Correlation between Experimental (x Values) and Theoretical (y Values) ^{13}C Chemical Shifts for the Conformers of β-D-Glucopyranose

conformer	method	slope (a)	intercept (b)	R^2
$^4C_1$ G^+	HF	0.901	1.443	0.999
	ONIOM2(MP2:HF)	1.088	−2.458	0.997
	MP2	1.078	−0.977	0.999
$^4C_1$ G^-	HF	0.970	−4.860	0.984
	ONIOM2(MP2:HF)	1.155	−8.770	0.994
	MP2	1.166	−8.955	0.986
$^4C_1$ T	HF	0.800	9.835	0.874
	ONIOM2(MP2:HF)	0.987	5.816	0.873
	MP2	0.961	8.778	0.873
$^1C_4$ G^+	HF	1.039	−12.632	0.871
	ONIOM2(MP2:HF)	1.224	−16.523	0.876
	MP2	1.234	−16.991	0.875
$^1C_4$ G^-	HF	0.787	7.624	0.663
	ONIOM2(MP2:HF)	0.986	2.760	0.706
	MP2	0.949	5.899	0.658

than those observed experimentally whereas the MP2-GIAO and ONIOM2(MP2-GIAO:HF-GIAO) ^{13}C chemical shifts are consistently higher than their experimental counterparts. The fact that MP2-GIAO often overestimates the correlation corrections to isotropic shieldings and chemical shifts is well known and is reflected in Chesnut's approximate infinite-order perturbation theory prescription for estimating isotropic NMR chemical shieldings,[13] according to which the MP2-GIAO corrections should be scaled down by a factor of $^2/_3$. It should be mentioned that, according to our results, the MP2-GIAO and ONIOM2(MP2-GIAO:HF-GIAO) approaches predict the experimental proton NMR data for the $^4C_1$ conformers with greater accuracy than the HF-GIAO method.

Inspection of the theoretical carbon and proton NMR data for the five β-D-glucopyranose conformers clearly shows that the results that most closely correspond to the experimental findings are those for the $^4C_1$ G^+ and $^4C_1$ G^- species. This is consistent with the work of Nishida[14] in which the $^4C_1$ G^+ and $^4C_1$ G^- conformers were experimentally determined to coexist in a 55:45 ratio in solution. It is evident that the theoretical chemical shifts correctly predict the trends in the experimental carbon and proton NMR data. This provides additional confidence for future calculations on carbohydrate molecules for which the experimental data is not as abundant and/or accurate as that for β-D-glucopyranose.

The chemical shifts for oxygen are not in good agreement with experiment for all three of the theoretical methods that we used. One reason for this is that our calculations were performed on single molecules in the gas phase whereas the experimental measurements were carried out in solution. Additionally, the experimental data for ^{17}O were determined with lower accuracy than the carbon and proton spectra, and the assignment of the oxygen signals has not been finalized and can be changed by more-accurate future experimental studies.

Although the absolute magnitudes of the ^{17}O chemical shifts are not reproduced accurately by the theoretical methods, the trends carried by the differences between the chemical shifts for the individual oxygens are predicted reasonably well. The calculated chemical shifts once again clearly differentiate between the $^4C_1$ and $^1C_4$ conformers, allowing the $^1C_4$ conformers to be disregarded as possible structures for β-D-glucopyranose in solution.

In a recent paper,[8] Kupka et al. report theoretical ^{17}O chemical shifts for β-D-glucopyranose obtained using HF and DFT methods that appear to be in better agreement with experimental data than our results in Tables 3 and 4. However, the ^{17}O chemical shifts in ref 8 were calculated relative to liquid water in which the absolute oxygen shielding was assumed to be 308 ppm.[15] To calculate comparable ^{17}O chemical shifts, we would need to subtract $324 - 308 = 16$ ppm and $342.53 - 308 = 34.53$ ppm, respectively, from the HF-GIAO and MP2-GIAO (and ONIOM2) ^{17}O chemical shifts listed in Tables 2 and 3. If we introduce these adjustments, then our HF-GIAO ^{17}O chemical shifts become very similar to those reported by Kupka et al. whereas their DFT-GIAO ^{17}O chemical shifts fall between our HF-GIAO and MP2-GIAO values.

To investigate the correlation between the theoretical and experimental ^{13}C and ^{17}O chemical shifts in the five β-D-glucopyranose conformers in greater detail, we subjected these data to a linear regression analysis. The results are summarized in Tables 5 and 6. The best correlations observed in the ^{13}C data are between the theoretical and experimental results for the $^4C_1$ G^+ conformer ($R^2 \geq 0.997$), which are closely followed by the corresponding correlations for the $^4C_1$ G^- conformer ($R^2 \geq 0.984$). This provides further confirmation of the already mentioned experimental finding[14] that in solution the $^4C_1$ G^+ and $^4C_1$ G^- conformers coexist in a very close ratio, slightly dominated by the $^4C_1$ G^+ species. It is straightforward to verify that the ONIOM2(MP2-GIAO:HF-GIAO) and MP2-GIAO regression lines specified in Table 5 are reasonably close in the important 60−100 ppm range that includes all of the experimental ^{13}C chemical shift data available for β-D-glucopyranose. This reinforces the conclusion that the ONIOM2(MP2-GIAO:HF-GIAO) construction represents a reliable approximation to the full MP2-GIAO treatment and should therefore be applicable to the post-HF calculation of ^{13}C NMR chemical shifts for other, more complex carbohydrate molecules where use of the full MP2-GIAO approach could be too computationally demanding or even unfeasible. The high R^2 values for all three theoretical approaches in the cases of the $^4C_1$ G^+ and $^4C_1$ G^- conformers suggest that the corresponding HF-GIAO, ONIOM2(MP2-

TABLE 6: Linear Regression ($y = ax + b$) Analysis of the Correlation between Experimental (x Values) and Theoretical (y Values) ^{17}O Chemical Shifts for the Conformers of β-D-Glucopyranose[a]

conformer	method	slope (a)	intercept (b)	R^2
$^4C_1$ G^+	HF	0.904	11.524	0.987
	ONIOM2(MP2:HF)	1.047	25.011	0.988
	MP2	1.124	25.670	0.974
$^4C_1$ G^-	HF	0.959	8.943	0.997
	ONIOM2(MP2:HF)	1.128	21.285	0.995
	MP2	1.188	22.580	0.990
$^4C_1$ T	HF	0.895	11.779	0.979
	ONIOM2(MP2:HF)	1.016	25.702	0.981
	ONIOM2(MP2:HF)[b]	1.086	25.680	0.969
	MP2	1.091	26.434	0.966
$^1C_4$ G^+	HF	0.250	26.798	0.288
	ONIOM2(MP2:HF)	0.414	39.136	0.618
	MP2	0.386	44.761	0.542
$^1C_4$ G^-	HF	0.392	28.251	0.537
	ONIOM2(MP2:HF)	0.608	40.426	0.850
	MP2	0.541	48.669	0.666

[a] Unless stated otherwise, the ONIOM2 results make use of the M1−M6 model systems. [b] ONIOM results making use of the larger model system M8 for the ring oxygen.

GIAO:HF-GIAO), and MP2-GIAO regression lines should predict very much the same value for the unavailable experimental C6 chemical shift. Indeed, the three $^4C_1$ G^+ regression lines yield 63.76 ppm (HF), 63.73 ppm (ONIOM2), and 62.95 ppm (MP2). This shows that for many carbohydrate molecules a regression line relating several HF-GIAO and experimental ^{13}C chemical shifts and characterized by a high coefficient of determination could prove sufficient for obtaining good estimates of any missing experimental ^{13}C chemical shifts for the same molecule.

The correlations between the theoretical and experimental ^{17}O chemical shifts (see Table 6) are not as good as in the case of the carbon data. The results for the $^1C_4$ conformers, especially those obtained at the HF-GIAO level of theory, are characterized by particularly low coefficients of determination. The R^2 values for all three $^4C_1$ conformers are rather similar, which indicates that the ^{17}O NMR data is less selective and does not discount the possible presence of the $^4C_1$ T conformer in a solution of β-D-glucopyranose.

The agreement between the ONIOM2(MP2-GIAO:HF-GIAO) and MP2-GIAO ^{17}O chemical shifts is not as close as in the case of the corresponding ^{13}C results. This is reflected by the larger differences in the slopes of the regression lines in Table 6 and is due to the insufficient accuracy of the value for the chemical shift of the ring oxygen calculated using an ONIOM2(MP2-GIAO:HF-GIAO) construction involving the three-carbon model system M5. Reevaluation of the O11 chemical shift by means of an ONIOM2(MP2-GIAO:HF-GIAO) scheme incorporating the larger model system M8 (see the additional ONIOM2 results for the $^4C_1$ T conformer) leads to a considerable reduction in the difference between the slopes of the ONIOM2(MP2-GIAO:HF-GIAO) and MP2-GIAO regression lines.

4. Conclusions

We have shown that the ONIOM2(MP2-GIAO:HF-GIAO) approach is capable of providing NMR isotropic chemical shieldings for all nuclei in the most important β-D-glucopyranose conformers, which are in very good agreement with the corresponding results coming from whole-molecule MP2-GIAO treatments. The ONIOM approach can therefore be regarded as a relatively inexpensive and efficient way of including MP2-level correlation effects in the calculation of NMR chemical shielding constants for larger carbohydrate molecules, for which the computational effort required by a full MP2-GIAO calculation can be prohibitively high.

The choice of model systems that adequately represent the chemical environments of the nuclei of interest within the whole molecule remains the crucial step in the construction of the ONIOM model for calculating nuclear shieldings. The results for the β-D-glucopyranose conformers show that acceptable agreement between the ONIOM2(MP2-GIAO:HF-GIAO) and whole-molecule MP2-GIAO shieldings for the carbon and hydrogen nuclei can be achieved through the use of relatively small model systems, each of which contains three carbon atoms only. The choice of model systems surrounding ^{17}O nuclei requires greater care. In general, if we are dealing with equatorial exocyclic oxygens, our results show that model systems with three carbon atoms provide reasonable approximations to their chemical environments and, consequently, ensure good agreement with the full MP2-GIAO nuclear shieldings. If the exocyclic oxygens are in axial positions, then larger model systems such as M9 are required to account for possible 1,3-diaxial interactions. The situation regarding the ring oxygen in pyranose rings proves to be dependent on the conformation of the ring and the relative positions of the substituents. Large model systems (e.g., M8) are required to produce reasonable agreement between the ONIOM2(MP2-GIAO:HF-GIAO) and full MP2-GIAO nuclear shieldings for the ring oxygen in the $^4C_1$ β-D-glucopyranose conformers whereas the small M5 model systems prove to be adequate for the $^1C_4$ β-D-glucopyranose conformers. As a general rule, when choosing a model system surrounding an oxygen atom participating in an intramolecular hydrogen bond, it is important to make sure that this bond is preserved. The model systems discussed in the present paper should be particularly useful in ONIOM-style calculations on di-, tri-, and polysaccharides in which even the largest model systems we have defined (M8, M9) would represent relatively small parts of the entire carbohydrate and ONIOM can become the only way of obtaining MP2-level chemical shieldings using present-day computational facilities and ab initio packages.

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Note Added after ASAP Posting

This article was released ASAP on 12/18/2002 with an error in Tables 1 and 3. In the footnote of Table 1, ONIOM2(MP2-GIAO) was corrected to ONIOM2(MP2-GIAO:HF-GIAO). In Table 3, row C1, column MP2:HF, under heading $^4C_1$ G^-, data was corrected from 102.16 to 102.61. The corrected version was posted on 12/27/2002.

References and Notes

(1) Gauss, J. *Chem. Phys. Lett.* **1994**, *229*, 198. Gauss J.; Stanton, J. *J. Chem. Phys.* **1995**, *103*, 3561. Gauss, J.; Stanton J. *J. Chem. Phys.* **1996**, *104*, 2574.

(2) Ahlrichs, R.; Bär, M.; Baron, H.-P.; Bauernschmitt, R.; Böcker, S.; Ehrig, M.; Eichkorn, K.; Elliott, S.; Furche, F.; Haase, F.; Häser, M.; Horn, H.; Huber, C.; Huniar, U.; Kollwitz, C. K. M.; Ochsenfeld, C.; Öhm, H.; Schäfer, A.; Schneider, U.; Treutler, O.; von Arnim, M.; Weigend, F.; Weis, P.; Weis, H. *TURBOMOLE,* version 5.1; program package for ab initio electronic structure calculations; Quantum Chemistry Group, University of Karlsruhe: Karlsruhe, Germany, 1999.

(3) Karadakov, P. B.; Morokuma, K. *Chem. Phys. Lett.* **2000**, *317*, 589.

(4) Svensson, M.; Humbel, S.; Froese, R. D. J.; Matsubara, T.; Sieber, S.; Morokuma, K. *J. Phys. Chem.* **1996**, *100*, 19357. Humbel, S.; Sieber, S.; Morokuma, K. *J. Chem. Phys.* **1996**, *105*, 1959.

(5) Barrows, S. E.; Dulles, F. J.; Cramer, C. J.; French, A. D.; Truhlar, D. G. *Carbohydr. Res.* **1995**, *276*, 219. Barrows, S. E.; Storer, J. W.; Cramer, C. J.; French, A. D.; Truhlar, D. G. *J. Comput. Chem.* **1998**, *19*, 1111.

(6) Csonka, G. I.; Éliás, K. I.; Csizmadia, G. *Chem. Phys. Lett.* **1996**, *257*, 49.

(7) Wladkowski, B. D.; Chenoweth, S. A.; Jones, K. E.; Brown, J. W. *J. Phys. Chem. A* **1998**, *102*, 5086.

(8) Kupka, T.; Pasterna, G.; Lodowski, P.; Szeja, W. *Magn. Reson. Chem.* **1999**, *37*, 421.

(9) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(10) Wasylishen, R. E.; Mooibroek, S.; Macdonald, J. B. *J. Chem. Phys.* **1984**, *81*, 1057.

(11) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; p 157.

(12) Hobley, P.; Howarth, O.; Ibbett. R. N. *Magn. Reson. Chem.* **1996**, *34*, 755. Schulte, J.; Lauterwein, J. *Magn. Reson. Chem.* **1996**, *34*, 527.

(13) Chesnut, D. B. *Chem. Phys. Lett.* **1995**, *246*, 235.

(14) Nishida, Y.; Ohrui, H.; Meguro, H. *Tetrahedron Lett.* **1984**, *25*, 1575.

(15) Ruud, K.; Helgaker, T.; Kobayashi, R.; Jorgensen, P.; Bak, K. L.; Jensen, H. J. A. *J. Chem. Phys.* **1994**, *100*, 8178.