

The Optical Rotation of Glucose Prototypes: A Local or a Global Property?

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Abstract: In this work, we present a quantum-mechanical study of the optical rotation (OR) of model systems representing glucose prototypes with one and two chiral centers. The ONIOM method is used to evaluate the property and to analyze its local or global character. Different ONIOM partitions are tested and compared to better appreciate differences and similarities between mono- and bichiral prototypes. The local versus global character of OR is investigated and compared to other properties such as energies and nuclear magnetic shieldings, which have been deeply studied in previous applications of the ONIOM method.

1. Introduction

Optical rotation (OR) plays a significant role in carbohydrate research. Both the high number of chiral centers present in these compounds and the relative ease of experimentally obtaining the OR values have been important factors. While in the sugar industry the OR facilitates an efficient way to measure concentrations, the scientific community has especially employed the relationship between OR and the compound's structure.^{1–10}

However, the development of theoretical [and especially quantum-mechanical (QM)] methods for the prediction of OR, from which carbohydrate research could greatly benefit, is quite difficult for different reasons. First of all, we have to consider the difficulty involved in the QM calculation of the optical rotation. Only in recent years have advances in the field of theoretical chemistry led to the development of new computational approaches for calculating OR at different levels of accuracy, including methods such as the Hartree–Fock (HF),¹¹ density functional theory,¹² and coupled cluster.¹³ This development of the theoretical background has been followed by a large number of papers using theoretical approaches,^{14–19} possibly including the effect of the solvent,^{20,21} to elucidate the factors that determine OR.

Generally, these studies have been limited to chiral systems with a single chiral center. Saccharides, on the contrary, are

systems with many chiral centers, and therefore, the complexity of the calculations is largely amplified. Additionally, such chiral centers can occur in different geometrical arrangements because saccharides present many conformations: all of these aspects make the calculation of OR for saccharides very difficult but, at the same time, a challenging test for QM approaches. Recently, we have presented a study on OR of glucose in aqueous solution showing that, indeed, QM methods can be reliably applied to the study of these kinds of systems (even including the effect of the solvent).²² Obviously, the extension to other saccharides (and especially oligosaccharides) is not straightforward. While a reliable conformational analysis is still possible using either less accurate QM approaches²³ or molecular mechanics,²⁴ the calculation of OR necessarily requires an extended QM description, and thus it becomes computationally quite demanding.

One possible approach to make accurate calculations on such kinds of systems feasible is the use of hybrid or layered methods. These methods partition the system into regions, each of them treated with a different level of accuracy. The justification for this approach is that the various parts of the system contribute to the property we are interested in, in different ways, and therefore they require different computational levels. A powerful version of this kind of approach is the ONIOM (our own n-layered integrated molecular orbital) method.²⁵ Over the years, ONIOM has been used to predict energies and geometries of a large number of

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chemical systems,²⁶ also involving solvent effects.²⁷ In addition, it has been successfully applied in the prediction of various molecular properties such as nuclear magnetic resonance (NMR) shieldings.²⁸

These previous studies suggest that ONIOM works well if the properties to be calculated are principally determined locally, that is, by a small part of a large system, with some corrections from the rest of the system. However, when the property is global, that is, the whole system largely contributes to its final value, ONIOM can still be used but in a different way. In these cases, only relative values can be reliably obtained, such as, for example, energy differences among different conformers or activation free energies.

Motivated by these results, an ONIOM procedure has been tried here to investigate two different but related aspects of optical rotation, one concerning its nature and the other its calculation. In particular, for the first time, the character of OR as a global or a local property is analyzed, and ONIOM is tested as a potential method to simulate OR in saccharide-like systems. If this would be the case in fact, it could represent an extremely useful tool to validate the structures selected by sampling potential energy surfaces.

The general ONIOM strategy, however, requires reconsideration in some aspects when applied to the calculation of OR in saccharide-like systems. In fact, because of the presence of multiple chiral centers, the preliminary identification of the part of the system which most contributes to the property required by any layered approach is not only not univocal but also questionable. In the following sections, the optical rotation of model systems representing glucose prototypes with one and two chiral centers are thus introduced, and different ONIOM partitions are tested and compared to better appreciate differences and similarities between the two classes of prototypes.

The paper is organized as follows: In section 2, we define the monochiral and bichiral prototypes studied and the ONIOM partition used, while in section 3, the calibration of the ONIOM method is performed in order to define the proper high and low levels of calculations. In section 4, the chosen ONIOM partitions and levels are applied to the calculation of the OR of the mono- and bichiral systems and the results compared with the high-level benchmarks. In section 5, two further ONIOM calculations of energy differences about the α and β anomers and NMR nuclear shieldings are presented and compared with the previous ones on OR to rationalize the results in terms of global and local character of the property. Finally, in section 6, some conclusive comments are reported.

2. The Definition of the Chiral Systems

In this study, we introduce simplified monosaccharide model systems, derived from glucose but with just one or two adjacent chiral centers; in the following, we shall refer to these systems as prototypes. By studying these simplified systems in which we have eliminated any conformational freedom (each prototype is considered as a rigid system) and reduced the number of chiral centers, we can simplify the analysis but still keep the same main structural and electronic aspects of the real systems.

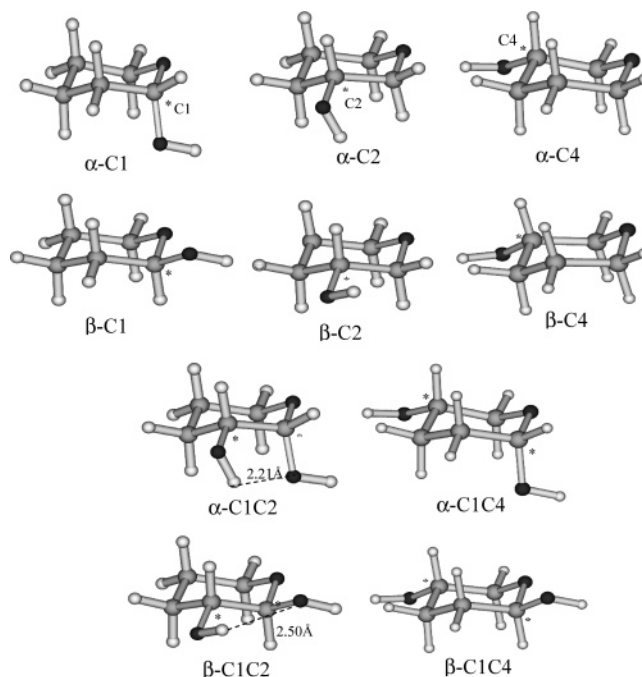


Figure 1. Glucose anomeric prototypes used in this work. The chiral centers are indicated by an asterisk. The hydrogen-bond distances are reported for the α and β C1C2 bicenter chiral prototypes.

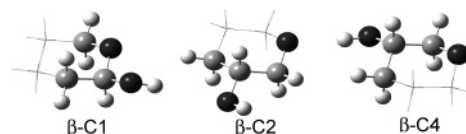


Figure 2. Scheme of the ONIOM partitions adopted to describe the OR in systems with just one chiral center.

Two sets of prototypes have been built starting from the two most abundant conformers of glucose in aqueous solution, one for the α anomer and one for the β anomer. These structures correspond to the GT conformation of the hydroxyl methyl group of each anomer of glucose. The geometries of the two conformers have been presented in a previous work on the OR.²²

From both structures, three monocenter and two bicenter chiral systems are obtained by replacing the hydroxymethyl and all of the hydroxyl groups, except one (monocenter) or two (bicenter), with hydrogen atoms. The structures of the different prototypes we have thus obtained are reported in Figure 1. We note that among all possible structures which can be obtained from glucose we have selected those that keep the chiral center on the anomeric carbon (indicated as C1) and/or on its vicinal carbon (C2) and/or on its opposite carbon (C4). This choice has been dictated by the fact that, here, we are interested in analyzing the local character of the OR and thus starting from the main chiral center (the anomeric carbon); C2 and C4 represent the two extremes (the closest and farthest).

In Figures 2 and 3, the ONIOM two-layer partition adopted in this work is presented, but for simplicity's sake, only for the β anomers. Figure 2 shows the ONIOM partitions adopted for the monochiral prototypes, while Figure 3 shows those for the bichiral ones. The ball-and-stick representation

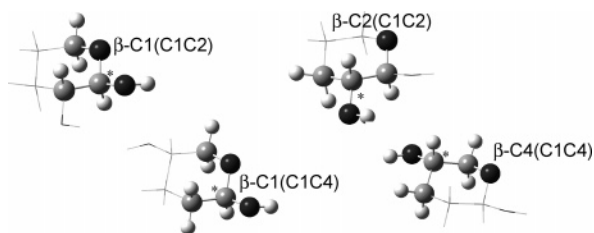


Figure 3. Scheme of the ONIOM partitions adopted to describe the OR in systems with two different chiral centers. In all systems, only one chiral center (*) is present in the HM layer.

regards the part of the system which is described at the high level and is usually indicated as the high-model (HM) layer in the ONIOM framework. All the link atoms, that is, the atoms that are bounded to the model to complete their valence when a bond is broken, are hydrogen atoms.

As can be seen from Figure 2, the HM layer has been chosen to include the proper chiral center of the monocenter chiral prototypes of Figure 1. We note that, for the C4 prototype, two different HMs are possible, one including the two carbons on the left of the chiral C4 and the other including one carbon and the oxygen on the right of C4; in the following analysis, we shall consider only the latter one because only this preserves the ring oxygen atom in the HM layer as the other C1 and C2 HM layers. The ring oxygen is in fact of fundamental importance in defining the nature of the sugarlike systems because it belongs to the moiety responsible for the anomeric effect.

The four structures of Figure 3 correspond to ONIOM calculations for the bichiral systems reported in Figure 1. They refer to ONIOM calculations where just one of the two chiral centers (that indicated in Figure 3 by an asterisk) present in the whole system is preserved in the HM layer. As already noted for C4, for C2, we can also define in principle two different HMs. Once again, we only consider that preserving the ring oxygen atom. We also note that both bichiral systems C1C2 and C1C4 present the same C1 HM layer; thus, in the Figure 3 and in the following analysis, we will use two labels, X-C1(C1C2) and X-C1(C1C4), to indicate such a layer in C1C2 and C1C4 systems, respectively.

3. Calibrating the Model

3.1. The QM Calculation of OR. The quantum-mechanical foundations of optical rotation are due to Rosenfeld,²⁹ who demonstrated that the electric dipole moment of a chiral molecule induced by a frequency-dependent electromagnetic field may be written as

$$\mu_a = \sum_b \left(\alpha_{ab} E_b - \beta_{ab} \frac{\partial B_b}{\partial t} \right) \quad (1)$$

where E and B represent the applied, time-dependent electric and magnetic field vectors and the α tensor denotes the usual molecular dipole polarizability. The key quantity introduced by Rosenfeld is the electric dipole-magnetic dipole polarizability β ; it is in fact its isotropic value which determines the OR of a chiral molecule.

From eq 1, it follows that, as the dipole μ and the polarizability α of the molecule can be properly defined in an ONIOM scheme,^{22d} it is also possible to define an ONIOM β as

$$\beta^{\text{ONIOM}} = \beta^{\text{LR}} + \beta^{\text{HM}} - \beta^{\text{LM}} \quad (2)$$

where a two-layer ONIOM has been used.

From a computational point of view, the calculation of each $\beta^{\text{level,system}}$ in eq 2 can be obtained, at least for variational wave functions in the limit of a static field, in terms of electric and magnetic field derivatives of the ground-state electronic wave function,³⁰ namely

$$\beta_{ab} = \frac{hc}{3\pi} \text{Im} \left\langle \frac{\partial \Psi}{\partial E_a} \left| \frac{\partial \Psi}{\partial B_b} \right. \right\rangle \quad (3)$$

The derivatives of the ground-state electronic wave function, $\partial \Psi / \partial E$ and $\partial \Psi / \partial B$, are calculated using analytical derivative methods and field-dependent atomic orbitals, in particular, gauge-invariant (or including) atomic orbitals (also referred to as London orbitals).³¹ This procedure has been generalized to the frequency-dependent case³² by extending the analytical derivative method to its time-dependent analogue.^{12,13}

As a matter of fact, in the following, the optical rotation will be analyzed in terms of the specific rotation $[\alpha]_D$ instead of the isotropic electric dipole-magnetic dipole polarizability β ; their simple relation is given by

$$[\alpha]_D = 13.43 \times 10^{-5} \frac{\beta \bar{\nu}^2}{M} \quad (4)$$

with β in atomic units, the molar mass M in grams per mole, and $\bar{\nu}$ (the wavenumber where optical rotation is measured) in cm^{-1} .

3.2. The Benchmarks and the Choice of the High Level.

Taking into account the studies performed by Stephens et al.¹² where the effects of considering different levels of QM descriptions were deeply investigated, the first reasonable choice to calculate the optical rotation for the glucose prototypes studied in this paper is to adopt the B3LYP density functional approach with the aug-cc-pVDZ basis set. An important characteristic of the correlated consisted (cc) group of basis is the ability to generate a sequence of basis sets which converges toward the basis set limit. However, small basis sets (that are needed in the low-level ONIOM layer) belonging to this family of bases are not available, and thus the use of ONIOM becomes useless if two time-demanding calculations must be done in both layers.

Therefore, it is mandatory to introduce, for the low level, another kind of basis set not belonging to the cc groups of basis. For this reason, it is interesting to test an alternative to the aug-cc-pVDZ for the high level, which is more coherent with the type of the basis set to be adopted for the low level. Still following the analysis by Stephens et al., we see that a valid alternative is represented by the split valence 6-311++G(2d,2p) basis set.

This basis sets, however, is quite large, and thus, in the view of future applications of the method to real mono- and disaccharides, we have tried to find a substitute which could correctly reproduce the behavior of the larger basis set but

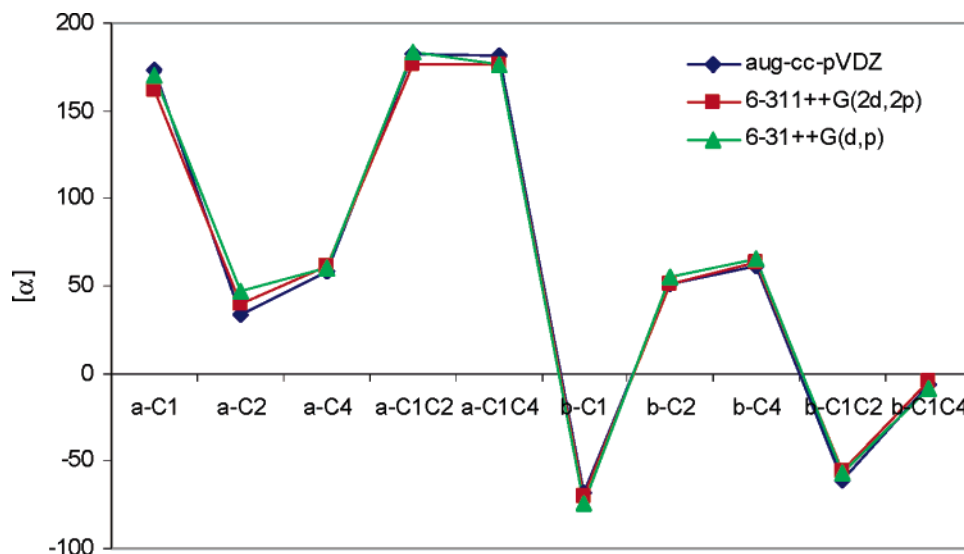


Figure 4. $[\alpha]_{\text{D}}^{20}$ values {in degrees/[dm(g/cm³)]} for 10 prototypes of glucose, at the B3LYP level, in the gas phase obtained with three different basis sets.

at a much lower computational cost. The selected basis set is the 6-31++G(d,p). We note that also in this second set we have maintained the presence of diffuse functions on both heavy and hydrogen atoms, as required to correctly describe the OR property.

The results obtained for the 10 prototypes with these three basis sets are reported in Figure 4. A local version of Gaussian 03 computational code³³ has been used for all the calculations.

Looking at data reported in Figure 4, it can be seen that the three basis sets give very similar OR values, with a single exception for α -C2, for which the 6-31++G(d,p) gives an OR value 30% higher than aug-cc-pVDZ.

Following this analysis, we have fixed the high-layer level of the next ONIOM calculations to B3LYP/6-31++G(d,p).

3.3. S Test for Monochiral Systems: The Choice of the Low Level. A systematic procedure to test the reliability of the level/model combination in ONIOM has been devised using the monochiral systems. The descriptions tested are HF/3-21G, HF/3-21+G, and B3LYP/3-21+G. All of the calculations performed did not involve any reoptimization of the geometries.

In the present application of the ONIOM method, $[\alpha]_{\text{D}}^{20}$ (high,real) is the target (or benchmark) calculation that $[\alpha]_{\text{D}}^{20}$ (ONIOM) is trying to reach. Let us define the S value at a given level as

$$S(\text{level}) = [\alpha]_{\text{D}}^{20}(\text{level,real}) - [\alpha]_{\text{D}}^{20}(\text{level,model}) \quad (5)$$

The S value, $S(\text{level})$, is the difference between the *real* and the *model* system, or the effect of the substituent (second layer) evaluated at a given level. It is obvious that if $S(\text{low}) \rightarrow S(\text{high})$, then $[\alpha]_{\text{D}}^{20}(\text{ONIOM}) \rightarrow [\alpha]_{\text{D}}^{20}(\text{high,real})$. Namely, if the S value evaluated at the low level is the same as that at the high level, the ONIOM property is the same as the target property; that is, the error of the ONIOM extrapolation, $[\alpha]_{\text{D}}^{20}(\text{ONIOM}) - [\alpha]_{\text{D}}^{20}(\text{high,real})$, is zero.

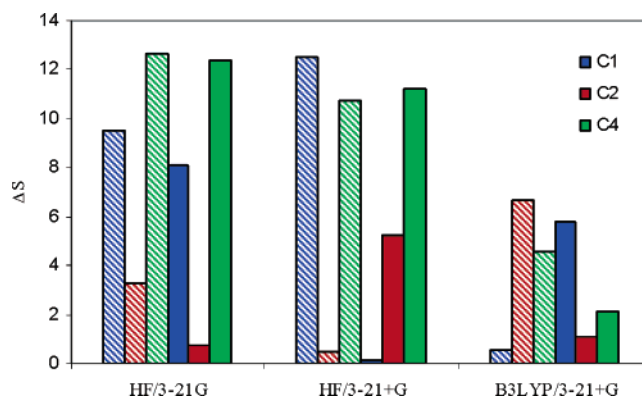


Figure 5. ΔS values for ONIOM(B3LYP/6-31++G(d,p):X) $[\alpha]_{\text{D}}^{20}$ {in degrees/[dm(g/cm³)]} for the monocenter prototypes. Striped and full columns refer to α and β anomers, respectively.

Taking into account these considerations, we prefer to visualize the results in terms of the $\Delta S = S(\text{low}) - S(\text{high})$ values, namely

$$\begin{aligned} \Delta S &= S(\text{low}) - S(\text{high}) = (\text{LR} - \text{LM}) - (\text{HR} - \text{HM}) \\ &= \text{LR} - \text{LM} - \text{HR} + \text{HM} = (\text{LR} + \text{HM} - \text{LM}) - \text{HR} \end{aligned} \quad (6)$$

where the quantity between the parentheses is exactly the integrated ONIOM property. In other words, the ΔS value is a straightforward and quantitative measurement of how much each OR ONIOM value is close to the respective benchmark. These quantities are reported in the graphs in Figures 5.

From Figure 5, it appears that the effects of the description of the low level (both the method and the basis set) are dependent on the conformation.³⁴ For example, the ΔS values when passing from HF/3-21G to HF/3-21+G increase for α C1 and decrease for β C1, while the opposite trend is found passing from HF/3-21+G to B3LYP/3-21+G. On the average, however, the B3LYP/6-31++G(d,p):B3LYP/3-21+G ONIOM combination significantly differs from the others giving small ΔS values for all prototypes.

Table 1. B3LYP/6-31++G(d,p) $[\alpha]_D^{20}$ Values {in degrees/[dm(g/cm³)]} for All Prototypes

prototype	OR	prototype	OR
Monochiral			
α -C1	170.53	β -C1	-74.02
α -C2	46.87	β -C2	55.53
α -C4	59.86	β -C4	64.9
Bichiral			
α -C1C2	183.09	β -C1C2	-56.44
α -C1C4	176.47	β -C1C4	-8.66

Table 2. ONIOM(B3LYP/6-31++G(d,p):B3LYP/3-21+G) $[\alpha]_D^{20}$ Values {in degrees/[dm(g/cm³)]} for the Different ONIOM Partitions Reported in Figure 2

	OR (degrees/[dm(g/cm ³)])			ONIOM
	LR	HM	LM	
α -C1	149.86	154.62	134.49	169.98
α -C2	45.13	17.61	9.23	53.50
α -C4	69.11	39.70	53.49	55.32
β -C1	-72.19	-86.24	-78.66	-79.77
β -C2	79.65	24.60	47.60	56.65
β -C4	74.11	47.56	54.67	67.00

It can thus be assumed that such a combination is the most suited for an ONIOM description of the present systems, and from now on, it will be the only one used.

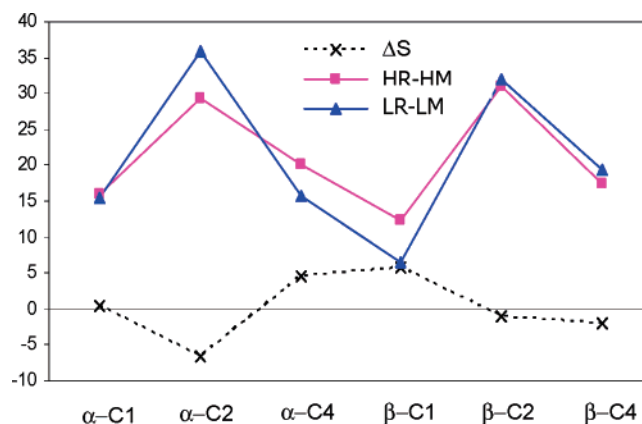
4. The ONIOM Analysis

In this section, we report the analysis of the results in three sections, one referring to the high-level (or benchmark) calculations and two to the ONIOM calculations for OR of mono- and bichiral prototypes, respectively.

4.1. OR Benchmark. All of the OR ($[\alpha]_D^{20}$) benchmark values obtained for all of the prototypes are reported in Table 1.

A first aspect to be underlined is the different behavior of OR in α and β prototypes. In the α series, the OR values are all positive, with α -C2 and α -C4 presenting smaller values. On the contrary, in the β series, both positive and negative values are found. We note, however, that despite this different behavior, in both series, the monochiral C1 system presents OR values very close to those of the bichiral system C1C2, principally for the α conformers. One possible interpretation of this fact is that the chiral centers do not equally contribute to the net chiral behavior, but instead the C1 center plays the major role, because, even when the chirality of C2 is eliminated by saturation, the monochiral C1 prototype presents an OR value very close to that presented by the C1C2 bichiral system. Complimentarily, when the chirality of C1 is eliminated, the results obtained for the OR of the monochiral C2 prototype are not comparable to the corresponding bichiral values.

This analysis can be applied also to C1C4 bichiral. In this case, the chiral centers are away from each other, and thus we can expect that the elimination of one chiral center (to build the corresponding monochiral prototype) should not largely affect the other chiral center. In this case, we should

**Figure 6.** Differences (HR - HM) and (LR - LM) and ΔS values {in degrees/[dm(g/cm³)]} for the different ONIOM partitions of the monochiral systems.

more easily find if one of the two centers is dominant or if, instead, both of them similarly contribute to the OR. For α conformers, it appears that C1 plays the dominant role. In fact, the C1 monochiral prototype practically has the same OR value as the bichiral C1C4 system, in both phases. By contrast, in the β conformer, the chirality of both centers seems to be additive, because the bichiral C1C4 OR value is approximately reproduced by the sum of the values found for each monochiral prototype.

It is important to recall that the α and β C4 monochiral systems have very similar OR values because the anomerism has been eliminated. The only differences are due to small geometric changes.

4.2. The Monochiral Prototypes. In Table 2, we report the ONIOM OR values for the four different monochiral systems C1, C2, and C4 (see Figure 2).

From the comparison of the results reported in Tables 1 and 2, it appears that the ONIOM method can be reliably used to compute the OR property for monochiral systems once the high/low combination is accurately defined on the basis of the S test (see section 2.2). For all systems, the difference between ONIOM and benchmark values is always below 6°/[dm(g/cm³)].

These results seem to suggest that OR behaves as a local property for these monochiral systems: one could observe that this is indeed a straightforward result as only one chiral center is present. This conclusion, however, is not correct as locality is not automatically determined by monochirality. Also, in the presence of a single chiral center, in fact, the OR can significantly depend on the structural and electronic properties of the whole molecule.

To verify if the good results obtained with ONIOM really imply a local character of the property or, instead, are due to a fortuitous cancellation of errors, we introduce here a further analysis.

In Figure 6, we report the ΔS value defined in eq 6 together with the differences between the real and the model systems (both at a low and at a high level of calculations).

The local character of OR is directly evaluated in terms of the difference between HR and HM descriptions. If the part of the system introduced in the model layer contains the whole effect responsible for the property, such a

Table 3. ONIOM(B3LYP/6-31++G(d,p):B3LYP/3-21+G) [α_D^{20} and ΔS Values {in degrees/[dm(g/cm³)}] for the Different Partitions of the Bichiral System (see Figure 3)

	LR	HM	LM	ONIOM	ΔS
α -C1(C1C2)	164.96	133.68	116.28	182.36	0.73
α -C2(C1C2)	164.96	15.22	7.98	172.20	10.89
α -C1(C1C4)	179.03	133.68	116.28	196.43	-19.96
α -C4(C1C4)	179.03	34.32	46.25	167.11	9.36
β -C1(C1C2)	-51.31	-74.56	-68.01	-57.86	1.42
β -C2(C1C2)	-51.31	21.27	41.15	-71.20	-14.76
β -C1(C1C4)	-4.84	-74.56	-68.01	-11.39	-2.73
β -C4(C1C4)	-4.84	41.12	47.27	-10.99	2.33

difference must be very small. From Figure 6, it can be seen that the “local” character decreases in the order C1, C4, and C2. We also note that the same ordering in “degree of locality” found from the HR – HM difference is obtained also in terms of LR – LM differences, generally a more accessible quantity for large systems when the RH calculations are prohibitive. However, the reliability of an ONIOM description depends not only on this degree of locality. As it can be seen from Figure 6, larger ΔS values (i.e., worse ONIOM descriptions) are obtained for α -C4 and β -C1, for which the HR – HM difference is relatively small.

Following this analysis, it seems that the performance of ONIOM to describe the OR of a chiral center depends on two different aspects, the “true locality” of the property for such a given chiral center and the different evaluation of the locality at low and high levels, or in other words the differences between HR – HM and LR – LM.

4.3. The Bichiral Prototypes. In Table 3, we report the ONIOM results for the bichiral systems C1C2 and C1C4 (see Figure 3), for the three ONIOM partitions considered.

In the previous section, we have shown that the ONIOM description is sufficiently accurate for monochiral systems and that the ΔS error found is always acceptable. On the contrary, for bichiral systems, the error associated with the ONIOM calculations can be large, as shown in Table 3, and it ranges from 2° to 20°/[dm(g/cm³)], depending on the system.

This result is not completely unexpected as the bichiral systems introduce a new aspect, which was not present in the monochiral systems. This aspect is related to the elimination of one of the two chiral centers in the HM layer and the consequences of this on the resulting OR value. Because of the limited dimensions of the prototypes studied, it is not possible to define an ONIOM model system including both chiral centers. However, we can try to approximately account for them by summing up the ONIOM results of the two complementary model systems [e.g., α -C1-(C1C2) and α -C2(C1C2)], namely:

$$\begin{aligned} \text{ONIOMbi} &= \text{ONIOMCx(CxCy)} + \text{ONIOMCy(CxCy)} - \text{LR} \\ &= (\text{LR} + \text{HMx} - \text{LMx}) + (\text{LR} + \text{HMy} - \text{LMy}) - \text{LR} \quad (7) \end{aligned}$$

where the subtraction of the value found for the low real system has been introduced to avoid its double counting. The ΔS values corresponding to this approximate description



Figure 7. Scheme of the additional ONIOM partitions adopted to describe the OR in the C1C2 system.

can be easily obtained from Table 3; the results obtained are -6.5, -8.0, 21.3, and 8.9 {in degrees/[dm(g/cm³)]} for α -C1C2, α -C1C4, β -C1C2, and β -C1C4, respectively. These values further confirm the nonlocality of the property because locality would also imply a limited coupling between the two chiral centers, and thus eq 7 (in which two separated ONIOM calculations, each one with a different model system, are combined) should reliably reproduce the benchmark.

To better analyze the real character of OR in these bichiral systems, we introduce now a different test based on the change of the ONIOM description as the model layer increases. We thus introduce two new ONIOM partitions, C1(OH) and C2(OH), in which the HM layer includes also the hydroxyl group bonded to the carbon atom adjacent to the chiral center kept active (see Figure 7 for a schematization of the β anomers).

One could expect that, if the OR for a bichiral system was a purely local property, the increase of the model system (for example, by including the OH groups) would imply an improvement in the description of the property.

From Figure 8, in which we report the ΔS values for the different ONIOM partitions used to describe the C1C2 bichiral system, one can see that it is not exactly what happens.

Passing from the partition C1(C1C2) to C1(OH), the HM becomes more “complete” but the ONIOM description becomes less accurate (the ΔS value increases) for both anomers.

To try to rationalize the results obtained for the bichiral systems, in the following section, we introduce two auxiliary levels of analysis.

5. A Further Analysis in Terms of Anomeric Energy Differences and NMR Shieldings

We introduce here two additional properties to be studied with ONIOM, one of global character, that is, the energy, and one of local character, that is, the nuclear shielding. Both these quantities have been deeply analyzed with ONIOM approaches in many previous papers. This experience will thus allows us to use them as a comparative tool to better appreciate the global/local character of the OR for bichiral systems and to rationalize the results obtained in the previous section.

5.1. Energy Differences. As far the energy is concerned, it is well-known that ONIOM can only be used to get relative values, and thus here we shall consider differences in the α and β anomers. In Figure 9, the (β – α) energy differences for different ONIOM partitions depicted in Figure 3 are reported.

As it can be seen from Figure 9, not all of the partitions properly describe the (β – α) energy difference. In particular,

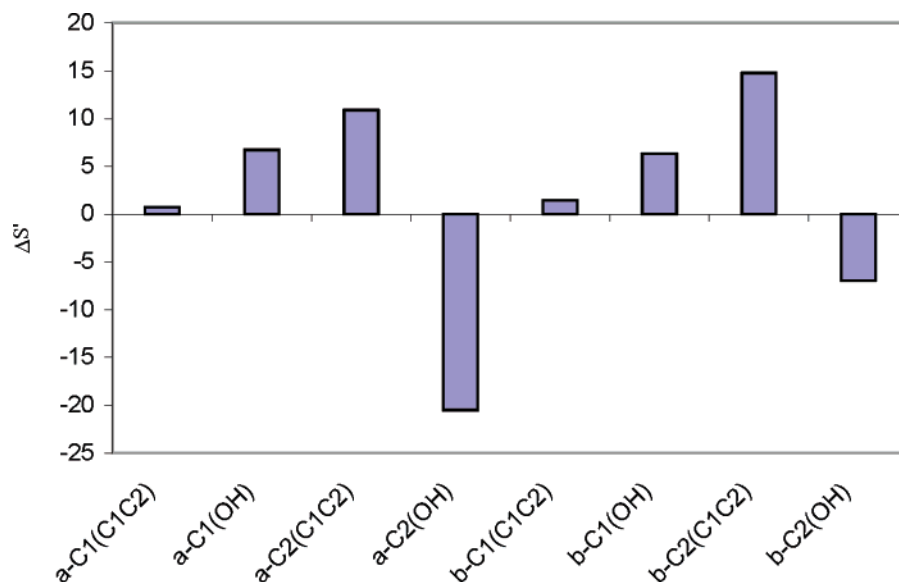


Figure 8. ΔS values {in degrees/[dm(g/cm³)]} for the different ONIOM partitions of the α (left) and β (right) C1C2 bichiral systems.

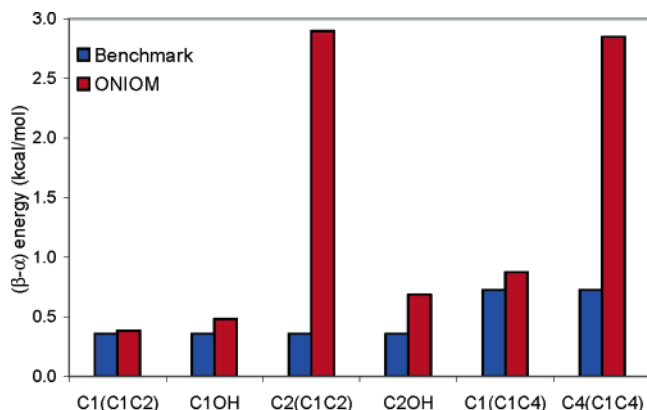


Figure 9. Benchmark and ONIOM values for the $(\beta - \alpha)$ energy difference in kcal/mol for the different ONIOM partitions.

the C2(C1C2) and C4(C1C4) give a completely wrong picture. To better understand this behavior, it is important to analyze the nature of these ONIOM partitions.

As can be seen from Figure 3, for the C4(C1C4) partition, the anomeric center (C1–OH) is not included in the HM; therefore, the anomeric $(\beta - \alpha)$ difference is described only at the low level (i.e., in the LR); this prevents a correct evaluation of the differential stability of the two anomers. By contrast, in the C2(C1C2) partition, the anomeric carbon is in the HM but not the corresponding hydroxyl group. As the anomeric effect represents the axial preference of such a OH, it is obvious that we cannot properly describe the differential stability of the two anomers without including the whole moiety in the HM. This is confirmed by the comparison of the C2(C1C2) and C2(OH) results; the latter partition in fact is exactly identical to the former with the only exception of the inclusion of the anomeric OH in the HM layer.

5.2. Carbon Nuclear Shieldings. We finally present the results for the “local” nuclear shieldings of the C1, C2, and C3 carbon atoms.

In Figure 10, we report the absolute ΔS values for the carbon nuclear shieldings of the α (left) and β (right) anomers corresponding to the different ONIOM partitions.

First of all, we note that for all the partitions the ONIOM error is always less than 5% (the absolute values of the nuclear shieldings for the various carbon atoms range from 90 to 160 ppm). This shows, once more, that ONIOM can be reliably used to compute nuclear shieldings also for cyclic systems.^{28b}

Going into more detail, we can observe that for C1 the largest error is found for C2(C1C2), that is, where the hydroxyl group is not included in the HM. For C2, on the contrary, the less accurate result is found for C1(C1C2); this can be due to two different effects, one, as in the previous case, related to the OH being excluded from the HM and the other related to what we can call a “border effect”, that is, the presence of the “cut” between low and high layers exactly at the C2 atom. By comparing with the C1(OH) result for the same C2 atom, we can observe that the OH effect is more intense than the “border” one, because in this partition the error in the ONIOM description diminishes with the inclusion of the OH group into the HM layer. For the C3 atom, we observe a regular behavior which can be easily explained in terms of border effect, the only active in this case.

From both the energy and the nuclear shielding analyses, it clearly comes out that the most important factor in these systems is the proper description of the anomeric moiety which can only be obtained by including all the related atoms in the HM.

In section 4.3, we have shown that this picture does not apply for the OR; there, however, we have implicitly assumed a “local” character of the property because the comparison was made using absolute values. It is thus worth checking if a different analysis, that is, assuming the OR as a global property, can help in rationalizing the ONIOM behavior for this property. To do that, we introduce here the difference of the OR values for α and β anomers using the

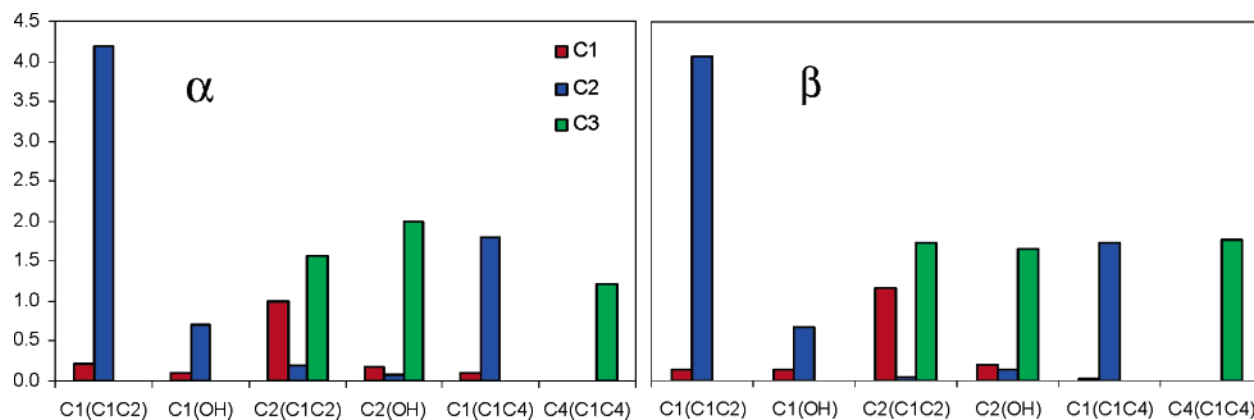


Figure 10. ΔS values (in ppm) for the C1, C2, and C3 carbon nuclear shieldings of the α and β anomers.

Table 4. ΔS Values {in degrees/[dm(g/cm³)]} for the Differences in the $[\alpha]$ of the Two Anomers ($OR_\alpha - OR_\beta$)

	$\Delta S([\alpha]_\alpha - [\alpha]_\beta)$
C1(C1C2)	0.69
C2(C1C2)	-3.87
C1(C1C4)	-22.69
C4(C1C4)	7.04

different ONIOM partitions. Let us analyze the data reported in Table 4 by considering first the C1C2 bichiral system.

In section 4.1, we have suggested that two chiral centers do not equally contribute to the net chiral behavior, but instead the C1 center plays the major role in both α and β anomers. This is confirmed by these results; in fact, the partition which includes C1 in the HM gives a very low error. By contrast, when we consider the nonadjacent C1C4 system for which, in section 4.1, we were not able to identify a dominant chiral center (at least not for both anomers simultaneously), a far more irregular behavior is found. In fact, a larger error is found passing from the C4(C1C4) not including the anomeric moiety in the HM to the complementary C1(C1C4), that is, a completely opposite behavior with respect to what is found for the energy difference (see Figure 9).

6. Conclusions

In this work, we have presented for the first time a study of the local or global character of the optical rotation of mono- and bichiral prototypes of glucose using the ONIOM method. The results obtained for monochiral systems seem to suggest that OR can be considered as a local property at least in the ONIOM sense, and thus it can be studied by applying the same strategy used for other local properties (like NMR), namely, a proper definition of the low and high partition and a correct combination of the corresponding levels of calculation in terms of the S test.

By contrast, the bichiral systems studied present a much more complex behavior. In these systems, the property is not well behaved; that is, it cannot be classified as a purely local or purely global property. The limited dimensions of the prototypes chosen allow only an approximated analysis of ONIOM partitions including both chiral systems, and thus the reasons for the observed behavior remain largely unclear.

Some guesses, however, can be given. First of all, it is immediate to accept that OR in chiral systems without asymmetric atom(s) (such as helicenes or similar systems) is necessarily nonlocal. By contrast, in the most common cases in which chirality is determined by one or more asymmetric atoms (like in the systems studied here), the local or nonlocal character strongly depends on the number of chiral centers and their proximity.³⁵ Further analyses on larger bichiral (cyclic and open) systems with different distances between chiral centers will surely lead to a more complete picture of the nature of OR and to verification of whether a layered method like ONIOM can be applied to the study of this property. These studies are in progress.

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