Letter

Orbital Analysis of Molecular Optical Activity Based on Configuration Rotatory Strength

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ABSTRACT: We present a method to analyze the origin of molecular optical activity in terms of orbital contributions and rotatory strength in configuration space. The method uses quantities already available at completion of standard linear-response calculations of specific rotation and requires minimal manipulation. Preliminary application to (1S,4S)-norbornenone and (P)-2,3-pentadiene shows that only a few orbitals (6 and 4, respectively) contribute significantly to the specific rotation and can be used directly for a qualitative interpretation of this fundamental property.
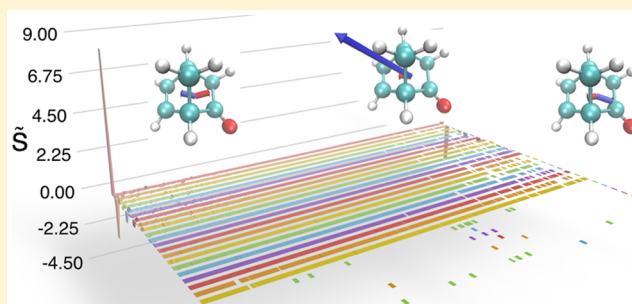
Chirality plays a fundamental role in chemistry and biology since the building blocks of life, i.e. amino acids and sugars, are chiral molecules.[1] Nature has selected a preferential enantiomer for each set, a phenomenon called homochirality, whose origin is still a matter of debate.[2] As a result, chemists often need to differentiate enantiomers, e.g. in the synthesis of natural products, since only one enantiomer will provide the desired interaction with a target biological environment. One of the most widely strategies to differentiate chiral molecules is through interaction with chiral light. Among these techniques, the oldest and still widely applied is the measurement of specific rotation.[3] This phenomenon refers to the rotation of the plane of polarization of linearly polarized light when it passes through a sample containing an excess of one enantiomer.[4] One enantiomer will rotate the polarization plane clockwise ("+" rotation), the other anticlockwise ("-" rotation). Experiment, however, cannot provide a direct link between the structural handedness of a chiral compound and the sign of the rotation. In the last two decades, theoretical calculations have provided such direct link more and more reliably, thus becoming a standard tool in organic synthesis research.[5,6] However, fundamental questions remain: What contributes to the overall sign and magnitude of the specific rotation? Can we make any prediction based on the molecular structure even without performing time-consuming calculations?

This communication proposes an approach to answer the first question as a first step to find an answer to the second one. This approach is based on a theoretical analysis of the specific rotation in terms of orbital contributions. Here we show that only a limited number of orbitals provide a significant contribution to this property, and we propose a simple visual technique to interpret the molecule interaction with the external field. Other strategies based on a sum-over-states (SOS) decomposition of the specific rotation have been proposed, but they are only applicable to special cases due to the slow convergence of the series expansion.[7−9] This is not the

first method based on orbital analysis of molecular properties that has been proposed. For specific rotation in particular, Autschbach and co-workers[10,11] have recently published an approach that is closely related to that shown here. The main difference is that the method in ref 10 focuses on individual diagonal elements of the linear response tensor, while our method directly considers the trace of the tensor as shown in detail below. This allows us to maintain a connection with the SOS approach, preserving its physical interpretation in terms of electric and magnetic moments albeit without its overwhelming computational effort. Our approach and Autschbach's will likely be complementary, and further study will help define the respective range of applicability. At the moment, our approach is intended as an interpretive tool of linear response (LR) results obtained at a certain level of theory, not as a predictive tool of what the outcome of a LR calculation may be. More experience on multiple systems, however, may allow us to predict the optical activity of other compounds from a (relatively) simple orbital analysis.

In order to describe our approach, let us start from the expression of the specific rotation written as a sum-over-states (SOS)[5]

$$[\alpha]_\omega \propto \sum_{n=1}^{N_{ex}} \left(\frac{R_n}{\omega_n - \omega} + \frac{R_n^*}{\omega_n + \omega} \right) \tag{1}$$

where n runs over the number of excited states (N_{ex}), ω_n is the corresponding transition energy, and ω is the frequency of the impinging light. R_n is the rotatory strength for the $0 \to n$ transition

$$R_n = \text{Im}\left\{ \sum_{i=1}^{3} \langle 0|\mu_i|\psi_n\rangle\langle\psi_n|m_i|0\rangle \right\} = \text{Im}\{\vec{\mu}_{0n}\cdot\vec{m}_{0n}\} \tag{2}$$

where μ_i and m_i are the Cartesian components of the electric and magnetic dipoles, and ψ_n is the n-th excited state. The rotatory strength is related to the differential absorption of left and right circularly polarized light, which is measured in circular dichroism experiments. In fact, specific rotation and circular dichroism are properties related through Kramers−Kronig relations.[12] The proportionality constant in eq 1 is irrelevant for a qualitative analysis. Also, the expression in eq 1 applies to the nonresonant case where ω is far from any transition energy ω_n. We will only consider this case here. We can rewrite this expression incorporating the denominator into the definition of the rotatory strength

$$[\alpha]_\omega \propto \sum_{n=1}^{N_{ex}} (\tilde{R}_n + \tilde{R}_n^*) \tag{3}$$

where we may interpret $\tilde{R}_n$ as a rotatory strength weighted over the excitation energy. As mentioned above, the SOS approach is of little use in practice for most cases due to its slow convergence and the cost associated with excited state calculations.

Alternatively, one can compute $[\alpha]_\omega$ with analytic linear response (LR) techniques.[6] For mean-field single-reference methods like Hartree−Fock (HF) and Kohn−Sham density functional theory (KS DFT), the LR expression of the specific rotation reads

$$[\alpha]_\omega \propto \mathrm{Im}\left\{ \sum_{i=1}^{3} \sum_{k=1}^{N_{ex}} (\langle 0|\mu_i|\phi_k\rangle\langle\phi_k|X_{m_i}^+|0\rangle + \text{c.c.}) \right\} \tag{4}$$

where i runs over Cartesian coordinates while k runs over singly excited configurations ϕ_k (i.e., excited Slater determinants). Obviously, the total number of excited configurations is equal to the total number of electronic excited states. The vectors $X_{m_i}^\pm$ are the perturbed densities obtained from the solution of the coupled-perturbed HF/KS equations:

$$\langle\phi_k|X_{m_i}^\pm|0\rangle = \sum_{l=1}^{N_{ex}} \langle\phi_k|(H - E_0 \mp \omega)|\phi_l\rangle^{-1}\langle\phi_l|m_i|0\rangle \tag{5}$$

The LR approach can be seen as a change of basis in the representation of the Hamiltonian from a diagonal (i.e., SOS) to a nondiagonal basis based on configurations.

Changing the order of summation in eq 4 we obtain

$$[\alpha]_\omega \propto \sum_{k=1}^{N_{ex}} (\tilde{S}_k + \tilde{S}_k^*) \tag{6}$$

where we have defined a rotatory strength in configuration space $\tilde{S}_k$:

$$\tilde{S}_k = \mathrm{Im}\left\{ \sum_{i=1}^{3} \langle 0|\mu_i|\phi_k\rangle\langle\phi_k|X_{m_i}^+|0\rangle \right\} \tag{7}$$

The weighting now is over the matrix elements of the nondiagonal Hamiltonian and is included in the $\vec{X}_m^\pm$ vectors, see eq 5. Since $\langle 0|\mu_i|\phi_k\rangle$ is a real symmetric matrix, we can consider only the symmetric combination of the $X_{m_i}^\pm$ matrices, and thus only one set of $\tilde{S}_k$s. With this set of rotatory strengths $\tilde{S}_k$ we can perform similar analyses to what is done for SOS. The advantage is that no excited state needs to be explicitly computed as all the quantities of interest are already computed in the LR calculation. In principle, one can write eq 4 in terms

of vectors $\vec{X}_\mu$ rather than $\vec{X}_m$ where the weighting is shifted from the magnetic to the electric perturbation. Therefore, one can define alternative configuration rotatory strengths:

$$\tilde{S}_k' = \mathrm{Im}\left\{ \sum_{i=1}^{3} \langle 0|X_{\mu_i}^-|\phi_k\rangle\langle\phi_k|m_i|0\rangle \right\} \tag{8}$$

In eqs 4, 7, and 8 we used the $2n+1$ rule of perturbation theory.[11,13] By comparing $\tilde{S}_k$ and $\tilde{S}_k'$ one could distinguish whether a particular value of the rotatory strength is due to the magnitude of the electric and magnetic dipoles, to the angle between them, or to the energy weighting.

We report preliminary results of $\tilde{S}_k$, eq 7, for two organic molecules: (1S,4S)-norbornenone and (P)-2,3-pentadiene. These systems present large and small specific rotation, respectively, representing two opposite case scenarios. All calculations were performed at the B3LYP/aug-cc-pVDZ[14] level with the GAUSSIAN suite of programs.[15] The geometries are taken from ref 16.

The data for $\tilde{S}_k$ is presented in 3D plots where the contribution for each excited determinant k is reported in terms of the corresponding occupied-virtual orbital pair (sorted in energy order) used to built the determinant. Only the alpha spin contribution to $\tilde{S}_k$ is considered since these molecules are closed shell. The sign is opposite to that of the specific rotation since we are ignoring a minus sign in the constant factor in eq 4.

(1S,4S)-Norbornenone presents an unusually large specific rotation compared to molecules of similar size: $[\alpha]_{355}^{exp} = -6310$ deg dm^{-1} (g/mL)$^{-1}$.[17] This fact has been experimentally known for a long time through measurements in solution[18] and more recently in gas phase.[17] The latter has also shown an unexpectedly large solvation effect, which is beyond the scope of this work. This behavior is due to the interaction between the C═C and C═O groups,[7,10,19] maintained in a favorable orientation by the rigid cage structure of this molecule. We also studied the norbornenone case with a SOS analysis,[9] and we showed that the C═C/C═O interaction can be unraveled by considering only the first electronic excited state and its associated rotatory strength. The rigid structure of norbornenone maintains these two groups fixed in an orientation where the transition electric and magnetic dipole moments have large magnitude and point in the same direction (remember that the rotatory strength in eq 2 is the inner product between the two dipole moments). At the B3LYP level of theory, however, the specific rotation is largely overestimated: $[\alpha]_{355}^{calc} = -11298$ deg dm^{-1} (g/mL)$^{-1}$. We refer the reader to ref 10 for a detailed discussion about the poor performance of B3LYP. In the context of this work, however, good accuracy is not crucial as long as the correct physics is described, which is the case with B3LYP.

In this work, we revisit the analysis of the specific rotation of norbornenone in terms of rotatory strength from the point of view of orbital contributions. Norbornenone has 29 alpha electrons, and with this choice of basis set there are 227 alpha virtual orbitals, which correspond to 6583 values of $\tilde{S}_k$. The individual values of $\tilde{S}_k$ obtained from excited determinants k for each pair of occupied-virtual orbitals is reported in Figure 1. The figure clearly shows that a very limited number of $\tilde{S}_k$ values contribute significantly to the total specific rotation of this molecules. In particular, the HOMO−1→ LUMO, HOMO→ LUMO, HOMO→ LUMO+2 determinants provide large contributions: $\tilde{S}_K = -2.36, 8.30, -1.74$ au, respectively. The
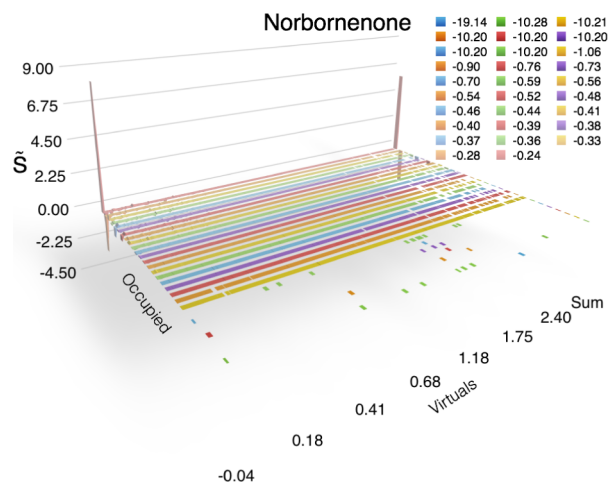
Figure 1. $\tilde{S}_k$ plot for (1S,4S)-norbornenone (au). Each determinant k is represented in terms of occupied-virtual orbital pairs. The orbitals are reported in energy order (au). The last row on the right edge of the plot ("Sum") reports the sum of $\tilde{S}_k$ over all virtual orbitals for each occupied orbital.

sum of these three contributions, 4.20 au, is about twice the total sum over $\tilde{S}_k$, 2.21 au. While these three values of $\tilde{S}_k$ are not enough for a quantitative account of the trace of the response tensor, they are all we need for understanding the origin of the large specific rotation of this compound. This is rather remarkable considering that over 6500 values of $\tilde{S}_k$ contribute to this property. This result is also consistent with our previous study on norbornenone in terms of excited state contributions[9] since these three determinants have the largest amplitudes in the formation of the first excited state (48% collectively).

For the interpretation of the values of $\tilde{S}_k$ for these determinants, we resort to a graphical representation of $\vec{\mu}$ and $\vec{X}_m$ from eq 7, shown in Figure 2. This approach is similar
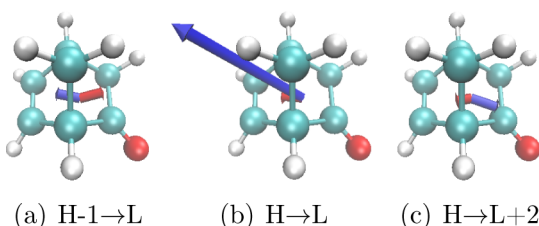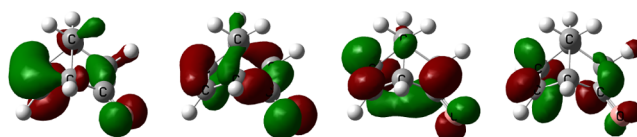

(a) H-1→L   (b) H→L   (c) H→L+2

Figure 2. Graphical representation of the $\vec{\mu}$ (red) and $\vec{X}_m$ (blue) vectors that give the largest contribution to the specific rotation of norbornenone. The length of the blue vectors is reduced by a factor of 5 in order to fit in the page size. H: HOMO, L: LUMO.

to that used in ref 9 except that here we are working in configuration space. The figures were produced with the VMD software.[20] The magnitude of the vectors for $\vec{X}_m$ (blue arrows) is reduced by a factor of 5 to allow the HOMO−LUMO case to fit in the page. Therefore, all blue arrows are considerably longer than the red arrows. The sign and magnitude of $\tilde{S}_k$ can be now directly correlated with the magnitude and relative orientation of the arrows. When the arrows point in the same direction (HOMO - LUMO case) the sign of $\tilde{S}_k$ is positive and vice versa. The HOMO - LUMO terms present the largest magnitude due to the large magnitude of $\vec{X}_m$. The direction and magnitude of these vectors can be interpreted by considering the orbitals involved, shown in Figure 3. The direction of the

(a) HOMO-1   (b) HOMO   (c) LUMO   (d) LUMO+2

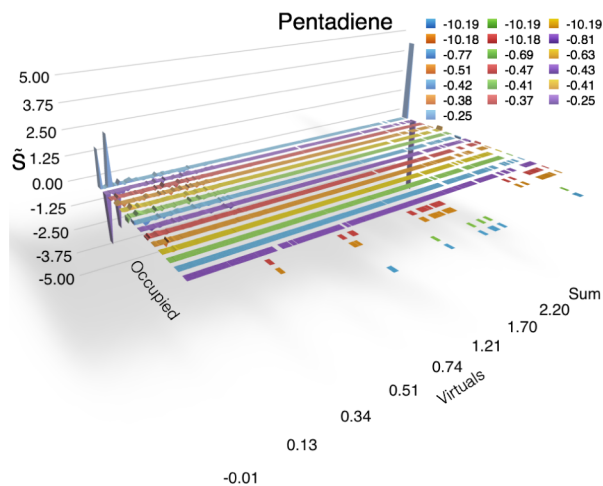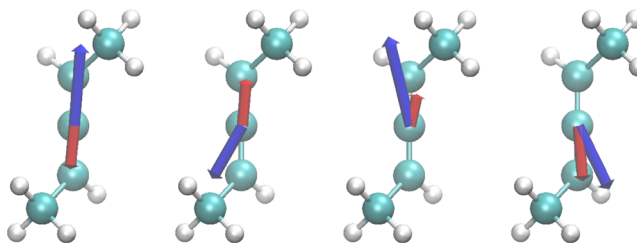**Figure 3.** Orbitals that give the largest contribution to the specific rotation of norbornenone.

Figure 4. $\tilde{S}_k$ plot for (P)-2,3-pentadiene (au). Each determinant k is represented in terms of occupied-virtual orbital pairs. The orbitals are reported in energy order (au). The last row on the right edge of the plot ("Sum") reports the sum of $\tilde{S}_k$ over all virtual orbitals for each occupied orbital.

(a) H-1→L+1   (b) H-1→L+5   (c) H→L   (d) H→L+4

Figure 5. Graphical representation of the $\vec{\mu}$ (red) and $\vec{X}_M$ (blue) vectors that give the largest contribution to the specific rotation of pentadiene. H: HOMO, L: LUMO.

blue arrows correlates with rotations of the density around the C=O group, which is directly involved in all four orbitals. The direction in the HOMO - LUMO+2 case is opposite compared to the other two because the density rotation is in the opposite direction as revealed by the opposite sign of the lobes on the LUMO and LUMO+2 orbitals. The considerably larger magnitude of the blue arrow for the HOMO - LUMO determinant is due to the larger value of electron density associated with the carbonyl group in these two orbitals compared to the other two. The directionality of the red arrows indicates partial electron transfer between the two chromophores. The magnitude is small since the two groups are two bonds apart, and electron delocalization is small. The direction of the electric dipole moment indicates a partial charge transfer toward the C=C group for the determinant than involve the HOMO since the latter has a large contribution from the lone
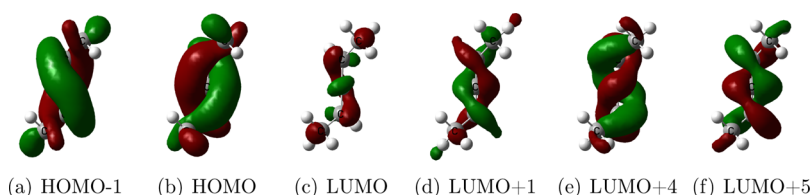
(a) HOMO−1 (b) HOMO (c) LUMO (d) LUMO+1 (e) LUMO+4 (f) LUMO+5

Figure 6. Orbitals that give the largest contribution to the specific rotation of pentadiene.

pair of the oxygen. The opposite is for the determinant that involves the HOMO−1 since the latter has a larger contribution from the C=C π density.

(P)-2,3-Pentadiene has axial symmetry (C_2 point group), and its optical activity is $[\alpha]_{355}^{exp} = +408$ deg dm^{-1} (g/mL)$^{-1}$,[16] which is more than an order of magnitude smaller than that of norbornenone. The calculated value is $[\alpha]_{355}^{calc} = +264$ deg dm^{-1} (g/mL)$^{-1}$, which is underestimated compared to experiment and about 2 orders of magnitude smaller than the corresponding calculated value for norbornenone. This molecule has also been studied experimentally and theoretically, including with a SOS approach that has shown slow convergence.[8]

The contributions to the specific rotation tensor in terms of $\tilde{S}_k$ are shown in Figure 4. There are 19 alpha electrons and 168 alpha virtual orbitals at this level of theory, which yields 3192 values of $\tilde{S}_k$. The trace of the tensor (i.e., the sum over all $\tilde{S}_k$) is -3.52×10^{-2} au, which is 2 orders of magnitude smaller than norbornenone. As shown in Figure 4, also in this case most $\tilde{S}_k$ contributions are really small. Only four terms are large in magnitude and opposite in sign, so that they compensate. However, we note that these terms are individually of the same order of magnitude of those of norbornenone, a fact previously not recognized. The determinants for these terms are the HOMO - LUMO and HOMO - LUMO+4, which give positive contributions (1.92 and 2.54 au, respectively), and the HOMO−1 - LUMO+1 and HOMO−1 - LUMO+5, which give negative contributions (−2.48 and −1.80 au, respectively).

The origin of the sign and magnitude of these terms can be studied again with a vectorial representation of $\vec{\mu}$ and $\vec{X}_m$ superimposed to the molecular structure, as shown in Figure 5. The figure shows that both vectors are rather aligned with the diene structure, and they are similar in magnitude (contrary to the previous case). When the two vectors point in the same direction, the sign of $\tilde{S}_k$ is positive, while it is negative otherwise. The orbitals involved are shown in Figure 6. Interestingly, all of these orbitals have a helical structure, and only those with same helicity can interact to give non-negligible values of magnetic moment (the HOMO with the LUMO and LUMO+4 and the HOMO−1 with the LUMO+1 and LUMO+5, respectively). The direction of the blue arrow is opposite for these two sets of determinants because the helicity of the orbitals involved is opposite. The red arrows also indicate that a significant charge transfer accompanies these excitations.

From a quantitative perspective, adding up $\tilde{S}_k$s that are within a factor of 10^{-3} from the total sum for norbornenone requires 834 configurations (out of 6583) for a relative error of 1.6%. For pentadiene, adding up $\tilde{S}_k$s within 10^{-2} from the total sum requires 1043 configurations (out of 3192) with an error of 0.8%. This indicates that a considerable computational effort is wasted in computing small values, a fact that may be used to reduce the computational cost of these calculations. This would be highly desirable, especially for accurate and expensive many-

body methods like those belonging to coupled cluster (CC) theory.

This preliminary data shows that an analysis of the contribution to the specific rotation in configuration space may only require a very limited number of elements. This allows a detailed study of such contributions in terms of electric and magnetic dipoles and in terms of a few molecular orbitals associated with the relevant excited determinants. This provides an extremely promising interpretative tool for chiroptical properties, more powerful than a typical SOS approach since it does not require the evaluation of thousands of excited states. We are currently working to extend this approach to methods beyond DFT (e.g., CC theory) and to study other molecular systems.

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Notes

The authors declare no competing financial interest.

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