Optical Properties of Artemisinin and Its Derivatives
Jialin Ma, Wenhua Qiao, Xijiao Mu,* Jun Dong,* Jun Quan,* and Chunhua Tian*

ABSTRACT: Artemisinin and its derivatives are of great research value in biology. In this work, we study their chiral and optical properties. The multidimensional multifunction analysis method is used to analyze the linear and nonlinear optical processes (one-photon and two-photon absorption: OPA and TPA), electronic circular dichroism (ECD), and Raman optical activity (ROA) mechanisms under light excitation. Transition dipole moments (TDMs) and charge difference density (CDD) are used to describe the electromagnetic interaction between ECD and ROA when a substance is excited by light. The theoretical research results of the study show that the dioxygen atoms provide an intermediary for the transfer between charges and also enhance the role of the TDMs. This generalized chiral theory can not only explain the traditional sources of chirality but also distinguish whether the molecule has chirality when the chiral center is not obvious. By analyzing ROA and different vibration modes, we can clearly observe that each part of the molecule responds differently when excited.

1. INTRODUCTION
Artemisinin (ART) is regarded as the first natural peroxide extracted from the Chinese herbal medicine Artemisia annua. Artemisinin and its derivatives are all sesquiterpene lactones. They are widely used to treat malaria due to their high antimalarial activity and low toxicity.1 With the safety record established in millions of malaria patients, artemisinin was reported for the first time in anti-tumor activity in 1993.2−4 Since then, numerous derivatives of artemisinin such as esters,5 ethers,6 dimers, trimers, and tetramers7 have been researched and expected to become anti-tumor drug candidates. We selected artemisinin and its two derivatives to study their optical properties, as shown in Figure 1. The chemical structural formulas and atomic schematic diagrams of molecule 1, 2, and 3 are shown in Figure 1a−c, respectively. First, all of them are sesquiterpene lactones, but they have their own characteristics. By comparing molecule 1 (R1) and molecule 2 (R2), it is observed that the structure of R1 consists of a ring containing dioxygen atoms, while the dioxygen atoms of R2 are on the branch. By comparing R2 and molecule 3 (R3), it is observed that R2 has a dioxygen atom structure, while R3 has two dioxygen atom structures. Since there are no other special atoms except oxygen in the studied molecules, it is very helpful for us to control the variable of atoms. It is precisely because they have similarities and differences, we chose these three molecules for research.

The dioxygen atoms have a special configuration, and there are no other special atoms in the chosen molecules, which makes it convenient for us to study the characteristics of the oxygen atoms and eliminate the interference of other atoms. The two-dimensional (2D) visualization method shows us which part of the atoms of the molecule responds to the light, and the direction of charge transfer is represented by the three-dimensional (3D) diagram.

When molecules are excited by light, charge transfer occurs. This phenomenon exists in many systems. What we want to study is the charge transfer characteristics in OPA and TPA. Compared with TPA, OPA directly transitions from the ground state to the final excited state, and the light absorption intensity is weaker.5 Hence, we also studied the TPA process. As a third-order nonlinear optical process, this process was proposed by Göppert-Mayer.9 TPA can be analyzed by the absorption cross section. Compared with OPA, TPA only needs to absorb one-half of the energy, so its electronic transition ability is stronger. In our research, we regard the transition between the ground state and the final excited state in TPA as two processes. The intermediate transition state can be directly obtained by quantum chemical calculation.10−13 TDMs in TPA usually contain two modes, a three-state model produced by the intermediate transition and a two-state model produced by the direct transition.14 TPA also has a wide range of applications in microcopy,15−17 solar cells,18,19 non-destructive imaging of biological tissues,20,21 and nanodevice manufacturing. Usually the chirality of the system can be achieved with the help of electronic circular dichroism (ECD).23,24 As we know, ECD is an asymmetric response between electromagnets, it is closely related to the transition magnetic dipole moment.
(TMDM) and the transition electric dipole moment (TEDM). Theoretically, the formula for calculating the ECD intensity is as follows:

\[ I \propto \langle \mu_e \Phi \rangle \langle \mu_m \Phi \rangle \]

\[ \propto \left| \sum_{j} \Phi_{ij} \sum_{i} | \langle \mu_e | \Phi_i \rangle |^2 \right| \]

\[ E_j^2 \]

where \( \mu_e \) and \( \mu_m \) are the TEDM and TMDM, respectively.

Raman optical activity (ROA) spectroscopy, a way to express the molecular vibration optics spectrum, has a high resolution in the frequency domain, and its intensity is determined by

\[ \sum \sum \mu_{\omega} \omega_{\mu} \omega_{\mu} \]

\[ \propto \sum_{\mu} | \langle \mu_e | \Phi_i \rangle |^2 | \langle \mu_m | \Phi_i \rangle |^2 \]

\[ E_j^2 \]

\[ E_j^2 \]

where different from the ECD, the tensor product of transition electric quadrupole moment (TEQM, \( \Theta \)) and TEDM determines the ROA intensity, and \( \omega_{\mu} \) is the gap of two energy levels. The first and second terms of eq 2 are Raman activity and ROA intensity, respectively. ROA is related to the product of TEDM and TMDM and the tensor product of TEQM and TEDM. Through the 2D color maps, we visualized the visual representation of TEDM and TMDM and their tensor product. Similarly, the tensor product of TEQM and TEDM can also be represented by a 2D color map.

This paper focuses on the comparative analysis of the response of oxygen atoms to light excitation at different positions of molecules and successfully confirms that the source of the molecular chiral center is not only the chiral center but also the asymmetric electromagnetic interaction in the whole system.

2. RESULTS AND DISCUSSION

2.1. OPA and TPA. Figure 2 displays the OPA and TPA spectra of these three molecules. The blue, red, and black lines represent R1, R2, and R3, respectively. As shown in Figure 2a, we selected the first excited state (\( S_1 \)) of R1, \( S_1 \) of R2, and \( S_1 \) and \( S_4 \) of R3 to study after observing the OPA diagram. We can observe that the wavelengths of the first excited states of molecules 1, 2, and 3 are 233, 226, and 244 nm, respectively. We also get information that there is \( S_4 \) of R3 at 215 nm. For \( S_1 \), the molar absorption coefficient of R1 is very small, and the one of R2 is still small but larger than the one of R1; the molar absorption coefficient of R3 is much larger than those of the other molecules. This indicates that R3 has a strong response to OPA. Figure 2b shows the TPA spectrum of these three molecules. The transition process of TPA requires two steps, that is to say, an intermediate state is necessary as a transfer station from the ground to final...
excited states. The ground state transition can choose different intermediate states, that is, when the ground state and the final state are the same, the intermediate state is not unique. We can calculate the intermediate state by employing quantum chemistry software. Through observation, we selected the first excited states of R1, R2, and R3 for TPA analyses. Since the studied TPA state is the first excited state, which has no intermediate state. Therefore, it directly transfers from the ground state to S1, which is the same as OPA transition characteristics. Then, the excited states to be studied in TPA are the same as OPA, so the analytical results are also the same.

By drawing the TDM and CDD diagrams of OPA, we can see more intuitively the position and direction of the electronic transition between excited states when molecules are excited by light, as shown in Figure 3. The positions of hole density and electron density are shown in green and red, respectively. Through the combination of 2D and 3D visualization methods, we can get a lot of information. Figure 3a is the transition density matrix of S1 of R1, which shows that weak charge transfer and strong local absorption are the main characteristics of the transition. This conclusion can obviously be confirmed by Figure 3c, which shows the charge difference density of S1 in R1. The localized excitation characteristics of the charge are obvious and are concentrated around the oxygen atoms. For S1 of R2, the charge transfer characteristic is localized excitation, as shown in Figure 3b. Figure 3d shows the atom positions where charge redistribution processes are concentrated on the oxygen atoms of the intermediate part. For S1 of R3, Figure 3e shows that the charge redistribution characteristic is localized excitation with weak charge transfer. As shown in Figure 3g, the localized excitation occurs on the benzene ring and the oxygen next to it. Moreover, for S4 of R3, Figure 3f shows that the charge transfer characteristic is localized excitation with weak charge transfer, which is confirmed in Figure 3h.
and the occurrence of localized excitation and charge transfer are observed. The atoms are concentrated on the ring containing the oxygen atoms and the benzene ring. By comparing the structure of the three molecules, we found that all of them have a dioxygen bridge structure, and it is the dioxygen bridge part that can be used as an intermediate for charge transfer.

2.2. ECD. Figure 4 shows the ECD spectra of the three molecules. We analyze the first excited states of these three molecules separately. The blue, red, and black curves represent R1, R2, and R3, respectively. By observing the molecular structure diagram, we can clearly observe that R1 and R2 have chirality, but we cannot see whether R3 has chirality. It can clearly conclude that R3 is also chiral. To confirm which part of the molecule contributes to the charge–hole interaction, we plotted the three-dimensional density of TEDM and TMDM, as well as the two-dimensional TEDM and TMDM and their tensor product.

The density of TEDM and TMDM component isosurface maps of R1 are shown in Figure 5a. The first row represents the TEDM density, where pink represents holes and blue represents electrons; the second row represents the TMDM density, where yellow represents holes and purple represents electrons. By comparison, it is found that the TMDM density and TEDM in each component are basically the same. For R1, the atoms that contribute more to electron and hole differential after photoexcitation are still concentrated around the dioxygen bridge. TEDM, TMDM, and their tensor product of R1 are shown in Figure 5b at different states. The first column represents TEDM, the second column represents TMDM, and the third column is the tensor product of TEDM and TMDM. The last column of Figure 5 shows the contribution of each atom to the ECD intensity, which is determined by the tensor product itself, that is, the quadrupole moment \( l(\mu_i)l(\mu_m)l^2 \). The density matrices indicate that the TEDM density is greater than the TMDM density.

The 3D TEDM and TMDM density maps of R2 are shown in Figure 6a. It can be observed that the TEDM density and the TMDM density are mainly concentrated in the dioxygen bridge part of R2 with a large value. The TEDM density in the X component is a little larger than the TMDM density, whereas in the Y and Z components, the TMDM density is greater than the TEDM density. So, in the density matrix, TEDM and TMDM have similar densities. Figure 6b shows the matrix filling diagrams of TEDM and TMDM, and their tensor product. The TDM density is mainly concentrated on the dioxygen bridge and its connected ring, and the difference between the intensity of TDM and TMDM is small.

Now let us also analyze the ECD of R3. Figure 7a shows that the TEDM density and the TMDM density of R3 are concentrated at the benzene ring and the oxygen atoms connected with it, and their values are large. As revealed in Figure 7b, we found a phenomenon that the intensity of TDM is much greater than that of TMDM, showing an order of magnitude difference. It is also obvious that the density of TDM is indeed concentrated at the benzene ring and its connected oxygen atom. The 2D and 3D visualizations make it convenient for us to study ECD. This method can be called generalized chirality theory. Using this method, we successfully distinguish R3 with chirality and found that the chirality of the system depends not only on the chiral center of the molecule but also on the magnetic transition of the entire system that determines the chirality.

2.3. Raman Spectroscopy and ROA. The Raman spectroscopies of the molecules were analyzed (see Figure 8). Figure 8a shows the resonance Raman spectrum of R1 with a strong Raman peak at a wavenumber of 915 cm\(^{-1}\), and its Raman activity is not high. Figure 8b shows the resonance Raman spectrum of R2 with a strong peak at the wavenumber of 898 cm\(^{-1}\), and its Raman activity is two orders of magnitude larger than that of R1. A strong Raman peak of R3 appears at 1653 cm, and the value of Raman activity reaches 10\(^3\), as shown in Figure 8c. At the same wavelength, the resonance Raman activity is not the same, which indicates that under the same incident light, different vibration modes of the molecule have different Raman spectral responses.

The second term of formula 2 indicates that the ROA spectrum relates to the TEDM, TEQM, and TDM of the molecules. We have also studied the Raman optical activity (ICPu/SCPu (180)) of these three molecules and still choose the first excited state. Figure 9a–c shows the ROA spectra of molecules 1, 2, and 3. The molecular vibration mode maps corresponding to these peaks of the three molecules are also shown in Figure 9d–f. Simultaneous analysis of the ROA spectrum and vibration modes at different frequencies allow us to get the response of each group of the molecules to light. As can be seen in Figure 9a, ROA is also very strong. As shown in Figure 9d, the vibration of R1 mainly exists in the ring where oxygen atoms exist, and there are many vibration positions. The main reason for this phenomenon might be the existence of lone pair electrons in oxygen, which play a more important role in electromagnetic interactions.28 In Figure 9b, we analyze a strong peak of R2 at a wavenumber of 1653 cm\(^{-1}\). The light response of R2 is mostly concentrated on the dioxygen bridge and its connected ring in Figure 9e. The results show that the oxygen atom plays an important role in TEDM and TMDM. ROA has different sensitivities to different incident light frequencies, which causes the relative intensity of the Raman peak to change when the Raman shift changes. When the wavenumber of R3 is 1653 cm\(^{-1}\), the maximum absolute value of the Raman optical activity is obtained in Figure 9c. As shown in Figure 9f, the vibration of R3 is mainly concentrated on the benzene ring and its connected oxygen atoms.
The strength of ROA is relative to the tensor product of TEDM and TMDM and the tensor product of TEQM and TEDM. Consequently, Figure 10 shows this process. The tensor product is calculated. As shown in Figure 10a, we can realize that the tensor of R1 at 233 nm is mainly donated by the oxygen-containing ring and the dioxygen bridge. In Figure 10b, the ROA of R2 is mostly contributed by the dioxygen bridge and its connected ring. Here, the oxygen atoms can act as intermediaries in the process of charge transfer and promote the interaction between TDMs. As shown in Figure 10c, the tensor product contribution of R3 mainly comes from the benzene ring. Consistent with eq 2, the product of two tensors determines the strength of ROA. One is the tensor product of TEDM and TMDM, and the other is the tensor product of TEDM and TEQM. In Figure 10, we can clearly see that for all the three molecules, the influence of the second term is greater than that of the first one.

3. CONCLUSIONS

In this paper, 2D and 3D visualization methods were utilized to analyze the physical mechanism of artemisinin and its derivatives under light excitation, including OPA, TPA, ECD, and ROA. For the three chosen molecules, the atoms that play an important role in charge redistribution in OPA and TPA are generally the same as those in ECD and ROA, which are principally the oxygen-containing ring and the dioxygen bridge. It can be concluded that dioxygen atoms can be regarded as a connection of charge transfer, which can also strengthen this effect. Using this method, we can not only explain the mechanism of traditional molecular chirality but also distinguish whether the molecules without the chiral center mark have chirality. Even if the wavelength of the incident light is the same, the responsivity of RRS to light excitation is different under different vibration modes, and the ring structure containing the dioxygen atom bridge can also enhance the dipole moment of the light-encouraged transition. The methods and conclusions in this paper provide theoretical help for studying the electromagnetic interaction and physical principle of chiral molecules excited by light. This method is suitable for different scale researches.

4. METHODS

4.1. Calculation Details. The quantum computing part is done with Gaussian 16 software. We use the framework of density functional theory (DFT) to combine B3LYP and 6-31(G) basis sets. The dispersion function in quantum chemistry calculation refers to a basis function with a small exponent and a wide spatial distribution range. The necessity

Figure 5. TEDM density (blue represents the positive isosurface and the pink represents negative isosurface) and TMDM density (purple represents the positive isosurface and yellow represents the negative isosurface) component isosurface maps for S1 of R1 (a); TEDM, TMDM, and their tensor product for S1 of R1 (b).
of adding a dispersion function is summarized based on a large number of theoretical calculation articles and practical experience as follows: Calculation of dipole moment, polarizability, hyperpolarizability, Rydberg excited state, anion system energy and electron affinity energy require a dispersion function, but our article does not discuss these.

Figure 6. TEDM density (blue represents the positive isosurface and pink represents the negative isosurface) and TMDM density (purple represents the positive isosurface and yellow represents the negative isosurface) component isosurface maps for S\textsubscript{1} of R2 (a); TEDM, TMDM, and their tensor product for S\textsubscript{1} of R2 (b).

Figure 7. TEDM density (blue represents the positive isosurface and pink represents the negative isosurface) and TMDM density (purple represents the positive isosurface and yellow represents the negative isosurface) component isosurface maps for S\textsubscript{1} of R3 (a); TEDM, TMDM, and their tensor product for S\textsubscript{1} of R3 (b).
contents, so the dispersion function is not considered. CAM-B3LYP was used to calculate and analyze the transition process and the obtained spectra. The TEDM density, the TMDM density, the distribution of electron–hole pair analysis, and the TDM density matrix are completed with the help of the Multiwfn 3.6 program. The VMD software was used to achieve the distribution of the isosurface of the TEDM density and TMDM density maps in a 3D space.

### 4.2. TPA

There are two transitions in TPA, one is a two-step transition through an intermediate excited state, and the other is a symmetrical fracture transition because of the huge difference. The quantification of the TPA process is defined by:

$$
\sigma_T = \frac{4\pi^2 \alpha_0^5 c_0^7 g(\omega)}{15 \varepsilon_0^4 \hbar^2} \delta_{T}\quad (3)
$$

where the first term is combined by the Bohr radius ($a_0$), speed of light ($c_0$), and the structure constant ($\alpha$). The second is controlled by the frequency of light ($\omega$) and excited-state lifetime (tie-bar-start). The profile of the spectral line is expressed by $g(\omega)$. If it is regarded as a $\delta$ function, the transition probability of formula 3 is revealed by:

$$
\delta_T = 8 \sum_{j \neq k \neq j} \frac{|\langle f | \mu | j \rangle|^2 |\langle j | \mu | g \rangle|^2}{(\omega_j - \omega_j/2)^2 + \Gamma_j^2} (1 + 2 \cos^2 \theta_j)
$$

$$
+ 8 \frac{|\Delta \mu_{fg}|^2 |\langle f | \mu | g \rangle|^2}{(\omega_j/2)^2 + \Gamma_j^2} (1 + 2 \cos^2 \phi)
$$

where the TPA probability consists of the ground ($|g\rangle$) and final states ($|f\rangle$), and $|j\rangle$ represents any state; $\mu$ and $\omega_j$ are the TEDM and energy of special excited states, and the difference between the permanent dipole moment can be expressed by $\Delta \mu_{fg} = |\langle f | \mu | j \rangle| - |\langle g | \mu | j \rangle|$; $\theta$ is the angle between the Dirac bracket $\langle | f \mu | j \rangle$ and $\langle | g \mu | j \rangle$. The angle between the Dirac bracket $\Delta \mu_{fg}$ and $\langle | f \mu | g \rangle$ is represented by $\phi$. From eq 4, it is confirmed that the TPA probability is determined by the TDM product during the two transitions. Compared
with the other methods, the results obtained in this paper are in good agreement with the experiment.8,10,36

4.3. TEDMs and TMDMs. TEDMs are expressed by the physics formula37

$$\chi = \langle |\mu| |\mu| \rangle + \sum_{\mu \neq \nu} \langle |\mu| |\mu| \rangle$$

where

$$P_{\mu \nu}^{\text{tran}}$$

is the TDM; the allocation coefficient from the occupied track to the virtual track is represented by \(w\). The linear combination coefficients of molecular orbitals are represented by \(C_{\mu i}\) and \(C_{\nu j}\), and \(\mu\) represent the amount of basis function \(\chi_{\mu}\). The contribution of atoms to TEDM can be calculated. TMDM is described as follows37

$$\chi = - \langle |\mu| |\mu| \rangle + \sum_{\mu \neq \nu} \langle |\mu| |\mu| \rangle$$

When \(D_{\mu}^{\nu}\) and \(M_{\mu}^{\nu}\) are known, their tensor product can be calculated.

### AUTHOR INFORMATION

#### Corresponding Authors

Xijiao Mu — School of Mathematics and Physics, University of Science and Technology Beijing, Beijing 100083, P. R. China; orcid.org/0000-0001-7226-613X; Email: muxijiao@gmail.com

Jun Dong — School of Electronic Engineering, Xi’an University of Posts and Telecommunications, Xi’an 710121, P. R. China; orcid.org/0000-0001-7226-613X; Email: dongjun@xupt.edu.cn

Jun Quan — School of Physics Science and Technology, Lingnan Normal University, Zhanjiang 524048, P. R. China; Email: Quanj@lingnan.edu.cn

Chunhua Tian — School of Physics Science and Technology, Lingnan Normal University, Zhanjiang 524048, P. R. China; Email: chunhuatian@lingnan.edu.cn

Jialin Ma — School of Physics Science and Technology, Lingnan Normal University, Zhanjiang 524048, P. R. China; School of Mathematics and Physics, University of Science and Technology Beijing, Beijing 100083, P. R. China

Wenhua Qiao — School of Mathematics and Physics, University of Science and Technology Beijing, Beijing 100083, P. R. China

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c03361

### Notes

The authors declare no competing financial interest.

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