#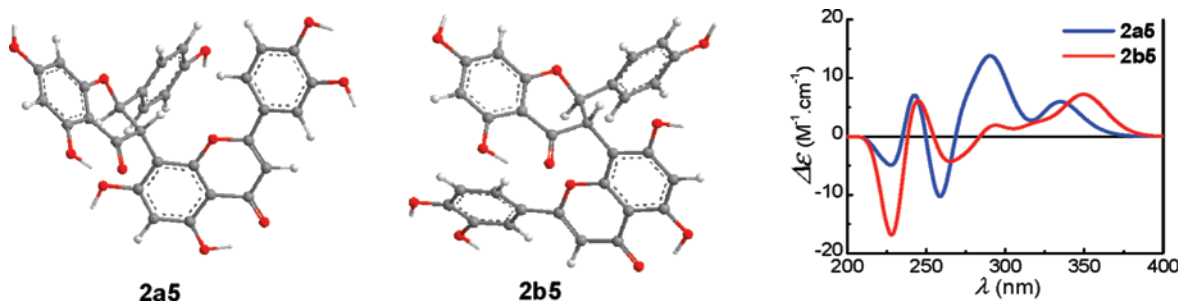 Theoretical Calculation of Electronic Circular Dichroism of the Rotationally Restricted 3,8″-Biflavonoid Morelloflavone

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Theoretical calculation of electronic circular dichroism (ECD) of the rotationally restricted 3,8″-biflavonoid (+)-morelloflavone using time dependent density functional theory (TDDFT), performed at 298 K at B3LYP-SCRF/6-31G*//B3LYP/6-31G* level with COSMO model, permitted unequivocal assignment of its 2R,3S absolute configuration. The experimentally observed Cotton effect (CE) around 290 nm is contributed by the acetophenone $\pi \rightarrow \pi^*$ transition of the ABC-flavanone moiety and the electronic transition within the DEF-flavone moiety, while another diagnostic positive CE around 350 nm is attributable to the electronic interaction between the ABC-flavanone moiety and the DEF-flavone moiety, as well as the electronic transition within the DEF-flavone moiety. The remarkable differences of the calculated ECD of its two rotamers indicate that the rotational restrictions significantly affect the ECD of 3,8″-biflavonoids. Empirical ECD rules derived from monomeric flavonoids may not be applicable to configurational assignment of complex 3,8″-biflavonoids. This study has provided new insights in interpreting the experimentally observed ECD spectra of this class of compounds.

Introduction

Recent advances on calculation of electronic circular dichroism (ECD) have greatly enhanced its value in determining absolute configuration of chiral molecules. Several quantum chemistry methods including time dependent density functional theory (TDDFT) can be used to calculate or predict the ECD of chiral molecules.[1]

The bioactive 3,8″-biflavonoids represent a small but biosynthetically important group of natural products.[2] They include two types: flavanone-(3 → 8″)-flavone (or flavonol) with two stereogenic centers and one chiral axis, and flavanone-(3 → 8″)-flavanone (or dihydroflavonol) with three (or four) stereogenic centers and one chiral axis, called the GB-series of biflavonoids (Figure 1). The restricted rotation about the C3—C8″ bond between the two flavanyl moieties significantly complicated assignment of their absolute configuration. Although empirical CD rules derived from monomeric chiral flavonoids have been used to address this issue, no unambiguous evidence, e.g., from total synthesis or X-ray crystallography, has been available to support the deduced absolute configuration for this class of compounds. In addition, conflicting interpretations leading to different configurational assignments for the same compound GB-2 (**3**) have been reported.[3] In the current study, the relatively simple flavanone-(3 → 8″)-flavone, (+)-morelloflavone (**2**), with two stereogenic centers and a chiral axis was selected for

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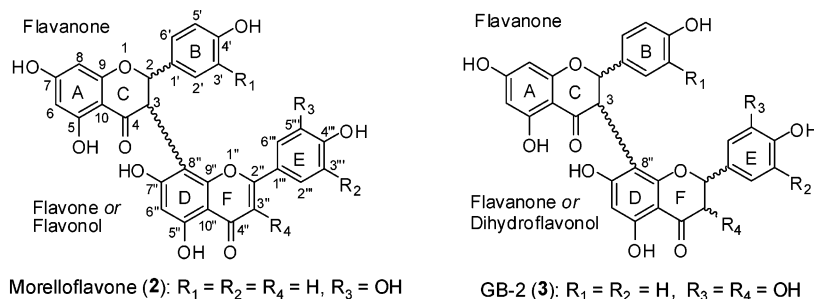
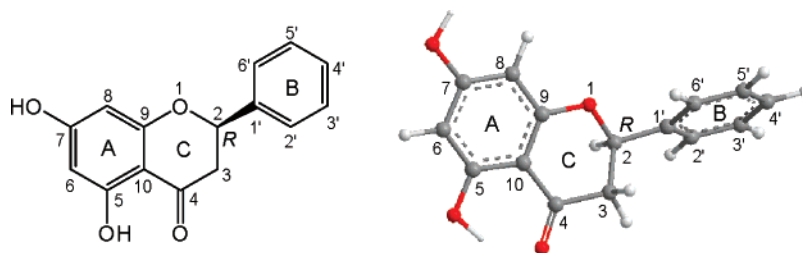**FIGURE 1.** Typical structures of 3,8″-biflavonoids.

FIGURE 2. Structure and optimized geometry of (2*R*)-pinocembrin (**1**) at B3LYP/6-31G* level.

TABLE 1. Total Energies (au), and Key Transitions and Their Related Rotatory and Oscillator Strengths, of (2*R*)-Pinocembrin at B3LYP/6-31G* Level

species	total energy	transition	ΔE^a (eV)	λ^b (nm)	f^c	$R_{vel}{}^d$	$R_{len}{}^e$
(2*R*)-**1**	−879.725485 2	67→68	3.91	317	0.05	−10.3	−10.9
		65→68	4.12	301	0.01	13.8	14.8
		66→68	4.65	267	0.23	43.5	44.3
		63→68	4.99	249	0.01	−16.0	−16.8

[a] Excitation energy. [b] Wavelength. [c] Oscillator strength. [d] Rotatory strength in velocity form (10^{-40} cgs). [e] Rotatory strength in length form (10^{-40} cgs).

theoretical calculation of its ECD by using the TDDFT method in order to unequivocally establish its absolute configuration and gain an understanding how the rotational achiral DEF-flavone unit affects the observed experimental ECD. The results provide new insights in interpreting the experimentally observed ECD spectra of this class of compounds.

Methods of Calculations

All calculations were performed at 298 K by the Gaussian03 program package.[4] A semiempirical AM1 method was employed to scan the potential energy surface (PES) to identify conformers. Ground-state geometries were optimized at the B3LYP/6-31G* level, total energies of individual conformers were obtained, and vibrational analysis was done to confirm these minima. TDDFT at the same level was employed to calculate excitation energy (in nm) and rotatory strength R in the dipole velocity form (R_{vel}) and dipole length form (R_{len}). The calculated rotatory strengths were simulated into an ECD curve by using the Gaussian function:

$$\Delta \in (E) = \frac{1}{2.297 \times 10^{-39}} \frac{1}{\sqrt{2\pi}\sigma} \sum_i^A \Delta E_i R_i e^{[-(E-\Delta E_i/2\sigma)]^2}$$

where σ is the width of the band at $1/e$ height and ΔE_i and R_i are the excitation energies and rotatory strengths for transition i, respectively. $\sigma = 0.10$ eV and R_{vel} were used in this work.

"Self-Consistent Reaction Field" method (SCRF) with "COn-ductor-like continuum Solvent MOdel" (COSMO) was further employed to perform the conformational analysis and ECD calcula-

tion of some conformers in methanol solution at B3LYP-SCRF/6-31G*//B3LYP/6-31G* level.[5]

Results and Discussion

ECD of the Flavanone, Pinocembrin (1). The empirical CD rules derived from chiral monomeric flavonoids indicate that (2*S*)-flavanones and (2*R*,3*R*)-dihydroflavonols give the same negative Cotton effect (CE) around 290 nm and a positive CE

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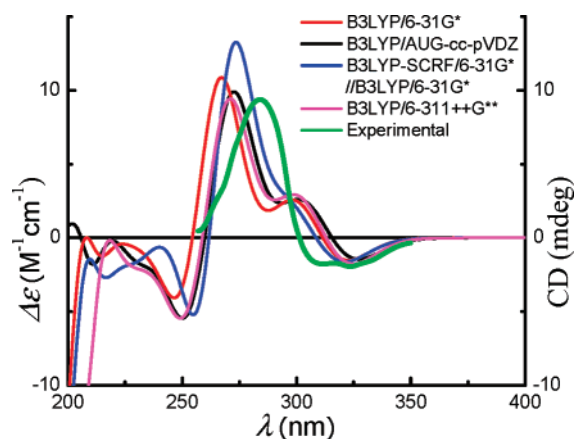
FIGURE 3. Calculated ECD spectra of (2R)-pinocembrin (**1**) at different levels in Δε values (M⁻¹ cm⁻¹) and its experimental ECD spectrum in the range of 260–350 nm in raw ellipiticiy (mdeg).[7]

around 330 nm, while their enantiomers give opposite CEs.[6] The CEs around 290 and 330 nm were considered to be associated with their acetophenone $\pi \rightarrow \pi^*$ and n $\rightarrow \pi^*$ electronic transitions, respectively.[6] To assess the feasibility and reliability of the TDDFT method in calculating ECD of chiral flavonoids, the simple monomeric flavanone pinocembrin (**1**), with published experimental ECD data,[7] was used as a model compound. The optimized geometry of (2R)-**1** at B3LYP/6-31G* level in the gas phase is shown in Figure 2. The heterocyclic ring adopts a half-chair conformation with an equatorial phenyl B-ring rotated to be almost perpendicular to the plane of the A/C rings. The dihedral angle, O1−C2−C1′−C2′, is 40.0°. The calculated total energies, important transitions, related rotatory strengths, and oscillator strengths of (2R)-**1** at B3LYP/6-31G* level are shown in Table 1, while the simulated ECD curve of (2R)-**1** is shown in Figure 3. It is evident that the calculated ECD spectrum is consistent with its experimental data in the region of 260–350 nm[7] (Figure 3), although the maximum absorption is shifted toward the low wavelength region, i.e., around 270 nm in the calculated ECD versus around 285 nm in the experimental ECD.

The molecular orbitals involved in key transitions for the ECD of (2R)-**1** are shown in Figure 4. The major positive rotatory strength at 267 nm results from the electronic transition from orbital 66 involving a delocalized $^{14}_{11}\pi$ bonding (a 14-electron π system involving 11 atoms) of the acetophenone moiety to its corresponding unoccupied orbital 68 (LUMO). This supports the classical interpretation that the diagnostic positive CE in the range of 280–290 nm for this class of compounds is a contribution from the $\pi \rightarrow \pi^*$ transition of the acetophenone moiety. However, the observation that the negative rotatory strength at 317 nm resulted from the transition from HOMO (Orb67), which excludes involvement of the electrons of the carbonyl group, to LUMO (Orb68) contradicts the classical interpretation that another diagnostic CE around 330 nm for this class of compounds is associated with the acetophenone n $\rightarrow \pi^*$ transition.[6]

The effects of different basis sets on ECD of (2R)-**1** in the gas phase were investigated using TDDFT at B3LYP/AUG-cc-pVDZ//B3LYP/6-31G* and B3LYP/6-311++G** levels. In

addition, B3LYP-SCRF/6-31G*//B3LYP/6-31G* was performed in methanol solution (dielectric constant ϵ = 32.63) with COSMO model to address the solvent effect on the ECD of (2R)-**1** since the experimental ECD is generally recorded in organic solvents. Comparison of the calculated ECD of (2R)-**1** in Figure 3 shows that there are no major differences among the four simulated ECD curves. The positive rotatory strength at 267 nm calculated by B3LYP/6-31G* are slightly shifted toward the high wavelength region at 270 nm by B3LYP/6-311++G**, 272 nm by B3LYP/AUG-cc-pVDZ//B3LYP/6-31G*, and 272 nm by B3LYP-SCRF/6-31G*//B3LYP/6-31G*, which better fits with the experimental data at 285 nm in solution. We also employed BHLYP/6-31G* and BLYP/6-31G* to calculate the ECD of (2R)-**1**. However, the calculated ECD spectra do not match the experimental ECD (refer to Figure S1 in Supporting Information). The above results indicate that TDDFT (B3LYP) should be an effective method for calculating/predicting the ECD of the monomeric flavonoids, with a larger basis set or consideration of the solvent effect further improving the method.

Conformational Analysis of (+)-Morelloflavone (2). Our previous study[2] by NMR and semiempirical AM1 calculations demonstrated that (+)-morelloflavone (**2**) possessed two preferred conformations about the interflavanyl bond in a ratio of 1:0.37 in solution, i.e., 73% to 27%. In the major and minor conformers **2a** and **2b**, respectively, the DEF-flavone moiety is extended above and below the plane of the A/C-ring of the ABC-flavanone moiety, respectively. Without considering the effects of rotation about the interflavanyl bond, **2** was assigned a 2R,3S absolute configuration based on comparison of its experimental CD with those of similar compounds.[2]

In this study, extensive conformational analysis of the arbitrarily assigned (2R,3S)-**2** was conducted as follows. Since **2** is a relatively big molecule and the availability of computational time is a consideration, the less accurate semiempirical AM1 method in the gas phase was initially used for conformational search by rotating the DEF-flavone moiety with a step increase of the key dihedral angle, C4−C3−C8″−C7″, in which two stable conformers **2a** and **2b** with dihedral angles around 60° and 225° (i.e., −135°), respectively, were obtained based on its potential energy surface (Figure 5A). For the major conformer **2a**-series, further search using the AM1 method by rotating the unsymmetric E-ring of the DEF-flavone moiety and considering the presence or absence of a hydrogen bond between C7″-OH and the C4 carbonyl group afforded eight conformers **2a1**−**2a8** (Figure 5B and 5C). Note that **2a1**−**2a4** have hydrogen bonding between C7″-OH and the C4 carbonyl group (Figure S2 in SI). In a similar way, the minor conformer **2b**-series also gave eight conformers **2b1**−**2b8** (Figure 5D and 5E). Optimizations of individual conformers were then performed at B3LYP/6-31G* level and harmonic frequencies analysis at the same level conducted to confirm these minima. Stable points on potential energy surfaces for **2a1**−**2a8** and **2b1**−**2b4** were relocated, but for **2b5**−**2b8** in Figure 5E, only two minima, **2b5** and **2b7**, were obtained (Figure S2).

Among these conformers, the key dihedral angles of C4−C3−C8″−C7″ vary from 50° to 61° in **2a1**−**2a8**, −80° to −83° in **2b1**−**2b4**, and −126° and −131° in **2b5** and **2b7**, respectively. The dihedral angles of H2−C2−C3−H3 for all conformers are almost 180°, supporting a large coupling constant (~12 Hz) between H2 and H3 observed in our previous NMR studies.[2] For all conformers, the atoms in rings A and C, except C2, are

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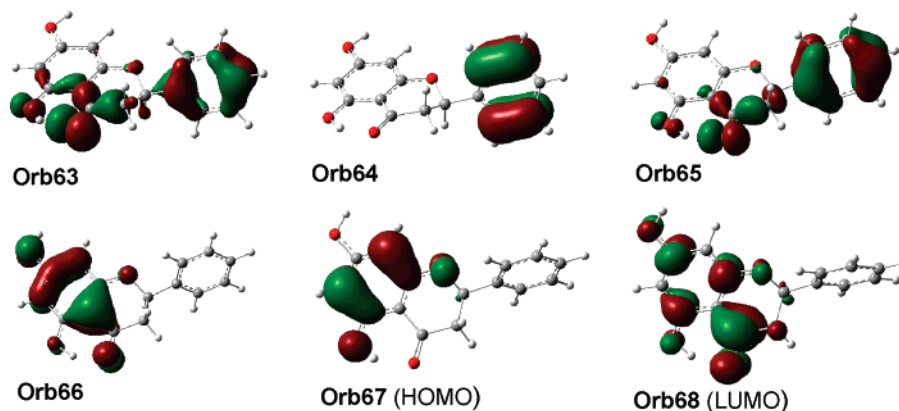(7) Caccamese, S.; Caruso, C.; Parrinello, N.; Savarino, A. *J. Chromatogr. A* **2005**, *1076*, 155.

FIGURE 4. Molecular orbitals involved in key transitions in the calculated ECD of (2*R*)-**1** at B3LYP/6-31G* level in gas phase.

TABLE 2. Conformational Analysis of (2*R*,3*S*)-2 in Gas Phase and in Methanol Solution

species	in gas phase						in methanol	
	ΔE^a	$P_E\%^b$	ΔE^c	$P_E\%^d$	ΔG^e	$P_G\%^f$	ΔEs^g	$P_{Es}\%^h$
2a1	0.41	10.0	0.39	7.8	1.30	3.2	2.86	0.3
2a2	0.00	19.8	0.02	14.7	1.07	4.7	2.44	0.5
2a3	0.67	6.4	0.51	6.4	0.88	6.5	3.85	0.1
2a4	0.11	16.6	0.00	15.2	0.63	9.9	2.87	0.2
2a5	0.53	8.2	0.23	10.2	0.78	7. 7	0.16	23.4
2a6	0.64	6.7	0.32	8. 9	0.39	14.7	0.00	30.8
2a7	0.43	9.6	0.15	11.8	0.00	28.6	1.29	3.5
2a8	0.37	10.5	0.08	13.3	0.25	18.7	0.42	15.2
2b1	2.84	0.2	3.06	0.1	4.15	0.0	4.84	0.0
2b2	5.12	0.0	5.17	0.0	5.77	0.0	8.42	0.0
2b3	2.52	0.3	2.71	0.2	3.34	0.1	6.42	0.0
2b4	4.85	0.0	5.04	0.0	6.11	0.0	6.99	0.0
2b5	0.31	11.7	0.16	11.5	0.93	5.9	0.10	26.1

a,c,e Relative energy, relative energy with ZPE, and relative Gibbs free energy, respectively (kcal/mol). *b,d,f* Conformational distribution calculated by using the respective parameters above at B3LYP/6-31G* level in the gas phase. *g,h* Relative energy (kcal/mol) and conformational distribution at B3LYP-SCRF/6-31G*//B3LYP/6-31G* level with COSMO model in methanol solution, respectively.

almost coplanar, which is similar to that in **1**. All atoms in rings D and F of the DEF-flavone moiety are coplanar, indicating the presence of an even more delocalized $^{16}_{13}\pi$ bonding in the D/F plane of **2** compared to the $^{14}_{11}\pi$ bonding in the A/C plane of **1**. For the DEF-flavone moiety in all conformers, the largest dihedral angle between ring E and the plane of D/F rings is 31°.

Since strong interactions between the multiple hydroxy groups in these conformers and the solvent may have a considerable influence on their minimum energies and possibly further affecting the ECD calculations, the single point energy (SPE) of every conformer in methanol was calculated at B3LYP-SCRF/6-31G*//B3LYP/6-31G* level with the COSMO model. The calculated thermodynamic parameters in gas phase and in methanol including total energy (*E*), zero point energy (ZPE), enthalpy (*H*), and Gibbs free energy (*G*) of **2a1**−**2a8**, **2b1**−**2b4**, **2b5**, and **2b7** are shown in Table S6 in the Supporting Information. The total energy of conformer **2b7** both in gas phase and in methanol was considerably lower than those of all others due to the formation of the hydrogen bond of C3′′′−OH···O−C5. Thus, inclusion of this conformer in the conformational analysis will result in a population of almost 100%, excluding the presence of all other conformers. **2b7** is the only conformer that possesses the hydrogen bonding between C3′′′−OH and C5−OH. However, it is reasonably perceived that this loose intramolecular hydrogen bond is unlikely to survive because of the rotating nature of the bulky flavanyl moieties and strong interaction between the C7′′−OH and the solvent.

Hence, the C7′′−OH that is presumably solvated has little chance to form a hydrogen bond with the C5−OH since the two flavanyl moieties are dynamically rotating to preclude a *frozen* conformer at that critical point. Thus, this unusual conformer **2b7** *ideally* generated by our theoretical models should not be significant in solution in real time. Surprisingly, the exclusion of **2b7** has made the conformational analysis using the SPEs of the remaining conformers in methanol in close agreement with the experimental data: a total of 73.9% population for major conformers **2a1**−**2a8** and 26.1% population for minor conformer **2b1**−**2b5** versus experimentally observed 73% to 27% for major and minor conformers (Table 2). Only three major conformers **2a5** (23.4%), **2a6** (30.8%), and **2a8** (15.2%) and one minor conformer **2b5** (26.1%) are predominant. The conformational analysis using Δ*E*, Δ*E*′, or Δ*G* in the gas phase did not match the experimental data (Table 2). At this point, it appears that consideration of the solvent effect is critical for the conformational analysis of such molecules.

ECD of (+)-Morelloflavone (2). On the basis of the conformational analysis of (+)-**2** in solution, we calculated the ECD of conformers **2a5**−**2a8** and **2b5** in methanol using TDDFT and COSMO model at B3LYP-SCRF/6-31G*//B3LYP/6-31G* level. Theoretically, an experimentally observed ECD of a chiral compound is the contribution of all preferred conformers in solution. Since the major and minor conformers of **2** were experimentally observed in a ratio of 73% to 27% in solution, it is reasonably perceived that the calculated ECD of
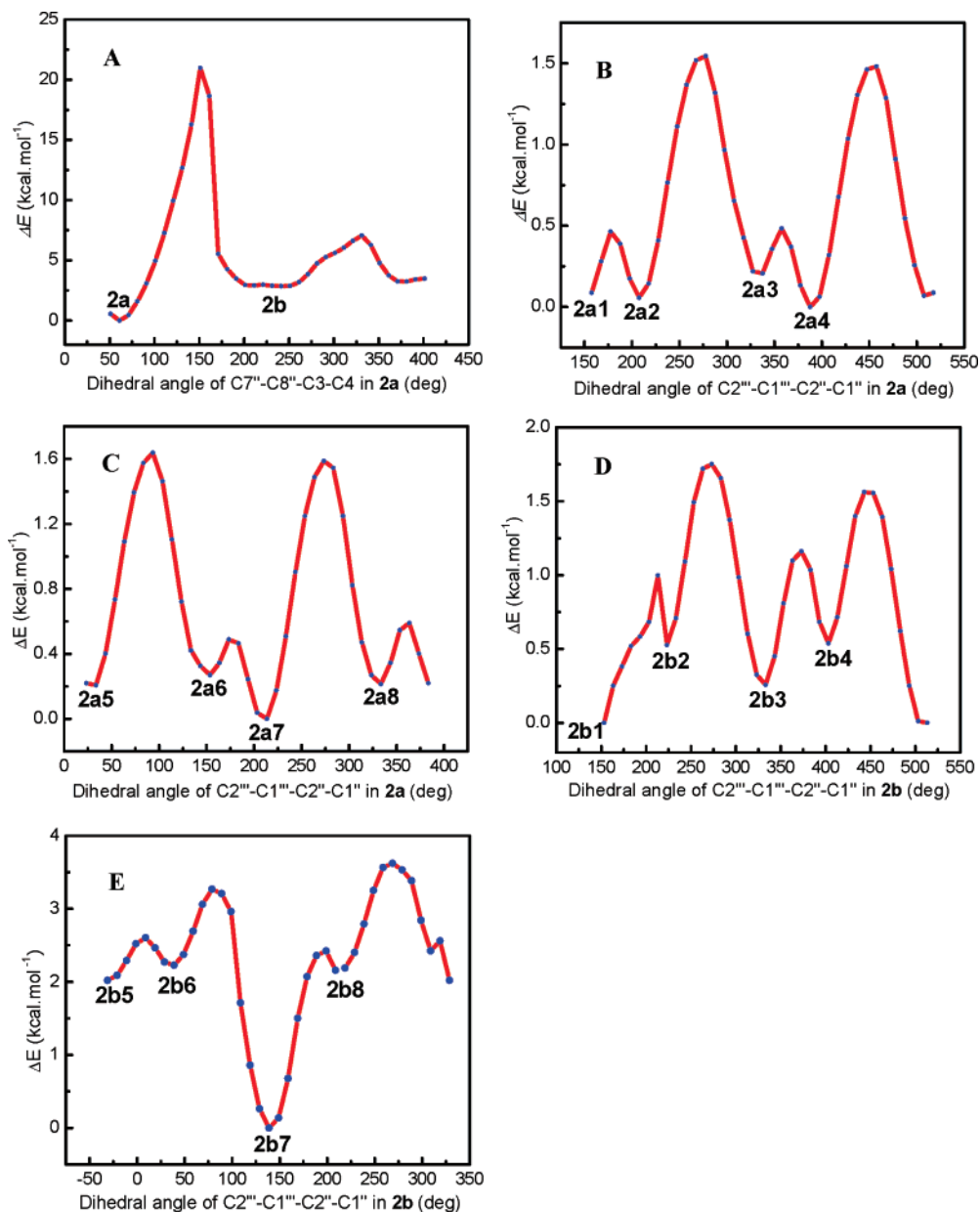
FIGURE 5. Potential energy surface of (2*R*,3*S*)-**2** scanned at AM1 level in the gas phase.

the major conformers should reflect the overall shape of the experimental one if the preassigned configurations are correct and the calculations are appropriately performed. The simulated CD curves of **2a5**−**2a8** and **2b5** are shown in Figure 6. It is evident that the ECD curve of conformer **2a5** (23.4%) in the major conformer series (Figure 6A), which shows positive CEs around 285 and 340 nm, is very similar to the experimental ECD in methanol[2] that displays positive CEs around 290 and 350 nm (Figure 6F). Another two major conformers, **2a6** (30.8%), and **2a8** (15.2%), also produce positive CEs around 285 and 340 nm (Figure 6B and 6D), while conformer **2a7** (3.5%) does not give similar CEs in that region (Figure 6C). The simulated ECD curve of conformer **2b5** (26.1%) representing the minor conformer series (Figure 6E) produces a strong CE around 350 nm, which may complement the positive CEs around 340 nm produced by the major conformers **2a5**, **2a6**, and **2a8**. A weighted ECD curve based on the populations of the above five conformers is finally generated as shown in

Figure 6F, which is overall consistent with the experimental ECD in methanol, particularly for the two diagnostic CEs around 290 and 350 nm. Therefore, it can be convincingly concluded that the (2*R*,3*S*)-absolute configuration assigned to (+)-**2** on the basis of empirical rules is correct.

Analysis of the ECD calculating results of **2a5**, **2a6**, **2a8**, and **2b5** has provided new insights in interpreting the experimentally observed ECD spectra of this class of compounds at real molecular level. Since **2a5**, **2a6**, and **2a8** generate similar ECD spectra (Figure 6), only **2a5** is used as a representative of the major conformer series for the following discussion. Table 3 lists the key transitions, oscillator strengths, and rotatory strengths of conformers **2a5** and **2b5**, while the molecular orbitals involved in the key transitions are shown in Figures 7 and 8. Table 3 showed that the experimentally observed CE around 290 nm in **2** is contributed by the positive rotatory strengths at 271 and 289 nm in **2a5**, resulting from the transitions from Orb140 to Orb146 and from Orb139 to Orb145 in Figure
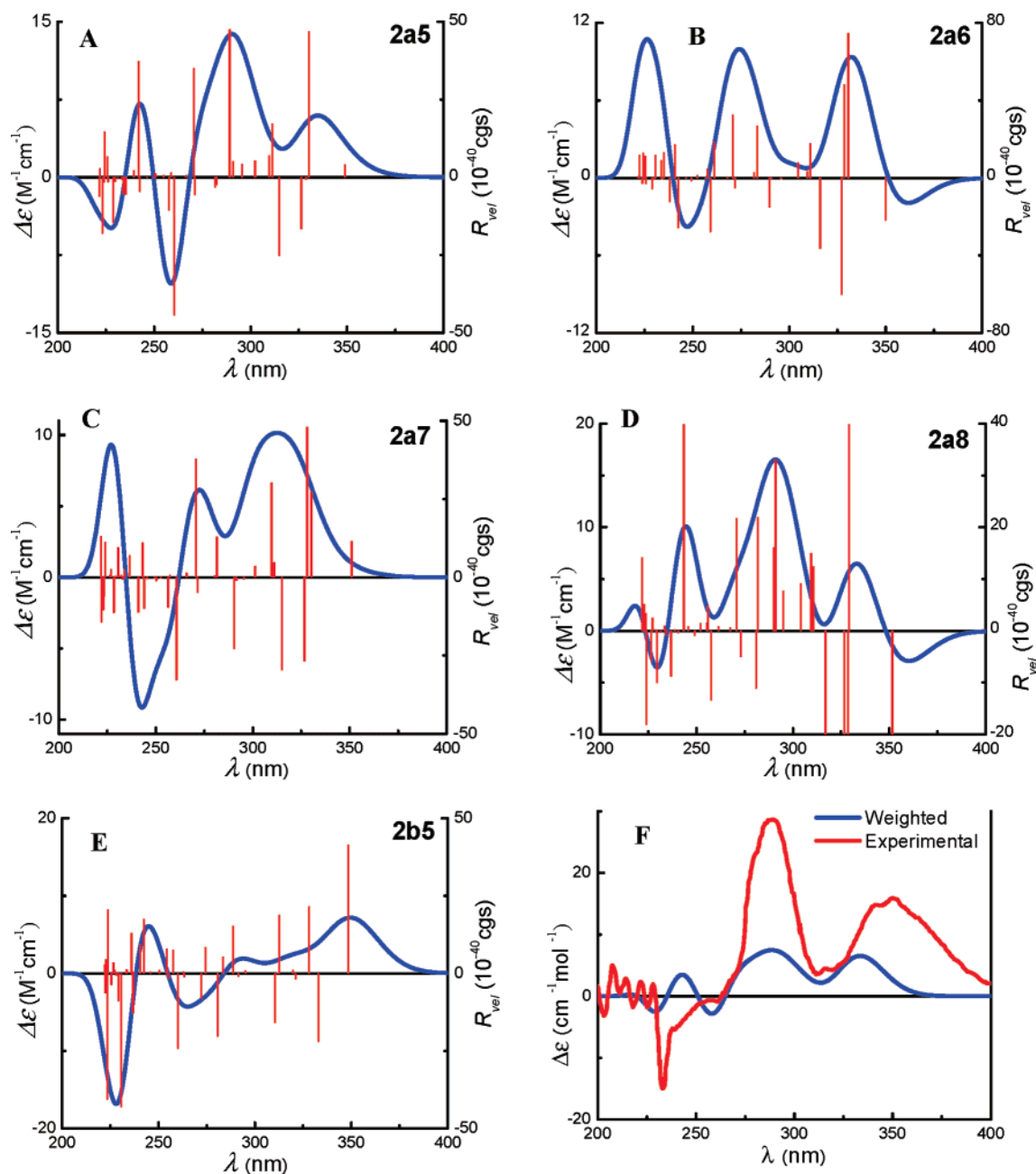
FIGURE 6. Calculated ECD of conformers **2a5**−**2a8** and **2b5** (A → E) by TDDFT at B3LYP-SCRF/6-31G*//B3LYP/6-31G* level in methanol and their weighted ECD (F) and the experimental ECD of (+)-**2** in methanol (F).[2]

7, respectively. The former corresponds to the acetophenone π → π* transition of the ABC-flavanone moiety, similar to **1** as discussed above, while the latter generating an even stronger positive rotatory strength is associated with the electronic transition within the DEF-flavone moiety. Another diagnostic positive CE around 350 nm in the experimental ECD would be contributed by the positive rotatory strength at 330 nm generated from the transition from Orb143 to Orb145 that reflects the electronic interaction between the ABC-flavanone moiety via the B-ring π electrons and the DEF-flavone moiety in major conformer **2a5**, which is further strengthened by the positive rotatory strength at 348 nm from the transition of Orb144 to Orb145 that involves the electrons within the DEF-flavone moiety in **2b5**. The results indicate that the electronic interaction between the ABC-flavanone moiety and DEF-flavone moiety

plays a critical role in generating the aforementioned two positive CEs. This supports an empirical interpretation that the positive CE around 350 nm for morelloflavone may be produced by the electronic transitions of the achiral DEF-flavone moiety chirally perturbed by the ABC-flavanone moiety.[8]

Without consideration of the solvent effect, the ECD spectra of conformers **2a1**−**2a8**, **2b5**, and **2b7** were also calculated using TDDFT at B3LYP/6-31G* level in the gas phase. The simulated ECD curves are hardly in agreement with the experimental ECD (refer to Figure S3 in Supporting Information). This strongly suggests that the utilization of the B3LYP-SCRF method with COSMO model in this study is critical. The solvent effect apparently plays a pivotal role in the case of **2** containing multiple hydroxy groups capable of forming inter- and intraunit hydrogen bonds when compared with the mono-
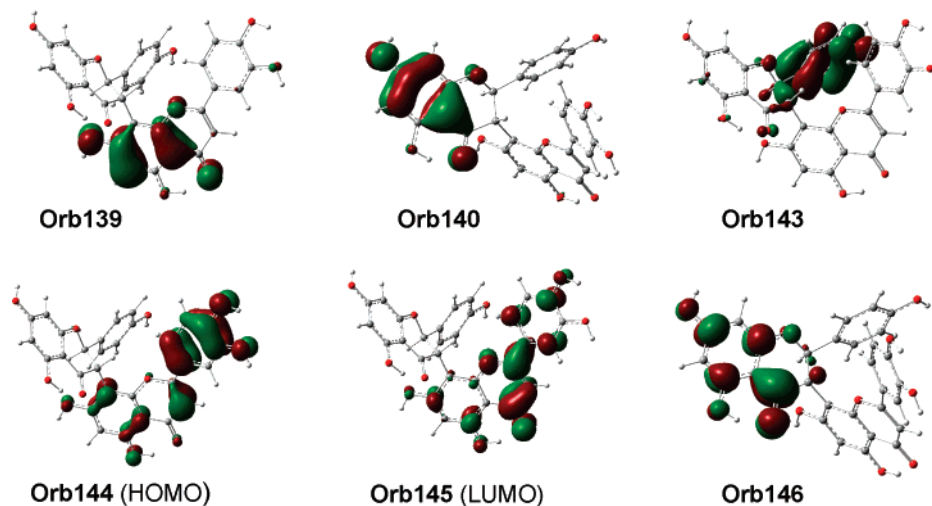
FIGURE 7. Molecular orbitals involved in key transitions in the calculated ECD of **2a5** at B3LYP-SCRF/6-31G*//B3LYP/6-31G* level in methanol.
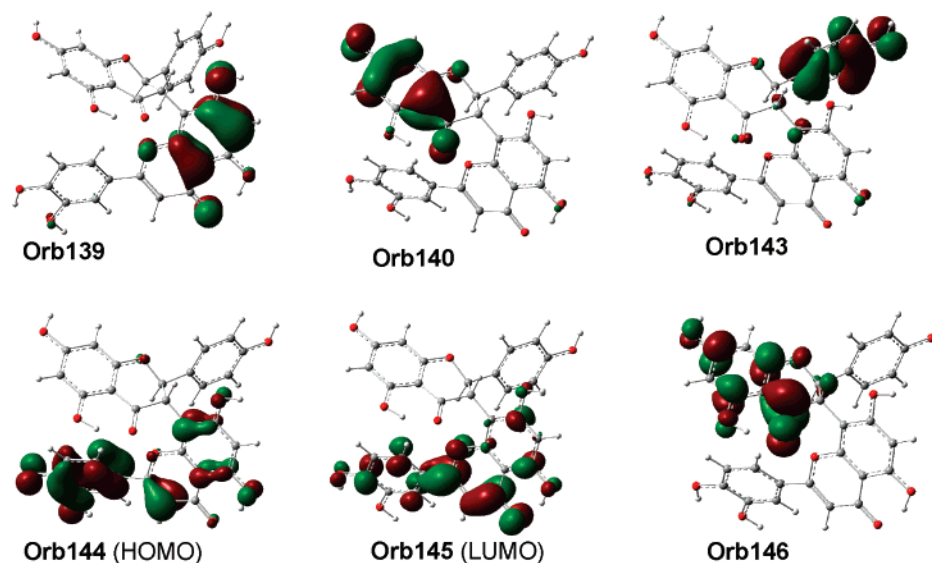

FIGURE 8. Molecular orbitals involved in key transitions in the calculated ECD of conformer **2b5** at B3LYP-SCRF/6-31G*//B3LYP/6-31G* level in methanol.

TABLE 3. Key Transitions and Their Related Oscillator and Rotatory Strengths in the ECD Spectra of (2*R*,3*S*)-Morelloflavone Conformers 2a5 and 2b5 at B3LYP-SCRF/6-31G*//B3LYP/6-31G* Level

transition	ΔE^a (eV)	λ^b (nm)	f^c	R_{vel}^d	R_{len}^e
		2a5			
143→145	3.75	330	0.089	46.9	50.5
139→145	4.29	289	0.094	47.5	48.3
140→146	4.58	271	0.347	35.0	31.5
		2b5			
144→145	3.56	348	0.309	41.5	47.6
143→145	3.78	328	0.137	21.5	24.2
143→146	3.96	313	0.043	18.8	17.7
139→145	4.29	289	0.077	15.2	15.1

^{a} Excitation energy. ^{b} Wavelength. ^{c} Oscillator strength. ^{d} Rotatory strength in velocity form (10^{-40} cgs). ^{e} Rotatory strength in length form (10^{-40} cgs).

permit a better comparison between experimental and theoretical chiroptical data as calculated for the isolated (solvent-free) molecule.[9]

It should be noted that the TDDFT calculations may not be accurate for transitions involving charge-transfer character, e.g., Orb143 to Orb145 in **2a5**.[10] However, we were able to obtain good results using the B3LYP-SCRF method with COSMO model, in contrast with the calculated results in the gas phase that do not agree with the experimental data. We also calculated the ECD of **2b7** in methanol with COSMO model at B3LYP-SCRF/6-31G*//B3LYP/6-31G* and B3LYP-SCRF/6-31G* levels. The simulated curves (Figure S3 in SI) do not match the experimental ECD of **2**, indeed exhibiting a high-amplitude negative CE near 290 nm, in contrast to the experimental high-amplitude positive CE in the same wavelength region. Such an

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meric **1** bearing fewer hydroxy groups that produces a calculated ECD spectrum in solution similar to that in gas phase (Figure 3). This is interesting in particular in view of recent studies demonstrating that solvents possessing high dielectric constants

observation, hence, supports our conjecture that **2b7** may not play a significant contributing role in solution.

The fundamental issue for ECD calculations is to use the conformers that best reflect their preferred conformers in solution, particularly for complex natural products like **2**. The B3LYP-SCRF method with COSMO model is proven to be critical in this regard. Our studies further indicate that the rotational restrictions significantly affect the ECD of 3,8″-biflavonoids, as demonstrated by the remarkable differences of the calculated ECD of two rotameric series (**2a5**, **2a6**, and **2a8** versus **2b5**). Empirical rules derived from monomeric flavonoids may thus not be applicable to configurational assignment of complex 3,8″-biflavonoids, particularly when the so-called major and minor conformers are in a ratio of nearly 1:1 in solution such as in GB-2.[3] This work has laid a foundation for the future study of the absolute configuration of more complex 3,8″-

biflavonoids with rotationally restricted chiral DEF-flavanone or dihydroflavonol structural moieties.

Supporting Information Available: Detailed computational calculating data of compounds **1** and **2**. This information is available free from the Internet at http://pubs.acs.org.

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