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Determining the absolute configuration of benzopyrenomycin by optical rotation, electronic circular dichroism, and population analysis of different conformations via DFT methods and experiments

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ABSTRACT

In this work, we have studied the absolute configuration of benzopyrenomycin using different density functional theory (DFT) methods, such as optical rotation (OR), electronic circular dichroism (ECD), and conformation distribution analysis for three kinds of Mosher esters at different levels, e.g., B3LYP/6-31G(d), B3LYP/6-311+G(d), and B3LYP/6-311++G(2d,p) in the gas phase and in solution, respectively. Careful investigations for different chiral Mosher esters using DFT theory exhibited the application conditions for certain chiral molecules in absolute configuration determination. Benzopyrenomycin possesses a unique benzo[a]pyrene-type skeleton and shows strong cytotoxicity against various tumor-cell lines.

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1. Introduction

It remains a challenge to determine the absolute configuration of complex compounds by both experimental and theoretical approaches. One potential solution is to use empirical methods such as the widely used Mosher method,¹ and optical rotation (OR) where the OR of an unknown chiral compound is compared with that of a structurally similar chiral compound. However, the wrongly assigned absolute configuration of oruwacin **1** has been predicted by comparing its OR with that of **2**.² Here we use density functional theory (DFT) method with different options (geometry optimizations, solvent model) to determine the absolute configuration of benzopyrenomycin (**3**). Additionally, we synthesized analog (**4A**) of **4** (including **4**) and compared **4A**'s OR and ECD

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0040-4020/\$ — see front matter @ 2013 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tet.2013.01.082 calculated with the experimental results, good agreements were recorded between the computational and experimental data.³ After combination of all evidences together, we demonstrated that the absolute configuration of **3** has been wrongly predicted as (2R,3S) by the empirical Mosher method and correlation of experimental OR.^{4a}

As the first example from nature, benzopyrenomycin (**3**) has a unique benzo[*a*]pyrene-type skeleton^{4b} and shows strong cytotoxic activity against various tumor-cell lines. For instance, benzopyrenomycin exhibited GI₅₀ of 3.2 µg/mL and 4.2 µg/mL for L-929 and K562 cell lines, respectively. The absolute configuration of benzopyrenomycin (**3**) was reported by Hertweck et al., which is the same as that of rubiginone A2 (**4**) (2*R*,3*S*), based on their similar molecular structures and close OR values (+38° for **3** and +50° for **4** in chloroform).^{4a,5} Meanwhile, Hosokawa et al. concluded that the absolute configuration of **3** was the same as that of **4** based on the ¹H NMR shift differences of the synthesized (*R*)- or (*S*)-Mosher ester of **5** whose structure was eventually converted to **3**.^{6a} However, when using Mosher ester to determine the absolute configuration

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of **5** analogs, wrong predictions could be made because these chiral molecules have a bulky group.^{6b} As a result, the absolute configuration of **3** might be wrongly determined, due to the incorrect distribution of the major and minor conformations predicted by Mosher method. Moreover, the synthetic results did not provide sufficient evidences to support the conclusion that (+)-**3** should have (2R,3S) configuration.⁷ In the present work, we have carefully investigated the ORs and ECDs of **3** and **4** using eight DFT methods (see the following Computational section for details) via Gaussian 03 package,⁸ and compared our results with the current OR computational methods that are reliable for rigid compounds.^{2,9,10}



2. Results and discussion

2.1. Computational methods

The methods used here are according to previous reports.^{9,10} First, conformational studies were performed using Amber and MMFF94S force field, respectively. We selected those geometries with relative energy from 0 to 5.5 kcal/mol using Amber force field for the optimizations at the B3LYP/6-31G(d) level. If the conformations obtained via MMFF94S force field were more than 300, only the first 100 geometries with lower energy were used in the computations at the B3LYP/6-31G(d) level. We made sure that all the conformations with very low energy were selected.

2.1.1. OR computation. The literature results showed that OR sign obtained at the lower level may differ from those predicted at higher basis sets.^{11a} Thus, we computed the ORs using eight methods, from

the low level to the high level. In our study, all geometries with relative energy at 0-2.5 kcal/mol were selected for OR computations at the B3LYP/6-311++G(2d,p) level in the gas phase (method 1). Sequentially, we used single point energy (SPE) data that were computed at the B3LYP/aug-cc-pVDZ level in CHCl₃ via PCM model in the OR computation (method 2). All B3LYP/6-31G(d)-optimized geometries were re-optimized at the B3LYP/6-31+G(d,p) level in the gas phase. The OR values were obtained at the B3LYP/6-311++G(2d,p) level (method 3), and SPE at the B3LYP/aug-ccpVDZ level in CHCl₃ via PCM model was then used in the OR computation again (method 4). To simulate the solvent effect on geometries, we performed the optimizations at the B3LYP/6-311+G(d)level in chloroform using PCM model for all conformers. ORs were then computed at the B3LYP/6-311++G(2d,p) level in the gas phase (method 5), followed by the OR calculations at the same level in CHCl₃ using PCM model (method 6). Furthermore, we investigated the effect of different optimization methods by computing all the geometries at the B3LYP/6-311++G(2d,p) level in the gas phase, and calculating their OR values at the B3LYP/6-311++G(2d,p) level (method 7). The SPE data were then used for OR computations (method 8). In our recent study, it was found that the use of total electronic energy (TEE), zero-point energy (ZPE, vibrational correction), and free Gibbs energy (GFE) in OR computations for small OR compounds gave good agreements in OR prediction.^{11b} Considering other results that ZPE (vibrational correction) is important for chiral compounds with small OR values, ^{11c} thus, TEE, ZPE, and GFE are also considered in OR computations.

2.1.2. Circular dichroism (CD) computation. The major conformations obtained at the B3LYP/6-311++G(2d,p) level were used in CD computation at the B3LYP/6-311++G(2d,p) level. Boltzmann statistics were used for final CD simulations. A total of 100 excited states were computed.

2.1.3. Conformational analysis. All B3LYP/6-31G(d)-optimized geometries of **6**, **7**, and **8** at the relative energy of 0-1.5 kcal/mol were re-optimized at the B3LYP/6-311+G(d) and B3LYP/6-311++G(2d,p) levels, respectively. TEE and GFE data were used to study the conformations with lowest energy for both major and minor conformations of **6** that were predicted by Mosher approach. It was found that TEE could also give good prediction for **6**. On the other hand, it

is impossible at the present to compute frequency to obtain the GFE and ZPE data for one more thousand of conformations of big molecule of Mosher esters of **7** and **8** at B3LYP/6-311+G(d) or B3LYP/6-311++G(2d,p) level. Thus, the TEE data were used for further conformation analyses for Mosher esters of **7** and **8**. The distribution of geometries with different energy at the B3LYP/6-31G(d) level can be found in Supplementary data.

2.2. Computational results for OR

The results are listed in Table 1.⁷ In all the methods, we found that (2R,3S)-**3** has negative OR values between -28° and -86° , mostly ranging from -28° to -50° , using the TEE. The OR values based on vibrational corrections (ZPE) are also negative and most of them are in the range of -16° to -32° . A +9.5 of OR was recorded when free energy was used for B3LYP/6-31G(d)-optimized geometries in method 1. However, other two ORs were -14 to -28, respectively, at the higher levels. It looks that the free energy data recorded at the B3LYP/6-31G(d) level was not the best in OR computations. Meanwhile, the predicted OR values for (2R,3S)-**4** are mostly in the range of $+2.1^{\circ}$ to $+104^{\circ}$ using TEE, ZPE, and GFE data, mostly from $+32^{\circ}$ to $+87^{\circ}$. The results are in good agreement with the experimental results. Relatively, to use the SPE in solutions predicted lower OR values such as the data in method 8.

Table 1

Computed OR values using different methods

	(2R,3S)- 3	(2R,3S)- 4
$[\alpha]_{D exp}$	+38	+50
Method 1 ^a	$-50.4/-16.2^{ m g}/+9.5^{ m h}$	$+48.7/+47.7^{ m g}/+87.2^{ m h}$
Method 2 ^b	-44.1	+18.7
Method 3 ^c	$-27.8/-26.8^{ m g}/-28.4^{ m h}$	$+33.4/+72.6^{g}/+104.7^{h}$
Method 4 ^b	-40.5	+34.1
Method 5 ^d	-28.9	+32.4
Method 6 ^e	-86.1	+2.12
Method 7 ^f	$-49.2/-28.6^{\text{g}}/-14.0^{\text{h}}$ (CHCl ₃)	$+38.4/+61.4^{\rm g}/+87.8^{\rm h}$
Method 8 ^b	-12.2	+13.5

^a B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d), total electronic energetics are used in OR computations.

^b Single point energy at the B3LYP/aug-cc-pVDZ level in chloroform via PCM model was used in OR computations.

^c B3LYP/6-311++G(2d,p)//B3LYP/6-31+G(d,p).

^d B3LYP/6-311++ $G(2d,p)//PCM(CHCl_3)/B3LYP/6-311+G(d)$.

^e PCM(CHCl₃)/B3LYP/6-311++G(2d,p)//PCM(CHCl₃)/B3LYP/6-311+G(d).

^f B3LYP/6-311++G(2d,p)//B3LYP/6-311++G(2d,p).

^g Vibration corrections are performed in OR computations.

^h Free energy data were used in OR computations.

To determine the correct or not of the methods used here for OR predictions of **3** and **4**, the best way is to synthesize **3** or **4** using standard methods. However, to synthesize 3 is a huge job. Thus, we decided to synthesize 4 via a commercially available (2R,5R)-(+)-dihydrocarvone (6). Unfortunately, it failed to obtain 4 in this route after we firstly synthesized **4A** as a model in study.³ Compound (2R,3S)-4A had the OR of +75 in chloroform, and (2R,3S)-4B had +79. Both had good agreement in ORs although 4A had no -OH on C-7. At the same time, (2R,3S)-4B just had no Me on –OH group of C-7 compared to (2R,3S)-4, both had the same skeleton. Therefore, it can be used as a standard sample to test the theoretical methods used here. The ORs for (2R,3S)-4B mostly were from +31 to +119 in the gas phase using methods 1, 3, 5, and 7, respectively. The computed OR sign for (+)-(2R,3S)-4B agreed well with experimental results.³ Very recently, **4** was obtained using the same methods that we used in syntheses of **4A** and **4B** (Scheme 1).³ Furthermore, in its ROESY experiments, the NOE between the H-3 and the -Me on C-2 was observed, it hints that the H-3 and -Me locate at the same side. Since C-2 has R configuration, C-3 should have *S* configuration. The recorded OR for (2R,3S)-**4** was +46, this is closer to the reported OR magnitude of +50 for (2R,3S)-**4**.^{4a-d} The data are almost the same as the OR of +47.^{4e} On the other hand, if it is (2R,3R) configuration, its OR should be –106 in chloroform that had been found in Yoshihama's reports.^{4e} The predicted OR for (2R,3S)-**4** is from +14 to +87, mostly in the range of +33 to +73. The predictions agree well with the experimental results. Therefore, the theoretical methods used here are reliable. In contrast, the predicted OR for (2R,3S)-**3** was in the range of -12 to -86, mostly, from -29 to -50. The OR sign is opposite to the experimental result (+50). Since the relative configuration of (+)-**3** was well established as (2R,3S)-**3** hints that the obtained (+)-**3** should be absolute configuration of (2S,3R).

2.3. Computational results for ECD

Evidences from OR support that (+)-**3** should have (2S,3R)mentioned above. Another independent evidence, such as ECD should be also important and valid. No experimental ECD was found. Thus, it is impossible to compare the ECD of (2R,3S)-3 with the experimental results when we can compare the predicted ECD of (2R,3S)-4 with the experimental ECD. However, if one method can predict the absolute configuration for (2R,3S)-4 well via comparing its ECD to the experimental results, in this case, it is possible to compare the predicted ECD for (2R,3S)-3 to the computed (2R,3S)-4 to see their differences. This is similar with the results happened in OR computations, the signs for the computed ORs of (2R.3S)-3 and (2R.3S)-4 are reversed. Therefore, the absolute configuration of (2R,3S)-3 was used in ECD computations first, and the same absolute configuration of (2R,3S)-4 was computed too using TEE, ZPE, and GFE data, respectively, in ECD simulations.^{2,10} Both ECDs looked like that compounds 3 and 4 had reversed stereo-structures using all three energy data in simulations (Fig. 1(a)-(c)). Especially, that the ECD simulated using GFE had large differences between 3 and 4. The ECD spectra indicate that the two compounds have different absolute configurations at C-2 and C-3. This independent evidence supports the conclusion from OR data.

Due to that (2R,3S)-**4** was not obtained at the first time as mentioned above, only an analog of **4**, (2R,3S)-**4A** was obtained.³ After that, (2R,3S)-**4B** was obtained. Thus, we study (2R,3S)-**4B**. The ECD was computed at the B3LYP/6-311++G(2d,p)//B3LYP/6-311++G(2d,p) level. The ECD of (2R,3S)-**4B** simulated using GFE was close to the experimental results (Fig. 1(d)). After UV corrections, the simulated ECD is much close to the experimental ECD (Fig. 1(e)). Also, the computed ECD of (2R,3S)-**4B** is also the same as the ECD computed for (2R,3S)-**4** using all of TEE, ZPE, and GFE data (Fig. 1(f)–(h)). After (2R,3S)-**4** was obtained recently, it was used for ECD determination again. Its ECD is the same as that of (2R,3S)-**4B**, and also almost the same as that of (2R,3S)-**4A** (Fig. 1(i)). Obviously, it indicates that **4A**, **4B**, and **4** have the same absolute configuration. It suggested that the methods used here are reliable for the predictions of ECD for **4** and **4A** and **4B**.

Based on the calculated ECD and OR results and the fact that the relative configuration of **3** was well established, we propose that the absolute configuration of (+)-**3** is (2S,3R), namely, (+)-(2S,3R)-**3**.

2.4. Computational results for conformation analysis

The difficulty is to understand why the Mosher method predicted a wrong result in absolute configuration determination for an intermediate **5** in total synthesis. Indeed, Mosher approach is a type of NMR method that has been used to determine the absolute configurations of secondary alcohols or amines. It has a very strict range used in absolute configuration determinations. It was introduced by Raban and Mislow,¹² and further developed by

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Scheme 1. The synthetic route to (2R,3S)-rubiginone A₂.



Lewis,¹³ Trost,¹⁴ Rigura,¹⁵ and other chemists.^{6b} In the existing protocol, predicting the absolute configuration requires the following two conditions: (1) atoms H1, C1, O1, C2, O2, C3, and C4 should be in the same plane (MTPA plane) as illustrated below, e.g., **10** in Fig. 2; (2) H1 and O2 must be at the same side (direction) of the major conformer so that the phenyl ring has proper effect on the electronic current induced proton resonance. If the populations of the major and minor conformations were not properly assigned, wrong prediction of the absolute configuration could be made by the Mosher (NMR) method.

To examine the existence of MTPA plane and the correct population of the major and minor conformations, both of which are required to predict the absolute configuration of chiral compounds correctly using NMR (Mosher) methods, we applied the computational methods to 10 first, whose conformational searches were carried out.⁷ Total electronic energy and free energy data were used in conformational analyses for Mosher esters 10a-1, 10a-2, 10b-1, and **10b-2**. It was found that major isomer was **10b-1** for (*S*)-ester predicted using total energy, which agreed with the Mosher's prediction. However, it changed to **10b-2** predicted by the relative energy data when B3LYP/6-31G(d)- and B3LYP/6-311++G(2d,p)optimized geometries were used (Fig. 3). The wrong prediction looks similar to that the wrong OR value of 3 using GFE data obtained at the B3LYP/6-31G(d) level. Indeed, to compute the GFE for all the Mosher esters of 11 and 12 is an extremely difficult task since their stable conformations are more than one thousand obtained at the B3LYP/6-31G(d) and B3LYP/6-311+G(d) levels. Indeed, to use TEE can also give good agreements at the B3LYP/6-311++G(2d,p)//

B3LYP/6-311+G(d) level.^{11b} Similar results that we recently reported in chiral catalysts conformation analyses had the same predictions using total energy data.¹⁶ Thus, TEE data were used in conformation analysis for other Mosher esters of **11** and **12**.

The computational results showed that the MTPA plane was present. The predicted major conformations of 10 were 10a-2 for (*R*)-Mosher ester at the B3LYP/6-31G(d) level. The predicted major one changed to 10a-1 using B3LYP theory at the basis sets of 6-311+G(d) and 6-31++G(2d,p) levels, respectively. Mosher method can be used to predict the absolute configuration of secondary aliphatic alcohols, e.g., **10**. Thus, the major conformation of **10** must be **10a-1** (Fig. 3).^{17a} Moreover, the ratio of the major (**10a-1**) to minor (10a-2) computed for (R)-Mosher ester 10 was 5.9:4.1 and 7.0:3.0 at the 6-311+G(d) and 6-31++G(2d,p) levels, respectively. Though compound 10 is different from cyclohexanol, the ratio of the major to minor conformation is almost the same as the experimental results using the band profile analysis of the IR adsorptions (in CCl_4) on the (R)-MTPA esters of several cyclohexanols, where the (*R*)-Mosher's conformation of the MTPA moiety is much more preferable (7:3) than the one with CF₃ groups anti to the ester carbonyl.^{17b} This observation lays the foundation for using the current Mosher method to derive the absolute configuration of secondary alcohols.

The same methods were used for the conformation searches for (*R*)- and (*S*)-Mosher ester of (2R,3S)-**11**. In total 726 geometries were computed at the B3LYP/6-31G(d) level. The conformations with relative energy of 0–1.5 kcal/mol were re-optimized at the B3LYP/6-311+G(d) level. Given the high cost and long time

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Fig. 1. Comparisons of the computed ECD spectra for (2*R*,3*S*)-**4** and (2*R*,3*S*)-**4** simulated using TEE (a), ZPE (b), and GFE (c). Comparisons of computed ECD for (2*R*,3*S*)-**4** and its experimental ECD without UV corrections (d) and with UV corrections (e). Comparisons of the computed CD spectra for (2*R*,3*S*)-**4** and (2*R*,3*S*)-**4B** using TEE (f), ZPE (g), and GFE (h). The experimental ECD for (2*R*,3*S*)-**4**, and (2*R*,3*S*)-**4B** (i).



Fig. 2. Mosher ester MTPA plane and its predominate conformations.

requirement for such a big molecule, we did not apply the method at the B3LYP/6-311++G(2d,p) level at present time. All the predicted major and minor conformations are illustrated below (Fig. 4).

If Mosher method could be modified to determine the absolute configuration of **11**, the correct major conformation should be **11a-1** for (*R*)-Mosher ester, and the major one for (*S*)-Mosher ester should be **11b-1**. Consequently, NMR can record the effect of electronic

current from phenyl ring on the proton resonance, as well as their differences.

The conformers with the lowest energy and second lowest energy for (*R*)-Mosher ester were **11a-1** and **11a-2**, at the B3LYP/ 6-31G(d) level, respectively. However, to correctly use Mosher methods, it requires **11a-1** being the minor isomer. Thus, the prediction does not agree with that the Mosher method predictions. The above two changed to 11a-2 (54%) and 11a-1 (46%) at the B3LYP/6-311+G(d) level, respectively. This does not match the prediction of Mosher method yet. The major and minor conformations for (S)-Mosher esters of 7 were 11b-1 and 11b-2, respectively, at the B3LYP/6-311+G(d) level, which do not meet the requirements of Mosher method. In the actual experiments performed for **11**, the observed $\Delta \delta$ sign caused by the effect of π -cloud of phenyl ring on the other ¹H shifts reversed, indicating that the predicted configuration was incorrect. The C-3 in 3 displays (R) configuration, which agrees well with the prediction using OR values. The population difference between (R)-11a-1 and (R)-11a-2 at the B3LYP/6-311+G(d) level is 8%. The population between (R)-10a-1 and (R)-10a-2 is 18%. The distribution differences between (S)-11b-1 and (S)-11b-2 (16%) are also less than one, such as 41% between (R)-10b-1 and (R)-10b-2. The small population differences indicate that the electronic effect recorded by NMR is small, which

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* Data in italic did not agree with the predicteion as the computed. ΔE : relative energy, ΔG : relative free energy. ΔE_1 and ΔG_1 : Energy at the B3LYP/6-31G(d) level; ΔE_2 and ΔG_2 : at the B3LYP/6-311+G(d) level; ΔE_3 and ΔG_3 : B3LY/6-311++G(2d,p)

Fig. 3. Predicted major and minor conformers for Mosher esters 10 by Mosher and DFT computations.



11, (R) or (S)-Mosher ester



 ΔE_1 : obtained at the B3LYP/6-31G(d) level. ΔE_2 : B3LYP/6-311+G(d)

Fig. 4. Differences of energy between two pairs of conformers for (R)- and (S)-Mosher esters 11.

is supported by the very small $\Delta\delta$ data (generally less than 0.01 ppm) except for CH₃-13.

Likewise, the correct major conformation is **12a-2** for (R)-Mosher ester, and **12b-2** for (S)-Mosher ester. Thus, the stable conformations of (R)- and (S)-Mosher ester (**12**) of (2R,3S)-**4** were searched using all three methods. Their relative energy data and populations are listed together with the corresponding geometries (Fig. 5).

The relative energy (ΔE) between **12a-1** and **12a-2** at the B3LYP/ 6-31G(d) level is close to zero, which also occurs to **12b-1** and **12b-2**. This difference increases to about 0.24 kcal/mol at the 6-311+G(d) and 6-311++G(2d,p) basis sets. The predicted major and minor conformations are those that the Mosher ester required. Compound **7** has a very long side chain and a bulky aromatic ring, and its $\Delta\delta$ may not obey the empirical rule, as pointed out by

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Fig. 5. Predicted major and minor conformers for Mosher esters of 4 (12a and 12b) by Mosher and DFT computations.



 $R^* = (R)$ - or (S)-Mosher ester moiety, the number labelled near atom is the $\Delta\delta$ value.



Fig. 6. Two pairs of stable conformations' OR, relative energy, and the contribution to the total OR.

Kakisawa.^{6b} For example, the $\Delta\delta$ values of sipholenol-A (**13**) and episipholenol-A (**14**)¹⁸ have exhibited random changes.

We point out that the OR values of **3** and **4** are determined by two parts: the two stereogenic centers and the helical structure. It

is well known that helical structures generally produce large OR values. Thus, the direction of OR value (positive or negative) depends on the OR magnitude of most stable helical conformation. As expected, the two helical geometries that are the most and second

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most stable conformations have shown opposite OR directions. For example, two pairs of B3LYP/6-311++G(2d,p)-optimized helical conformations have almost the same absolute OR values but opposite directions for **3**, and they make over 70% contribution to the total OR. Similarly, four conformations have made about 80% contributions to the total OR of **4**. The results are summarized in Fig. 6.

3. Conclusion

Empirical methods mentioned in the text have played important roles in determinations of absolute configurations. However, their use conditions block their more widely uses. In contrast, quantum methods have more widely use ranges than the empirical methods. With the development of supercomputers, quantum methods including other mathematic methods should be encouraged in assignment of absolute configuration for chiral compounds.

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Supplementary data

Material of computed OR, ECD, and experimental results for all compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.01.082.

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