

# Conformer Pair Contributions to Optical Rotations in a Series of Chiral Linear Aliphatic Alcohols

ZHAO Dan<sup>1</sup>, REN Jie<sup>1</sup>, XIONG Yongfei<sup>1</sup>, DONG Mengxiang<sup>1</sup>,  
ZHU Huajie<sup>1\*</sup> and Charles U. PITTMAN, Jr.<sup>2</sup>

1. School of Pharmacy, Hebei University, Baoding 071002, P. R. China;

2. Department of Chemistry, Mississippi State University, Starkville 39762, MS, US

**Abstract** The chain length effect of four chiral aliphatic alcohols, (*S*)-2-butanol, (*S*)-2-pentanol, (*S*)-2-hexanol and (*S*)-2-heptanol, on their specific optical rotations(OR) was studied experimentally and theoretically *via* quantum theory. Many conformations of each chiral alcohol exist as conformer pairs in solution. The OR sum from these pairs of conformers has much smaller contributions to OR values than that contributed by the most stable conformation. These four alcohols' OR values were also investigated using the matrix model, which employs each substituent's comprehensive mass, radii, electronegativity and symmetry number as the elements in the matrix. These are all particle properties. This matrix determinant is proportional to its OR values within a closely related structural series of chiral compounds. The experimental OR values and the matrix determinants of these four alcohols were compared with the predicted OR values obtained from quantum theory wave functions. The ORs predicted by the matrix method, which is based on particle function statistics, agreed with the results from quantum theory. The agreement between OR predictions by the matrix method and DFT calculations illustrates the wave-particle duality of polarized light that is operating in these predictions.

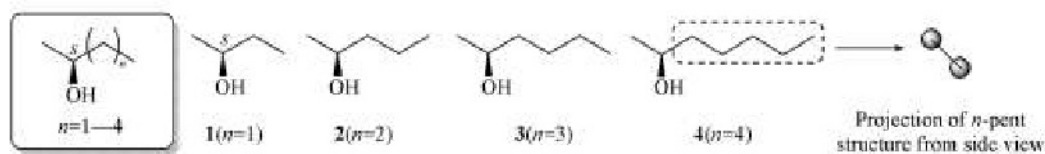
**Keywords** Optical rotation; Absolute configuration; Conformer pair; Matrix model; Quantum computation

## 1 Introduction

The effect of the chain lengths of four different substituents on the dissymmetric carbon in a chiral molecule on that molecule's optical characteristics is an important research target in organic stereochemistry. When the number of carbons in a substituent increases, the number of stable conformations will increase sharply. This causes difficulties in quantum mechanics calculations of optical rotation(OR), electronic circular dichroism(ECD) or vibrational circular dichroism(VCD) of a chiral compound containing a long chain. Therefore, researchers frequently shorten the substituent's chain length in OR, ECD or VCD calculations during absolute configuration(AC) determinations while hoping that the OR, ECD or VCD calculation accuracy does not decrease markedly<sup>[1,2]</sup>. However, what the fundamental theoretical basis is for using such simplified model molecules has long puzzled scientists. In this study, the effects of the longest substituent chain length[from 2(ethyl) to

5(*n*-pentyl)] on the four chiral alcohols, (*S*)-2-butanol(**1**), (*S*)-2-pentanol(**2**), (*S*)-2-hexanol(**3**) and (*S*)-2-heptanol(**4**), were investigated by studying their ORs using DFT and matrix determinants<sup>[3]</sup>, respectively, and comparing these data.

Quantum mechanical predictions of OR<sup>[4]</sup> are based on the wave properties of polarized light and the electrons of the chiral molecule. In contrast, the matrix method<sup>[3]</sup> employs particle properties including comprehensive substituents' mass and radii as inputs for predicting OR. Herein, we demonstrated that both methods predicted that the major contribution to OR was from the most stable conformation of the substituent chain. If both approaches can be successful for predicting OR, this would illustrate the unity of wave-particle duality within these predictions. Indeed, we showed both the matrix approach and quantum theory based on wave functions can both achieve such OR predictions. Quantum mechanical calculations showed that the conformation having the chain substituent with the smallest radii is the most stable one in each case(Scheme 1).



Scheme 1 Most stable conformation structures

\*Corresponding author. Email: hjzhu2017@163.com

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## 2 Theoretical and Computational Details

A complete conformational search was conducted on each of the four chiral alcohols using the MMFF94S force field<sup>[5]</sup>. The two packages, Barista and Computer VOA, were employed, respectively. All conformations of the entire molecules for compounds **1**–**4** were found and then optimized at the B3LYP/6-31G(*d*) level in the gas phase, respectively. All these geometries were then further optimized at the B3LYP/6-311++G(2*d,p*) level in the gas phase. These structures were then used for OR computations at the B3LYP/6-311++G(2*d,p*) level in the gas phase (Method 1). These B3LYP/6-311++G(2*d,p*)-optimized geometries were then re-optimized at the B3LYP/6-311++G(2*d,p*) level in the liquid(CHCl<sub>3</sub>) using the PCM model<sup>[6–11]</sup>, and all these molecular conformers were used in the OR computations at the B3LYP/6-311++G(2*d,p*) level in chloroform using the PCM model (Method 2). All the B3LYP/6-311++G(2*d,p*)-optimized geometries of each entire molecule were then re-computed at the B3LYP/6-311++G(2*d,p*) level in the gas phase. These recomputed structures were the used for OR computations at the B3LYP/6-311++G(2*d,p*) level in the gas phase (Method 3). Boltzmann statistics were applied throughout all the OR simulations. The Boltzmann statistics formula is illustrated below:

$$Q_i = ke^{\frac{-\Delta E_i}{RT}} \quad (1)$$

where  $Q_i$  is the fraction of *i*th conformation,  $k$  is a constant,  $R$  is the gas constant (8.314 J·mol<sup>-1</sup>·K<sup>-1</sup>), and  $T$  is the absolute temperature (298 K),  $\Delta E_i$  is the energy difference between the *i*th conformation's energy versus the lowest conformation's energy. Final OR( $[\alpha]_D$ ) calculations were performed as illustrated below.

**Table 1** Predicted  $[\alpha]_D$  values for the four (*S*)-chiral alcohols

Compound	Reported <sup>[23]</sup>	Exp.(CHCl <sub>3</sub> ) <sup>a</sup>	Predicted		
			Method 1 <sup>b</sup>	Method 2 <sup>c</sup>	Method 3 <sup>d</sup>
<b>1</b>	+13.0	+11.7	+19.45	+11.05	+16.49
<b>2</b>	+13.0	+11.0	+21.60	+13.19	+20.62
<b>3</b>	+11.0	+13.2	+18.75	+8.05	+20.62
<b>4</b>	+9.5	+9.7	+19.07	+11.86	+21.35

*a.* The OR values were measured in our lab; *b.* B3LYP/6-311++G(2*d,p*)/B3LYP/6-311++G(2*d,p*); *c.* (PCM)/B3LYP/6-311++G(2*d,p*)/(PCM)/B3LYP/6-311++G(2*d,p*); *d.* B3LYP/6-311++G(2*d,p*)/B3LYP/6-311++G(2*d,p*).

It is important and necessary to analyze the relationship between two different conformations' structures, their  $[\alpha]_D$  values, and the relationship between  $[\alpha]_D$  values and their relative energy. *n*-Butane and chiral 2-chlorobutane were discussed previously<sup>[13–17]</sup>. *n*-Butane (**5**) was selected as the first example to illustrate the relationships mentioned above. It has one pair of conformers that are enantiomers **5a** and **5b** with the same energy and mirror-image structures (Fig.1). Conformers **5a** and **5b** have the opposite OR signs. Therefore, the sum of the contributions to OR of this pair of conformations is zero. Its other conformation **5c** has a symmetric structure, so its OR contribution is zero. The final *n*-butane OR, therefore, equals zero. In this example, it is important to recognize the fact that conformations **5a** and **5b** are mirror-images. In the next example,

$$[\alpha]_D = (Q_1 \times [\alpha]_{D1} + Q_2 \times [\alpha]_{D2} + Q_3 \times [\alpha]_{D3} + \dots) / (Q_1 + Q_2 + Q_3 + \dots) = \sum(Q_i \times [\alpha]_{Di}) / \sum Q_i \quad (2)$$

where  $[\alpha]_{Di}$  is the *i*th conformation's OR value.

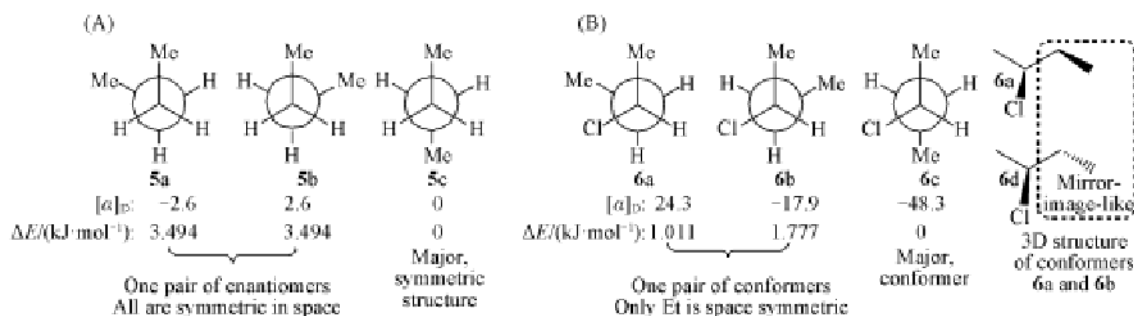
## 3 Results and Discussion

### 3.1 Effect of Chain Length on OR Values

OR values are sensitive to substituent geometries in many cases and play an important role in AC assignments<sup>[12]</sup>. A given substituent can exist in many conformations. The numbers of possible conformations increase rapidly with substituent size and complexity. Many contributions to OR study have been developed by different research groups<sup>[13–17]</sup>. When a chiral compound has a long chain attached to a chiral center, a shorter chain with fewer possible conformations is often used to replace the long chain in order to simplify the calculations<sup>[18–20]</sup>. After this simplification, the model compound is considered to be the representative of the original structure<sup>[18–20]</sup>, and it is used in OR, ECD or VCD simulations during AC assignment<sup>[3,21]</sup>. Why is such a substitution possible? In order to answer this question, it is imperative to understand the basic underlying concepts. A systematic study of the relationship between OR and the length of linear carbon substituent chain bound to a chiral carbon could permit an understanding of these fundamental principles. This requires performing conformational analyses to look for the most stable conformation. It is the most stable conformation which exerts the largest contribution to its OR( $[\alpha]_D$ ) in solution since the contributions to  $[\alpha]_D$  from the all conformation pairs are cancelled in Boltzmann statistics<sup>[22]</sup>. The three DFT computational methods introduced above were used to predict  $[\alpha]_D$  values for the four chiral alcohols **1**–**4**. These are summarized in Table 1.

(*R*)-2-chlorobutane has one pair of conformers (**6a** and **6b**) that have symmetric substituent structures with very similar, but not identical, energies. Also, conformations **6a** and **6b** have opposite OR signs. This looks very similar to the case in conformations **5a** and **5b**, which are complete mirror-images. The symmetric structures that appear in conformations **6a** and **6b** exist within their Et substituents. Therefore, the sum of the OR contributions of conformations **6a** and **6b** have a very small magnitude of only 6.4, calculated from their individual OR values at the B3LYP/6-31G(*d*)/B3LYP/6-31G(*d*) level and based on their relative energies. Thus, the calculated OR( $[\alpha]_D$ ) contribution (6.4) of this pair of conformers **6a** and **6b** was only 13% of the OR value of -48.3 from conformation **6c**.

Conformer pairs like **5a** and **5b**, or **6a** and **6b** are expected



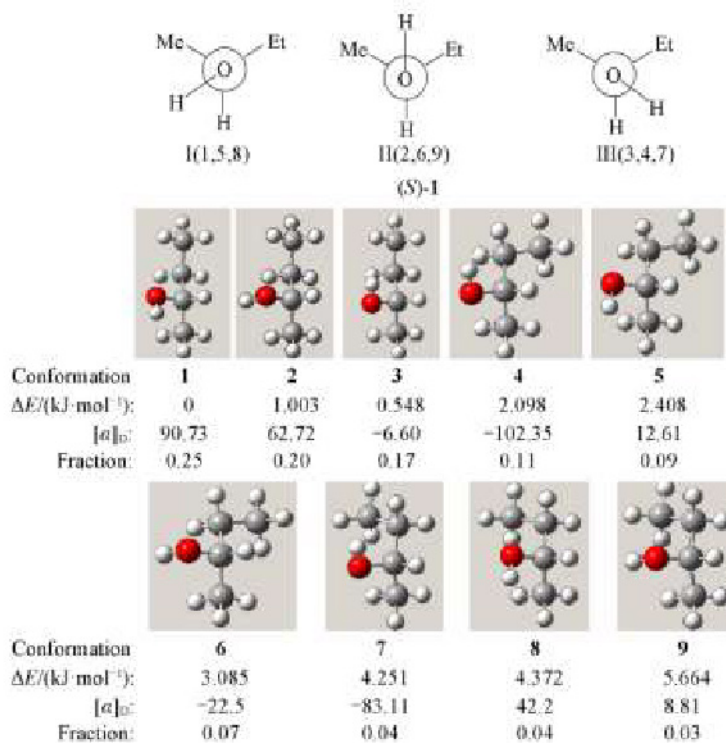
**Fig.1 Conformations of *n*-butane(A) and (*R*)-2-Cl-butane(B)**

The OR values were computed at the level of B3LYP/6-31G(*d*)/B3LYP/6-31G(*d*) in order to exhibit the contributions to molecular ORs played by all the enantiomer conformations, including the very similar existing conformers. The long chain substituent Et structures (in the dashed line) in conformers 6a and 6b of (*R*)-2-chlorobutane are mirror-image-like.

in any chiral linear molecules existing in solution. The final contribution from a summation of all the enantiomeric conformer pairs and the closely symmetric pairs will only represent a small fraction of the total measured molecular  $[\alpha]_D$  value. The major  $[\alpha]_D$  contribution is from the most stable conformer as illustrated by conformer 6c in (*R*)-2-chlorobutane.

Chiral alcohols **1**–**4** are the examples used here to study the effect of symmetric substituents on OR values. The single bond O—C rotation in chiral 2-butanol gives three rotational conformations (types I, II and III, Fig.2). Conformation optimizations of all the molecular conformers associated with each of the three types of distinct O—C rotational positions were

performed using method 1[B3LYP/6-311G++(2*d,p*)/B3LYP/6-311G++(2*d,p*)](Fig.2). The molecular conformations **1**, **2** and **3** have the lowest energies of the molecular conformations within the groups having the O—C type I, II and III orientations, respectively. The numbers in parentheses (1, 5, 8) after type I designate the conformations numbered 1, 5, and 8. Similarly, the conformations numbered 2, 6, 9 and 3, 4, 7 in parentheses after the types II and III are the corresponding conformation numbers that designate the specific molecular conformations having the types II and III rotational orientations around the O—C bond, respectively.



**Fig.2 All nine conformations of (*S*)-**1** and their computed relative energetics and predicted OR values  $\{[\alpha]_D$  calculated via B3LYP/6-311++G(2*d,p*)/B3LYP/6-311G++(2*d,p*)**

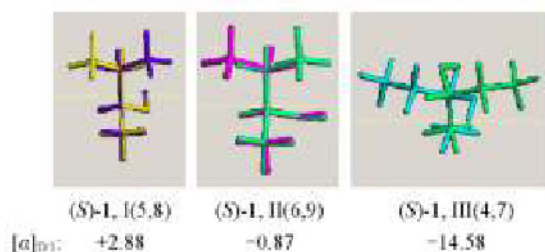
The numbers in brackets below the Newman structures I, II and III are the specific conformation numbers 1–9. “Fraction” represents the amount of each conformation that would be present at 298 K based on the Boltzmann distribution from their calculated relative energies. The sum of the total fractions is 1.00.

There is one most stable conformation in each type series of conformations. For example, the most stable conformation of type I is the conformer **1**, which has the lowest energy

among the conformations **1**, **5** and **8**. Its OR value is labeled  $[\alpha]_{D01}$ . The most stable type II conformation is conformer **2** with its OR value labeling  $[\alpha]_{D0II}$ . It has the lowest energy

among the conformers **2**, **6** and **9**. Conformer **3** is the most stable conformer of the type III conformers(**3**, **4** and **7**). Its OR value labeled as  $[\alpha]_{D,0III}$ . The concept of “the most stable conformer” will be frequently mentioned below in discussion of the OR contributions from the different type of conformers for (S)-**1** to (S)-**4**. Among all nine conformers of the three types(I, II, and III) of conformers, conformer **1** has the lowest energy in (S)-**1**. Thus, conformer **1** is both the most stable conformer of type I and also is more stable than all types II and III conformers. The “net OR value” designates the Boltzmann sum of OR values for the selected conformers, which could be one pair of conformers(represented as  $[\alpha]_{D,1}$ ), or all conformer pairs ( $[\alpha]_{D,2}$ ), or all paired conformers and the most stable conformers in the type II and type III designated as  $[\alpha]_{D,3}$ .

The orientation of the ethyl substituent in alcohol **1** in the conformer pairs(**5** and **8** of type I, **6** and **9** in type II, **4** and **7** in type III) exhibit almost mirror-image-like structures that are shown as superimposed images for the three types of O—C rotational orientations(types I, II and III) in Fig.3. A total of three pairs of conformations, related to the **6a** and **6b** space-symmetric conformations of (*R*)-2-chlorobutane, were found for (S)-**1**. The sum of the OR contributions(net OR,  $[\alpha]_{D,1}$ ) of type I conformations **5** and **8** was only +2.88. In the type II O—C group conformers, the net OR contribution ( $[\alpha]_{D,1}$ ) summed from the pair of conformations **6** and **9** was only -0.87. Similarly, the net OR( $[\alpha]_{D,1}$ ) contribution from pair conformers **4** and **7**(type III) was -14.58. Finally, the sum of the OR contributions( $[\alpha]_{D,2}$ ) was -12.57 from all three of these conformer pairs. The sum of the OR contributions( $[\alpha]_{D,3}$ ) was -3.23 from all three of these conformer pairs and conformations **2** and **3**(all eight conformations **2**—**9**) to the entire OR. The most stable conformation **1** has the OR( $[\alpha]_{D,0I}$ ) of 90.73. Its contribution to entire OR after accounting for its fraction of the population *via* the Boltzmann distribution is 22.68. Thus, the final Boltzmann statistics from all geometries from **1** to **9** is 19.45( $[\alpha]_D$ ). The OR contribution from all pair conformers( $[\alpha]_{D,2}$ ) is -12.57. This is about 64% of entire OR value ( $[\alpha]_D=19.45$ ) summed from all conformations. The OR contribution from all the paired conformations and the most stable type II and III conformations is -3.23( $[\alpha]_{D,3}$ ), which is only



The  $[\alpha]_{D,3}$  from conformations **2**—**9** is -3.23; the  $[\alpha]_{D,0I}$  of most stable conformation **1** is 90.73.

**Fig.3 Superimposed pairs of conformations of (S)-1 and their summed OR values using Boltzmann statistics**

The ethyl group in each pair of conformations exhibits mirror-image-like structures. See the structure above the yellow-dashed-line in each plot. Summary: the  $[\alpha]_D$  of (S)-**1** is 19.45 based on  $(90.73 \times 0.25 - 3.23)$ .

16.6% of the OR contribution of 19.45( $[\alpha]_D$ ), or only 14.2% of the OR contribution( $[\alpha]_{D,0I}=22.68$ ) from the most stable conformation **1**. The major OR contribution is from the most stable conformation **1** in the type I group.

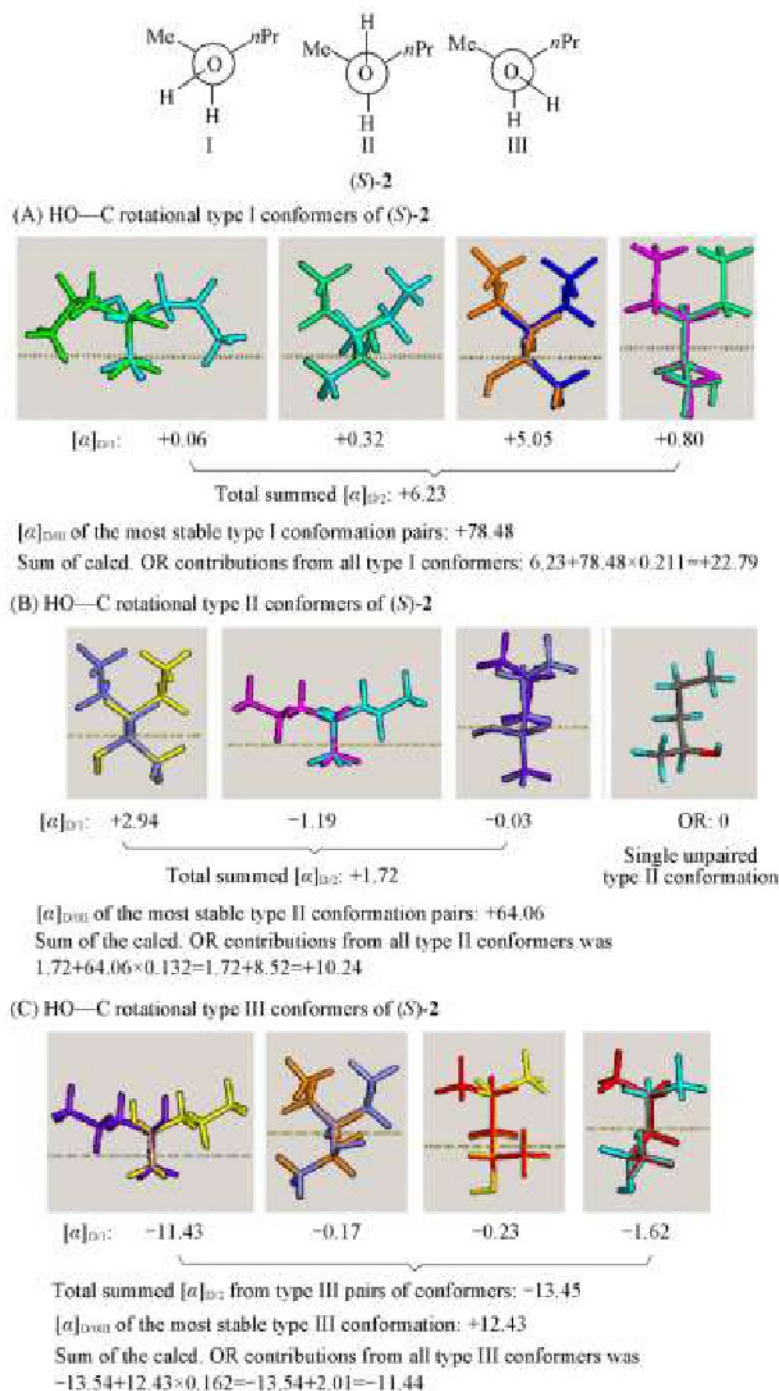
The similar results were expected and found during conformational analyses for (S)-**2**, where the substituent is *n*-propyl. A conformational search identified a total of 26 conformations and each was used in optimizations using computational methods 1 to 3, respectively. The geometries obtained *via* method 1 were used as a typical example of conformation analysis for (S)-**2**. A total of eleven pairs of conformations(22 conformers) were identified out of the 26 total that were found. The 26 conformations also contain the three most stable conformations in types I, II and III, and one unpaired conformation in type II. To clearly illustrate the “symmetric substituents” in these 22 conformations, the conformational analysis was performed again based on rotation of the C—O bond. The O—H bond axis in the orientations is depicted in the conformer types I, II and III shown below. Conformation numbers and their relative energy values are not listed in Fig.4 for clarity and simplicity. Only the superimposed conformer pairs and the net OR values are illustrated in Fig.4.

The OR value( $[\alpha]_{D,0I}$ ) of the most stable conformation in the type I conformations was 78.48( $[\alpha]_{D,0I}$ ), its fractional population is 0.211]. It was +64.06(0.132) in type II( $[\alpha]_{D,0II}$ ). The OR of the most stable type III conformation was +12.43(0.162)( $[\alpha]_{D,0III}$ ) using method 1. The most stable three conformations and their OR values will be used in the following discussion.

In summary, the OR contribution( $[\alpha]_{D,2}$ ) from all the paired conformers is 5.50. The OR value summed from all conformations is 21.60. The OR contribution from all the pair conformers is only 25.46% of the entire OR value, or 33.2% of the most stable conformer’s OR contribution(16.56). The OR contribution( $[\alpha]_{D,3}$ ) from all paired conformations and the most stable conformations in types II and III is 5.04, which is 23.3% of the entire OR value( $[\alpha]_D=21.60$ ), or only 30.4% of the most stable conformer’s OR contribution( $[\alpha]_{D,0I}=16.56$ ). The sum of the contributions to OR from all the conformer pairs only contributes a small fraction to the molecular OR. The major OR contribution is from the most stable conformation’s OR(16.56).

It should be pointed out that conformational searching of one conformation did not locate a pair for this conformation. This occurred in the type II classification in (S)-**2**(Fig.4). The OR( $[\alpha]_{D,4}$ ) of this unpaired conformation was zero. It is possible that the two computational softwares/packages used in the conformational searches were unable to find a conformer to pair with this conformation. As the chain length increases, it is possible that all the existing conformers may not be found by these software packages. Furthermore, the number of missed conformers might increase as the chain length increases.

A similar computational analysis of the conformations and OR was performed for (S)-**3**, where the long chain substituent is *n*-butyl. Very similar results to those exhibited by (S)-**2** were obtained. Seven conformer pairs were found for both types I



**Fig.4 Net OR values of the eleven pairs of (S)-2 conformers and single unpaired conformation for a type II O—C orientation where it pair was not found**

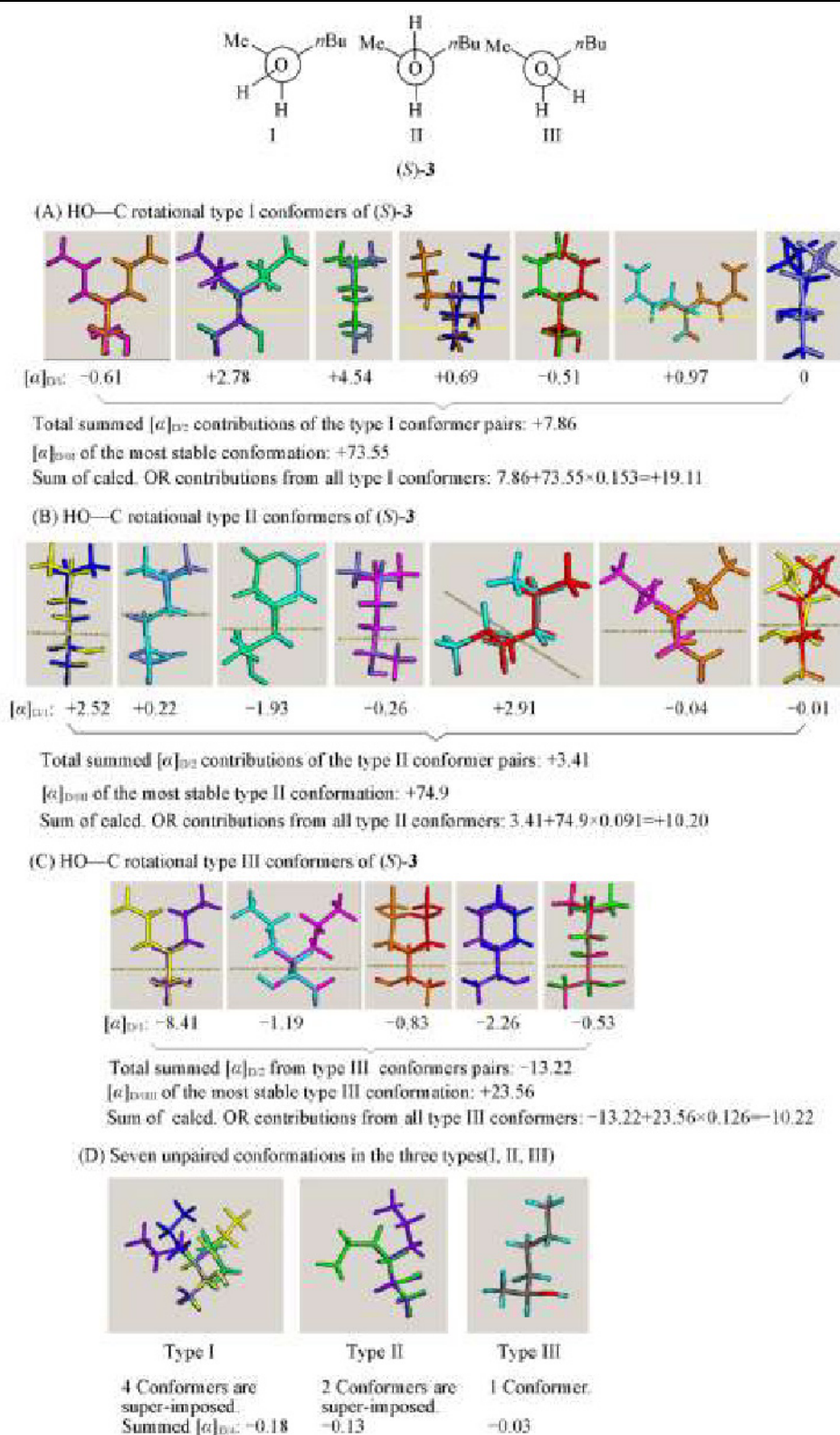
The *n*-propyl substituent in each pair of conformations exhibits mirror-image-like structures. See the structures above the yellow-dashed-line in each plot. Summary: total summed OR contribution from all conformations(not including the most stable conformations) among all three types is 5.04. The  $[\alpha]_{D(01)}$  of the most stable conformation among the three types is 78.48, which has a fractional population of 0.211. Finally, the total  $[\alpha]_D$  for (S)-2 is 21.60 ( $78.48\times 0.211+6.23+10.24-11.44$ ).

and II conformers(14 pairs, 28 total). Furthermore, five pairs of type III conformers were found(10 total). All are summarized in Fig.5.

The OR value( $[\alpha]_{D(01)}$ ) of the most stable type I conformation of (S)-3 was +73.55 with fraction of 0.153 using method 1. It was +74.9(0.091) for the most stable type II conformation( $[\alpha]_{D(0II)}$ ). The OR of the most stable conformer of type III was +23.56(0.126)( $[\alpha]_{D(0III)}$ ) using method 1. These three most

stable conformations and their OR values will be used in the following discussion.

A total seven unpaired conformations were also found for (S)-3. They were super-imposed according to their type (Fig.5), although their contributions to OR were very small. This analysis of (S)-3 clearly showed that as chain length increases, the total number of conformers that the computational package cannot find would increase.

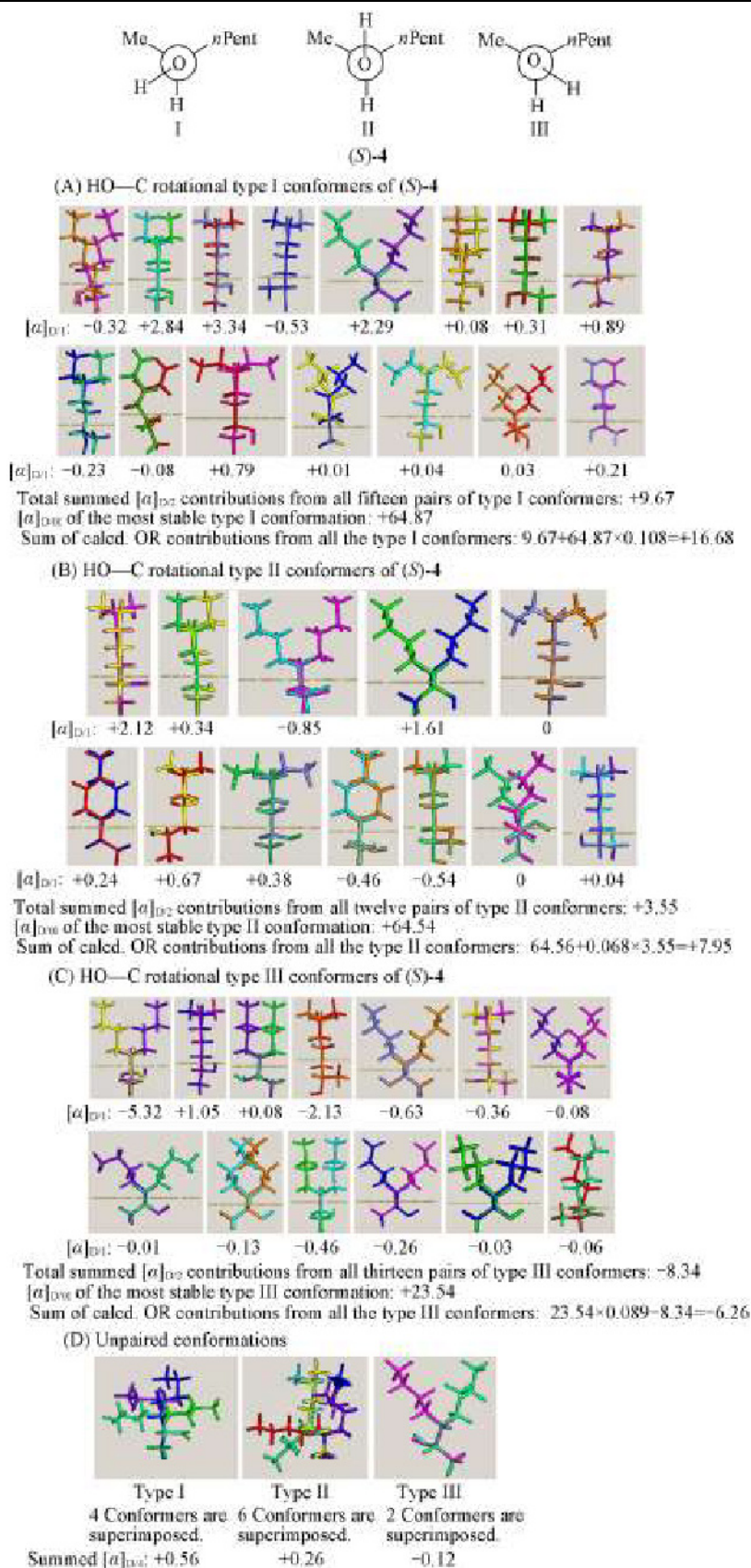


**Fig.5 Total net OR values summed from nineteen pairs of conformers and seven unpaired conformations illustrated in chiral compound (S)-3**

The *n*-butyl substituent in each pair of conformations exhibits mirror-image-like structures. See the structures above the yellow-dashed-line in each plot. Summary: total summed  $[\alpha]_{D25}$  is 7.50.  $[\alpha]_{D01}$  of the single most stable conformation among all three types is 73.55, which has a fractional population of 0.153. Finally, the total  $[\alpha]_D$  value of (S)-3 from all conformations is 18.75( $73.55 \times 0.153 + 7.05$ ).

The largest chiral alcohol in the group studied here is (S)-4, where the substituent chain is *n*-pentyl. Fifteen conformer pairs were found in the type I O—C rotational orientations group of (S)-4(Fig.6). Also, twelve conformer pairs of types II

and thirteen conformer pairs of type III(25 pairs and 50 total conformations) were found for (S)-4. These are also summarized in Fig.6.



**Fig.6 Net OR contribution values summed from the forty one conformer pairs of chiral compound (S)-4 and twelve unpaired conformations that were found**

All 52 conformations are illustrated. The substituent (*n*-pentyl) in each pair of conformations exhibits mirror-image-like structures. See the structures above the yellow-dashed-line in each plot. Summary: total summed  $[\alpha]_{D15}$  from conformations (not including the most stable one) is 12.06.  $[\alpha]_{D15}$  of the most stable conformation among the three types is 64.87, where the fractional population is 0.108. Finally, the total  $[\alpha]_D$  of (S)-4 from all conformers is  $19.07(64.87 \times 0.108 + 12.06)$ .

The OR value( $[\alpha]_{D,01}$ ) of the most stable type I conformation of (*S*)-**4** was +64.87, considering its fractional population of 0.108 using method 1. The  $[\alpha]_{D,01}$  was +64.54(0.068) for the most stable type II conformation. The  $[\alpha]_{D,01}$  was +23.54(0.089) using method 1. These three most stable conformations and their OR values will now be used below.

The data of net OR contribution for the fifteen type I pairs were +64.87, its contribution to OR in type I was  $64.87 \times 0.108 = 7.01$ . The data of net OR contribution values for the thirteen type II and thirteen III conformer pairs were +4.39 and +2.09, respectively. All the OR contribution of the conformation pairs were 4.88(−8.34+3.55+9.67). The OR value from the pair conformations and the most stable conformation in types II and III is 12.06. The final OR predicted from the simulation from all the conformations is +19.07. The contribution from the pair conformations is just about 25.6%.

**Table 2** OR values summed from paired conformers, and stable conformers of types II and III, unpaired conformers, and their contributions to OR using method 1

Conformation	( <i>S</i> )-1	( <i>S</i> )-2	( <i>S</i> )-3	( <i>S</i> )-4
$[\alpha]_{D,01}$ (fraction) <sup>a</sup>	90.73(0.250)	78.48(0.211)	73.55(0.153)	64.87(0.108)
$[\alpha]_{D}$ <sup>b</sup>	22.68	16.56	11.25	7.01
$[\alpha]_{D,2}$ <sup>c</sup>	−12.57	−5.5	1.85	4.88
$[\alpha]_{D,3}$ <sup>d</sup>	−3.23	5.04	7.84	11.36
$[\alpha]_{D,4}$ <sup>e</sup>	0	0	−0.34	0.70
$[\alpha]_{D}$ <sup>f</sup>	19.45	21.60	18.75	19.07
$([\alpha]_{D,2})/([\alpha]_{D})(\%)$	64.6	25.5	9.9	25.6
$([\alpha]_{D,2})/([\alpha]_{D,01})(\%)$	55.4	33.2	16.4	69.6
$([\alpha]_{D,3})/([\alpha]_{D})(\%)$	16.6	23.3	41.8	59.6
$([\alpha]_{D,3})/([\alpha]_{D,01})(\%)$	14.2	30.4	69.7	162.1

a. The OR value of the most stable conformation. Its fractional population is listed in parentheses; b.  $[\alpha]_{D} = [\alpha]_{D,01} \times \text{fractional population}$ ; c.  $[\alpha]_{D,2}$ : all paired conformers' OR contributions; d.  $[\alpha]_{D,3}$ : OR contributions from all paired conformers plus the most stable conformers of types II and III; e.  $[\alpha]_{D,4}$ : unpaired conformers' OR.  $[\alpha]_{D}$ : total summed OR using all conformations.

### 3.2 Equivalent Radius of Substituents

Some conformations may never be found during the conformational searching for a chiral compound that has one or more long chains connected to the stereogenic carbon when using the very best current software packages. This is a key problem. Therefore, contributions to OR from such un-found conformers of these compounds[as noted in (*S*)-**3** and (*S*)-**4**] cannot be estimated in OR simulations. This may be the one of the major reasons that the quantum mechanical calculations using DFT or other methods have resulted in high or low estimations of OR values for both (*S*)-**3** and (*S*)-**4**.

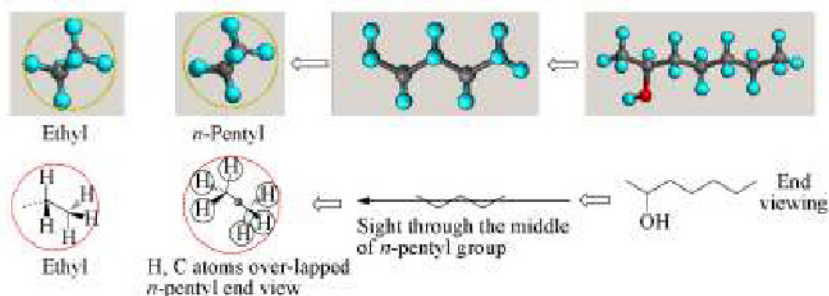
The major contributions from the ethyl to *n*-pentyl substituents continuing to the OR values of the four linear alcohols come from the substituents' most stable conformations. In this case, the radii of ethyl or *n*-pentyl substituents have been well discussed in our early reports<sup>[3]</sup>, and can be estimated in their most stable conformations. For example, the methyl radii is its van der Waals radii, and phenyl ring's radii is also equal its van der Waals radii. For a big substituent, like *n*-butyl, the distance of its center of mass to the closest proton is the smallest radii, and a value of 0.08 nm is added in a small contact radii calculation<sup>[3]</sup>(Generally, the van der Waals' radius of any atom is about 0.08 nm larger than the same atom's valence radius. We used the average value 0.08 nm as the plus value in the calculation

The different OR values are summarized for (*S*)-**1** to (*S*)-**4** in Table 2. It is clear that the OR contributions of paired conformers are only about 10% to 26% of the total for (*S*)-**2** to(*S*)-**4**. (*S*)-**1** is the exception, where the pair conformations contribute about 64.6% to the OR using method 1. The longer the side chain carbon number is, the smaller the contribution from the paired conformers. After considering the OR contributions of all conformations( $[\alpha]_{D,3}$ ) except that of the most stable conformation( $[\alpha]_{D,01}$ ), the most stable conformation's contribution increases from 16.6% to 59.6% with the side chain carbon number increasing from (*S*)-**1** to (*S*)-**4**. The effect from all the paired conformers on OR are expected to be small as chain length increases. When the carbon chain number increases, the OR signs of  $[\alpha]_{D,2}$  and  $[\alpha]_{D,3}$  tend to exhibit the same direction with the molecule's  $[\alpha]_{D}$ (e.g., the Boltzmann sum from all conformations).

of radius of the substituents). Since the contributions of conformer pairs to OR are essentially cancelled in Boltzmann statistics, the most stable conformation contributes the largest amount the OR. The vibrations of the substituent under the most stable conditions also cause the *n*-butyl group's radius to be a little larger in size than the ethyl group's radius. Therefore, the radius of the most stable *n*-butyl conformation of (*S*)-**4** is close in length to the radius of the ethyl substituent in (*S*)-**1**(Fig.7), but it must be a little larger than ethyl's radius.

Full conformational searches are absolutely necessary and extremely important for achieving accurate OR studies of chiral compounds since OR is sensitive to geometry changes. If all conformations cannot be found, then OR calculations using any quantum theory will not necessarily match well with experimental results. As the number carbons of a chain increase, the number of stable conformations increase by  $3^{(n-2)}$ (here *n* is the number of single bond rotations and *n* must be larger than 3). This formula is applicable to many chiral linear compounds like (*S*)-**1** to (*S*)-**4**, where no double bonds are present in the chain. A total of 92 conformations were found using Barista via the MMFF94S force field for (*S*)-**4**(Fig.8). The empty regions of these (*S*)-**4** conformation superimposed plots suggest that some conformations might have been missed in this search for all existing conformations. However, the lowest energy conformation has been recorded. The core section in Fig.7(in the

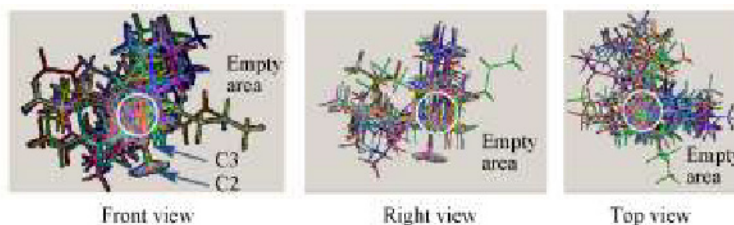




**Fig.7 Side view of the most stable conformation(with anti-arrangement of C—C bonds) of (S)-4 and a comparison of its radius to that of the ethyl group**

white circled region) is the most densely packed volume in the molecule when considering all 92 conformations. The radius of this volume region is designated as the contact radius. This core area should have the largest density. The velocity of left and right circularly polarized light are retarded in this volume, the most, as is the difference in these velocity. Hence, the plane of the resulting polarized light is rotated most strength in this

volume. Thus, this volume should give the largest contribution to OR values. This core section is only a little larger than the radii of the ethyl group. Namely, this contact radius region has the largest contributions to the molecule's OR value. Indeed, because of the existence of conformer pairs, it is the most stable conformer that has the biggest OR contribution to the entire molecular OR.



**Fig.8 Superimposed view of all 92 conformers of (S)-4 found in the conformation search using the MMFF94S force field**

The C2 and C3 atoms of (S)-4 were fixed in the same location for every conformation in these super-imposed images.

### 3.3 Matrix Model Predictions and Comparisons

As already mentioned, a long chain attached to a stereogenic carbon is often artificially shortened to reduce the computational time and complexity in AC determinations. The gamble taken is that the computational accuracy does not decrease significantly. However, the fundamental theoretical basis for why this model simplification often works reasonably well has not been explained. The experimental OR values tend to be an approximately “constant” value for a chiral molecule when its chain length increases. This is observed for the ORs of compound **1**, 2-(S)-octanol, which has an OR of +11.7, compound **4**, 2-(S)-heptanol(OR of +9.7), and 2-(S)-octanol(OR of +9.5)<sup>[24]</sup>. This study shows that the fundamental reason for the OR values remaining similar is the existence of conformer pairs, which tend to cancel out their individual OR contributions. These pairs have small net contributions to a molecule's OR values. The final Boltzmann statistics combined with this cancellation tendency resulted in the small OR contributions in practice. The major contribution to the OR is from the conformer that has the lowest energy and the highest population, like examples **1—4** already discussed. The most stable conformation of the *n*-pentyl substituent in (S)-4, has a radius similar to the ethyl and propyl substituent radii in (S)-1 and (S)-2, respectively.

A molecule can be treated as a small particle<sup>[25,26]</sup>. On the other hand, light and electrons have wave-particle duality. Like light, the electrons with a tiny mass, have this wave-particle

duality. We can treat the electrons' behavior using wave-functions in optical spectroscopy studies. However, as a single entity, the entire molecule must have some different characteristics from its individual isolated electrons. Currently, light's particle function is unknown. The interaction of a molecule with polarized light can be regarded as the interaction of two small particles. A molecule's particle nature can be characterized by independent variables like comprehensive mass, radii, electronegativity and symmetry number or other such factors. This concept was initially developed and published by our group<sup>[3,21]</sup>. When polarized light interacts with a molecule (*e.g.*, a particle), the characteristics of this interaction, such as OR, should satisfy statistics principles as observed for light diffraction fringes for example. This requires a mathematical treatment. It is this fundamental consideration, which is involved in the construction of the matrix method<sup>[3,21]</sup>. When the light frequency is fixed(the sodium D line is used) and both solvent and measurement temperature are held constant in OR determination, the function *F* is the function of a polarized light photon(particle) interacting with a chiral molecule. This interaction should have the following expression<sup>[3,21]</sup>, where 1—4 indicate that matrix elements *m*, *r*,  $\chi$  and *s* with these sub-numbers represent the four substituents bound to the stereogenic center

$$F = k \begin{vmatrix} m_1 & r_1 & \chi_1 & s_1 \\ m_2 & r_2 & \chi_2 & s_2 \\ m_3 & r_3 & \chi_3 & s_3 \\ m_4 & r_4 & \chi_4 & s_4 \end{vmatrix} \begin{vmatrix} a_1 \\ a_2 \\ a_3 \\ a_4 \end{vmatrix}$$

Here, *k* is a constant, *m* is the comprehensive mass, *r* is the

smallest contact radius, or van der Waals radii for an atom or a substituent,  $\chi$  is the Pauling electronegativity and  $s$  is a symmetry number; and  $a_1$ — $a_4$  (where  $a_1 \neq a_2 \neq a_3 \neq a_4$ ) are the weighting factors for each of the matrix elements. The weighting factors represent the magnitudes of these particle effects exerted by the mass, radius, electronegativity and symmetry of each of the substituents, respectively, on the function  $F$ . Function  $F$  is not a scalar number. It is defined as  $[\alpha] = |F|$ , when D line of Na is used. Thus,

$$[\alpha]_D = k \times a_1 \times a_2 \times a_3 \times a_4 \times \det(D) = k_0 \times \det(D)$$

where

$$\det(D) = \begin{vmatrix} m_1 & r_1 & \chi_1 & s_1 \\ m_2 & r_2 & \chi_2 & s_2 \\ m_3 & r_3 & \chi_3 & s_3 \\ m_4 & r_4 & \chi_4 & s_4 \end{vmatrix}$$

and  $k_0$  equals to  $k \times a_1 \times a_2 \times a_3 \times a_4$ , namely,  $k_0 = a_1 a_2 a_3 a_4 k$ . This approach is fully discussed in our earlier matrix model publication<sup>[21]</sup>.

It's impossible to obtain  $a_1$ ,  $a_2$ ,  $a_3$  and  $a_4$  and  $k$  values at

**Table 3 Det(D) values estimated for the four chiral alcohols (S)-1—(S)-4**

Compound	det(D)	Exp. $[\alpha]_D$	$k_0^a$	$k_{0, \text{reported}}^b$
1	$\begin{vmatrix} 16.3 & 1.4 & 3.5 & 0.0 \\ 13.0 & 2.0 & 2.5 & 0.44 \\ 13.6 & 2.1 & 2.5 & 0.0 \\ 1.0 & 1.2 & 2.1 & 1.0 \end{vmatrix} = +14.33$	+11.7	0.82	0.91
2	$\begin{vmatrix} 16.3 & 1.4 & 3.5 & 0.0 \\ 13.0 & 2.0 & 2.5 & 0.44 \\ 14.1 & 2.2 & 2.5 & 0.0 \\ 1.0 & 1.2 & 2.1 & 1.0 \end{vmatrix} = +14.69$	+11.0	0.75	0.88
3	$\begin{vmatrix} 16.3 & 1.4 & 3.5 & 0.0 \\ 13.0 & 2.0 & 2.5 & 0.44 \\ 14.5 & 2.2 & 2.5 & 0.0 \\ 1.0 & 1.2 & 2.1 & 1.0 \end{vmatrix} = +13.51$	+13.2	0.98	0.97
4	$\begin{vmatrix} 16.3 & 1.4 & 3.5 & 0.0 \\ 13.0 & 2.0 & 2.5 & 0.44 \\ 14.7 & 2.3 & 2.5 & 0.0 \\ 1.0 & 1.2 & 2.1 & 1.0 \end{vmatrix} = +14.75$	+9.7	0.66	0.66

*a.*  $k_0$  is computed from the formula  $[\alpha]_D = k_0 \times \det(D)$  using the OR values that we determined experimentally and listed in Table 1; *b.* these  $k_{0, \text{reported}}$  values were the  $k_0$  values using the reported OR values in references listed in column three of Table 1 under the title of "Reported OR" for the four alcohols *via* the same formula  $[\alpha]_D = k_0 \times \det(D)$ .

In this study, the  $\det(D)$  values are very sensitive to the changes of the substituent radii values in the (S)-chiral alcohols(1—4). For example, when the radii of ethyl group changes from 0.22 nm to 0.21 nm, the  $\det(D)$  value of (S)-1 decreased from 16.16 to 14.33 (After the study of the matrix model was published<sup>[3]</sup>, some scholars pointed out there were some errors or disagreements of the radii in the earlier reports. We found some minor errors reported in the original study. These included the comprehensive mass of  $n\text{-C}_5\text{H}_{10}$  that was reported as 14.7 and the radii reported as 0.29 nm. The corrected comprehensive mass and radii values for  $n\text{-C}_5\text{H}_{10}$  were 14.9 and 0.23 nm, respectively).

Among the  $\det(D)$  values of the chiral (S) alcohols 1—4, the  $k_0$  values tend to be close to a constant value using the OR values (Exp.  $[\alpha]_D$ ) determined in chloroform at room temperature. These OR values for (S)-1 to (S)-4 were +11.7, +11.0, +13.0 and +9.7, respectively, in our measurements. The corresponding  $\det(D)$  values are close to the 0.80 using these OR values. However, when the reported ORs were used in  $k_0$  value computation, the averaged  $k_{0, \text{reported}}$  was 0.86. When the carbon chain length increases, the OR may decrease since the value of

this point. Therefore, there is no absolute value for  $[\alpha]_D$ . However, the relative values of  $[\alpha]_D$  for a given chiral molecule can be obtained by computing  $\det(D)$ , since  $\det(D)$  is characteristic of the molecule and proportional to the optical rotation values when the frequency, temperature and other factors are fixed. These values represent relative optical rotation values, which are distinct from those obtained by quantum chemistry methods. For a closely related series of chiral compounds, like the four (S)-alcohols 1—4, their  $k_0$  values should be different but close to a constant. Thus, the  $\det(D)$  values were estimated by inputting the comprehensive mass, radii, Pauling electronegativity and symmetry number for each substituent. These parameters are copied from the reference published in matrix study<sup>[3]</sup>. All the experimental OR values in Table 1 were obtained at room temperature, in the solvent, chloroform, and using the sodium D line to obtain rotation. The  $\det(D)$  values are illustrated in Table 3. For chiral alcohols 1—4, the  $\det(D)$  values are remarkably similar in value.

the large substituent's radii value does not increase quickly and its comprehensive mass ( $m$ ) just increases slightly. Thus, the  $\det(D)$  values increase only slightly. Therefore, the OR values remain almost the same in this series. For example, (S)-2-octanol's OR value is only +9.5, which is the same as the reported OR(+9.5) of (S)-2-heptanol and very close to our measured values of +9.7 of (S)-2-heptanol.

## 4 Conclusions

It is clear that the OR values calculated from wave functions(DFT) match the experimental values well. Pairs of conformers exist for a chiral compound with a long chain connected to stereogenic center. The contributions of these conformer pairs to OR is small since they tend to cancel each other. The major contribution to the molecule's OR is from the most stable conformer's OR. The most stable conformation has the smallest radii in solution. At the same time, we have confirmed that the OR values could be obtained using the matrix method<sup>[3]</sup> that is constructed from particle functions. Each substituent attached to the chiral center is represented by elements that are particle properties of that substituent. Only the van der Waals

radius for simple substituents or the smallest radii for other substituents were used in the determinant for the matrix model computations, where that determinant is proportional to its OR value. Both wave and particle characteristics of light and electrons are manifest in these optical rotation determinations. The ability to use either quantum theory wave mechanics methods (based on electron characteristics) or the particle-based matrix method (based on the entire molecule particle characteristics) to calculate OR using the four chiral linear alcohols (*S*)-**1** through (*S*)-**4** demonstrates wave particle unity in OR.

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