

Stereochemical Determination of Dexlansoprazole by Optical Rotation, ECD and ^{13}C -NMR

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Abstract

Dexlansoprazole is an outstanding proton pump inhibitors, which is a chiral sulfoxide. We firstly report determination of the absolute configuration (AC) of dexlansoprazole by the combination of experimental and calculated optical rotation (OR), electronic circular dichroism (ECD) and ^{13}C -NMR. The high agreement between theoretical and experimental data illustrates that this method would be used to determine the absolute configuration of chiral sulfoxide.

Keywords: Dexlansoprazole; Chiral sulfoxide; DFT; Optical rotation; ECD; ^{13}C -NMR

Introduction

Lansoprazole is a new addition to the proton pump inhibitor (PPI) class and is approved for the treatment of heartburn associated with non-erosive gastroesophageal reflux disease (GERD) and healing all grades of erosive esophagitis (EE) [1,2]. Dexlansoprazole (dex), the dextrorotatory enantiomer of lansoprazole, was developed by Takeda Pharmaceutical Co., Ltd. US Food and Drug Administration (FDA) approved dex in 2009. Canada and Mexico have approved dex in Canada and Mexico in 2010 and 2011, respectively [3]. Dex is used in clinically administration, which shows excellent superiority in higher efficacy, lower elimination rate and less side effects than S-(-)-lansoprazole (levo) [4]. Hence, it is essential to determine the absolute configuration of lansoprazole.

Now a days, numerous approaches to determine the absolute configuration of chiral molecules have been promoted. X-ray crystallography determines the ACs unambiguously if a single crystal is available for molecules [5,6]. The Mosher ester has become a widely used method in organic chemistry. It is a type of NMR method for the determination of the AC of secondary alcohols or amines [7-9]. If X-ray crystallography is not accessible, the optically active compound can be researched by optical rotation (OR) [10,11] electronic circular dichroism (ECD) [12,13] and vibrational circular dichroism (VCD) [14-16]. In general, AC of a chiral molecule can be deduced directly from its OR and/or its ECD spectrum using semiempirical correlations [12,17-24]. But, this empirical approach was not always being successful and couldn't be relied on, unless structural analogs exhibiting comparable chiroptical property were available [25]. Therefore, quantum chemical calculations have been extensively used for calculating optical rotation and ECD spectrum simulation, the correct absolute configuration can be obtained even without reference molecule [5,6,26-30]. In principle, theoretical calculation can simulate ECD spectra of any compounds if correct conformational analysis is achieved. Besides, a new view has been put forward that differences between the chemical shifts of similar carbons should be calculated more accurately than the shifts themselves because of cancellation of systematic errors [31]. Therefore, ^{13}C -NMR is a useful tool for stereochemical assignment lansoprazole not only has a chiral sulfur atom, but also is a flexible molecule. Currently, there are several studies having been performed on the absolute configuration of asymmetric sulfur atom, however, few reported on the flexible molecule. On the absolute configuration of flexible chiral sulfur atom, the stereochemical assignment of omeprazole enantiomers has been determined by X-ray crystallography of a fenchyloxymethyl derivative of (R)-omeprazole [32]. Rabeprazole has been determined by X-ray crystallography of an intermediate [33]. Not with standing, there is

only one paper reporting the absolute configuration of lansoprazole enantiomers by similar experimental ECD curve to omeprazole [34]. Thence, the aim of this paper is to determine the absolute configuration of lansoprazole by the combination of experimental and theoretical calculation. Furthermore, a new approach to determine the dominant conformation of flexible chiral compound has been pointed out.

Materials and Methods

General remarks

Mass spectra (MS) was taken in ESI mode on Agilent 1100 LC-MS (Agilent Technologies, USA). HR-TOF-MS data was obtained by using an Agilent Accurate-Mass-Q-TOF LC/MS 6520 instrument (Agilent Technologies, USA). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE-600 MHz NMR spectrometer (Bruker, Germany) with tetramethylsilane (TMS) as an internal standard. Analytical HPLC was performed on an Agilent 1200 HPLC systems (Agilent, USA) with UV detection at 285 nm. The column temperature was 30 °C. The S-isomer determination was performed on an AGP chiral column (Daicel CHIRALPAK, 150 mm × 4.6 mm, 5 μm). The mobile phase was acetonitrile-pH 6.0 sodium phosphate buffer (10:90) at the flow rate of 0.5 mL/min. An Agilent C18 column (150 mm × 4.6 mm ID, 5 μm) was used for the other impurities determination. The mobile phase was composed of 1 volume of triethylamine and 60 volumes of water and adjusted to pH 6.2 with phosphoric acid and then mixed with 40 volumes of acetonitrile. The flow-rate was 1.2 mL/min. ECD spectra was recorded on a MOS-450 circular dichroism spectrometer spectropolarimeter (Biologic, France). The spectra was measured at solute concentration of 0.2 mg/mL using a 1 mm path length quartz cuvette at 25°C in a wavelength range of 190 to 400 nm, and methanol was used as solvent. All materials were obtained from commercial suppliers and were used without further purification. Column chromatography was run on silica gel (200-300 mesh) from Qingdao Ocean Chemicals (Qingdao, China).

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Preparation of dexlansoprazole

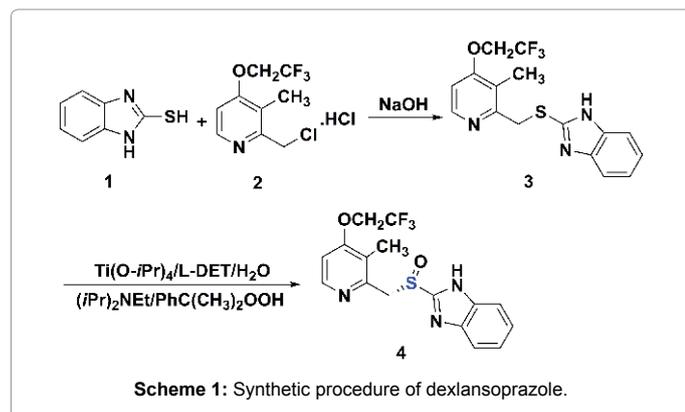
The synthetic process of these compounds referred to literatures [35,36] (Scheme 1).

1H-benzo[d]imidazole-2-thiol (1) (3.14 g, 20.9 mmol) was added to a solution of sodium hydroxide (2.91 g, 72.7 mmol) and water (50 mL) at 25°C, then the solution was stirred to homogeneous solution. Add 2-(chloromethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride (25.00 g, 18.2 mmol) to the mixture at 30°C. After stirring for 3 hours, the solution was then filtered followed by being leached with water (25 mL), and finally dried under reduced pressure to afford 2-(((3-methyl-4-(2,2,2-trifluoro-ethoxy)pyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (3) (5.68 g) as white solid. Titanium propoxide (0.90 mL, 3 mmol) and water (54 mg, 3 mmol) were added to a solution of diethyl L-tartrate (1.23 g, 6 mmol) and (3) (3.53 g, 10 mmol) in toluene (20 mL) at 80°C. The solution was stirred for 60 min., after which diisopropylethylamine (1.75 mL, 10 mmol) was added to the mixture, and the solution was stirred for another 30 min. Next, the temperature was adjusted to 30°C, after which cumene hydroperoxide (80%, 3.6 mL, 20 mmol) was slowly added. After 1 h with the temperature of 30°C, the solution was added to 20% aqueous sodium thiosulfate (15 mL). The aqueous phase was extracted with dichloromethane (20 mL, 3). The combined organic solutions were dried with anhydrous sodium sulfate, filtered, and the filtrate was distilled under reduced pressure. The residue was purified by chromatography on silica gel with ethyl acetate/petroleum ether (2:1) as the eluent to afford dexlansoprazole (42.84 g) as white solid. (68% yield, 99.8% purity, 100% ee). MS (ESI) *m/z*: 370.0 [M+H]⁺. ¹H NMR (600 MHz, CDCl₃) δ 8.29 (d, *J*=5.6 Hz, 1H), 7.62 (dd, *J*=6.2, 3.2 Hz, 2H), 7.28 (dd, *J*=6.1, 3.1 Hz, 2H), 6.63 (d, *J*=5.7 Hz, 1H), 4.82 (dd, *J*=35.8, 13.7 Hz, 2H), 4.35 (q, *J*=7.7 Hz, 2H), 2.21 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 161.83, 152.94, 150.60, 148.37, 143.85, 134.42, 124.28, 123.76, 123.25, 121.91, 120.36, 112.22, 106.02, 65.35, 60.74, 10.95.

The similar procedure was conducted to afford S(-)-Lansoprazole by diethyl D-tartrate. The theoretical mass of [M+Na]⁺ is 392.0656 amu. The high-resolution mass spectrum shows the [M+Na]⁺ at *m/z*=392.0646 amu. ¹³C NMR (150 MHz, CDCl₃) δ 161.86, 152.99, 150.61, 148.41, 143.86, 134.44, 124.31, 123.76, 123.30, 121.92, 120.34, 112.18, 106.04, 65.38, 60.80, 10.99.

Computational details

The conformational analysis was firstly performed by arbitrarily fixing the absolute configuration of target compound, using the Spartan 08 program [37] with the MMFF [38,39] molecular mechanics force field. Then all of the possible conformers were optimized at B3LYP level of theory using 6-311++G^{**} [40,41] basis sets under PCM model



[42,43] in Gaussian 09 package [44]. Frequency calculations based on previously optimized geometries were performed in order to ensure the minimum energy of the structure. Relative population of each conformer was valued on the basis of Boltzmann weighting factor at 298K which was also calculated at the same level in order to simulate OR, ECD and ¹³C-NMR.

Results and Discussions

Conformational searching

In principle, the conformation of a molecule critically influences its physical and chemical properties [45-47]. Thus, reliable conformational analysis has fundamentally importance for computational results close to the experimental ones. It is shown that even minor changes in molecule conformer would lead to a significant data of theoretical OR and CD, in particularly, for simple nonpolar compounds [48-53]. Kwit et al. have summarized three frequently used approaches for conformational searching of chiroptical flexible molecules [54]. A crucial issue to be addressed is that, the rotatable single bonds around chiral centre would show predominant role in the chiroptical properties of flexible molecules. Taking these aspects into account, a conformational searching of the title compound was performed by Spartan 08 program [37] with MMFF [38,39] molecular mechanics force field. Then, geometry optimizations and frequency calculation of all the possible conformers were performed using DFT/B3LYP/6-311++G^{**} [40,41] under PCM model [42,43] in Gaussian 09 package [44]. Boltzmann distribution [55] has been obtained according to the Gibbs free energies which were also calculated at the same level in order to simulate OR, ECD and ¹³C NMR. The correctness of conformational determination in flexible chiral compound can be achieved by the calculation results in the following, noting that it is a reasonable method for the conformational searching of flexible chiral molecule. OR value was calculated by DFT/B3LYP/6-311++G^{**}, ECD was simulated by TDDFT/B3LYP/6-311++G^{**} and ¹³C-NMR was performed by GIAO/B3LYP/6-311++G^{**}. The calculated data (OR, ECD and NMR) of dex is the Boltzmann-weighted average of all possible conformers. The relative Gibbs free energies and Boltzmann distribution of dex are shown in Table 1, and the conformers of dex is presented in Figure 1. The similar process was performed on the calculation of levo and the result is shown in Table 1 and Figure 2.

Optical rotation analysis

According to the literature, the AC of lansoprazole is R(+)/S(-) which are shown in Table 2. Specific optical rotation of dex and levo at 589.3 nm have been predicted using B3LYP method and 6-311++G^{**} as basis set, with the measured data given in Table 2. Under this circumstance, theoretical [α] findings show good agreement with experimental optical rotation at 589.3 nm if the AC is R(+)/S(-) [34], the differences between theoretical and calculated [α] values are 204.6° and 173.9° for dex and levo, respectively. For the assignment R(-)/S(+), the deviations are 519.6° and 488.9° for dex and levo, respectively. It is worth noting that the bias between experimental and calculated data confirms the AC of lansoprazole is R(+)/S(-) and DFT/B3LYP/6-311++G^{**} in PCM model is accurate to predicted optical rotation values.

ECD analysis

Although, electronic circular dichroism (ECD) is one of the most ideal techniques for the AC of molecule which has chromophores nearby chiral centre, however, calculations of ECD with density functional theory (DFT) using B3LYP/6-311++G^{**} in PCM model have not been reported for chiral sulfoxides. The simulated ECD spectrum for dex which has been re-plotted with population weighting along

| Conf. | G (kcal/mol) | ΔG (kcal/mol) | P% |
|--------|--------------|---------------|------|
| Dex-1 | -1023249.80 | 0 | 79.8 |
| Dex-2 | -1023247.80 | 1.001 | 14.5 |
| Dex-3 | -1023247.26 | 1.542 | 5.7 |
| Levo-1 | -1023249.71 | 0 | 79.9 |
| Levo-2 | -1023247.67 | 1.039 | 13.6 |
| Levo-3 | -1023247.24 | 1.465 | 6.5 |

^awhich related to the most stable conformer.
^bBoltzmann weighting factor (P%) based on ΔG.

Table 1: Gibbs free energies (G), relative Gibbs free energies (ΔG)^a and Boltzmann weighting factor (P%)^b of Dex and Levo conformers by using the DFT/B3LYP/6-311++G(d,p) method.

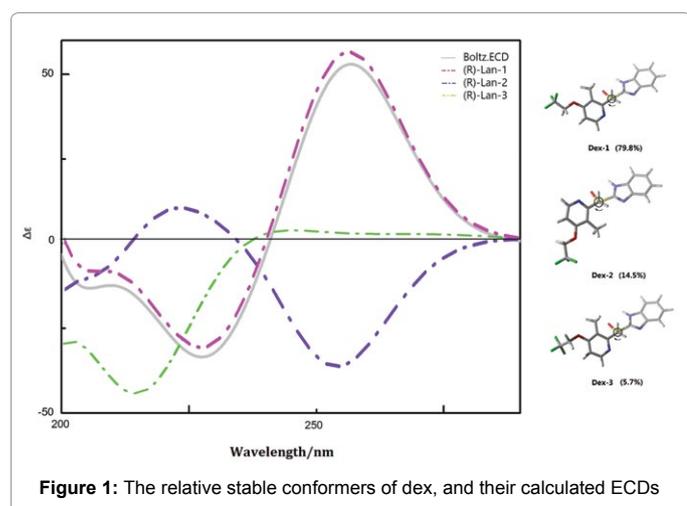


Figure 1: The relative stable conformers of dex, and their calculated ECDs

with experimental spectrum is shown in Figure 3. It can be seen that TDDFT calculations provided excellent agreement to the measured ECD band shape in spite of blue-shift which stem from the system error caused by theoretical calculations. The calculated ECD of dex showed a strong positive Cotton effect (CE) at 267 nm and a negative CE at 228 nm, similar to the curve in the experimental spectrum of dex. The simulated ECD of levo mirrored by that of dex, showing a positive CE at 228 nm, a negative CE at 267 nm, is shown in Figure 3. Similar to the OR calculations, the best agreement between the calculated and the experimental data illustrates the combination of measured and theoretical ECD can be used as a tool to determine the absolute configuration of chiral sulfoxide

The origin of the CEs in ECD spectrum can be explained by molecular orbital (MO) analysis at the same level of ECD calculation (Figure 4). The conformer 1 is the most populated conformer of dex which Boltzmann population is 79.8%, hence, the electron transition analysis of dex is based on Conf.1. As inferred from the MO analysis, the significant positive CE at 267 nm was contributed by the electronic

transition (ET) from MO 95 to MO 96 involving $\pi \rightarrow \pi^*$ transitions of benzimidazole ring and pyridine ring and sulfoxide $n \rightarrow \pi^*$ transition. The negative CE at 228 nm is mainly dominated by transitions from MO 95 to MO 97, which could be ascribed to the electronic transitions from the chiral centre to the benzimidazole ring and $\pi \rightarrow \pi^*$ transitions of pyridine ring (Figure 4).

On the side of ECD calculation it is important to note that the experimental and calculated ECD spectrum showed high degree of agreement, clarifying that the conformers of dex is correct.

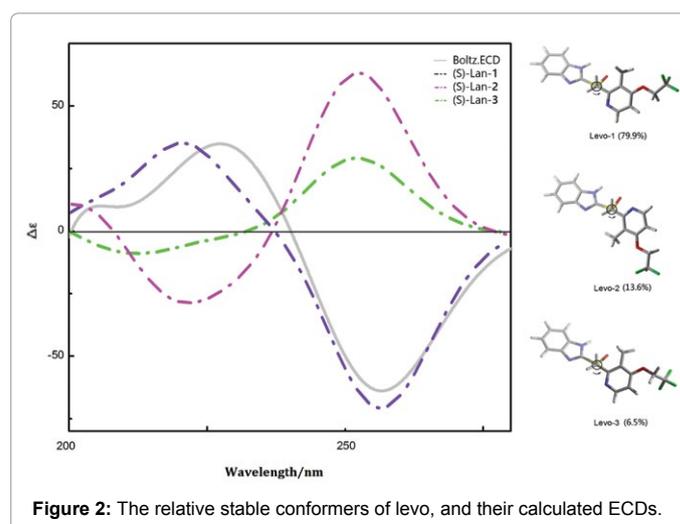


Figure 2: The relative stable conformers of levo, and their calculated ECDs.

| No. | Theoretical OR(°) | Experimental OR(°) |
|------|-------------------|--------------------|
| Dex | 356.6 | 152T |
| Levo | -336.9 | -163 |

Table 2: The calculated and experimental optical rotation (OR) of dex and levo.

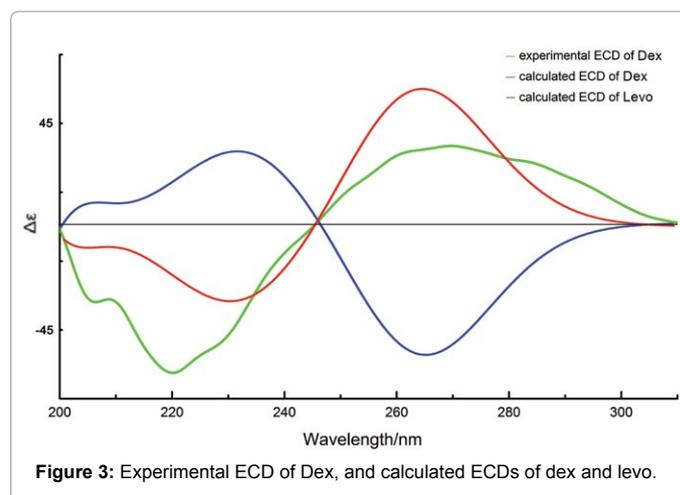


Figure 3: Experimental ECD of Dex, and calculated ECDs of dex and levo.

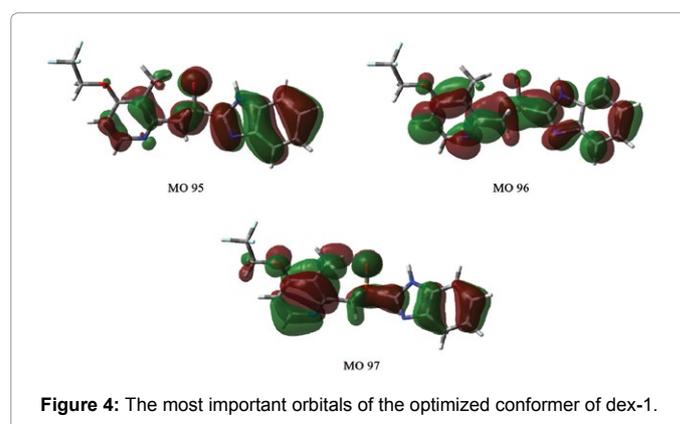


Figure 4: The most important orbitals of the optimized conformer of dex-1.

¹³C-NMR analysis

¹³C-NMR was simulated to support the stereochemical assignment, which can determine the stereocentre by chemical shifts of carbon atoms

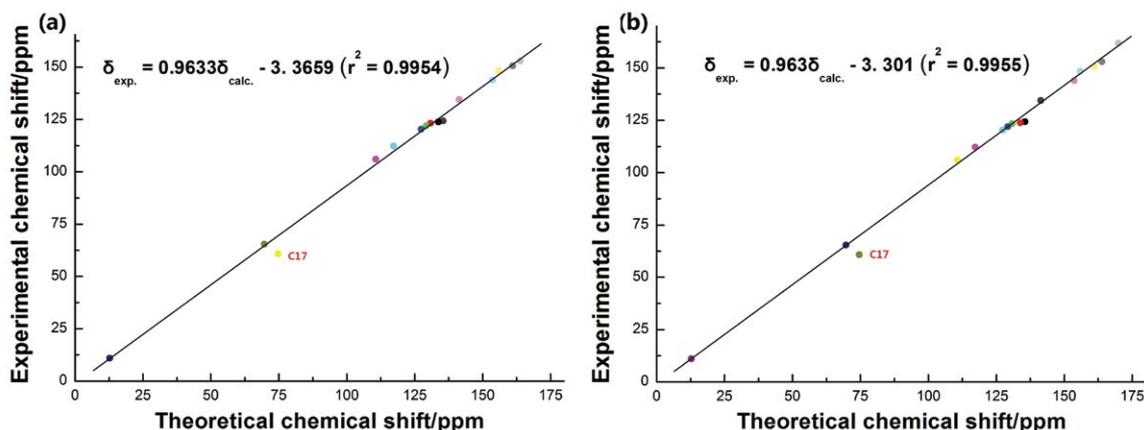


Figure 5: Correlations of ¹³C chemical shifts of dex and levo.

| Assignments | Dex (δ_{iso}) | | Levo (δ_{iso}) | | Deviation (δ_{iso}) | |
|-------------|------------------------|---------|-------------------------|---------|------------------------------|---------------|
| | ^a Calc. | Exp. | ^a Calc. | Exp. | Δ calc. | Δ exp. |
| C25 | 160.13 | 161.83 | 160.11 | 161.86 | 0.02 | -0.03 |
| C14 | 154.36 | 152.94 | 154.38 | 152.99 | -0.02 | -0.05 |
| C20 | 151.70 | 150.6 | 151.75 | 150.61 | -0.04 | -0.01 |
| C24 | 146.78 | 148.37 | 146.79 | 148.41 | -0.01 | -0.04 |
| C6 | 144.74 | 143.85 | 144.78 | 143.86 | -0.04 | -0.01 |
| C9 | 133.08 | 134.42 | 133.10 | 134.44 | -0.02 | -0.02 |
| C36 | 127.54 | 124.28q | 127.58 | 124.31q | -0.04 | -0.03 |
| C22 | 125.91 | 123.76 | 125.96 | 123.76 | -0.05 | 0 |
| C8 | 123.18 | 123.25 | 123.15 | 123.3 | 0.03 | -0.05 |
| C7 | 121.64 | 121.91 | 121.64 | 121.92 | 0.01 | -0.01 |
| C4 | 119.84 | 120.36 | 119.86 | 120.34 | -0.02 | 0.02 |
| C5 | 110.26 | 112.22 | 110.28 | 112.18 | -0.03 | 0.04 |
| C21 | 104.07 | 106.02 | 104.11 | 106.04 | -0.04 | -0.02 |
| C17 | 70.16 | 60.74 | 70.03 | 60.8 | 0.13 | -0.06 |
| C33 | 65.36 | 65.35q | 65.37 | 65.38q | -0.01 | -0.03 |
| C28 | 11.53 | 10.95 | 11.56 | 10.99 | -0.03 | -0.04 |

^aThe theoretical chemical shifts were empirically scaled by using the following equation: $\delta_{scaled} = (\delta_{calc.} - \text{intercept})/\text{slope}$.

Table 3: The experimental and calculated ¹³C-NMR of dex and levo.

in different stereo environments [31]. Among several computational means to calculate ¹³C-NMR, the “gauge-independent atomic orbital” (GIAO) method is one of the most common methods for predicating isotropic nuclear magnetic and it has been proven to be accurate and computational expensive [56]. The experimental and theoretical chemical shifts of dex and levo in ¹³C-NMR spectrum and the spectral assignments are presented in Table 3.

The differences in calculated and experimental chemical shift ($\delta_{dex} - \delta_{levo}$) between dex and levo have been plotted in Table 3. It is obviously shows that the chemical shift deviations of C14 and C17 which are linked to chiral S atom are bigger than others in measured spectrum. However, the other carbons which show little difference in chemical shift seem less useful for structure assignment. The same phenomenon also occurs in theoretical spectrum. Hence, the chemical shifts of the carbon which are around chiral sulfur atom can be used as an approach to judge chiral atom. The experimental shifts were plotted against the calculated shifts, and the least-squares fit values of slope, intercept, and correlation factor (r^2) were determined (dex: slope=0.9633, intercept=-3.3659, $r^2=0.9954$; levo: slope=0.963, intercept=-3.301, $r^2=0.9955$). Besides, the some conspicuous discrepancies for the atoms were evident. This is

chiefly owing to the role of the electron correlation associated with the presence of the lone pairs on the sulfur atom bonded to carbon atom of C17. Notwithstanding the bias, the measured and predicted chemical shifts present highly relevance (Figure 5). These findings show that the proposed structures match the authentic structures very well.

Conclusion

In conclusion, we have conducted conformational searching to establish the stable conformations of dexlansoprazole. Then, optical rotation, electronic circular dichroism and ¹³C-NMR were simulated by DFT/B3LYP method at 6-311++G(d,p) basis set. Configuration assignments were confirmed by the strong correlation between measured and calculated OR data, ¹³C-NMR and ECD. Therefore, this approach should be promoted to determine the absolute configuration of chiral sulfoxide.

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References

- Caldwell J (1992) The importance of stereochemistry in drug action and disposition. *J Clin Pharmacol* 32: 925-929.
- Drayer DE (1986) Pharmacodynamic and pharmacokinetic differences between drug enantiomers in humans: an overview. *Clin Pharmacol Ther* 40: 125-133.
- Sekharan CB, Rao MP, Naseema S, Kumar GS, Alekha B, et al. (2015) Application of Ion-Pair Complex Formation in Spectrophotometric Analysis of Dexlansoprazole. *App Sci Report* 10: 105-111.
- Abel C, Desilets AR, Willett K (2010) Dexlansoprazole in the treatment of esophagitis and gastroesophageal reflux disease. *Ann Pharmacother* 44: 871-877.
- Ladd MFC, Palmer RA (1985) Structure determination by X-ray crystallography. Springer.
- Harada N (2008) Determination of absolute configurations by X-ray crystallography and ¹H NMR anisotropy. *Chirality* 20: 691-723.
- Zhu HJ (2015) Organic Stereochemistry: Experimental and Computational Methods. John Wiley & Sons.
- Zhang Y, Wang JS, Gu YC, Wang XB, Kong LY, et al. (2014) Diverse pteridinium-type limonoid derivatives from the fruits of *Aphanamixis grandifolia* and their absolute configuration determination. *Tetrahedron* 70: 6594-6606.
- Iwai T, Kubota T, Kobayashi J (2014) Absolute configuration of amphidinin A. *J Nat Prod* 77: 1541-1544.
- Polavarapu PL (2002) Optical rotation: recent advances in determining the absolute configuration. *Chirality* 14: 768-781.
- Polavarapu P (2002) Optical rotation: Recent advances in determining the absolute configuration. *Chirality* 14: 768-781.
- Berova N, Nakanishi K, Woody R (2000) Circular dichroism: principles and applications. (2nd edn), John Wiley & Sons.
- Harada N, Nakanishi K (1983) Circular dichroic spectroscopy: exciton coupling in organic stereochemistry. Univ Science Books, USA.
- Cerda-Garcia-Rojas CM, Bucio MA, González SB, Garcia-Gutierrez HA, Joseph-Nathan P, et al. (2015) Absolute configuration of esquelane derivatives from *Adesmia boronioides* by vibrational circular dichroism. *Tetrahedron Asymmetry* 26: 136-140.
- Sanchez-Castellanos M, Bucio MA, Hernandez-Barragan A, Joseph-Nathan P, Cuevas G, et al. (2015) Vibrational Circular Dichroism (VCD), VCD Exciton Coupling, and X-ray Determination of the Absolute Configuration of an α , β -Unsaturated Germacranolide. *Chirality* 27: 247-252.
- Sherer EC, Lee CH, Shpungin J, Cuff JF, Da C, et al. (2014) Systematic Approach to Conformational Sampling for Assigning Absolute Configuration Using Vibrational Circular Dichroism. *J Med Chem* 57: 477-494.
- Mislow K, Green MM, Laur P, Melillo JT, Simmons T, et al. (1965) Absolute Configuration and Optical Rotatory Power of Sulfoxides and Sulfinate Esters. *J Am Chem Soc* 87: 1958-1976.
- Donnoli MI, Giorgio E, Superchi S, Rosini C (2003) Circular dichroism spectra and absolute configuration of some aryl methyl sulfoxides. *Org Biomol Chem* 1: 3444-3449.
- Rosini C, Donnoli MI, Superchi S (2001) Towards a Correlation of Absolute Configuration and Chiroptical Properties of Alkyl Aryl Sulfoxides: A Coupled-Oscillator Foundation of the Empirical Mislow Rule? *Chemistry* 7: 72-79.
- Djerassi C (1960) Optical rotatory dispersion; applications to organic chemistry.
- Lightner DA, Gurst JE (2000) Organic conformational analysis and stereochemistry from circular dichroism. John Wiley & Sons.
- Snatzke G (1979) Circular dichroism and absolute conformation: Application of qualitative MO theory to chiroptical phenomena. *Angewandte Chemie International (edition in English)* 18: 363-377.
- Schellman JA (1975) Circular dichroism and optical rotation. *Chem Rev* 75: 323-331.
- Moscowitz A (1961) Some applications of the Kronig-Kramers theorem to optical activity. *Tetrahedron* 13: 48-56.
- Rinderspacher BC, Schreiner PR (2004) Structure-property relationships of prototypical chiral compounds: Case studies. *J Phys Chem A* 108: 2867-2870.
- Polavarapu PL, He J (2004) Peer Reviewed: Chiral Analysis Using Mid-IR Vibrational CD Spectroscopy. *Anal Chem* 76: 61 A-67 A.
- Freedman TB, Cao X, Dukor RK, Nafie LA (2003) Absolute configuration determination of chiral molecules in the solution state using vibrational circular dichroism. *Chirality* 15: 743-758.
- Diedrich C, Grimme S (2003) Systematic investigation of modern quantum chemical methods to predict electronic circular dichroism spectra. *J Phys Chem A* 107: 2524-2539.
- Polavarapu BPL (1997) Ab initio molecular optical rotations and absolute configurations. *Molecular Physics* 91: 551-554.
- Cheeseman J, Frisch M, Devlin F, Stephens P (1996) Ab initio calculation of atomic axial tensors and vibrational rotational strengths using density functional theory. *Chemical physics letters* 252: 211-220.
- Bifulco G, Bassarello C, Riccio R, Gomez-Paloma L (2004) Quantum mechanical calculations of NMR J coupling values in the determination of relative configuration in organic compounds. *Org Lett* 6: 1025-1028.
- Von Unge S, Langer V, Sjölin L (1997) Stereochemical assignment of the enantiomers of omeprazole from X-ray analysis of a fenhyloxymethyl derivative of (+)-(R)-omeprazole. *Tetrahedron: Asymmetry* 8: 1967-1970.
- Nochi S, Kawai T, Kawakami Y, Asakawa N, Ueda N, et al. (1996) Preparation and Absolute Configurations of Optical Isomers of Sodium 2-[[4-(3-Methoxypropoxy)-3-methylpyridin-2-yl] methylsulfonyl]-1H benzimidazole (E3810). *Chem Pharm Bull* 4400: 1853-1857.
- Andersson S, Nelander H, Öhlén K (2007) Preparative chiral chromatography and chiroptical characterization of enantiomers of omeprazole and related benzimidazoles. *Chirality* 19: 706-715.
- Che G, Xiang J, Tian T, Huang Q, Cun L, et al. (2012) Catalytic asymmetric oxidation of 1H-benzimidazolyl pyridinylmethyl sulfides with cumene hydroperoxide catalyzed by a titanium complex with (S, S)-N, N'-dibenzyl tartramide ligand. *Tetrahedron: Asymmetry* 23: 457-460.
- Raju MN, Kumar NU, Reddy BS, Anitha N, Srinivas G, et al. (2011) An efficient synthesis of dexlansoprazole employing asymmetric oxidation strategy. *Tetrahedron Letters* 52: 5464-5466.
- Deppmeier B, Driessen A, Hehre T, Hehre W, Johnson J, et al. (2008) Wavefunction Inc, Irvine, CA.
- Bosnich B (1994) Molecular mechanics force fields for cyclopentadienyl complexes. *Chem. Soc. Rev* 23: 387-395.
- Huang N, Kalyanaraman C, Bernacki K, Jacobson MP (2006) Molecular mechanics methods for predicting protein-ligand binding. *Phys Chem Chem Phys* 8: 5166-5177.
- Koch W, Holthausen MCA (2001) chemist's guide to density functional theory. (2nd edn) Wiley-Vch Weinheim.
- Geerlings P, De Proft F, Langenaeker W (2003) Conceptual density functional theory. *Chem Rev* 103: 1793-1873.
- Miertuš S, Scrocco E, Tomasi J (1981) Electrostatic interaction of a solute with a continuum. A direct utilization of AB initio molecular potentials for the prevision of solvent effects. *Chemical Physics* 55: 117-129.
- Miertus S, Tomasi J (1982) Approximate evaluations of the electrostatic free energy and internal energy changes in solution processes. *Chemical physics* 65: 239-245.
- Frisch M, Trucks G, Schlegel H, Scuseria G, Robb M, et al. (2010) Gaussian Inc, Wallingford, PA.
- Mori T, Inoue Y, Grimme S (2006) Time dependent density functional theory calculations for electronic circular dichroism spectra and optical rotations of conformationally flexible chiral donor-acceptor dyad. *J Org Chem* 71: 9797-9806.
- Marchesan D, Coriani S, Forzato C, Nitti P, Pitacco G, et al. (2005) Optical rotation calculation of a highly flexible molecule: the case of paraconic acid. *J Phys Chem A* 109: 1449-1453.
- Kwit M, Sharma ND, Boyd DR, Gawronski J (2008) Determination of absolute configuration of conformationally flexible cis-dihydrodiol metabolites: Effect of diene substitution pattern on the circular dichroism spectra and optical rotations. *Chirality* 20: 609-620.
- Grimme S, Mück-Lichtenfeld C (2008) Calculation of conformational energies and optical rotation of the most simple chiral alkane. *Chirality* 20: 1009-1015.

-
49. Kundrat MD, Autschbach J (2006) Time dependent density functional theory modeling of specific rotation and optical rotatory dispersion of the aromatic amino acids in solution. *J Phys Chem A* 110: 12908-12917.
50. Wiberg KB, Wang YG, Wilson SM, Vaccaro PH, Jorgensen WL, et al. (2008) Optical rotatory dispersion of 2,3-hexadiene and 2,3-pentadiene. *J Phys Chem A* 112: 2415-2422.
51. Wiberg KB, Vaccaro PH, Cheeseman JR (2003) Conformational effects on optical rotation. 3-substituted 1-butenes. *J Am Chem Soc* 125: 1888-1896.
52. Pecul M, Ruud K, Rizzo A, Helgaker T (2004) Conformational effects on the optical rotation of alanine and proline. *J Phys Chem A* 108: 4269-4276.
53. Specht KM, Nam J, Ho DM, Berova N, Kondru RK, et al. (2001) Determining absolute configuration in flexible molecules: a case study. *J Am Chem Soc* 123: 8961-8966.
54. Kwit M, Rozwadowska MD, Gawronski J, Grajewska A (2009) Density functional theory calculations of the optical rotation and electronic circular dichroism: the absolute configuration of the highly flexible trans-isocytosone revised. *The J org chem* 74: 8051-8063.
55. Barone G, Duca D, Silvestri A, Gomez-Paloma L, Riccio R, et al. (2002) Determination of the Relative Stereochemistry of Flexible Organic Compounds by Ab Initio Methods: Conformational Analysis and Boltzmann-Averaged GIAO ¹³C NMR Chemical Shifts. *Chemistry* 8: 3240-3245.
56. Bifulco G, Gomez-Paloma L, Riccio R (2003) Configurational analysis of the natural product passifloricin A by quantum mechanical ¹³C NMR GIAO chemical shift calculations. *Tetrahedron letters* 44: 7137-7141.