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Absolute configuration of 4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one by circular dichroism.

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Abstract

The absolute configuration (AC) of synthetic 4-Methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one was confirmed by comparison of the experimental circular dichroism with theoretical curves generated from the density functional theory (DFT) calculations. Initial analysis were carried out by Sybyl simulated annealing at force field MMFF94s.All the conformers were optimized by B3LYP/6-31G(d) level of theory. Electronic excitation energies (wavelength) and rotational strengths R (cgs) were calculated by time dependent density functional theory using density functional B3PW91 and bases set TZVP. Agreement between theoretical and experimental CD curves verified the R configuration of synthetic 4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one.

Introduction

Many biologically-active molecules are chiral, including the naturally-occurring amino acids, and sugars. Enantiomers are identical with respect to ordinary chemical reactions, but differ in their optical activity and effects as drugs. It is generally known that often only one of the enantiomers shows the desired biological activity. Many chiral drugs are made with high enantiomeric purity due to potential side-effects of the other enantiomer. e.g. Ethambutol one enantiomer is used to treat tuberculosis [1] the other causes blindness. So determination of absolute configuration of biologically active compound is of great importance.

CD spectroscopy is a powerful analytical technique for investigating the secondary structure of proteins and for determining the absolute configurations of chiral compounds. Advancement of the computational methods in the last two decades made quantum mechanical computational calculation much faster and more reliable. We can predict the chiroptic properties of chiral compounds with DFT calculation more accurately. Theoretical calculations of chiroptic properties, such as optical rotatory dispersions, [2], vibrational circular dichroism, [3] and electronic CD spectra, [4,5] – especially by the time-dependent density functional theory (TDDFT) – have recently

been applied successfully to the assignment of the absolute configuration of small- to medium-sized chiral organic molecules [6].

The benzodiazepine skeleton (Fig.1) is widely used as therapeutic agents for the treatment of anxiety and neuroses. For years, benzodiazepines were regarded exclusively as synthetic products, until diazepam, lorazepam and N-desmethyldiazepam were found in brain and other peripheral tissues of untreated human subjects and animals [7]. Several benzodiazepines have been identified in wheat grains as well as in potatotuber [8,9].
In 1995 experimental CD and UV studies on 41 derivatives of chiral benzodiazepinones have been reported [10]. The absolute configuration of these can be obtained by the comparison of calculated and experimental CD Spectra. In continuation of our computational approach for the determination of the absolute configuration of natural products, we present here some preliminary results on ab initio DFT studies performed for of 4-Methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (R and S enantiomer).

A **B**

Figure 1.

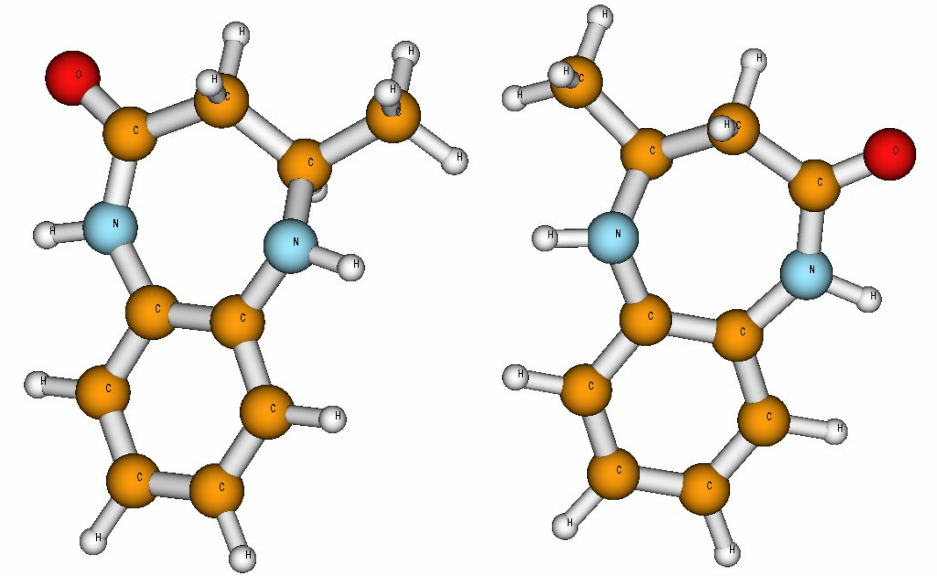
A: (S) 4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one

B: (R) 4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one

Computational detail

Starting structures (R) and (S) stereoisomers of 4-Methyl-1,3,4,5-tetrahydro-2H-1,5 benzodiazepin-2-one were created with the Sybyl molecular modeling package [11]. Ten conformation of each analogue were obtained by Sybyl simulated annealing using the force field MMFF94s followed by .B3LYP/6-31G(d) optimization [12,13]. Electronic excitation energies (wavelength λ /nm) and rotational strengths R (cgs) were calculated

by TDDFT[14-21] using the B3PW91 functional and *TZVP* basis sets. Bulk solvent effects (CH_3CN) were approximated by the polarizable continuum model (IEF-PCM)[22]. The Gaussian 03 program was used [23] for all DFT calculations. CD spectra was simulated as sums of Gaussians [23] centered at the wavelengths of the responding electronic transitions and multiplied by the calculated rotational strength by using the program Shape.[24]



R **S**

Figure 2. Molden [25] plots of calculated [B3LYP/6-31G(d)] structures for (R) and (S) 4-Methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one

Results and discussion

The reported experimental data [10] for 4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one has Cotton effects at 217 nm (-5.74), 232 nm (3.38), 250 nm (0.39) and 384nm (-1.40). Besides the existence of two enantiomers (R)- and (S) 4-Methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one can also adopt several different ring conformations. The CD spectra of all unique conformations obtained by the procedure described above were simulated in gas phase and CH_3CN on the basis of electronic

excitation energies (wavelength) and rotational strengths R (cgs). The calculated CD spectra for all these conformers of the R enantiomer in gas phase are presented in Fig.3. Clearly, the simulated CD spectra strongly depend on the respective ring conformation. Thus, Boltzmann-averaging over the simulated CD spectra for the various ring conformations was done (Fig. 4). Comparison of this averaged CD curve with the experimental data unambiguously establishes the absolute configuration of 4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one as (R). Therefore, as this compound was taken as starting material in the synthesis of the 41 derivates described in [10], these also have to be in R configuration as the only chiral center was not disturbed during synthesis.

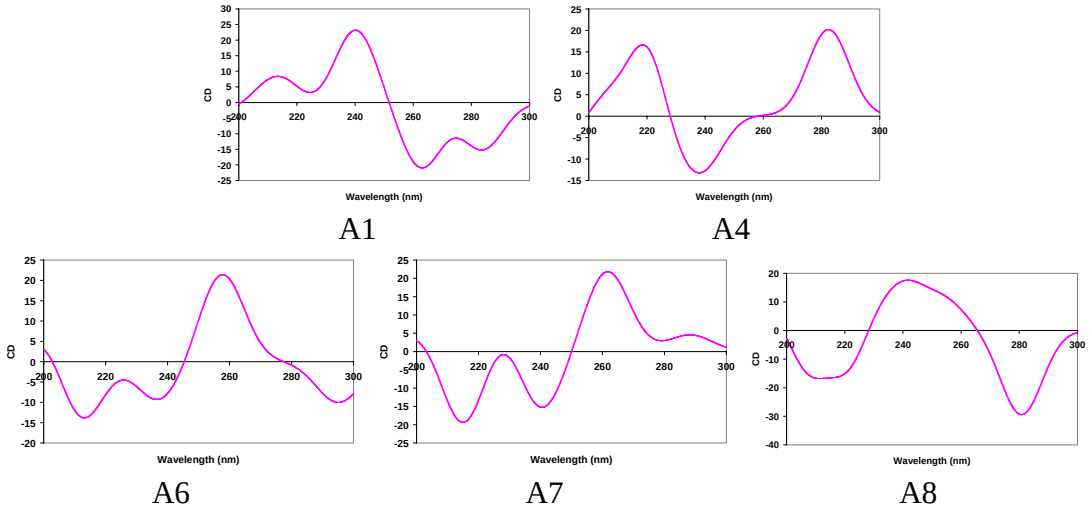


Figure 3. Simulated CD (B3PW91/TZVP) spectra of R configuration in gas phase

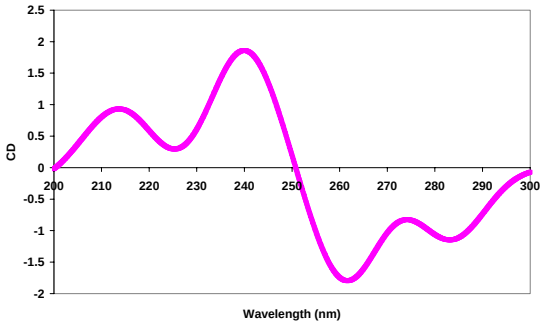


Figure 4. Boltzmann weighted CD spectrum of (R)-4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one

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