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Absolute configuration of 1,5-diazepin-2-ones: A critical test case for density functional theory

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ABSTRACT

The absolute configuration of a series of 4(*R*)-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-ones is assigned by comparison of experimental and calculated CD spectra using time-dependent density functional theory (TDDFT) in combination with four different functionals (B3PW91, CAM-B3LYP, M06-2X, BMK). Closest agreement with experiment is obtained with B3PW91. All compounds except those bearing an acyl group at N5 exist in two nearly isoenergetic conformations of the seven-membered ring ($G \leqslant 0.5$ kcal mol^{-1} with the local pair natural orbital coupled-electron pair approximation LPNO-CEPA/1/def2-TZVPP//B3LYP/6-311G(d,p)). Agreement between simulated and experimental CD spectra was found to critically depend on a proper description of conformer population as well as the position of the calculated longest-wavelength transitions of the individual conformers.

1. Introduction

Benzodiazepinones, especially 1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-ones, are of significant pharmacological importance [1–3]. From structure–activity studies [4] the stereochemistry of the seven-membered ring had been found to play a significant role for the biological activity; consequently, conformational properties of this important subclass of benzodiazepines have been extensively studied by NMR spectroscopy and semiempirical calculations [4–6]. Furthermore, the existence of these drugs in solution as single non-converting conformer has been postulated to improve the biological activity [4]. The stability of the two main conformations (P and M, defined by the torsional angle C2—C3—N4—C5, see Fig. 1 for atom numbering) [7,8] of the seven-membered ring in 1,4-diazepam derivatives and barriers of interconversion between them have been calculated by density functional methods (B3LYP) [9,10]. B3LYP calculations also have been used to establish tautomeric equilibria of 1,3-dihydro-2H-benzodiazepin-2-ones and –thiones [11]. Recently, quantitative structure–toxicity studies of benzodiazepines have been published [12,13]. In view of this importance of 1,5-benzodiazepin-2-ones a number of differently substituted derivatives have been synthesized [14,15] and characterized by their electronic circular dichroism as well as X-ray structure determination [16,17].

Meanwhile, the assignment of the absolute configuration of optically active compounds has been greatly facilitated by computational chemistry, mainly by comparison of simulated with experimental electronic circular dichroism (ECD) curves [18–23]. In continuation of our previous work on the absolute configuration of natural products [24–26] here we present a detailed computational study concerning the absolute configuration of a series of substituted 4-methyl-1,3,4,5-tetrahydro-2H-1,5 benzodiazepin-2-ones (Scheme 1) with special emphasis on the effect of substituents, either at the aromatic and/or the seven-membered ring on both molecular structure and ring conformation as well as chiroptic properties.

2. Computational details

Starting structures for each 1,3,4,5-tetrahydro-2H-1,5 benzodiazepin-2-one derivative were created with the Sybyl molecular modeling package [27] followed by a conformational search using the simulated annealing procedure (50 cycles with 1 ps at 1000 K followed by 1 ps cooling to 200 K) with the MMFF94s force field [28]. Each unique conformation obtained thereby was then reoptimized by B3LYP/6-311G(d,p) [29–31] and characterized by frequency calculations as true minimum. Final relative Gibbs free energies were obtained from local pair natural orbital

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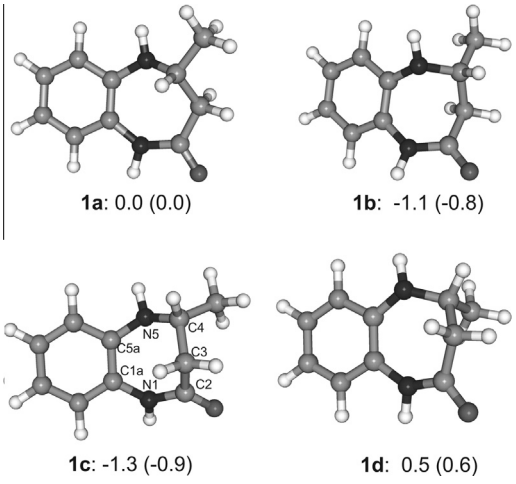
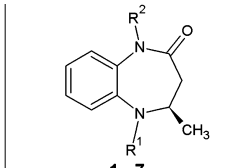
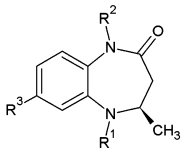


Fig. 1. Low-energy conformations and relative Gibbs free energies in gas phase and acetonitrile solution (values in parentheses) for compound **1**.



	R^1	R^2
1	H	H
2	H	CH_3
3	CH_3	H
4	CH_3	CH_3
5	$CH_3C{=}O$	H
6	$CF_3C{=}O$	H
7	CH_3	$CH_3C{=}O$



	R^1	R^2	R^3
8	CH_3	H	Cl
9	H	CH_3	Cl
10	CH_3	CH_3	Cl
11	H	H	NH_2
12	CH_3	CH_3	NH_2
13	H	H	CH_3O
14	CH_3	H	CH_3O
15	CH_3	CH_3	CH_3O
16	$CH_3C{=}O$	CH_3	CH_3O
17	H	H	NO_2
18	H	CH_3	NO_2
19	$CH_3C{=}O$	CH_3	NO_2
20	$CF_3C{=}O$	H	NO_2

Scheme 1.

coupled-electron pair approximation (LPNO-CEPA/1) single point calculations [32–35] using the def2-TZVPP basis set [36,37] combined with unscaled B3LYP/6-311G(d,p) ZPE and thermal corrections. Solvent effects (CH_3CN as the solvent) were taken into account by the SMD-M06-2X/6-31G(d) solvation model [38]. Electronic excitation energies and rotational strengths were calculated by time-dependent density functional theory (TDDFT) [39–43] using the B3PW91 [29,44], BMK [45], M06-2X [46–48], and CAM-B3LYP [49] functionals and the TZVP basis set [36] except BMK where the DGTZVP basis set [50] was used. This latter functional combined with the DGDZVP (or DGTZVP) basis set had been shown to give excellent absorption energies for a series of organic dyes [51]. Solvent effects (CH_3CN) on electronic transition energies were approximated by the IEFPCM procedure [52,53]. Based on the calculated rotational strengths of the individual conformers of each benzodiazepinone the CD spectra of the respective conformations were simulated using Gaussian line shapes. These simulated CD spectra were then Boltzmann-weighted to yield the final simulated CD curves. From these final simulated curves the respective extrema (maxima and minima) presented in Table 1 in Section 3.3 were derived. Programs used were: ORCA [54,55], GAMESS [56,57], and Gaussian09 [58]. UV/Vis and CD spectra were simulated with the programs Orca_asa [59] and Shape [60] using half widths of 1200 cm^{-1} and 10 nm, respectively. Visualization was done with Molden [61] and MOLEKEL [62].

3. Results and discussion

The four unique ring conformations resulting for the parent 1,3,4,5-tetrahydro-2H-1,5 benzodiazepin-2-one **1** after an extensive conformational search by simulated annealing followed by B3LYP/6-311G(d,p) optimization are shown in Fig. 1.

It is well known that the appearance of simulated electronic circular dichroism curves of biaryl atropisomers may strongly depend on molecular conformation [63–65]. This is also evident for the present molecules: the seven-membered diazepine ring is known to exist in two isoenergetic mirror-image boat-type conformations [7,8,10]. The chiral center at e.g. C3 of 1,4-benzodiazepines or C4 of 1,3,4,5-tetrahydro-2H-1,5 benzodiazepin-2-ones **1**–**20** induces slightly different energies of these two conformations. Consequently, the two lowest energy structures **1b** and **1c** yield nearly mirror-image CD curves (Fig. 2).

Therefore, proper Boltzmann-weighting of the various conformations is essential to providing reliable simulated CD spectra. For this purpose we have chosen the LPNO-CEPA/1/def2-TZVPP procedure which is expected to provide energies close to those obtained with CCSD(T) calculations [32–35]. For the calculation of geometries as well as ZPE and thermal corrections to Gibbs free energies the B3LYP/6-311G(d,p) model was used which is known to yield usually quite good geometries as well as ZPE corrections [66,67]. Hence we consider that combining CEPA/1 electronic energies with B3LYP ZPE and thermal corrections will give sufficiently reliable conformer populations. Experimentally, the CD curves of the investigated compounds were recorded in acetonitrile [16], hence solvent effects on relative energies were also taken into account [SMD-M06-2X/6-31G(d)]. In the following, we will first briefly describe the molecular structure of the investigated compounds, especially the effect of substituents on seven-membered ring conformation, and then proceed to a presentation and discussion of the UV/Vis absorption spectra, including an estimation of the reliability of the density functionals used. Finally, comparisons of experimental and simulated ECD spectra will be used to establish respectively corroborate the experimental assignment of the absolute configuration [16,17] of these important compounds.

3.1. Molecular structures

Relevant structural parameters obtained for the lowest energy conformation (*R*)-**1c** of the parent 1,3,4,5-tetrahydro-2H-1,5 benzodiazepin-2-one **1** and 7-chloro -4(*R*),5-dimethyl-1,3,4,5-tetrahydro-2H-1,5 benzodiazepin-2-one **8** are compared with the corresponding X-ray data for (*S*)-**1** [68] and (*R*)-**8** [17] in Table S1 of the Supplementary materials. Most importantly, the calculated dihedral angles of **1c** and **8c** describing the seven-membered ring conformation perfectly match the experimental values. In analogy to diazepam and its derivatives, the torsional angle $\tau_3 = \tau$(C2—C3—C4—N5) is used for the notation of the individual conformations [7,8,10]. Calculated relative Gibbs free energies in the gas phase and acetonitrile solution as well as torsional angles τ_1–τ_7, describing the structure of the seven-membered ring of the individual unique conformations, are provided in Table S2 of the Supplementary materials. With the exception of derivatives