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The absolute configuration of streptonigrin

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In memoriam Professor Vinayak V. Kane

Abstract

A theoretical study of the molecular circular dichroism (CD) of the antitumor antibiotic natural product streptonigrin is described, aiming at the secure assignment of its absolute configuration by comparison of the CD spectra predicted for *M* and *P*, with the experimental one. The stereostructure of streptonigrin was previously investigated by two other groups, yet leading to two different attributions. Although streptonigrin possesses two biaryl axes, only the 'southern' one is configurationally stable and thus responsible for the chiroptical properties, since the 'northern' **AB**-ring system of the molecule is kept in plane with ring **C** by hydrogen bonding. All computational methods applied within this work to simulate the CD spectrum—semiempirical approaches and time-dependent density functional theory (TDDFT)—consistently attribute the *M*-configuration to streptonigrin.

Keywords: Axial chirality; Circular dichroism; Hetero biaryl; Quantum chemical calculations; Time-dependent density functional theory

1. Introduction

The history of streptonigrin (**1**) has its origin in the year 1959, when a dark-brown, crystalline solid was isolated from cultures of *Streptomyces flocculus*.[1] Later on, the same compound was obtained from *Streptomyces rufochromogenes* and *Streptomyces chinatues*[2] and from a strain of *Actinomyces albus* var. *bruneomycini*,[3] but was named rufochromomycin and bruneomycin, respectively. Soon, streptonigrin (**1**) attracted attention, due to its broad antiviral and, in particular, antibiotic activities against both Gram-positive and Gram-negative bacteria.[4] Furthermore, it was found to be highly active against several animal and human tumor cell lines.[5,6] Unfortunately, **1** failed to get into clinical use, because of its toxicity[6,7] causing severe side effects.[8,9] Nonetheless, streptonigrin (**1**) inspired generations of synthetic and biosynthetic chemists, pharmacologists, and physicians.[5,10]

The gross structure of **1** was established in 1963, based on degradative procedures and ^{1}H NMR spectroscopic studies.[11] Later on, comprehensive ^{13}C NMR experiments[12] and an X-ray structure analysis[13] confirmed its constitution as displayed in Figure 1.

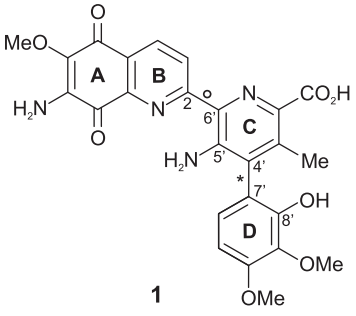

Figure 1. Constitution of streptonigrin (**1**).

Although devoid of stereogenic centers, streptonigrin (**1**) is a chiral compound, due to the presence of a rotationally hindered (hetero) biaryl axis between the rings **C** and **D**. Earlier

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stereochemical investigations gave contradictory results: a first, rather arbitrary attribution based on a merely empirical analysis of the CD spectrum of **1** suggested the *P*-configuration,[14] whereas a later, more in-depth investigation hinted at an *M*-configuration.[15] In this paper, we describe the unambiguous assignment of the absolute configuration of streptonigrin (**1**) as *M*, by quantum chemical CD calculations in combination with CD measurements, following earlier examples of investigations like molecules owing their chirality not (only) to stereogenic centers, but also to chiral axes,[16] 'planes',[17] helices[18] or to the presence of an intrinsic molecular helicoidal shape as in small fullerenes like, e.g., C_{78}.[19]

2. Previous investigations on the absolute configuration of streptonigrin

Although the above-mentioned X-ray crystallographic investigation[13] could not establish the absolute configuration of **1**, it gave further valuable stereochemical information. Thus, the **AB**-ring system was found to be almost coplanar to the **C** ring in the solid state, emphasizing the molecular chirality to result from the pyridyl-phenyl axis (**CD**) exclusively, which exhibits a near-orthogonal array, with a dihedral angle of 85°.[13] By variable-temperature NMR spectroscopy, these conformational features were found to be basically conserved in solution.[20] In both phases the coplanarity of the heterocyclic quinolinequinone system (**AB**) with the pyridyl ring (**C**) was explained by hydrogen bonding between the nitrogen of ring **B** and the amino function at C-5′ of ring **C**.

The first investigations on the absolute axial configuration of streptonigrin (**1**) were reported by Dholakia and Gillard in 1981.[14] From the empirical interpretation of its experimental CD spectrum measured in ethanol (Fig. 2b), they assumed

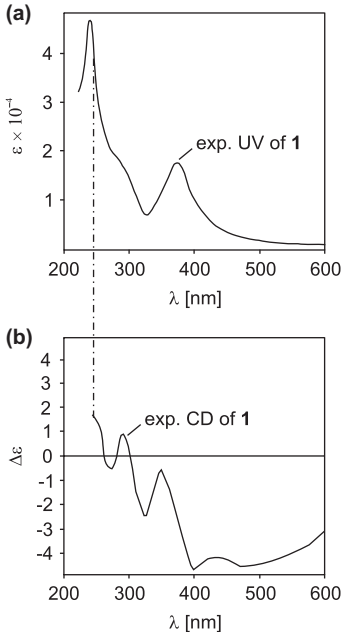

Figure 2. UV (a) and CD spectra (b) of streptonigrin (**1**) in ethanol as reported by Dholakia and Gillard in 1981.[14] The dashed line corresponds to a wavelength of 245 nm.

the natural product to be *P*-configured,[21] because of the occurrence of a negative Cotton effect at shorter wavelengths, which was associated with the 'biphenyl conjugated band at about 245 nm'. This interpretation, however, has to be critically reviewed in several respects. Firstly, the Cotton effect at the referred wavelength is positive, not negative as stated by the authors, and moreover 'incomplete', since located at the margin of the measured wavelength array (see Fig. 2b). Secondly, to compare **1** with a (symmetrically substituted) biphenyl, great caution has to be taken, because the signs of the Cotton effects strongly depend on the respective substitution pattern and on the nature of the attached groups.[22] And thirdly, a basic precondition for the attribution of the absolute configuration from the sign of a Cotton effect is the applicability of the exciton chirality method,[23] which requires the availability of two identical—or at least very similar—chromophores whose degenerated electric dipole moments interact with each other. This results in two energetically different transitions (Davydov split)[24] that lead to the characteristic exciton couplet in the CD spectrum. A significant feature of such a couplet is its symmetric location around the wavelength of the non-perturbed transition, i.e., the corresponding UV maximum[25] has to parallel the inflection point of the excitonic couplet in the CD curve. The direct comparison of the UV (Fig. 2a) and CD spectra (Fig. 2b) of **1**, however, reveals that no UV maximum in the shorter wavelength range (up to ca. 325 nm) corresponds to a point of inflection in the CD curve, but only to extrema.

Furthermore, besides the facts that the CD spectrum is only shown down to the mentioned region of 245 nm, and that the nearest negative Cotton effect lies at about 270 nm, the absence of an exciton couplet is not surprising, since streptonigrin (**1**) is structurally far from being a biphenyl or from possessing two very similar chromophores at the chiral axis between the rings **C** and **D** (Fig. 1). In fact, the linkage between C-4′ and C-7′ connects a phenyl and a pyridyl residue, which are, in addition, differently substituted. The latter one is even conjugated to a quinolinequinone chromophore. Consequently, there is no justified reason for the application of the exciton chirality method to streptonigrin (**1**).

This fact was also realized by Tennant and Rickards, who investigated the absolute configuration of **1** in 1997,[15] again by CD spectroscopy. Their first observation was that the CD curve of streptonigrin (**1**), although likewise measured in ethanol (Fig. 3b), significantly differed from the one recorded by Dholakia and Gillard before,[14] whereas the UV spectra looked almost the same in both cases (Fig. 3a).

Because of the absence of structurally closely related reference substances of known absolute configuration, Tennant and Rickards attached two identical chromophores, viz. *p*-nitrobenzoyl residues, to the 5′-amino and 8′-hydroxy groups of streptonigrin methyl ester, in order to produce a derivative with an expectedly clear excitonic couplet in the CD spectrum, thus permitting application of the exciton chirality method. Indeed, the experimental CD curve of the obtained 5′,8′-di-*N*,*O*-*p*-nitrobenzoyl streptonigrin methyl ester (**2**) exhibited an intense couplet around 260 nm (Fig. 4b), i.e., at the wavelength where *p*-nitrobenzoyl is known to absorb.[15] The new

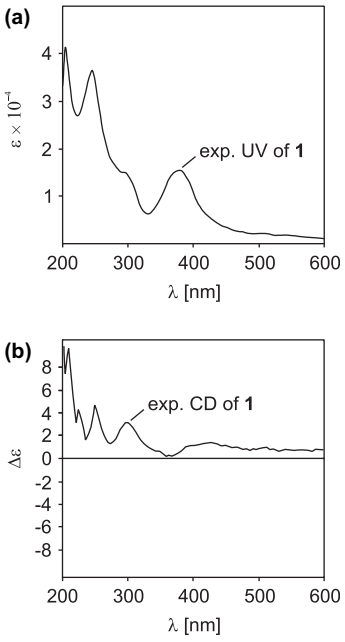

Figure 3. UV (a) and CD spectra (b) of streptonigrin (**1**) in ethanol as reported by Tennant and Rickards in 1997.[15]

couplet was attributed to originate from the excitonic coupling of the introduced *p*-nitrobenzoyl chromophores, because the respective point of inflection now paralleled the expected maximum in the corresponding UV spectrum of **2** (Fig. 4a).

The observed first negative Cotton effect at around 270 nm hinted at a so-called 'negative chirality' of the *p*-nitrobenzoyl substituents (Fig. 4c), i.e., these chromophores should be located in a way that their transition moments form an anti-clockwise twist, here corresponding to an *M*-configuration for **2** and thus for streptonigrin (**1**) itself, in contrast to the original attribution by Dholakia and Gillard (see above).

However, as already pointed out by Tennant and Rickards, themselves, this stereochemical assignment might not be entirely secure due to the additional presence of the strong quinolinequinone chromophore, its superimposing absorption, and, in particular, its hard-to-predict interaction with the *p*-nitrobenzoyl auxiliary chromophore, thus making their configurational attribution to be only tentative. Consequently, a secure, independent elucidation of the absolute stereostructure of genuine streptonigrin (**1**) still seemed necessary and rewarding.

3. Results and discussion

In order to surely determine the three-dimensional structure of **1**, we predicted the molecular CD of its two atropo-enantiomers, (*M*)-**1** and (*P*)-**1**, by quantum chemical calculations[26] and compared these theoretical spectra with the CD curve measured in our laboratory. This experimental spectrum (Fig. 6) was found to be similar[27] to the one reported by Tennant and Rickards (cf. Fig. 3). Arbitrarily starting with the *M*-enantiomer of **1**, the conformational space was screened first by means of PM3.[28] For this purpose reaction coordinates covering the flexible parts of streptonigrin (**1**) were defined (Fig. 5) and investigated in order to locate all minimum dihedral angles (Table 1).

The permutation of these independently variable minimal angles resulted in 1536 possible conformers. After PM3 optimization, 390 of them remained within an energy gap of 3 kcal/mol above the global minimum thus found.[29] For

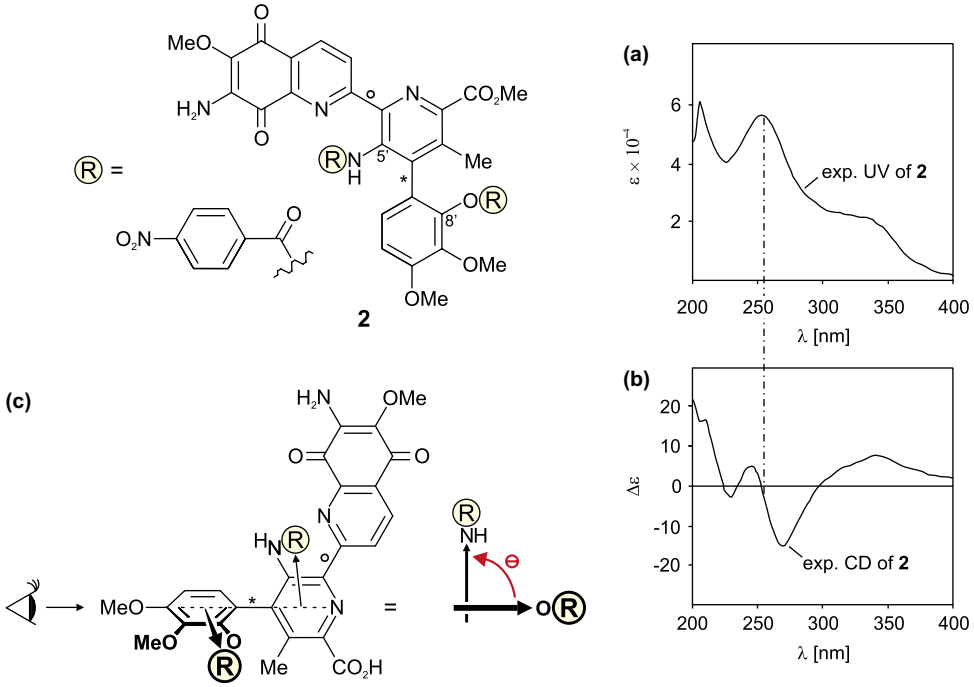

Figure 4. UV (a) and CD spectra (b) of 5′,8′-di-*N*,*O*-*p*-nitrobenzoyl streptonigrin methyl ester (**2**) in ethanol as received by Tennant and Rickards;[15] the dashed line connects a UV maximum to the inflection point of the supposed exciton couplet at about 260 nm, (c) 'negative chirality' of **2** as a consequence of the observed negative exciton couplet in its experimental CD spectrum.

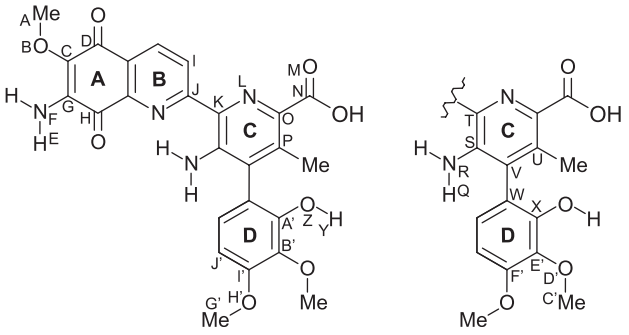

Figure 5. Definition of the dihedral angles investigated in the semiempirical conformational analysis of **1**.

each of these structures a single CD spectrum was computed using the semiempirical CNDO/S[30] and OM2[31] Hamiltonians. In both cases the individual spectra were summed energetically weighted, following the Boltzmann statistics, subsequently UV corrected,[32] and finally compared with the experimental CD curve of **1**. In the case of CNDO/S, this comparison revealed an acceptable agreement for the computed CD spectrum of (*M*)-**1** (Fig. 6a, left), yet only in the shorter wavelength array up to ca. 320 nm, while the curve calculated for the atropo-enantiomer, (*P*)-**1**, was almost opposite in that particular range (Fig. 6a, right).

The results obtained with OM2 were in principle the same, i.e., a basic agreement for the computed curve of (*M*)-**1** (Fig. 6b, left) between 200 and up to 300 nm and the expectedly inverse course for (*P*)-**1** (Fig. 6b, right). Thus, the two semiempirical approaches assigned the axial *M*-configuration to streptonigrin (**1**), but both failed to reproduce the experimental CD spectrum for longer wavelengths and with respect to the intensities of the transitions.

To overcome these deficiencies, more sophisticated calculations seemed desirable, both, concerning the structural optimization and the computation of the electronic transitions. Unfortunately, the molecular size and the very high number of minimum conformers strongly hampered the applicability of such calculations. Therefore, an approximation procedure

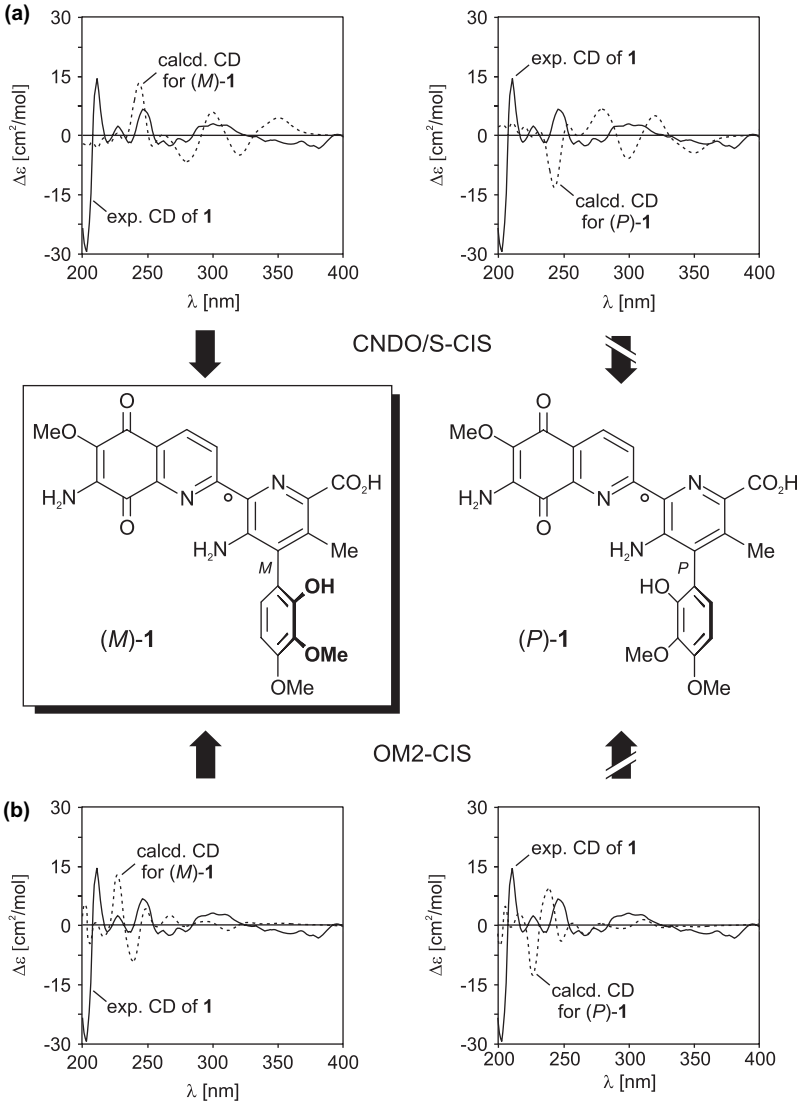

Figure 6. Attribution of the absolute configuration of **1** by comparison of the CNDO/S (a) and OM2 (b) calculated CD spectra of its enantiomers, (*M*)-**1** and (*P*)-**1**, with the experimental CD curve.

Table 1
Minimum dihedral angles of the flexible substituents of **1**[a]

[ABCD]	[EFGH]	[IJKL]	[MNOP]	[QRST]	[UVWX]	[YZA′B′]	[C′D′E′F′]	[G′H′I′J′]
80	−10	170	90	0	−65	175	90	175
−80	−160	120	20	−170		5	−90	95
		−100	−40					5
			−90					−100

[a] All values (in degrees) represent average data, with deviations of ca. ±5° in the final structures.

became necessary in order to decrease the number of minimum structures to be treated at a higher computational level. Thus, in a first step, the discrete, semiempirically calculated CD spectra were screened, revealing that the overall simulated CD curve is basically composed of three types of single spectra (Fig. 7). Each of these were found to possess one of the three possible minimum dihedral angles, [IJKL], at the configurationally unstable 'northern' biaryl axis (ca. −100°, ca. +120°, ca. +170°, see Table 1), which connects the quinolinequinone portion with the pyridyl moiety. This result was not surprising, since it is expected that the presence of an additional non-planar—and therefore chiral—axis should have a more pronounced effect on the molecular CD than the mere variation of the dihedral angle of a substituent that is devoid of a chromophore.

In the next step, the respective lowest-energy conformer from each of the three aforementioned groups of minimum

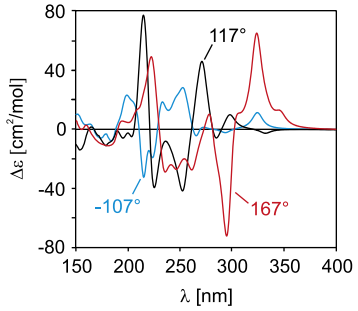

Figure 7. The CNDO/S calculated single CD spectra of those three lowest-energy minimum structures that each possess one of the three possible minimal dihedral angles, [IJKL], at the 'northern' axis.

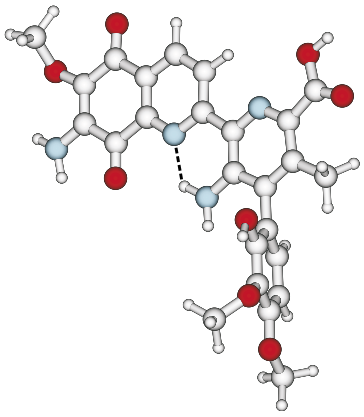

Figure 8. Calculated (B3LYP/6-31G*) global minimum structure of **1**, exhibiting a planar **ABC**-ring system, which is structurally stabilized by a strong hydrogen bond (dashed line).

structures was further optimized using DFT. The corresponding B3LYP[33]/6-31G*[34] calculations resulted in a convergence of the different dihedral angles at the 'northern' biaryl axis. This led to a planar structure of the **ABC**-ring system (Fig. 8), as previously also found in the solid state[13] and in solution,[20] and consequently gave almost identical CD spectra.[35]

This convergence permitted to perform the following more sophisticated TDDFT computations of the excited states only for one single minimum structure, which was done by using the B3LYP hybrid functional and a basis set of triple-zeta quality (TZVP),[36] with consideration of the first 100 excitations. The comparison of the UV-corrected CD spectra thus obtained with the measured curve showed a good agreement in the case of (*M*)-**1** (Fig. 9, left) and an almost perfect mirror image for (*P*)-**1** (Fig. 9, right), thus unambiguously confirming the above results of the semiempirical CD computations (Fig. 6).

4. Conclusions

Although the antitumor antibiotic natural product streptonigrin (**1**) has been known for almost 50 years, its absolute configuration at the configurationally stable 'southern' biaryl axis has as yet not been unambiguously established, with two controversial configurational suggestions in the literature. While the first, empirical assignment by Dholakia and Gillard[14] seems to be arbitrary, the later attribution by Tennant and Rickards,[15] who applied the exciton chirality method to a derivative of **1**, appears to be more substantiated, but is still not unambiguous.

Within this paper a third, non-empirical approach is presented, now based on the comparison of the quantum chemically computed CD spectra of (*M*)- and (*P*)-**1** with the experimental curve. At the levels of semiempirical (CNDO/S and OM2) and ab initio (TDDFT) calculations these comparisons revealed a satisfactory to excellent agreement for the simulated CD spectrum of the *M*-atropo-enantiomer of streptonigrin (**1**), thus clearly and conclusively assigning this absolute configuration to the natural product, and additionally verifying the result of the second, more solid previous attempt.[15]

5. Experimental section

5.1. General experimental procedures

A sample of streptonigrin (**1**) was purchased from Fluka and its purity was verified by HPLC analysis on a chiral phase, using a Chiralcel OD-RH column (150×4.6 mm) and water/acetonitrile (3:7) as the eluent. The UV spectrum of **1** was

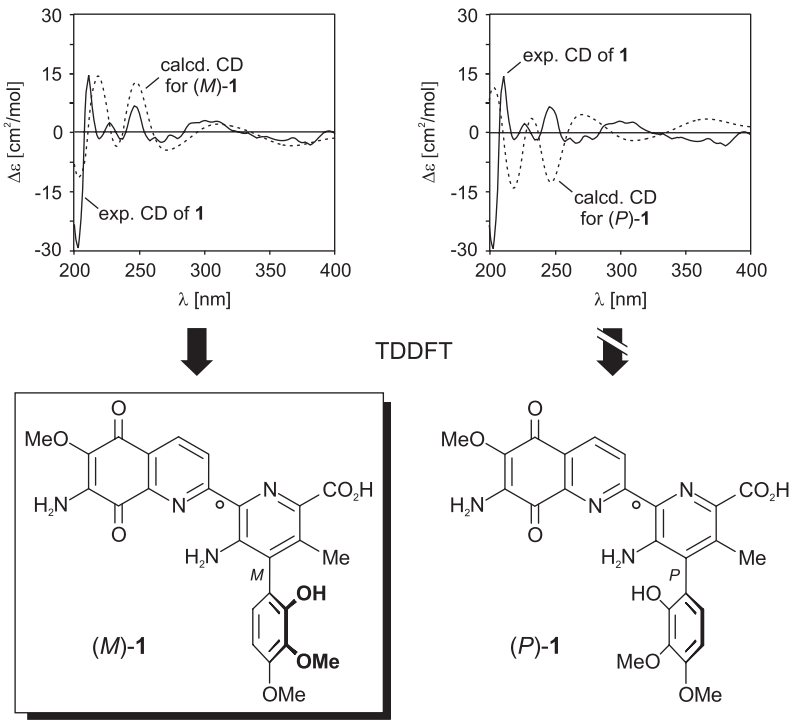

Figure 9. Unambiguous assignment of the absolute configuration of **1** by comparison of the TDDFT (B3LYP/TZVP) calculated CD spectra of (*M*)-**1** and (*P*)-**1** with the experimental curve.

recorded on a Varian Cary 50 spectrophotometer. Its CD spectrum was measured on a Jasco J-715 spectropolarimeter at room temperature using a 0.2 cm standard cell and spectrophotometric grade MeOH, and is reported in units of $\Delta\varepsilon$ (cm^2/mol) at the given wavelength λ (nm).

5.2. Electronic excitation spectra of *1*

UV (MeOH) λ_{max} 212, 244, 296, 374 nm; CD (MeOH): $\Delta\varepsilon_{203}$ −29.4, $\Delta\varepsilon_{211}$ +14.2, $\Delta\varepsilon_{219}$ −1.8, $\Delta\varepsilon_{227}$ +2.2, $\Delta\varepsilon_{236}$ −1.8, $\Delta\varepsilon_{246}$ +6.5, $\Delta\varepsilon_{258}$ −2.3, $\Delta\varepsilon_{267}$ −2.8, $\Delta\varepsilon_{280}$ −1.8, $\Delta\varepsilon_{290}$ +2.1, $\Delta\varepsilon_{300}$ +3.0, $\Delta\varepsilon_{310}$ +2.7, $\Delta\varepsilon_{355}$ −2.3, $\Delta\varepsilon_{381}$ −3.4.

5.3. Computational methods

The conformational analysis of **1** was performed by means of the semiempirical PM3[28] method and a DFT approach (B3LYP[33]/6-31G*[34]), as implemented in the program package GAUSSIAN 03,[37] starting from pre-optimized geometries generated by the TRIPOS[38] force field as part of the molecular modeling package SYBYL 7.2.[38]

The wave functions required for the computation of the respective oscillator and rotational strengths of the electronic transitions from the ground state to excited states were obtained by CNDO/S-CIS[30] and OM2-CIS[31] calculations, using the ground state determinants and 784 and 900 singly occupied configurations, respectively, resulting from the excitations of one electron from one of the 14 (or 15 in the case of OM2) highest occupied molecular orbitals into one of the 14 (OM2: 15) lowest unoccupied ones, thus taking into account only π- and non-bonding electrons of **1**. These calculations were carried out by using the BDZDO/MCDSPD[39] and MNDO99[40] software packages. Furthermore the oscillator and rotatory strengths for the first 100 transitions were calculated by means of TDDFT using the B3LYP[33] hybrid functional and a TZVP[36] basis set as implemented in TURBOMOLE 5.6.[41] The oscillator and rotatory strengths, thus obtained for the individual structures, were summed energetically weighted, following the Boltzmann statistics. Finally, the overall UV and CD spectra were simulated as sums of Gaussian functions centered at the wavelengths of the respective electronic transitions and multiplied by the corresponding oscillator or rotatory strengths—transformed into absorption and $\Delta\varepsilon$ values, respectively.

Acknowledgements

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