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Quantumchemical Calculation of CD Spectra: the Absolute Configuration of Palmarumycins CP_3 and C_2

Gerhard Bringmann* and Stefan Busemann
Institut für Organische Chemie, Universität Würzburg,
Am Hubland, D-97074 Würzburg, Germany

Karsten Krohn and Karsten Beckmann
Fachbereich Chemie und Chemietechnik der Universität-Gesamthochschule Paderborn,
Warburger Straße 100, D-33098 Paderborn, Germany

Abstract: The quantumchemical calculation of the CD spectra of two representatives of palmarumycins, biologically active compounds from *Coniothyrium* species, is described, allowing, for the first time, the elucidation of the absolute configuration of two representatives of this class of compounds without the use of empirical rules or reference material.

INTRODUCTION

A substantial precondition for directed structure-activity investigations is the unambiguous knowledge of the 3-dimensional geometry of the active substance including, in particular, its absolute configuration. An important method for the attribution of the stereostructure of a chiral compound is the investigation of its circular dichroism (CD). Its broad and general applicability, however, is severely hampered by the sometimes difficult interpretation of the CD effects if novel classes of compounds are dealt with, *i.e.* if no structural analogs are available with comparable chiroptical properties or if empirical rules are not applicable, so that theoretical methods are increasingly essential.[1,2] This is the case for the palmarumycins, secondary metabolites from various species of the fungal genus *Coniothyrium*. Thus, Krohn *et al.* isolated several representatives of the general structure **1**, among them palmarumycins CP_3 and C_2, which were attributed the constitutions **2** and **3**, respectively.[3,4] They were shown to exhibit a high biocidal activity against different bacteria, fungi, and algae.[3,4] From other fungal species, some of which are as yet unidentified, compounds of type **1** were also isolated.[5-11] They are all characterized by a 1,8-dihydroxynaphthalene-derived subunit as a joint structural element, attached to a second, partially reduced analog by a spiroacetal function.

The relative configurations of palmarumycins were established by NMR and, in single cases, by X-ray structure analyses.[3,4] Due to the novelty of the structures, there was no possibility of interpreting their CD spectra by comparison with those of similar compounds of known absolute configuration. For the application of the exciton chirality method,[12,13] an important precondition is the presence of two identical or at least similar chromophores with an intensive electric transition dipole moment, which, however, is not *a priori* fulfilled for the palmarumycins. As some representatives of this class of compounds have two (or more) hydroxy

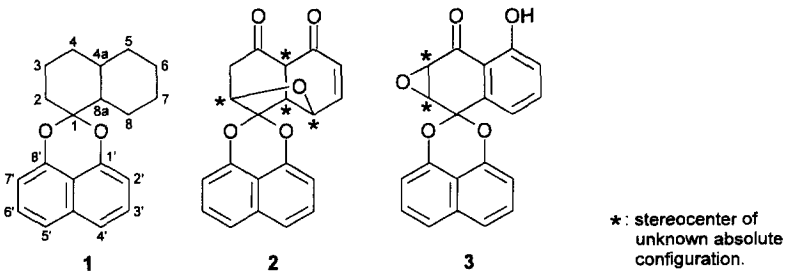

Fig. 1. Joint structural element **1** of palmarumycins and constitutions of palmarumycins CP_3 (**2**) and C_2 (**3**).

groups, this precondition was attained for a few special cases (*e.g.* for **4** and **5**), by introduction of the required chromophores into the molecule through derivatization to the corresponding di- (or even tri-) *p-N,N*-dimethylaminobenzoates.[5,14] That work was based on the assumption that the observed CD effect depends on the orientation of the benzoate groups towards each other, exclusively – interactions between the benzoates and other pronounced chromophores, *e.g.* the naphthalene unit, were neglected. Furthermore, in the case of more than two hydroxy groups, it will have to be demonstrated that the interpreted effects[5] are really caused by the exciton interaction between the two *neighboring* benzoate groups at C-4 and C-5 (and not with the one at C-8).

Thus, for the elucidation of the absolute configuration of palmarumycins, no generally applicable, independent procedure has so far been available, only special solutions for particular single compounds within this class of substances, based on empirical rules. In this paper, we describe our combination of the quantumchemical calculation and Boltzmann-weighted addition of CD spectra[1,2,15–19] as the first means for the elucidation of the absolute configuration of palmarumycins, exemplarily to the elucidation of the absolute stereostructures of palmarumycins CP_3 and C_2 as **2a** and **3b**.

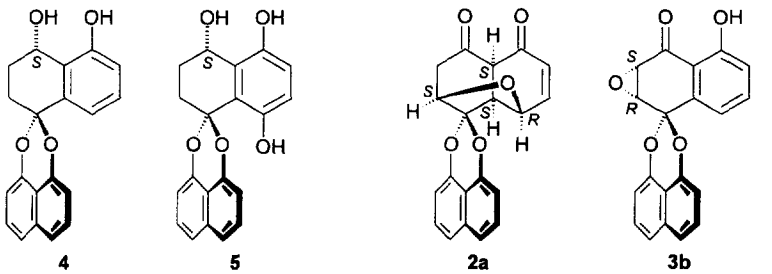

Fig. 2. Two single representatives **4** and **5** whose absolute configurations were attributed after derivatization into their di- resp. tri-*p-N,N*-dimethylaminobenzoates by application of the exciton chirality method, and absolute configuration of palmarumycins CP_3 (**2a**) and C_2 (**3a**) attributed in this paper, by quantumchemical calculation of CD spectra.

QUANTUMCHEMICAL CALCULATION OF CD SPECTRA

The elucidation of the absolute configuration by quantumchemical calculation of CD spectra consists of four principal parts: In the first step (**I**), a conformational analysis is performed. Since the CD spectrum of a compound is largely depending on the molecular geometry, the experimental CD spectrum in particular of a flexible molecule has to be considered as the averaged overall CD behavior of all of the relevant conformational

species. For this reason, the second step (**II**) is the calculation of the CD spectra of all the conformers that are populated to a given degree. From these single spectra, the theoretical overall spectrum is subsequently obtained by a Boltzmann-weighted averaging (**III**), *i.e.* according to their heats of formation ΔH_f. By comparison of the CD spectra calculated for the proposed structure resp. for its enantiomer, with the experimental spectrum (**IV**), an assignment of the absolute configuration of the chiral compound is possible. In previous papers, we have applied this technique to the elucidation of the absolute stereostructure of axially chiral biaryl alkaloids such as naphthylisoquinolines[1,2,15,16] and biscarbazoles,[17] as well as biaryl compounds of merely synthetic origin.[18] Here, we report on the extension of this useful method to the structural elucidation of palmarumycins, natural products with stereogenic *centers*, exclusively.

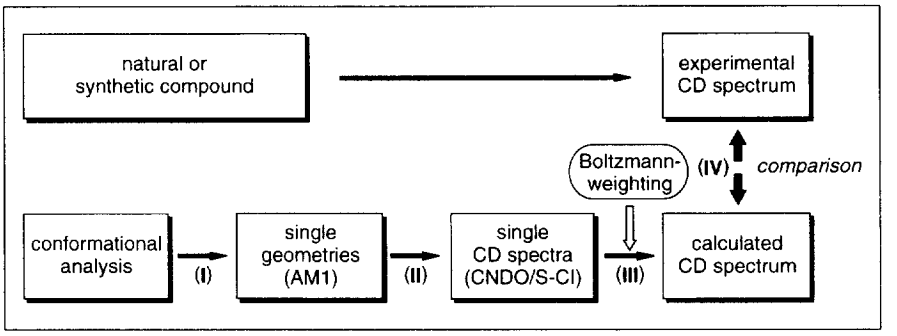

Fig. 3. The quantumchemical calculation of CD spectra – general procedure.

RESULTS AND DISCUSSION

1. Palmarumycin CP_3

From previous NMR investigations by Krohn *et al.* and confirmed by an X-ray structure analysis, the constitution and the relative configuration of palmarumycin CP_3 were reliably known.[3] Accordingly, the natural product was either 2*S*,4a*S*,8*R*,8a*S*-palmarumycin CP_3 (**2a**) or the enantiomeric compound 2*R*,4a*R*,8*S*,8a*R* (**2b** = *ent*-**2a**).

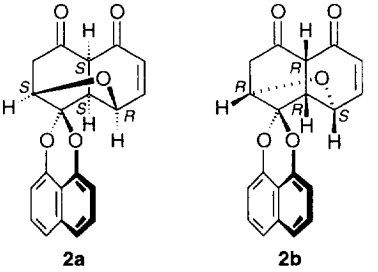

Fig. 4. Possible enantiomeric absolute stereostructures **2a** and **2b** of palmarumycin CP_3.

The calculations were started with the 2*S*,4a*S*,8*R*,8a*S*-enantiomer **2a**, arbitrarily. The conformational analysis revealed a pronounced molecular flexibility particularly in the region of the spiroacetal, whereas the oxygen-bridged molecular part was found to be quite rigid. For this reason, a 'motion coordinate' was calculated in the

course of which the dihedral angle ϑ [ABCD] is varied in 5° steps, within margins of 120° to 240°. By this procedure, the folding movement of the aromatic ring system relative to the *O*-bridged 'upper' part of the molecule, about the sp^3-type 'hingejoint' of the two acetal oxygen atoms (Fig. 5), should be appropriately described.

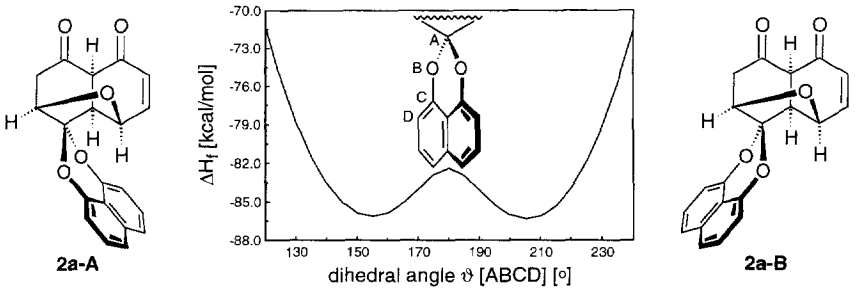

Fig. 5. 'Motion coordinate' for the partial rotation about the dihedral angle ϑ [ABCD].

The calculations revealed the existence of two conformers **2a-A** and **2a-B**, their structures are shown in Fig. 6 (left part and middle). The comparison of their computed geometries with the data previously obtained from the X-ray structure analysis shows a very good match (RMS value = 0.134) between the calculated structure and the geometry of palmarumycin CP_3 in the crystal (Fig. 6, right part).

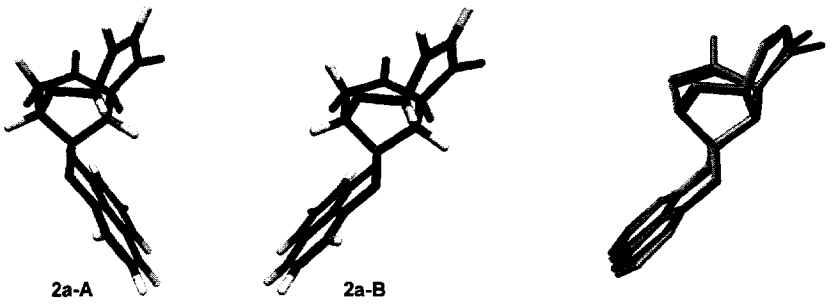

Fig. 6. Calculated geometries to the conformers of palmarumycin CP_3 (**2a**), **2a-A** (left) and **2a-B** (middle); matchplot of the conformer **2a-B** (light) of palmarumycin CP_3 and its structure in the crystal (right); for the experimental structure, arbitrarily the same 2*S*,4a*S*,8*R*,8a*S*-enantiomer is shown.

This good agreement revealed the high reliability for the calculation of the molecular structure of this compound using the semiempirical approach. Table 1 shows the calculated dihedral angles and the heats of formation ΔH_f of **2a-A** and **2a-B**.

Table 1. Characteristic structural and energetic data of the two conformers of the palmarumycin CP_3 enantiomer **2a**.

conformer	ϑ [ABCD] [°]	ΔH_f [kcal mol^{-1}]
2a-A	155.18	−85.68
2a-B	205.47	−85.90

The presence of only two conformational minimum structures reveals the rigidity of the molecular framework of palmarumycin CP_3. For both conformers, the single CD spectra were calculated (Fig. 7, left part) and subsequently added up according to their energies following the Boltzmann statistic, to give the calculated overall spectrum of **2a** (Fig. 7, right part).

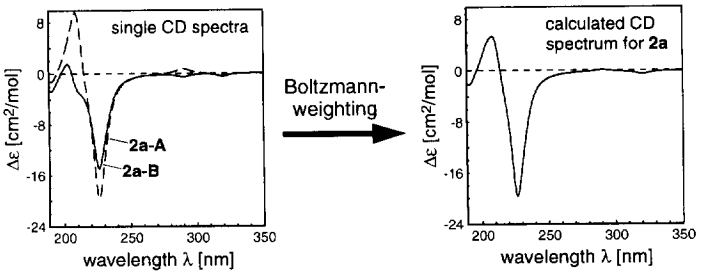

Fig. 7. Single CD spectra of the two conformers **2a-A** and **2a-B** and the Boltzmann-averaged overall spectrum.

Subsequent to the calculation of the CD spectrum of **2a**, the circular dichroism of natural palmarumycin CP_3 was investigated experimentally. Fig. 8 shows the near-exact agreement between the experimental spectrum thus obtained with the one predicted for **2a**. By contrast, the theoretical spectrum predicted for the enantiomeric structure **2b**, as obtained by multiplication of the $\Delta\varepsilon$-values calculated for **2a**, by a factor of -1, is virtually opposite to the experimental spectrum. This allows the unambiguous assignment of structure **2a** to palmarumycin CP_3, *i.e.* with 2*S*,4a*S*,8*R*,8a*S* configuration (Fig. 8).

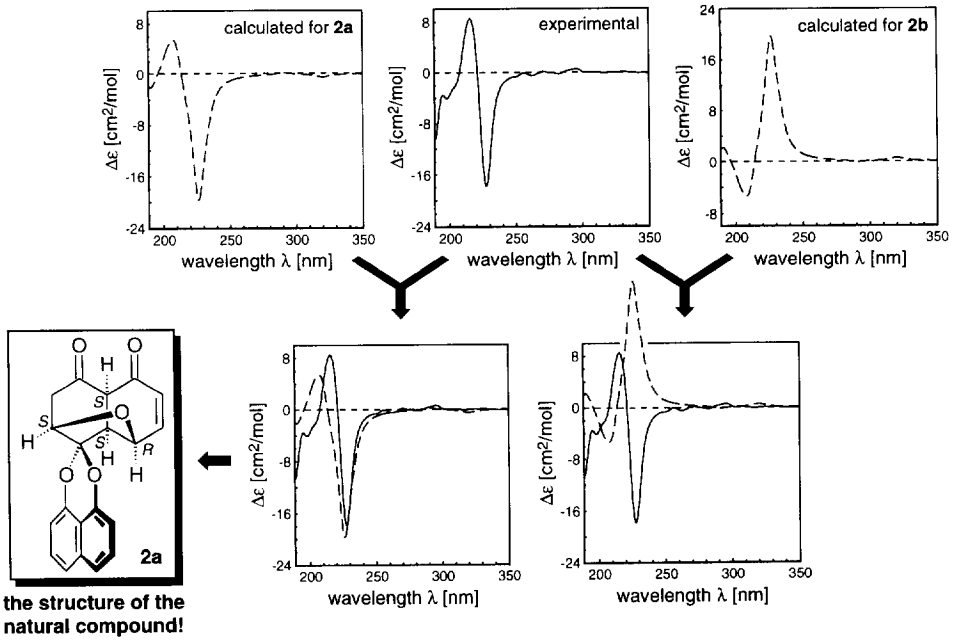

Fig. 8. Attribution of the absolute stereostructure of palmarumycin CP_3 as **2a**, by comparison of the theoretically predicted CD spectrum for the two possible enantiomers **2a** and **2b** with the experimental one for the natural product.

This elucidation of the absolute stereostructure of palmarumycin CP_3 is remarkable since the CD spectra were calculated *before* the natural compound was available for CD measurements, so that the calculations constitute true theoretical predictions. Palmarumycin CP_3 (**2a**) is thus the first representative of this class of compounds whose full stereostructure was elucidated based on theoretical calculations and not on empirical rules (which would not have been applicable, anyhow).

2. Palmarumycin C_2

The structure of the second palmarumycin, named C_2, which again was confirmed by an X-ray structure analysis,[4] is characterized by the presence of an epoxide function, giving rise to the existence of two stereogenic centers. The absolute stereostructure of palmarumycin C_2 was arbitrarily drawn as **3a** (Fig. 9), *i.e.* with 2*S*,3*R* configuration **3a**,[4] but might likewise be represented by the enantiomeric 2*R*,3*S* structure **3b** (= *ent*-**3a**).

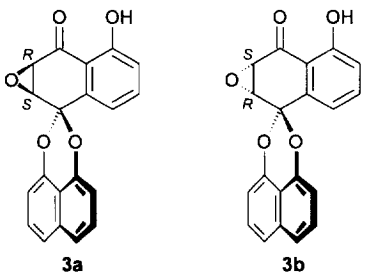

Fig. 9. Possible enantiomeric absolute stereostructures **3a** and **3b** of palmarumycin C_2.

The CD behavior of palmarumycin C_2 was calculated, exemplarily, for the 2*S*,3*R*-enantiomer **3a**. In analogy to the calculations described above for palmarumycin CP_3, again the 'motion coordinate' for the internal molecular movement that converts the two conformers with respect to the folding at the 'hingejoint' of the spiroacetal function was calculated. For this purpose, the dihedral angle ϑ [ABCD] was varied from 120° up to 240°, proceeding in 5° steps (Fig. 10).

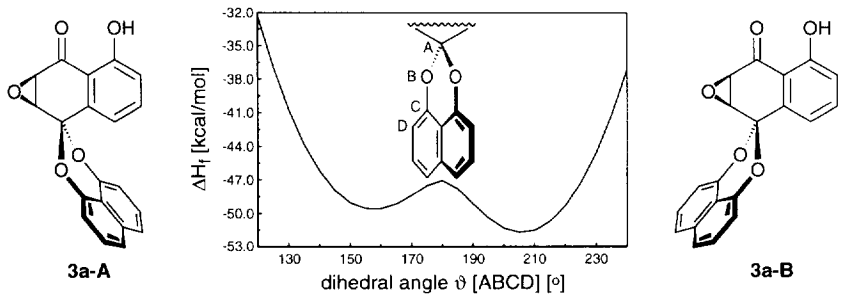

Fig. 10. 'Motion coordinate' for the partial rotation about the dihedral angle ϑ [ABCD].

The calculations revealed the existence of two conformers **3a-A** and **3a-B** (Fig. 11), which correspond to those of palmarumycin CP_3 (**2a**) concerning the geometry of the dihedral angle ϑ [ABCD]. A very good

agreement between the calculated molecular geometry of one of the two conformers and the experimental crystal structure of palmarumycin C_2 was found in this case, too (RMS value = 0.112). Table 2 shows characteristic structural and energetic data of the **3a** conformers.

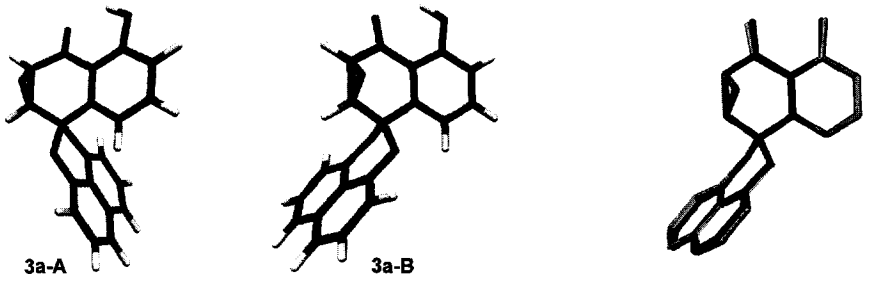

Fig. 11. Calculated geometries to the conformers of palmarumycin C_2 (**3a**), **3a-A** (left), and **3a-B** (middle); matchplot of the conformer **3a-B** (light) of palmarumycin C_2 and its structure in the crystal (right).

Table 2. Characteristic structural and energetic data of the conformers of the palmarumycin C_2 enantiomer **3a**.

conformer	ϑ [ABCD] [°]	ΔH_f [kcal mol^{-1}]
3a-A	154.48	−49.69
3a-B	205.24	−51.72

Again, the single CD spectra were calculated for both conformers and were then Boltzmann-averaged to give the theoretical overall spectrum of 2*S*,3*R*-palmarumycin C_2 (**3a**) (Fig. 12).

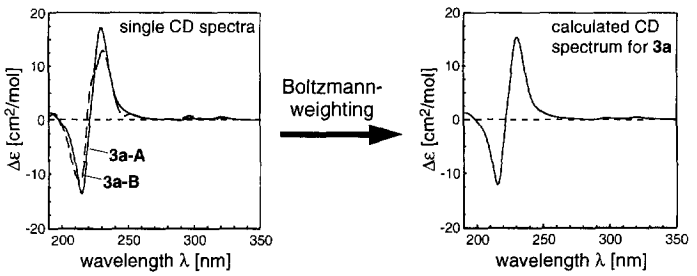

Fig. 12. Single CD spectra of **3a-A** and **3a-B** and their Boltzmann-weighted averaging to give the overall CD spectrum of 2*S*,3*R*-palmarumycin C_2 (**3a**).

The comparison of the theoretical CD spectra of **3a** and its enantiomer **3b** with the experimental one of the natural product (Fig. 13) shows that in this case, the initially calculated spectrum for **3a** is virtually opposite to the experimental one, while the theoretical spectrum for the enantiomer **3b** matches nearly perfectly. From this, the natural product can unambiguously be deduced to be 2*R*,3*S*-configured and to be represented by structure **3b**.

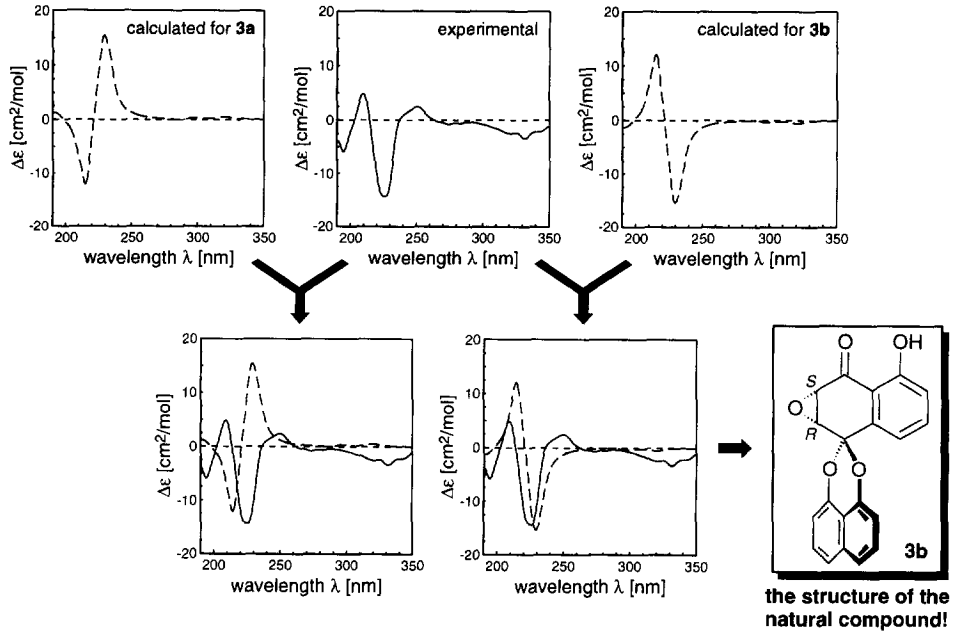

Fig. 13. Attribution of the absolute stereostructure of palmarumycin C_2 as **3b**, by comparison of the theoretically predicted CD spectrum for the two possible enantiomers **3a** and **3b**, with the experimental one for the natural product.

CONCLUSIONS AND FURTHER PERSPECTIVES

In this paper, the method for the determination of the absolute configuration by CD calculations, which had previously given excellent results mainly for biaryl compounds,[1,2,15–18] has now demonstrated its applicability to the efficient structure elucidation within the palmarumycins. With comparatively low efforts, the absolute configurations of two representatives of this new class of compounds were attributed, which had so far not been possible with conventional methods. In the case of palmarumycin CP_3, the CD spectrum was even theoretically predicted *before* the CD behavior of the natural product had been investigated experimentally, subsequently revealing the nearly perfect agreement of the theoretical spectrum for the 2*S*,4a*S*,8*R*,8a*S*-enantiomer **2a** with the experimental one. Whereas previously the absolute configurations of few, special representatives of palmarumycins have been elucidated, the results described in this paper now allow a general procedure for the rapid and unequivocal attribution of the absolute configuration within this class of natural products, without having to rely on empirical data or reference material. The quantumchemical attribution of the absolute stereostructures of further representatives of this class of compounds, is underway.

COMPUTATIONAL METHODS

Conformational analyses

The conformational analyses were performed on Silicon Graphics IRIS 4D, INDIGO (R4000) workstations. For the AM1[20] calculations the program package VAMP 5.0[21] was used, starting from structures preoptimized by the TRIPOS force field as implemented in the molecular modelling program SYBYL.[22]

Calculation of CD spectra

The rotational strength R_{0a} of an electric transition from the groundstate ψ_0 to an excited state ψ_a, which is proportional to the experimental observable $\Delta\varepsilon$, is given as:

$$R_{0a} = \Im\{\langle\psi_0|\hat{\mu}|\psi_a\rangle \cdot \langle\psi_a|\hat{m}|\psi_0\rangle\} = \Im\{\mu_{0a} \cdot m_{a0}\}. \quad (1)$$

Inserting the dipol velocity formalism

$$\mu_{0a} = \frac{e\hbar}{im(E_a - E_0)} p_{0a}, \quad (2)$$

called Bohm-formula, transforms equation (1) into

$$R_{0a} = \Im\left\{\frac{e\hbar}{im(E_a - E_0)}\langle\psi_0|\hat{p}|\psi_a\rangle \cdot \langle\psi_a|\hat{m}|\psi_0\rangle\right\} = \Im\left\{\frac{e\hbar}{im(E_a - E_0)} p_{0a} \cdot m_{a0}\right\}. \quad (3)$$

By using this term, the rotational strength R_{0a} can be calculated, giving origin-independent results even for approximated wavefunctions ψ_0 and ψ_a. The wavefunctions of the excited states ψ_a were obtained by a *CNDO/S*-CI calculation,[23] where the CI expansion includes the ground state determinant and 400 singly occupied configurations. These calculations were carried out on LinuX workstations using the BDZDO/MCDSPD progam package.[24] The size of the investigated molecules does not yet permit the application of *ab initio* CI calculations.

All calculated single CD spectra were then averaged to the theoretical overall spectrum by the means of the Boltzmann statistic according to the calculated heats of formation of the corresponding geometries. For a better visualization of the theoretical CD spectra, $\Delta\varepsilon$ curves were calculated from the rotational strengths:

$$\Delta\varepsilon(\nu) = \frac{6.909 h c_o \nu \sqrt{\varepsilon_0}}{8\pi^2 1000 N_A \sqrt{\mu_0}} \sigma_{0a}(\nu) R_{0a}, \quad (4)$$

where σ_{0a} denotes a Gaussian band shape function according to the formula:

$$\sigma_{0a}(\lambda) = -\frac{1}{\Delta m\sqrt{\pi}} e^{-\left(\frac{\lambda - \lambda_a}{\Delta m}\right)^2}. \quad (5)$$

For the halfband width Δm, a value of 5 nm was chosen.

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