Determination of the Absolute Configurations of γ-Rubromycin and Related Spiro Compounds by Quantum Chemical CD Calculations

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Dedicated to Professor Richard Neidlein on the occasion of his 70th birthday

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The absolute configurations of the spiro compounds γ- and β-rubromycin (**2** and **3**), natural antibiotics derived from actinomycetes, have been elucidated as (*S*) by quantum chemical calculations of their chiroptical properties and comparisons with the respective experimental CD spectra. Surprisingly, their spiro centers show an absolute configuration opposite to that of heliquinomycin (**1**), the only related spiro compound for which the configuration has hitherto been assigned. By further quantum chemical CD calculations, we were likewise able to confirm the absolute stereostructure of heliquinomycin (**1**), previously assigned by X-ray structural and degradative studies, thus providing independent corroboration of our results for γ- and β-rubromycin (**2** and **3**). Accordingly, it has emerged that diverse actinomycetes can generate different acetal configurations.

Introduction

The rubromycins[1,2] are antibacterially and cytostatically active microbial secondary metabolites[3] containing a hydroxynaphthoquinone chromophore and an isocoumarin moiety connected through a spiro acetal system. Structurally related to the rubromycins are purpuromycin,[4] the griseorhodins,[5–9] the DK-7814 compounds,[10] and heliquinomycin (**1**, see Figure 1),[11] all of which are isolated from actinomycetes. The numerous structural investigations on these dyes were followed by detailed work on the mode of action,[12–14] the chemical reactivity,[15] the biosynthesis,[3,16] and the total synthesis[17] of selected representatives of this so-called rubromycin group of antibiotics. However, until now, the absolute configuration has been established only for one single representative, heliquinomycin (**1**), which was accomplished by X-ray crystallographic analysis coupled with the fortuitous presence of a sugar moiety of which the absolute configuration could be established through degradation experiments.[11] This was, however, not possible for γ-rubromycin (**2**), nor for another naturally occurring derivative β-rubromycin (**3**, see Figure 1), which may be converted into the stereochemically identical **2** by acid-catalyzed transformation without loss of optical purity.[3] Moreover, attempts to crystallize brominated rubromycin derivatives failed,[18] so that neither **2** nor **3**, nor any of the other naturally occurring spiro acetals have yet been assigned stereochemically. In this paper, we describe the elucidation of the absolute configuration of **2** (and thus also of **3**) as (*S*), i.e. opposite to that of **1**, by quantum chemical CD calculations.[19–23] Furthermore, the stereostructure of

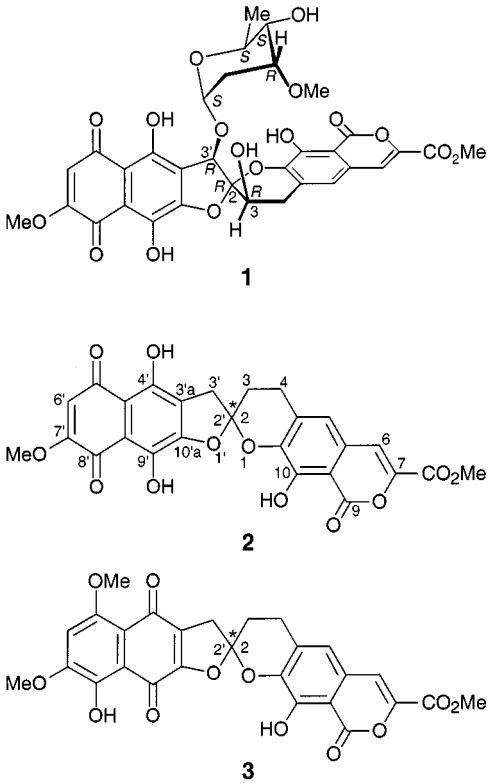

Figure 1. Absolute configuration of heliquinomycin (**1**), and the constitution of γ-rubromycin (**2**) and β-rubromycin (**3**)

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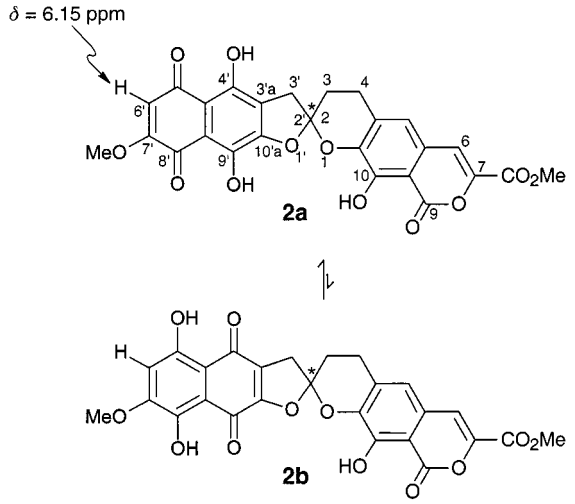
1 with the (*R*)-configuration at the acetalic stereocenter has been confirmed by the same computational method.

Results and Discussion

γ-Rubromycin (**2**) might, in principle, be represented by one of the two tautomeric forms, **2a** or **2b**. As can be deduced from the chemical shift of 6′-H (δ = 6.15 in $CDCl_3$),[1] the tautomeric equilibrium almost completely favors **2a**, i.e. the form with the distal naphthalene ring in the quinoid form (see Scheme 1), hence the calculations centered on this tautomer.



Scheme 1. Equilibrium of the two possible tautomeric forms of γ-rubromycin (**2**)

Starting with the arbitrarily chosen (*S*)-enantiomer, a semiempirical conformational analysis using the AM1 parameterization[24] was performed. This revealed the presence of the following six flexible parts:

- The spiro acetal part consisting of five- and six-membered heterocyclic rings; of these, the dihydropyran moiety adopts either a half-chair (C-3 out of plane) or a boat conformation (O-1 and C-3 out of plane, energetically preferred), whereas the dihydrofuran part is nearly planar due to the spiro-like linkage and the unsaturation at C-3′a and C-10′a.
- An ester function at C-7, existing in four different orientations.
- Three OH groups at C-10, C-4′, and C-9′ showing two possible alignments each, which differ in their dihedral angles relative to the respective aromatic ring by approximately 180° and in the H−O distance of the hydrogen bond formed:
  - $OH_{C\text{-}10} - O_{C\text{-}9} \approx 204$ pm,
  - $OH_{C\text{-}10} - O\text{-}1 \approx 227$ pm,
  - $OH_{C\text{-}9'} - O\text{-}1' \approx 243$ pm,
  - $OH_{C\text{-}9'} - O_{C\text{-}8'} \approx 198$ pm, and
  - $OH_{C\text{-}4'} - O_{C\text{-}5'} \approx 194$ pm.

The energy gained through a hydrogen-bonding interaction increases with decreasing bond length. Note that, in contrast to the two other OH functions, the OH group at C-4′ has only one possibility of forming a hydrogen bond.

- 7′-OCH_3 lies in the plane of the quinoid ring system, with the methyl group oriented towards either 6′-H or the oxygen at C-8′.

Because of the largely unsaturated character, the two portions of the γ-rubromycin (**2**) molecule are both almost planar, with the exception of the heterocyclic six-membered ring of the spiro acetal moiety. The combination of all of the possible orientations of all six aforementioned flexible parts, which are independent of one another, leads to an overall number of 2 × 4 × 2 × 2 × 2 × 2 = 128 possible conformers. Each of these was optimized semiempirically (for the 3D structure of the energetically most favorable conformer, see Figure 2).

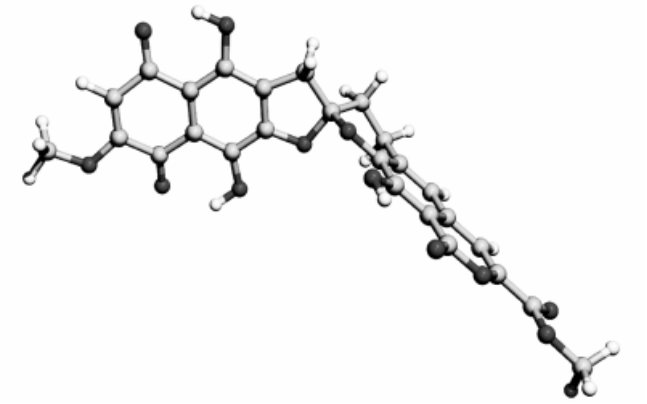


Figure 2. 3D structure of the calculated conformer of **2** lowest in energy

Assuming a Boltzmann distribution of the conformers, only those minimum structures for which the energies are no higher than 3 kcal/mol above the global minimum can be expected to show significant contributions to the overall CD spectrum.

Based on this criterion, only 10 of the 128 conformers were considered in the calculations of the chiroptical properties. The other optimized minimum structures were discarded, either because their energies were found to be too high due to fewer hydrogen bonds, or because of the presence of weaker hydrogen bonds, i.e. those with hydrogen−oxygen distances longer than 220 pm.

The individual calculated CD spectra for these 10 energetically favorable conformers were Boltzmann-weighted, added up, and subsequently "UV-corrected" [19] to give the computed overall CD spectrum for (*S*)-**2** (Figure 3, left). By reflection at the zero line, the theoretical spectrum for (*R*)-**2** was obtained (Figure 3, right). Comparison of the two calculated spectra with the experimental one shows a convincing agreement in the case of (*S*)-**2**, whereas the theoretical spectrum for (*R*)-**2** is virtually opposite to the experimental one. Thus, the configuration of the spiro center of γ-rubromycin (**2**) can be unequivocally assigned as (*S*).

On the basis of this result, the absolute configuration of β-rubromycin (**3**), which can be converted into **2**[3] and the CD spectrum of which (see Figure 4) is very similar to that of γ-rubromycin (**2**), can likewise be assigned as (*S*).

The spiro centers of both **2** and **3** have thus been found to exhibit an absolute configuration opposite to that of the

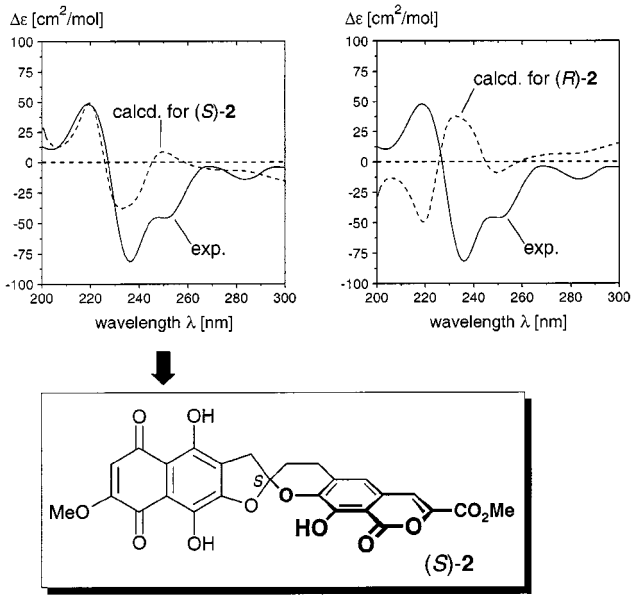


Figure 3. Attribution of the absolute configuration of γ-rubromycin (**2**) by comparison of the calculated CD spectra with the experimental one (in MeOH)

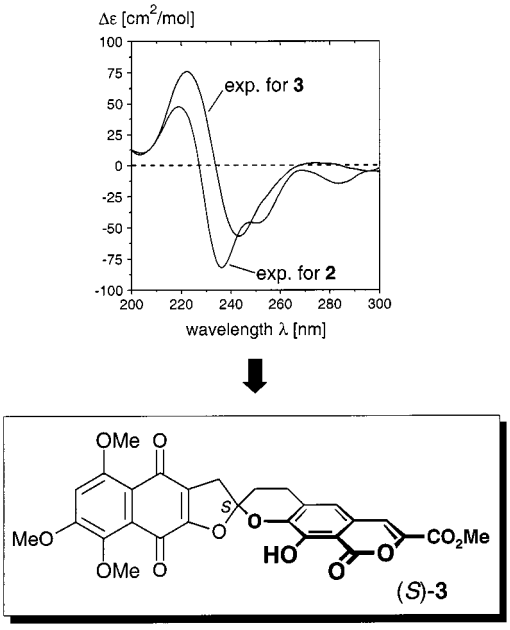


Figure 4. Attribution of the absolute configuration of β-rubromycin (**3**) by comparison of its experimental CD spectrum with the one of γ-rubromycin (**2**) (both in MeOH)

only other related spiro acetal configurationally assigned, i.e. heliquinomycin (**1**, see Figure 1), which is (*R*). This finding was unexpected and warranted further corroboration, although it could not, of course, be ruled out that different actinomycetes might generate diverse acetal configurations. A confirmation of our assignment was expected to be provided by the experimental CD spectrum of heliquinomycin (**1**), which, with its reportedly (*R*)-configured spiro center, should be essentially opposite to that of γ-rubromycin (**2**). Unfortunately, no CD spectrum of **1** has hitherto been published in the literature, but thanks to the courtesy of Prof. T. Takeuchi, we obtained a sample of authentic natural **1**. As expected on the basis of our quantum chemical stereoassignment, the experimental CD spectrum of **1** [i.e. with the (2*R*)-configuration] (see Figure 4) was found to be opposite to that of **2** [i.e. with (2*S*)-configuration], thus confirming the high predictive and diagnostic value of our calculations.

As an additional control "experiment", we analogously calculated the chiroptical properties of heliquinomycin (**1**) to see whether we would, independently, obtain a CD curve opposite to that for **2**, thereby allowing assignment of the spiro center of this compound as (*R*). The conformational analysis, performed analogously to that of γ-rubromycin (**2**), showed that the sugar moiety of **1**, which is devoid of a major chromophore, has only a negligible influence on the calculated overall spectrum. Substitution of this moiety by a hydrogen atom or a methyl group leads to nearly identical CD spectra to those of **1** itself. In contrast, the conformational behavior of the dihydropyran ring, as already

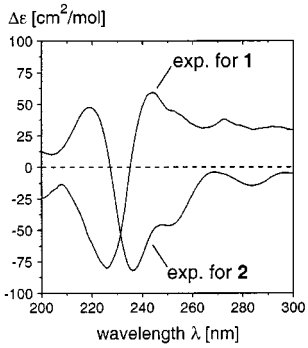


Figure 5. Comparison of the experimental CD spectrum of heliquinomycin (**1**) with that of γ-rubromycin (**2**) (both in MeOH)

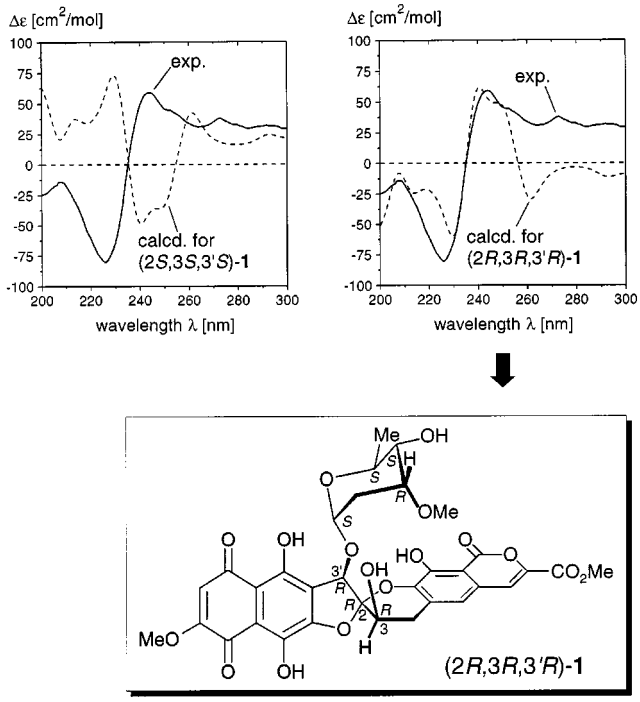


Figure 6. Renewed investigation − and confirmation − of the absolute configuration of heliquinomycin (**1**), by comparison of the calculated CD spectra with the experimental one

found for γ-rubromycin (**2**), is seen to have a strong influence on the chiroptical properties of the molecule. Comparison of the theoretical spectra of **1** with the experimental spectrum (see Figure 6) reveals a good agreement with that calculated for the enantiomer with an (*R*)-configuration at C-2, i.e. for (2*R*,3*R*,3′*R*)-**1**, which thus independently confirms the results obtained previously by X-ray structure analysis in combination with degradation experiments,[11] and simultaneously supports our calculations on **2**. As already observed for the experimental spectra (Figure 5), the calculated spectra of (2*R*,3*R*,3′*R*)-**1** (Figure 6) and (*S*)-**2** (Figure 3) are opposite to each other.

Conclusion

This work constitutes the first assignment of the absolute stereostructure of γ-rubromycin (**2**), and thus that of β-rubromycin (**3**) too. It also confirms the configuration of heliquinomycin (**1**) without relying on X-ray crystallographic and degradative methods. These studies also confirm the, at first sight surprising, fact that **1** and **2** have opposite configurations at their spiro centers. Furthermore, the results demonstrate, once again, the high reliability of the computational method used, allowing confidence in future assignments of the absolute configurations of further rubromycin derivatives.

Experimental Section

General Remarks: The CD spectra were measured on a J-715 spectropolarimeter (JASCO, Gross-Umstadt, Germany) at room temperature in methanol. Due to the moderate solubility of **1**−**3** in this solvent, no absolute Δε values could be obtained. Therefore, the range from −100 to 100 cm^2/mol was arbitrarily chosen for the measured Δε values. Using solvents in which **1**−**3** are readily soluble (e.g. CH_2Cl_2 or $CHCl_3$), the wavelength range below ca. 230 nm was not accessible due to the high UV absorptions of these media. The isolation of **2** and **3** from *Streptomyces* sp. (strain A1) was carried out as described previously.[3]

Computational Section. − Conformational Analyses: The conformational analyses of heliquinomycin (**1**) and γ-rubromycin (**2**) were performed on Silicon Graphics OCTANE R10000 workstations by means of the AM1[24] parameterization as implemented in the program package VAMP6.5,[25] starting from pre-optimized geometries generated by the TRIPOS[26] force field.

CD Calculations: Due to the size and flexibility of the studied molecules, the application of modern ab initio or DFT methods[27−29] would have required a too-large demand of CPU time and thus was not possible in this case. Therefore, we chose the semiempirical method CNDO/S,[30] which, as shown in the successful application to similar problems, is well suited to the calculation of π→π* transitions of compounds with a large system of conjugated double bonds.[20,22,31] As a consequence, the wavelength range from 200 to 300 nm, which is mainly dominated by π→π* transitions in the case of **2** and **3**, is decisive for the attribution of their absolute configurations. This assumption was supported by the assignment of UV bands observed experimentally in this region to the π→π* type of compounds that have similar chromophores as **2** or **3** (e.g. isocumarin,[32] 8-hydroxy-3-methyl-isocumarin[32] and 5,8-dihydroxy-1,4-naphthoquinone[33]). The calculated rotational strengths that are responsible for the significant CD effects at approximately 220, 240, and 260 nm in the spectra of **2** and **3**, can be considered as a contribution of several transitions differing in their source and/or target molecular orbital, which were likewise identified as π→π* transitions.

The CNDO method is based on a drastic approximation of the two-electron integrals (integrals over s- and p-AO functions are averaged) and is therefore not suitable for the calculation of states dominated by lone-pair→π* transitions. Consequently, CD bands in the region above 300 nm resulting from n→π* transitions of the unsaturated carbonyl groups of **2** and **3** were not considered for the stereochemical assignment.

The calculations of the chiroptical properties were performed on LinuX PentiumPro workstations by means of the BDZDO/MCDSPD[34] program package, which allows the calculation of excitation energies and rotational strengths for a given molecular geometry. For the calculation of the rotational strengths R_{0a} of an electronic transition 0→a we used, instead of Equation (1)

$$R_{0a} = \mathrm{Im}\{<\psi_0|\vec{\mu}|\psi_a \cdot <\psi_a|\vec{m}|\psi_0\} \quad (1)$$

as first derived by Rosenfeld,[35] the equivalent expression [Equation (2)]:

$$R_{0a} = \mathrm{Im}\left\{\frac{e\hbar}{im\,(E_a - E_0)} <\psi_0|\vec{p}|\psi_a> \cdot <\psi_a|\vec{m}|\psi_0>\right\} \quad (2)$$

In contrast to Equation (1), this expression is origin-independent and is also valid for approximate wave functions ψ_0 and ψ_a for the ground state and the excited states.[36] $\vec{\mu}$, $\vec{m}$ and $\vec{p}$ are the operators of the electric dipole, the magnetic dipole, and the linear momentum, respectively. *Im* in Equation (1) and (2) represents the imaginary part.

The complete parameter set from Ridley and Zerner[37] is listed in Table 1. The two-center electron repulsion integrals γ_{AB} are calculated by an extended Mataga-Nishimoto[38] approximation [Equation (3)]:

$$\gamma_{AB} = \frac{1}{\left(\frac{R_{AB}}{f_\gamma} + \frac{2}{\gamma_{AA}+\gamma_{BB}}\right)} \quad (3)$$

where Ridley and Zerner[35] introduced the parameter $f\gamma = 1.2$. R_{AB} is the distance between the atoms A and B, γ_{AA} and γ_{BB} are the one-center electron repulsion integrals. For the calculation of the nondiagonal H^{core} integrals, the scaling parameters $f_\pi = 0.585$

Table 1. Parameter set of the CNDO/S program (Slater exponent α_x, one center electron repulsion integral γ in eV, β^0 in eV, ionization potential *I* and electron affinity *A* for s- and p-orbitals)

Atom X	H	C	N	O
α_x	1.2	1.625	1.95	2.275
γ_{xx}	12.85	11.11	12.01	13.00
β^0	−12.0	−17.0	−26.0	−34.00
$1/2(I + A)_s$	7.176	14.051	19.316	25.390
$1/2(I + A)_p$	−	5.572	7.275	9.111

(Jaffé et al.[30]) and f_σ = 1.267 (according to Ridley and Zerner[37]) were used.

The wave functions required for the calculation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained by CNDO/S-CI calculations[30] with a CI expansion including 576 singly occupied configurations and the ground state determinant. All single CD spectra thus obtained were added up by the Boltzmann statistics using appropriate heats of formation, to give the calculated overall CD spectrum. Mainly due to the neglect of doubly excited configurations by the BDZDO/MCDSPD program, the calculated transition energies show a systematic shift,[39] whose sign and magnitude can be obtained by the comparison of the theoretical UV spectrum (to be calculated by the same program) with the experimental one. By taking into account this systematic shift, the virtually identical shift of the computed overall CD spectrum can be compensated and thus corrected. An example of this "UV-correction"[19] is shown in Figure 7. The bands of the theoretical UV spectrum of **2** within the decisive range from 200 to 300 nm show a systematic shift of about 20 nm to higher wavelengths compared to the experimental one. The shifting of the computed UV spectrum of **2** about 20 nm to lower wavelengths eliminates this "red-shift" and leads to a good agreement with the experimental one of **2**. With the knowledge of the sign and magnitude of the error of the calculated transition energies, the theoretical overall CD spectrum has to be corrected likewise for a meaningful comparison with the experimental one. UV spectra are more suitable as a basis for this process, because CD spectra will often show bands of different signs following each other within a small range of wavelengths thus complicating significantly the establishment of the calculated systematic shift. For a better visualization, the rotational strengths were transformed into Δε values and superimposed with a Gaussian band shape function (Figure 7).

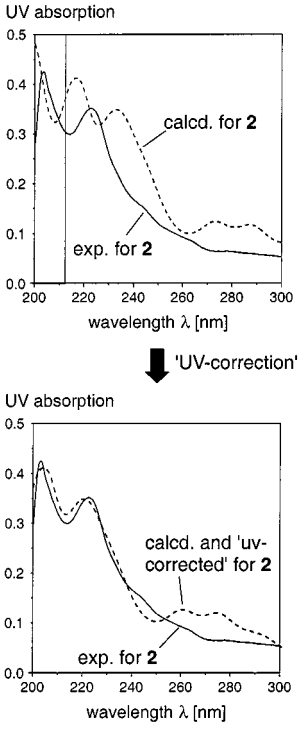


Figure 7. Example of the correction of the systematic shift for the calculated transition energies by comparison of the experimental UV spectrum of **2** with the calculated one

Acknowledgments

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