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Calculation of circular dichroism spectra of michellamines A and C, based on a complete conformational analysis☆

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Abstract—The first quantum chemical calculation of the circular dichroism (CD) spectra of michellamines has been achieved, based on a complete quantum chemical conformational analysis. Michellamines are dimeric naphthylisoquinoline alkaloids and thus naturally occurring quateraryls, with a large molecular size and flexibility and equipped with stereogenic centers and axes.

1. Introduction

Michellamines A (**1a**), B (**1b**), and C (**1c**, see Fig. 1),[2,3] isolated from the 'new' Cameroonian liana *Ancistrocladus korupensis* (Ancistrocladaceae), constitute structurally and biosynthetically intriguing secondary metabolites. Their promising anticytopathic activity against HIV-1 and -2 has triggered numerous efforts to provide more such alkaloids or their structural analogs both, by partial or total synthesis[4,5] and by isolation from other Ancistrocladaceae plants.[6] Structurally, most of the michellamines known to date are constitutionally symmetric 'dimeric'[7] naphthylisoquinoline alkaloids and, due to the presence of six free hydroxy functions and two secondary amino groups, highly polar natural products. They occur together with their molecular 'halves', the—still quite polar—monomeric naphthylisoquinoline (NIQ) alkaloids,[8] named korupensamines A (**2a**) and B (**2b**).[9]

Stereochemically, the michellamines are characterized by the presence of six stereogenic elements: the four stereocenters and the two outer biaryl axes, which are rotationally hindered. The central biaryl axis, by contrast, which joins together the two molecular halves, is configurationally unstable. With the constitutions and the configurations at all of the stereocenters identical, viz R, michellamines A (**1a**), B (**1b**), and C (**1c**) constitute a complete[10] set of all three possible atropo-diastereomeric forms of **1**. The relative configuration at the axes vs the centers within the molecular halves was assigned through NOE investigations,[2] from which, in conjunction with the absolute configuration at the stereocenters as established through chemical degradative methods,[3,11] the absolute axial configurations were deduced. Accordingly both, michellamines A (**1a**) and C (**1c**), with their homochiral biaryl axes (two times *P* for **1a** and two times *M* for **1c**) consist of two homomorphous halves and are thus C_2-symmetric, in agreement with the spectroscopic identity of the two molecular portions in NMR, while michellamine B (**1b**) has two differently configured axes and therefore shows a full set of signals in both the ^{1}H and the ^{13}C NMR spectra.[2,3]

A reliable knowledge of the absolute stereostructure of such bioactive compounds is an important precondition for the directed further improvement of the bioactivity by directed synthetic modifications. For this reason, we additionally chose the method of quantum chemically calculating CD spectra, as a most useful tool for the elucidation of the absolute stereostructures of unknown, structurally novel compounds.[12] Due to our at first restricted computational resources,[13] we initially had to proceed indirectly, by first calculating the expected CD spectra for the monomeric halves, the korupensamines,[9] and then—empirically—investigating the additivity of the chiroptical contributions to the overall spectrum of the entire dimeric natural product.[14] In this paper, we now describe, for the first time, the successful quantum chemical calculation of the CD spectra for the genuine, entire dimers, the michellamines. The calculations confirm the absolute stereostructures of these remarkable compounds and, simultaneously, demonstrate the value of this computational method as a

☆ Acetogenic isoquinoline alkaloids, part 153.[1]

Keywords: circular dichroism; quantum chemical CD calculations; conformational analysis; biaryls; naphthylisoquinoline alkaloids; michellamines.

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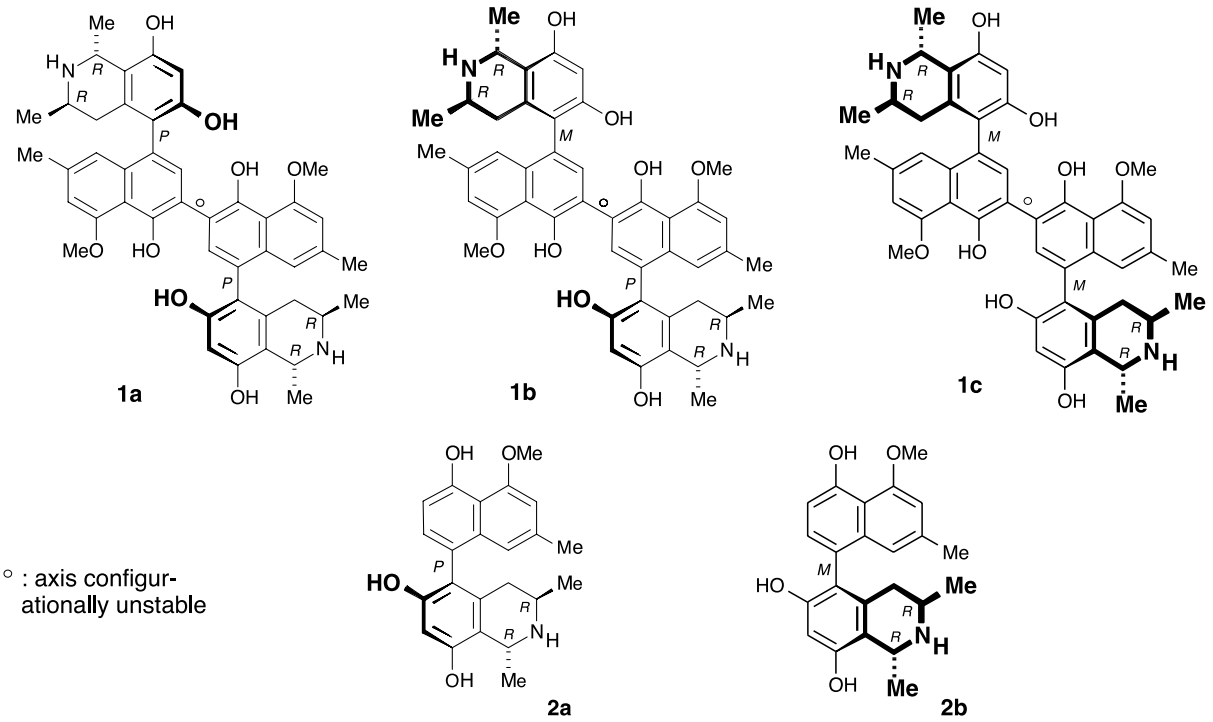


Figure 1. Structures of michellamines A–C (**1a**–**c**) and of their natural monomeric portions, korupensamines A and B (**2a** and **2b**).

powerful tool for the elucidation of the absolute configuration even of molecules as large and flexible as these naturally occurring quateraryls.

2. Results and discussion

2.1. Quantum chemical conformational analysis: general approach

A fundamental prerequisite for the computational calculation of CD spectra is the knowledge of all CD-relevant conformational species of the respective molecule. In the present case, the conformational analysis of michellamines A and C was performed using the quantum chemical semiempirical AM1 method.[15] In order to save CPU time, the search for energetic minimum structures was done via the 'detour' of first considering partial systems, as obtained by disconnecting the biaryl bonds, separately.

Bond disconnection at the two outer biaryl axes (disconnection **A**, see Fig. 2, full line) led to the binaphthalene partial system **3**; rupture of the central axis (disconnection **B**, dotted line) yielded two (here constitutionally identical) naphthylisoquinoline (NIQ) portions, korupensamines (**2**), simply named 'NIQ partial system' in the following.

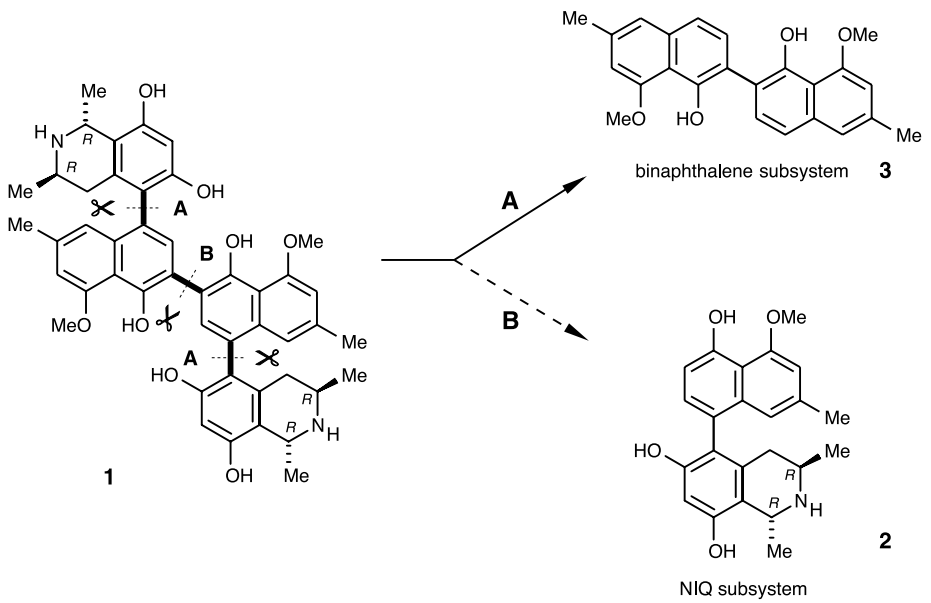
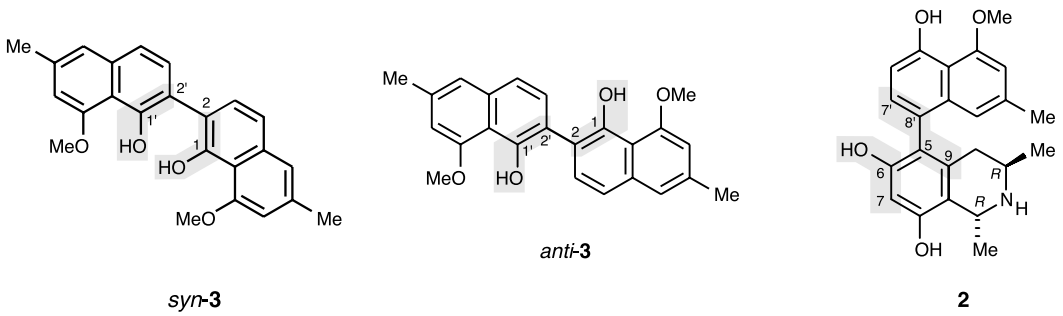


Figure 2. Illustration of schematic bond ruptures **A** and **B** on the quateraryl **1**, leading to simplified biarylic subsystems.



syn-**3** *anti*-**3** **2**

Figure 3. Michellamine fragments that were investigated regarding their conformational behavior.

At the sites of bond rupture, the open valences were 'saturated' by a hydrogen atom, each. Compared to the intact, entire michellamine molecules, the partial systems thus formed are not only smaller than the parent molecule, but also distinctly less flexible, so that their conformational analysis could be performed with significantly lower computational effort. Furthermore, the calculations were simplified by the following heuristical axioms:

1. The aromatic systems are quite rigid.
2. The flexibility at the axes is determined only by the sizes of the *ortho*-substituents.
3. For 1,3-dimethyl substituted tetrahydroisoquinoline alkaloids, CD-relevant contributions are to be expected only from the most stable conformation in the tetrahydroisoquinoline ring.

After the conformational analysis of the partial systems **2** and **3**, all conformer permutations of **2** and **3** were transferred into the michellamine basic structure. This resulted in a complete set of raw geometries of all of the michellamines A (**1a**), B (**1b**), and C (**1c**). From the subsequent geometry optimization of these crude michellamine geometries, during which all molecule-internal parameters were allowed to get optimized, ultimately those conformers were obtained that were finally taken for the CD calculations.

2.2. Conformational analysis of the subsystems

It had to be analyzed how far changes of the two dihedral angles ∢ ($H,O_{C\text{-}1'},1',2'$) and ∢ ($H,O_{C\text{-}1},1,2$) in the case of the binaphthyl partial system **3** (see Fig. 3), and the dihedral angle ∢ ($H,O_{C\text{-}6},6,7$) in the case of the naphthylisoquinoline partial system **2** would influence the preferred conformer geometry of the respective axes.

In the binaphthyl partial system **3**, the two hydroxy functions in adjacent *ortho*-positions next to the central axis influence the conformation; therefore, the computational investigation had to be differentiated into two different conformational cases: (i) a cisoid conformation, subsequently named the '*syn*-array' (*syn*-**3**), in which the two free OH groups are, within a dihedral angle ∢ ($1',2',2,1$) between −90° and +90°, 'on the same side' of the axis, and (ii) a transoid conformation, the '*anti*-array' (*anti*-**3**), in which the two OH groups are, now within a dihedral angle ∢ ($1',2',2,1$) between +90° and +270° (=−90°) away from each other, located on opposite sides of the biaryl axis. The three resulting model systems, *anti*-**3**, *syn*-**3**, and **2** (see Fig. 3) were investigated for their conformational flexibility (within the gray areas).

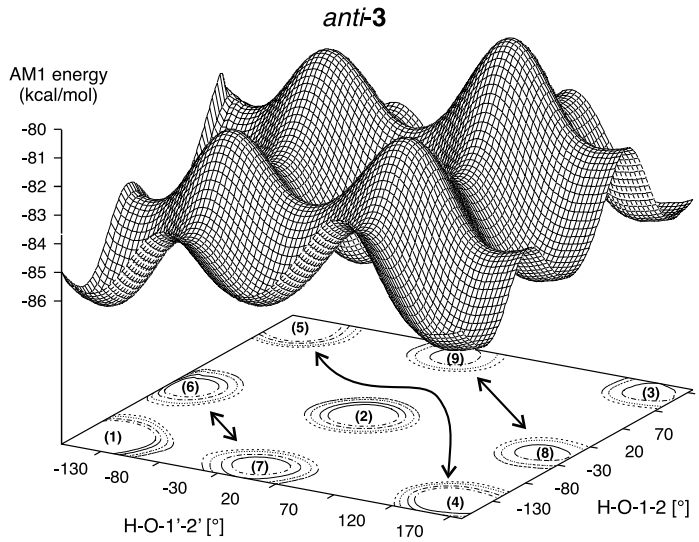
The energy hypersurfaces of these model systems, by which the local minimum structures were to be found, were constructed using the 'unidirectional' GridSearch modification:[16] Starting from an initial geometry, one of the two parameters to be varied (*P*1) is fixed at a particular value, while the other one (*P*2) is modified in incremental steps over the range of definition. Before the next cycle, *P*1 is discretely modified and is then taken as a constant value in the ensuing calculations with stepwise variation of *P*2. As soon as all pairs of values (*P*1/*P*2) are available, the energetic surface can be constructed. For an identification of the particular conformers, the minima roughly taken from the potential surfaces were further energy-minimized within separate calculations. All geometries were computed using the semi-empirical parameterization AM1[15] within the program package VAMP 5.0.[16]

2.2.1. The transoid binaphthyl partial system *anti*-3. The uniform appearance of these energy functions (Fig. 4, top) reveals that the hydroxy functions are energetically independent. The table right hand beside to the potential surface shows the conformers identified.

As can be seen, the conformational pairs *anti*-**3** (4) / *anti*-**3** (5), *anti*-**3** (6) / *anti*-**3** (7), and *anti*-**3** (8) / *anti*-**3** (9) have identical energies and the same dihedral angles at the axis, with the dihedral angle at the two OH groups pairwise interchanged. This shows that the considered pairs constitute homomeric conformers, so that the conformational denotations *anti*-**3** (5), *anti*-**3** (7), *anti*-**3** (9) are redundant; still, for reasons of population statistics, these denotations were kept.

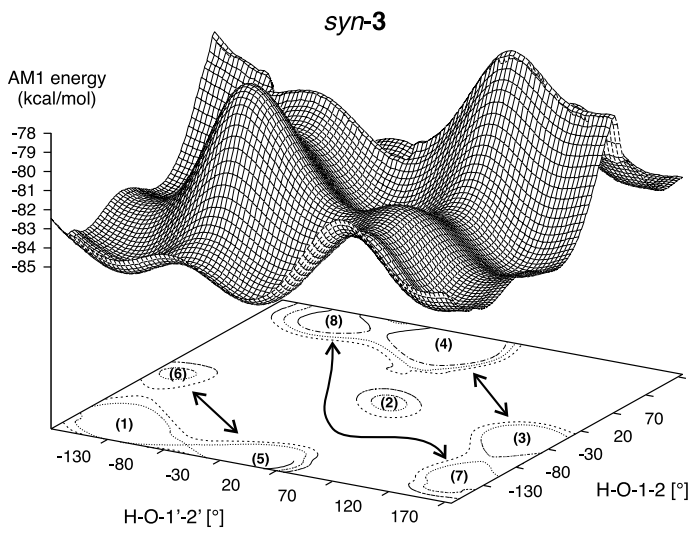
For the minimum structures *anti*-**3** (1), *anti*-**3** (2), and *anti*-**3** (3), no homomeric counterparts can be found. As evident from the identical dihedral angle for the two hydroxy functions, these conformers are C_2-symmetric.

All of the six conformers *anti*-**3** (1), *anti*-**3** (2), *anti*-**3** (3), *anti*-**3** (4/5), *anti*-**3** (6/7), and *anti*-**3** (8/9) are chiral. Consequently, for the assembly of the partial systems to give the 'intact' michellamines, the conformers *anti*-**3*** (1–9), which are the respective enantiomers relative to the geometries mentioned here, must be taken into consideration, too, because the central axis in michellamines is



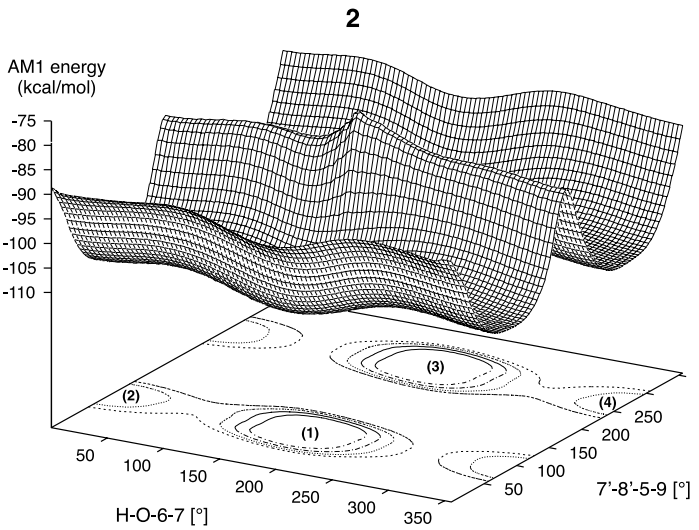
Minima *anti*-**3**	∢ OH 1 H-O-1'-2' [°]	∢ OH 2 H-O-1-2 [°]	∢ axis 1'-2'-2-1 [°]	AM1 [kcal/mol]
anti-**3** (1)	-142.7	-142.7	134.3	-86.4
anti-**3** (2)	-2.0	-2.0	115.6	-85.7
anti-**3** (3)	152.3	152.3	131.7	-84.9
anti-**3** (4)	151.3	-141.2	133.0	-85.8
anti-**3** (5)	-141.2	151.3	133.0	-85.8
anti-**3** (6)	-144.7	-11.0	126.5	-85.4
anti-**3** (7)	-10.9	-144.9	126.4	-85.4
anti-**3** (8)	-153.1	-11.3	126.1	-85.0
anti-**3** (9)	-11.3	-153.0	126.1	-85.0

⟷ Identical conformers



Minima *syn*-**3**	∢ OH 1 H-O-1'-2' [°]	∢ OH 2 H-O-1-2 [°]	∢ axis 1'-2'-2-1 [°]	AM1 [kcal/mol]
syn-**3** (1)	-131.9	-131.9	41.1	-85.8
syn-**3** (2)	9.7	9.6	55.2	-85.7
syn-**3** (3)	142.6	-11.4	54.8	-86.2
syn-**3** (4)	-11.4	142.6	54.8	-86.2
syn-**3** (5)	-10.5	-161.4	55.2	-85.4
syn-**3** (6)	-161.5	-10.5	55.2	-85.4
syn-**3** (7)	147.0	-120.6	46.2	-85.0
syn-**3** (8)	-120.6	147.0	46.2	-85.0

⟷ Identical conformers



Minima **2**	∢ OH 1 H-O-6-7 [°]	∢ axis 7'-8'-5-9 [°]	AM1 [kcal/mol]
2 (1)	179.4	99.0	-115.7
2 (2)	2.0	99.3	-112.7
2 (3)	179.9	262.9	-115.6
2 (4)	358.6	261.4	-112.6

Figure 4. Energy surfaces and tables of conformers of *anti*-**3** (top), of *syn*-**3** (center), and of **2** (bottom).

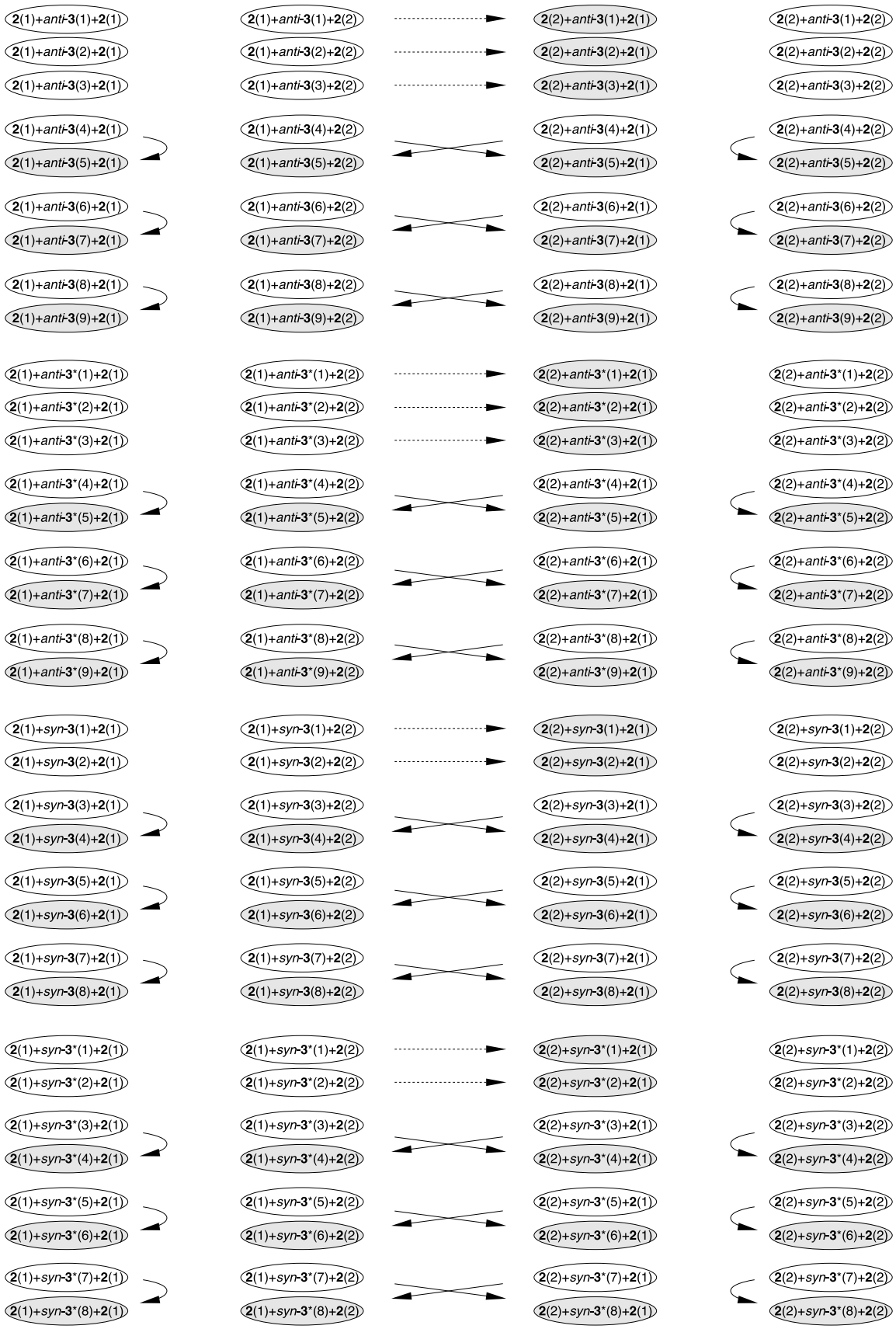


Figure 5. Conformers of michellamine A (**1a**) that result from the combination of the minimum geometries of the subsystems. Nomenclature: first part denotes the geometry parameters of the NIQ subsystem **2**; the central part indicates the binaphthalene subsystem *anti*/*syn*-**3**; the last part denotes the geometry parameters of the other NIQ subsystem **2** (see Fig. 4). Dotted arrows connect homomeric conformers that result from the C_2 symmetry of the corresponding binaphthalene subsystems. Arrows with full lines denote conformers that are homomers, because of homomeric binaphthalene subsystems.

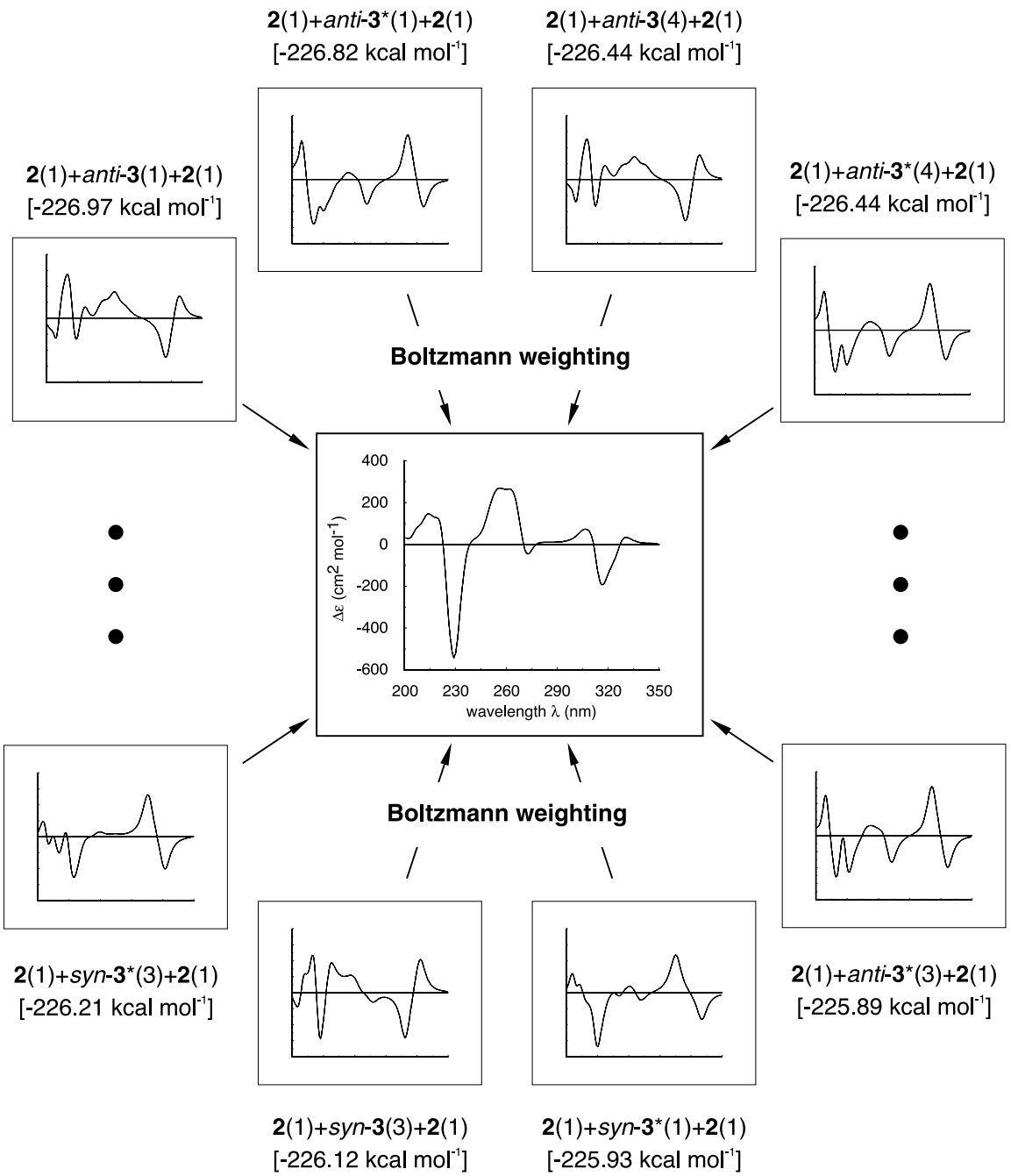


Figure 6. Calculated CD spectra of single conformers of michellamine A (**1a**) (only the spectra of the 8 energy-poorest conformers are shown; AM1 heats or formation in brackets) and their Boltzmann-weighted addition to give the theoretical overall CD spectrum of **1a**.

stereochemically unstable. These enantiomeric conformers *anti*-**3*** (1–9) were easily obtained, just mechanically, by simple reflection of the conformers *anti*-**3** (1–9) at the *xy*-plane.

2.2.2. The cisoid binaphthyl partial system *syn*-3. For *syn*-**3**, the unidirectional GridSearch method as performed in analogy to the transoid binaphthyl partial system *anti*-**3**, initially failed, probably because of the fact that in this case the motion of the two *ortho*-positioned hydroxy functions is no longer energetically decoupled: Within certain ranges of dihedral angles, these steric interactions get so strong that the system escapes into an *anti*-conformation. For this reason, the dihedral angle at the central axis was kept constant at 50° during the scanning of the energetic hyper surface. From the two-dimensional energetic hyper surface thus obtained (see Fig. 4, center), eight minimum conformations were obtained (see the table next to the potential surface).

Similar to the transoid binaphthyl partial system *anti*-**3**, again homomeric pairs of structures were found, here as well: *syn*-**3** (3/4), *syn*-**3** (5/6), and *syn*-**3** (7/8). The conformers *syn*-**3** (1) and *syn*-**3** (2) possess C_2-symmetry. Since all conformers located must again be chiral, in each case the respective enantiomeric molecular conformations

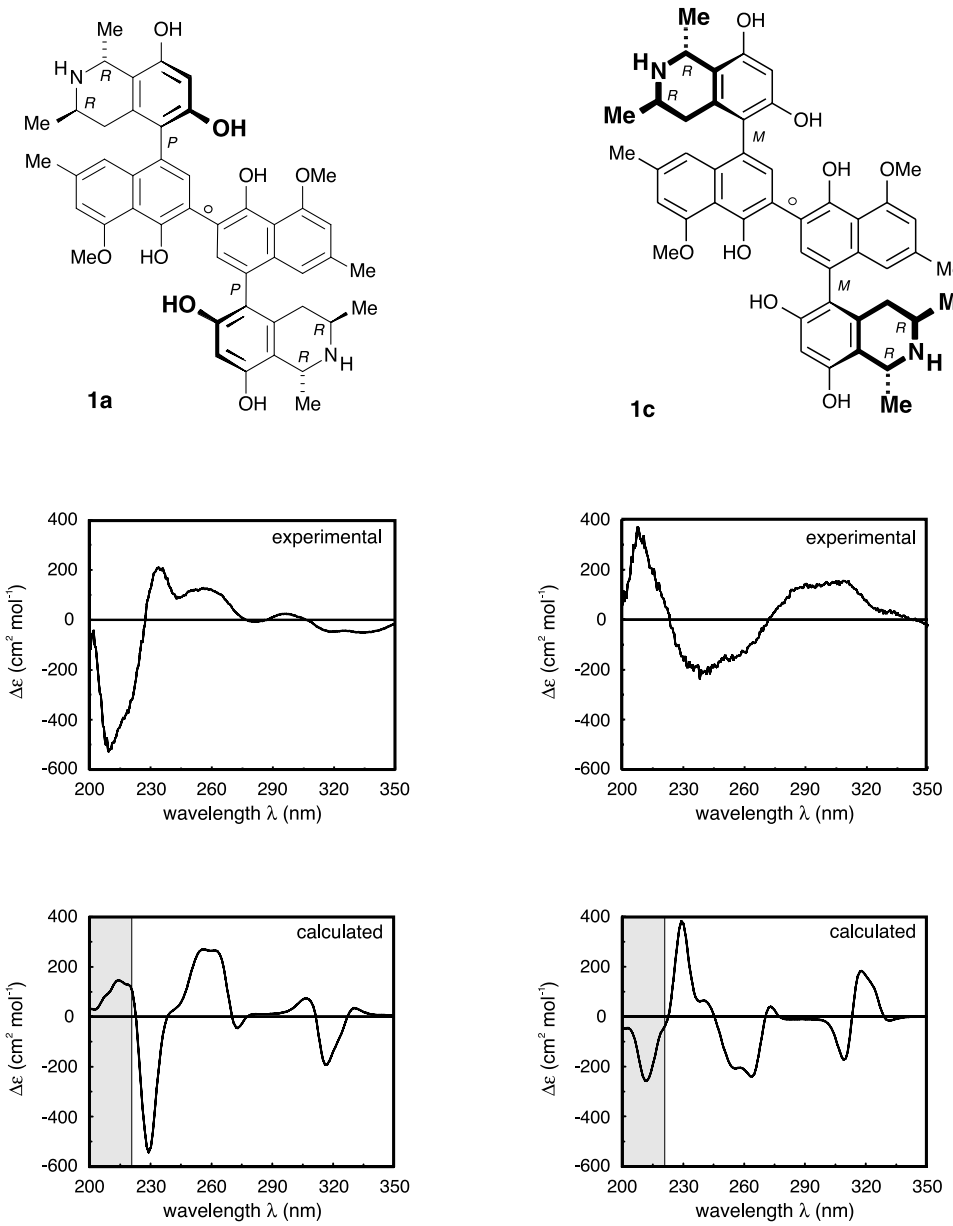


Figure 7. Comparison of the theoretical spectra (bottom) calculated for **1a** and **1c**, with the experimental ones (center); the systematically occurring shift difference of ca. 24 nm of experimental and theoretical spectra is 'optically subtracted' by hatching.

syn-**3*** (1–8) have to be taken into consideration during the composition of the intact michellamine framework.

2.2.3. The NIQ partial system 2. A conformational analysis of the NIQ partial system **2**, during which the dihedral angle ∢ (9,5,8′7′) at the biaryl axis (cf. Fig. 3) was varied on the one hand, and the dihedral angle ∢ (H,$O_{C\text{-}6}$,6,7) on the other, gave rise to four minimum structures (see Fig. 4, bottom left).

2.3. Conformers of the intact michellamines

By the different combinations of a structure of the binaphthyl partial system **3** (energy-minimized with respect to the central axis) with each two minimum structures of the NIQ partial system **2**, 'crude geometries' of the intact michellamine molecules were obtained. These were found to be already very close to the actual conformers of the michellamines and converged distinctly more rapidly during the subsequent geometry optimizations (using VAMP 5.0[16]) than newly constructed michellamine geometries.

Including the (not explicitly calculated) enantiomeric minimum conformations of the binaphthyl partial systems *anti*-**3*** (1–9) and *syn*-**3*** (1–8), formally (18 '*anti*'×4' NIQ1'×4'NIQ2')+(16 '*syn*'×4'NIQ1'×4'NIQ2')=544 michellamine geometries were obtained, merely statistically. Corresponding to the absolute configurations at the biaryl axes and within the naphthylisoquinoline fragments, 136 structures each correspond to michellamines A (**1a**, see Fig. 5) and C (**1c**), the remaining 272 structures constitute conformers of michellamine B (**1b**).

Taking into account the homomeric relationships between

some of the minimum geometries of the binaphthyl partial system **3**, one can conclude the following: a given conformer in the intact michellamine molecule is homomeric to another one if the binaphthyl fragments are homomeric to each other and the conformers of the NIQ fragments are either

1. *identical* like, e.g. [**2**(1)+*anti*-**3** (4)+**2**(1)]⇔[**2**(1)+*anti*-**3** (5)+**2**(1)], or
2. *crosswise interchanged* like, e.g. [**2**(1)+*anti*-**3** (4)+**2**(2)]⇔[**2**(2)+*anti*-**3**(5)+**2**(1)],

which is indicated by full-line arrows for michellamine A (**1a**) in Figure 5.

Moreover, the partial system minima *anti*-**3** (1-3), *anti*-**3*** (1-3), *syn*-**3** (1,2), *syn*-**3*** (1,2) are C_2-symmetric, which leads to the fact that those conformers in the intact michellamine molecule for which the minimum conformers in the NIQ fragment are exchanged, are homomeric to each other, too. For michellamine A (**1a**), this stereochemical relationship is indicated by dotted arrows in Figure 5.

Summarizing, from these homomeric and enantiomeric interrelationships one can conclude that for michellamines A (**1a**) and C (**1c**) only 78 structures each have to be calculated within the final geometry optimization.

Figure 5 schematically reflects all these relationships for michellamine A (**1a**). The conformers not explicitly computed still played an important statistical role: the CD spectra of those conformers that are connected by an arrow with a conformer marked in gray (i.e. not calculated), needed to be weighted by a factor of 2.

For reasons of completeness, the respective matter for michellamine B (**1b**) should at least be briefly explained, even though no CD spectrum was calculated for this alkaloid. Exactly half of the 272 michellamine B conformers to be expected, are redundant, so that the number of conformers is again reduced down to 136. Since this quateraryl is composed of two diastereomorphous molecular moieties, no symmetry relationships can be found for a further reduction of the conformers to be computed, so that, in this case, the full number of 136 geometries would have to be calculated.

2.4. CD spectra of michellamines and conclusions

The single CD spectra obtained for the conformers thus calculated were subsequently weighted according to their energetic content following the Boltzmann statistics and, if relevant, applying the above mentioned statistical correcting factor of 2, to give the overall computed CD spectra of michellamines A (**1a**) and C (**1c**). In Figure 6, this Boltzmann-weighted addition of the single spectra is shown, exemplarily for michellamine A (**1a**). Theoretical details for the calculation of the CD spectra are described in Section 3.

Figure 7 compares the theoretical spectra thus obtained, with those experimentally taken in ethanolic solution. As for previous calculations,[12–14] a red shift of the calculated spectra vs the experimental ones is observed, as indicated by the gray hatching. In this case, different from the usual shift of about 14 nm,[13] the shift amounts to ca. 25 nm, thus being nearly two times larger than usually. The CNDO/S method used, calculates the naphthyl part energetically too favorable. Apparently the larger wave length shift of ca. 25 nm observed here, is due to the presence of now two such naphthyl fragments as compared to the naphthyl portions in 'normal', i.e. monomeric naphthylisoquinoline alkaloids.

Considering the fact that the molecules computed here possess a critical size for such calculations, and, moreover, an enormous flexibility, the agreement between theory and experiment has to be judged as excellent. This agreement again confirms the configuration at the axes previously determined and, in addition, demonstrates the efficiency of the method.

3. Experimental and computational section

3.1. Experimental

The natural products michellamine A (**1a**) and C (**1c**) were isolated and purified using procedures described earlier.[2] CD and UV spectra of these alkaloids were recorded in ethanolic solution on a Jobin Yvon Model CD6 spectrograph at room temperature within the range of 200–350 nm. Selected UV data of the michellamines: UV λ_{max} (ϵ): 228.0 (71915), 237.5 (65480), 260.5 (35957). For further spectroscopic data of michellamines A–C, see Ref. 3.

3.2. Computational

The rotational strength values R_{0a} for the electric transitions $0 \longrightarrow a$ were calculated according to the dipole velocity formalism, which, in contrast to the formula primarily derived by Rosenfeld,[17] delivers origin-independent results even for approximated wave functions ψ_0 and ψ_a:

$$R_{0a} = \mathrm{Im}\left\{\frac{e\hbar}{\mathrm{im}(E_a - E_0)}\langle\Psi_0|\vec{p}|\Psi_a\rangle\cdot\langle\Psi_a|\vec{m}|\Psi_0\rangle\right\}.$$

The wave functions ψ_0 and ψ_a were obtained by a CNDO/2S-CI calculation,[18,19] where the CI expansion consists of the ground state determinant and 576 singly occupied configurations. In order to get $\Delta\varepsilon$ curves from the calculated rotational strength values, the following formula was used:

$$\Delta\varepsilon(\lambda) = \sum_a \frac{16\pi^2\lambda N_A R_{0a}\sigma_{0a}(\lambda)}{3(2303)\hbar c},$$

where N_A denotes the Avogadro number and $\sigma_{0a}(\lambda)$ a Gaussian band shape function.[20] The single spectra thus obtained where then added up to give the predicted overall spectrum by Boltzmann-weighted averaging according to the calculated energies of the corresponding geometries.

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