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Circular Dichroism of Naphthyltetrahydroisoquinoline Alkaloids: Calculation of CD Spectra by Semiempirical Methods[1]

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In memoriam G. Snatzke.

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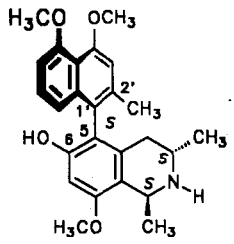
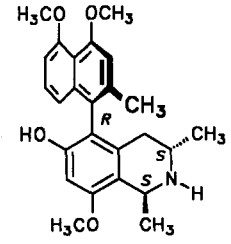
Abstract: The circular dichroism (CD) of the naturally occurring biaryls ancistrocladine and hamatine – the most important representatives of naphthylisoquinoline alkaloids – has been studied. Semiempirical all valence electron calculations using the CNDO/2S method have been applied to reproduce the experimental CD spectra of the two alkaloids with known absolute configuration at the biaryl axis. Based upon the good agreement of experimental and calculated data, a more reliable assignment of axial chirality for so far undetermined structures of natural as well as synthetic compounds may be expected.

INTRODUCTION

During the past 20 years, the rapidly growing group of naphthylisoquinoline alkaloids, structurally unusual biaryls of plant origin, has been investigated intensively.[2,3] The structures *e.g.* of ancistrocladine (**1a**) and its naturally occurring atropisomer hamatine (**1b**) have been elucidated by Govindachari, who did pioneering work in this field.[4,5]



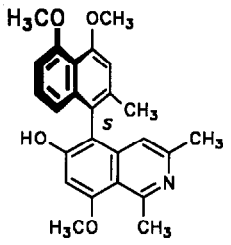
1a



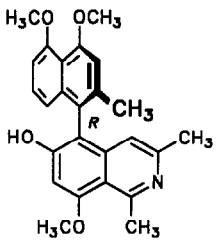
1b

The configurations at the biaryl linkages of **1a** and **1b** have been established by application of the exciton chirality method[6] to the corresponding fully aromatized, merely axially chiral naphthyliso-

quinolines **2a** and **2b**, as obtained by dehydrogenation of **1a** and **1b**, respectively.[4] For this empirical procedure, biaryl systems like **2a** and **2b** constitute nearly ideal substrates, because of the close structural and electronical similarity between the two molecular "halves" – a naphthalene and an aza-naphthalene, which are characterized by nearly identical predominant B_b-transitions according to the Platt notation.[7] Such a far-reaching similarity of the two chromophores is the fundamental precondition for the exciton chirality approach.[6]



2a



2b

Consequently, the application of the exciton chirality method to **2a** and **2b** led to the correct attribution of the configuration at the axis, which has later fully been confirmed by an X-ray structure analysis.[4] For a direct treatment of the corresponding tetrahydroisoquinolines, *e.g.* of the genuine, naturally occurring alkaloids **1a** and **1b**, the above mentioned electronic precondition for the two aryl moieties (the similarity of the B_b-transitions) is not given, so that the exciton chirality method is not applicable to these compounds. This, however, would be highly desirable, since in many cases the often anyhow tedious and substance-consuming dehydrogenation procedure can not be realized, either because of the presence of an *N*-methyl substituent or because of the too low atropisomerization barrier at the axis, which may lead to a complete racemization under the required reaction conditions.[8]

Hence, the availability of a theoretical method for the unambiguous calculation and thus prediction of CD spectra even for biaryls with largely different chromophores is required. Recently, we have developed a procedure for the prediction of CD spectra by semiempirical calculations, exemplarily starting with the dehydrogenated systems **2a** and **2b**,[9] since these allow the direct comparison with the results of the "classical" exciton chirality method. Encouraged by the good agreement between the calculated and the experimental CD spectra for these naphthylisoquinolines, we have now embarked on the extension of this procedure also to the hitherto critical tetrahydroisoquinoline derivates, **1a** and **1b**, themselves.

CALCULATIONS

The calculations of the chiroptical properties of **1a** and **1b** were performed by means of the program package DZDO/MCD3SP.[10] It allows the calculation of excitation energies and rotational strengths for a given molecular geometry. We chose the semiempirical method CNDO/2S,[11] which has been successfully applied to similiar problems by other authors.[12] Details like the amount of single excited configurations and the parameters are described in the appendix.

The geometries of **1a** and **1b** were calculated by energy optimization with the AM1 method,[13] as contained in the MOPAC 6.0 program package.[14] Starting with a half-chair conformation for the tetrahydroisoquinoline moiety with a methyl group in an equatorial position at C-3,[15] ancistrocladine (**1a**) and hamatine (**1b**) revealed only one minimum with respect to the dihedral angle at the axis (Fig. 1). This is in contrast to other biaryl compounds,[16] where we have found two minima with different torsion angles for each atropisomer. Due to the fact that transition energies and especially the rotational strengths of biaryl compounds strongly depend on the dihedral angle ϑ (defined by the atoms 2',1',5,6) of the two aromatic chromophores,[12] we performed a variation of this angle and an energy optimization for each chosen angle using AM1. Figure 1 shows the results.

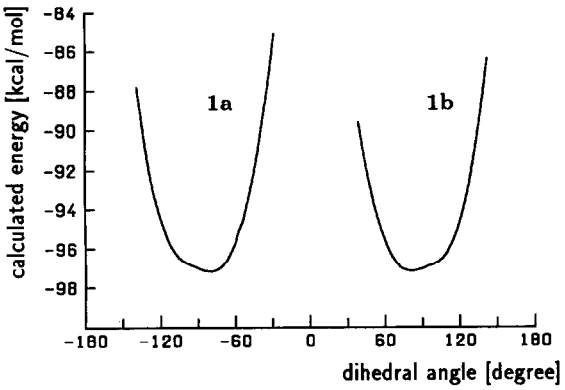


Fig. 1. AM1 energies in dependence of the biaryl angle $\sphericalangle$(2',1',5,6) for ancistrocladine (**1a**) and hamatine (**1b**).

Despite the above mentioned fact that there is only one minimum for ancistrocladine ($\vartheta = -80.2°$ and $\Delta H_F = -97.16$ kcal/mol) and for hamatine ($\vartheta = 80.7°$ and $\Delta H_F = -97.15$ kcal/mol), the flatness of the graphs near the minima indicates an unexpected flexibility of the molecules. Furthermore, these curves are not symmetric with respect to the minima. Therefore, we did not only consider the CD contribution of *the* minimum structure, but rather took into account a whole series of other conformations, by calculating the excitation energies and the rotational strengths for all angles ϑ, for which an energy optimization had been done. Finally, we performed a Boltzmann weighting based on the AM1 energies (see Figure 2).

For the visualization of the results, the $\Delta\varepsilon$ curves were constructed with Gaussian functions.[17] Other representations, *e.g.* bars with a length proportional to the corresponding rotational strength, would be too confusing, because for each of the nearly 40 structures, about 20 transitions were found to exist in the range of the experimental spectra.

The procedure of superimposing the single CD spectra according to the Boltzmann factors is demonstrated in Figure 2. It is impressing how the strongly different angle-depending single spectra add up to give a calculated overall spectrum so closely related to the experimental one.

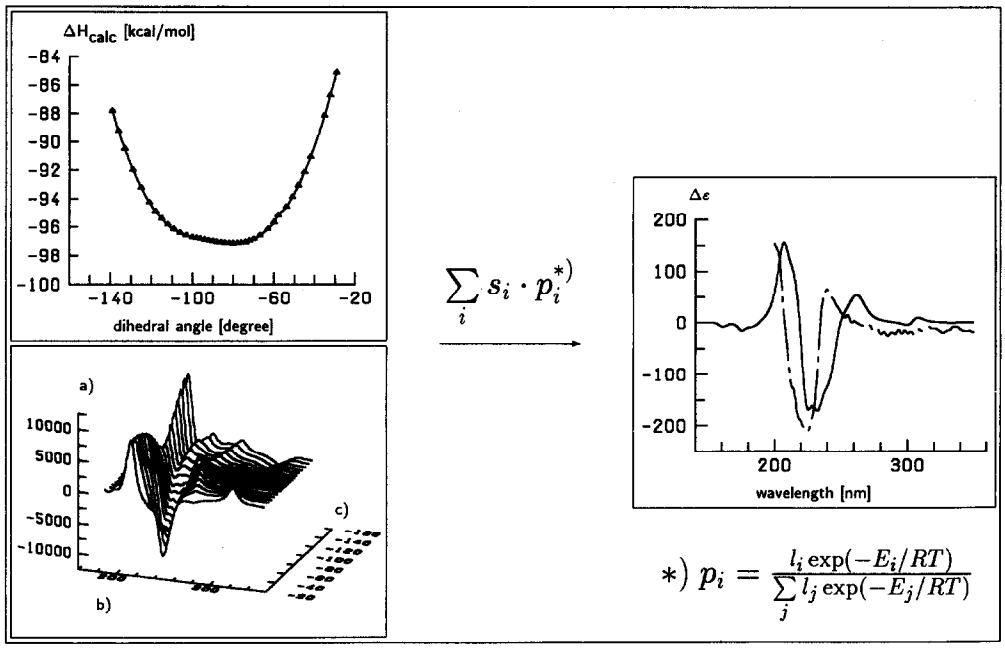


Fig. 2. Schematic procedure for calculating the CD spectrum of ancistrocladine (**1a**) — Left top: Energy profile — left bottom: Single calculated CD spectra s_i, description of the axes are as follows: a) intensity [DBM/100], b) wavelength [nm], c) dihedral angle $\sphericalangle$(2',1',5,6), right: Experimental CD (——— – ———) and calculated Boltzmann weighted overall CD spectrum (———). l_i is the width of the ϑ-interval of the ith structure. The theoretical CD has been scaled by a factor of 3.

COMPARISON OF EXPERIMENTAL AND CALCULATED SPECTRA

Preparation and Measurements. Ancistrocladine (**1a**) and hamatine (**1b**) were available by total synthesis,[18,19] as well as by isolation from *Ancistrocladus abbreviatus*.[20] Their CD spectra (from 350 to 200 nm) were measured on a JOBIN YVON Model CD6 Spectrograph at room temperature, in ethanol as the solvent, and are shown in Figures 2 and 3 (together with the calculated spectra, which are discussed below).

The two compounds exhibit first CD effects in the near UV at 239 nm and 226 nm (signs: ancistrocladine +/–, hamatine –/+, see Figure 2 and 3).

In the UV spectra,[5] only one single band at 231 nm corresponds to both CD effects. At about 211 nm only hamatine (**1b**) exhibits one further significant transition (sign: +), whereas in the ancistrocladine spectrum only a shoulder (sign: –) appears in this region. Here the diastereomeric character distorts the mirror image behavior of the two CD curves. At 200 nm, the CD ends with a large negative $\Delta\varepsilon$ value in the case of hamatine, for ancistrocladine with opposite sign. Further UV transitions in the region 270 – 330 nm have no characteristic counterparts in the CD.

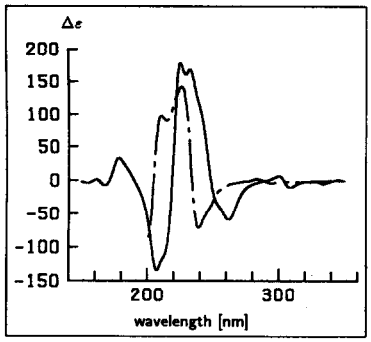


Fig. 3. Calculated (——) and experimental (—— – ——) CD spectra of hamatine (**1b**).

Theoretical Results. The large bands in the calculated CD spectra of both compounds at 261, 232, 226 (only for hamatine), and 207 nm (Figure 2 and 3) can be assigned directly to the experimental bands at 239, 226, 211 (again only for hamatine) and the behavior near the end of the spectrum at 200 nm. In analogy to the measured spectrum around 211 nm, the calculations produce a shoulder at 226 nm.

Although there to a red shift of about 7 to 22 nm, the calculated CD bands do not only show the correct sign, but also the same relations between each other as in the experimental spectra. A little draw back is the fact that the calculated intensities are too small (30% of the measured intensity). But this does not diminish the value of this procedure for an unambiguous assignment of the absolute configuration at the biaryl axis.

The importance of taking into account also structures with higher energies is illustrated by the good agreement of experimental and calculated data particularly for wavelengths from 270 to 330 nm. The small intensities experimentally found in this region, can be reproduced in the calculations by superposition of significant calculated bands, yet of opposite signs that add up to values near zero.

FURTHER PERSPECTIVES

CNDO/2S calculations with doubly excited configurations are in progress, which might correct the intensities and the red shift of the energies.

Furtheron we will repeat our investigations with the Tinoco theory[21] and the so–called matrix method.[22] Both are implemented in the program package MATMAC.[23] These methods allow an easier analysis of intrachromophoric transitions.

APPENDIX

Rotational Strength. For the calculation of the rotational strength R_{0a} of an electronic transition $0 \rightarrow a$ we used instead of the equation

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

as first derived by Rosenfeld,[24] the equivalent expression:

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

In contrast to formula (1), this expression is origin-independent also for approximative wavefunctions ψ_0 and ψ_a for the ground state and the excited states.[25] $\vec{\mu}$, $\vec{m}$ and $\vec{p}$ are the operators of the electric dipole, the magnetic dipole moment and the linear momentum. *Im* in eq. (1) and (2) represents the imaginary part.

In order to obtain the wavefunctions of the ground state and the excited states, we used the semi-empirical CI method CNDO/2S, since our alkaloids are far too large to apply *ab initio* methods.

CNDO/2S. The complete parameter set from Ridley and Zerner[26] is listed in Table 1. The two center electron repulsion integrals γ_{AB} are calculated by an extended Mataga–Nishimoto[27] approximation:

$$\gamma_{AB} = 1/(R_{AB}/f_\gamma + 2/(\gamma_{AA} + \gamma_{BB})), \quad (3)$$

where Ridley and Zerner[26] introduced the parameter $f_\gamma = 1.2$. R_{AB} is the distance between the atoms A and B, and γ_{AA}, γ_{BB} are the one center electron repulsion integrals. For the calculation of the nondiagonal H^{core} integrals, the scaling parameters $f_\pi = 0.585$ (Jaffé et al.[11]) and $f_\sigma = 1.267$ (according to Ridley and Zerner[26]) are used. In our calculations the CI expansion included the ground state determinant and 100 singly occupied configurations.

Table 1. Parameter set of the CNDO/2S program (Slater exponent α, 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_x^0	-12.0	-17.0	-26.0	-34.0
$\frac{1}{2}(I+A)_s$	7.176	14.051	19.316	25.390
$\frac{1}{2}(I+A)_p$	–	5.572	7.275	9.111

Gaussian Bandshapes. In order to get $\Delta\varepsilon$ curves from the calculated rotational strength values, we used the following formula:[17]

$$\Delta\varepsilon(\lambda) = \sum_a \frac{16\pi^2\lambda N_A R_{0a}\sigma_{0a}(\lambda)}{3(2303)\hbar c}, \quad (4)$$

where N_A is Avogadro's number and $\sigma_{0a}(\lambda)$ a Gaussian band shape function:

$$\sigma_{0a}(\lambda) = \frac{1}{\Delta m\sqrt{\pi}}\exp[-(\frac{\lambda - \lambda_a}{\Delta m})^2], \quad (5)$$

where Δm is the exponential half-width. The calculated CD spectra in Figure 2 and 3 were generated with $\Delta m = 5$ nm.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. "Novel Concepts in Directed Biaryl Synthesis", part 18; for part 17, see Peters, K.; Peters E.-M.; von Schnering, H.G.; Bringmann, G.; Göbel, L. *Z. Kristallogr.* **1993**, *203*, 265–268. – "Acetogenic Isoquinoline Alkaloids", part 46; for part 45, see Grimm, C.; Proksch, P.; Gramatzki, S.; Schneider, C.; Bringmann, G. *Planta Med.* **1992**, *58(Suppl.1)*, 630.

2. Bringmann, G. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, Vol. 29, 1986, pp. 141–184.

3. Bringmann G.; Rübenacker, M.; Weirich, R.; Aké Assi, L. *Phytochemistry* **1992**, *31*, 4019–4024, and literature cited therein.

4. Govindachari, T.R.; Nagarajan, K.; Parthasarathy, P.C.; Rajagopalan, T.G.; Desai, H.K.; Kartha, G.; Lai Chen, S.; Nakanishi, K. *J. Chem. Soc., Perkin Trans. I* **1974**, 1413–1417.

5. Govindachari, T.R.; Parthasarathy, P.C.; Rajagopalan, T.G.; Desai, H.K.; Ramachandaran, K.S.; Lee, E. *Indian J. Chem.* **1975**, *13*, 641–643.

6. Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy — Exciton Coupling in Organic Stereochemistry*, University Science Books: Mill Valley, CA, and Oxford University Press: Oxford, 1983.

7. Platt, J.R. *J. Chem. Phys.* **1949**, *17*, 484–495.

8. (a) Lavault, M.; Bruneton, J. *C. R. Acad. Sci. Ser. C* **1978**, *287*, 129–131.
   (b) Bringmann, G.; Rübenacker, M.; Jansen, J.R.; Scheutzow, D. *Tetrahedron Lett.* **1990**, *31*, 639–642.

9. Fleischhauer, J.; Kramer, B.; Zobel, E.; Bringmann, G.; Gulden, K.-P.; Ortmann, T.; Peter, B. *Z. Naturforsch.* **1993**, in press.

10. The programs DZDO and MCD3SP were written by J. Downing and J. Michl, University of Colorado at Boulder and modified by J. Fleischhauer, W. Schleker, and B. Kramer.

11. Del Bene, J.; Jaffé, H.H. *J. Chem. Phys.* **1968**, *48*, 1807–1813.

12. (a) Rashidi-Ranjbar, P.; Sandstrøm, J. *Collection of Lectures at the "4th Int. Conference on Circular Dichroism"*, Bochum, FRG, **1991**, 152–159.
   (b) Buss, V.; Kolster, K. *Z. Phys. Chem. Neue Folge* **1989**, *162*, 73–82.
   (c) Buss, V.; Klein, M. *Chem. Ber.* **1988**, *121*, 89–93.

13. Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

14. QCPE#455 MOPAC: A General Molecular Orbital Package (Version 6.0) Stewart, J.J.P.; J. Frank Seiler Research Laboratory, United Air Force Academy, CO 80840.

15. Random search forcefield calculations, X-ray analyses, and NMR experiments of ancistrocladine[4] and several related alkaloids[28] show this conformation to be the most stable one. For this reason, it was taken as the starting geometry for the MOPAC calculations.

16. AM1 and forcefield calculations *e.g.* on the related naphthylisoquinoline alkaloid dioncophylline A, which has only 3 *ortho*-substituents next to the axis, even showed two minima: Bringmann, G.; Gulden, K.-P., unpublished results.

17. Schellman, J.A. *Chem. Rev.* **1975**, *75*, 323–331.

18. (a) Bringmann, G.; Jansen, J.R.; Rink, H.-P. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 913–915.
(b) Bringmann, G.; Jansen, J.R. *Heterocycles* **1989**, *28*, 137–142.

19. Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977–991.

20. Bringmann, G.; Zagst, R.; Reuscher, H.; Aké Assi, L. *Phytochemistry* **1992**, *31*, 4011–4014.

21. Tinoco, I., jr. *Adv. Chem. Phys.* **1962**, *4*, 113–160.

22. Bayley, P.M.; Nielsen, E.B.; Schellman, J.A. *J. Phys. Chem.* **1969**, *73*, 228–243.

23. (a) Kramer, B. Ph.D. Dissertation; RWTH Aachen, FRG, 1991.
(b) Zobel, E. Diploma Thesis; RWTH Aachen, FRG, 1989.

24. Rosenfeld, L. *Z. Phys.* **1929**, *52*, 161–174.

25. Moscowitz, A. In *Modern Quantum Chemistry*; Sinanoglu, O., Ed., John Wiley and Sons, Inc.: New York, 1965, Vol. 3, p. 21.

26. Ridley, J.; Zerner, M. *Theor. Chim. Acta* **1973**, *32*, 111–134.

27. Nishimoto, K.; Mataga, N. *Z. Phys. Chem. Neue Folge* **1957**, *13*, 140–157.

28. Bringmann, G.; Zagst, R.; Schöner, B.; Busse, H.; Hemmerling, M.; Burschka, C. *Acta Cryst.* **1991**, *C 47*, 1703–1705.