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Circular Dichroism of Naphthyldihydroisoquinoline Alkaloids: Determination of the Axial Configuration of Yaoundamine A[1]

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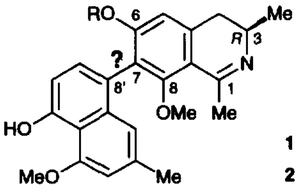
Abstract: The absolute axial configuration of yaoundamine A, a naphthyldihydroisoquinoline alkaloid recently isolated from *Ancistrocladus korupensis*, was elucidated by comparison of experimental and theoretical Circular Dichroism (CD) spectra. An extensive semiempirical (AM1) analysis of the conformational properties of yaoundamine A and its atropo-diastereomer revealed an interesting long-range mutual interaction of the local conformations in the axis and of the dihydroisoquinoline system *via* the 8-methoxy group as a "molecular clutch". Subsequent calculation and Boltzmann-weighting of single-conformation CD spectra (CNDO/2S - C.I.) gave a thermal average CD spectrum matching the experimental one very closely. © 1997 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

During the last years, the number of naphthylisoquinoline compounds isolated from plants of the genus *Ancistrocladus* has increased steadily.[2] The need for a reliable method to determine not only their constitution, but also their configuration is therefore obvious. While the absolute configuration of possible stereocenters can be elucidated by means of a specially designed oxidative degradation process,[3] the configuration at the biaryl axis can be determined by CD spectroscopy, which is connected with little experimental effort and requires only minute amounts of substance. Similar compounds with the same type of connection between the naphthyl and isoquinoline halves of the molecule often give similar CD spectra. In some cases, however, a definite assignment of the stereo array at the axis is possible only when theoretical CD spectra of reliable quality can be compared with the experimental ones. We report here on the effective application of a previously established method[4-10] to the determination of the axial configuration of yaoundamine A (**1**), a natural product recently isolated from *Ancistrocladus korupensis*,[11] along with its L-rhamnoside, named yaoundamine B (**2**). At the beginning of our calculations, only the configuration of the chiral center C-3 was known from degradative work,[11] while attempts to determine the axial configuration by long-range NOE investigations, as developed recently,[12] had failed.



1 R = H
2 R = rhamnose

CONFORMATIONAL ANALYSIS

For other related alkaloids, yet with a *tetra*hydroisoquinoline unit, a working protocol of the following kind has been established in our group[4,8–10]:

- Find the global minimum of the molecule with respect to all degrees of freedom, using the semiempirical AM1 method.[13] For a tetrahydroisoqinoline system this is a half-chair conformation with the methyl group at C-3 in an equatorial position. Other conformations of the *N*-heterocycle, however close in energy to the global minimum, can be neglected, as they lead to almost identical CD spectra: The conformationally labile heterocycle is not part of the chromophor.
- Calculate a one-dimensional potential curve for the hindered rotation around the biaryl axis, using a cut-off of 3 kcal/mol above the global minimum. A reasonable step size for these calculations is 2 degrees.
- Calculate the CD spectra of all geometries on the potential curve by means of the programs BDZDO and MCDSPD within the CNDO/2S approximation[14] and determine the Boltzmann-weighted average spectrum.

The results described here for yaoundamine A were obtained using the same semiempirical programs. All geometry optimizations were performed to a gradient norm of 0.01 using the VAMP 5.0[15] program. In principle, the procedure applied was the same as described above. However, the calculation of the CD spectrum of yaoundamine A proved to be more demanding. First, the molecule contains a dihydro- instead of a tetrahydroisoquinoline moiety. As the imino group is part of the π system, its orientation was supposed to play a major role in the rotational strengths of the transitions. In the isolated half **3**, two conformations can be found, which are only 0.25 kcal/mol apart from each other (cf. Fig. 1).

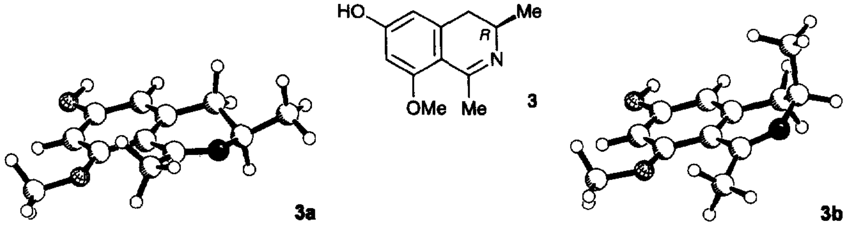


Fig. 1. Ball-and-stick plots of both conformers of the yaoundamine A dihydroisoquinoline system **3** with the methyl group at C-3 equatorial (**3a**) resp. axial (**3b**).

The energetically lower conformation **3a** contains a pseudo-equatorial methyl group at C-3, whereas the second conformation, **3b**, carries a pseudo-axial methyl group (Fig. 1). In the following, we will refer to these structures as the axial and the equatorial conformations. Because of the small energy difference between the two conformers, both of them must be considered in a complete conformational analysis.

A second factor which makes the determination of the theoretical CD spectrum less straightforward, is the fact that it is impossible to obtain steady potential curves for the rotation around the axis from the calculation of only one reaction coordinate, *i.e.* the rotation around the biaryl axis. Obviously, the preferred conformation of the MeO group at C-8 changes during the rotation. We therefore calculated two AM1 energy hypersurfaces for yaoundamine A, for both the axial and the equatorial conformation of the dihydroisoquinoline system and for both the *M*- and *P*-isomers. Here, we discuss only the two surfaces for the *M*-atropisomer, as the same qualitative picture applies to the *P*-atropisomer. We used the angles ABCD and EAFG as driving parameters in the range from -20 to -160 and 40 to 320 degrees, respectively (Fig. 2). The evaluation of these potential surfaces yields the following results:

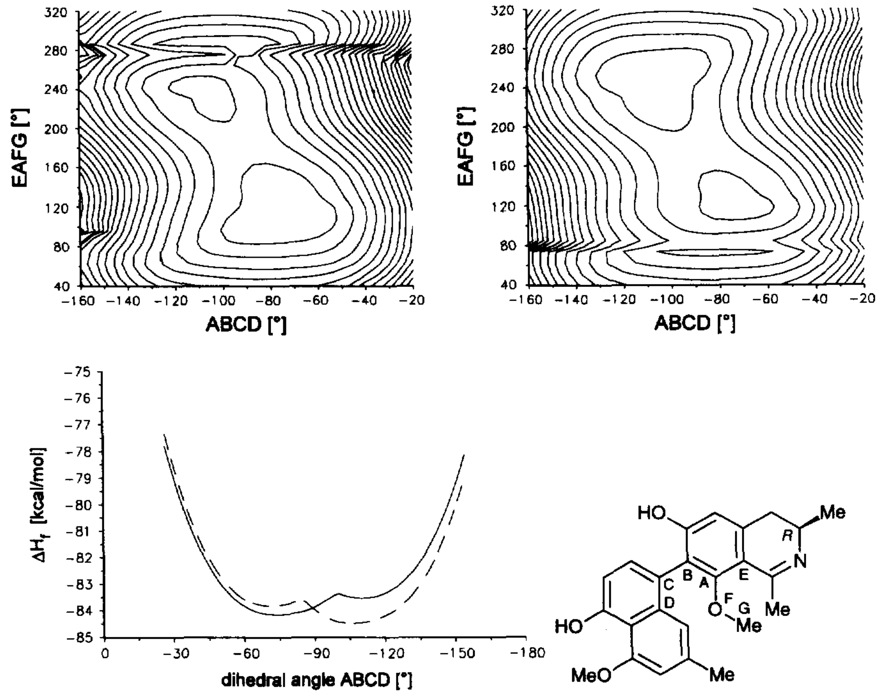


Fig. 2. Top: contour plots of both energy surfaces of the yaoundamine A *M*-isomer, axial conformation (left) and equatorial conformation (right) obtained by rotating simultaneously around the angles ABCD and EAFG. The contour lines are in distances of 1.0 kcal/mol. Below: lowest-energy potential curves for the rotation around the biaryl axis of the *M*-isomer of yaoundamine A (— : axial conformation, - - - : equatorial conformation of Me-3). Qualitatively, the same picture applies to the *P*-isomer.

For each conformation of the *N*-heterocycle, there exist two very shallow local minima with distinctly different angles ABCD as well as EAFG. The relative energies of the local minima are not the same for the two surfaces. Hence, it can be concluded that there is a strong interdependence of the angle at the biaryl axis and the conformation of the dihydroisoquinoline system. This interaction is mediated by the C-8 MeO group, which is situated between those two conformationally labile reagions of the molecule and therefore interacts with both of them. On the one side, there is the naphthyl system rotating around its pivot and on the other side, the methyl group at C-1 adopts a position above or below the plane of the dihydroisoquinoline system depending on its conformation. Accordingly, the preferred orientation of the methyl group changes from above to below the plane of the dihydroisoquinoline system as well. From the hypersurfaces, it is possible to construct minimum energy pathways for the rotation around the biaryl axis. This leads to two W-shaped potential curves with cusps at those points where the MeO group changes its position. The curves reveal that yaoundamine A is indeed a very fexible molecule as far as the rotation around the axis is concerned: The potential energy stays within 1 kcal/mol of the global minimum in a region of almost 60 degrees.

CD SPECTRA

A series of test calculations gave almost identical single CD spectra when only the position of the MeO group was varied and the remainder of the molecule was kept rigid. They changed, however, to a great extent with the conformation of the dihydroisoquinoline system. This showed that it sufficed to calculate single CD spectra of the conformations along the minimum potential paths. Therefore, CD spectra for both the equatorial and the axial conformations were calculated at each discrete value of the angle ABCD in steps of 2°. A total of 65 spectra was calculated for each conformation of the dihydropyridine ring, such that the complete range of conformations up to 4.5 kcal/mol above the global minima is represented in the spectra. Boltzmann-weighted spectra were then generated from these spectra. This procedure was carried out for both atropisomers. For the calculation of all spectra, a C.I. basis of 100 singly excited configurations plus the ground state were taken into account. Figure 3 shows how the total spectrum for the *P*-isomer can be regarded as a sum of the individual spectra for the local conformers of the dihydropyridine ring. There is a drastic difference between the CD properties of these two local conformers, as was supposed in the beginning.

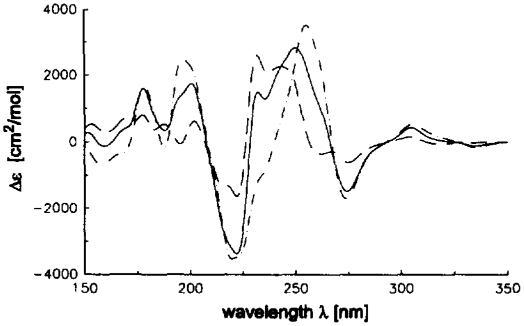
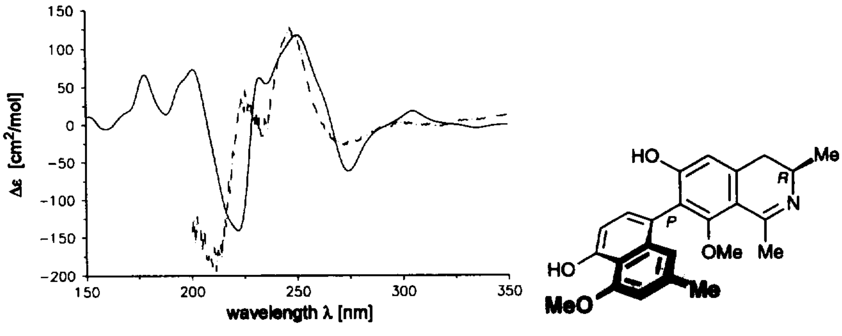


Fig. 3. Boltzmann-weighted CD-spectrum of yaoundamine A (*P*-isomer) (—), Boltzmann-weighted spectra calculated from conformations of the axial conformer only (- - -), and of the equatorial conformer only (– · –).

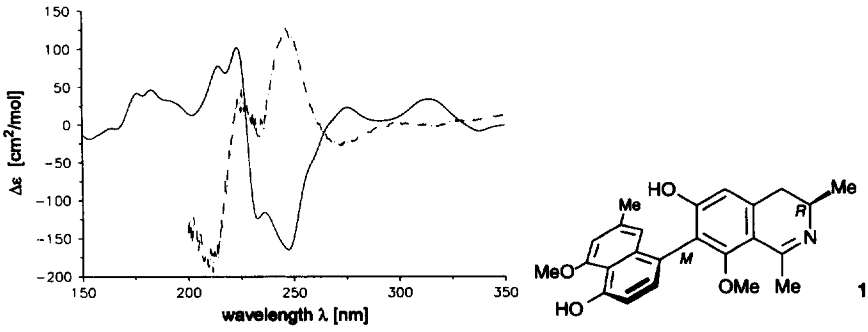
A comparison of both calculated spectra for the *M*- and *P*-models (Figs. 4 and 5) with the experimental spectrum of the natural product makes it easy to identify yaoundamine A as an alkaloid with *P*-configuration at the biaryl axis. The calculated spectrum for the *P*-structure matches very well with the experimental spectrum, whereas the theoretical spectrum of the *M*-isomer possesses nearly opposite Cotton effects. Still, the diastereomeric character of the two species is evident from the calculated spectra. A red-shift of 10 - 15 nm can be observed for the theoretical spectrum.

This is normally the case with results on this theoretical level[4] and might be tentatively attributed to the fact that, using only singly excited states in the C.I. calculation, the excited states might be lowered too much relative to the ground state, which does not mix with the rest of the C.I. basis (Brillouin theorem[16]).



1a

Fig. 4. Match plot of the calculated CD spectrum of the yaoundamine A *P*-atropisomer, **1a** (—), and experimental spectrum of the alkaloid (– · –).



1b

Fig. 5. Match plot of the calculated CD spectrum of the yaoundamine A *M*-atropisomer, **1b** (—), and experimental spectrum (– · –) of the alkaloid.

The work described in this paper clearly establishes the full stereostructure of yaoundamine A as **1a**, *i.e.* with *P*-axial configuration. From this, the same axial stereo array can be deduced for its L-rhamnoside yaoundamine B. For formal reasons, this glycoside has *M*-configuration at the axis.

Furthermore, a most striking feature was found in the conformational behavior of yaoundamine A: the rotation around the biaryl axis and the local conformation of the dihydroisoquinoline system, two *a priori* independent degrees of freedom, are strongly coupled through the methoxy group at C-8, which works as a "molecular clutch".

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