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# Quantum chemical CD calculations of dioncophylline A in the solid state

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ABSTRACT

Although dioncophylline A (**1**) is the certainly best-investigated naphthylisoquinoline alkaloid, it still represents a challenging case for theoretical stereochemical investigations. Its biaryl axis, although being configurationally stable, still has a certain degree of rotational flexibility, rapidly twisting within certain margins, and thus, exerting a dramatic influence on the CD behavior of **1**. Therefore, solid-state CD spectroscopy might provide a unique chance to study this flexible compound in a conformationally 'frozen' form, as fixed in the crystal. Based on the X-ray derived coordinates of the single conformer found in the crystalline state, CD calculations were performed by three different approaches, viz. by CNDO/S-CI, TD-B3LYP, and DFT/MRCI, each permitting the unambiguous attribution of the absolute axial configuration of dioncophylline A (**1**) as *P*, which is in full agreement with the previous assignments. Furthermore, to examine a possible influence of the neighboring molecules in the crystal on the CD behavior of **1**, a set of dyads, each consisting of a given 'central' molecule and a second one from the nearest neighborhood, were considered at a semiempirical level, as well as a 'one-piece' cluster of 16 molecules from the crystal. The results were compared with those obtained by solution and solid-state CD spectroscopy, which confirmed the configurational assignment.



## 1. Introduction

The secure, unambiguous elucidation of the absolute stereostructures of chiral molecules of natural or synthetic origin is one of the central topics of modern organic chemistry. Along with traditional methods of determining the absolute configuration by total synthesis,[1,2,3] chemical degradation[4,5] or X-ray structure analysis,[6,7] chiroptical approaches, and in particular circular dichroism (CD) spectroscopy[8] have emerged as the currently most effective tools. In combination with methods for the online measurement of CD spectra, immediately from the peak in the chromatogram by HPLC–CD coupling[9] and with ever-developing quantum chemical calculations,[10] they permit to distinguish between stereoisomers without major experimental effort and dissipating only minuscule amounts of substance. Usually, experimental CD spectra, which serve as a basis for comparison with the theoretically predicted curves, are measured in solution. Since circular dichroism, more than any other spectroscopic method, strongly depends on the orientation of the chromophores to each other and, thus, on the conformational behavior, the calculation of the CD spectra requires the consideration of all possible conformational species that occur in solution, and hence do contribute to the molecular CD. This task may become very difficult in the case of highly flexible compounds. Recently, the method of determining the absolute configurations by CD calculations has been extended to the crystalline state.[11,12] Evidently, the theoretical CD study of a chiral compound in the crystal has a substantial advantage over that in solution, since solid-state samples provide one or only few conformers, whose geometries and relative orientations can be easily and unambiguously revealed by X-ray crystallography—provided that crystals of sufficient quality can be obtained. On the other hand, due to the dense 'packing' of the molecules in the crystal, intermolecular interactions, which are much stronger as compared to those occurring in solution, may have an additional influence on the resulting CD spectrum. Furthermore, to measure solid-state CD spectra, great care is needed to avoid or/and eliminate the inevitably expected artifacts.[13,14,15]

In this paper, we describe the first theoretical and experimental solid-state CD investigations on the well-known natural product dioncophylline A (**1**)[16,17,18,19] as a model compound, which consists of two substantially different chromophoric units, viz. a naphthalene part and an isoquinoline portion, linked through a rotationally

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flexible, but still configurationally stable biaryl axis. The axial chirality of dioncophylline A (**1**)—here even in connection with stereogenic centers—is a particular challenge for CD studies. According to semiempirical gas-phase computations, this molecule may, even for the same absolute axial configuration, adopt two different minimum conformations with divergent orientations at the stereogenic axis, which, although both *P*-configured, provide virtually opposite CD spectra, as normally to be expected for enantiomers. This makes an interpretation of the experimental CD spectrum measured in solution extremely difficult and insecure. In the crystalline state, however, dioncophylline A (**1**) adopts only one of these two conformations, which, thus, should facilitate theoretical CD investigations considerably.

Furthermore, we have examined whether the neighboring molecules of dioncophylline A (**1**) in the crystal do affect its CD behavior and whether consideration of a single molecule is indeed sufficient for predicting its solid-state CD spectrum. For this purpose, the semiempirical CD computations were performed for all possible dyads, i.e., all combinations of each, one 'central' molecule of **1** and one neighbor, followed by an averaging of the obtained CD spectra and a comparison with the experimental KBr-based CD curve. Moreover, the CD spectrum was calculated for a fragment of the crystal lattice including 16 molecules of dioncophylline A (**1**).

## 2. Results and discussion

### 2.1. Dioncophylline A as a rewarding model compound

Dioncophylline A (**1**)[16] is a well-known naphthylisoquinoline alkaloid possessing both central and axial chirality. Its full absolute stereostructure, with 1*R*,3*R*,7*P*-configuration (Fig. 1a), has been established by one of our groups, using a broad variety of most different analytical, chemical, X-ray crystallographic, and computational methods, namely by NMR,[16,20] oxidative degradation,[4] by stereoselective total synthesis,[21] by X-ray diffraction analyses both in the absence or presence of heavy atoms,[22,23] by circular dichroism spectroscopy (after dehydrogenation) with application of the exciton chirality method,[16] and by semiempirical CD calculations (of the authentic alkaloid) based on a molecular dynamics (MD) approach.[24] Dioncophylline A (**1**) is thus a valuable model compound with an unambiguously known absolute stereostructure, and, thus, a test case for new methods for the assignment of absolute configurations, but simultaneously, it still exemplifies the need for improved stereochemical methods due to its flexible stereogenic biaryl axis, whose orientation has a drastic influence on the CD spectrum. Thus, partial rotation around this axis by varying the dihedral angle ABCD ($30^\circ<\theta_{ABCD}<135^\circ$, Fig. 1a)—yet without changing its *P*-configuration—followed by CD calculations of the single rotamers thus obtained revealed a far-reaching change in the CD behavior of dioncophylline A (**1**). Under these conditions, even fully mirror-like, opposite CD spectra were obtained for different conformers, although all possessing the same absolute configurations at axis and centers (Fig. 1b). The semiempirical AM1-based[25] screening of the reaction coordinate for the rotation around the axis of **1** (Fig. 1c) showed two energetically nearly identical ($\Delta\Delta E$ 0.2 kcal/mol)—and thus similarly populated!—minimum conformers (Fig. 1d) with dihedral angles $\theta_{ABCD}$ of 106° and 78°,[26] whose CD spectra were found to be nearly opposite to each other (Fig. 1e). Further optimization of these two minima at the DFT level (BLYP/6-31G**) gave, on the other hand, only one minimum structure with an angle of 105°, proving the second conformer with $\theta_{ABCD}$ of 78° to be unstable, which might thus be considered as an artifact of the AM1 calculations. Still, in agreement with the semiempirical calculations, the respective energy profile predicted by DFT (Fig. 1f) indicated a substantial rotational flexibility at the axis of **1**, resulting in very similar energies within a quite broad range of dihedral angles. As a consequence, the resulting overall theoretical CD curve of **1**, which is substantially determined by the conformer distribution, will strongly depend on the accuracy of the method used for the conformational analysis and for the calculation of the energies of the respective minimum conformers.

In the crystals, by contrast, as obtained from dichloromethane/ethanol, dioncophylline A (**1**) was found to adopt only one conformation, viz. with a dihedral angle $\theta_{ABCD}$ of 115° (Fig. 2),[22] which does not correspond to any of the two preferential angles predicted at the AM1 level to occur in solution (106° and 78°), but should, due to the rigid structure, permit an unequivocal prediction of the CD spectrum. According to the DFT calculations, this conformer has an energy of 0.7 kcal/mol higher than the lowest-energy structure (Fig. 1f). The geometry of this conformer, as known from the X-ray diffraction experiment, can be directly used as an input for the excited states' energy calculations. Thus, solid-state CD spectroscopy in combination with CD calculations could provide an attractive additional tool for the attribution of the absolute axial configuration of conformationally flexible compounds that have chiroptically different, but energetically similar conformers, like dioncophylline A (**1**).

### 2.2. Experimental solid-state CD investigations

Solid-state CD measurements on dioncophylline A (**1**) were carried out on the Universal Chiroptical Spectrophotometer (UCS-1), designed and constructed by one of our groups in 2001.[15] The instrument is able to measure all the polarization phenomena, i.e., linear birefringence (LB), linear dichroism (LD), circular birefringence (CB), and CD, simultaneously. Using this apparatus and especially devised Stokes–Müller matrix analysis[15] for the solid samples, artifact-free CD spectra can be obtained, without any macroscopic anisotropies typical of the solid-state samples such as LD and LB. Details of the instrumentation and the analytical procedure for obtaining artifact-free CD spectra have been already reported.[15]

The transmittance CD spectrum of the microcrystalline material obtained by the KBr matrix method is shown in Figure 3. It comprises two peaks with positive Cotton effects at 280 and 245 nm, separated by a low-intensity negative band at 260 nm and followed by a broad, strongly negative signal at 227 nm (Fig. 3). Similar transmittance CD and absorption spectra were obtained for both, the solid (KBr disk) and the solution (EtOH) states, thus indicating related conformational patterns in the solid (as a KBr pellet) and in solution.

### 2.3. CD calculations of a single molecule of 1

Based on the X-ray derived coordinates of the single conformer of **1** found in the crystal, CD calculations were performed by using three different approaches: the semiempirical CNDO/S-CI[27] method, which had previously shown good results for a large variety of axially chiral biaryls,[28,29,30,31] the more accurate ab initio approaches based on a time-dependent density functional theory (TDDFT,[32,33] B3LYP/TZVP[34,35,36]), and on a multireference configuration interaction procedure (DFT/MRCI,[37] BHLYP/SVP[38,39]). For the latter two approaches, the initial X-ray based geometry was additionally re-optimized by DFT at the B3LYP/TZVP level with regard to all bond lengths of **1** while preserving the whole set of valence and dihedral angles and hence saving the overall conformation.[12] This optimization led to an increase of the bond lengths between heavy atoms by 0.3–0.5% and by 10–15% for the bonds involving hydrogen atoms.

The comparison of the experimental solid-state CD curve of dioncophylline A (**1**) with the spectra calculated for a single molecule of (*P*)-**1** is shown in Figure 4. The first positive band observed

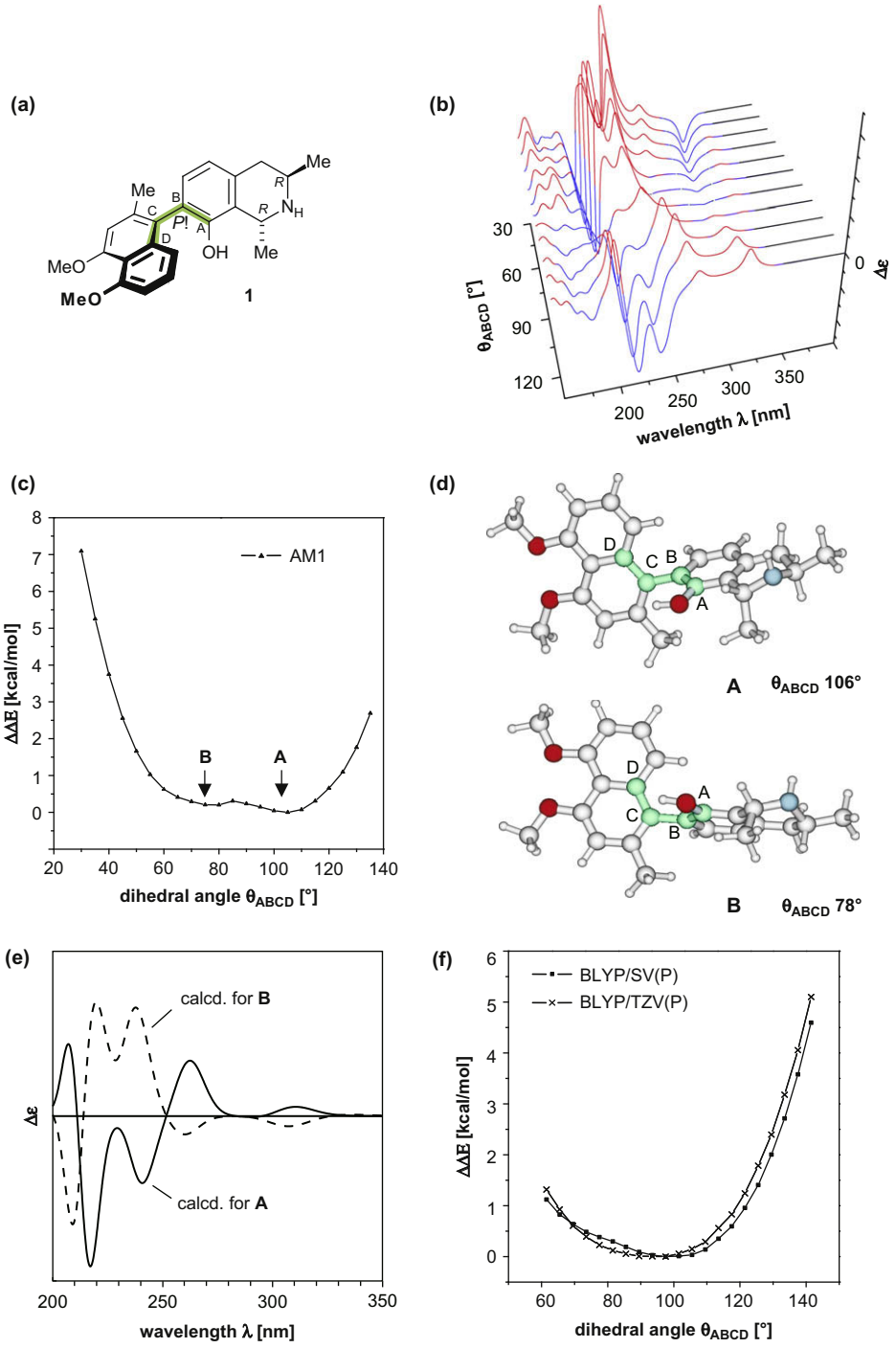


**Figure 1.** One absolute 'configuration' (1*R*,3*R*,7*P*), but two chiroptically opposite conformers. Dioncophylline A (**1**) with its absolute stereostructure (a), a series of CNDO/S calculated CD spectra (red and blue areas correspond to positive and negative $\Delta\varepsilon$ values, respectively) of its rotamers (b), and reaction coordinate (AM1) for the partial (twisting) rotation around the biaryl axis (c), revealing two minimum conformers **A** and **B**, with dihedral angles $\theta_{ABCD}$ of 106° and 78°(d), respectively; the CD spectra of these conformers are almost mirror-image like (e); the energy profiles for the axial rotation calculated at the DFT level (f).

experimentally at 280 nm was predicted by each theoretical method with a too low intensity. The best overall match between theory and experiment was achieved in the case of DFT/MRCI methodology (Fig. 4c), whereas TDDFT calculations revealed the first positive and second negative signals to be substantially shifted to the region of shorter wavelengths (Fig. 4b). The repeated TD-B3LYP computations on the original structure obtained from X-ray diffraction analysis did not yield any substantial improvement in the spectrum (Fig. S1, Supplementary data). Nevertheless, the overall agreement between the experimental (KBr) curve of **1** and all simulated spectra permitted an unambiguous attribution of the axial configuration of dioncophylline A (**1**) as *P*, which again, independently, confirmed the previous assignments.[16,21,22,24]

Although the combination of solid-state CD spectroscopy and CD computations of a single X-ray derived molecule proved its applicability for the attribution of the absolute configuration of this axially chiral alkaloid, dioncophylline A (**1**), it was still of interest how the closest neighbors of any molecule of **1** in the crystal affect its CD behavior, and whether the quantum chemical treatment of larger systems, e.g., of the dyads of **1** or of an integral, 'one-piece'

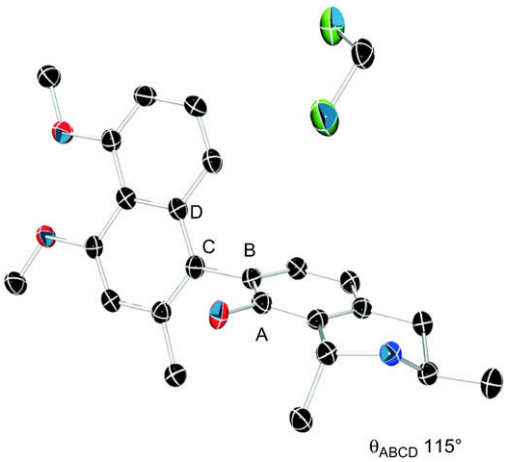


**Figure 2.** Single conformer of dioncophylline A (**1**) as found in the crystal (likewise present in the crystal: a molecule of $CH_2Cl_2$).[22]

cluster with several molecules, can improve the quality of the above-presented results. In the case of dioncophylline A (**1**), neighboring effects seemed to be of particular importance, since this relatively large molecule, comprising two electronically different, almost orthogonally oriented chromophores, should 'see' its different closest neighbors in the crystal differently. Thus, depending on the direction in the crystalline structure, the one or the other chromophoric units of two individual molecules (isoquinoline to isoquinoline, naphthalene to naphthalene, or isoquinoline to naphthalene) will be oriented at different distances and angles, thus providing a set of certainly most diverse intermolecular interactions, which may affect the CD behavior of **1**, possibly even substantially. Thus, to investigate this effect, CD calculations were first performed for all imaginable dyads, each comprising one 'central' molecule of **1** and its closest neighbor (see below).

### 2.4. CD calculations on the dyads of 1 and on the cluster from the crystal

The unit cell of dioncophylline A (**1**) contains four molecules, which were named **I**, **II**, **III**, and **IV**, as shown in Figure 5a. The molecules formally generated by the translation along the principal axes *x*, *y*, and *z* were given the respective indexes **x**, **y**, and **z**. It was shown that each of the molecules of **1** in the crystal has the same molecular environment. For the comprehensive investigation of the neighboring effect one molecule with all its neighbors can therefore be chosen randomly. Thus, CD computations were performed on all possible dyads, which always consisted of the molecule **Ix** as the center (Fig. 5b, pink; for interpretation of the references to color in the text and in the figure legends, the reader is referred to the web version of this article) and, in turn, all its neighboring molecules, viz. **Ix-I**, **Ix-Iz**, **Ix-Ixz**, **Ix-II**, **Ix-IIx**, **Ix-IIz**, **Ix-IIxz**, **Ix-III**, **Ix-IIIx**, **Ix-IIIy**, **Ix-IIIxy**, **Ix-IVy**, **Ix-IVxy**, **Ix-IVyz**, **Ix-IVxyz** (Fig. 5b). The coordinates of each of the dyads were obtained as a result of constructing the desired fragment of the crystal structure of **1** and

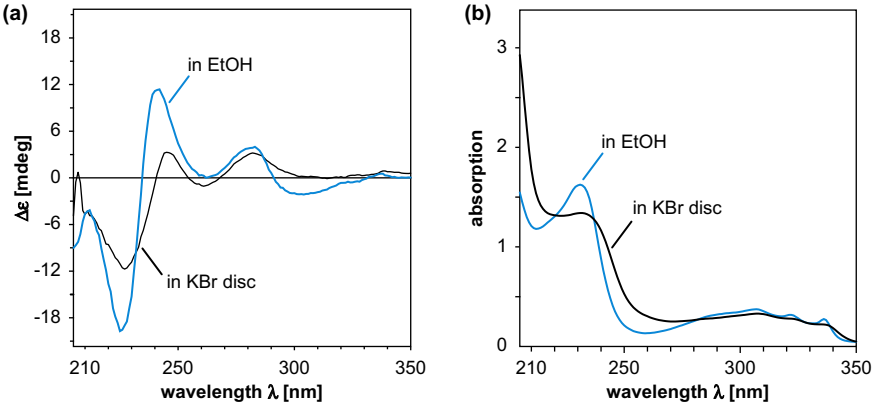


**Figure 3.** Transmittance CD (a) and UV spectra (b) of dioncophylline A (**1**) as measured in ethanol solution, and in the solid state as a KBr pellet.

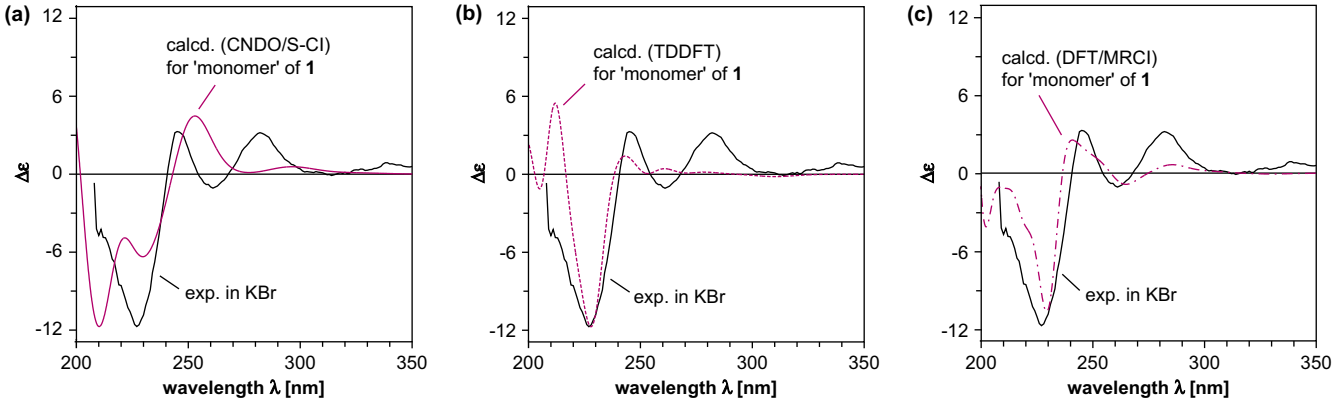


**Figure 4.** Comparison of the experimental CD curve of dioncophylline A (**1**, in KBr) with the spectra calculated for a single molecule of (*P*)-**1** by using CNDO/S-CI (solid line) (a), TDDFT (dotted line) (b), and DFT/MRCI (dash-dotted line) (c).

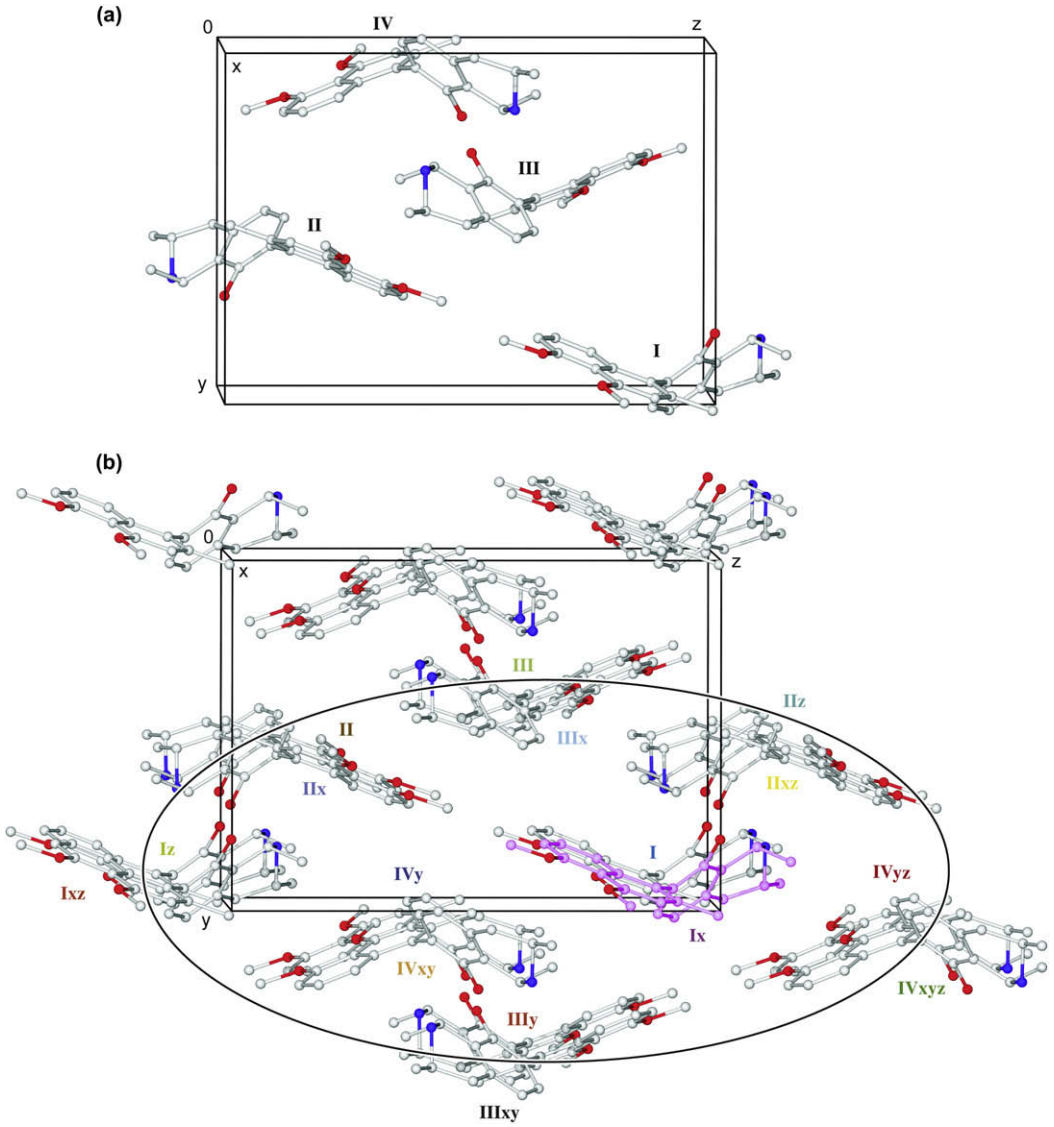


**Figure 5.** A simplified representation of the unit cell of dioncophylline A (**1**), containing four molecules labeled as **I**, **II**, **III**, and **IV** (a), and a fragment of the crystal lattice of **1** demonstrating the 'central' molecule **Ix** (pink) and all its neighbors taken into account (b). For reasons of clarity, solvent molecules and all hydrogen atoms of **1** were omitted.

subsequent canceling of all atoms of the other molecules, while leaving those of the two molecules of interest (for details, see Section 4). The CD spectra were calculated only by using the computationally inexpensive semiempirical CNDO/S-CI method, which had also shown a good agreement concerning the predicted wavelengths and the relative intensities for the 'monomer' of **1**. In order to simplify a comparative analysis of the obtained CD curves, they were grouped in accordance to the same molecular number given and, additionally, compared with the CD spectrum of the single conformer found in the crystal ('monomer'). Despite the fact that some of the dyads appeared geometrically identical and hence provided the same CD spectra, they are still presented in the paper for reasons of completeness.

The comparison of the CD curves calculated for the dyads with the neighbors of type I (i.e., the dyads **Ix**+**I**, **Ix**+**Iz**, **Ix**+**Ixz**, Fig. 6, left) and the spectrum predicted for the single conformer showed that this type of neighborhood does not influence the CD behavior (Fig. 6, right), clearly indicating a negligible intermolecular interaction, which can be explained in the case of the molecules **Iz** and **Ixz** with a too large spatial distance from **Ix** and, in the case of molecule **I**, with the parallel orientation of the molecular chromophores of **I** and **Ix**, which prevents them from interaction.

From the CD plot for the neighbors of type II (Fig. 7, right) it can be seen that taking molecule **II** as the neighbor (i.e., the dyad **Ix**+**II**) gave the same CD spectrum as taking the molecule **IIx** (i.e., the dyad **Ix**+**IIx**). Moreover, the CD behavior of these dyads did not differ substantially from that of the CD of the monomer. This observation can be interpreted by the weak interaction of the almost parallelly arranged naphthalene chromophores of **Ix** and **II**, and of **Ix** and **IIx** (Fig. 7, left). In the cases of the dyads with the molecules **IIz** and **IIxz** (i.e., the dyads **Ix**+**IIz** and **Ix**+**IIxz**), their CD spectra were also identical with each other, but differed from the CD curves of the first pairs of dyads and from the CD of the monomer in the intensities being switched for the negative peak at 230 nm. This revealed a noticeable interdependency between the overlaying naphthalene and isoquinoline moieties, viz. the isoquinoline part of **Ix** with the naphthalene portion of **IIz**, and the naphthalene unit of **Ix** with the isoquinoline half of **IIxz** (Fig. 7, left).

The neighbors of type III are located above the molecule **Ix**, as **III** and **IIIx**, and below, as **IIIy** and **IIIxy** (Fig. 8, left). In this case, the dyad with the molecule **III** as the neighbor (i.e., the dyad **Ix**+**III**) was identical to the one with the molecule **IIIy** (i.e., the dyad **Ix**+**IIIy**) and hence, they resulted in the same CD spectrum.

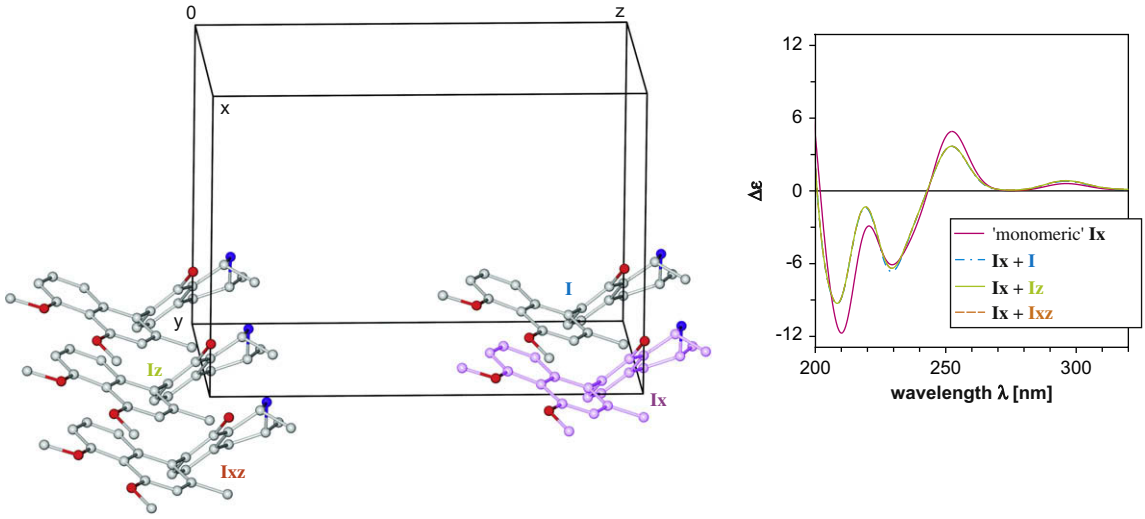


**Figure 6.** Plot of the 'central' molecule **Ix** with the neighbors of type I (viz. **I**, **Iz**, and **Ixz**) and CD spectra of the corresponding dyads.

Consequently, the neighbors **IIIx** and **IIIxy** (i.e., the dyads **Ix**+**IIIx** and **Ix**+**IIIxy**) exhibited an equal CD behavior as well, so that the below-lying neighbors, **IIIy** and **IIIxy** (i.e., the dyads **Ix**+**IIIy** and **Ix**+**IIIxy**), did not cause any changes in the CD behavior in comparison to the respective molecules of type III lying above. On the other hand, the CD curves for the dyads including the molecules **III** and **IIIx** strongly differed from each other, with some signals even possessing opposite signs, and furthermore they were distinct from the CD spectrum of the monomer (Fig. 8, right). This might be due to the presence of different types of interactions, namely a naphthalene–naphthalene one in the case of the overlaying naphthalene portions of **IIIx** or **IIIxy** and that of the molecule **Ix** (naphthalene centroid–naphthalene centroid, ca. 7.0 Å, and the closest interatomic distance, ca. 5.4 Å), isoquinoline–naphthalene ones for the isoquinoline half of the molecule **III** or **IIIy** and the naphthalene part of **Ix** (centroid–centroid, ca. 8.0 Å, and the closest interatomic distance, ca. 3.7 Å), and vice versa for the isoquinoline moiety of **Ix** and the naphthalene parts of **III** or **IIIy** (centroid–centroid, ca. 8.0 Å).

In the cases of the neighbors of type IV, which are located on the right (**IVyz**, **IVxyz**) and on the left (**IVy**, **IVxy**) side of the molecule **Ix** (Fig. 9, left), the following situation occurred: considering the molecules **IVy** and **IVyz** as the neighbors (i.e., the dyads **Ix**+**IVy** and **Ix**+**IVyz**) resulted in identical CD spectra, which were furthermore similar to the spectrum of the monomer (Fig. 9, right), thus clearly indicating marginal interactions between these molecules and **Ix**. Furthermore, **IVxy** and **IVxyz**, each in combination with **Ix**, likewise gave geometrically the same dyads (i.e., the dyads **Ix**+**IVxy** and **Ix**+**IVxyz**), whose CD spectra revealed a substantially different behavior as compared to the spectra of the first pairs of dyads and that of the monomer of **1** (Fig. 9, right), viz. showing the signals at 300 and 230 nm to be of opposite signs. As evident from Figure 9 (left), this behavior can be explained by remarkably strong intermolecular naphthalene–isoquinoline interactions: naphthalene (**Ix**)–isoquinoline (**IVxy**) and isoquinoline (**Ix**)–naphthalene (**IVxyz**) (with a centroid–centroid distance of ca. 5.4 Å).

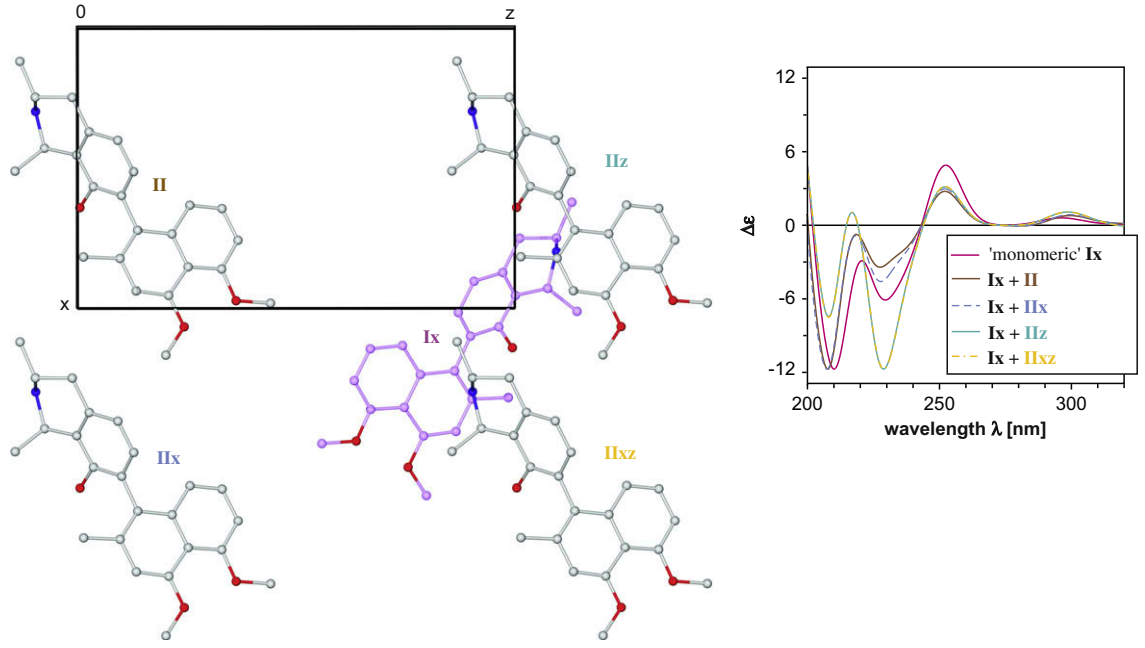


**Figure 7.** Plot of the neighbors of type II (viz. **II**, **IIx**, **IIz**, **IIxz**) in the *xz* plane of the unit cell of **1** and CD spectra of the corresponding dyads.

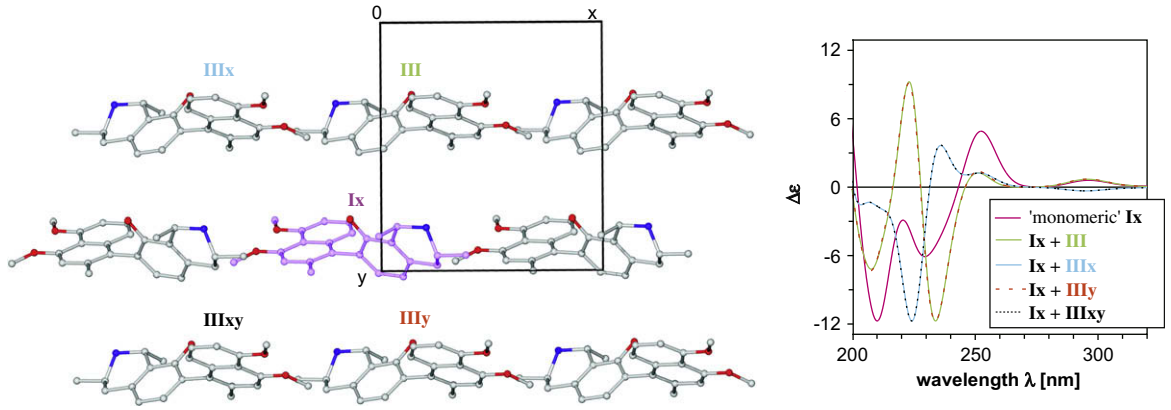


**Figure 8.** Neighbors of type III (viz. **III**, **IIIx**, **IIIy**, **IIIxy**) as depicted in the *xy* plane of the unit cell of **1** and comparison of the respective CD spectra.

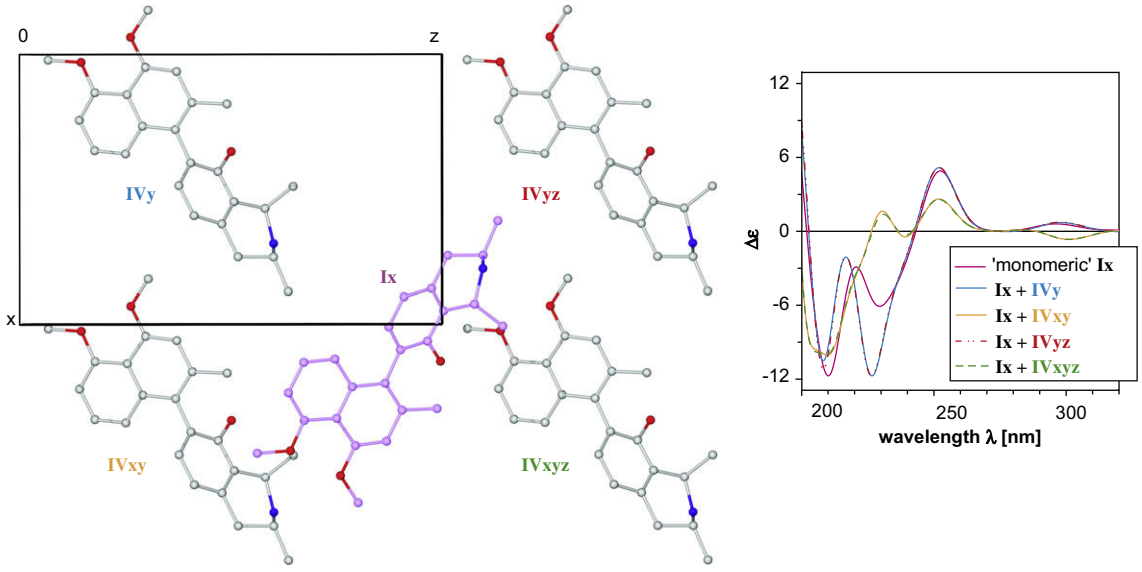


**Figure 9.** Plot of the neighbors of type IV (namely **IVy**, **IVxy**, **IVyz**, and **IVxyz**) in the *xz* plane of the unit cell of **1** and comparison of the CD spectra of the corresponding dyads.

Thus, the calculations described above have proven that the surrounding effects should indeed have a certain influence on the CD behavior of dioncophylline A (**1**) in the solid state, namely for one molecule of **1** (here presented for **Ix**) four of the neighboring molecules—**IIz** (same effect as **IIxz**), **III** (same effect as **IIIy**), **IIIx** (same effect as **IIIxy**), and **IVxy** (same effect as **IVxyz**) have a substantial impact, while the other neighbors—**I**, **Iz**, **Ixz**, **II** (analogous to **IIx**), **IVy** (analogous to **IVyz**)—possess little or no influence.

The spectrum obtained by the arithmetical average over the CD curves of all dyads considered, however, did not show any substantial change in comparison to the spectrum of 'monomeric' **1**

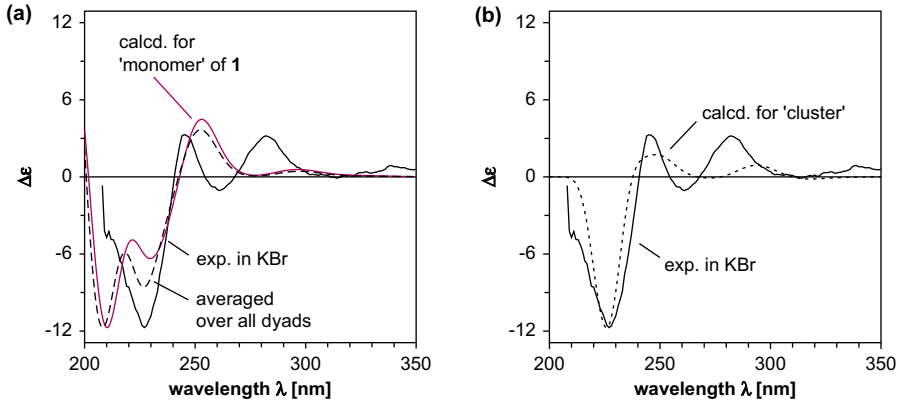


**Figure 10.** (a) Comparison of the experimental solid-state (KBr matrix) CD spectrum of dioncophylline A (**1**) with the curve predicted (CNDO/S) for one single molecule, and with the calculated spectrum obtained as an average over all treated dyads, and also (b) with the curve calculated (ZINDO/S) for the cluster of 16 molecules as experimentally found in the solid state of **1**.

(Fig. 10a). Thus, since no improvements were achieved with these dyads as compared to the aforementioned results (see Section 2.3), CD calculations were performed for a significantly larger aggregate, including 16 molecules of dioncophylline A (**1**) (these are the molecules shown in Fig. 5b, except for molecules **IIz**, **IIIy**, **IIIxy**, **IVxy**, and **IVxyz**). Because of the too large size of the system, the CD spectrum was now calculated by using ZINDO/S[40] implemented in ORCA.[41] For a single molecule of **1**, CNDO/S and ZINDO/S methods provided very similar CD spectra, only slightly differing in the excitation energies (Fig S3, Supplementary data). Comparison of the CD spectrum calculated for the cluster taken from the crystal, with the experimental solid-state CD curve (Fig. 10b) showed only minor improvements, viz., the higher intensity of the peak at about 280 nm. Nonetheless, these results showed that there is indeed an effect on the CD spectrum from the crystalline state; but according to the calculations, this effect is negligible. Therefore, in the case of dioncophylline A (**1**) the consideration of only one molecule is sufficient for an assignment of its absolute axial configuration by means of solid-state CD spectroscopy.

The effect of neighboring molecules on the solid-state CD spectrum has already been investigated by Antus and Kurtán for naphthylethylidene ketals of glycosides by using an approximate method.[42] The present work, with its in-depth, systematic study of the possible surrounding effects should further contribute to the problem of intrinsic solid-state CD effects, and the results found so far should give a higher security for configurational assignment with the solid-state CD method, as first reported by Krohn.[11,12]

## 3. Conclusion

The recently introduced method of determining the absolute stereostructure of chiral compounds by a combination of solid-state CD spectroscopy and quantum chemical CD calculations was successfully applied for the attribution of the axial configuration of the conformationally flexible naphthylisoquinoline alkaloid, dioncophylline A (**1**). Along with a prediction of the CD spectrum for the single conformer of **1** found in the crystal by using three different theoretical approaches (viz. CNDO/S-CI, TD-B3LYP, DFT/MRCI), we have furthermore investigated, for the first time, an influence of the neighboring molecules of dioncophylline A (**1**) in the solid state on its CD behavior by calculating the CD spectra for all possible dyads, each composed of one 'central' molecule plus one neighbor, and also by predicting the CD spectrum for a 16-molecule fragment of the crystal structure of **1**. Despite the fact that in this particular case and at the semiempirical level such consideration of the surrounding effect did not improve the final result, we consider this approach as highly promising, especially for higher-level computations on large chiral molecules with several chromophoric units being distant from each other.

## 4. Computational

Screening of the reaction coordinate for the biaryl axis of **1** was performed at the semiempirical AM1[25] level with the Gaussian 03[43] program by varying the dihedral angle at the axis with an interval of 5° ($30°<\theta_{ABCD}<135°$). Analogous DFT computations using the RI-BLYP/SV(P) and RI-BLYP/TZV(P) methods were done with ORCA.[41] The CD spectra for the rotamers thus obtained were calculated by using the semiempirical CNDO/S-CI[27] method within the BDZDO/MCDSPD[44] program package, with a CI expansion including 28 occupied and unoccupied orbitals.

CD computations of the single conformer of **1** obtained from the solid-state structure were performed by the CNDO/S-CI method and also by using TDDFT (B3LYP/TZVP)[34,35,36] and DFT/MRCI (BHLYP/SVP)[37,38,39] approaches, which considered 40 and 35 energetically lowest excites states, respectively. For the TDDFT and DFT/MRCI-based CD calculations, the initial X-ray deduced structure was additionally re-optimized by a DFT method at the B3LYP/TZVP level with regard to all bond lengths of **1** while 'freezing' a whole set of valence and dihedral angles using the ModRedundant[43] option of Gaussian 03. The DFT/MRCI calculations were performed with a configuration selection cut-off of $0.8E_h$,[45] which permitted to reduce the computational costs substantially. The dipole-velocity representation[46] of the rotatory strengths was chosen for all methods. To simulate the CD curves, a Gaussian band-shape function[47] was applied with the exponential half-width of 0.1 eV in the case of the spectra of the 'monomeric' **1** and of 0.08 eV for the curves of all dyads. To compensate an error in the prediction of the energies of the excited states, the calculated CD spectra were shifted in accordance with a UV correction[28] by 6 nm (blue shift, CNDO/S-CI), 8 nm (red shift, TDDFT), and 15 nm (red shift, DFT/MRCI) as compared to the experimental KBr-based curve. Simulation of all band-shape spectra and their comparison with the experimental ones were performed with SpecDisc.[48]

Coordinates of the dyads of **1** were obtained by constructing the required fragment of the crystalline structure of **1** within the ORTEP[49] program, followed by the cancellation of all atoms of currently unneeded molecules, while saving those of the two molecules of interest. The CD spectra of the dyads were calculated by the semiempirical CNDO/S-CI method as described above. For calculation of the 'one-piece' fragment with 16 molecules of **1** taken from the crystal, the ZINDO/S approach was used, treating 120 singly excited configurations. The resulting spectrum was blue-shifted by 20 nm.

## 5. Solid-state CD measurements

The transmittance solid-state CD and absorption spectra were recorded using UCS-1.[15] A crystal of dioncophylline A (**1**) (ca. 50 μg) and dry KBr (125 mg) were finely ground, and the powder was pressed at 4.8 MP/cm$^2$ in vacuum for 10 min to prepare a transparent disk of 1 cm diameter. The KBr disk, held by a specially designed disk holder, was placed normal to a light beam. The wavelength scan CD spectrum was recorded over a wavelength range of 350–207 nm with 'standard' sensitivity at 50 nm/min with 1 nm resolution, time constant of 1 s. The true CD spectrum in the solid state was obtained by a specially devised set of procedures based on the Stokes–Müller matrix method.[15] For comparison, CD and absorption spectra of dioncophylline A in ethanol were recorded at a concentration of 0.296 mM using a quartz cell of 1 mm optical length.

The transmittance solid-state CD spectrum was checked for the effect of artifact signals, which arise from the interaction between the macroscopic anisotropies of the sample and the non-ideal characteristics of the polarization-modulation instruments.[15] The artifact signals have terms dependent and independent on the sample rotation in the plane perpendicular to the light beam.[15] The CD signal of the prepared KBr disk hardly changed with rotation (data not shown), and hence the angular-dependent terms multiplied by the polarization characteristics of the detector were negligible. LB and LD values of the current sample were measured to be of $6\times10^{-3}$ and the order of $10^{-3}$ OD, respectively. Thus, the angular-independent terms are 10–100 times smaller than the true CD signal (the order of $10^{-4}$ OD=5–10 mdeg). Therefore, one can conclude that the transmittance solid-state CD spectra of **1** recorded on UCS-1 are free from LD and LB effects. This was achieved by a careful preparation of the sample, and due to the use of UCS-1, which was specially made to possess little non-ideal polarization characteristics. The effect of large artifacts to CD spectra can be seen in the literature.[15,50,51]

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.024.

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