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The Assignment of Absolute Stereostructures through Quantum Chemical Circular Dichroism Calculations

Gerhard Bringmann,*[a] Torsten Bruhn,[a] Katja Maksimenka,[a] and Yasmin Hemberger[a]

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The determination of the absolute configuration of a chiral compound of synthetic or natural origin is a problem that every organic chemist willl certainly have to face some day. An efficient and reliable method for the assignment of absolute stereostructures, independent of empirical CD rules, is the combination of experimental circular dichroism (CD) investigations with quantum chemical CD calculations. The availability of a broad variety of quantum chemical methods and the continuing appearance of new approaches permits – but also requires – the most appropriate method to be selected in each particular case, with respect to accuracy, time consumption, and computational resources. With examples of selected chiral compounds of the most diverse structures and origins, and inclusion of several methods based on substantially different theoretical backgrounds, this review describes the basic principles and concepts of quantum chemical CD calculations for the configurational assignment of chiral compounds with stereogenic centers and/or elements of axial or planar chirality.

1. Introduction

Absolute configuration is a fundamental structural feature of chiral compounds and determines their pharmacological activities and other properties.[1] Its safe assignment is thus an important – and sometimes challenging – task. For this purpose it is possible to apply not only (sometimes tedious) total or semisynthetic approaches, but also NMR and X-ray crystallography. These, however, usually require the presence or introduction either of stereogenic centers of known configuration or (in the latter case) of heavy atoms, as well as the availability of crystals of suitable quality. Chiroptical methods, in particular electronic circular dichroism (CD) spectroscopy, are inexpensive and easy to perform, variously for pure synthetic or isolated compounds or in mixtures, in conjunction with chromatographic methods (HPLC-CD), and are ideal in that they give mirror image CD spectra for the individual members of pairs of opposite enantiomers. The interpretation of the spectra is usually done by comparing them with the chiroptical data for related, structurally known compounds or by applying CD rules such as the octant rule[2,3] or the exciton chirality method,[4,5] although these require the fulfillment of particular structural preconditions.[6] This can make the configurational assignment difficult, especially for structurally novel compounds. Quantum chemical calculation of the CD spectra predicted for the corresponding enantiomers (in a very few cases even for different diastereomers) and their comparison with the experimental spectrum is thus of particular value. This approach is not restricted to any structural preconditions (except for the molecular size) and has thus become a valuable tool for the assignment of the absolute stereostructures of a broad spectrum of chiral compounds.[7–9]

However, there are several other chiroptical properties that can also be calculated by quantum chemical methods, such as vibrational CD (VCD),[10] optical rotation (OR),[11] or optical rotation dispersion (ORD).[12] These methods are also well suited for determining absolute configurations of unknown compounds and are very reliable, particularly in cases in which CD, VCD, and OR predictions all lead to the same result.[13] Nonetheless, especially in natural products chemistry, in which the investigated compounds in most cases possess significant chromophores but are available only in low quantities, CD is usually the more appropriate method, due to its need for only very small quantities (0.1–1 mg, whereas VCD measurements require at least 10 mg).

In this review, the general applicability of CD calculation is illustrated mainly for unprecedented structures from nature and may encourage experimental chemists to take advantage of this useful analytical tool.

2. Concept

The chiroptical behavior of a chiral compound depends on the spatial orientation of its chromophoric groups and

[a] Institute of Organic Chemistry, University of Würzburg, Am Hubland, 97074 Würzburg, Germany
Fax: +49-931-888-4755
E-mail: bringman@chemie.uni-wuerzburg.de
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thus on its molecular flexibility. CD is, therefore, more conformation-dependent than any other spectroscopic method. In many cases, consequently, it will not be sufficient simply to consider the global minimum but it will also be necessary to take into account the CD contributions of all conformational species that are significantly populated. This, in turn, requires a detailed conformational investigation beforehand. For the screening of the particular potential energy surface (i.e., for a conformational search), different approaches can be used. Figure 1 illustrates, in a schematic, generalized way, the different approaches and the overall calculation strategy described in this chapter.

A different, more specialized approach, as proposed by Krohn et al.,[14] takes advantage of the presence of only one single configuration in the solid state. If this structure is known from X-ray diffraction analysis, the CD spectrum calculated for this conformer can be compared with the solid-state CD spectrum for configurational assignment, thus making a conformational analysis unnecessary. The method, however, requires the availability of the solid-state CD methodology and is based on the assumption that the molecules in the crystals do not interact significantly with each other. The criteria for the quantum chemical methods and density functionals to be chosen and used for this approach are similar to those for the molecules described in this review.

2.1. The Boltzmann-Weighted Conformational Analysis Approach

Starting with an arbitrarily chosen stereoisomer of a chiral compound, all possible conformations are generated manually by systematic analysis of the degrees of freedom – in particular, dihedral angles – of each flexible part of the molecule, for calculation of the internal rotation energy profile, usually performed at a semiempirical level (AM1,[15] PM3[16]). The conformers thus found are further optimized at a higher level of theory [e.g., by means of the density functional theory (DFT), mainly with use of the B3LYP[17,18] or the BLYP[19,17] functional, often together with the resolution of identity (RI)[20] approximation and

Gerhard Bringmann received his Ph. D. (porphyrin chemistry) at the University of Münster. After his postdoctoral stay with Sir D. H. R. Barton in Gif-sur-Yvette (France), he passed his habilitation (isoquinoline chemistry) in 1984. Since 1987 he has been a professor of organic chemistry at the University of Würzburg. He works in the field of analytical, synthetic, and computational natural products chemistry. Recent awards have been the Adolf-Windaus Medal (2006), the Honorary Doctorate of the University of Kinshasa, D.R. of Congo (2006), the Paul-J.-Scheuer Award (2007), and the Honorary Guest Professorship of Peking University (2008).

Torsten Bruhn obtained his PhD in 2006 from the University of Oldenburg under the supervision of Dr. Rainer Koch and Prof. Manfred Weidenbruch. His graduate research dealt with computational studies on reactive group-14 systems. Since 2006 he has been a postdoc at the University of Würzburg with Prof. G. Bringmann, where he focuses on the quantum chemical prediction of circular dichroism and NMR properties.

Katja Maksimenka studied chemistry at the Belarusian State University in Minsk (Belarus). She completed her diploma in 2002 at the Organic Chemistry Department under the guidance of Prof. Oleg G. Kulinkovich and Ass. Prof. Nikolai N. Sokolov. During her Ph.D. study at the University of Würzburg under the direction of Prof. G. Bringmann she worked on the elucidation of absolute configurations by means of quantum chemical CD calculations.

Yasmin Hemberger studied chemistry at the University of Würzburg, where she received her diploma in 2008. She is currently pursuing her Ph.D. studies under the supervision of Prof. G. Bringmann on the quantum chemical calculation of spectroscopic properties of chiral natural products.

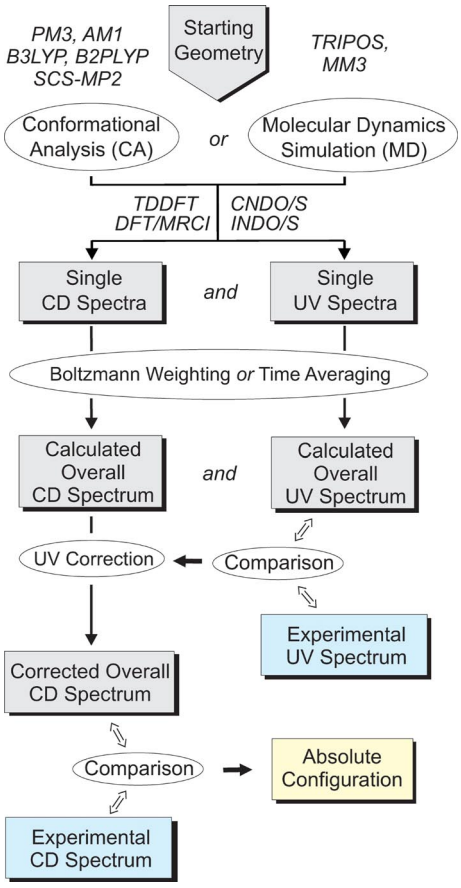

Figure 1. The principal approaches for the assignment of absolute stereostructures of chiral compounds by quantum chemical CD calculations in combination with experimental CD measurements; the conformation-dependent chiroptical behavior is interpreted by conformational analysis or by MD simulation.

with use of a split-valence double-zeta basis set such as 6–31G*[21]] to locate all minimum conformers that are significantly populated at ambient temperature. According to Boltzmann statistics, these are the conformers within an energy cut-off of 3 kcal mol^{-1}. These energetically favorable minimum structures are then subjected to the actual calculations of excited states.

2.2. The Molecular Dynamics (MD) Approach

For investigation of the conformational spaces of highly flexible molecules, the MD procedure is an efficient, time-saving alternative. In this approach, a single structure of one enantiomer is exposed to a force field, usually TRIPOS[22] or MM3,[23] for a defined span of time. During this period, the Newton equations of motion are solved and the single geometries are extracted at given intervals.[24] The chosen temperature is controlled and kept constant by coupling to a virtual thermal bath.[25] An essentially complete sampling of the conformational space of the molecule can be achieved either by increasing the duration of the MD run or by varying the temperature. The CD spectra for all of the "stroboscopically" collected structures are calculated at a semiempirical level and are then added arithmetically, one by one, and thus averaged over time.[26] Alternatively, the force-field-generated conformers are subjected to further optimization steps, based on either ab initio or DFT procedures, and the subsequently computed CD spectra are again weighted according to Boltzmann statistics.

2.3. Calculation of Electronic Transitions

The second step of the computations comprises the calculation of the electronic transitions from the ground to the excited states. In the simulation of the molecular CD, the decisive quantity is the rotatory strength R.[27] For its calculation, two formalisms are in use: the dipole length and the velocity formalisms. The use of the dipole length form results in rotatory strengths that are origin-dependent,[28] whereas the velocity representation is origin-invariant, but violates the rotational-strength sum rule.[29] For this reason, the matter of which approach should be preferred is a subject of controversy in the literature.[8,30] In our experience, though, the differences between the rotatory strengths calculated by the two different methods are negligible.

Experimentally, the molecular CD is usually measured in units of $\Delta\varepsilon$ (i.e., the difference between the extinction coefficients for left- and right-circularly polarized light). For this purpose, the computed rotatory strengths R_{0k} are accordingly transformed and superimposed with Gaussian functions,[31] centered at the respective wavelengths λ_k of the electronic transitions, to give the calculated single CD spectrum Equation (1).

$$\Delta\varepsilon(\lambda) = \frac{16\pi^2\beta N_A\lambda}{6909\hbar c}\cdot\sum_k R_{0k}\frac{e^{-\left(\frac{\lambda-\lambda_k}{\Gamma_k}\right)^2}}{\Gamma_k\sqrt{\pi}} \quad (1)$$

In this equation, β means the Lorentz correction, which considers the perturbation of the external field by the local one of the chromophore,[32] N_A is the Avogadro constant, and Γ_k is the exponential half-width, which is used as an adjustable parameter for reproducing the experimentally observed CD features. Normally, a default value of 0.08 eV is used for Γ_k, but it still has to be fitted for every molecule and may range from 0.05–0.2 eV.

The simulation of the CD spectrum is accompanied by the calculation of the UV curve, because the electric transition dipole moments are integral parts of both. In the case of the UV spectrum, the basic quantity is the electric dipole strength D. More familiar, however, is the oscillator strength f, which is easily obtained from D.

In order to obtain the UV curve, one has to convert the calculated oscillator strengths f_{0k} into units of the extinction coefficient ε, and again, as in the case of CD, then has to overlay them with Gaussian functions Equation (2).

$$\varepsilon(\lambda) = \frac{4\pi^2\beta N_A\lambda}{6909\hbar c}\cdot\sum_k D_{0k}\frac{e^{-\left(\frac{\lambda-\lambda_k}{\Gamma_k}\right)^2}}{\Gamma_k\sqrt{\pi}} \quad (2)$$

In the MD approach, the single UV and CD curves of all conformers are superposed to give the overall simulated UV and CD spectra, respectively, whereas in the case of the Boltzmann procedure they are summed energetically weighted (i.e., in accordance with the heats of formation of the corresponding structures).

In the calculation of electronic transitions, the major challenge is the reliable consideration of (dynamic) electron correlations. In order to obtain trustable wavefunctions for the ground state and the excited ones, together with the corresponding energies, one can apply several methods.[33] The most common one is a configuration-interaction (CI) procedure.[34]

For such an approach we have frequently applied the semiempirical CNDO/S,[35] ZINDO/S,[36] and OM2[37] Hamiltonians with a CI expansion that covers single excitations. However, to account for the dynamic electron correlation discussed above, at least the double excitations have to be included in the CI progression, because, according to the Brillouin theorem, the mere single excitations do not interact with the ground state wavefunction.[38]

Another technique employed to compute electronic transitions uses the propagator method, which applies a time-dependent (TD) perturbation to the system. This method has been applied to both HF and DFT; the latter approach – TDDFT[39] – is superior and nowadays the most frequently used.[40]

A third method that fruitfully combines two different techniques is a DFT/MRCI approach developed by Grimme and Waletzke.[41] This method uses a multi-reference (MR) wavefunction in the CI expansion that covers single and double excitations. The orbitals are obtained by means of DFT, with application of the BHLYP[17,42] hybrid functional together with the RI approximation. With regard to the basis set size, it has recently been shown by Marian et al.[43] that the use of the small SVP basis, which drastically reduces the computational time, has a negligible effect on the excitation energies and oscillator strengths relative to the larger TZVP basis, so that the DFT/MRCI/SVP approach becomes applicable to rather large molecules. Unlike a single-reference ansatz such as TDDFT, DFT/MRCI also takes account of the static electron correlation, therefore providing highly accurate predictions. Another method used in our group is the MRCI approach as implemented in the ORCA software package,[44] in which Kohn–Sham's reference functions can also be used. This DFT-MRCI approach, which differs from Grimme's method, likewise yields comparably good calculations of excited states.

An essential step in assigning the absolute configuration from CD calculations is the comparison of the predicted overall UV spectrum with the experimentally measured one. By this strategy, systematic errors in the prediction of the excited-state energies (and thus the wavelengths) that are present in *both* calculated spectra can be estimated and thus eliminated by adjusting the calculated overall CD spectrum by the same shift. This so-called UV correction[9] hence permits a better agreement with the experiment and a greater reliability and predictability for the subsequent assignment. An unambiguously determined UV shift is an important precondition for obtaining an unequivocal elucidation of the absolute configuration. The aim of this review is the comparative presentation of the elucidation of the absolute configurations of natural products through calculation of the UV and CD spectra by several approaches, and not to focus too much on the theoretical background of the methods used. For further, more in-depth details, we therefore instead quote recent reviews describing the computation of chiroptical properties,[33] and again point to the references mentioned in this chapter.

3. Elucidation of Absolute Configurations

For the quantum chemical calculation of the CD behavior of concrete chiral molecules to be configurationally assigned, one has to validate the numerous theoretical chemical methods. One of the decisions to be taken is to find a realistic compromise between the accuracy of the methods used and the computational costs, because these may rise dramatically with increasing molecular size. In the early 1990s, when our group started calculating CD spectra, only semiempirical methods were feasible, whereas today semiempirical methods are mainly used for the calculation of excited states of very large structures, for which ab initio and DFT appear impracticable due to very high computational costs.

3.1 Semiempirical Methods: Configurational Assignment at the Chiral Axis of Abyquinone A (1)

The first example of semiempirical CD calculations in combination with the Boltzmann approach was the assignment in 1993 of the absolute configurations of the naphthylisoquinoline alkaloids ancistrocladine and its atropo-diastereomer hamatine.[45] A detailed computational analysis of these natural biaryls revealed that the CD spectra expected for different conformational species – just differing in the dihedral angles at the biaryl axis – gave nearly opposite CD spectra, even if belonging to the very same atropo-diastereomer! It was thus only by taking all of these structures into account by Boltzmann weighting that a reliable prediction of the CD behavior succeeded. A series of successful elucidations of absolute configurations mainly of axially chiral compounds followed, among them the determination of the biaryl axes of michellamines[46] and of bismurayaquinone A.[47] In 1997[48] the palmarumycins then provided the first example of a more complex system containing several stereogenic centers (with known relative configuration) that could be stereochemically assigned by quantum chemical CD calculations, while no other methods had, at that time, succeeded in establishing their absolute configurations. Semiempirical methods – CNDO/S,[35] INDO/S,[36] MNDO-based (e.g., OM2),[37] and SCF-CI-DV MO[5] approaches – have been widely applied, and many research groups have used them as tools for the determination of the absolute configurations of a great variety of chiral com-

pounds, such as vinblastine alkaloids, by Berova et al.,[49] bridged biphenyls, by Sandström,[50] or fullerenes, by Diederich et al.[51] In 1997, the concept of UV correction for achieving better agreement between the theoretical UV and CD spectra and the experimentally measured ones, introduced by our group, was a further significant improvement.[9] Many configurational assignments followed, relating mainly to rotationally hindered biaryl axes such as in dioncophylline A[52] or murastifoline F,[53] but also to "molecular chiralities" as in isoplagiochins C and D,[54,55] or to twofold alkylidene-bridged biaryls possessing both planar-chiral elements and chiral axes.[56]

Unfortunately, the determination of the UV shifts is not always a trivial matter when applying semiempirical methods. In our experience, semiempirical approaches may have difficulties in reproducing the longer-wavelength region (i.e., the range above 300 nm), which may be attributed to the poor description of n–π* transitions in these methods. Therefore, in ambiguous cases, the UV shift is better determined by taking account of the UV bands in the 200 to 300 nm range, while disregarding the match in the higher regions. In such cases, however, higher-level methods are generally more appropriate.

A more recent example of semiempirical CD calculation is provided by the elucidation of the absolute configurations of abyquinone A (**1**, Figure 2) and related natural bisanthraquinones[57] obtained from the fruits of *Bulbine abyssinica*. The conformational analysis of abyquinone A

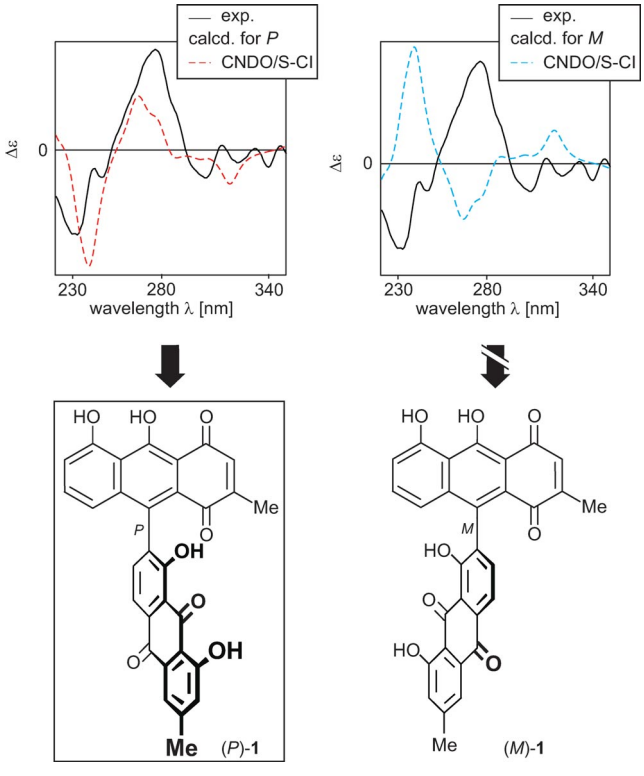

Figure 2. Absolute configuration of abyquinone A (**1**) attributed by comparison of the experimentally measured CD curve with the spectra calculated for the *P* and the *M* enantiomers by the CNDO/S method.[57]

(**1**) with the AM1 Hamiltonian, arbitrarily for the *P* atropoenantiomer, yielded eight minimum structures within the energetically relevant range of 3 kcal mol^{-1} above the global minimum. From the conformers thus identified, the single UV and CD spectra were calculated by use of CNDO/S and OM2 and were then added up in energetically weighted fashion according to the Boltzmann statistics and UV corrected (see above). The CD spectrum of (*M*)-**1** was generated by mirroring the spectrum predicted for the *P* configuration at the zero line. A comparison of the CD spectra thus computed for the two enantiomers of **1** with the experimentally measured one showed a good agreement in the case of the *P*-configured abyquinone A (**1**), whereas the CD curve calculated for the *M* configuration was virtually opposite (Figure 2).

3.2 Time-Dependent Density Functional Theory (TDDFT)

TDDFT is currently one of the most popular methods for quantum chemical calculations of CD and UV spectra. The accuracy of the predicted spectra depends strongly on the functional and the basis set used. Therefore, the first – and most important – step in TDDFT calculations is the choice of an appropriate functional and a basis set, always keeping the computational costs in mind. The hybrid B3LYP or the BLYP functionals, together with at least a double-zeta basis set, thus yield sufficiently good results for the elucidation of the absolute configurations of chiral molecules. An increase in the size of the basis set leads to smaller systematic errors in the prediction of the excited state energies and, thus, to smaller required UV shifts. The combination of B3LYP with 6–31G*, SVP, or TZVP[58] basis sets seems to be the most suitable, as verified for several examples from our group and others.[8,59]

TDDFT in particular gives good results for the low-lying states. Consequently, the UV shift, in contrast to the semiempirical methods, should in ambiguous cases be determined in the higher-wavelengths region, and not for smaller wavelengths, where Rydberg states are involved and the TDDFT results get slightly worse. Again, these cases are hints that a more appropriate functional or – if applicable – an MRCI approach should be used.

3.2.1 Several Stereogenic Centers in One Molecule: Gephyromycin (2)

Gephyromycin (**2**, Figure 3) from *Streptomyces* strain NTK 14,[60] the first bridged angucyclinone, is one of those cases in which assignment of the absolute configuration by semiempirical methods proved rather difficult, whereas TDDFT calculations provided an unequivocal attribution. The unique constitution of **2** and its relative configuration were determined by extensive NMR measurements and further corroborated by a "normal" X-ray structure analysis (i.e., without a heavy atom).[60] Accordingly, its absolute configuration could have been either 3*S*,4a*S*,6a*S*,12a*R*,12b*R* or, fully opposite, 3*R*,4a*R*,6a*R*,12a*S*,12b*S*. To decide between these two enantiomeric possibilities, the quantum chemical calculation of the CD spectra for both pos-

sible stereostructures and their comparison with the experimentally measured curve for **2** seemed to be the method of choice.

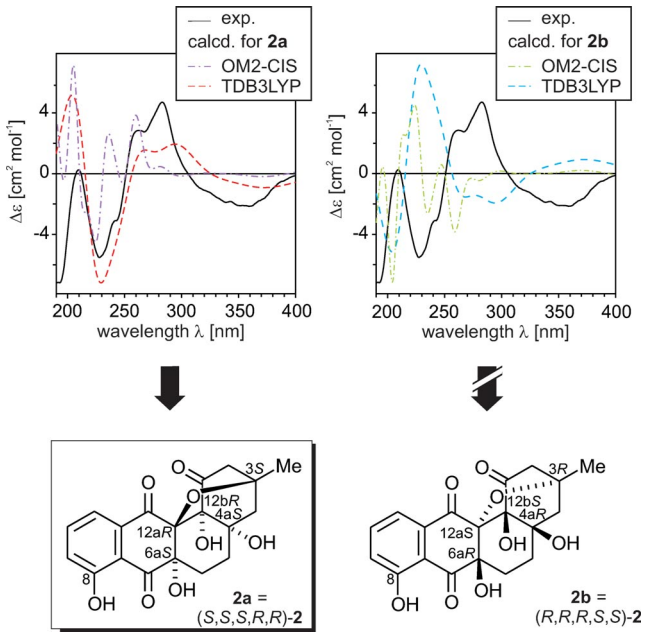

Figure 3. Elucidation of the absolute stereostructure of gephyromycin (**2**) by semiempirical OM2 calculations and, more successfully, by TDB3LYP/TZVP investigations.

The conformational analysis of gephyromycin (**2**) at the AM1 level followed by CD calculations by CNDO/S and OM2, however, gave only ambiguous results. Some improvements were obtained with the tetra-*O*-acetyl derivative of gephyromycin,[60] but for a solid confirmation of the configurational assignment of **2**, a more exact theoretical approach had to be applied. Therefore, the AM1-predicted structures of gephyromycin (**2**) were further optimized at the higher RI-BLYP/SVP level, resulting in only one relevant conformer. The CD and UV spectra of **2** were now calculated with use of the hybrid B3LYP functional and the TZVP basis set. After a UV correction of 16 nm (blue shift), the accordingly adapted CD spectrum predicted for "*S*,*S*,*S*,*R*,*R*" now perfectly reproduced the experimentally measured one, including the broad low-intensity band, with a negative Cotton Effect (CE), at about 350 nm (Figure 3), which does not appear in the semiempirical calculations. Analysis of the electronic excitations and the most significant molecular orbitals involved showed that all bands in the CD spectrum of **2** include large numbers of n–π* transitions, which might be the reason for the failure of the semiempirical approaches described above.

3.2.2 Pseudo-Enantiomeric (and Energetically Similar!) Conformers: Neoechinulin A (3)

DFT-based CD calculations have also proven superior to the semiempirical methods for the assignment of the absolute configuration of neoechinulin A (**3**, Figure 4). This diketopiperazine alkaloid from various *Aspergillus*[61] and *Eurotium*[62] species, together with its closest analogue, neoechinulin B, has recently been identified in the fungal strain R04–3-14, available from the marine sponge *Axinella damicornis*.[63] These natural products show promising UV-A protective,[64] antioxidant,[65] and also neuroprotective activities,[66] which made stereochemical investigations into the diketopiperazine unit of **3** potentially rewarding. Neoechinulin A (**3**) had been assumed to be *S*-configured on the basis of feeding experiments,[67] as has been confirmed recently by the total synthesis of (–)-**3**,[68] whereas the *Z* configuration of the C^8=C^9 double bond of **3**, as deduced from NMR experiments,[69] has been corroborated by an X-ray structure analysis.[63]

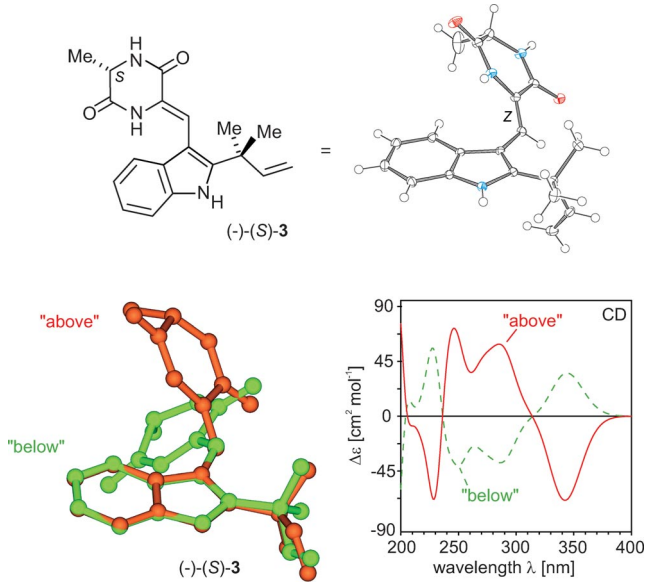

Figure 4. X-ray structure (top, right) and two conformers of neoechinulin A (**3**) of the same absolute configuration (here arbitrarily *S*), but with pseudo-enantiomeric chromophoric frameworks (red and green; bottom, left), thus providing mirror-image-like CNDO/S-predicted CD spectra (bottom, right).

Starting with the *S* enantiomer of **3**, the AM1-based conformational search concentrated on two flexible groups: the isoprenyl substituent at C-2 and the diketopiperazine ring. The latter adopted two preferential orientations, one above (red in Figure 4, left) and one below (green) the plane of the indole ring. Semiempirical excited state energy calculations of the AM1-simulated structures, however, gave unclear results. The problems in the prediction of the CD spectrum of **3** arise from the presence of two sets of helical conformers, which, although possessing the same absolute configuration at the stereogenic center and hence being diastereomers, still adopt near-enantiomeric orientations of the chromophores, thus providing virtually opposite CD spectra (Figure 4, right, red and green curves). Because the predicted overall CD curve is, due to the Boltzmann statistics, highly sensitive to the accuracy of the calculated relative energies of the conformers, the more exact DFT approach for the structure and energy optimization was required.

The BLYP/TZVP optimization reduced the number of the conformers and, furthermore, gave relative energies for the pseudo-enantiomeric structures substantially different

from those obtained with the AM1 results. The CD spectrum of (*S*)-**3**, calculated at the TDDFT level by use of the B3LYP/TZVP method, properly reproduced the experimentally measured CD spectrum of (–)-neoechinulin A (**3**), whereas the one predicted for (*R*)-**3** clearly showed opposite behavior (Figure 5). From this, the absolute configuration of the naturally predominant enantiomer of natural neoechinulin A, (–)-**3**, was unambiguously determined to be *S*, which also confirmed the assignment provided by the synthetic work.

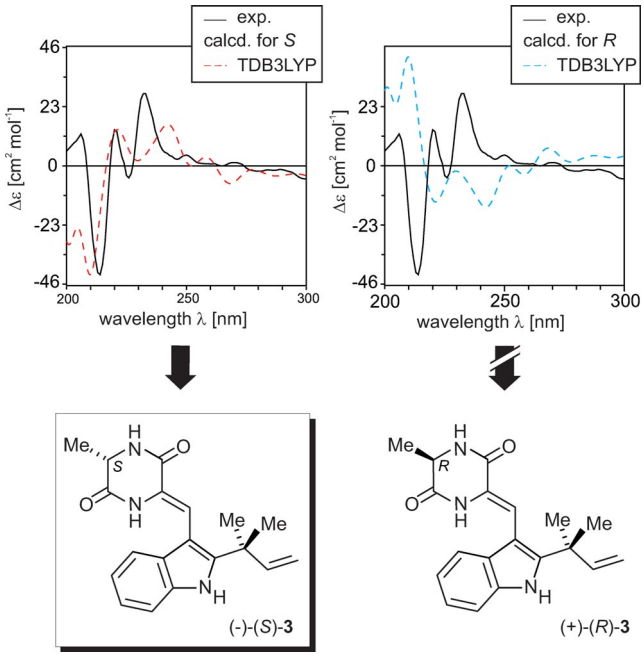

Figure 5. Elucidation of the absolute configuration of (–)-neoechinulin A (**3**) by comparison of its experimentally measured CD spectrum with the TDDFT-predicted curves.

3.2.3 The Importance of Solvent Effects: The Cationic Alkaloid Ancistrocladinium B (4), Incorporating a Chiral N,C-Axis

Ancistrocladinium B (**4**, Figure 6) is one of the first *N*,*C*-coupled representatives of the structurally, biosynthetically, and pharmacologically remarkable class of naphthylisoquinoline alkaloids,[70] discovered most recently in Congolese *Ancistrocladus* lianas.[71] Besides a stereogenic center at C-3, it possesses a chiral, but configurationally semi-stable iminium-aryl axis and thus occurs as a mixture of slowly interconverting atropo-diastereomers, which can be resolved by HPLC. Thus, whereas the *S* configuration at C-3 was determined by ruthenium-mediated oxidative degradation[72] directly on the atropisomeric mixture of **4**, the other stereochemical investigations were performed individually on each of the two atropisomers, in conjunction with HPLC resolution.[73] For the interpretation of the CD spectra thus measured online, quantum chemical calculations were performed. The conformational analysis based on DFT (B3LYP/6–31G*) led to four relevant conformers for each of the two possible atropo-diastereomers, (*M*,3*S*)-**4** and (*P*,3*S*)-**4**. TDB3LYP CD calculations performed on these conformers did permit an initial assignment of the absolute configurations, but the agreement between the theoretical spectra and the experimentally measured ones, especially in the case of (*P*,3*S*)-**4**, was not perfect at all (Figure 6). Improved results were achieved by taking account of solvent effects through the use of the COSMO approach, which provided a better match, while requiring only slightly higher computational costs. In the spectrum thus calculated for (*P*,3*S*)-**4** (Figure 6), the strong double band around 210–240 nm and the peak at 350 nm with a positive sign were only reproduced when the COSMO model was applied, whereas the gas-phase computations had led to opposite Cotton effects at 230 nm and had not predicted any positive signals at 350 nm. Therefore, the exciton couplet at 340 nm (resulting from the interaction between the naphthalene and the isoquinoline chromophores), which is in agreement with a "positive chirality" corresponding to the *P* configuration of **4**, was only reproduced by TDB3LYP calculations in combination with COSMO. Furthermore, consideration of the solvent effects both for (*M*,3*S*)-**4** and for (*P*,3*S*)-**4** resulted in much more accurate excitation energies, which further demonstrated the advantage of the method.[74] The example of ancistrocladinium B (**4**) shows that the COSMO calculations yield results either better than or at least similar to those obtained from the gas-phase calculations, which, together with the only negligibly higher computational costs, suggests that solvent effects might profitably be taken into account regularly, in particular for ionic structures. The absolute axial chirality thus determined by quantum chemical CD calculations finally confirmed parallel results of online NMR investigations, by LC-ROESY coupling.

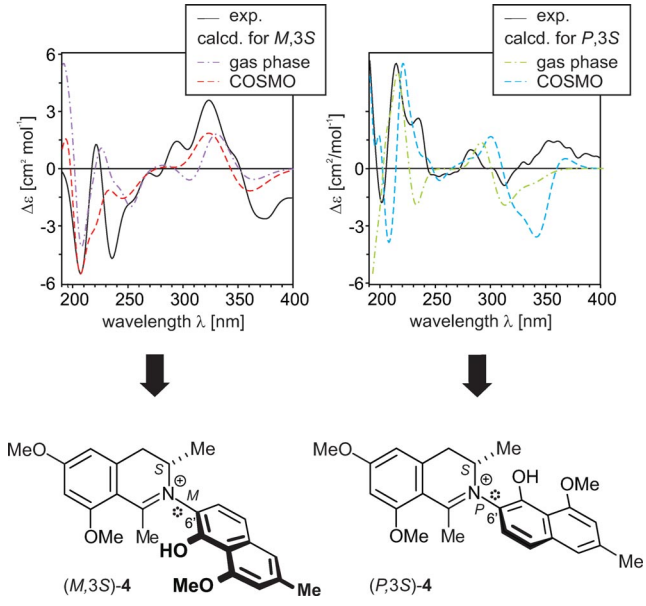

Figure 6. Elucidation of the absolute axial configuration of ancistrocladinium B (**4**) by comparison of its experimentally measured CD spectrum with curves predicted by TDB3LYP gas-phase and COSMO methods (methanol/water 1:1, ε = 56.52, refraction index 1.33).

3.3 Even More Demanding, but Sometimes Necessary: MRCI Approaches

In cases in which the elucidation of absolute configurations with TDDFT has been difficult or even impossible, either due to an ambiguous UV shift or because comparison of the calculated CD spectrum with the experimentally measured one has not given sufficient agreement, multireference CI (MRCI) approaches may be helpful. Generally, MRCI calculations require far larger computational resources than TDDFT methods. Nevertheless, the combined DFT/MRCI approach[41] seems to be an advantageous exception, because it uses a combination of Kohn–Sham's technique with the MRCI, together with an iterative procedure to find the active space of the molecule. The calculation times are thus reduced to a certain degree, making the computation of the excited states possible even for larger molecules.[75] Another option is the MRCI package in the ORCA software package, which utilizes a complete active space (CAS). The difficulty here is that the definition of the CAS is not trivial, because it differs from molecule to molecule. It thus has to be found by trial and error in each case.

3.3.1 A Difficult Case Requiring Higher-Level Methods: Knipholone Anthrone (5)

Knipholone anthrone (**5**, Figure 7) is one of the best-known representatives of the young class of naturally occurring 4-phenylanthraquinones, first isolated in 1993 by Dagne and Yenesew from the Ethiopian torch lily, *Kniphofia foliosa*,[76] and later from several other *Kniphofia* and *Bulbine* species.[77] Its absolute configuration at the rotationally hindered biaryl axis was investigated by quantum chemical CD calculations[78] based on semiempirical methods, which, in combination with some experimental difficulties, led to the (wrong) assignment of an *M* configuration for (+)-knipholone anthrone. A renewed, more in-depth investigation of the absolute configuration of **5**, based on advanced, higher-level methods, was thus inevitable.[79] The DFT-based conformational analysis revealed substantial differences in the arrangement of the main chromophores of knipholone anthrone (i.e., the anthraquinone portion and the acetophenone ring) in relation to the semiempirical results, providing only one major conformer for excited states calculations. The DFT/MRCI (BHLYP/SVP) method appeared to be more exact in reproducing the CD signals of (+)-**5** than TDDFT calculations, which were not able entirely to simulate some important CD features. In particular, the CD split at 290 nm, which is an exciton couplet from the interaction between the acetophenone and anthrone chromophores, hinting at a "positive chirality" for **5** [i.e., corresponding here to (*P*)-**5**], was simulated only by the DFT/MRCI calculations (Figure 7). Finally, comparison of the CD spectra calculated for the *M* and the *P* atropo-enantiomers of **5** with the experimentally measured curve for (+)-knipholone anthrone showed that the naturally predominant, dextrorotatory form of knipholone anthrone has the *P* configuration.[79]

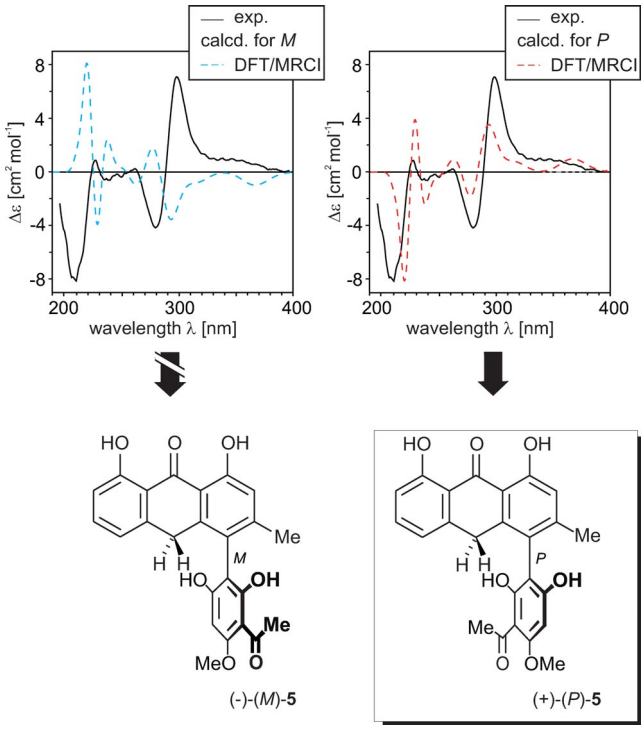

Figure 7. Revised assignment of the absolute axial configuration of (+)-knipholone anthrone (**5**) by DFT/MRCI calculations.

3.3.2 Distinction between Diastereomers: Xylogranatine F (6)

Another recent example in which TDDFT revealed major difficulties was that of xylogranatine F (**6**).[80] As can be seen in Figure 8, the theoretical simulation of the region

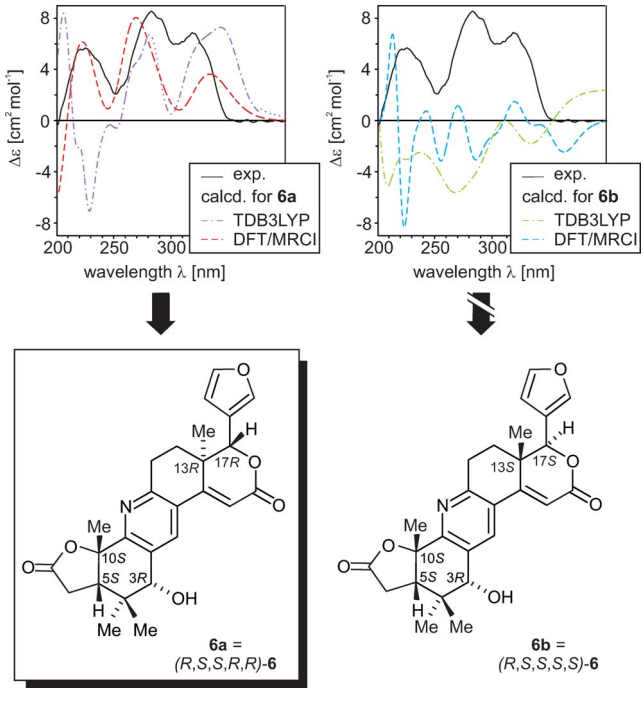

Figure 8. Assignment of the absolute axial configuration of xylogranatine F (**6**) by TDDFT and DFT/MRCI calculations.

below 250 nm failed to reproduce the experimentally measured CD spectrum: the calculated Cotton effect is opposite to the measured one. In combination with NMR investigations, these results were, nonetheless, still sufficient to elucidate the absolute configuration of the naturally occurring xylogranatine F (**6**) as 3*R*,5*S*,10*S*,13*R*,17*R*. For a further solid confirmation, DFT/MRCI calculations were performed, yielding a nearly perfect fit of the theoretical spectrum for (*R*,*S*,*S*,*R*,*R*)-**6** with the measured curve.

3.4 Conclusion: Semiempirical Methods, DFT, or MRCI?

The tremendous progress in computer technologies and computational chemistry increasingly permits reasonably accurate and, at the same time, relatively inexpensive calculations of CD spectra for sufficiently large molecules through the use of high-level methods such as TDDFT or MRCI for determination of their absolute stereostructures. The semiempirical calculations generally show good results in determining absolute configurations of simple axially chiral biaryl systems, although TDDFT calculations are still preferable even in these cases, because they provide significantly higher accuracies at moderate computational costs. Nonetheless, there are a few examples, such as those of knipholone anthrone (**5**) or xylogranatin F (**6**), for which TDDFT calculations are not sufficient to reproduce the experimentally measured spectra, so that the MRCI approach is an advantageous – and sometimes even essential – alternative. The results obtained for gephyromycin (**2**), neoechinulin A (**3**), and knipholone anthrone (**5**) clearly show the necessity of good and reliable conformational analysis. For this a scan of the potential energy surface by DFT methods is recommended. In general, B3LYP/6-31G* has proven to be a reliable method, and the subsequent excited states calculation on the structures thus found by TDB3LYP and SVP or TZVP have yielded reasonably accurate UV and CD spectra. An important aspect is the inclusion of solvent effects by application of, for example, COSMO calculations, which appear particularly important for charged molecules. In the future, recently developed functionals such as the double hybrid B2PLYP[81] and dispersion corrected density functional methods[82] should become increasingly commonly considered for conformational analyses and CD calculations.

In summary, comparison of calculated and experimentally measured CD spectra provides an excellent and efficient analytical tool for the assignment of the absolute configurations of chiral compounds of virtually any structure. In many cases it is even the only possible means to elucidate the absolute configuration of a newly isolated and/or synthesized compound, in particular if novel, unprecedented structures are concerned. For a few further selected

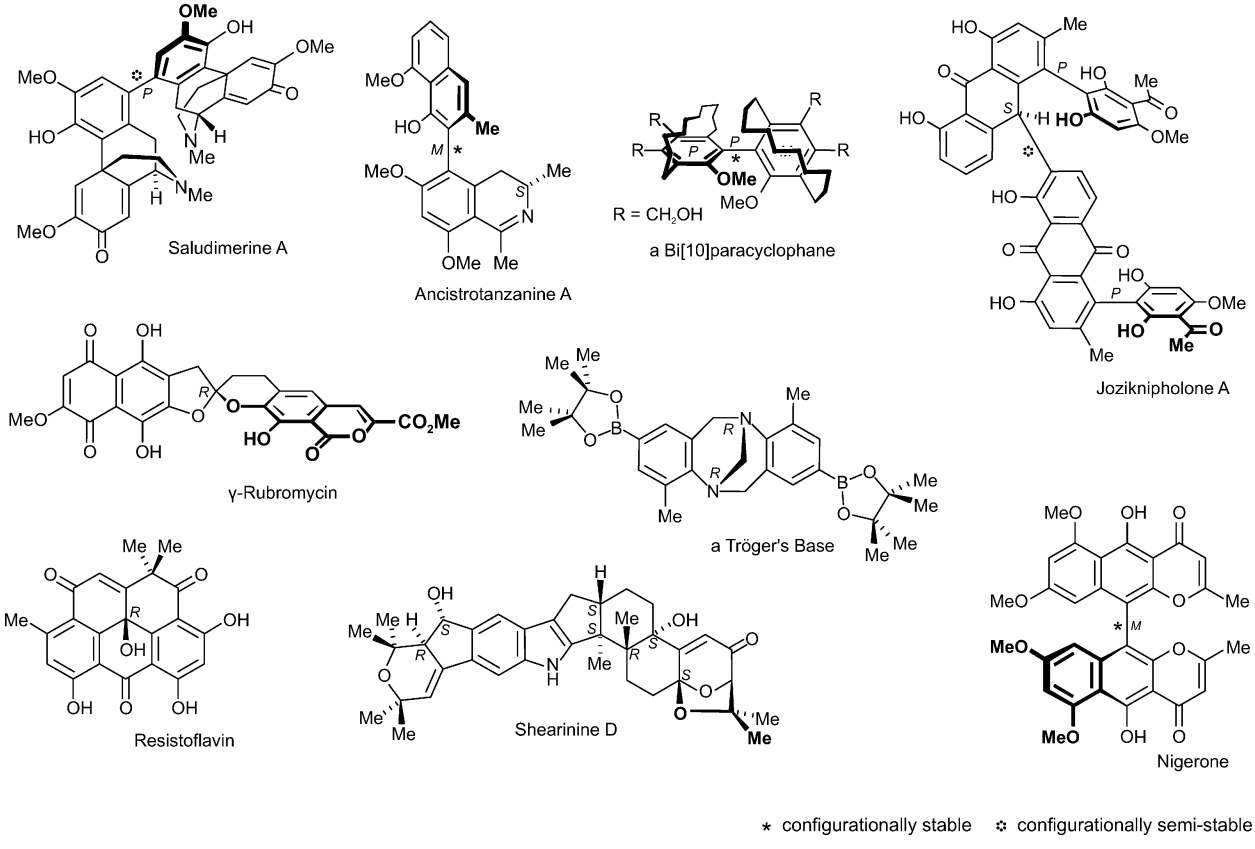

Figure 9. Further selected examples of structurally diverse compounds with different types of stereogenic elements, the absolute configurations of which were established by quantum chemical CD calculations (saludimerin A,[83] ancistrotanzanin A,[84] bi[10]paracyclophanes,[56] joziknipholone A,[85] γ-rubromycin,[86] a Tröger's base derivative,[87] resistoflavin,[88] shearinine D,[89] nigerone;[90] for other examples see ref.[91]).

examples established in the authors' group more recently, involving cases of stereogenic centers (both *C*- and *N*-centered), axes (configurationally stable or semi-stable, sp^2–sp^2 or sp^2–sp^3, *C*,*C*- or *C*,*N*-coupled), or "planes", or combinations thereof, see Figure 9.

Supporting Information (see also the footnote on the first page of this article): Computational details, relative energies and population of the conformers of the compounds **2**, **3**, and **4**.

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