Absolute Configurational Assignment in Chiral Compounds through Vibrational Circular Dichroism (VCD) Spectroscopy

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Trends and perspectives of the IR/VCD chiroptical technique in configurational and conformational assignment of chiral compounds are illustrated with significant examples from literature reports within 2003-2008 period. The advantages, as well as inherent limitations of VCD as complementary or competing technique to the classical chiroptical methods are underlined.

Keywords: VCD spectroscopy, absolute configuration, ab initio DFT calculations

The determination of the absolute configuration is a major goal in stereochemical analysis. The main traditional methods for establishing absolute configuration include X-ray crystallography, synthesis of the target-molecule through a series of stereochemically controlled steps, optical rotation (OR) and electronic circular dichroism (CD).

Among these methods, only X-ray crystallography is an absolute method. Although straightforward and highly reliable, this method operates with single crystals, a requirement which is not easily met and often may be even precluded. In order to unambiguously determine the absolute configuration of the crystal, a „heavy" atom must be present in the molecule or must be incorporated into the molecule by derivatization, without alteration of the investigated chirality.

The stereochemically-controlled synthesis is prone to error if an unexpected reversal in stereochemistry occurs at any step and, in addition, is time- and effort-consuming.

Several rules or correlations have been established for relating the sign of the measured optical activity to the absolute configuration in a variety of structural motifs. In spite of their usefulness, such empirical methods should be carefully addressed since might be contaminated by incorrect assignments.

CD has been used as a relative method, based on chirality rules. Unfortunately, all these rules involve exceptions and this fact places some doubt on the results obtained thereby.

The CD exciton chirality method is claimed to be an absolute method in configurational assignment, being based on comparison between measured and calculated spectra. Still, the calculations are based on a model in which the location and the direction of the electronic transition moments have to be correctly assigned.

For carrying out ab initio calculations of the electronic CD spectra, the difficulties in describing electronically excited states of the molecules are still to be overcome.

Vibrational circular dichroism (VCD) became lately an increasingly popular method for the unambiguous assignment of absolute configuration in chiral molecules. The accessibility to VCD spectra greatly enhanced since FT-VCD instrumentation became commercially available (1997).

However, the real impetus came into play when a reliable structure-spectra algorithm based on ab initio density functional theory (DFT) has been developed [1]. Ever since, the continuous improvement in computational hardware and software extended the applicability of this methodology to ever larger molecules or to compounds containing atoms far beyond second row.

VCD is the extension of electronic CD into the infrared region, where fundamental vibrational transitions occur. It measures the difference in the absorbance of left-(LCP) and right-circularly polarized (RCP) infrared radiation for a vibrational transition. VCD has a number of advantages over all previous methods of absolute configuration assignment, but has some limitations as well. Like X-ray

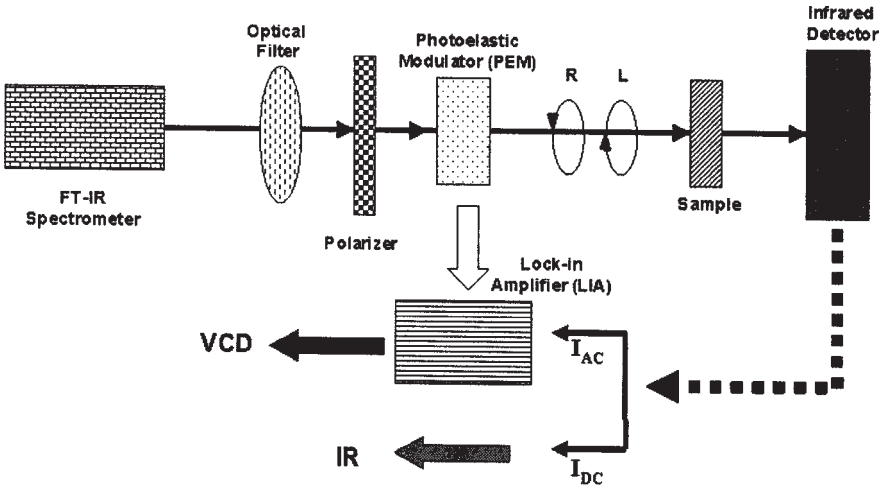

Fig. 1. Schematic representation of the block-diagram of FT-VCD spectrometer

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crystallography, VCD is an absolute not a relative method, but unlike X-ray analysis does not require the presence of a heavy atom in the molecule and is not restricted to single crystals. VCD spectra are recorded for neat liquid or solution in suitable solvents ($CDCl_3$, CCl_4, CS_2) and no derivatization of the molecule is needed prior to analysis.

The VCD method of analysis involves comparison of the experimentally measured VCD spectrum to the one calculated from ab initio quantum chemistry. If close agreement between the measured and calculated IR and VCD spectra is achieved, the absolute configuration is established by comparing the signs of the experimental VCD to the signs of the spectrum calculated for a particular choice of absolute configuration. Should these signs be the same, the absolute configuration is the calculated one; if the signs are reversed, the absolute configuration is the opposite of the calculated configuration.

Recently, specific applications and performances of the VCD technique have been presented in an international symposium, organized in Bucharest [2].

Methodology of experimental VCD measurements

The schematic representation of the block diagram of a FT-VCD spectrometer is given in figure 1. The IR radiation coming from a glower source passes through an interferometer which encodes each spectral point using a Fourrier frequency.

The interferometer radiation passes subsequently through an optical filter being linearly polarized in order to define a single state of polarization. The resulting IR beam passes through a photoelastic modulator (PEM) when sine-wave modulates the polarization between LCP and RCP states in the frequency range of tens of kilohertz. The beam then is propagated through the sample, which imposes an intensity modulation on the beam at the PEM frequency at Fourier frequencies in the spectrum where there is VCD. The intense IR beam is converted into an electrical signal by a cooled detector. This is processed by electronic devices being possible two electronic path-ways: i) the usual pathway for the measurement of the IR spectrum, and ii) other pathway that include a lock-in amplifier tuned to the PEM frequency, which demodulates the spectral information at the frequency leading to VCD spectrum.

Methodology of VCD calculations

The key of the successful application of VCD spectroscopy is the ability to accurately predict VCD spectra. The VCD spectra are always measured simultaneously with IR spectra and together, they provide more information than the VCD spectrum alone.

The prediction of the harmonic absorption spectrum requires firstly the calculation of the harmonic force field (HFF) from which the normal mode frequencies and coordinates are obtained and secondly the calculation of the atomic polar tensors (APT). Furthermore, the prediction of the harmonic VCD spectrum requires an additional task, namely calculation of the atomic axial tensors (AAT).

Ab initio calculations of HFFs, APTs and AATs are most accurately and efficiently carried out using analytical derivative (AD) methods, together with perturbation dependence (PD) basis functions. The practical options for caring out the calculations are: i) Hartree-Fock (HF) / self-consistent field (SCF) theory; ii) second-order Moller-Plesset perturbation theory (MP2); iii) density functional theory (DFT). In terms of relative accuracy the order is HF/SCF<MP2~DFT. In terms of computational cost, HF/SCF~DFT<MP2. Thus, DFT is the most cost-effective of the three methods.

The calculation of DFT HHFs, APTs and AATs using AD methods together with PD basis sets has been implemented within the GAUSSIAN program system. While HFFs and APTs were implemented in the early 1990s, AATs were implemented in 1996. The capabilities are now available in GAUSSIAN 98 updated by now to GAUSSIAN 03 version.

The second step in VCD analysis is to assess the conformational flexibility and to determine which conformers are significantly populated under the experimental measurements conditions. To identify low-energy conformations, a conformational search can be carried out at the molecular mechanics level, with software such as HyperChem (Hypercube, Gainesville, FL), Spartan (Wavefunction, Irvine, CA), Macro-Model (Schrödinger, Portland, OR), Irsight II (Accelrys, San Diego CA) or Confort (Tripos, St. Louis, MO). For molecules with few conformers, it is often beneficial to calculate the optimized conformers and energies at a semiempirical level (PM3 or AM1) in order to identify the starting conformations for DFT calculations.

For identification of dominant solution conformations, the observed IR and VCD spectra are compared with overlays of the calculated spectra for a group of low-energy conformers. Based on the calculated relative energies for conformers (usually within 1 kcal/mol above the lowest energy conformer), the fractional Boltzmann populations at the measurement temperature is calculated:

$$\frac{N_i}{N_0} = \exp(-\Delta E_i / RT) \quad \sum_i N_i = 1$$

N_0 = population of the lowest energy conformer

N_i = population of conformer i

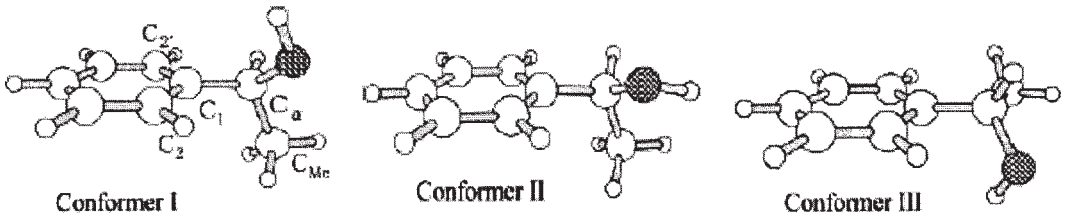
Composite IR and VCD spectra are generated by weighting with Boltzmann populations and are afterwards compared with their experimental counterparts. Such comparison allows identification of the dominant conformations in solution, besides the absolute configuration. This is one of the major advantages of the VCD technique over X-ray analysis, the latter providing only the lattice conformation.

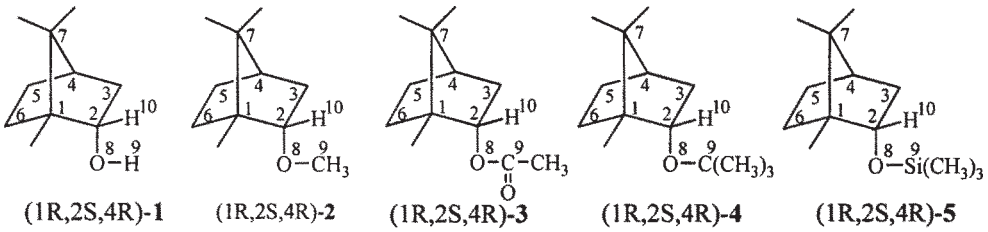
When large deviations are found in comparing composite calculated spectra with experimental spectra, the presence of additional conformations and/or unanticipated solvent effects should be explored. Such events are usually met when molecules prone to hydrogen bonding or other strong intermolecular associations are investigated. Several procedures for overcoming such difficulties, recently described in the literature, are presented in the following.

Matrix-Isolation Infra-red and Vibrational Circular Dichroism (MI-VCD)

When a chiral molecule has several conformers and is capable of strong intermolecular interactions, interpretation of its VCD spectrum is far from straightforward. The spectra of either neat liquid or solution in polar solvents present broad, featureless signals, with low information content. The theoretical modeling of VCD spectra is also more complicated and less accurate, since the intermolecular interactions and/or the solvent effects should be taken into account. Under these conditions, comparison between experimental and calculated VCD spectra for assigning absolute configuration is difficult, unreliable or even completely impossible. The matrix-isolation procedure successfully solved the configurational assignment in two simple chiral compounds, namely 1-phenylethanol [3] and 2-amino-1-propanol [4].

Three conformers (I-III) were found by DFT calculations for (S)-1-phenylethanol. The calculated IR spectrum of the





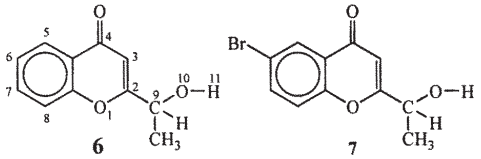
most stable conformer I reproduced very well the Ar matrix-isolated IR spectra recorded at 12 and 33 K. The spectra of diluted solutions in non-polar solvents (CCl_4, CS_2) were in excellent agreement with conformer I with a trace amount of conformer II. A composite spectrum of dimmers stabilized by intermolecular H bonding reproduced well the VCD spectrum of the neat liquid sample. Such a detailed examination allowed a very interesting observation: two key-VCD bands were found, which are insensitive to both conformational changes and intermolecular H-bonding in concentrated solutions. These bands appeared at 1011 and 901 cm^{-1} in (-) (S)-1-phenylethanol, and are due to the C=C stretching and CH bending (in plane) of the phenyl ring. Such key-bands are most useful in assigning absolute configuration even in condensed phases (liquid state) [3].

Chemical derivatization methodology

Although it was stated in the introduction that VCD technique does not require prior derivatization of the investigated compound, in some instances a derivatization step is beneficial.

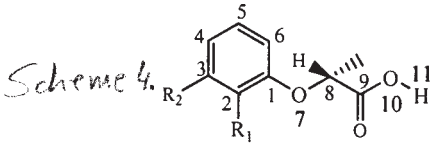
Broadly speaking, the application of chirooptical methods in conjunction with DFT calculations becomes increasingly unreliable as the number of populated conformations increases. A strategy for diminishing the conformational flexibility via chemical derivatization was proposed [5]. The basic idea is to add a bulky group to the molecule of interest, without affecting its absolute stereochemistry, in such a way as to diminish the number of accessible conformations. It has been demonstrated that derivatization of the OH group of *endo*-borneol **1** leads to conformational rigidification and simplifies the chirooptical spectroscopy. Indeed, while DFT calculations predicted equilibrium of three conformers for borneol **1**, the number of stable conformations is reduced to two for the methyleter **2** and only one stable conformer is predicted for acetate **3,** t-buthylether **4** and trimethylsilyl derivative **5**. The agreement between predicted and experimental spectra for derivatives **3-5** was excellent, confirming the benefit of rigidification.

A similar strategy has been used in assigning the absolute configuration to 2-(1-hydroxyethyl)-chromen-4-one **6** and its 6-bromoderivative **7** [6]. Both alcohols have been acetylated and the IR, VCD spectra of the acetates were examined in the C=O stretching modes alone. The excellent agreement between experimental and calculated spectra allowed the assignment R-(-)/S-(+) for **6** and R-(+)/S-(-) for **7**. It is interesting to note that the previous X-ray crystallographic analysis gave the same assignment for compound **7** (possessing a heavy Br atom) but the opposite assignment for **6**. This is one of the (rare) cases in which the X-ray crystallography gave a wrong result, corrected afterwards due to VCD technique.



Derivatization has also been used in absolute configuration determination of chiral carboxylic acids. At the concentrations used for VCD measurements, mono-carboxylic acids are substantially dimerized and the analysis of their spectra requires calculations for an equilibrium mixture of monomer and dimmer species. The derivatization into methyl esters prevents aggregation, enabling the analysis of the experimental data on the basis of isolated molecule calculations. The results reported in the class of α-aryloxypropanoic acids (chiral herbicides) are most instructive [7,8]. The chiral acids **8a**, **b** were separated into enantiomers and converted into the

Scheme 4.



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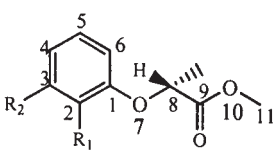
a: R_1=Cl, R_2=H
b: R_1=H, R_2=Cl



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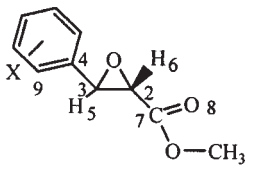


(+)-(2S, 3R) **10** X = *o*-Br
(+)-(2S, 3R) **11** X = *p*-CH_3
(+)-(2S, 3R) **12** X = *m*-F

corresponding methyl esters **9a**, **b**. The absorbance and VCD spectra for both enantiomers of acids **8** and esters **9** were measured in $CDCl_3$ and CCl_4, respectively. The ab initio DFT calculations used B3LYP functional with 6-31G* basis set, choosing arbitrarily (R) configuration.

The geometry-optimization gave the same number of stable conformers in each acid/ester pair: four conformers in **8a**/**9a** pair and five in **8b**/**9b** pair. However, comparing the population-weighted absorbance and VCD spectra with the experimental data, the results for acids and for esters were quite different. Notable differences appeared between experimental and predicted absorbance spectra for acids **8a**, **8b**; also, the predicted VCD spectra for (R)-configuration did not match the experimental VCD of neither (+) nor (-) enantiomers of **8a**, **8b**. On the contrary, the experimental and predicted absorbance spectra of esters **9a**, **9b** agreed very well, and the VCD spectra of (+) **9a**, (+) **9b** enantiomers matched those calculated for (R)-configuration [7].

The same derivatization procedure was used in configurational assignment of *trans*-phenylglycidic acid derivatives, based on a VCD study of the corresponding methyl esters **10**-**12** [9].

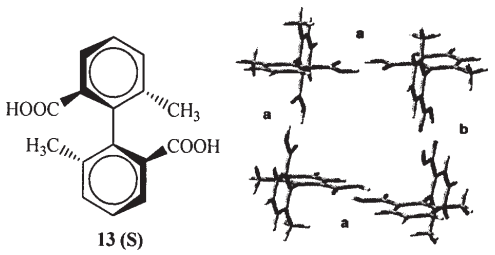
Isotope labeling

Absolute configuration assignment by VCD spectroscopy can be done via isotopic substitution which leads to an isotopic difference spectra. The IR and VCD spectra are in this case computed as a difference between individual VCD and IR spectra, namely a difference of parent and isotopic spectra. This difference spectrum is accurately reproduced by density functional theory calculations. For instance, the functionalized nonamethoxy cyclotriveratrylene was isotopically labeled both with ^2H and ^{13}C at the ring methylenes [10]. Comparison between the intensity scales for the IR, VCD difference spectra relative to those of the parent structures reveals an intensity difference of approximately four times smaller. The agreement between both IR and VCD difference spectra determined for the measurements and the calculations supports the presence of a single dominant conformer. Analogous difference spectra were observed for the deuterium isotopomers. Again, both the match between calculated and observed IR and VCD as well as their respective isotopic difference spectra is very close. The effect of the selective isotopic substitution on the IR and VCD spectra is somewhat larger for deuterium substitution than it is for ^{13}C substitution, although overall relatively minor changes were observed compared to the IR and VCD of the parent isotopomer. The degree of agreement for the deuterium substitution is qualitatively as good as that observed for the ^{13}C-substitution. In the case of isotopic substitution with ^{13}C at chiral centres, enhanced selectivity is expected for IR and VCD difference spectra from vibrational modes that are structurally associated with the chiral centre of the molecule [10].

Self-assembling of chiral molecules in solution (supramolecular structures)

A reversal in the derivatization strategy, in which aggregation is avoided, may be identified in the first VCD study on a supramolecular species in solution [11]. Indeed, the paper reports on self-assembling of the chiral molecules of 2,2'-dimethylbiphenyl-6,6'-dicarboxylic acid **13** into cyclotetramers, through hydrogen (H)-bonded $(COOH)_2$ moieties.

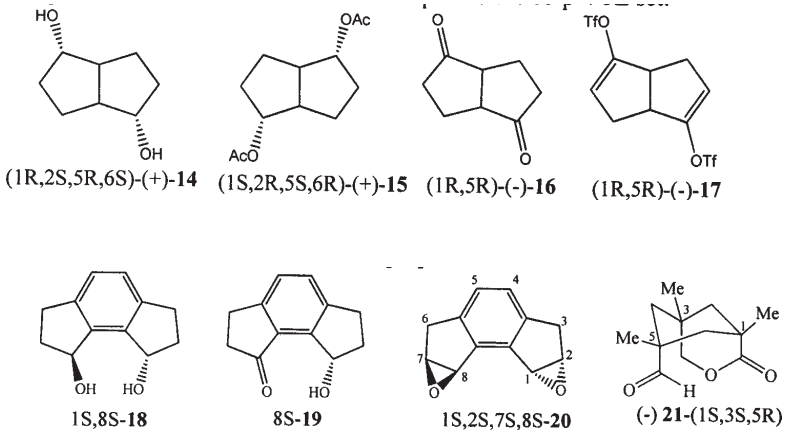
The experimental IR and VCD spectra of optically pure (S)(+)-**13** were recorded in concentrated $CDCl_3$ solution, in order to favor oligomerization. The DFT calculations started with prediction of IR spectra for an aggregation-model, namely the benzoic acid dimmer, involving two equi-energetic tautomeric forms. In the conformational analysis of the cyclotetramer (S-**13**)$_4$, structures of six different conformers, involving two energetically non-equivalent tautomers (denoted **a** and **b**), have been built and optimized at B3LYP/6-31G* level. It is interesting to note that ordering of the conformers by relative energies and by relative free energies was different. When comparing IR and VCD spectra, the best qualitative agreement between theory and experiment was obtained for the conformer with the lowest **free** energy (labeled **aaab**, with C2 symmetry), while all the others exhibited poor agreement. However, the conformer with the lowest **relative** energy (labeled **aaaa**, with D4 symmetry) coresponds to the structure of the (R-**13**)$_4$ tetramer identified in solid state by X-ray crystallography (distortion from D4 symmetry is presumably caused by crystal-packing forces) [11]. In other words, although the supramolecular structures had the same degree of association in solution and in solid state, their conformational assembly was different. This work demonstrates the potential utility of VCD spectrometry in the field of supramolecular chemistry.



13 (S)

VCD spectroscopy was also used to describe the intermolecular hydrogen bonding interaction between solute-solvent molecules. This was exemplified on the hydrogen bonded achiral NH_3 ("solvent" molecule) to hydroxyl group in a chiral conformation of the benzoyl-benzoic acid ("solute" molecule) [12]. Six cases were distinguished regarding the perturbation of the VCD signals, ranging from no or very small changes in the rotational strengths of solute modes (case **A**) to changes of sign of rotational strengths (case **B**), changes in magnitude (case **C**), nonzero rotational strengths for modes of the achiral solvent ("transfer of chirality", case **D**), large frequency shifts accompanied by giant enhancements of the IR and VCD intensities of modes involved in hydrogen bonding (case **E**), and emergence of new peaks (case **F**). The VCD rotational strength output is important when the angle between the electric and magnetic transition dipole moments is far from 90° because only the "robust modes" are used for the determination of absolute configuration.

Chiral C_3-symmetrical discotic molecules, based on trialkybenzene-1,3,5-carboxamide, form supramolecular polymeric stacks with a right-handed helical structure in solution due to intermolecular hydrogen bonds. The N-H stretching vibration at 3235 cm^{-1} and the carbonyl stretching vibration at 1642 cm^{-1} indicate the presence of hydrogen-bonded species in solution, and correspond with the values measured in the solid state for (R)-stack, 3225 and 1636 cm^{-1}, respectively. Furthermore, the N-H stretching vibration at 3235 cm^{-1}, measured in decahydronaphthalene, corresponded nicely to the value of 3242 cm^{-1} that was previously reported for (S)-isomer when performed in hexane (at 10^{-4} M) [13]. The formation of a right-handed



helical structure, which was concluded from the CD measurements, was further studied by VCD spectroscopy, since the preferred handedness of the stacks implies that the hydrogen-bonded amide groups in these stacks also must have a chiral orientation. Different concentrations were used in order to obtain the best signal-to-noise value and to observe the VCD signals, especially the carbonyl stretching vibration, which presents a (+,-,+) pattern [14]. These patterns were observed even at low concentration ($1.6x10^{-3}$ M). VCD spectroscopy combined with DFT calculations resulted in a R-structure for the stacks that is in agreement with the structure determined by X-ray for a related benzene-1,3,5-tricarboxamide[15]being concluded that in the stack, there is a preference for a chiral and nonplanar orientation of the carbonyl groups, which are involved in the hydrogen bonding interaction.

Fragmentation of large chiral molecules

For many chiral molecules of pharmaceutical interest or natural compounds, calculations on the entire structure are prohibitive. In such cases, fragments of the molecule that include the chiral centers and relevant substituents are used for calculating the IR and VCD spectra. It is obvious that the success of the configurational assignment crucially depends on the cutting ability and simulation of inter- or intramolecular interactions expected to occur with/in the whole molecule. For example, a cyclohexapeptide-cyclo (Phe-^{D}Pro-Gly-Arg-Gly-Asp) has been used as a test of density functional theory level predictions of spectral intensities for a constricted conformation in VCD and IR spectra. Stepwise full DFT simulation of spectra was performed for various sequences with the same backbone geometry but based on: i) solely Gly residues, ii) Ala substitution except Gly and Pro, and iii) complete sequence with side-chains. The Ala model for the cyclohexapeptide gives the clearest representation of the amide VCD band. Nevertheless, the final data favors a mixture of structures that fits to experimental sign pattern for the amide band [16].

Recent applications in absolute configuration assignment

Several authoritative reviews have been published so far on the absolute configuration determination in solution using VCD[1,17-22].

The purpose of the present report is to sum-up the major contributions in the field issued from 2003 till 2008. The classification of the material follows the major trend detected, namely an extension from central chirality towards more complex types of molecular chirality (axial, planar, helical, globular, etc). The increase in diversity of the constituting atoms and/or in the size of the investigated molecules is also illustrated. Whenever possible, particular stereochemical problems or special approaches are briefly commented.

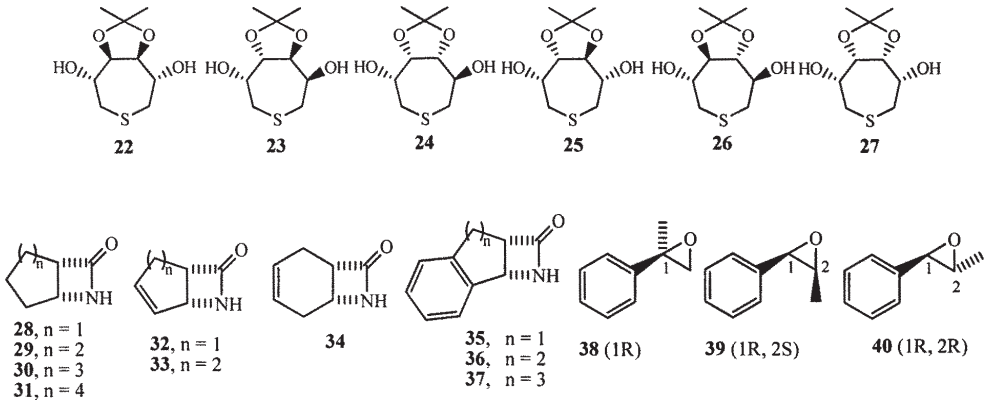
Compounds with several chiral centers

The absolute configuration in compounds containing only one stereogenic center are determined on an almost routine basis. Nevertheless, compounds with several chiral centers have been fully assigned as well. Prior information on the relative configuration by other techniques is helpful, reducing thereby the number of computed isomers. The strategy consists in enumeration of all possible optically active diastereomers. Conformational analysis of each stereoisomer provides the significant conformers, their relative free energies and the corresponding equilibrium populations. The Bolzmann-weighted IR and VCD spectra are compared one by one with the experimental spectrum of the enantiopure isomer. A reliable assignment means not only a good agreement between experimental and theory for one diastereomer, but also a much poorer agreement for all the others. Several examples are presented in the following, underlying special features or observations from the original papers.

The bicyclo [3.3.0] octane derivatives **14**-**17** are interesting intermediates in asymmetric synthesis of enantiomerically pure natural products and chiral ligands for asymmetric catalysis [23]. The absolute configurations of chiral centers (given in brackets) were established by VCD. For symmetry reasons, the number of calculated diastereomers was four for **14** and **15**, and only one for **16** and **17**.

The conformational landscape was firstly explored by molecular mechanics and subsequently optimized by DFT calculation. The simulation of IR, VCD spectra was performed with B3LYP functional using 6-31G* and cc-p VTZ basis sets. The correlation factors between dipole and rotational strengths and the experimental values were rather low for all compounds **14 – 17**, not unexpected for molecules of this size. However, these quantitative comparisons were not decisive, once a good fit between experiment and calculation was found for one stereoisomer, whereas all the others gave a poor fit (case of compounds **14** and **15**). Focus on the most intense peaks was practiced when more detailed features in the spectra disagreed between experiment and theory (case of the compound **17**). For each molecule, the 6-31G* basis set was sufficient for configurational assignment and no large differences were observed with respect to the cc-p VTZ set.

Under a similar treatment, compounds **18-20** with a rigid 1,8- disubstituted as-hydrindacene skeleton have been



assigned [24]. The results obtained by VCD were found to be in agreement with CD measurements and/or predictions based on the asymmetric method used in the synthetic route.

Lactone **21** has been designed as candidate for the study of synergistic effects in the interactions between adjacent functional groups upon the reactions of other neighboring groups. Utilization of this synergistic effect required the optical resolution and knowledge of the absolute configurations of the chiral centers in the molecule [25].

Racemate **21** has been resolved by chiral HPLC into (+) and (-) enantiomers. The UV and CD spectra of (+) **21** indicated very week absorption bands, discouraging this approach in configurational assignment. Application of VCD technique unambiguously established the configuration (1S, 3S, 5R) to (-) **21**. The DFT calculation predicted two stable conformers of **21** with opposite orientations for the 5-formyl group, one prevailing. In discussing the corresponding predicted VCD spectra, the authors made an interesting comment: conformations that differ significantly at the center(s) of chirality often have opposing VCD intensities that tend to diminish the intensities of VCD bands. This fact increases the difficulty of obtaining an accurate ab initio representation of the spectrum. However, in favorable cases of rigid molecules with only one significantly populated conformation in solution (such as **21**), very close agreement between experiment and theory can be routinely achieved [25].

Polyhydroxylated thiepane derivatives are of the great therapeutic interest as glycosidase inhibitors. In searching new structures expected to possess optimized inhibitory activity, the target molecule 3,6-dihydro-4,5-O-isopropylidine-thiepane has been designed [26]. This compound with four chiral centers presents six diastereomers two meso **22**, **27** and four enantiomeric pairs of chiral **23**, **24**, **25** and **26**. Since compounds (±) **23**, (-) **25**, (±) **26** had already been described, only (+) **24**, (-) **24**, (+) **25**, **22** and **27** had to be prepared and characterized. For overcoming the difficulty of obtaining precursors with the correct stereochemistry and for reducing the synthetic efforts, the authors adopted the following strategy: a library containing all the individual stereoisomers was synthesized from commercially available precursors, and then a two-step chromatographic procedure was performed for isolation of library members. A first step over non-enantioselective stationary phases provided the six diastereomers and a second step over enantioselective phases gave the individual enantiomers of the four chiral members. The configurational assignment was performed in the enantiomeric pair (+)/(-) **24** by VCD. The conformationally averaged B3LYP/TZ2P VCD spectrum calculated for (3R, 4S, 5R, 6R) configuration was in good agreement with the experimental spectrum of (+) **24**.

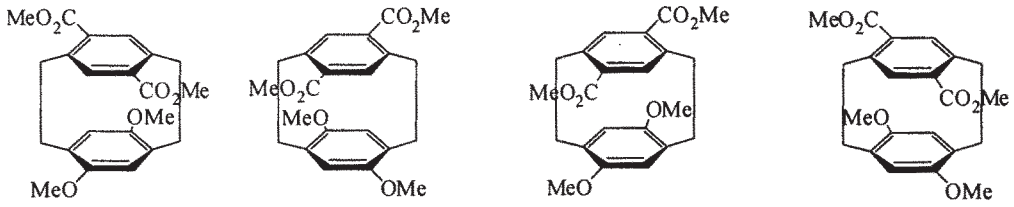
A highly enantioselective enzymatic procedure provided simultaneously cyclic β-aminoacids and bicyclic β-lactams enantiomers, possessing two chiral centers. The absolute configuration and conformation of a series of ten β-lactams (**28**-**37**) were successfully established by comparing experimental and computed VCD spectra with DFT calculations at BPW91/6-31G(d,p) and B3LYP/6-31G(d) levels. The comparison allowed a reliable population analysis of the ring conformers and detected a cyclic H-bonded dimeric structure in the spectra of **32**. The series of β-lactams was found to be homochiral, in agreement with the expected stereochemical demands around the chiral centers in the enzymatic process [27].

Studies of small synthetic molecules continue to contribute to the refinement of theoretical approach in VCD spectroscopy, as illustrated for the methyl-substituted phenyloxiranes **38**-**40** sharing 1-R configuration [28]. Geometry optimization and calculation of the IR and VCD spectra were performed at B3LYP level using three different basis sets: 6-31++G**, aug-cc-pVDZ and aug-cc-pVTZ. Comparison between calculated spectra for each compound disclosed differences among these three basis sets, which were commented upon. Comparison between isomers, based on simulations with the largest basis set, allowed the configurational assignment at each chiral center. Changes occurring both in structures and in IR, VCD spectra disclosed the substituent effects on the oxirane ring.

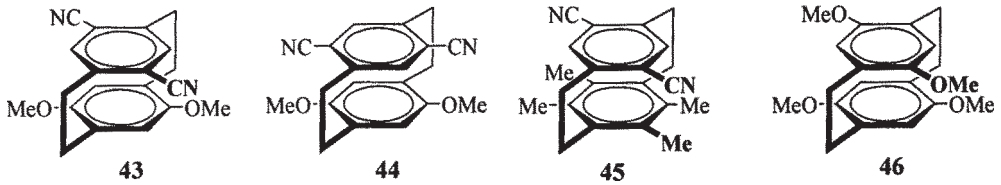
The concept of „vibrational chirality probe" is related to assigning the absolute configuration of a single chiral center in molecules with several such centers. It is based on a characteristic VCD peak, whose sign solely reflects the absolute configuration of the single chiral center. In the VCD spectra of a series of six methyl pyranosides, a band near 2840 cm^{-1} was found to be positive for R-configuration at C-1 (α-anomers for D-sugars and β-anomers for L-sugars) and negative for S-configuration. This band was assigned to the symmetric methyl stretching in the „probe" methoxy group [29]. This approach could be particularly useful for large or flexible molecules (including carbohydrates), since theoretical calculations are generally difficult in these cases.

Molecules with planar chirality (cyclophanes)

A considerable interest has been paid lately to a variety of substituted cyclophanes because of their planar chirality, which was found to behave quite differently from conventional central chirality in asymmetric reactions, catalysis and host-guest interactions. The method of choice in assigning absolute configuration in cyclophanes is the CD exciton chirality method. However, it was found that the exciton chirality does not give the correct absolute



$(4R_p;12R_p)$ (-) $(4S_p;12S_p)$ (+) **41** $(4S_p;12R_p)$ (+) $(4R_p;12S_p)$ (-) **42**



43 **44** **45** **46**

configuration for some donor-acceptor cyclophanes. This failure originates in the intramolecular charge-transfer (CT) interactions and/or deformation of the aromatic rings, leading to significantly distorted transition moments.

Recently, successful assignment of absolute configuration of donor-acceptor [2.2] paracyclophanes **41** and **42** was achieved by VCD/DFT method [30]. The DFT calculation performed at B3LYP/6-31G(d) level gave six optimized conformers for both **41** and **42**, in which the orientation of the methoxy and methoxycarbonyl substituents play an important role in the stability of each conformer. The theoretical IR spectra enabled the recognition of the major bands, while the theoretical VCD spectra allowed the assignment of the absolute configuration in each enantiomeric pair +/- **41**; +/- **42**, displaying excellent agreement between experimental and calculated spectra.

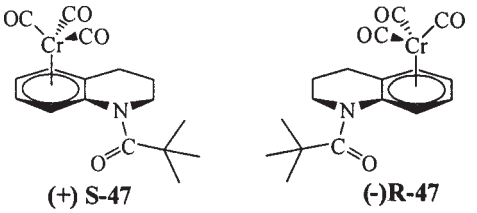
The first comparative study of the experimental and simulated chirooptical properties (optical rotations, vibrational and electronic CD spectra) of paracyclophanes with and without donor-acceptor interactions gives an interesting perspective on the bias performance/limitations of the methods involved [31]. The compounds under investigation were the CT cyclophanes **43**-**45** and the non-CT cyclophane **46**.

The concluding remark of the paper is that one should be cautious in assigning the absolute configuration of chiral cyclophanes by comparing the theoretical and experimental VCD spectra, since disagreement in signal intensity and pattern is often observed in several transitions. Better performance was obtained with CD (when appropriate), compared to specific rotation and VCD, in terms of computational time and accuracy [31].

The determination of absolute configuration in organometallic compounds is straightforward *via* X-ray crystallography. However, when X-ray diffraction is not practicable, VCD offers a viable alternative, as recently illustrated for the enantiomers of the planar chiral arene chromium tricarbonyl complex **47** [32].

The racemate has been resolved by chiral HPLC and IR, VCD spectra were recorded in $CDCl_3$ (with precautions to minimize chemical and photochemical decomposition). The DFT calculations were carried out with B3LYP and B3PW91 functionals, using 6-31G*, TZVP and 6-311++G (2p,2d) basis sets. The goal was to examine the dependence of the reliability of the calculated VCD spectra on the basis set and density functional used, an issue not studied for the organometallics until this publication.

The predicted VCD spectrum of S-**47** using B3PW91 functional with 6-311++G (2d,2p) basis set was in excellent agreement with the experimental VCD spectrum of (+)**47**, leading unambiguously to (S)-(+) assignment. However, the authors draw attention that extension of such studies is required if complexes of second- and third-row transition metals are to be assigned. Otherwise, the optimum functional and basis set found in this report might be restricted to first-row transition metals, such as Cr.



(+) S-47 (-)R-47

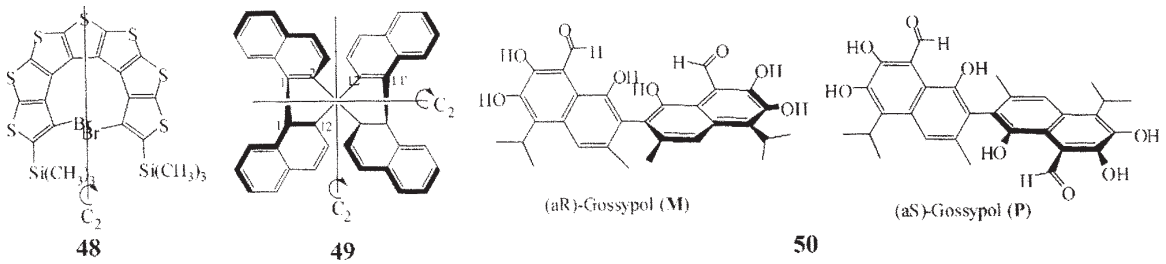
Absolute configuration of molecule with chiral axes, helical chirality or globular chirality; macrocycles

The absolute configurations of two large molecules that possess chiral axes have been determined by VCD: the annelated heptathiophene **48** (a helical molecule with C-2 symmetry) and a π-conjugated chiral derivative of o-tetraphenylene (with D-2 symmetry) [33].

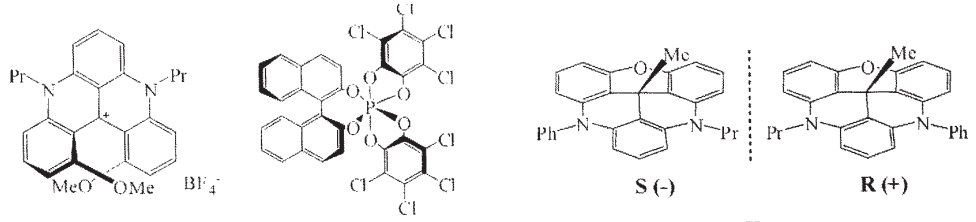
The DFT calculations at the B3LYP/6-31G* level provided almost perfect band-to- band fit with the experimental spectra. The superb agreement easily provided R-configuration for (-) **48** and (+) **49**.

It is worth mentioning that previous tentative of absolute configuration assignment in **48** by X-ray crystallography was hampered by the difficulty in growing suitable crystals. The X-ray structure for **49** has been obtained, but the data were not complete enough for determination of absolute configuration. The CD spectra have been measured for both **48** and **49**, but conjugation of the cromophores precluded the application of the exciton coupling model in order to determine the absolute configuration. Therefore in this case, the DFT/VCD procedure was indeed a simpler and highly reliable alternative.

An experimental detail related to the amount of the sample required in experimental measurements is also relevant: the sample of (-) **48** was as small as 3 mg, of 84 ± 5% ee (for reducing the VCD noise because of the small sample, an acquisition time of 18 h was required).



48 49 50



51 52 53

An interesting compound of plant origin, gossypol **50** (an axial chiral compound) has been intensively studied due to its pharmacological properties [34]. The compound is rather unstable and presents tautomeric equilibria in solution: in $CDCl_3$ solution, only the aldehyde tautomer is present, but in other solvents the aldehyde and lactol tautomers are in equilibrium. The VCD spectra in $CDCl_3$ for the two enantiomers are near mirror images. The excellent agreement between the observed IR and VCD spectra and the ab initio calculation at B3LYP/6-31G* level established P absolute configuration for (+) gossypol and M for (-) gossypol (the physiologically active enantiomer). The assignment agrees with the previous one, based on coupled oscillator theory applied to the electronic CD spectrum. Other structural details have also been established: two different orientations of the isopropyl group relative to the naphthyl plane as well as intramolecular hydrogen-bonded forms (in agreement with data from X-ray structure and NMR studies).

The first application of VCD in the study of chiral helical derivatives reports on dimethoxyquinacridinium salt **51**. Due to strong steric repulsion between the methoxy substituents, the molecule adopts a twisted helical conformation typical of helicene derivatives. The resolution of this chiral cation had been achieved by coupling with the enantiopure anion **52**, followed by chromatographic separation of the diastereomeric salts [35].

The absolute configuration of the separated enantiomers of **51** (as PF_6 salt) was determined by VCD, using for DFT calculation the molecular structure determined by X-ray analysis. Overall, a good agreement between the experimental and calculated spectra gave P configuration for the carbenium ion in the (+) [**51**] $[PF_6]$ salt. Subsequent studies on racemization of the (-) **51** $[PF_6]$ by chiral HPLC demonstrated a very high configurational stability for this helical species (interconversion between M and P enantiomers was observed above 200 ^{0}C).

The absolute configuration of the nonracemic novel diazaoxatricornan, namely 12*c*-methyl-12-phenyl-8-propyl-12, 12*c*-dihydro-8*H*-4-oxa-8, 12-diazadibenzo[*cd,mn*] pyrene **53,** was established by comparing experimental and theoretical VCD spectra. The novel chiral cup-shaped compound was isolated in racemic form by classical means from unsymmetrical diazaoxatriangulenium cation and the enantiomers were separated by chiral HPLC. Isolation of (-)-(S) and (+)-(R)- represents the first literature report of a nonracemic closed-capped chiral bowl molecule for which the chirality is due to the intrinsic dissymmetry of the central core of the structure [36].

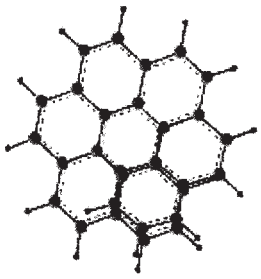
The absolute configuration of heptahelicene **54** enantiomers has been unambiguously established by VCD, after resolution by chiral HPLC [37]. VCD spectra were calculated at DFT B3LYP (B3PW91) level. The comparison with experimental data gave the unequivocal assignment (-)**54**/M, (+)**54**/P.

The use of 2,2'-diphenyl-[3,3'-biphenanthrene]-4,4'-diol, known as VAPOL **55**, as chiral ligand for enantioselective catalysis necessitates the reliable determination of its absolute configuration. The crystal chemistry of VAPOL has been intensively investigated. Remarkably, the melting point of racemic VAPOL is 86 °C higher than that of the S-enantiomer, and there is a 2.0 kcal/mol difference in stability at room temperature, favoring the racemate. These values are at the upper end of reported differences between a racemic/chiral pair [38].

The experimental VCD, ECD and optical rotatory dispersion (ORD) spectra, and the corresponding quantum mechanical prediction data were used to determine the absolute configuration of VAPOL. In general, while reliable VCD prediction can normally be obtained at B3LYP/6-31G* level of theory, ECD and ORD predictions require higher level of theory. Therefore, the absolute configuration was sustained by correlation among the VCD signals in experimental and predicted spectra when it was unambiguously established that the (aR)-configuration corresponds to (-) enantiomer of VAPOL [39].

One of the largest molecules investigated by ab initio calculation and VCD spectroscopy for determination of absolute configuration are the enantiomers of the cryptophane-A **56** (R=OCH_3) [40].

The rigid bowl-shape structure of cryptophane A makes this molecule very attractive for the investigations of host-guest interaction (such as complexes with halogeno-methanes or xenon atom). The IR and VCD spectra of (+) and (-) **56** were measured in $CDCl_3$, CD_2Cl_2 or $C_2D_2Cl_4$ solution. The effort in ab initio calculation was impressive. Calculation of the optimized geometry of the empty cryptophane A (120 atoms) required 702 basic function, 1152 primitive Gaussians for the 3-21G basis set, and 1098 basis functions, 2064 primitive Gaussians for the 6-31G* basis set. Calculation of the optimized geometry of the chloroform-cryptophane A Complex (125 atoms) required 1172 basis functions and 2252 primitive Gaussians for the 6-31G* basis set (calculations performed on up to four



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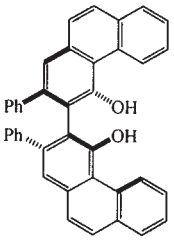

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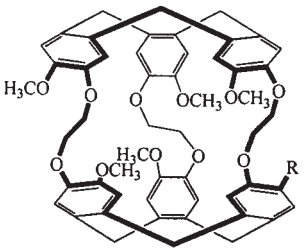
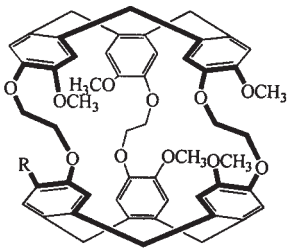


(-) 56



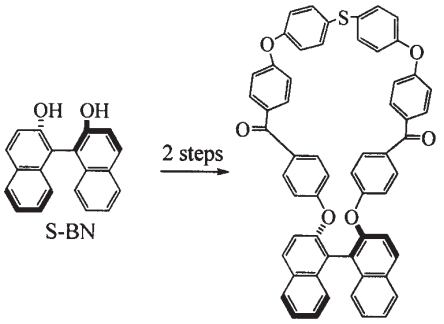
(+) 56

processors on a SGI Altix 3300). Despite the high computation time needed, the authors showed that even a small basis set (6-31G*) allows one to calculate, with a good degree of precision, the IR and VCD spectra of the cryptophane A and thus to predict its absolute configuration.

New enantiopure monofunctionalized cryptophanes with C_1-symmetry (R= OH, OCH_2COOCH_3, OCH_2COOH, OSO_2CF_3, bis-cryptophane) were synthesized and their absolute configuration was assigned using VCD measurements associated with DFT calculations. A comparison between ECD and VCD techniques reveals the versatility of the last method. The ECD spectra of cryptophanes are sensitive to the bulk properties of the solvents rather than to the ability of certain solvents to insert in the cavity. The ECD spectra are the result of six nondegenerate components with different intensities and polarization, according to the studies in several solvents when Cotton bands of different magnitude and intensities are obtained. Therefore, the interpretation of the ECD results is more difficult and required an additional chiroptical technique. The VCD measurements were reproduced accurately by ab initio calculated bands, revealing the easy and unambiguous determination of the absolute configuration in these cryptophane series [41]. These last measurements were performed both in solvents that can enter in the cavity of the cryptophanes ($CHCl_3$) as well as in solvents which do not enter in the cavity ($C_2D_2Cl_4$). In both cases a good agreement between experimental and calculated VCD spectra was obtained, although the conformation of the aliphatic linkers is very dependent on the used solvent and its ability to enter or not in the cavity.

The change in conformation of the ethoxy linkers upon guest encapsulation was addressed for the cryptophane R=H. These linkers can adopt a gauche or anti orientation which leads to changes in the VCD spectra. Closer examination of the VCD spectra of R=H cryptophane revealed an overall decrease of the bands intensities. This feature was not observed for monofunctionalized cryptophane with electron-donating substituents, hence the spectral modifications could not be attributed to the lack of symmetry. In this case, DFT calculations associated with VCD experiments help to provide a detailed and accurate description of the conformation of optically pure cryptophane R=H. The host molecule adopts a preferential *anti* conformation of the aliphatic linkers in the complex with $CDCl_3$. In contrast, a preferential *gauche* conformation of the aliphatic linkers has been revealed for empty cryptophane [42].

Knowledge of the absolute configuration is of great importance when exploring the mechanism of chiral recognition based on chiral macrocycles. An interesting example is provided by a chiral rigid bisetherketone containing a C-2 symmetrical binaphtyl with S-configuration and thioether moieties (S-PENEKSC-**57**) [43].



S-BN

S-PENEKSC **57**

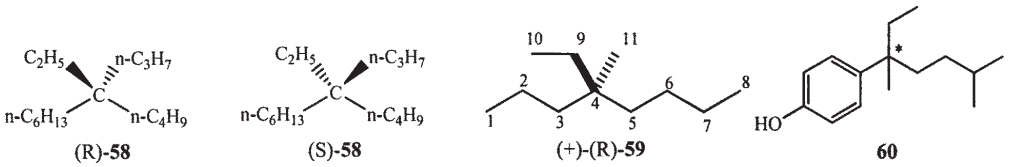
The experimental IR and VCD spectra were in good agreement with those calculated at B3LYP/6-31 g (d) level. The detailed assignment of the bands allowed identification of the spectral signatures of the hydrophobic (binaphtyl core and phenyls) and hydrophilic (C=O, C-O (aryl), C-S (aryl)) groups in the macrocycle. This finding is of great significance in the research on the chiral recognition properties of such macrocycles.

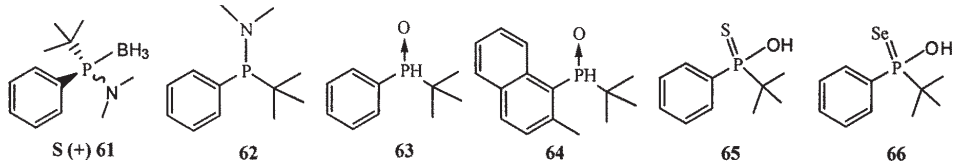
Chiral saturated hydrocarbons

Chiral saturated hydrocarbons form a class of compounds whose chiral discrimination has been very difficult to establish or has not been possible at all. A representative example is the quaternary hydrocarbon 5-ethyl-5-propylundecane **58**: the enantiomers of **58** exhibit practically no optical rotation ($|\alpha| < 0.001$ between 280 and 580nm). The configurational assignment for enantiomers of **58** and for several related tertiary hydrocarbons was made only recently, by asymmetric autocatalysis [44].

The enatiopure (+) 4-ethyl-4-methyloctane **59**, the simplest chiral saturated hydrocarbon with a quaternary stereogenic center, was synthesized using chiral 2-methoxy-2-(1-naphthyl) propionic acid. The absolute (R) configuration was established by ^{1}H-NMR spectroscopy and X-ray crystallography for the (+) enantiomer. The assignment has been checked by VCD technique. The calculated spectrum of (R)-**59** at B3PW91/6-31G(d,p) level agrees well with the experimental spectrum recorded with the neat sample (+)-**59**, especially in the 1100-900 cm^{-1} range [45].

Nonylphenols represent a class of compounds widely used as surfactants in industrial and institutional cleaning products. These compounds possess large endocrine disrupting effect which is very much dependent on the structure of the alkyl chain. Hence, enantiomeric-specific determination is of great interest. Since their crystallization is not an easy target, the question of absolute configuration was addressed only by solution methods. In the case of compound **60**, the experimental rotation data were





considered inconclusive. However, comparison between experimental and calculated VCD data allowed the determination of the absolute configuration in the alkyl side-chain [46].

Compounds with a heteroatom as chiral center

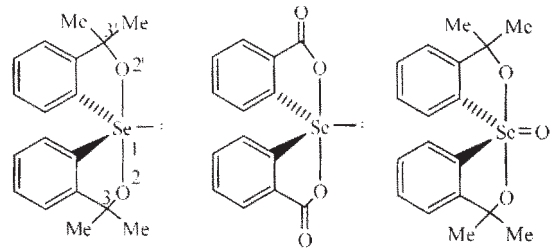
Phosphorus

The first phosphorus compound investigated by VCD was *tert*-butyl(dimethylamino)phenylphosphine-borane complex **61** [47]. The enantiomers were separated by chiral HPLC. The borane protection could be removed without racemization and the configuration of the free aminophosphine **62** was found to be stable in solution. The DFT calculation at B3LYP/6-31+G9d) level predicted three significantly populated conformers. The conformational flexibility of the molecule was detrimental to signal intensity in the experimental VCD spectrum. The comparison theory-experiment unambiguously provided (s)-(+) **61** assignment, in agreement with X-ray crystallography.

VCD spectroscopy in conjugation with DFT calculations has been used to establish the equilibrium between tautomeric structures, the dominant conformations and phosphorus absolute configuration in *tert*-butylphenyl-phosphine oxide **63**, *tert*-butyl-(2-methylnaphthyl)-phosphine oxide **64**, *tert*-butylphenyl-phosphinothioic acid **65**, *tert*-butylphenylphosphino-selenoic acid **66** [48,49]. A single tautomeric form has been found (pentavalent phosphorus derivatives) and the configurational assignment was supported by results obtained through other chiroptical methods.

Selenium

Chiral spiroselenuranes constitute a family of hypervalent selenium compounds which have scarcely been characterized in optically active form. The enantiomers of 3,3,3',3'-tetramethyl-1,1'-spiro[3*H*,2,1] benzoselenone **67** were separated by chiral HPLC and the configurational assignment (S)/(-) at 589 nm has been established independently by VCD, ECD and ORD calculations at B3LYP/6-31G* level) [50]. The combined approach allowed also the following observation: spiro-selenoderivatives **67**, **68**, **69**, sharing common (S)-configuration, present different signs of rotation (at the

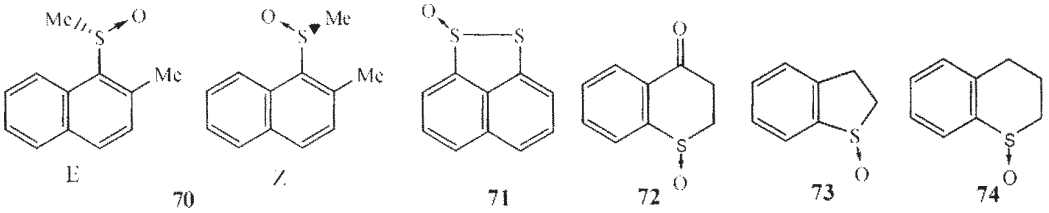


same λ value). It recalls again that rules relating absolute molecular configuration to the sign of rotation should be carefully elaborated and applied.

Sulfoxides

Chiral sulfoxides are of considerable importance as bioactive compounds,[51,52] synthetic intermediates[53] and ligands[54] for asymmetric synthesis, but determination of their absolute configuration was limited due to the low application of typical chirooptical methods.[55]. In general, their absolute configuration was established by conversion of the appropriated diastereomeric or enantiomeric sulfinic acid derivatives (sulfinates, thiosulfinates, sulfinamides) into sulfoxides with various types of organometallic reagents[56] which produced large controversy [57-60]. The discrepancy of the absolute configuration assignment for enantiomerically pure sulfoxide has disappeared when the VCD spectra of the (+)/(R) enantiomer of n-butyl tert-butyl sulfoxide was published [48], in agreement with X – ray assignment in the mercury chloride complex of the S-(-) isomer [61]. Similar results have been reported for absolute configuration assignment in the case of *tert* butyl methyl sulfoxide. Using DFT-GIAO methodology, theoretical VCD spectra of the sulfoxide has been predicted, demonstrating the reliability and the convenience of the VCD spectroscopy as a tool for determining the absolute configuration of the chiral sulfoxides [62].

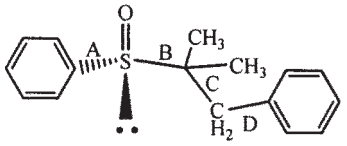
More complicated sulfoxide molecules have been studied by *ab initio* methodology. Using potential energy surface, different dihedral angles involving the sulfur atom are taken into account, with energy minima corresponding



to E and Z conformations. Comparison between predicted and experimental IR-VCD spectra lead to unequivocally assignment of the absolute configuration of 1-(2-methylnaphtyl) methyl sulfoxide **70** as being R-(+) / S-(-)[63,64], in agreement with ulterior electronic circular dichroism experiments [65].

The general use of VCD methodology to determine the absolute configuration is confirmed by absolute configuration assignment of cyclic thiosulfinate**71** as (+)-S/(-)-R relationship,[66] for 1-thiochromanone S-oxide (**72**) as S(+) configuration [67] and sustained by R-(-)/ S-(+) assignment for 1-thiaindan S-oxide (**73**) and 1-thiochroman S-oxide (**74**) [68].

The absolute configuration and the predominant conformations were also determined by means of VCD for (+)-1,1-dimethyl-2-phenylethyl phenyl sulfoxide **75**. Additionally, two other chiroptical methods, namely ECD and specific rotation, were used to assign its absolute configuration. Considering free rotations around labeled bonds, variation of four dihedral angles are possible. Comparison of experimental with the predicted spectrum calculated for individual conformers showed the absolute configurations as (+)-R/(-)-S [69].



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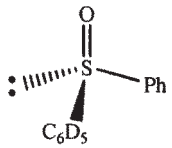

(+) S 76

The first isotopically chiral sulfoxide studied by VCD was perdeuteriophenyl-phenyl sulfoxide **76,** for which (S)(+)/(R)(-) assignment was established[70].

Finally, successful assignment in sulfoxides possessing also other stereogenic sources are quoted: α-chlorinated α-phosphoryl sulfoxides[71], N-α-phenylethyl-tert-butylsufinamide [72] and a new bicalutamide analog, an androgen receptor antagonist [73]. These examples emphasize the versatility of the VCD technique for absolute configuration assignment in sulfoxide series.

Miscellaneous

Successful assignment of absolute configuration by IR/VCD method have been accomplished for a large diversity of compounds: enatiopure chiral oxorhenium (V) complexes containing hydrotris (1-pyrazolyl) borate ligand,[74] chlorofluoroiodomethane,[75] Δ-TRISPHAT[tris (tetrachlorobenzenediolato)-phosphate(V)]anion [76], 3-chloro-1-butyne,[77] chiral pyrazoles derived from (5R)-dihydrocarvone [78] and 2-substituted-3(2H)-furanone derivatives which posses significant aroma properties [79].

Configurational assignment in natural products

The survey of recent literature reveals an increase in the number of papers dealing with configurational assignment in natural products by VCD technique. This fact may be easily explained from the experimental point of view: there is not restriction for the physical state of the compound, a small amount of sample is required and compounds only enriched in one enantiomer, not enantiomerically pure, are still acceptable. However, the ab initio calculations might be much more difficult since the molecules are generally large, involve several chiral motifs and may adopt unexpected conformations. An usual strategy used in these cases is the fragmentation of the molecule, selecting a core structure relevant for the chirality of the whole molecule and calculation of the fundamental vibrational modes in the selected moiety. The power of VCD spectroscopy in determining the absolute configuration for large organic molecules and for conformationally-flexible organic molecules is well documented [22].

The technique seems most appropriate for determination of stereochemistry of the sugar anomers; it has been reported that axial aromatic glycosides exhibit a negative band at around 1230 cm^{-1} while equatorial ones show a flat feature in this region [80].

Several examples of naturally occurring compounds possessing biological activity which were studied by VCD techniques are given below:

- a new cytotoxic iridoid (prismatomerin with 5 chiral centers) analyzed as acetate derivative [81,82];
- a new dihydrofuranocoumarin, (+)-alternamin, exhibiting antidote activity against snake venom [83];
- a verticillane diterpenoid (with 3 chiral ceneters) [84];
- eudesmanolides from Mikania genus [85];
- marine endoperoxides, with potential anti-tumor and anti-malarian biological activity [86];
- brominated sesquiterpenes, with moderate antibacterial activity against marine bacteria [87];
- citrinadins (pentacyclic indolinone alkaloid) [88];
- nyasol and hinokiresinol, with antiplasmodial activity [89];
- 6-hydroxyeuryopsin and other derivatives with hypoglycemic activity [90];
- novofumigatonmin – a new metabolite from *Aspergillus novofumigatus* [91];
- africanane and lippifoliane sesquiterpenes from *Lippia integrifolia* [92];
-isoschizogaline and isoschizogamine with antimicrobial activities [93];
- sex pheromone of the obscure mealybug[94] and
- naringenin (4',5,7-trihydroxyflavanone) [95].

Configuration assignment in chiral drugs and pharmaceutical intermediates

In 2005, worldwide sales of single-enantiomer drugs reached $ 225 billion. A glance at the top 10 best selling prescription drugs shows that eight are chiral and all are small molecules. Another sign indicative of growing importance of chirality in the pharmaceutical industry: the best-selling drug in the world is Lipitor (treating high cholesterol) and it is marketed as a single enantiomer, providing annual sales of $ 12.9 billion.

The growing demand for highly pure enantiomers in the pharmaceutical and fine chemicals industries gave an impetus to the developpment of analytical techniques for chiral compounds as well. Among other chiroptical methods, the VCD technique adequately responded to this signal. Recent reports dealing with configurational assignment in synthetic drugs or natural compound with pharmacological activity are given below:

- GT-2331, a potent histamine H3 receptor antagonist [96];
- phenylglycidols, substituted with halogens in the phenyl ring [97];
- chiral oxadiazol-3-one, calcium channel blocker [98];
- precursors of CCR2 receptor antagonist [99];
- L-type calcium entry blockers [100];
- antifungal agents ketoconazole, intraconazole and miconazole [101];
- a high-affinity ligand for the serotonin transporter in mammalian brain [102].

Paclitaxel is an excellent anti-cancer drug extracted from the leaves of yew trees. In the search of more efficient drugs, functionalization of the natural product yielded a

more potent cytostatic and anti tumoric product. The VCD spectra of the two drugs are similar and reflect the structural property of the family. Nevertheless, conformational change of paclitaxel corresponding to a switch through binding with β-tublin (nucleotide binding) and intermolecular interactions might explain the superior cytostatic activity [103].

The VCD technique was also used for introducing enantiopure nonsteroidal compounds for steroid sulfatase. Letrozole is an oral non-steroidal aromatase inhibitor that has been introduced as adjuvant treatment of hormonally-responsive breast cancer. Functionalization of this product as sulfamate derivative has yielded the most potent steroid sulfatase compound when is used as (S) enantiomer. The absolute configuration has been established by VCD-ECD techniques [104].

Conclusion

The present report illustrates, with significant examples, the trends and perspectives of the chiroptical technique IR/VCD in the stereochemical analysis of chiral compounds. The advantages as well as inherent limitations of the VCD as complementary or competing technique to the classical chiroptical methods are underlined.

The report has been elaborated by a group of researchers currently involved in implementing the IR/VCD technique in the "C. D. Nenitzescu" Center of Organic Chemistry of the Romanian Academy.

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