Absolute configurational assignment in chiral compounds through vibrational circular dichroism (VCD) spectroscopy

1. Introduction

The determination of the absolute configuration of chiral molecules is an important aspect of molecular stereochemistry. The main traditional methods for establishing absolute configuration include X-ray crystalography , synthesis of the molecule under study through a series of stereochemically- controlled steps, optical rotation (OR) and electronic circular dichroism (CD).

Among these methods, only X-ray crystalography is an absolute method. Although straightforward and highly reliable, this method requires a single crystal of the sample of sufficient size and quality, a requirement which is not easily met and often may be even precluded. In order to determine the absolute configuration of the crystal unambigously, an atom heavier than oxygen must be present in the molecule or must be incorporated into the molecule by derivatization. Here again, the derivatization step should not alter the chirality under investigation.

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.

For relating the sign of the measured optical activity to absolute configuration, several rules or useful correlations have been established for a variety of structural motifs. However, such empirical methods should be carefully addresed since might be contaminated by incorrect assignments.

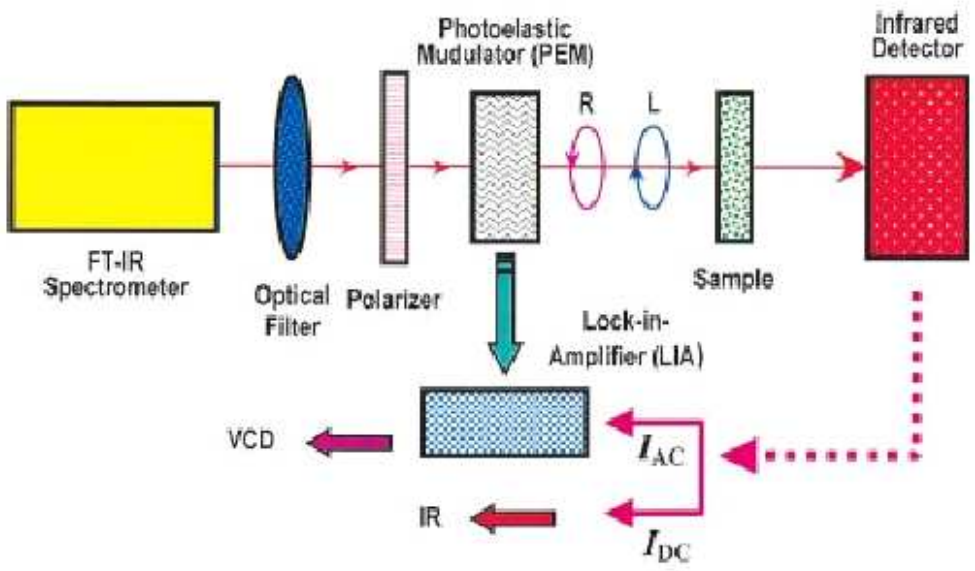
CD has been used as a relative method, based on chirality rules. Unfortunately, all these rules involve exceptions and this fact places some doubt on the use of empirical rules.

Vibrational circular dichroism (VCD) became lately an increasingly popular method for the unambigous assignment of absolute configuration in chiral molecules. VCD is the extension of electronic CD into the infrared region, where fundamental vibrational transitions occur. VCD has a number of advantages over all previous methods of absolute configuration assignment, but has some limitations as well. Like X-ray crystalography , 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.

2. Methodology of experimental VCD measurements

The block diagram for the optical layout of a FT-VCD spectrometer is given in Figure 1. IR radiation from a glower source is directed through an interferometer that encodes each spectral point with a Fourrier frequency. The radiation from the interferometre is then passed through an optical filter and is then linearly polarized to define a single state of polarization.



The IR beam then passes through a photoelastic modulator (PEM) that sine-wave modulates the polarization between LCP and RCP states in the frequency range of tens of kilohertz. The beam then propagates through the sample, which imposes an intensity modulation on the beam at the PEM frequency of Fourrier frequencies in the spectrum where there is VCD. A cooled infrared detector then converts the IR beam intensity to an electrical signal that is processed by the subsequent electronics. There are two electronic path-ways. One is the usual pathway for the measurement of the IR spectrum, and the other pathway includes a lock-in amplifier tuned to the PEM frequency, which demodulates the spectral information at the frequency and leads to the VCD spectrum.

3. 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 absorbtion spectrum requires the calculation of 1) the harmonic force field (HFF) from which the normal mode frequencies and coordinates are obtained and 2) the atomic polar tensors (APT) . The prediction of the harmonic VCD spectrum requires the additional task of calculating 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 carring out the calculations are 1) Hartree-Fock (HF) /self-consistent field (SCF) theory; 2) second-order Moller-Plesset perturbation theory (MP2); 3) density functional theory (DFT). In terms of relative accuracy, 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.

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 conformation, 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 (Schrodinger, 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 conformers),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.

4. Recent application of stereochemical determination

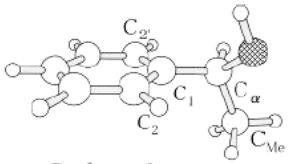
Several authoritative reviews have been published so far on the absolute configuration determination in solution using VCD.[56, 47, 46, 44, 36,12, 58]

The purpose of the present review is to sum-up the major contributions in this field issued in the last five years (2003-2007). For convenience, the references were numbered starting from the most recent ones.

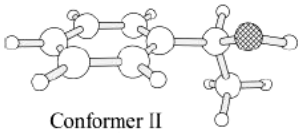
4.1. Matrix-Isolation Vibrational Circular Dichroism (MI-VCD)

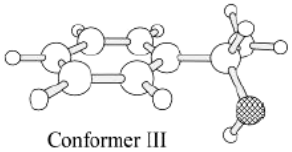
When a chiral molecule has several conformers and is capable of strong intermolecular interactions, interpretation of its VCD spectrum is far from strightforward. The spectra of either neat liquid or solution in polar solvents present broad, featureless signals, with low information content. The theoretical 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. For overcoming these difficulties , the noble gas (Ar) matrix-isolation VCD procedure has been used successfully for two simple chiral compounds, namely (S) -1-phenylethanol [4] and (R)-2-amino-1-propanol.[28]

Three conformers (I-III) were found by DFT calculations for 1-phenyl ethanol. The calculated IR spectrum of the most stable conformer I reproduced very well the Ar matrix-isolated IR spectrum. The spectra of diluted solutions in CCl_4 and CS_2 were in excellent agreement with conformer I with a trace amount of conformer II. A composite spectrum of dimers reproduces well the VCD spectrum of the neat liquid sample.



Conformer I

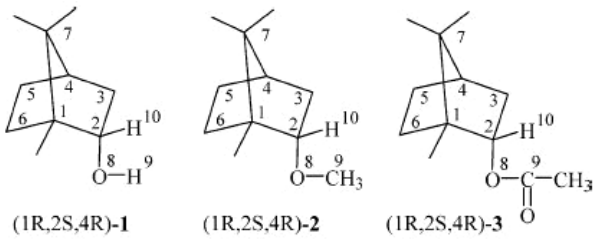

Conformer II

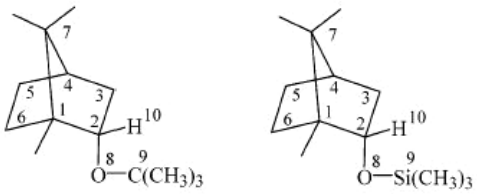

Conformer III

It is interesting to note that two key-VCD bands were found, which are insensitive to both conformational changes and intemolecular 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). [4]

4.2. Protocol for conformational rigidification via chemical derivatization (CRDC)

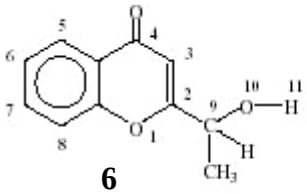
Broadly speaking, the application of chirooptical methods in conjunction with DFT calculations becomes increasingly unreliable as the number of populated conformations increases. A strategy for diminishing the conformational flexibility via chemical derivatization was proposed.[42] The basic idea is to add a bulky group to the molecule of interest, without affecting its absolute stereochemistry, in such a way as to diminsh 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 an equilibrium of 3 conformers for borneol **1** , the number of stable conformations is reduced to 2 for the methyleter **2** and only one stable conformer is predicted for acetate **3,** t-buthylether **4** and trimiethylsilyl derivative **5**.


(1R,2S,4R)-**1** (1R,2S,4R)-**2** (1R,2S,4R)-**3**


(1R,2S,4R)-**4** (1R,2S,4R)-**5**

The agreement between predicted and experimental spectra for derivatives **3-5** is excellent, confirming the benefit of rigidification. A supplemental benefit of derivatizing the OH group of alcohol is the elimination of intermolecular H-bonding at medium-to-high concentrations in nonpolar solvents.

A similar strategy has been used in assigning the absolute configuration to 2-(1-hydroxyethyl)-chromen-4-one **6** and its 6-bromoderivative **7.**[41] 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 following assignment: R-(-) / S-(+) for **6** and R-(+) / S-(-) for **7**. It is interesting to note that the previous X-ray crystalographic analysis gave the same assignment for compound **7** but the opposite assignment for **6**. This is one of the rare cases in which the X-ray crystallography gave an incorrect result. Indeed, while molecule **7** has a heavy atom (Br) and the X-ray analysis gave the correct assignment, the molecule **6**, with no heavy atom, was not correctly assigned by X-ray analysis.



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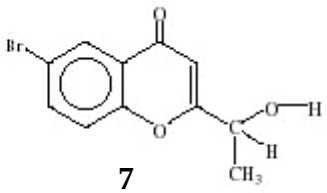

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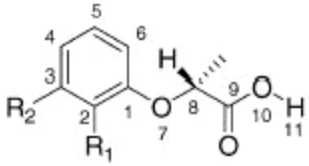
The experimental absorbance and VCD spectra of α-aryloxypropanoic acids **8a**, **8b** did not match well the predicted spectra for isolated monomeric acid, due to intermolecular hydrogen bonding in solution. These effects were eliminated by conversion into the corresponding methyl esters **9a**, **9b** through reaction with diazomethane, which does not change the absolute configuration in the parent acid.



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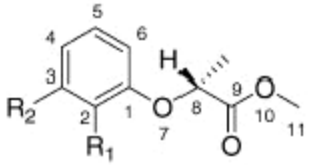


9

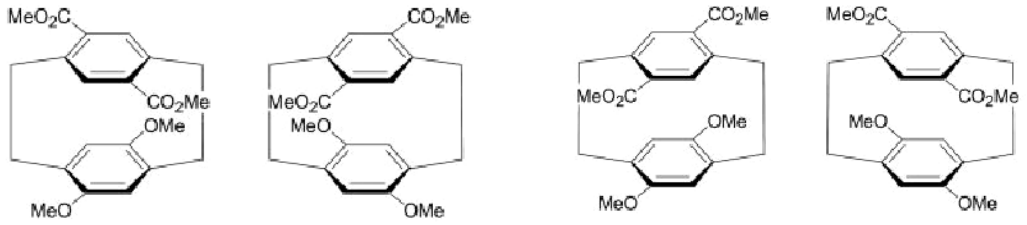
The positive and negative VCD signs of the major peaks measured in $CDCl_3$ solution in the 2000-900 cm^{-1} region are similar with ab initio predicted spectra of the esters **9a**, **9b** (only small discrepances have been found). However, taking into account the general agreement between experiment and calculation, (+) **8a** and (+) **8b** were assigned (R)-configuration.

This study is important, being related to detection of chiral herbicides,[40, 34] which can become an enviromental hazard when used in excess quantities.

4.3. Absolute configuration of molecules with planar chirality (cyclophanes)

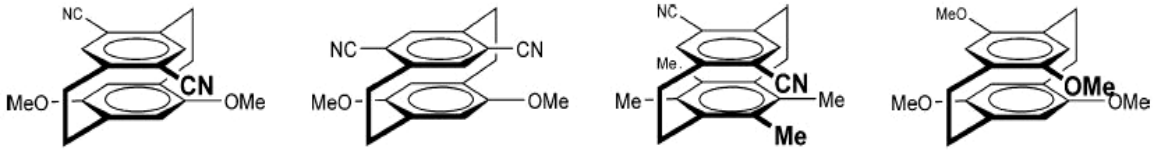
A considerable interest has been paid lately to a variety of substituted cyclophanes because of their planar chirality, which was found to behave quite differently from conventional point chirality in asymmmetric reactions, catalysis and host-guest interactions. The method of choice in assigning absolute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

Very recently, successful assignment of absolute configuration of donor-acceptor [2.2] paracyclophanes **10** and **11** was achieved by applying the VCD/DFT method. [27] The DFT calculation performed at the B3LYP/6-31G(d) level gave six optimized conformers for both **10** and **11**, 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 +/- **10**; +/- **11**, displaying excellent agreement between experimental and calculated spectra.



10 **11**

The first comparative study of the experimetal and simulated chirooptical properties (optical rotations, vibrational and electronic CD spectra) of paracyclophanes with and without donor-acceptor interactions gives an interesting evaluation of balance between performance and limitations of the methods involved. [6] The compounds under investigation were the CT cyclophanes **12**-**14** and the non-CT cyclophane **15**.

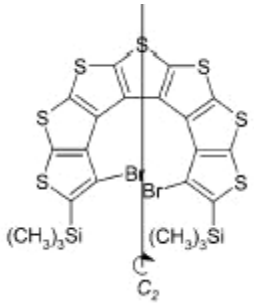


12 **13** **14** **15**

The concluding remark of the paper is that VCD spectra simulated at the B3-LYP/6-31G(d) level are not always consistent with the experimental data. Indeed, disagreement in signal intensity and pattern is often observed in several transitions. Nevertheless, for the VCD bands that have mirror images for the enantiomers, the agreement between theoretical and experimental VCD signs appears to be sufficient enough to suggest the absolute configuration.[6]

4.4. Absolute configuration of molecule with chiral axes, helical chirality or globular chirality; supramolecular species; macrocycles.

The absolute configuration of two large molecules that possess chiral axes, but not chiral centers, have been determined by VCD: the annelated heptathiophene **16** (a helical molecule with C-2 symmetry) and a π-conjugated chiral derivative of o-tetraphenylene (with D-2 symmetry).[52]



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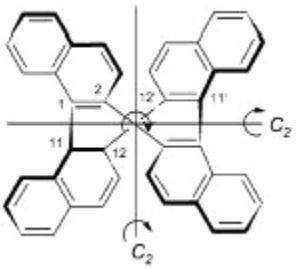


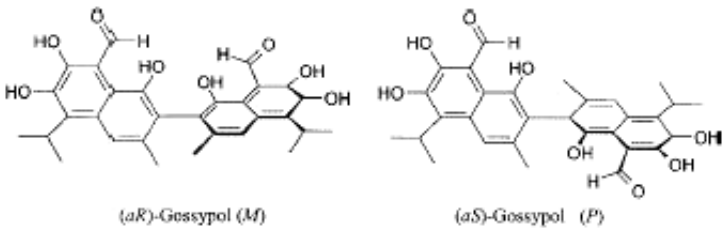
17

The DFT calculations at the B3LYP/6-31G* level provided almost perfect band-to- band fit with the experimental spectra. The superb agreement easly provided R-configuration for (-) **16** and (+) **17**.

It is worth mentioning that previous tentative of absolute configuration assignment in **16** by X-ray crystalography were hampered by the difficulty in growing suitable crystals. The X-ray structure for **17** has been obtained, but the data were not complete enough for determination of absolute configuration. On the other hand, although CD spectra have been measured for both **16** and **17**, the conjugation of the cromophores precludes the application of the exciton coupling model to the UV-visible CD spectra in order to determine the absolute configuration. Therefore, the DFT/VCD procedure was indeed a richer, simpler and highly reliable alternative in this case.

Another advantage is related to the amount of the sample required in experimental measurements. The sample of (-) **16** was as small as 3 mg, of 84 ± 5% ee. For reducing the VCD noise because of the small sample, an aquisition time of 18 h was required.

An interesting compound of plant origin, gossypol **18** has been intensively studied due to its pharmacological properties. [57] This compound is rather unstable and presents tautomeric equilibria in solution. In $CDCl_3$ solution, the aldehyde tautomer is present, but in other solvents the aldehyde and lactol tautomer 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. Two different orientations of the isopropyl group relative to the naphthyl plane as well as intramolecular hydrogen-bonded forms were found, in agreement with data from X-ray structure and NMR studies.



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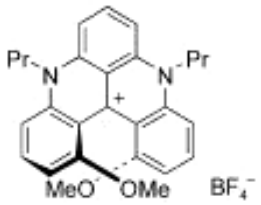
In the dimethoxyquinacridinium salt **19**, the strong steric repulsion between the methoxy substituents forces the molecule to adopt a twisted helical conformation typical of helicene derivatives. The resolution of

this chiral cation has been achieved by coupling with an enantiopure anion, namely **20**, followed by chromatographic separation of the diastereomeric salts.[54]



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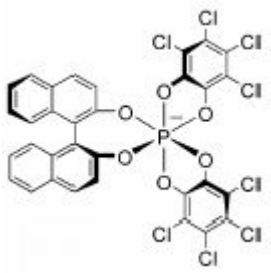
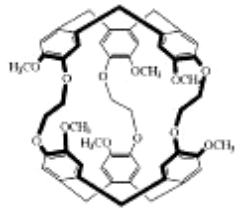


20

The absolute configuration of the separated enantiomers of **19** (PF_6 salt) was determined by VCD, using for DFT calculation the molecular structure determined by X-ray analysis. Overall, a good ageement between the experimental and calculated spectra gave P configuration for the carbenium ion in the (+) [**19**] [PF_6] salt. Subsequent studies of racemization of the (-) **19** [PF_6] by CSP-HPLC demonstrated a very high configurational stability for this helical species (interconversion between M and P enantiomers was observed above 200 ^{0}C).

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 **21**.[25]

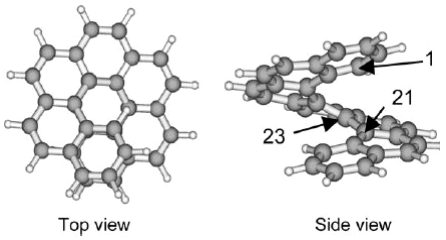


(-) 21

(+)21

The rigid bowl-shape structure of cryptophane A makes this molecule very attractive for the investigations of host-guest interaction (such as complexes with halogenomethanes or even xenon atom). The IR and VCD spectra of (+) and (-) **21** 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. t, 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 processors ou 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.

The absolute configuration of heptahelicene **22** enantiomers has been unambigously established by VCD. The resolution of enantiomers was performed by chiral HPLC on Chiralcel OD column, eluting with hexane/2-propanol (9/1). The VCD spectra of the firstly eluted (H1) and secondely eluted (H2) enantiomers were recorded in CH_2Cl_2 solution. The reliability of the measurement was confirmed by the mirror-image-like VCD spectra of H1 and H2. VCD spectra were calculated using GAUSSIAN 98, at DFT B3LYP (B3PW91) levels. The comparison with experimental data gave the unequivocal assignment H1/M and H2/P (H2 is dextrorotatory at 590 nm).[61]



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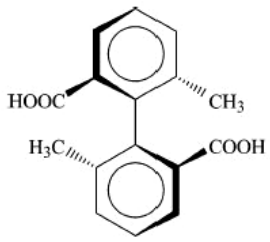
The first study using VCD spectroscopy in order to establish the structure of a supramolecular species was published in 2005.[62] The IR and VCD spectra of S-2,2'-dimethyl-biphenyl-6,6'-dicarboxylic acid (S-**23**) in $CDCl_3$ solution are concentration-dependent, indicating that oligomerization occurs with increasing concentration.



23

DFT calculations supported the conclusion that the oligomer formed is the cyclic tetramer (S-**23**)$_4$ in which the monomers are linked by hydrogen-bonded $(COOH)_2$ moieties. The conformational analysis of (S-**1**)$_4$ established that six different and energetically unequivalent supramolecular species are possible. DFT calculations at B3LYP/6-31G* level predicted the lowest free energy conformation and its corresponding IR/VCD spectra. Examination of the experimental data indicated an excellent agreement in the C=O stretch modes and a good fit in the range 1100-1600 cm^{-1} for the favoured conformer denoted (aaab).

An interesting example is provided by a chiral rigid macrocyclic compound containing a C-2 symmetrical binaphthyl with S-configuration and thioether moieties. The IR and VCD spectra calculated at B3LYP/6-31G level were in good agreement with the experimental data. The vibrational modes of both hydrophobic (binaphtyl core and phenyls) and hydrophilic (C=O, C-S, C-O) groups were identified. This finding is of great significance in research on the chiral recognition properties of such macrocycles.[38]

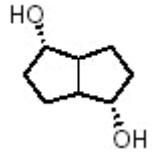
4.5. Absolute configuration of compounds with several chiral centers

The absolute configurations in compounds containing only one stereogenic center are determined on an almost routine basis. A step ahead was made by determination of absolute configurations of compounds with several chiral centers. Two situations have been encountered:

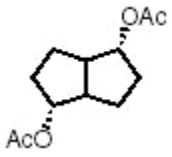
a) molecules with relative configuration known in advance by other techniques; [59]

b) molecules lacking any prior stereochemical information.[14,19]

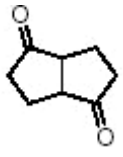
The second situation is illustrated by the configurational assignment in the bicyclo [3.3.0] octane derivatives **24**-**27**.



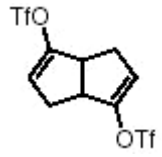
(+) –(!R,2S,5R,6S)-24



(+)- (1S, 2R, 5S, 6R)-25



(-)-(1R,5R)-26



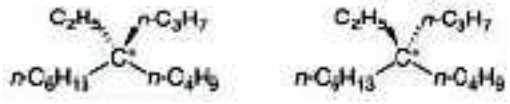
(-)-(1R,5R)-27

The strategy consisted in enumeration of all possible optically active diastereomers (for symmetry reasons, these numbers are 4 for **24**, **25** and only 1 for **26** and **27**). Conformational analysis of each stereoisomer provides the significant conformers, their relative free energies and the corresponding Boltzmann population. The Boltzmann-weighted IR and VCD spectra were calculated at B3LYP/6-31G* level. The calculated spectra were compared one by one with the experimental spectrum of (+) **24**, (+) **25**, (-) **26** and (-) **27**. Reliable assignments has been made (given in the formulas) since only **one** of the computed spectra could be linked band-by-band with the experimental spectrum.

A concept *of vibrational chirality probe* from a single chiral center in the presence of numerous such centers has been implemented in a study on carbohydrates.[45] In methyl glycosides, the symmetric methyl stretching reflects only the anomeric stereochemistry, with peaks simply displaying in the opposite sign for the reversal of C-1 configuration. This band appears near 2840 cm^{-1} and shows a positive sign for the R-configuration at C-1 and a negative sign for the S-configuration. This approach of vibrational chirality probe could be particularly useful for large and flexible molecules, such as carbohydrates.

4.6. Absolute configuration of chiral saturated hydrocarbons

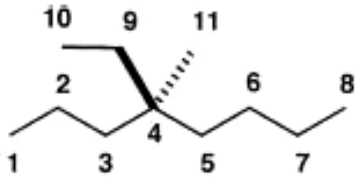
Chiral saturated hydrocarbons form a class of compounds whose chiral discrimination has been very dificult to establish or has not been possible at all. A representative example is the quaternary hydrocarbon 5-ethyl-5-propylundecane **28**, a naturally occuring compound isolated from bean. The enantiomers of **28** exhibit practically no optical rotation ($|\alpha| < 0.001$ between 280 and 580nm). Mislow called such hidden chirality „cryptochirality" and reffered to the corresponding measurements as the „operational null".The configurational assignment for enantiomers of **28** wad made only recently, by asymmetric autocatalysis. The same procedure was successfully used for several tertiary hydrocarbons. [60]



(S)-**28** (R)-**28**

28

The enatiopure (+) 4-ethyl-4-methyloctane **29**, 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 1H-NMR spctroscopy and X-ray crystalography for the (+) enantiomer. The assignment has been checked by VCD technique. The calculated spectrum of (R)-**29** at B3PW91/6-31G(d,p) level agrees well with the experimental spectrum recorded with the neat sample (+)-**29**, especially in the 1100-900 cm^{-1} range.[11]



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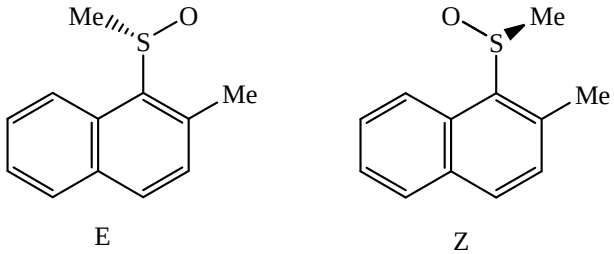
4.7. Absolute configuration of chiral sulfoxides

Chiral sulfoxides are of considerable importance as bioactive compounds[63], synthetic intermediates[64] and ligands[65] for asymmetric synthesis. There are numerous examples in which chiral sulfoxides play a major role in preparing a final chiral product. Much effort has been devoted to the development of synthesis methods in order to isolate sulfoxides of high enantiomeric purity. Nevertheless, prior to their application, it is important to determine their absolute configuration. Determination of the absolute configuration was

limited due to the low application of typical chirooptical methods.[66] The commonly used method to assign the absolute configuration of enantiomerically pure sulfoxides was based upon the synthetic pathway used to isolate them. In instance, conversion of the appropriated diastereomeric or enantiomeric sulfinic acid derivatives (sulfinates, thiosulfinates, sulfinamides) were converted into sulfoxides with various types of organometallic reagents[67]. The absolute configuration of the sulfoxides obtained by this methodology was assigned by assuming inversion of configuration at the sulfinyl sulfur atom in the nucleophilic substitution step. Controversy in the assignment of absolute configuration has been published before 20th century for n-butyl *tert*-butyl sulfoxide[68]. The discrepancy of the absolute configuration assignment for this sulfoxide has disappeared when Drabowicz *et al.* published the VCD spectra of the (+)- enantiomer of n-butyl tert-butyl sulfoxide[69,see also, 13]. Firstly, crystallographic determination of absolute configuration has been performed for (–) sulfoxide enatiomer. The molecular structure has been determined by X – ray crystallography on the mercury chloride complex formed between sulfoxide and the inorganic salt. Mercury chlorides can form solid complexes with liquid sulfoxides[70] through coordination of the Hg ion to the sulfoxide oxygen atom. In this case, X-ray crystal structure determination on such a crystalline compounds has revealed unequivocally the S-(-) absolute configuration of n-butyl *tert*-butyl sulfoxide. For the (+) - enantiomer, the absolute configuration has been assigned by vibrational circular dichroism measurements. The unpolarized experimental absorption spectra showed the specific stretching vibrations of the molecule. The experimental VCD spectra of (+) n-butyl *tert*-butyl sulfoxide was obtained at two concentrations: 0.823 M and 0.421 M. The significant VCD bands are: ii) a positive band at 1067 cm^{-1} and ii) a positive-negative couplet with positive maximum at 1028 cm^{-1} and negative maximum at 1014 cm^{-1}. The same features were observed in the calculated VCD spectra of R - n-butyl *tert*-butyl sulfoxide which predicted the positive band at 1055 cm^{-1} and the positive-negative couplet was resolved as two positive bands at 1014 and 1028 cm^{-1} and the negative maximum at 1001 cm^{-1}. The simulated theoretical spectrum has been obtained by *ab initio* calculations using density functional theory (DFT) - GIAO (gauge invariant atomic orbitals), the last being widely used in *ab initio* calculations of NMR shielding constants. In conclusion, the VCD spectrum was a definitive proof of the absolute configuration of the exemplified sulfoxide indicating that the + enantiomer has the R configuration.

Similar results have been previously reported for absolute configuration assignments in the case of *tert* butyl methyl sulfoxide[71]. Using similar 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. The authors have also studied the aggregation of the sulfoxide molecules at higher concentrations by observing the increase in intensity of the specific sulfoxide band at 1060 cm^{-1}. Excellent agreement between experimental and theoretical data has led to the final assignment of the absolute configuration for the given sulfoxide as being R-(-)/ S-(+).

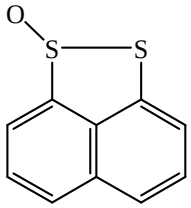
More complicated sulfoxide molecule has been studied by Stephens et al.[72]. Involving the same *ab initio* methodology, the absolute configuration has been determined in the case of 1-(2-methylnaphtyl) methyl sulfoxide **30**. In this case two conformations are possible, namely E and Z as it was also observed by NMR spectroscopy[73].



E Z

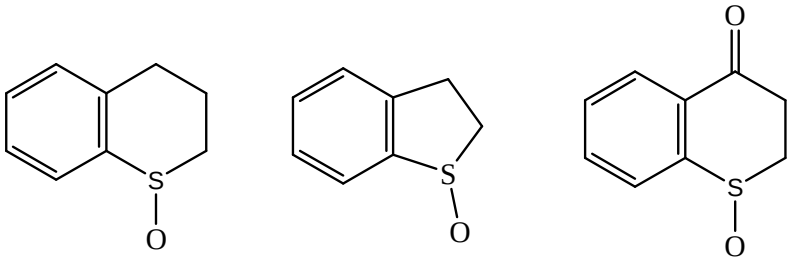
30

The authors have studied the assignment of the absolute configuration for both – and + sulfoxide by use of VCD spectroscopy on CCl_4 solutions. It has been observed the variation of the intensity bands, the experimental VCD spectrum being dominated by two features at ~ 950 cm^{-1} and ~ 1070 cm^{-1}, respectively. The later corresponds to the S-O stretching vibration. The analysis of the experimental spectrum starts with the prediction of the more stable conformation. Using potential energy surface, different dihedral angles involving the sulfur atom are taken into account with energy minima corresponding to E and Z conformations, where the latter is lower in energy. Prediction of the spectra has been based on vibrational frequencies and dipole strength, calculated using GAUSSIAN functions. Secondly, the spectra are synthesized using Lorentzian band shapes. Comparison between predicted E/Z IR spectrum and the experimental one had helped the authors to assign the bands. Later, comparison between predicted and experimental VCD spectra has led to their final goal, namely the assignment of the absolute configuration of 1-(2-methylnaphtyl) methyl sulfoxide as being R-(+) / S-(-). This assignment has been later confirmed by electronic circular dichroism[51]. Moreover, VCD spectroscopy proved to be a useful tool to determine the absolute configuration of a cyclic thiosulfinate of type naphto[1,8-cd]-1,2-dithiole 1-oxide[53] (**31**). In this case an excellent agreement has been observed between experimental and calculated VCD spectra showing a (+)-S/ (-)-R relationship for the conformationally rigid thiosulfinate.



31

Elucidation of the absolute configuration has been also published for 1-thiochroman S-oxide[74]. The experimental VCD spectrum has been recorded in CCl_4 and analyzed using density functional theory which predicts three stable conformations separated by 1 kcal/mol. The theoretical VCD spectra calculated with DFT/GIAO methodology has predicted for the equilibrium mixture of the three conformations the S absolute configuration which was in agreement with the experimental spectrum of the (+) enantiomer. One year later, the authors examined the absolute configuration of the 1-thiochromanone S-oxide[75] using VCD spectroscopy. DFT/GIAO methodology predicts two stable conformations of the chiral sulfoxide, separated by less than 1 kcal/mol. The experimental VCD spectrum for (+) enantiomer is in good agreement with the DFT predicted spectrum for the equilibrium mixture of the two conformations of the S isomer. Therefore, the absolute configuration of 1-thiochromanone S- oxide is definitively R-(-)/ S-(+). A detailed *ab initio* density functional theory calculation is described by Devlin *et al*. for chiral cyclic sulfoxides: 1-thiochroman S-oxide, 1-thiaindan S-oxide and 1-thiochromanone S-oxide[76] (**32, 33, 34**).

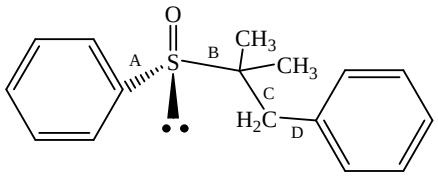


32 **33** **34**

Vibrational unpolarized absorption (IR) and vibrational circular dichroism (VCD) spectroscopies have been employed to determine the exact absolute configuration of the above mentioned chiral sulfoxides. DFT

calculations have predicted two conformations for 1-thiochroman S-oxide and 1-thiaindan S-oxide and three conformations for 1-thiochroman S-oxide. Harmonic IR and VCD spectra of the conformations of these sulfoxides, predicted using DFT, are sensitive to conformational structures. The complex predicted IR and VCD spectra of the three sulfoxides are averaged spectra. These spectra were compared to experimental spectra recorded in CCl_4 and CS_2 in the mid IR-region. A good agreement between the two types permitted the assignment of the experimental bands and unambiguously confirmed the predicted conformations.

The absolute configuration and the predominant conformations were also determined by means of VCD for (+)-1,1-dimethyl-2-phenylethyl phenyl sulfoxide **35**. Additionally, two other chiroptical spectroscopic methods, namely ECD and specific rotation were used to assign its absolute configuration[39]. Considering free rotations around labeled bonds, variation of four dihedral angles are possible, suggesting around 81 possible conformations.



35

Each dihedral angle can be incrementally rotated giving: plus *gauche*, minus *gauche* and *anti* conformations around each bond. Comparison of experimental spectrum with the predicted spectrum, calculated for individual conformers, showed the correspondence between predicted and experimental recorded vibrational band positions. The characteristic VCD signature of this molecule, respectively the negative-positive VCD couplet seen in the experimental spectrum at 1466-1454 cm^{-1} was correctly reproduced in the predicted theoretical spectrum at around 1480-1461 cm^{-1}. The agreement seen between predicted and experimental VCD bands suggested that the absolute configurations are (+)-R or (-)-S. The information was corroborated with electronic circular dichroism and optical rotation measurements, that led to similar assignments.

4.8. 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, [15] enantiopure cyclic β-lactams,[17] a novel disubstituted phenyloxiranes,[21] *tert*-buthyl (dimethylamino)phenylphosphine–borane complex,[22] chlorofluoroiodomethane,[26] rigid 1,8-disubstituted as- hydrindacene compounds, [29] methylesters of three *trans*-phenylglycidic acid derivatives,[32] Δ-TRISPHAT[tris(tetrachlorobenzenediolato)-phosphate(V)]anion,[35] C-2 symmetric spiroselenurane derivatives,[37] 3,6-dihydroxy-4,5-O-isopropylidene-thiepane,[43] *tert*-butylphenylphosphino-selenoic acid,[48] 3-chloro-1-butyne,[49] 5-formyl-cis,cis-1,3,5-trimethyl-3-hydroxymethylcyclohexane-1-carboxylic acid lactone,[50] chiral pyrazoles derived from (5R)-dihydrocarvone.[77]

5. 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 easly explained from the experimental point of view: there are 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 fragmentations 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.

Several examples of naturally occuring compounds possessing biological activity which were studied by VCD techniques are given below:
- a new cytotoxic iridoid (prismatomerin with 5 chiral centers) analysed as acetate derivative;[3, 7]
- a new dihydrofuranocoumarin, (+)-alternamin, exhibiting antidote activity against venom;[5]
- a verticillane diterpenoid (with 3 chiral ceneters);[8]
- endesmanolides from Mikania genus;[9]
- marine endoperoxides, with potential anti-tumor and anti-malarian biological activity;[23]
- brominated sesquiterpenes, with moderate antibacterial activity against marine bacteria;[24]
- citrinadinus (pentacyclic indolinone alkaloid);[30]
- nyasol and hinokiresinol, with antiplasmodial activity;[31]

6. Configuration assignment in chiral drugs and pharmaceutical intermediates

In 2005, worlwide 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;[1]
- phenylglycidols, substituted with halogens in the phenylring;[2]
- chiral oxadiazol-3-one, calcium channel blocker;[10]
- precursorsof CCR2 receptor antagonist;[16]
- L-type calcium entry blockers;[20]
- antifungal agents ketoconazole, intraconazole and miconazole;[33]
- a high-affinity ligand for the serotonin transporter in mammalian brain.[55]

7. Conclusion

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

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