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Advanced Spectra Analysis to Determine Complex Structure and Chirality

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Summary

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This thesis describes the measurement, computation, method development and analysis of several spectroscopic techniques that probe the structure of molecules and supramolecular complexes using their vibrational fingerprints. The technique that is primarily used for that purpose is vibrational circular dichroism (VCD) spectroscopy. What makes this technique so special is that it combines a number of characteristics that are almost impossible to find together in a single technique. It is sensitive to the chirality of the molecule, it probes the many possible vibrations occurring within molecular frameworks, it can be measured in solution, and it is highly sensitive to the exact molecular structure. This makes VCD ideal for studying the structure of molecules and in particular to identify the absolute configuration of chiral molecules.

Despite that the technique might seem to be the answer to all problems regarding chiral molecular structures, it nevertheless also has its downsides. Firstly, signals are very small. Although over the past decades extensive progress has been made in clever designs of spectrometers, at the end of the day the fact remains that the recording of a spectrum still is not straightforward and requires extensive averaging. Secondly, on itself an experimental VCD spectrum does not reveal very much about the molecular structure. It is only when it is compared with theoretically predicted spectra that the full amount of information hidden in the spectrum can be unveiled. Such calculations are very well possible and have indeed been incorporated into a number of well-known quantum chemical software packages, but in applying these methodologies one also is confronted with challenges to resolve. For example, as yet, the molecules that have been investigated, have been largely restricted to rigid systems with relatively few low-energy conformations. Nature is, however, not rigid but flexible, and very often exploring large conformational heterogeneities. Another issue is that so far molecules have been considered with only a few chiral centres. In practice, there is, however, a plethora of systems with many chiral centres, and also for such systems one would like to be able to get a grip on their absolute configuration. Finally, until now predominantly relatively small molecular systems have been studied. Being able to apply VCD to larger molecular systems would be extremely rewarding, and provide access to polymeric systems and novel molecular architectures. This thesis aims to develop and apply novel methodologies to address these issues. What is necessary for this is to develop a fundamental understanding of the physics that underlie VCD signal intensities and clever approaches to analyse VCD spectra for such flexible and conformationally heterogeneous systems. In the present thesis it is shown how such challenges can be met.

As already remarked, in order to interpret VCD spectra, quantum chemical computations are required. Within these computations the high sensitivity to structure becomes problematic as small differences between calculations introduced by the various approximations associated with different levels of theory can lead to large deviations in the computed spectrum. The origin of this high sensitivity to structure is theoretically well understood and is due to the general coupled oscillator (GCO) mechanism. The GCO mechanism dictates that large VCD signals can arise from the vibrational coupling between

different parts of the molecule. The signals stemming from the GCO mechanism are highly dependent on both the relative orientation of the coupled groups and to what extent these vibrations interact. Both features depend strongly on the precise structure of the molecule and are easily influenced by phenomena that are ignored in calculations such as large-amplitude motions in flexible molecules or interactions with the solvent.

In chapter 3 the graphical user interface (GUI) implementation of VCDtools into the ADF software suite is described. VCDtools is an analysis toolbox with the purpose to gain more physical insight in the origins of the computed VCD spectra. At the core of the program is the GCO formalism which enables to analyse computed VCD signals in terms of the interaction between the motions of two or more molecular fragments. By analysing these interactions, differences between computed and experimental spectra can often be explained and subsequently resolved. In addition it provides a clear indication on the origin of the intense VCD signals which can be used to determine if the signal is representative for the entire molecular structure and whether small changes in the structure could induce sign changes, potentially leading to the incorrect assignment of the absolute configuration. In the chapter it is demonstrated how the GUI implementation of VCDtools can be used to detect and resolve differences between theory and experiment arising from incorrect molecular structures and large amplitude motions, and most importantly, how it can be used to prevent incorrect enantiomeric assignments. The GUI implementation of VCDtools has been used heavily to interpret and analyse the VCD spectra in the other chapters.

In chapter 4 we use eight conformers of ForValNHMe as a model peptide to investigate both the GCO mechanism itself and how the GCO mechanism affects the characteristic amide I and amide II bands. This study has revealed which electronic and spatial parameters are critical in the context of the intensity of these bands, and highlighted the importance of intramolecular hydrogen bonds. As the GCO mechanism was responsible for all intense VCD bands, both amide I and amide II modes were found to be very sensitive to the relative orientation of the amide groups and the normal mode localisation on these groups. As is shown, this is important as it has direct consequences on the robustness of the computed VCD bands. In addition we found that the standard coupled oscillator (CO) approach, which is normally employed, does not always give the main contribution to neither the VCD signal or the GCO contribution. This CO model should thus be employed with caution.

In chapter 5 we investigate a benzyl α-hydroxysilane whose VCD spectrum very recently has been used to determine whether the Brook rearrangement of tertiary benzylic α-hydroxylsilanes occurs with or without inversion of the chiral centre. Although the larger part of the VCD spectrum of this molecule are well reproduced by calculations, striking differences occur between computed and experimental spectra in the entire O-H and C-H bending region. It is shown that this regional mismatch is caused by the GCO mechanism in combination with the dispersion of the O-H bending vibration over a large spectral region. As the GCO contribution is very sensitive to normal mode localisation, small changes in the angle of the O-H group were found to be able to induce drastic changes in the computed spectra. Taking the flexibility of the bending of the O-H group explicitly into account allowed us to greatly improve the match between theory and experiment in the problematic spectral region.

In chapter 6 a novel genetic fitting algorithm is introduced that fits the conformational energies to the experiment. This algorithm allows for a straightforward analysis of the effect of the relatively large uncertainty in the conformational energies on the computed VCD spectrum. This results in significant improvements in the overlap between the experimental and computed spectra but more importantly provides a quantitative measure of the probability that an incorrect assignment of the absolute configuration can occur due to the uncertainty in energy. In order to judge overfitting with the algorithm, K-fold cross-validation studies have been performed demonstrating to what extent the fitted results are statistically justified. Finally, a new method to estimate the energy uncertainty is introduced where the Boltzmann weights based on the energies are compared with a `wisdom of the crowd' approach.

In chapter 7 the capabilities of VCD to distinguish and assign without any prior knowledge of the absolute configuration of a molecule with many chiral centres is explored. Studies on dydrogesterone, containing six chiral centres, and its diastereomer 6-dehydroprogesterone show that these stereoisomers can easily be identified amongst the possible 64 stereoisomers by using a single VCD measurement and the computed spectra of all stereoisomers. Moreover, both diastereomers could be identified in an equimolar mixture. When using calculated spectra to interpret diastereomeric mixtures between dydrogesterone and 6-dehydroprogesterone it was found that diastereomeric contaminations down to 25% could be detected. When using the experimental spectra of the pure compounds as a reference much lower levels of contaminations could be detected as even a contamination level of 5% could be easily found back in its VCD spectrum. This shows that VCD can be quite useful for quantitative analytical applications.

In chapter 8 the helical supramolecular polymerisation process of triarylamine tris-amides (TATA) is investigated with both VCD and electronic circular dichroism (ECD). The intriguing observation that was made in these studies is that under certain experimental conditions the VCD spectrum changed sign while the ECD spectrum remained constant. This conflicting behaviour could only be understood through an in-depth theoretical analysis of both spectroscopic techniques. Computations based on quantum chemical calculations of oligomers and on a coupled oscillator model that allowed us to simulate spectra of large stacks, provided the necessary insight into the experimental results. It was concluded that the observed sign changes directly reflect the pathway complexity in the supramolecular assembly process. When the polymers were cooled below room temperature, the initial arrangement of the amide groups in the stacks changes, leading to an opposite helicity of the fibres and associated VCD signals. The ECD signals, on the other hand, were not affected by this change because ECD intrinsically probes much larger dipole couplings. This makes the technique more susceptible to the helicity of the overall polymer bundles, which remained the same after the rearrangement of the single fibres as this would require significant larger deformations. As a result, the ECD signal thus did not change sign. Apart from demonstrating how circular dichroism techniques are able to elucidate complex self-assembly processes, the chapter also shows how the combination of probing in the electronic and vibrational domains is able to bring so much more than each of the techniques on its own.

In chapter 9 an in-depth VCD study has been performed on the chirality of mechanically planar rotaxanes. This showed that VCD is very well suited to determine the absolute configurations of these mechanically interlocked molecules. By using the GUI implementation of VCDtools in ADF the source of the intense VCD bands has been investigated together with its dependency on the absolute configuration of the chiral sources. This has led to a picture in which the VCD signal does not directly originate from the chiral sources but rather is a consequence of the asymmetrical configuration of the molecule that is enforced by these sources. Moreover, it appeared that the asymmetry introduced by the asymmetric carbon atom has far less influence than the asymmetry from the mechanically planar chirality. Finally, clear evidence was found for interactions between the two mechanically interlocked parts of the rotaxanes, both in terms of vibrational coupling and electronic intermolecular interactions.

In chapter 10 it is not the circular dichroism but the vibrational absorption is used to investigate structure and its evolution. Rapid-scan Fourier transform infra-red spectroscopy has been used here to elucidate the photoswitching pathways of donor acceptor Stenhouse adducts (DASAs) and in particular the multitude of thermal molecular conversions that follow after the initial photon absorption and relaxation back to the electronic ground state. To be able to interpret these measurements a complete theoretical mapping has been performed of the switching pathways, the energies of the conformers along these pathways and the barriers between them. These results have provided key insights in the reaction mechanism and show which barriers and intermediates are crucial for steering and optimizing the photoswitching behaviour of DASAs. The `instruction manual' that has now been compiled on how to control these switches is a powerful means to rationally design derivatives for specific purposes and to extend their large variety of possible applications.

This thesis has shown the wealth of information that vibrational fingerprints of molecules are able to provide. Several challenges that so far have been restricting the use of their circular dichroism have been taken up and met. First, methodologies have been developed to understand the very fundamentals of how VCD intensity is generated. Second, the molecular flexibility was explored, both from a structural as conformational point of view. Third, the ability to go beyond `small' molecular systems was investigated. Fourth, molecules with many chiral sources have been studied. And last, several spectroscopic techniques were used to trace the behaviour of molecules in time. Overall, the studies reported in this thesis have contributed to bring VCD to a new level. A level at which it does no longer need to be considered as a scientific curiosity, but as a mature and powerful means to perform research and analysis in a large range of fundamental and applied areas.