Chapter 7

Summary and Conclusions

Determination of the absolute configuration (AC) of chiral molecules is of utmost importance in the pharmaceutical industry since the enantiomers of chiral drugs can have completely different biological and pharmacological properties (e.g. while one enantiomer has the desired pharmacological activity, the other one may be less active, inactive, or even toxic).

Vibrational Circular Dichroism spectroscopy is a powerful tool for determination of AC. In VCD spectroscopy the AC of a compound is determined based on a comparison of its experimental and calculated spectra. Thus, in order to have reliable VCD predictions, it is imperative to understand the differences between the experimental and calculated VCD spectra, and the mechanisms that induce these changes.

This thesis deals with the various aspects related to the calculation and interpretation of VCD spectra.

Chapter 1

Chapter 1 gives a brief introduction of chirality and optical activity phenomena. After summarizing the implication of chirality in chemistry, biology and pharmaceutical industry, a short overview of the chiroptical spectroscopic techniques with emphasis on VCD is given.

Chapter 2

In Chapter 2 the theory of vibrational circular dichroism is presented. After deriving a general quantum mechanical expression for rotational strength, i.e. the quantity that determines the circular dichroism intensities, the properties of rotational strength are discussed. Then, the expression for rotational strength is
cast into a form implementable in computer programs, i.e. Stephens’ equations for VCD, by making successive approximations.

Chapter 3

Chapter 3 describes the implementation of Stephens’ equations for VCD in the Amsterdam Density Functional (ADF) program package and the validation of our implementation.

Analytical derivatives techniques have been employed for the calculation of APTs, AATs and harmonic force fields (HFF). Slater-type orbitals have been used for the calculation of APTs and HFF, whereas STO based London-atomic orbitals, the so called GIAO (gauge included atomic orbitals), have been used for the calculation of the AATs.

One complication encountered during the implementation process was the dependence of the AATs on the occupied–occupied (occ–occ) block of the \( U^{(1)}_{\lambda \alpha} \) and \( U^{(1)}_{\beta} \) matrices, i.e. the derivatives of the eigenvectors of the unperturbed Kohn-Sham equations with respect to a nuclear displacement and a magnetic field, respectively. For degenerate orbitals, the denominator of the occ–occ off-diagonal matrix elements of both \( U^{(1)}_{\lambda \alpha} \) and \( U^{(1)}_{\beta} \) matrices will diverge causing numerical problems. However, as demonstrated in section 3.2.5, the contributions from these off-diagonal matrix elements of the occ–occ blocks can be expressed in terms of the perturbed overlap matrices thereby avoiding any complication.

The validation of the implementation was done in two steps. First, we have verified the internal consistency of the code by investigating 1) the degree of origin independence of our calculated rotational strengths, and 2) to what extent the APTs and AATs sum rules are satisfied. Thus, we have shown that 1) the common origin gauge and the distributed origins gauge yield practical identical AATs, which proofs that our implementation yields rotational strengths that are origin independent [20], and 2) the sum rules for the AATs and APTs convergence to a stable limit as the size of the basis set is increased and are practically satisfied when using the large ET-pVQZ basis set, which is a good approximation of the basis set limit.

Then, we have shown that our implementation yields VCD spectra that reproduce very well the experimental VCD spectra. Using \( \alpha \)-pinene and Troger’s base as test molecules, we have tested the performance of various combinations of functionals and basis sets by comparing our calculated VCD spectra to experimental VCD spectra. We found that the BP86 and OLYP functionals in combination with TZP basis set yield VCD spectra that are in very good agree-
ment with experiments. The good agreement obtained between calculated and experimental spectra is the ultimate proof for the usefulness and correctness of the code.

Finally, we have also compared our BP86 and OLYP VCD spectra to the VCD spectra obtained with the hybrid functionals B3LYP and B3PW91 which are the most popular exchange–correlation functionals for VCD calculations. As shown, the non-hybrid functionals, i.e. BP86 and OLYP, have yielded frequencies and rotational strengths that are at least as good as the ones calculated with hybrid functionals.

Chapter 4

In Chapter 4 the effects induced by complex formation in VCD spectra have been investigated. Formation of molecular complexes between solute and solvent molecules is the most important interaction that affects the experimental VCD spectra measured in solution. Therefore, to correctly interpret the differences between gas phase calculations and experimental VCD spectra measured in solutions, it is crucial to identify and understand the mechanisms that induce changes in VCD spectra upon complex formation.

Using benzoyl-benzoic acid (BBA) hydrogen bonded to the achiral NH$_3$ as an example, 6 types of differences have been encountered when comparing the VCD spectrum of free BBA to the VCD spectrum of BBA–NH$_3$, i.e. very small changes in the rotational strengths of solute modes (case A), changes of sign of rotational strengths (case B), changes in magnitude (case C), non-zero 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).

By monitoring the changes of the APTs, AATs, and normal modes, when going from the free molecule (BBA) to the molecular complex (BBA–NH$_3$) we have been able to understand all these differences. The results of our detailed analysis have highlighted the role played by the angles $\xi$ between the electric and magnetic dipole transition moments, and clearly showed how knowledge of the values of the angles $\xi$ of the modes in the VCD spectrum can aid the interpretation of the VCD spectra. Thus, based on the value of its angle $\xi$ a normal mode can be classified as robust or non-robust. Robust modes have angles $\xi$ that are far from 90°. The sign of the rotational strength of a robust modes can be trusted since it is not easily affected by the small perturbation present in experiment. Non-robust modes, on the other hand, have angles $\xi$ that are close to 90°. The sign of the rotational strength of a non-robust mode should not be trusted since
it can be affected even by small perturbations. Clearly, only robust modes should be considered for determining the AC using VCD.

Chapter 5

In Chapter 5 we have investigated further the concept of robust modes introduced in Chapter 4. Using a test group of 27 molecules, ranging from small (5 atoms) to relatively large (44 atoms) molecules, and computational parameters that are known to yield converged APTs, AATs and normal mode frequencies, we have investigated 1) the distribution of the values taken by the angles $\xi$, and 2) the dependence of the distributions of the values taken by the $\xi$ angle on the exchange-correlation functional used in the calculation (BP86 vs. OLYP). We have found that in order to be classified as robust a normal mode should have significantly large electric and magnetic dipole transition moments, i.e. intense VCD signal, and an angle $\xi$ that differs from 90° by at least 30°.

Further, we have also shown that due to constraints imposed by symmetry on the orientations of the electric and magnetic dipole transition moments, chiral molecules that have symmetry have many normal modes with angles $\xi$ that are far from 90° (e.g. 0° or 180°). As a result, it is to be expected that under normal conditions chiral molecules with symmetry have many robust modes and therefore a better agreement between calculation and experiment should be obtained for them in comparison to molecules without symmetry.

Chapter 6

In Chapter 6 we have investigated further the mechanism responsible for the giant enhancements of the IR and VCD intensities of modes involved in hydrogen bonding. Using tris(ethylenediaminato)cobalt(III) complex with two associated chloride ions along the $C_3$ symmetry axes as an example, we have first investigated the enhancement mechanism by looking at the nuclear and electronic components of the total and atomic electric and magnetic dipole transition moments. This analysis has highlighted 1) the close relation between electric and magnetic phenomena, and 2) the constraints imposed by symmetry on the orientation of the electric and magnetic dipole transition moments and their consequences for the magnitudes of the IR and VCD intensities, which increased greatly our understanding of the enhancement mechanism.

Then, we have analyzed in detail the donor-acceptor interactions between the $3p_z$ orbitals of the $\text{Cl}^-$ associated ions (as donor) and the $\sigma^*$ molecular orbital localized on the $\text{N}–\text{H}_{axial}$ bonds (the bonds involved in the intermolecular hydro-
gen bonds). We have shown that upon stretching of the N–H$_{\text{axial}}$ bonds, charge flows from the the 3$p_z$ chloride orbitals into the N–H$_{\text{axial}}$ bonds.

Finally, by looking at the contributions to the atomic tensors (AATs and APTs) from occupied MOs, we have shown that the observed sign change of the electronic components of the electric and magnetic dipole transition moments is a direct consequence of the charge transfer phenomena. We have found that in most of the cases when the tensor components of the APTs and AATs of the hydrogen atoms involved in the intermolecular bond have significantly different values in the free molecule and in the complex (which also correlates to the sign changes of the electronic components), the components to the total AATs and APTs associated to the 8 occupied chloride valence orbitals of the complex (3$s$ and 3$p$ orbitals) have significantly large magnitudes.

The results of our analysis are consistent with the following simple physical picture of the enhancement mechanisms: the transfer of charge induced upon elongation of the N–H$_{\text{axial}}$ bond counteracts the movement of negative electronic charge dragged along by the motion of the H nuclei. Depending on the amount of charge that flows into the N–H$_{\text{axial}}$ bonds, the total electronic contributions of the electric dipole transition moments either have much smaller magnitudes and therefore are unable to counteract the nuclear contributions anymore, or change sign and therefore will reinforce the nuclear parts. Since the electric and magnetic phenomena are intimately related, a sign change of the electronic contribution of the electric dipole transition moment will induce a sign change of the electronic contribution of the (perpendicular) magnetic dipole transition moment. As a result, the nuclear and electronic components of both dipole transition moments will reinforce each other in the complex. This clearly explains the large enhancements observed for the IR and VCD intensities. The very good agreement obtained between the experimental and calculated (OLYP/TZP) VCD spectra has validated further the conclusions of this study.