

Theoretical studies of EPR parameters of spin-labels in complex environments

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Abstract

This thesis encloses quantum chemical calculations performed in the framework of density functional response theory for evaluating electron paramagnetic resonance (EPR) spin Hamiltonian parameters of various spin-labels in different environments. These parameters are the well known electronic g-tensor and the nitrogen hyperfine coupling constants, which are extensively explored in this work for various systems. A special attention was devoted to the relationships that form between the structural and spectroscopic properties that can be accounted for as an environmental influence. Such environmental effects were addressed either within a fully quantum mechanical formalism, involving simplified model structures that still capture the physical properties of the extended system, or by employing a quantum mechanics/molecular mechanics (QM/MM) approach. The latter implies that the nitroxide spin label is treated quantum mechanically, while the environment is treated in a classical discrete manner, with appropriate force fields employed for its description. The state-of-the art techniques employed in this work allow for an optimum accounting of the environmental effects that play an important role for the behaviour of EPR properties of nitroxides spin labels. One achievement presented in this thesis includes the first theoretical confirmation of an empirical assumption that is usually made for inter-molecular distance measurement experiments in deoxyribonucleic acid (DNA), involving pulsed electron-electron double resonance (PELDOR) and site-directed spin labeling (SDSL) techniques. This refers to the fact that the EPR parameters of the spin-labels are not affected by their interaction with the nucleobases from which DNA is constituted. Another important result presented deals with the influence of a supramolecular complex on the EPR properties of an encapsulated nitroxide spin-label. The inclusion complex affects the hydrogen bonding topology that forms around the $R_2NO\cdot$ moiety of the nitroxide. This, on the other hand has a major impact on its structure which further on governs the magnitude of the spectroscopic properties. The projects and results presented in this thesis offer an example of successful usage of modern quantum chemistry techniques for the investigation of EPR parameters of spin-labels in complex systems.

List of publications

- Paper I.** B. Frecus, Z. Rinkevicius and H. Ågren, **Π stacking effects on the EPR parameters of a prototypical DNA spin label**, *submitted*.
- Paper II.** B. Frecus, Z. Rinkevicius, N. Arul Murugan, O. Vahtras, J. Kongsted and H. Ågren, **EPR spin Hamiltonian parameters of encapsulated spin-labels: Impact of the hydrogen bonding topology**, *Phys. Chem. Chem. Phys.*, **15**, pp. 2427 - 2434 (2013).
- Paper III.** Z. Rinkevicius, B. Frecus, N. Arul Murugan, O. Vahtras, J. Kongsted and H. Ågren, **Encapsulation influence on EPR parameters of spin-labels: 2,2,6,6-tetramethyl-4-methoxypiperidine-1-oxyl in cucurbit[8]uril**, *J. Chem. Theory Comput.*, **8**, pp. 257–263 (2012).
- Paper IV.** Z. Rinkevicius, N. Arul Murugan, J. Kongsted, B. Frecus, A. Steindal and H. Ågren, **Density functional restricted-unrestricted/molecular mechanics theory for hyperfine coupling constants of molecules in solution**, *J. Chem. Theory Comput.*, **7**, pp. 3261–3271 (2011).

Own contribution

For all papers I participated in analysis, discussion and interpretation of results. For *papers I, II and III* I did most of the work, and was responsible for writing the first versions of the manuscripts, as well as carrying out most of the calculations. For *paper IV* I was responsible for carrying out part of the calculations and for the analysis of the results.

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Chapter 1

Introduction

Magnetic resonance spectroscopy techniques represent important and widely used tools in the investigation of matter. This field has emerged with the pioneering work of I.I. Rabi *et al.* [1], who investigated the influence of a static magnetic field on the interaction of molecular beams with oscillating fields. For this work, I.I. Rabi was awarded the 1944 Nobel Prize in Physics. The technique was subsequently extended for use on liquids and solids by E.M. Purcell *et al.* [2] and independently by F. Bloch *et al.* [3]. The Nobel Prize in Physics in 1952 was jointly awarded to F. Bloch and E.M. Purcell for their work. Inspired by the advances in the newly emerged nuclear magnetic resonance (NMR) field, E. Zavoisky [4, 5] developed the first successful electron paramagnetic resonance (EPR) experiment in 1945. Since then, these techniques were subsequently refined and extended, and employed in a wide area of fields, ranging from chemistry and biomedical research to solid state physics, to mention a few of many examples. A common motivation that stands behind these spectroscopies is the desire to attain microscopic information and physical understanding of matter. However, extracting information from a NMR or EPR experiment is not a trivial task. One usually employs the spin Hamiltonian in order to relate experimental spectra to phenomenologically introduced parameters. Further on, empirical relationships between these parameters and structural properties are drawn. At this point, quantum chemistry can be employed to give a theoretical insight into these relationships, and broaden the understanding and interpretation of NMR and EPR measurements. Recently, theoretical evaluations of EPR parameters (more specifically, the electronic g -tensor and the nitrogen hyperfine coupling constants) of nitroxide spin-labels [6] have extensively been performed in gas-phase or in solution [7, 8, 9] but few such studies have addressed the influence of different environments on the spectroscopic properties. With the advent of site-directed spin labeling (SDSL) techniques [10, 11, 12] which can employ nitroxides spin-labels as paramagnetic probes, in order to investigate the structure and dynamics of various biomolecules (e.g. proteins, lipids, nucleic acids etc...), theoretical studies aimed at a better understanding of the behaviour of

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these probes in more realistic environments become more demanding. In this respect, theoretical tools can provide valuable information for experimentalists, allowing them to design better spin-labels with extended life-time (since nitroxide spin-labels can easily get reduced to EPR silent hydroxylamines in biological systems [13, 14, 15]) or with increased binding affinities, besides the invaluable insight gained through a theoretical microscopic investigation of matter. In this respect, the present thesis represents an approach in which state-of-the art quantum chemistry techniques are employed to calculate EPR parameters of spin-labels in complex environments, shedding light onto the relationships that form between structural data and spectroscopic properties from an *ab initio* viewpoint. Moreover, special attention has been devoted to the environment influence on the EPR parameters, and structure - spectroscopic properties relations were drawn for several nitroxides evidencing the crucial role of the environment on the behaviour of the spin label performance. The thesis is organised as follows: after a short introduction, the basics of electron paramagnetic resonance (also known as electron spin resonance - ESR) experiments are discussed, and an overview of the spin Hamiltonian is presented. In order to facilitate the understanding, a simple example (a system containing an unpaired electron in the presence of a spin one-half nucleus) is given, and discussed in the framework of the EPR spin Hamiltonian. Then, in the next three chapters the quantum chemistry framework in which the EPR parameters are theoretically computed is presented. In chapter three, a brief overview on the theory of electron spin is given, along with a discussion of the theory from which it naturally emerged, i.e. the Dirac theory. Since the full Dirac theory manifests several inconveniences for quantum chemical calculations (e.g. the coupling between positron and electron states), a transformation of the four-component Dirac equation to a two-component form is derived. Then, the Foldy-Wouthuysen transformed Dirac Hamiltonian is employed in a many-body formalism, with the help of the Breit two-body interaction term. The resulted Breit-Pauli Hamiltonian is discussed, in terms of its components that govern the magnetic interactions which are of interest in EPR spectroscopy. In chapter four an overview of the computational methods is presented, with a focus on density functional theory (DFT), which offers a good alternative to the *ab-initio* methods, and allows the study of larger systems, especially when coupled in a quantum mechanics/molecular mechanics (QM/MM) approach. Moreover, an introduction to response theory and QM/MM methods is given. In chapter five, the theoretical evaluation of electronic g-tensors and hyperfine coupling constants are presented using a perturbational approach, involving the relevant terms of the Breit-Pauli Hamiltonian. In the last chapter a short summary of the papers included in the thesis is given.

Chapter 2

Electron paramagnetic resonance spectroscopy

Electron paramagnetic resonance (EPR) or electron spin resonance (ESR) spectroscopy represents a technique for studying systems which have at least one unpaired electron in their composition. The principle behind this technique is the interaction between the unpaired electron spin with an external magnetic field. When subjected to an external uniform magnetic field, the absorption of electromagnetic radiation by molecules with unpaired electrons gives rise to transitions between energy levels that are degenerate in absence of the field, but become split in its presence, the splitting being proportional to the field strength (see Figs. 2.1 and 2.2). The transitions between these levels are evidenced by subjecting the system to another magnetic field (an oscillating one, and perpendicularly oriented with respect to the uniform field) if a resonance condition is satisfied. The existence of minimum one unpaired electron is crucial, and since most stable molecules exist in singlet state (having all their electrons paired), the applicability of EPR techniques is reduced. This limitation may be viewed as an advantage, since it allows the study of specific molecules enclosed in otherwise EPR silent materials, provided the life-time of the unpaired electron is long enough.

With the basics of EPR experiments being outlined, the next step would be to address the interpretation of such experiments. In this respect, an important tool which allows relationships between the spectral features and molecular spin levels to be made, is the spin Hamiltonian concept. This represents a theoretical model which allows experimental data to be related to phenomenologically introduced parameters, which can also be subjected to theoretical evaluation. The spin Hamiltonian summarizes the relevant interactions in terms of these parameters, an external magnetic field and effective electronic and nuclear spins operators. The eigenvalues that correspond to this spin Hamiltonian give the allowed energy levels in an EPR experiment. Usually, for a system containing

CHAPTER 2. ELECTRON PARAMAGNETIC RESONANCE SPECTROSCOPY

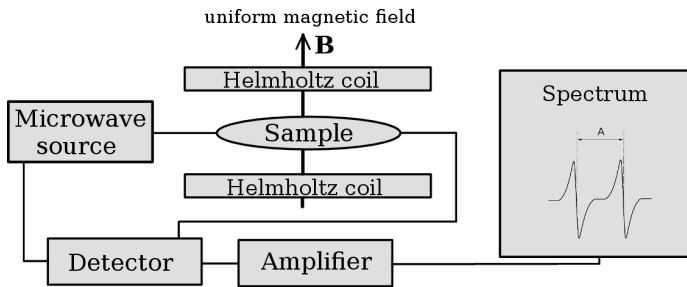


Figure 2.1: Scheme of an EPR experimental setup.

at least one unpaired electron the spin Hamiltonian is defined as [16, 17]:

$$\begin{aligned}
 H = & \sum_i \mu_B \mathbf{B}^T \cdot \mathbf{g} \cdot \mathbf{S}_i + \sum_{iI} \mathbf{S}_i^T \cdot \mathbf{A}_{iI} \cdot \mathbf{I}_I + \sum_{i \neq j} \mathbf{S}_i^T \cdot \mathbf{D}_{ij} \cdot \mathbf{S}_j \\
 & - \sum_I \gamma_I \mathbf{B}^T \cdot (1 - \boldsymbol{\sigma}_I) \cdot \mathbf{I}_I + \frac{1}{2} \sum_{I \neq J} \gamma_I \gamma_J \mathbf{I}_I^T \cdot (\mathbf{D}_{IJ} + \mathbf{K}_{IJ}) \cdot \mathbf{I}_J, \quad (2.1)
 \end{aligned}$$

where the summation normal indices, i, j , account for all the unpaired electrons in the system, while the capital indices, I, J , account for all non-zero nuclear spins present in the system (this summation convention will be used throughout the whole thesis), μ_B being the Bohr magneton, and γ_I the nuclear gyromagnetic ratio. The first term in the above equation describes the electronic Zeeman effect, which governs the interaction between the uniform external magnetic field, \mathbf{B} , and the electron spin, \mathbf{S}_i , through the electronic g-tensor, \mathbf{g} . The second term describes the hyperfine interaction between electron spin, \mathbf{S}_i , and nuclear spin, \mathbf{I}_I , through the hyperfine tensor, \mathbf{A}_{iI} . The third term describes the interaction between unpaired electrons spins, $\mathbf{S}_i, \mathbf{S}_j$, which is not dependent on any external field, through the zero-field splitting tensor, \mathbf{D}_{ij} . The fourth term describes the nuclear Zeeman effect, where the nuclear shielding tensor, $\boldsymbol{\sigma}_I$, appears, and accounts for the magnetic shielding effects of the surrounding electrons. The last term describes the direct classical dipolar interactions between nuclei spins \mathbf{I}_I and \mathbf{I}_J through the classical nuclear dipolar spin-spin coupling tensor, \mathbf{D}_{IJ} (note the capital indices, not to be confused with the zero-field splitting tensor), and the indirect couplings of the nuclear dipoles, mediated by the surrounding electrons, through the reduced indirect nuclear spin-spin coupling tensor, \mathbf{K}_{IJ} .

The above defined spin Hamiltonian is well suited for describing interactions occurring in EPR and nuclear magnetic resonance (NMR - a technique analogue to EPR but here nuclei are excited instead of electrons) experiments. As opposed to NMR spectroscopy, where usually the complete spin Hamiltonian

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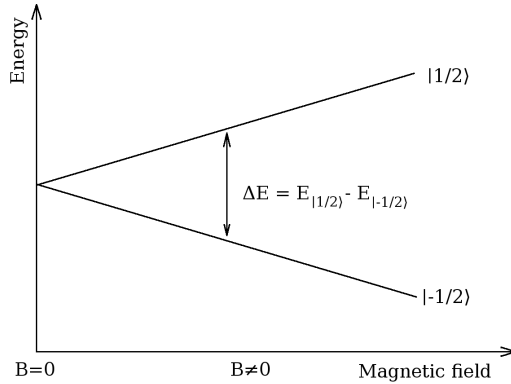


Figure 2.2: Splitting of the energy levels as a function of the external magnetic field strength for a system with one unpaired electron.

is needed in order to properly describe the spectra, in EPR spectroscopy only the relevant terms from the spin Hamiltonian can be employed for a successful description of experimental data. When more than one unpaired electron exists, the first three terms are usually employed, and in the case where only one unpaired electron exists, the first two terms are sufficient for a good description of the spectra. Although useful in the interpretation of experimentally obtained spectra, the spin Hamiltonian is though incapable in providing a direct relationship between the structure of the system under investigation and the tensorial parameters, \mathbf{g} , \mathbf{A} , ..., directly from measured spectra [18]. A way to obtain such informations is by employing quantum chemistry techniques. In this way, a direct connection between the structural data and the spectroscopic parameters can be achieved. However this is not an easy task, since real systems impose certain difficulties, which mainly relate to the computational cost as well as the accuracy of the obtained results. Before discussing these aspects, let us consider an illustrative example where the EPR spin Hamiltonian can be employed to get an insight on the problem studied.

2.1 The EPR spin Hamiltonian

For a spin one-half system the EPR spin Hamiltonian can be written in the following form:

$$H_{EPR} = g_{iso}\mu_B B S_z + \sum_{N=1}^{N_{total}} A_N \mathbf{S} \cdot \mathbf{I}_N, \quad (2.2)$$

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where the first term from the right hand side represents the electronic Zeeman interaction, with g_{iso} denoting the isotropic electronic g-factor, μ_B the Bohr magneton, B , the external, static magnetic field (assumed to be in the z direction). The second term corresponds to the hyperfine interaction, where the summation over N accounts for the coupling between the electron spin \mathbf{S} with every nuclei whose spin are denoted with \mathbf{I}_N . Making use of the creation and annihilation operators:

$$S_{\pm} = \frac{1}{\sqrt{2}}(S_x \pm iS_y) , \quad (2.3a)$$

$$I_{\pm} = \frac{1}{\sqrt{2}}(I_x \pm iI_y) , \quad (2.3b)$$

the dot product can be expressed as:

$$\mathbf{S} \cdot \mathbf{I} = S_z I_z + \frac{1}{2}(S_+ I_- + S_- I_+) . \quad (2.4)$$

In order to show the usefulness of the spin Hamiltonian concept in the analysis of EPR measurements, let us now consider the interaction between a system containing one unpaired electron with a single nucleus whose spin is also one-half. In the spin basis, $|S, m_S; I, m_I\rangle = |1/2, m_S; 1/2, m_I\rangle \equiv |m_S, m_I\rangle$, the non vanishing matrix elements of the EPR spin Hamiltonian, $\langle m'_S, m'_I | H_{EPR} | m_S, m_I \rangle$, can be written:

$$\langle 1/2, 1/2 | H_{EPR} | 1/2, 1/2 \rangle = \frac{1}{2} E_Z + \frac{1}{4} A , \quad (2.5a)$$

$$\langle 1/2, -1/2 | H_{EPR} | 1/2, -1/2 \rangle = \frac{1}{2} E_Z - \frac{1}{4} A , \quad (2.5b)$$

$$\langle 1/2, -1/2 | H_{EPR} | -1/2, 1/2 \rangle = \frac{1}{2} A , \quad (2.5c)$$

$$\langle -1/2, 1/2 | H_{EPR} | 1/2, -1/2 \rangle = \frac{1}{2} A , \quad (2.5d)$$

$$\langle -1/2, 1/2 | H_{EPR} | -1/2, 1/2 \rangle = -\frac{1}{2} E_Z - \frac{1}{4} A , \quad (2.5e)$$

$$\langle -1/2, -1/2 | H_{EPR} | -1/2, -1/2 \rangle = -\frac{1}{2} E_Z + \frac{1}{4} A , \quad (2.5f)$$

with the Zeeman energy, $E_Z = g_{iso} \mu_B B$. The two diagonal states, $|1\rangle = |1/2, 1, 2\rangle$ and $|4\rangle = |-1/2, -1, 2\rangle$ do not couple with any other off-diagonal state. For the remaining two states a diagonalization of a 2×2 matrix (see the four middle terms in Eq. 2.5) is needed. Defining the angle $\theta = \frac{1}{2} \tan^{-1} \frac{|A|}{E_Z}$, the

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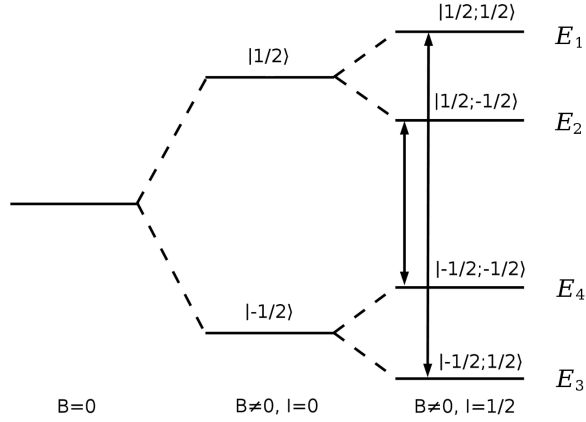


Figure 2.3: Magnetic energy levels and allowed transitions for a system with an unpaired electron and a nucleus with one-half spin.

diagonalization yields the remaining eigenstates:

$$|2\rangle = \cos \theta |1/2, -1/2\rangle + \sin \theta | -1/2, 1/2\rangle , \quad (2.6a)$$

$$|3\rangle = -\sin \theta |1/2, -1/2\rangle + \cos \theta | -1/2, 1/2\rangle , \quad (2.6b)$$

with the corresponding eigenvalues:

$$E_2 = \frac{1}{2} \sqrt{E_Z^2 + A^2} - \frac{1}{4} A , \quad (2.7a)$$

$$E_3 = -\frac{1}{2} \sqrt{E_Z^2 + A^2} - \frac{1}{4} A . \quad (2.7b)$$

In the high field limit, $g_{iso}\mu_B B \gg A$, as it is usually the case in typical EPR experiments, the eigenstates $|2\rangle$ and $|3\rangle$ can be expressed in a much simple mode, only in terms of single spin functions, with the corresponding energies written as:

$$|2\rangle \approx |1/2, -1/2\rangle , E_2 \approx \frac{1}{2} E_Z - \frac{1}{4} A , \quad (2.8a)$$

$$|3\rangle \approx | -1/2, 1/2\rangle , E_3 \approx -\frac{1}{2} E_Z - \frac{1}{4} A , \quad (2.8b)$$

In Fig. 2.3 an energy level diagram showing the subsequent splitting of initially degenerate levels due to the Zeeman effect, which are further split due to the hyperfine interaction (in the high field limit) is presented. The selection

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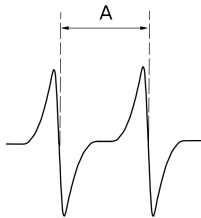


Figure 2.4: EPR spectrum for a system with an unpaired electron and a nucleus with one-half spin, showing the magnitude of the isotropic hyperfine coupling constant as the difference between the two recorded peaks.

rule, $\Delta m_S = \pm 1$, yields the allowed transitions in typical EPR spectroscopy. In the presence of a spin one-half nucleus only transitions between states with the same spin projection are observed. This gives the possibility to evaluate the isotropic hyperfine coupling constant, A , as an energy difference between the energies that correspond to the two possible transitions. In the high field limit these can be expressed:

$$\Delta E_{1-3} = E_1 - E_3 \approx E_Z + \frac{1}{2}A, \quad (2.9a)$$

$$\Delta E_{2-4} = E_2 - E_4 \approx E_Z - \frac{1}{2}A, \quad (2.9b)$$

and consequently, A , can be evaluated as:

$$A = \Delta E_{1-3} - \Delta E_{2-4}. \quad (2.10)$$

Moreover, one can estimate the intensities that characterize the possible transitions. These transitions are triggered by an external electromagnetic field in the radio frequency range, applied perpendicularly to $\mathbf{B} \equiv B_z \cdot \hat{\mathbf{z}}$, for example, along the x axis. The intensities can be then evaluated as:

$$|\langle 1|S_x|3\rangle|^2 = |\langle 2|S_x|4\rangle|^2 = \cos^2\theta, \quad (2.11)$$

yielding the two transitions intensities equal. A typical EPR spectrum for systems with a doublet ground state and one nucleus with one-half spin is shown in Fig. 2.4. It consists of two almost identical peaks split by the magnitude of the isotropic hyperfine coupling constant. Thus, from this simple example and the subsequent analysis, one is able to extract important information about the system studied.

Chapter 3

The molecular Hamiltonian

In the previous chapter we saw how the energy levels are split when a system containing at least one unpaired electron is subjected to a uniform magnetic field. This suggests that elementary particles possess an intrinsic property (the spin) that makes them interact with the external perturbing field. Since our aim is the theoretical evaluation of the EPR spin Hamiltonian parameters within an *ab-initio* approach, it is necessary to have a quantum mechanical framework in which the particle's spin explicitly appears. In electronic structure calculations the molecular Hamiltonian that appears in the Schrödinger equation, usually accounts only for the kinetic energies of the constituents (electrons and nuclei ¹) as well as the Coulomb interaction terms, without any reference to the spin of the particles. The aim of this chapter is to obtain such a molecular Hamiltonian which will include the particles' spin as explicit variables.

3.1 The electron spin

In quantum mechanics physical quantities are represented by hermitian (or self-adjoint) operators. More specifically, for such operators associated to these physical observables, the following relation holds, $\mathbf{A} = \mathbf{A}^\dagger \equiv (\mathbf{A}^*)^T$, and their expectation values, $\langle \mathbf{A} \rangle = \langle \psi | \mathbf{A} | \psi \rangle \in \Re$, should yield real numbers. More specifically, the operator that corresponds to the position observable is just a multiplicative operator, $\mathbf{r} \rightarrow \mathbf{r}$, the one that corresponds to the classical momentum is related to the gradient operator, $\mathbf{p} \rightarrow -i\hbar\nabla$, while for the total energy of a system the operator $E \rightarrow i\hbar\frac{\partial}{\partial t}$ is employed (with \hbar being the reduced Planck constant). Usually, the transition from the classical world to the quantum world is thus made by ways of analogy. For example, the operator that corresponds to the angular momentum can be constructed as $\mathbf{L} = \mathbf{r} \times \mathbf{p} \rightarrow -i\hbar\mathbf{r} \times \nabla$, for the energy of a free moving particle one has $E_k = \frac{p^2}{2m} \rightarrow -\frac{\hbar^2}{2m}\nabla^2$. However, there

¹This is further simplified in the Born-Oppenheimer [19] approximation, where the nuclei are considered at rest.

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is no way to make such an analogy with the classical world for the intrinsic angular momentum that is carried by elementary particles. Almost a century ago, in 1922, Stern and Gerlach [20] have shown that the splitting of a beam of silver atoms when shot through an inhomogeneous magnetic field suggested that particles should possess some intrinsic property like an angular momentum. At that time, one would have expected no interaction of the $5s^1$ electron with the external magnetic field, since its orbital angular momentum is zero. Few years later, in 1925 Uhlenbeck and Goudsmit [21, 22] have performed similar Stern-Gerlach experiments, but with electrons, pointing out that this intrinsic property, which is not related in any way to the orbital angular momentum, can be thought just as the magnetic moment that arises from a spinning charged classical object. In other words, Uhlenbeck and Goudsmit just postulated the existence of the electron *spin*, and since it should behave like an angular momentum, one can write its associated magnetic moment as:

$$\boldsymbol{\mu} = \frac{g\mu_B}{\hbar} \mathbf{S} , \quad (3.1)$$

with \mathbf{S} being the intrinsic electron angular momentum, or simply put, the spin operator, g denotes the g-factor - a constant value close to 2 and μ_B being the Bohr magneton. However, there was not yet any theoretical model that described particle's spin. The Schrödinger equation for a particle of mass m and charge q moving in an electric field is:

$$H\psi(\mathbf{r}, t) \equiv \left[-\frac{\hbar^2}{2m}\nabla^2 + q\Phi(\mathbf{r}, t) \right] \psi(\mathbf{r}, t) = i\hbar \frac{\partial}{\partial t} \psi(\mathbf{r}, t) , \quad (3.2)$$

with H denoting the Hamiltonian, $\Phi(\mathbf{r}, t)$ being the scalar electric potential and $\psi(\mathbf{r}, t)$ representing the wave function. The above equation describes the time evolution of the system, but has no connection with the spin of the moving particle. Or, as Schrödinger puts it [23]:

"But in what way the electron spin has to be taken into account in the present theory is yet unknown."

An attempt to make the connection between Schrödinger's theory and the electron spin has been subsequently made by Pauli [24] in 1927. The Schrödinger-Pauli equation now reads:

$$\left[\frac{1}{2m}(\boldsymbol{\sigma} \cdot \boldsymbol{\pi})^2 + q\Phi \right] |\psi\rangle = i\hbar \frac{\partial}{\partial t} |\psi\rangle , \quad (3.3)$$

with

$$\boldsymbol{\pi} \rightarrow \mathbf{p} - q\mathbf{A} = -i\hbar\nabla - q\mathbf{A} , \quad (3.4)$$

being the momentum in an electromagnetic field described by the scalar, Φ , and vector, \mathbf{A} , potentials respectively, and with $\boldsymbol{\sigma} = (\sigma_x, \sigma_y, \sigma_z)$ being a vector whose three components are the 2×2 Pauli matrices:

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$$\sigma_x = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}, \sigma_y = \begin{pmatrix} 0 & -i \\ i & 0 \end{pmatrix}, \sigma_z = \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}. \quad (3.5)$$

It is worth noting that in Eq. 3.3, $|\psi\rangle$ now represents a two-component spinor wavefunction, or a column vector:

$$|\psi\rangle = \begin{pmatrix} \psi_\alpha \\ \psi_\beta \end{pmatrix}, \quad (3.6)$$

as opposed to the Schrödinger equation (see Eq. 3.2) where ψ denotes a scalar wavefunction. Now, since the electron spin, \mathbf{S} , is an angular momentum, one can write the eigenvalue equation for its square:

$$\mathbf{S}^2|s, m_s\rangle = \hbar^2 s(s+1)|s, m_s\rangle, \quad (3.7)$$

and for the z component:

$$S_z|s, m_s\rangle = \hbar m_s|s, m_s\rangle. \quad (3.8)$$

Since electrons have half integer spin, there are only two possible eigenstates: spin up and spin down, and one can write the matrix elements of S_z as $\langle 1/2, m_{s'} | S_z | 1/2, m_s \rangle = \hbar m_s \delta_{m_{s'}, m_s}$. In this basis we can express S_z in terms of the Pauli σ_z matrix, $S_z = \frac{\hbar}{2} \sigma_z$. The eigenspinors are column matrices, $\chi_+ = \begin{pmatrix} 1 \\ 0 \end{pmatrix}$, $\chi_- = \begin{pmatrix} 0 \\ 1 \end{pmatrix}$, for spin up, and spin down respectively. The creation and annihilation operators that act on the state $|s, m_s\rangle$ are introduced as follows:

$$S_+|s, m_s\rangle \equiv \frac{1}{\sqrt{2}}(S_x + iS_y)|s, m_s\rangle = \frac{\hbar}{\sqrt{2}}\sqrt{(s-m_s)(s+m_s+1)}|s, m_s+1\rangle, \quad (3.9a)$$

$$S_-|s, m_s\rangle \equiv \frac{1}{\sqrt{2}}(S_x - iS_y)|s, m_s\rangle = \frac{\hbar}{\sqrt{2}}\sqrt{(s+m_s)(s-m_s+1)}|s, m_s-1\rangle, \quad (3.9b)$$

in terms of the first two Pauli matrices, $S_x = \frac{\hbar}{2}\sigma_x$, $S_y = \frac{\hbar}{2}\sigma_y$. Consequently, the total spin operator, \mathbf{S} , can be expressed using Pauli matrices as:

$$\mathbf{S} = \frac{\hbar}{2}\boldsymbol{\sigma}. \quad (3.10)$$

With the help of the identity

$$(\boldsymbol{\sigma}\mathbf{A}) \cdot (\boldsymbol{\sigma}\mathbf{B}) = \mathbf{A} \cdot \mathbf{B} + i\boldsymbol{\sigma} \cdot (\mathbf{A} \times \mathbf{B}), \quad (3.11)$$

let us explicit the square product $(\boldsymbol{\sigma} \cdot \boldsymbol{\pi})^2$ in Eq. 3.3 :

$$\begin{aligned}
 \left[\boldsymbol{\sigma}(\mathbf{p} - q\mathbf{A}) \right]^2 &= \mathbf{p}^2 + (q\mathbf{A})^2 - q\boldsymbol{\sigma}\mathbf{p}\boldsymbol{\sigma}\mathbf{A} - q\boldsymbol{\sigma}\mathbf{A}\boldsymbol{\sigma}\mathbf{p} \\
 &= \mathbf{p}^2 + (q\mathbf{A})^2 - q \left[-i\hbar \left(\boldsymbol{\sigma}\nabla(\boldsymbol{\sigma}\mathbf{A}) + \boldsymbol{\sigma}\mathbf{A}\boldsymbol{\sigma}\nabla \right) \right] \\
 &= \mathbf{p}^2 + (q\mathbf{A})^2 - q \left[-i\hbar \left(\boldsymbol{\sigma}(\nabla\boldsymbol{\sigma})\mathbf{A} + \boldsymbol{\sigma}\boldsymbol{\sigma}\mathbf{A}\nabla + \boldsymbol{\sigma}\boldsymbol{\sigma}(\nabla\mathbf{A}) + \boldsymbol{\sigma}\mathbf{A}\boldsymbol{\sigma}\nabla \right) \right] \\
 &= \mathbf{p}^2 + (q\mathbf{A})^2 - q \left[\boldsymbol{\sigma}\mathbf{p}\boldsymbol{\sigma}\mathbf{A} + \boldsymbol{\sigma}\boldsymbol{\sigma}\mathbf{A}\mathbf{p} + \boldsymbol{\sigma}\boldsymbol{\sigma}\mathbf{A}\mathbf{p} \right] \\
 &= \mathbf{p}^2 + (q\mathbf{A})^2 - 2q\mathbf{A}\mathbf{p} - q(\boldsymbol{\sigma}\mathbf{p})(\boldsymbol{\sigma}\mathbf{A}) \\
 &= \pi^2 - q \left(-i\hbar\nabla\mathbf{A} + i\boldsymbol{\sigma}(-i\hbar\nabla \times \mathbf{A}) \right) \\
 &= \pi^2 - q\hbar\boldsymbol{\sigma} \cdot \mathbf{B} ,
 \end{aligned} \tag{3.12}$$

where the magnetic field is expressed in terms of the vector potential (i.e. $\mathbf{B} = \nabla \times \mathbf{A}$) and the Coulomb gauge is considered (i.e. $\nabla \cdot \mathbf{A} = 0$). One can now rewrite the Hamiltonian in Eq. 3.3 :

$$H = \frac{1}{2m}\pi^2 - \frac{q\hbar}{2m}\boldsymbol{\sigma}\mathbf{B} + q\Phi , \tag{3.13}$$

with $q = -e$ for the electron. The second term from the right hand side of the above equation is the so-called spin-Zeeman term, which governs the interaction of the electron spin with an external magnetic field. If no such external field exists, the Hamiltonian will be the same as the one in Eq. 3.2. One might think that the theoretical framework from which electron's spin arises naturally was just found in the shape of the Schrödinger-Pauli equation (see Eq. 3.3). But this is not entirely the case, since the Pauli matrices were introduced "by hand", instead of arising naturally from the theory itself.

3.2 The Dirac equation

The emergence of the electron's spin comes naturally when one accounts for the principles of special relativity into the framework of quantum mechanics formalism. The first attempts in this direction, were made by Gordon [25] and Klein [26] in 1926. Their claim that what is now known as the Klein-Gordon equation (see. Eq. 3.15) was a relativistic description of the electron is not correct. Rather than a description of the relativistic electron (spin one-half particle), a relativistic description of the spinless pion was achieved. By substituting energy and momentum in the relativistic energy-momentum equation:

$$E^2 = p^2c^2 + (mc^2)^2 , \tag{3.14}$$

c being the speed of light, with their quantum mechanical corresponding operators, one easily arrives at the Klein-Gordon equation:

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$$-\hbar^2 \frac{\partial^2}{\partial t^2} \psi = \left[-\hbar^2 c^2 \nabla^2 + (mc^2)^2 \right] \psi = H^2 \psi . \quad (3.15)$$

One should note that the presence in the above equation of the second derivative with respect to time implies a non-conserving probability density (since the integral of $|\psi|^2$ varies with respect to time), hence, it cannot be interpreted similarly as the Schrödinger equation for a quantum state. To overcome this problem, Dirac [27] came with a different approach. He chose the Hamiltonian in such a way that:

$$H_D^2 \equiv (\boldsymbol{\alpha} \mathbf{p} c + \beta m c^2)(\boldsymbol{\alpha} \mathbf{p} c + \beta m c^2) = p^2 c^2 + (m c^2)^2 , \quad (3.16)$$

is satisfied, and thus, the Dirac equation would be:

$$H_D \psi \equiv (\boldsymbol{\alpha} \mathbf{p} c + \beta m c^2) \psi = i \hbar \frac{\partial}{\partial t} \psi . \quad (3.17)$$

In the above equations, the 4×4 matrices $\boldsymbol{\alpha} = (\alpha_1, \alpha_2, \alpha_3)$ and β appear, as well as the four-component wave function ψ (implied from the fact that the $\boldsymbol{\alpha}$ and β are 4×4 matrices). The $\boldsymbol{\alpha}$ and β matrices have to be chosen so that their squares are equal to the identity matrix, i.e. $\alpha_i^2 (i=1,2,3) = \beta^2 = I_4$, and the following anticommutation relations hold:

$$\{\alpha_i, \alpha_j\} = \alpha_i \alpha_j + \alpha_j \alpha_i = 0 , \quad (3.18a)$$

$$\{\alpha_i, \beta\} = \alpha_i \beta + \beta \alpha_i = 0 , \quad (3.18b)$$

with $i, j = 1, 2, 3$. One should note that the $\boldsymbol{\alpha}$ and β matrices should be independent with respect to position and momentum, since the Dirac equation describes an electron in isotropic space. The most common representation of these matrices is the following:

$$\alpha_i = \begin{pmatrix} 0 & \sigma_i \\ \sigma_i & 0 \end{pmatrix} , \beta = \begin{pmatrix} I_2 & 0 \\ 0 & -I_2 \end{pmatrix} , \quad (3.19)$$

with $i = 1, 2, 3$, and σ_i being the Pauli 2×2 matrices. In this way, a direct connection between the Dirac equation and the particle's spin arises. It is useful, for the future presentation, to introduce now the 4×4 ρ_i matrices, defined as:

$$\rho_1 = \begin{pmatrix} 0 & I_2 \\ I_2 & 0 \end{pmatrix} , \rho_2 = i \begin{pmatrix} 0 & -I_2 \\ I_2 & 0 \end{pmatrix} , \rho_3 = \begin{pmatrix} I_2 & 0 \\ 0 & -I_2 \end{pmatrix} , \quad (3.20)$$

and γ matrices (with $i = 1, 2, 3$):

$$\gamma_0 = \beta , \gamma_i = \beta \alpha_i , \quad (3.21)$$

with the help of which, the Dirac equation can be cast in the highly symmetric form:

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$$(-i\hbar\gamma_\mu\partial_\mu + mc)\psi = 0 . \quad (3.22)$$

Let us now consider a free electron at rest, Eq. 3.17 now reads:

$$H_D\psi = \beta mc^2\psi = E\psi , \quad (3.23)$$

with the eigenvectors (four-component vector columns or bispinors) $\psi_+ = \begin{pmatrix} \chi_\pm \\ 0 \end{pmatrix}$ yielding positive energy eigenvalues, $E = mc^2$, and with the eigenvectors $\psi_- = \begin{pmatrix} 0 \\ \chi_\pm^* \end{pmatrix}$ yielding negative energy eigenvalues, $E = -mc^2$ (which, as in the case of the Klein-Gordon equation, cannot be discarded). Here, the 4 fundamental solutions are described in terms of the Pauli two-component spinors denoting spin-up, $\chi_+ = \begin{pmatrix} 1 \\ 0 \end{pmatrix}$, and spin-down, $\chi_- = \begin{pmatrix} 0 \\ 1 \end{pmatrix}$, positive energy states, and spin-up, $\chi_+^* = \begin{pmatrix} 1 \\ 0 \end{pmatrix}$, and spin-down, $\chi_-^* = \begin{pmatrix} 0 \\ 1 \end{pmatrix}$, negative energy states. These negative energy states require a little bit of thinking since one can expect that an electron in a positive energy state can make a transition into one of the negative energy states, which clearly would lead to some stability problems. In this respect, Dirac postulated that all the negative energy levels are occupied in the vacuum state. Due to the fermionic nature of the electron, the transition into one of this negative energy state would be forbidden. But an electron coming from this negative energy sea can make a transition into one positive energy state, leaving a hole in the sea. One can view this hole in the negative energy and negatively charged sea as a positive energy positively charged particle. Thus, the hole in the negative energy sea can be interpreted as a positron (electron with positive charge). It is worth noting that the positron was experimentally observed by Anderson in 1932. Therefore, the Dirac equation not only describes the electron, but also its anti-particle, the positron whose solutions correspond to negative energy eigenvalues. Besides the theoretical prediction of the electron's antiparticle, another important aspect arising from the Dirac equation is that the dynamics of an electron implies a set of three independent variables, namely, position, \mathbf{r} , momentum, \mathbf{p} , and the velocity $c\boldsymbol{\alpha}$. This latter variable arises when one considers the equation of motion for the position z component, in the Heisenberg picture:

$$\dot{z} = \frac{i}{\hbar}[H_D, z] = \frac{i}{\hbar}[\beta mc^2 + c\boldsymbol{\alpha}\boldsymbol{\pi}, z] = \frac{i}{\hbar}c\alpha_z[p_z, z] = c\alpha_z , \quad (3.24)$$

with the eigenvalues of α_z being ± 1 , a measurement of the v_z component for a moving electron would yield the speed of light, c . One can now write the equation of motion for the velocity α_z :

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$$\begin{aligned}
 \dot{\alpha}_z &= \frac{i}{\hbar} [H_D, \alpha_z] = \frac{i}{\hbar} (H_D \alpha_z - \alpha_z H_D) \\
 &= \frac{i}{\hbar} (H_D \alpha_z - 2\alpha_z H_D + \alpha_z H_D) \\
 &= \frac{i}{\hbar} \left(-2\alpha_z H_D + \{H_D, \alpha_z\} \right) = \frac{i}{\hbar} (-2\alpha_z H_D + 2c p_z) , \tag{3.25}
 \end{aligned}$$

where use has been made of the commutation relations expressed in Eqs. 3.18. If we now consider the momentum to be constant in time, $\dot{p}_z = 0$, a second differentiation for α_z will yield $\ddot{\alpha}_z = -2\frac{i}{\hbar}\dot{\alpha}_z H_D$, since $\dot{H}_D = 0$, or, $\dot{\alpha}_z(t) = \dot{\alpha}_z(0)e^{-2iH_D t/\hbar}$, $\dot{\alpha}_z(0)$ being a constant time-independent value of $\dot{\alpha}_z$. Consequently, if we consider a stationary state for which E is an eigenvalue of the Dirac Hamiltonian, H_D , from the above equations, one can write:

$$\alpha_z(t) = \frac{i\hbar}{2E} \dot{\alpha}_z(0) e^{-\frac{2iEt}{\hbar}} + \frac{c p_z}{E} , \tag{3.26}$$

and thus, for the velocity $c\boldsymbol{\alpha}$ one has:

$$c\boldsymbol{\alpha} = \frac{i\hbar}{2E} c\dot{\boldsymbol{\alpha}}(0) e^{-\frac{2iEt}{\hbar}} + \frac{c^2 \mathbf{p}}{E} . \tag{3.27}$$

In the above equation the first term represents a rapid oscillatory motion which averages out, while the second term represents just the classical velocity. The first term represents the so-called *zitterbewegung* motion of the electron. The intrinsic angular momentum of the electron, or the spin, is intimately connected with this motion, as it can be viewed as the orbital angular momentum arising from the *zitterbewegung*, while the magnetic moment of the electron can be thought of as arising from the current produced by it [28, 29]. As we previously stated, we showed that the electron spin and magnetic moment beautifully arise from the Dirac theory, as a consequence of the mixing between special relativity and quantum mechanics.

Let us now consider an electron in a uniform magnetic field, described by the vector potential, \mathbf{A} , and taking the scalar potential to vanish, i.e. $\phi = 0$, we can write the Dirac equation in matrix form, in terms of the "positive" (also known in literature as "upper" or "large") and "negative" ("lower" or "small") components:

$$\begin{pmatrix} mc^2 & c\boldsymbol{\sigma} \cdot \boldsymbol{\pi} \\ c\boldsymbol{\sigma} \cdot \boldsymbol{\pi} & -mc^2 \end{pmatrix} \begin{pmatrix} \psi_+ \\ \psi_- \end{pmatrix} = E \begin{pmatrix} \psi_+ \\ \psi_- \end{pmatrix} , \tag{3.28}$$

it becomes clear that a mixing between the positive and negative components will occur. Generally, in quantum chemistry problems one is only concerned with the positive energy states (i.e. electron states). Fortunately there are

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ways which can be employed to decouple the upper and lower components, but unfortunately exact transformations can be made for special cases only, i.e. a free electron or an electron in a uniform magnetic field with vanishing scalar potential (as in the above example). Even though, when one deals with non vanishing electric fields, one can make a series of transformations up to a given desired order.

3.3 The Foldy–Wouthuysen transformation

One way to transform the four component Dirac equation into a pair of two uncoupled two component equations is by employing the so-called Foldy-Wouthuysen transformation [30]. This is achieved by performing a canonical transformation on the Dirac equation, for which the transformed Hamiltonian becomes free of odd operators. Then, one can subsequently represent the positive and negative energy states only by two component wave functions. The term "odd operator" introduced above represents an operator which connects the "upper" and "lower" components (or the positive and negative energy states) of the wave function. An "even operator" on the other hand connects only "upper" – "upper" or "lower" – "lower" components of the wave function. The simplest matrix representation of an odd operator can be written:

$$\mathcal{O} = \begin{pmatrix} 0 & \mathbf{a} \\ \mathbf{b} & 0 \end{pmatrix}, \quad (3.29)$$

while, for an even operator one can write:

$$\mathcal{E} = \begin{pmatrix} \mathbf{a} & 0 \\ 0 & \mathbf{b} \end{pmatrix}. \quad (3.30)$$

It becomes clear now that the Dirac Hamiltonian appearing in Eq. 3.17 contains odd operators through the components of the operator $\boldsymbol{\alpha}$. As previously stated, there are some cases for which a canonical transformation can be made completely (i.e. free electron, electron moving in uniform magnetic field with $\phi = 0$.) or approximately, when electric fields are present. We shall now turn our attention to the first case, and consider a moving electron in a uniform magnetic field.

Let S be a Hermitian operator, so that the unitary transformation:

$$\psi' = e^{iS}\psi, \quad (3.31a)$$

$$\begin{aligned} H_D\psi &= i\hbar\frac{\partial}{\partial t}(e^{-iS}\psi') = i\hbar e^{-iS}\frac{\partial}{\partial t}\psi' + i\hbar\left(\frac{\partial}{\partial t}e^{-iS}\right)\psi', \\ i\hbar\frac{\partial}{\partial t}\psi' &= \left(e^{iS}H_De^{-iS} - i\hbar e^{iS}\frac{\partial}{\partial t}e^{-iS}\right)\psi' = H\psi' \Rightarrow \\ H &= e^{iS}H_De^{-iS} - i\hbar e^{iS}\frac{\partial}{\partial t}e^{-iS}, \end{aligned} \quad (3.31b)$$

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would yield a Hamiltonian, H , which does not contain any odd operators. It is worth mentioning that in this representation any operator that in Dirac theory is A , now becomes $A' = e^{iS} A e^{-iS}$. Using the above mentioned unitary transformation, the Dirac equation, $H_D \psi = i\hbar \frac{\partial}{\partial t} \psi$, becomes $H \psi' = i\hbar \frac{\partial}{\partial t} \psi'$. If one choses S to be not explicitly depending on time and of the form:

$$S = -\frac{i}{2mc} \beta \boldsymbol{\alpha} \cdot \boldsymbol{\pi} f(\boldsymbol{\sigma} \cdot \boldsymbol{\pi}) , \quad (3.32)$$

with f being a real function of $\boldsymbol{\sigma} \cdot \boldsymbol{\pi}$, one can show that for the transformed Hamiltonian the following relation holds:

$$H = e^{iS} H_D e^{-iS} = e^{2iS} H_D . \quad (3.33)$$

To prove the above statement let us write the exponential expansions:

$$H_D e^{-iS} = H_D \sum_k \frac{(-iS)^k}{k!} , \quad (3.34a)$$

$$e^{iS} H_D = \sum_k \frac{(iS)^k}{k!} H_D , \quad (3.34b)$$

and, since S and H_D anticommute, $\{S, H_D\} = S H_D + H_D S = 0$, one has $H_D (-S)^k = S^k H_D$, hence $H = e^{2iS} H_D$. Now, with the operator S taking the form expressed in Eq. 3.32, we can expand the exponential in terms of even and odd powers [31]:

$$\begin{aligned} e^{2iS} &= \sum_{n=0}^{\infty} \frac{1}{n!} \left[\frac{1}{mc} \beta \boldsymbol{\alpha} \boldsymbol{\pi} f \right]^n \\ &= \sum_{k=0}^{\infty} \frac{1}{(2k)!} \left[\left(\frac{1}{mc} \beta \boldsymbol{\alpha} \boldsymbol{\pi} f \right)^2 \right]^k + \sum_{k=0}^{\infty} \frac{1}{(2k+1)!} \frac{\beta \boldsymbol{\alpha} \boldsymbol{\pi} f}{mc} \left[\left(\frac{1}{mc} \beta \boldsymbol{\alpha} \boldsymbol{\pi} f \right)^2 \right]^k . \end{aligned} \quad (3.35)$$

Keeping in mind the properties of the $\boldsymbol{\alpha}$ and β matrices, let us express the square of the operator:

$$\begin{aligned} \left(\frac{1}{mc} \beta \boldsymbol{\alpha} \boldsymbol{\pi} f \right)^2 &= \left(\frac{f}{mc} \right)^2 \beta \boldsymbol{\alpha} \boldsymbol{\pi} \beta \boldsymbol{\alpha} \boldsymbol{\pi} \\ &= -\left(\frac{f}{mc} \right)^2 \beta^2 \rho_1^2 \boldsymbol{\sigma} \boldsymbol{\pi} \boldsymbol{\sigma} \boldsymbol{\pi} = -\left(\frac{f}{mc} \right)^2 (\boldsymbol{\sigma} \boldsymbol{\pi})^2 , \end{aligned} \quad (3.36)$$

with $\boldsymbol{\alpha}$ expressed in terms of the ρ_1 matrix, the product becomes $\beta \boldsymbol{\alpha} \boldsymbol{\pi} = \beta \rho_1 \boldsymbol{\sigma} \boldsymbol{\pi}$. With the help of Eq. 3.36, we can further write the exponential:

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$$\begin{aligned}
 e^{2iS} &= \sum_{k=0}^{\infty} \frac{(-1)^k}{(2k)!} \left(\frac{f}{mc} \boldsymbol{\sigma} \boldsymbol{\pi} \right)^{2k} + \beta \rho_1 \sum_{k=0}^{\infty} \frac{(-1)^k}{(2k+1)!} \left(\frac{f}{mc} \boldsymbol{\sigma} \boldsymbol{\pi} \right)^{2k+1} \\
 &= \cos \left(\frac{f}{mc} \boldsymbol{\sigma} \boldsymbol{\pi} \right) + \beta \rho_1 \sin \left(\frac{f}{mc} \boldsymbol{\sigma} \boldsymbol{\pi} \right).
 \end{aligned} \tag{3.37}$$

Consequently, we can write the Hamiltonian in the new representation:

$$\begin{aligned}
 H &= e^{2iS} H_D = \left[\cos \left(\frac{f}{mc} \boldsymbol{\sigma} \boldsymbol{\pi} \right) + \beta \rho_1 \sin \left(\frac{f}{mc} \boldsymbol{\sigma} \boldsymbol{\pi} \right) \right] (\beta mc^2 + c \boldsymbol{\alpha} \cdot \boldsymbol{\pi}) \\
 &= (\beta mc^2 + c \rho_1 \boldsymbol{\sigma} \cdot \boldsymbol{\pi}) \cos(f') + \beta \rho_1 \beta mc^2 \sin(f') + \beta \rho_1^2 c \boldsymbol{\sigma} \cdot \boldsymbol{\pi} \sin(f') \\
 &= (\beta mc^2 + c \rho_1 \boldsymbol{\sigma} \cdot \boldsymbol{\pi}) \cos(f') - (mc^2 \rho_1 - c \beta \boldsymbol{\sigma} \cdot \boldsymbol{\pi}) \sin(f') \\
 &= \beta c \left[mc \cos(f') + \boldsymbol{\sigma} \cdot \boldsymbol{\pi} \sin(f') \right] + c \rho_1 \left[\boldsymbol{\sigma} \cdot \boldsymbol{\pi} \cos(f') - mc \sin(f') \right],
 \end{aligned} \tag{3.38}$$

where we used the notation $f' = \frac{f}{mc} \boldsymbol{\sigma} \cdot \boldsymbol{\pi}$, and the fact that ρ_1 and $\boldsymbol{\sigma}$ commute, ρ_1 and β anti-commute, and $\rho_1^2 = I_2$. With the transformed Hamiltonian written in this form, it becomes clear that for it to be even, the second term from the right hand side should vanish, since ρ_1 is the only odd operator involved in the equation. This condition is fulfilled if $\frac{\sin(f')}{\cos(f')} = \frac{\boldsymbol{\sigma} \cdot \boldsymbol{\pi}}{mc}$, and thus f becomes:

$$f(\boldsymbol{\sigma} \cdot \boldsymbol{\pi}) = \frac{mc}{\boldsymbol{\sigma} \cdot \boldsymbol{\pi}} \tan^{-1} \frac{\boldsymbol{\sigma} \cdot \boldsymbol{\pi}}{mc}. \tag{3.39}$$

Taking now into account the trigonometric identities:

$$\cos(\tan^{-1} x) = \frac{1}{\sqrt{1+x^2}}, \quad \sin(\tan^{-1} x) = \frac{x}{\sqrt{1+x^2}}, \tag{3.40}$$

we have:

$$\cos(f') = \frac{mc}{\sqrt{(mc)^2 + (\boldsymbol{\sigma} \boldsymbol{\pi})^2}}, \quad \sin(f') = \frac{\boldsymbol{\sigma} \boldsymbol{\pi}}{\sqrt{(mc)^2 + (\boldsymbol{\sigma} \boldsymbol{\pi})^2}}, \tag{3.41}$$

and the transformed Hamiltonian, H , becomes:

$$H = \beta c \sqrt{(mc)^2 + (\boldsymbol{\sigma} \boldsymbol{\pi})^2}, \tag{3.42}$$

providing thus independent equations for the positive and negative energy components, due to the fact that it is comprised only from even operators. For the general case, when one deals with the presence of electric fields (as it is the case in quantum chemistry problems) the Foldy-Wouthuysen (FW)

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transformation can be also employed, but there is no representation which would yield the Hamiltonian free of odd operators. Still, one can perform successive FW transformations up to a given desired order in $\lambda = \frac{1}{mc^2}$, in order to reduce the odd operators that arise up to that order. In the general case, the Dirac Hamiltonian has the form:

$$\begin{aligned} H_D &= \beta mc^2 + c\boldsymbol{\alpha}\boldsymbol{\pi} + q\phi, \\ H_D &= \frac{1}{\lambda}\beta + \mathcal{O} + \mathcal{E}, \end{aligned} \quad (3.43)$$

where we recall that for an electron we shall consider $q = -e$, while ϕ, \mathbf{A} denote the scalar and vector potentials respectively, with the odd operator, $\mathcal{O} = c\boldsymbol{\alpha}\boldsymbol{\pi}$, and the even operator being $\mathcal{E} = q\phi$. We can perform a similar unitary transformation as the one expressed in Eqs. 3.31, and we will expand the exponentials that arise in an infinite series of commutators, as follows:

$$e^{iS}H_De^{-iS} = H_D + i[S, H_D] + \frac{i}{2}[S, i[S, H_D]] + \frac{i}{3}\left[S, \frac{i}{2}[S, i[S, H_D]]\right] + \dots, \quad (3.44)$$

and if we replace the Dirac Hamiltonian in the above equation with the operator $\partial/\partial t$ we can also write:

$$e^{iS}\frac{\partial}{\partial t}e^{-iS} = -i\frac{\partial S}{\partial t} - \frac{i}{2}\left[S, i\frac{\partial S}{\partial t}\right] - \frac{i}{3}\left[S, \frac{i}{2}\left[S, i\frac{\partial S}{\partial t}\right]\right] - \dots. \quad (3.45)$$

Consequently, we can perform the first transformation of the Hamiltonian:

$$\begin{aligned} H' &= e^{iS}H_De^{-iS} - i\hbar e^{iS}\frac{\partial}{\partial t}e^{-iS} \\ &= \frac{1}{\lambda}\beta + \mathcal{O} + \mathcal{E} + i[S, H_D] + \frac{i}{2}[S, i[S, H_D]] + \frac{i}{3}\left[S, \frac{i}{2}[S, i[S, H_D]]\right] + \dots \\ &\quad - \hbar\dot{S} - \frac{i}{2}\hbar[S, \dot{S}] + \dots, \end{aligned} \quad (3.46)$$

and, since the aim is to reduce the odd operator, we use the following operator $S = -i\frac{\lambda}{2}\beta\mathcal{O}$. Bearing in mind the commutation and anticommutation relations involving β and $\alpha_{i=1,2,3}$ matrices, and that even operators commute while an even and an odd operator anti-commute, let us now evaluate the first commutator:

$$\begin{aligned} i[S, H_D] &= \frac{\lambda}{2}\left[\beta\mathcal{O}, \frac{1}{\lambda}\beta + \mathcal{O} + \mathcal{E}\right] \\ &= -\mathcal{O} + \lambda\beta\mathcal{O}\mathcal{E} + \lambda\beta\mathcal{O}^2. \end{aligned} \quad (3.47)$$

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For the second commutator in Eq. 3.46 we have:

$$\begin{aligned} \frac{i}{2} [S, i[S, H_D]] &= \frac{i}{2} [S, -\mathcal{O} + \lambda\beta\mathcal{O}\mathcal{E} + \lambda\beta\mathcal{O}^2] \\ &= -\frac{\lambda}{2}\beta\mathcal{O}^2 - \frac{\lambda^2}{2}\mathcal{E}\mathcal{O}^2 - \frac{\lambda^2}{2}\beta\mathcal{O}^3, \end{aligned} \quad (3.48)$$

while for the third and fourth:

$$\frac{i}{3} \left[S, \frac{i}{2} [S, i[S, H_D]] \right] = \frac{\lambda^2}{6}\mathcal{O}^3 + \frac{\lambda^3}{6}\beta\mathcal{E}\mathcal{O}^3 - \frac{\lambda^3}{6}\beta\mathcal{O}^4, \quad (3.49)$$

$$\frac{i}{4} \left[S, \frac{i}{3} \left[S, \frac{i}{2} [S, i[S, H_D]] \right] \right] = \frac{\lambda^3}{24}\beta\mathcal{O}^4 + \frac{\lambda^4}{24}\mathcal{E}\mathcal{O}^4 + \frac{\lambda^4}{24}\mathcal{O}^5. \quad (3.50)$$

The commutators involving time derivatives of S are:

$$-\hbar\dot{S} = i\hbar\frac{\lambda}{2}\beta\dot{\mathcal{O}}, \quad (3.51)$$

$$-\frac{i}{2}\hbar[S, \dot{S}] = -i\hbar\frac{\lambda^2}{8}[\mathcal{O}, \dot{\mathcal{O}}]. \quad (3.52)$$

Writing $\mathcal{O}^2\mathcal{E} = 1/4[\mathcal{O}, [\mathcal{O}, \mathcal{E}]]$ and $\mathcal{O}\mathcal{E} = 1/2[\mathcal{O}, \mathcal{E}]$, the Hamiltonian, H' , becomes (note that several λ^3 or higher order terms have been discarded):

$$\begin{aligned} H' &= \beta\left(\lambda^{-1} + \frac{\lambda}{2}\mathcal{O}^2 - \frac{\lambda^3}{8}\mathcal{O}^4\right) + \left[\mathcal{E} - i\hbar\frac{\lambda^2}{8}[\mathcal{O}, \dot{\mathcal{O}}] - \frac{\lambda^2}{8}[\mathcal{O}, [\mathcal{O}, \mathcal{E}]]\right] \\ &+ \left\{ \frac{\lambda}{2}\beta[\mathcal{O}, \mathcal{E}] - \frac{\lambda^2}{3} + i\hbar\frac{\lambda}{2}\beta\dot{\mathcal{O}} \right\} \\ &= \beta m' c^2 + \mathcal{E}' + \mathcal{O}'. \end{aligned} \quad (3.53)$$

Now, the new odd operator in the above equation is the one between the braces, and a subsequent FW transformation can be made in order to reduce it, $H'' = e^{iS'}(H' - i\hbar\partial/\partial t)e^{-iS'}$, making use of the new operator $S' = -i\frac{\lambda}{2}\beta\mathcal{O}'$. The operation can be performed until the desired order will be achieved. Further on, with the help of Eq. 3.12, let us evaluate the even operators involved in the first term of Eq. 3.53 :

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$$\begin{aligned}\frac{\lambda}{2}\mathcal{O}^2 &= \frac{\lambda}{2}(c\rho_1\boldsymbol{\sigma}\boldsymbol{\pi})^2 = \frac{\lambda}{2}c^2\rho_1^2(\boldsymbol{\sigma}\boldsymbol{\pi})^2 \\ &= \frac{1}{2m}(\pi^2 - q\hbar\boldsymbol{\sigma} \cdot \mathbf{B})\end{aligned}\quad (3.54)$$

$$\begin{aligned}\frac{\lambda^3}{8}\mathcal{O}^4 &= \frac{\lambda^3}{8}(c\rho_1\boldsymbol{\sigma}\boldsymbol{\pi})^4 = \frac{\lambda^3}{8}c^4(\boldsymbol{\sigma}\boldsymbol{\pi})^4 \\ &= \frac{1}{8m^3c^2}(\boldsymbol{\sigma}\boldsymbol{\pi})^4.\end{aligned}\quad (3.55)$$

The even operators appearing in the second term of Eq. 3.53:

$$\frac{\lambda^2}{8}\left\{[\mathcal{O}, [\mathcal{O}, \mathcal{E}]] + i\hbar[\mathcal{O}, \dot{\mathcal{O}}]\right\} = \frac{\lambda^2}{8}\left[\mathcal{O}, [\mathcal{O}, \mathcal{E}] + i\hbar\dot{\mathcal{O}}\right], \quad (3.56)$$

involve several commutators. The first one can be evaluated as:

$$[\mathcal{O}, \mathcal{E}] = [c\boldsymbol{\alpha}\boldsymbol{\pi}, q\phi] = -i\hbar cq\boldsymbol{\alpha}\nabla\phi, \quad (3.57)$$

since the vector, \mathbf{A} , and scalar, ϕ , potentials are even operators, and so, their commutator vanishes, $[\mathbf{A}, \phi] = 0$. Consequently, one can write:

$$[\mathcal{O}, \mathcal{E}] + i\hbar\dot{\mathcal{O}} = -i\hbar cq\boldsymbol{\alpha}\nabla\phi - i\hbar cq\boldsymbol{\alpha}\frac{\partial\mathbf{A}}{\partial t} = i\hbar cq\boldsymbol{\alpha} \cdot \mathbf{E} \quad (3.58)$$

Evaluating the second commutator gives:

$$\begin{aligned}\left[\mathcal{O}, [\mathcal{O}, \mathcal{E}] + i\hbar\dot{\mathcal{O}}\right] &= [c\rho_1\boldsymbol{\sigma} \cdot \boldsymbol{\pi}, i\hbar cq\boldsymbol{\alpha} \cdot \mathbf{E}] \\ &= i\hbar c^2q[\rho_1\boldsymbol{\sigma} \cdot \boldsymbol{\pi}, \rho_1\boldsymbol{\sigma} \cdot \mathbf{E}] \\ &= i\hbar c^2q(\rho_1\boldsymbol{\sigma} \cdot \boldsymbol{\pi}\rho_1\boldsymbol{\sigma} \cdot \mathbf{E} - \rho_1\boldsymbol{\sigma} \cdot \mathbf{E}\rho_1\boldsymbol{\sigma} \cdot \boldsymbol{\pi}) \\ &= i\hbar c^2q\left[\boldsymbol{\pi}\mathbf{E} + i\boldsymbol{\sigma}(\boldsymbol{\pi} \times \mathbf{E}) - \mathbf{E}\boldsymbol{\pi} - i\boldsymbol{\sigma}(\mathbf{E} \times \boldsymbol{\pi})\right] \\ &= i\hbar c^2q\left[-i\hbar\nabla\mathbf{E} + i\boldsymbol{\sigma}(\boldsymbol{\pi} \times \mathbf{E}) - i\boldsymbol{\sigma}(\mathbf{E} \times \boldsymbol{\pi})\right],\end{aligned}\quad (3.59)$$

where use has been made of Eq. 3.11 and the fact that the vector potential, \mathbf{A} , and the electric field, \mathbf{E} , are even operators and thus commute. Consequently, one has:

$$-\frac{\lambda^2}{8}\left[\mathcal{O}, [\mathcal{O}, \mathcal{E}] + i\hbar\dot{\mathcal{O}}\right] = -\frac{\hbar^2q}{8m^2c^2}\nabla\mathbf{E} + \frac{\hbar q}{8m^2c^2}\boldsymbol{\sigma}(\boldsymbol{\pi} \times \mathbf{E}) - \frac{\hbar q}{8m^2c^2}\boldsymbol{\sigma}(\mathbf{E} \times \boldsymbol{\pi}), \quad (3.60)$$

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and thus, the FW transformed Dirac Hamiltonian becomes:

$$\begin{aligned}
 H_D^{FW} &= \beta mc^2 + \frac{1}{2m} \beta \pi^2 - \frac{1}{8m^3 c^2} \beta (\boldsymbol{\sigma} \boldsymbol{\pi})^4 \\
 &+ q\phi - \frac{q}{2mc^2} \beta \boldsymbol{\sigma} \mathbf{B} - \frac{\hbar^2 q}{8m^2 c^2} \nabla \mathbf{E} \\
 &+ \frac{\hbar q}{8m^2 c^2} \boldsymbol{\sigma} (\boldsymbol{\pi} \times \mathbf{E}) - \frac{\hbar q}{8m^2 c^2} \boldsymbol{\sigma} (\mathbf{E} \times \boldsymbol{\pi}) .
 \end{aligned} \tag{3.61}$$

The first three terms represent the energy at rest, the non relativistic kinetic energy and the relativistic correction to the kinetic energy respectively, the fourth and fifth represent the energy of a particle with charge q and spin $\boldsymbol{\sigma}$ in an external electromagnetic field, the sixth term represents the so-called Darwin correction [32], while the last two terms represent the spin-orbit interaction.

3.4 The Breit-Pauli Hamiltonian

So far we have addressed only the one-body problem, but quantum chemistry in general does not deal with such simple (yet complicated) problems. The fully-relativistic quantum mechanical ² description of the electron given by the Dirac theory can be yet very useful in this respect, although difficult to implement due to the four-component nature of the bispinors involved. The Foldy-Wouthuysen transformation provides the necessary decoupling between the positive and negative energy components of the wave-function, yielding a quasi-relativistic limit for the Pauli theory, or a non-relativistic limit for the Dirac theory. The drawback of the aforementioned transformation relies on the fact that when electric fields are present (as it is usually the case), the FW transformation can not be precisely made, but rather up to a given order in $\lambda = (mc^2)^{-1}$. Up to second order, one reaches the Pauli theory. The natural next step would be to include the single-particle Dirac Hamiltonian (or the FW transformed one) into a many-body formalism. This is not a trivial task since the Coulomb interaction between the electrons does not propagate instantaneously and retardation effects should be accounted for, as required by special relativity. There are two ways in which the two-body problem can be treated, and which can be extended to a many-body formalism. In principle, the approach proposed by Salpeter and Bethe [33] can provide more accurate results, but we will focus on the approach proposed by Breit [34], even though it is of limited accuracy, due to the fact that it is more convenient for our purposes. A many-body Hamiltonian extension of the two-body Breit Hamiltonian would read:

$$H = \sum_i H_D^i + \frac{1}{2} \sum_{i \neq j} H_{Breit}^{ij} , \tag{3.62}$$

² Actually, the term "fully-relativistic quantum mechanical" might be misleading, since in the Dirac theory the fields are treated classically rather than quantum mechanically.

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with, H_D^i denoting the Dirac Hamiltonian for particle i , and the potential term ³ :

$$H_{Breit}^{ij} = \frac{1}{r_{ij}} - \frac{1}{2r_{ij}} \left(\boldsymbol{\alpha}_i \boldsymbol{\alpha}_j + \frac{(\boldsymbol{\alpha}_i \cdot \mathbf{r}_{ij})(\boldsymbol{\alpha}_j \cdot \mathbf{r}_{ij})}{r_{ij}^2} \right), \quad (3.63)$$

where the first term represents the Coulomb interaction, while the second is the two-body Breit operator which accounts for the retardation effects of the interaction. In this operator, the Dirac $\boldsymbol{\alpha}$ matrices corresponding to electrons i and j appear. The wave-function corresponding to the Breit Hamiltonian is a 4^N -component spinor, with N being the total number of electrons considered in the system, since each electron in Dirac theory is described by a four component vector or bispinor, hence the total wave-function is a tensor product involving N bispinors. Consequently the many-body Dirac-Coulomb-Breit Hamiltonian (which denotes the many-body extension of the two-body Breit Hamiltonian) can be written:

$$H_{DCB} = \sum_i H_D^i + \frac{1}{2} \sum_{i \neq j} \left[\frac{1}{r_{ij}} - \frac{1}{2r_{ij}} \left(\boldsymbol{\alpha}_i \boldsymbol{\alpha}_j + \frac{(\boldsymbol{\alpha}_i \cdot \mathbf{r}_{ij})(\boldsymbol{\alpha}_j \cdot \mathbf{r}_{ij})}{r_{ij}^2} \right) \right]. \quad (3.64)$$

Although the Dirac-Coulomb-Breit Hamiltonian can be in principle employed to solve problems in quantum chemistry, a practical approach would be to reduce the four-component spinors involved for each particle in the above equation into one which involves only two-component spinors. As already mentioned, the FW transformation can be employed in this respect. For the single-particle Dirac Hamiltonian we have already achieved this transformation, up to second order in λ . The FW transformation of the two-body interaction term has been accomplished by Chraplyvy [35, 36], Barker and Glover [37], but since the algebra is more complicated it will not be reproduced here. Consequently, a FW transformation of the Dirac-Coulomb-Breit Hamiltonian would yield the so-called Breit-Pauli Hamiltonian:

³ We should make one comment about the formulas appearing in this section. In previous sections of this Chapter the formulas were expressed in the *international system of units* to facilitate the physical understanding of the terms, through the constants that appear. Moreover, the charge q has not been explicitly replaced with the elementary charge of the electron, $q \rightarrow -e$, since the equations also apply for positively charged fermions. However, we will renounce to do so further on. Instead, in order to make the formulas look more clear we are opting for the *atomic units system* where the reduced Plank's constant, \hbar , the electron mass, m_e , elementary charge, e , and Coulomb's constant, $1/4\pi\epsilon_0$, are all equal to unity. Moreover, $\lambda = (mc^2)^{-1}$ will be expressed in terms of the fine structure constant, $\alpha = c^{-1} \approx 1/137$.

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$$\begin{aligned}
H_{BP} = & \sum_i \left(c^2 + \frac{1}{2}\pi_i^2 - \frac{\alpha^2}{8}\pi_i^4 - \phi_i - \boldsymbol{\mu}_i \cdot \mathbf{B} + \frac{\alpha^2}{2}\pi_i^2 \boldsymbol{\mu}_i \cdot \mathbf{B} \right. \\
& + \frac{\alpha^2}{8} \nabla \mathbf{E}_i + \frac{\alpha^2}{4} \boldsymbol{\mu}_i \cdot (\boldsymbol{\pi}_i \times \mathbf{E}_i - \mathbf{E}_i \times \boldsymbol{\pi}_i) \\
& + \sum_{i \neq j} \left[\frac{1}{2r_{ij}} - \frac{\alpha^2}{4} \left(\frac{\boldsymbol{\pi}_i \cdot \boldsymbol{\pi}_j}{r_{ij}} + \frac{(\boldsymbol{\pi}_i \cdot \mathbf{r}_{ij})(\mathbf{r}_{ij} \cdot \boldsymbol{\pi}_j)}{r_{ij}^3} \right) \right. \\
& + \frac{\alpha^2}{2} \left(\frac{\boldsymbol{\mu}_j \cdot (\mathbf{r}_{ij} \times \boldsymbol{\pi}_j)}{r_{ij}^3} + \frac{2\boldsymbol{\mu}_i \cdot (\mathbf{r}_{ij} \times \boldsymbol{\pi}_i)}{r_{ij}^3} \right) \\
& + \frac{\alpha^2}{2} \left(\frac{r_{ij}^2 \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_j - 3(\boldsymbol{\mu}_i \cdot \mathbf{r}_{ij})(\mathbf{r}_{ij} \cdot \boldsymbol{\mu}_j)}{r_{ij}^5} - \frac{8\pi}{3} \delta(\mathbf{r}_{ij}) \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_j \right) \\
& \left. - \frac{\alpha^2 \pi}{2} \delta(\mathbf{r}_{ij}) \right], \tag{3.65}
\end{aligned}$$

where $\boldsymbol{\mu}_i = -2\mu_B \mathbf{S}_i$ represents the magnetic moment of electron i associated with its spin \mathbf{S}_i . The first summation goes for the FW transformed Dirac Hamiltonian expressed in Eq. 3.61, while the second summation represents the FW transformed two-body interaction, and is comprised of several terms: (i) the Coulomb repulsion between electrons, (ii) the orbit-orbit interaction which accounts for the interaction between the magnetic dipole moments, arising from the orbital motion of charged particles, (iii) the spin-other orbit interaction which accounts for the interaction between the spin magnetic moment of one particle with the orbital moment of another particle, (iv) the spin-spin interaction which consists of two terms, the first can be thought of as a classical dipole-dipole interaction between magnetic moments, the second being a contact interaction, since it vanishes when particles are not at the same position due to the appearance of the δ -Dirac function, and lastly (v) the relativistic two-electron Darwin term. Except the first two terms, all the others are written on separate lines in the above equation. Although we made some simplifications in order to reach the Breit-Pauli Hamiltonian, with the aim of having a Hamiltonian suitable for electronic structure calculations, its direct usage in the field of quantum chemical calculations has several drawbacks, since some terms of H_{BP} are divergent rendering the Hamiltonian variationally unstable [31, 38]. However, in the framework of perturbation theory, for the evaluation of EPR spin Hamiltonian parameters several terms of the Breit-Pauli Hamiltonian can be successfully used. More explicitly, a set of four Hamiltonians can be formed, which will govern the behaviour of EPR spin Hamiltonian parameters (electronic g-tensor and hyperfine coupling constants), which represent the subject of this thesis. These Hamiltonians describe the following interactions: (i) Zeeman, (ii) spin-orbit, (iii) spin-spin, and (iv) diamagnetic interactions respectively [38].

The Zeeman Hamiltonian is written as:

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$$H_Z = \frac{1}{2} \sum_i \mathbf{B} \cdot \mathbf{l}_{iO} - \sum_i \boldsymbol{\mu}_i \cdot \mathbf{B} - \frac{\alpha^2}{2} \sum_i \nabla_i^2 \boldsymbol{\mu}_i \cdot \mathbf{B} . \quad (3.66)$$

The first term describes the interaction between the magnetic moment generated by the orbital motion, represented by the angular momentum operator, \mathbf{l}_{iO} , with an external magnetic field, \mathbf{B} . The second term describes the interaction between the magnetic moment associated with the electron spin with the external magnetic field. The third term represents the so-called "mass-velocity" correction, which accounts for the relativistic correction to the kinetic energy.

The spin-orbit Hamiltonian is written as:

$$H_{SO} = \frac{\alpha^2}{4} \sum_i \boldsymbol{\mu}_i \cdot (\mathbf{p}_i \times \mathbf{E}_i - \mathbf{E}_i \times \mathbf{p}_i) - \frac{\alpha^2}{2} \sum_{iI} \frac{Z_I \boldsymbol{\mu}_i \cdot \mathbf{l}_{iI}}{r_{iI}^3} + \frac{\alpha^2}{2} \sum_{i \neq j} \frac{(\boldsymbol{\mu}_i + 2\boldsymbol{\mu}_j) \cdot \mathbf{l}_{ij}}{r_{ij}^3} , \quad (3.67)$$

where the first term describes the spin-orbit interaction governed by the external electric field, \mathbf{E} , the second term describes the spin-orbit interaction governed by the magnetic field arising from nuclei, while the third term accounts for the two-body spin-orbit operator accounting for the interaction between the i -th electron magnetic moment associated with its spin with the magnetic field generated by the j -th electron's motion.

The spin-spin Hamiltonian is written as:

$$H_{SS} = \alpha^2 \sum_{i \neq j} \left(\frac{r_{ij}^2 \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_j - 3(\boldsymbol{\mu}_i \cdot \mathbf{r}_{ij})(\mathbf{r}_{ij} \cdot \boldsymbol{\mu}_j)}{r_{ij}^5} - \frac{8\pi}{3} \delta(\mathbf{r}_{ij}) \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_j \right) + \alpha^2 \sum_{iI} \left(\frac{r_{iI}^2 \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_I - 3(\boldsymbol{\mu}_i \cdot \mathbf{r}_{iI})(\mathbf{r}_{iI} \cdot \boldsymbol{\mu}_I)}{r_{iI}^5} - \frac{8\pi}{3} \delta(\mathbf{r}_{iI}) \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_I \right) . \quad (3.68)$$

The first term describes a summation that goes over the dipole-dipole like interaction between the magnetic moments of electrons i and j and the contact interaction. The second term describes the same dipole-dipole and Fermi contact interactions, but involve the magnetic moments of electron i and nucleus I .

The diamagnetic Hamiltonian describes the interaction which has the origin in the vector potential, \mathbf{A} , which is included in the kinetic momentum (see. Eq. 3.4) and is comprised of several terms. One of these, which governs to some extent the EPR parameters which are under investigation in this thesis (electronic g-tensors and hyperfine coupling constants) consists of three spin-orbit Zeeman gauge corrections operators, that correspond to interactions with external electric fields, fields arising from nuclei and other electrons respectively,

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which affect only the electronic g-tensors. The spin-orbit Zeeman gauge correction Hamiltonian is written as:

$$\begin{aligned}
 H_{SOGC} = & -\frac{\alpha^2}{4} \sum_i (\mathbf{B} \times \mathbf{r}_{iO})(\boldsymbol{\mu}_i \times \mathbf{E}_i) \\
 & - \frac{\alpha^2}{4} \sum_{iI} \frac{Z_I (\mathbf{B} \times \mathbf{r}_{iO})(\boldsymbol{\mu}_i \times \mathbf{r}_{iI})}{r_{iI}^3} \\
 & + \frac{\alpha^2}{4} \sum_{i \neq j} \frac{(\mathbf{B} \times \mathbf{r}_{iO})(\boldsymbol{\mu}_i + 2\boldsymbol{\mu}_j) \times \mathbf{r}_{ij}}{r_{ij}^3} . \quad (3.69)
 \end{aligned}$$

Another diamagnetic interaction which governs to some extent the hyperfine coupling between electron and nuclei spin, can be described in the following Hamiltonian:

$$\begin{aligned}
 H_{A(dia)} = & -\frac{\alpha^2}{2} \sum_{iI} \frac{(\boldsymbol{\mu}_I \times \mathbf{r}_{iI})(\boldsymbol{\mu}_i \times \mathbf{E}_i)}{r_{iI}^3} \\
 & - \frac{\alpha^4}{2} \sum_{iIJ} \frac{Z_J (\boldsymbol{\mu}_J \times \mathbf{r}_{iI})(\boldsymbol{\mu}_i \times \mathbf{r}_{iJ})}{r_{iI}^3 r_{iJ}^3} \\
 & + \frac{\alpha^4}{2} \sum_{i \neq j, I} \frac{(\boldsymbol{\mu}_I \times \mathbf{r}_{iI}) [(\boldsymbol{\mu}_i + 2\boldsymbol{\mu}_j) \times \mathbf{r}_{ij}]}{r_{ij}^3 r_{iI}^3} . \quad (3.70)
 \end{aligned}$$

With the help of these Hamiltonians, in the framework of density functional response theory (for which a short overview will be given in the next chapter), one can evaluate the EPR parameters of interest.

Chapter 4

Electronic structure methods

Traditional *ab initio* methods based on the Hartree-Fock theory and its descendants rely on the finding of the many-body wave-function of the system. A variational principle problem is solved within an appropriate trial space once the Hamiltonian of the system is introduced. A problem arises when one is interested in realistic systems, because these theories are difficult to be applied due to the computational cost of post Hartree-Fock methods or the reduced accuracy inherent in Hartree-Fock theory which poorly accounts for electron correlation. Therefore, a different approach comes at hand, namely the density functional theory (DFT). This represents a remarkable break-through in electronic structure calculations, since it aims at the solving of the many-body problem within an one-body formalism. This, coupled with the fact that the theory is exact in principle, represents a remarkable achievement. However, the drawback of this theory is that it relies on the knowledge of an universal functional which is unknown. As we shall see, approximations for this functional exist, and they permit the calculation of various physical quantities sufficiently accurate.

4.1 Density functional theory

One of the ideas behind DFT is to consider the energy of a system as a functional of the electron density rather than as an eigenvalue of the ground state wave function, as it is done in traditional methods. Within the Born-Oppenheimer approximation, traditional *ab-initio* methods describe the system under investigation using the time-independent Schrödinger equation, $H\psi = E\psi$, where E gives the energy of the system and ψ represents its wave-function, and depends on the spatial and spin coordinates of electrons ($3N + N$ total variables, assuming N to be the number of electrons in the system). H denotes the Hamiltonian of the system, and in its most simplistic form it can be expressed as:

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$$H = -\frac{1}{2} \sum_i \nabla_i^2 + \frac{1}{2} \sum_{i \neq j} \frac{1}{r_{ij}} - \sum_{iI} \frac{Z_I}{r_{iI}} . \quad (4.1)$$

The first term denotes the kinetic energy of electrons, the second describes the Coulomb repulsion between the electrons, while the last term gives the Coulomb attraction between the nuclei and electrons in the system. By solving the Schrödinger equation one is able to obtain the wave-function and the energy of the system, as well as any other properties of interest. However, we are not interested in this approach, but on a different one, which as already has been mentioned, relies on the usage of the electron density. The idea to use the electron density instead of the wave-function in order to gain knowledge about the system studied is traced back in the early days of quantum mechanics development in the twenties, especially from the Thomas-Fermi model [39, 40]. Consequently, instead of being interested in finding the many-body wave function of the system, the new approach proposes that the energy of the system can be expressed as a functional of the one-electron density:

$$\rho(\mathbf{r}) = N \int |\psi(\mathbf{r}_1 \cdots \mathbf{r}_N, s_1 \cdots s_N)|^2 ds_1 \cdots ds_N d\mathbf{r}_1 \cdots d\mathbf{r}_{N-1} , \quad (4.2)$$

which gives the probability of finding an electron with arbitrary spin at point \mathbf{r} in space. Although the roots of DFT were set with the Thomas-Fermi model, the theoretical legitimacy of the theory was achieved with the pioneering work of Hohenberg and Kohn [41], and subsequently by that of Kohn and Sham [42]. It is stated that the problem of interacting particles within an external static potential can be reduced to a non-interacting problem, where the energy is a functional of the local density. In the non-interacting problem, the particle move within a local effective potential, which can be expressed as a functional of the local density. The ground-state density can be obtained variationally by finding the density which minimises the total energy, this density being the exact ground-state density. Hohenberg and Kohn prove the existence of a unique functional of the density which determines exactly the external potential, and thus the ground-state energy, but gives no recipe on how this functional should look like. Let us consider the energy as a functional written in terms of the kinetic, electron-electron interaction and potential parts:

$$E[\rho(\mathbf{r})] = T[\rho(\mathbf{r})] + V_{ee}[\rho(\mathbf{r})] + V_{eN}[\rho(\mathbf{r})] . \quad (4.3)$$

The first two are system independent parts, and thus comprise the universal Hohenberg-Kohn functional, which is usually written as:

$$F[\rho(\mathbf{r})] = T[\rho(\mathbf{r})] + V_{ee}[\rho(\mathbf{r})] . \quad (4.4)$$

The last term in Eq. 4.3 is system dependent, and can be written as:

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$$V_{eN}[\rho(\mathbf{r})] = \int \rho(\mathbf{r})v(\mathbf{r})d\mathbf{r} , \quad (4.5)$$

with the external potential $v(\mathbf{r}_i) = -\sum_I \frac{Z_I}{r_{iI}}$. It is important to note here that this external potential, $v(\mathbf{r})$, needs not necessarily be a Coulomb potential. This external potential is determined by the electron density (within a trivial additive constant), as the 1st Hohenberg-Kohn theorem states. To prove this theorem let us consider the electron density, $\rho(\mathbf{r})$, corresponding to the non degenerate ground state of an arbitrary N -electron system. N is straightforwardly determined by the density, i.e. $N = \int \rho(\mathbf{r})d\mathbf{r}$. The density should also determine the external potential, and hence all the properties. Let us assume that there are two external potentials, v and v' which differ by more than a trivial additive constant, each of them giving the same electron density for the ground state. Hence, one would have two Hamiltonians, say H and H' , that would yield two different wave-functions, ψ and ψ' which would give the same electron densities in the ground state. If one takes the second wave-function, ψ' , as a trial function for the first Hamiltonian, H , one can write:

$$\begin{aligned} E_0 &< \langle \psi' | H | \psi' \rangle = \langle \psi' | H' | \psi' \rangle + \langle \psi' | H - H' | \psi' \rangle \\ &= E'_0 + \int \rho(\mathbf{r})[v(\mathbf{r}) - v'(\mathbf{r})]d\mathbf{r} , \end{aligned} \quad (4.6)$$

with E_0 and E'_0 denoting the ground state energies that correspond to H and H' Hamiltonians. Now, if one takes the first wave-function as a trial function for the second Hamiltonian, one can write:

$$\begin{aligned} E'_0 &< \langle \psi | H' | \psi \rangle = \langle \psi | H | \psi \rangle + \langle \psi | H' - H | \psi \rangle \\ &= E_0 - \int \rho(\mathbf{r})[v(\mathbf{r}) - v'(\mathbf{r})]d\mathbf{r} . \end{aligned} \quad (4.7)$$

Adding the above equations we would obtain a contradiction, i.e. $E_0 + E'_0 < E'_0 + E_0$, so our initial assumption that there exist two different external potential that would yield the same electron density for the ground state is invalid. We have just proved the 1st Hohenberg-Kohn theorem.

The variational problem implied by the 2nd Hohenberg-Kohn theorem states that for a trial ¹ non-vanishing electron density, $\rho'(\mathbf{r}) \geq 0$, for which the integral over coordinate space gives the number of electrons in the system, one can write:

¹ We should address some subtle aspect of the Hohenberg-Kohn theorems. These imply that the density associated with the ground state should be *v-representable*. This has the meaning that such a density is one that is essentially connected with an antisymmetric ground-state wave function that corresponds to a Hamiltonian like the one expressed in Eq. 4.1. Thus, the first theorem states that there is a one-to-one mapping between the ground state wave function and a *v-representable* density. When we consider a trial density in the second theorem, then this necessarily needs to be *v-representable*. If it is not (e.g. when one has

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$$E_0 \leq E[\rho'(\mathbf{r})] = \int \rho'(\mathbf{r})v(\mathbf{r})d\mathbf{r} + F[\rho'(\mathbf{r})] . \quad (4.8)$$

Thus, the energy functional for the trial density, $E[\rho'(\mathbf{r})]$, is always larger than the actual ground state energy of the system, E_0 . From the 1st Hohenberg-Kohn theorem we know that any trial density, ρ' , determines its own external potential, v' , and thus Hamiltonian, H' , and wave function, ψ' . Taking ψ' as a trial function for the problem involving the external potential v , one can write:

$$\langle \psi' | H | \psi' \rangle = E_v[\rho'] = \int \rho'(\mathbf{r})v(\mathbf{r})d\mathbf{r} + F[\rho'(\mathbf{r})] \geq E_v[\rho] = \langle \psi | H | \psi \rangle , \quad (4.9)$$

where we put the index v to the energy functional to stress its connection with the external potential ($E_v[\rho] \equiv E[\rho]$). Hence, we have just proved the 2nd Hohenberg-Kohn theorem.

The variational principle (see Eq. 4.8) can be formulated as a stationary principle [43]:

$$\delta \left\{ E[\rho(\mathbf{r})] - \mu \int \rho(\mathbf{r})d\mathbf{r} \right\} = 0 , \quad (4.10)$$

which can be rewritten as the Euler-Lagrange equation:

$$\mu = \frac{\delta E[\rho(\mathbf{r})]}{\delta \rho(\mathbf{r})} = v(\mathbf{r}) + \frac{\delta F[\rho(\mathbf{r})]}{\delta \rho(\mathbf{r})} , \quad (4.11)$$

for determination of the Lagrangian multiplier, μ , which has the physical meaning of *chemical potential* and is associated with the constraint, $N = \int \rho(\mathbf{r})d\mathbf{r}$.

However, as previously noted, Hohenberg and Kohn give us no clue onto how to construct this universal functional, F . From Eq. 4.4 we know that this functional comprises several parts, the only one which we can express in terms of the electron density being the Coulomb one:

$$V_{ee}^{Coulomb}[\rho(\mathbf{r})] = \frac{1}{2} \iint \frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r} d\mathbf{r}' . \quad (4.12)$$

The kinetic part, as well as the quantum mechanical contributions (which accounts for exchange and correlation effects) have no known explicit form. To solve the problem of the kinetic energy functional Kohn and Sham [42] came with an interesting idea. Rather than trying to search for an explicit density functional that determines the kinetic energy, one should compute it exactly for

degenerate ground-states), one would face serious problems (see also the discussion in Ref. [43], p. 54). However, it is shown [44] that the requirement of *v-representability* should be changed with a more weaker condition, namely *N-representability*. This means that the density should be obtained from *some* antisymmetric wave function, condition which is satisfied for any reasonable density.

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a simpler problem - a non interacting system [45]. They proposed the idea to evaluate this contribution in an orbital basis, as it is usually done in conventional ab-initio methods. In the last approach the kinetic energy is expressed as:

$$T = -\frac{1}{2} \sum_i^N n_i \langle \psi_i | \nabla^2 | \psi_i \rangle , \quad (4.13)$$

where ψ_i denotes a spin-orbital, and n_i the occupation number of this orbital (with $0 \leq n_i \leq 1$ as required by Pauli's principle). In the Kohn-Sham (KS) approach, the kinetic energy functional is introduced:

$$T_s[\rho] = -\frac{1}{2} \sum_i^N \langle \psi_i | \nabla^2 | \psi_i \rangle , \quad (4.14)$$

with the electron density given in terms of the KS orbitals, $\psi_i(\mathbf{r}, s)$:

$$\rho(\mathbf{r}) = \sum_i^N \sum_s |\psi_i(\mathbf{r}, s)|^2 . \quad (4.15)$$

It becomes clear that the KS kinetic energy functional is just a special case of the traditional way in which the kinetic energy is expressed. In this case, the kinetic energy functional exactly represents the kinetic energy for a Slater determinant-like wave-function that describes N noninteracting electrons. Then, in the KS approach, a Hamiltonian of the form is considered:

$$H_s = -\frac{1}{2} \sum_i^N \nabla_i^2 + \sum_i^N v_s(\mathbf{r}) , \quad (4.16)$$

which corresponds to a noninteracting (meaning that there is no electron-electron Coulomb repulsion term) problem, for which the exact ground state wave-function can be expressed:

$$\Psi_s = \frac{1}{\sqrt{N!}} \det \left[\psi_1 \psi_2 \cdots \psi_N \right] . \quad (4.17)$$

Here, ψ_i are the spin-orbitals that correspond to one-body Hamiltonians:

$$\left[-\frac{1}{2} \nabla^2 + v_s(\mathbf{r}) \right] \psi_i = \epsilon_i \psi_i . \quad (4.18)$$

The connection between this non-interacting system and the real system in which electrons interact can be made by choosing the non-interacting potential, v_s , in such a way that the ground state densities of the non-interacting and real systems will be the same. With the kinetic energy functional defined as in Eq. 4.14, let us rewrite the universal functional as:

$$F[\rho] = T_s[\rho] + J[\rho] + E_{xc}[\rho] . \quad (4.19)$$

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The first term denotes the kinetic energy functional for the non-interacting system, the second defines the Coulomb repulsion between the electrons, while the last represents the *exchange-correlation* energy functional:

$$E_{xc}[\rho] = T[\rho] - T_s[\rho] + V_{ee}[\rho] - J[\rho] , \quad (4.20)$$

which accounts for the difference between the interacting and non-interacting kinetic energies, as well as the quantum mechanical part of the electron-electron interaction. Eq. 4.11 becomes:

$$\begin{aligned} \mu &= v(\mathbf{r}) + \frac{\delta J[\rho]}{\delta \rho} + \frac{\delta E_{xc}[\rho]}{\delta \rho} + \frac{\delta T_s[\rho]}{\delta \rho} \\ &= v(\mathbf{r}) + \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' + v_{xc}(\mathbf{r}) + \frac{\delta T_s[\rho]}{\delta \rho} \\ &\equiv v_{eff}(\mathbf{r}) + \frac{\delta T_s[\rho]}{\delta \rho} . \end{aligned} \quad (4.21)$$

For a given effective potential, v_{eff} , one is able to obtain the density, $\rho(\mathbf{r})$, that can be evaluated according to Eq.4.15, by solving N one-body equations similar to Eq. 4.18 where the non-interacting potential, v_s , is replaced with the effective one, v_{eff} ²:

$$\left[-\frac{1}{2}\nabla^2 + v_{eff}(\mathbf{r}) \right] \psi_i = \epsilon_i \psi_i , \quad (4.22)$$

which is known as the Kohn-Sham equation. Since v_{eff} depends on $\rho(\mathbf{r})$, the equations must be solved until the self-consistency is reached, by varying the spin-orbitals, ψ_i . Usually, one begins with a trial density from which the effective potential can be constructed: $v_{eff}(\mathbf{r}) = v(\mathbf{r}) + \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' + v_{xc}(\mathbf{r})$. Then, a new density can be found following the process described above until convergence is reached. The total energy is [43]:

$$\begin{aligned} E &= \sum_i^N \langle \psi_i | -\frac{1}{2}\nabla^2 + v_{eff} | \psi_i \rangle \\ &\quad - \frac{1}{2} \int \frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' d\mathbf{r} + E_{xc}[\rho] - \int v_{xc}(\mathbf{r})\rho(\mathbf{r}) d\mathbf{r} \\ &= T_s[\rho] + \int v_{eff}(\mathbf{r})\rho(\mathbf{r}) d\mathbf{r} \\ &\quad - \frac{1}{2} \int \frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' d\mathbf{r} + E_{xc}[\rho] - \int v_{xc}(\mathbf{r})\rho(\mathbf{r}) d\mathbf{r} , \end{aligned} \quad (4.23)$$

showing that it depends on the kinetic energy of the non interacting system, the effective potential, v_{eff} , and exchange-correlation functional which is yet

²Actually $v_s \equiv v_{eff}$.

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unknown. Indeed, one can show that the above energy corresponds to the one of the real interacting system:

$$\begin{aligned}
 E &= T_s[\rho] + \int \left[v(\mathbf{r}) + \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' + v_{xc}(\mathbf{r}) \right] (\mathbf{r}) \rho(\mathbf{r}) d\mathbf{r} \\
 &\quad - \frac{1}{2} \int \frac{\rho(\mathbf{r}) \rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' d\mathbf{r} + E_{xc}[\rho] - \int v_{xc}(\mathbf{r}) \rho(\mathbf{r}) d\mathbf{r} \\
 &= T_s[\rho] + \int v(\mathbf{r}) \rho(\mathbf{r}) d\mathbf{r} + J[\rho] + T[\rho] - T_s[\rho] + V_{ee}[\rho] - J[\rho] \\
 &= V_{eN}[\rho] + T[\rho] + V_{ee}[\rho] .
 \end{aligned} \tag{4.24}$$

This represents a nice way to solve a many-body problem by involving only one-body equations. In this respect KS theory resembles the Hartree-Fock theory. Whereas the first one is an exact theory provided that the exchange correlation functional, E_{xc} , is known, the latter is an approximate theory since it doesn't account for a major part of the electron correlation from the way it is defined. In order to better account for the electron correlation, the quest for more accurate methods in the post HF methods manifests in approaches which include linear combinations, as in configuration interaction (CI) method, or exponential expansions, as in the coupled cluster (CC) method, of Slater determinants (to mention a few of the available approaches). On the other hand, in KS DFT the effort is spent (amongst other directions) onto the finding of more and more accurate exchange-correlation functionals. Before getting to this point let us bring into discussion the electron spin. As can easily be seen, the effective potential has no dependence on spin, making the solutions of the KS equations doubly degenerate. For a system with even number of electrons the spin up (α) and spin down (β) electron densities are usually equal, and the total density is the double of spin up (or spin down) density. For a system with unpaired number of electrons a slightly different type of energy functional must be employed:

$$E[\rho_\alpha, \rho_\beta] = T_s[\rho_\alpha, \rho_\beta] + J[\rho_\alpha + \rho_\beta] + E_{xc}[\rho_\alpha, \rho_\beta] + \int v(\mathbf{r}) [\rho_\alpha(\mathbf{r}) + \rho_\beta(\mathbf{r})] d\mathbf{r} . \tag{4.25}$$

The spin up and spin down densities are:

$$\rho_\alpha(\mathbf{r}) = \sum_i n_{\alpha i} |\psi_i(\mathbf{r}, \alpha)|^2 , \rho_\beta(\mathbf{r}) = \sum_i n_{\beta i} |\psi_i(\mathbf{r}, \beta)|^2 , \tag{4.26}$$

with the coefficients, $n_{\alpha i}, n_{\beta i}$, being zero or one, denoting the spin-orbital occupation number. In this case the kinetic energy functional can be written:

$$T_s[\rho_\alpha, \rho_\beta] = -\frac{1}{2} \sum_{i\sigma} \langle \psi_i(\mathbf{r}, \sigma) | \nabla^2 | \psi_i(\mathbf{r}, \sigma) \rangle . \tag{4.27}$$

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In open shell system, there are two possible ways in which the variational principle can be employed, which differ in the constraints imposed during the energy functional minimisation procedure. This necessarily leads to different Kohn-Sham equations, that will still resemble Eq. 4.38. The two approaches are the so-called unrestricted method, widely used to tackle different problems in quantum chemistry, and the spin-restricted method, which has become increasingly popular due to the spin contamination problem which is inherent in the former one [46, 47, 48]. The unrestricted KS approach implies two different constraints, which set the number of α and β electrons constant through the minimization procedure:

$$\int \rho_\alpha(\mathbf{r}) d\mathbf{r} = N_\alpha , \quad (4.28a)$$

$$\int \rho_\beta(\mathbf{r}) d\mathbf{r} = N_\beta , \quad (4.28b)$$

with the total number of electrons, $N = N_\alpha + N_\beta$. This leads to the following KS equations which involve the spin orbitals $\psi_i(\mathbf{r}, \alpha)$ and $\psi_i(\mathbf{r}, \beta)$ respectively:

$$\left[-\frac{1}{2}\nabla^2 + v_{eff}^\alpha(\mathbf{r}) \right] \psi_i(\mathbf{r}, \alpha) = \frac{\epsilon_{\alpha i}}{n_{\alpha i}} \psi_i(\mathbf{r}, \alpha) , \quad (4.29a)$$

$$\left[-\frac{1}{2}\nabla^2 + v_{eff}^\beta(\mathbf{r}) \right] \psi_i(\mathbf{r}, \beta) = \frac{\epsilon_{\beta i}}{n_{\beta i}} \psi_i(\mathbf{r}, \beta) , \quad (4.29b)$$

It is obvious that one can write N_α and N_β equations for the first and second equation depicted above, that correspond to each spin up and spin down electron in the system. The effective potentials involved in the above equations are:

$$v_{eff}^\alpha(\mathbf{r}) = v(\mathbf{r}) + \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' + \frac{\delta E_{xc}[\rho_\alpha, \rho_\beta]}{\delta \rho_\alpha} , \quad (4.30a)$$

$$v_{eff}^\beta(\mathbf{r}) = v(\mathbf{r}) + \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' + \frac{\delta E_{xc}[\rho_\alpha, \rho_\beta]}{\delta \rho_\beta} , \quad (4.30b)$$

where $\rho(\mathbf{r}') = \rho_\alpha(\mathbf{r}') + \rho_\beta(\mathbf{r}')$.

The spin restricted method implies an additional constraint during the variational procedure, beside the constraints implied by Eq. 4.28, that is, the spatial part of alpha and beta spin orbitals should remain the same. Considering a molecule with N_d doubly occupied orbitals (half alpha and half beta spin), and N_s singly occupied ones (with alpha spin), the KS equations for the spin

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restricted method become:

$$\left[-\frac{1}{2}\nabla^2 + v_{eff}^d(\mathbf{r}) \right] \psi_k(\mathbf{r}) = \sum_{i=1}^{N_d+N_s} \epsilon_{ki} \psi_i(\mathbf{r}) , \quad k = 1, 2, \dots, N_d , \quad (4.31a)$$

$$\left[-\frac{1}{2}\nabla^2 + v_{eff}^s(\mathbf{r}) \right] \psi_i(\mathbf{r}) = \sum_{i=1}^{N_d+N_s} \epsilon_{ki} \psi_i(\mathbf{r}) , \quad k = 1, 2, \dots, N_s . \quad (4.31b)$$

The effective potentials involved in the above equations are:

$$v_{eff}^d(\mathbf{r}) = v(\mathbf{r}) + \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' + \frac{1}{2} \frac{\delta E_{xc}[\rho_\alpha, \rho_\beta]}{\delta \rho_\alpha} \quad (4.32a)$$

$$+ \frac{1}{2} \frac{\delta E_{xc}[\rho_\alpha, \rho_\beta]}{\delta \rho_\beta} , \quad (4.32b)$$

$$v_{eff}^s(\mathbf{r}) = v(\mathbf{r}) + \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' + \frac{1}{2} \frac{\delta E_{xc}[\rho_\alpha, \rho_\beta]}{\delta \rho_\alpha} , \quad (4.32c)$$

where by ρ we denote the sum between the alpha, ρ_α , and beta, ρ_β , densities, which are:

$$\rho_\alpha(\mathbf{r}) = \sum_{i=1}^{N_d} |\psi_i(\mathbf{r})|^2 + \sum_{i=1}^{N_s} |\psi_i(\mathbf{r})|^2 , \quad (4.33a)$$

$$\rho_\beta(\mathbf{r}) = \sum_{i=1}^{N_d} |\psi_i(\mathbf{r})|^2 . \quad (4.33b)$$

So far we have discussed the general ideas behind DFT, the KS formalism with the two different approaches (unrestricted vs. spin-restricted one). As already mentioned, the many-body problem is elegantly solved within an one-body formalism. Exactly! But this is far from true, since the exact solution, in principle, relies on the knowledge of the exact Hohenberg-Kohn universal functional, F , that depends on the exchange-correlation term, E_{xc} , which captures the difference between the kinetic energy of the real system and the non-interacting one, plus all the quantum mechanical bi-electronic interactions which are not accounted for in the Coulomb repulsion functional, J . And with all the effort that has been put to develop better and better exchange-correlation functionals, the exact universal functional has not yet been found, and most probably will never be. Moreover, since the only unknown part is the exchange-correlation term, the quality of the results depends on the quality of the approximations made for E_{xc} . The development of exchange-correlation functional which has been made so far can be classified into several major directions.

The most simple type of functional is represented by the *local density approximation* (LDA) functional. These functionals depend only on the electron

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density, which may sound a little strange, since every functional should depend on the electron density. This aspect will be clarified further on. Although several functionals of these type have been developed, the combination of Dirac exchange [49] (which, in the Thomas-Fermi model represents an approximation of the exchange interaction with a density dependent functional of the form $C\rho^{4/3}$) with the Vosko-Wilk-Nussair [50] correlation functional stands now as the standard LDA exchange-correlation functional. The main reason for this association is that this exchange-correlation functional provides the most accurate results from the family of LDA functionals. An extension of the LDA functionals to spin-polarized system is represented by the local-spin-density approximation (LSDA) functionals. The general expression for these functionals can be expressed as:

$$E_{xc}^{LDA}[\rho(\mathbf{r})] = \int f(\rho(\mathbf{r}))d\mathbf{r} , \quad (4.34a)$$

$$E_{xc}^{LSDA}[\rho_\alpha(\mathbf{r}), \rho_\beta(\mathbf{r})] = \int f(\rho_\alpha, \rho_\beta)d\mathbf{r} . \quad (4.34b)$$

The next type of functionals is represented by the *generalized gradient approximation* (GGA) family of functionals. As the name suggests, these functionals not only have a dependence on the electron density but also on the gradients, $\nabla\rho(\mathbf{r})$, in order to better account for the bonding regions in molecules (the description of which represents the main drawback of the LDA functionals), where high variations of the density are expected:

$$E_{xc}^{GGA}[\rho_\alpha, \rho_\beta] = \int f(\rho_\alpha, \nabla\rho_\alpha; \rho_\beta, \nabla\rho_\beta)d\mathbf{r} . \quad (4.35)$$

The first attempts in this direction (see Sham [51] and Herman [52]) were rather unsuccessful, but significant improvements have been made with the appearance of the exchange functional proposed by Becke [53] and the correlation functional proposed by Lee, Yang and Parr [54]. Coupled together, these functional form the well known BLYP exchange-correlation functional. Another successful exchange-correlation functional from the GGA family is the one proposed by Perdew, Burke and Ernzerhof [55].

Another type of functionals are the *meta-GGA* ones, which include also a dependence on the divergence of the electron density gradients:

$$E_{xc}^{m-GGA}[\rho_\alpha, \rho_\beta] = \int f(\rho_\alpha, \nabla\rho_\alpha, \nabla^2\rho_\alpha; \rho_\beta, \nabla\rho_\beta, \nabla^2\rho_\beta)d\mathbf{r} . \quad (4.36)$$

Another important class is represented by the *hybrid* functionals type, which includes a fraction of the exact Hartree-Fock exchange, with Becke [53] and LDA exchange contributions to the exchange functional [56]. One of the most

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successful functional of this type is the B3LYP one, which couple the former exchange functional with the correlation functional of Lee, Yang and Parr and that of Vosko, Wilk and Nusair:

$$E_{xc}^{B3LYP} = a_{xc}E_x^{Dirac} + (1 - a_{xc})E_x^{HF} + a_xE_x^B + E_c^{VWN} + a_cE_c^{LYP} . \quad (4.37)$$

4.2 Response theory

Since we are interested in computing molecular properties of systems, a method for computing electronic g-tensors and hyperfine coupling constants in the density functional theory framework is needed. One can employ the response approach which is based on a perturbative treatment of the time-dependent Kohn-Sham equations:

$$f_{KS}(\mathbf{r}, t)\psi_i(\mathbf{r}, t) \equiv \left[-\frac{1}{2}\nabla^2 + v_{eff}(\mathbf{r}, t) \right] \psi_i(\mathbf{r}, t) = i \frac{\partial \psi_i(\mathbf{r}, t)}{\partial t} , \quad (4.38)$$

which assumes that a small time-dependent perturbation is turned on when the system is in its ground state. The relevant terms from the Breit-Pauli Hamiltonian (see. Eq. 3.65) which give a contribution to the EPR properties of interest (electronic g-tensors and hyperfine constants) are considered as such perturbations.

The behavior of a given system to an excitation determined by an operator, G , is characterized by the response function. The Hamiltonian, H_{int} , that describes the interaction between the system and an external field which oscillates in time with frequency ω , is given by [57]:

$$H_{\text{int}} = \lambda(G^\dagger e^{(\varepsilon - i\omega)t} + G e^{(\varepsilon + i\omega)t}) , \quad (4.39)$$

where the coupling strength is controlled by λ , and the exponential $e^{\varepsilon t}$ (with $\varepsilon > 0$ sufficiently small) ensures that at $t \rightarrow -\infty$ the system is in its ground state, $|0\rangle$, and is described by the unperturbed Hamiltonian, H . The time dependence of the perturbed system is given by the Schrödinger equation:

$$(H + H_{\text{int}})|\tilde{0}\rangle = i \frac{\partial}{\partial t} |\tilde{0}\rangle , \quad (4.40)$$

where $|\tilde{0}\rangle$ represents the N -body wave-function of the system, while the unperturbed Hamiltonian, H , has a set of eigenstates $|n\rangle$ defined from the equation:

$$H |n\rangle = E_n |n\rangle , \quad (4.41)$$

with E_n denoting the corresponding eigenvalues. The average value of an arbitrary operator, F , can be expressed:

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$$\langle \tilde{0} | F | \tilde{0} \rangle = \langle 0 | F | 0 \rangle + F_+ e^{-i\omega t} e^{\varepsilon t} + F_- e^{i\omega t} e^{\varepsilon t} . \quad (4.42)$$

Assuming that the interaction is sufficiently weak, the system response to the external field is determined by the linear response function:

$$\langle \langle F; G \rangle \rangle_\omega = \lim_{\lambda \rightarrow 0} \frac{F_+}{\lambda} . \quad (4.43)$$

Let us consider solutions of the following form:

$$|\tilde{0}\rangle = \sum_n a_n(t) e^{-iE_n t} |n\rangle , \quad (4.44)$$

with the boundary condition, $a_n(-\infty) = 1$ if $n = 0$ and $a_n(-\infty) = 0$ if $n \neq 0$. Making use of the usual techniques of perturbation theory and retaining only the terms in λ in first order, we get:

$$a_n(t) = \lambda \left[\frac{\langle n | G^\dagger | 0 \rangle}{\omega - \omega_{n0} + i\varepsilon} \exp[(-i\omega + i\omega_{n0} + \varepsilon)t] - \frac{\langle n | G^\dagger | 0 \rangle}{\omega - \omega_{n0} + i\varepsilon} \exp[(-i\omega + i\omega_{n0} + \varepsilon)t] \right] , \quad (4.45)$$

where $\omega_{n0} = E_n - E_0$ is the excitation energy. At first order in λ , Eq. 4.42 can be cast in the form:

$$\langle \tilde{0} | F | \tilde{0} \rangle = \langle 0 | F | 0 \rangle + \sum_n \left[\langle 0 | F | n \rangle a_n(t) e^{-i\omega_{n0} t} + \langle n | F | 0 \rangle a_n^\dagger(t) e^{i\omega_{n0} t} \right] . \quad (4.46)$$

Substituting the expression of the coefficients $a_n(t)$ into the above equation, by separating the coefficients of the exponential $\exp(-i\omega t)$ from those of the exponential $\exp(i\omega t)$ the linear response function (see Eq. 4.43) can be written:

$$\langle \langle F; G \rangle \rangle_\omega = \sum_n \left[\frac{\langle 0 | F | n \rangle \langle n | G^\dagger | 0 \rangle}{\omega - \omega_{n0} + i\varepsilon} - \frac{\langle 0 | G^\dagger | n \rangle \langle n | F | 0 \rangle}{\omega + \omega_{n0} + i\varepsilon} \right] ,$$

where we made use of the following relation:

$$\langle 0 | G | n \rangle^* = \langle n | G^\dagger | 0 \rangle . \quad (4.47)$$

In Eq. 4.47 the poles of the response function, $\langle \langle F; G \rangle \rangle_\omega$, represent the excitation energies, while the matrix elements between the ground and excited states are determined by the residues in the poles of $\langle \langle F; G \rangle \rangle_\omega$. Therefore, the knowledge of the response function gives knowledge of both the poles and the

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residues in the poles of $\langle\langle F; G \rangle\rangle_\omega$. Considering now F to be hermitian and equal to G , the response function can be written in a simplified form:

$$\langle\langle F; F \rangle\rangle_\omega = 2 \sum_n \omega_{n0} \frac{|\langle n|F|0 \rangle|^2}{(\omega + i\varepsilon)^2 - \omega_{n0}^2} . \quad (4.48)$$

In Kohn-Sham DFT response formalism, the time evolution of the KS determinant can be more conveniently expressed by an exponential expansion:

$$|\tilde{0}\rangle = \exp[-i k(t)]|0\rangle , \quad (4.49)$$

where the anti-Hermitian operator $k(t)$ has the expression:

$$k(t) = \sum_{rs\sigma} k_{rs}(t) E_{rs}^\sigma , \quad (4.50)$$

in terms of the so-called orbital rotations $k_{rs}(t)$, with the operator $E_{rs}^\sigma \equiv a_{r\sigma}^\dagger a_{s\sigma}$ expressed in terms of creation and annihilation operators. In this representation the alpha and beta spin densities have the form:

$$\rho_\sigma(\mathbf{r}, t) = \langle\tilde{0}|\rho_\sigma(\mathbf{r})|\tilde{0}\rangle = \langle 0|e^{ik(t)}\rho_\sigma(\mathbf{r})e^{-ik(t)}|0\rangle , \quad (4.51)$$

where the spin density, $\rho_\sigma(\mathbf{r})$, can be expressed in second quantization formalism as:

$$\rho_\sigma(\mathbf{r}) = \Psi_\sigma^\dagger(\mathbf{r})\Psi_\sigma(\mathbf{r}) = \sum_{pq} \varphi_p^*(\mathbf{r})\varphi_q(\mathbf{r})E_{pq}^\sigma , \quad (4.52)$$

in terms of the fermion field operator $\Psi_\sigma(\mathbf{r}) = \sum_i \varphi_i(\mathbf{r})a_{i\sigma}$. One can employ the Ehrenfest theorem [58] and show that the linear response function for an arbitrary operator A can be written (recall Eqs. 4.39 and 4.40):

$$\langle\langle A; H_{int} \rangle\rangle_\omega = \langle 0|[k^\omega, A]|0\rangle , \quad (4.53)$$

where the right hand side of the equation contains the commutator involving operator A and the Fourier transformed operator $k(\omega) = \int k(t)e^{i\omega t}dt$.

4.3 Solvent and environment models

The main purpose of this thesis is to study the EPR properties of various nitroxides in complex environments. The environment plays an important role due to the interaction between the probe and the molecules surrounding it. Similarly as the electronic g-tensor changes when going from the free electron to a radical with an unpaired electron, changes in the g-tensor also occur when going from the radical to the radical in solution, or enclosed into a molecular cage, protein pocket etc.. To be able to study such changes in the spectroscopic

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properties one needs a proper way to describe the environment. In some cases it is possible to treat the environment and the probe using quantum mechanical approaches, making use of simplifying models which include at maximum around a hundred atoms. In most cases one cannot find a satisfactory model which would capture the influence of the environment without significant loss in the accuracy of its description due to the simplification. When such approximative models cannot be found, one needs to treat the environment using different approaches. It is obvious that in such cases a quantum mechanical description of the medium is out of the question, due to the size of the system and the computational cost. Therefore one may treat the environment using simplified methods if a proper description of the interactions between it and the probe (which is treated quantum mechanically) is achieved. There are two ways in which one can treat the environment: (i) considering it as a continuum medium, and (ii) using a discrete particle approach. In the first method the environment is considered a homogeneous dielectric continuum medium which interacts with the probe charge distribution by generating a reaction field, which in turn reacts with the probe changing its charge distribution, the scenario repeating itself until self-consistency is reached. In the second method, the environment is treated using explicit molecules for which classical electric charges, dipole moments, polarizabilities etc. are usually assigned through a force-field, which has different energy terms for bonded and non-bonded interactions. The bonded interactions are described by stretching, bending or torsion terms, while the non-bonded ones include the electrostatic and van der Waals interactions. The sampling of the probe-environment configurational space is usually performed by molecular dynamics (MD) simulations, which allows the determination of the trajectories resulted by integration of the equations of motion, performed using Newtonian, Lagrangian or Hamiltonian formalisms. The first method can be employed without significant loss in accuracy to treat only solvents. For other environments (e.g. like inclusion complexes) one necessarily needs to employ the second approach. Consequently, in such an approach, the quantum mechanical treatment of the probe is combined with the classical treatment of the environment, in which a force field is considered to represent the interaction. Usually, the total Hamiltonian of the system comprised from the quantum mechanical (QM) region and the molecular mechanics (MM) one is written:

$$H_{total} = H_{MM} + H_{QM} + H_{QM/MM} , \quad (4.54)$$

where the first term describes the Hamiltonian of the classical region (intra-/inter-molecular interactions in/between the molecules in the MM region which account for the well known stretching, bending, torsion, van der Waals and electrostatic interactions, as well as the coupling between them), the second one describes the QM region, while the last term describes the interaction between the two systems.

The accuracy of the QM/MM method is given by the accuracy of the three Hamiltonians described above. Several studies aimed towards the modeling of

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EPR parameters of spin-labels in solution were recently carried out using various QM/MM approaches. Nevertheless, the description of the interaction between the QM and MM regions in terms of point charges that interact with the density of the QM system, [59] or by an approximate interaction between a fitted multipole expansion, determined from the electron density of the QM region, with an expansion of multipoles in the MM region [9] are rather rudimentary. To overcome the drawbacks of previous descriptions, we shall employ the so-called integrated approach developed by Barone *et al.* [60, 61], taking into account a more advanced treatment of the interaction between the QM and MM regions, using the general DFT/MM polarizable embedding response formalism, which is suitable for computing spectroscopic properties of molecular systems, in terms of linear, quadratic and cubic response functions and their residues [62]. The first step of this approach implies carrying out a molecular dynamics simulation at ambient temperature. The second step consists of extracting a set of uncorrelated snapshots from the MD trajectory generated at the previous step, in order to compute instantaneous spectroscopic properties. For the second step of this approach, in second quantization Kohn-Sham formalism the terms appearing in Eq. 4.54 can be expressed. For H_{QM} one can write:

$$H_{QM} = \sum_{rs} f_{rs} E_{rs} = \sum_{rs} (h_{rs} + j_{rs} + v_{rs}^{xc}) E_{rs} , \quad (4.55)$$

where the singlet excitation operator $E_{rs} = a_{r,\alpha}^\dagger a_{s,\alpha} + a_{r,\beta}^\dagger a_{s,\beta}$ is expressed in terms of the creation and annihilation operators, h_{rs} accounts for the kinetic energy and nuclear attraction operators, j_{rs} for the Coulomb repulsion between the electrons, while the last term accounts for the exchange correlation potential, v_{rs}^{xc} . The coupling Hamiltonian, $H_{QM/MM}$, includes electrostatic and polarization interactions between the QM and MM regions, and can be written as [62]:

$$H_{QM/MM} = \sum_{pq} \sum_s M_{s,pq} E_{pq} - \sum_{pq} \sum_a \boldsymbol{\mu}_a^{ind} \mathbf{t}_{pq}^a E_{pq} . \quad (4.56)$$

The first term accounts for the electrostatic embedding potential introduced as a set of localized multipole moments, $M_{s,pq}$, while the second term describes the polarization of the environment by the electron density, with $\boldsymbol{\mu}_a^{ind}$ denoting the induced dipole moments, while \mathbf{t}_{pq}^a denotes the interaction tensors which are defined as $\mathbf{t}_{pq}^a = \nabla^a \frac{1}{|\mathbf{r}_q - \mathbf{r}_p|}$.

The coupling between the MM and QM regions can be accounted using different levels of approximations. The most basic approach would be to describe the MM molecules in terms of a set of point charges located on the atoms from which the molecules are comprised, these charges being provided by the TIP3P [63] force field, which also implicitly accounts for the media polarization effects. An advanced approach would be to explicitly include polarization/induction interactions between the QM and MM regions. This can be achieved by including, besides the point charges assigned to every atom in the MM molecules, isotropic

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polarizabilities according to the Ahlström force field [64] to specific atoms in the MM molecules. The natural next step, in order to have a better approximation of the MM region, would be to consider explicit polarizability tensors distributed over all atoms in the MM molecules. Further improvements on the MM region description would be achieved by assigning dipole and quadrupole moments to every atom in the MM molecules, besides the point charges and the explicit polarizability tensors, and to the midpoints of the bonds. For an even better description of the electrostatic potential of the MM region, distributed octopoles can also be accounted for every atom as well as on the midpoints of the bonds. For a schematic overview of the force fields employed to describe the MM region one can refer to Fig. 1 from Ref. [65] and Table 1 from Ref. [66]. The force fields employed in this work are generated using the LoProp [67] procedure, and are usually evaluated separately for each snapshot resulting from the MD trajectory. In this way, a proper accounting for the molecular distortions of the environment is achieved.

Chapter 5

Evaluation of EPR parameters

5.1 Electronic g-tensors

The Zeeman term in the spin Hamiltonian:

$$H_Z = \mu_B \mathbf{S} \mathbf{g} \mathbf{B} , \quad (5.1)$$

governs the interaction between the unpaired electron spin, \mathbf{S} , and the external magnetic field, \mathbf{B} , through the electronic g-tensor, \mathbf{g} , μ_B denoting the Bohr magneton. The electronic g-tensor is comprised of two contributions, the first arising from the free electron g-factor, $g_e = 2.002319\dots$, the second accounting for the interaction between the unpaired electron spin and its local environment, giving a valuable insight into the properties of the system. The deviation of the free electron g-factor from the value predicted by Dirac theory (which is exactly 2) comes from the neglect of the quantum electrodynamics (or radiative) corrections. The leading order radiative correction has been firstly computed by Schwinger [68], in terms of the fine structure constant, α , as:

$$\frac{g_e}{2} = 1 + \frac{\alpha}{2\pi} = 1.001161 . \quad (5.2)$$

This value of the free electron g-factor is simply taken for granted in quantum chemical calculations. Deviations from this value can give valuable information about the system studied (since the local environment around the unpaired electron can be linked to the magnitude of the g-tensor shift), and therefore it is convenient to separate the free electron g-factor from the electronic g-tensor, \mathbf{g} , as:

$$\mathbf{g} = g_e \mathbf{I}_3 + \Delta \mathbf{g} . \quad (5.3)$$

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Moreover, it is important to note that the diagonal elements of the g-tensor shift (second term in the above equation) account for the anisotropy of the studied system, which can be probed in EPR experiments of cooled solutions or crystals. In EPR experiments performed in solution at room temperature, due to the random thermal motion of the paramagnetic probe it is convenient to define the isotropic g-tensor shift as:

$$\Delta g_{iso} = \frac{\Delta g_{xx} + \Delta g_{yy} + \Delta g_{zz}}{3} . \quad (5.4)$$

A theoretical evaluation of the electronic g-tensor can be made, in accordance with Eq. 5.1, as a second derivative of the energy with respect to the electronic spin and external magnetic field:

$$\mathbf{g} = \frac{1}{\mu_B} \frac{\partial^2 E}{\partial \mathbf{B} \partial \mathbf{S}} \Big|_{\mathbf{B}=0, \mathbf{S}=0} . \quad (5.5)$$

The usual approach is to calculate the ground state wave function, $|0\rangle$, for an isolated system, while all relevant terms of the Breit-Pauli Hamiltonian that have a contribution to the g-tensor can be considered as perturbation operators. Up to second order in the fine structure constant, α , the g-tensor shift can be written as:

$$\Delta \mathbf{g} = \Delta \mathbf{g}_{RMC} + \Delta \mathbf{g}_{GC} + \Delta \mathbf{g}_{SO} , \quad (5.6)$$

where the first term represents the so-called "mass-velocity" correction, the second term represents the gauge correction contribution while the third denotes the spin-orbit corrections. The first two terms are evaluated just as the expectation value of the corresponding terms from the Breit-Pauli Hamiltonian on the unperturbed ground state wave function, $|0\rangle$. For the mass-velocity g-tensor shift one has:

$$\Delta \mathbf{g}_{RMC} = \frac{1}{\mu_B} \frac{\partial^2}{\partial \mathbf{B} \partial \mathbf{S}} \langle 0 | H_{RMC} | 0 \rangle \Big|_{\mathbf{B}=0, \mathbf{S}=0} , \quad (5.7)$$

where H_{RMC} represents the relativistic mass correction term from the Zeeman Hamiltonian (see Eq. 3.66):

$$H_{RMC} = -\frac{\alpha^2}{2} \sum_i \nabla_i^2 \boldsymbol{\mu}_i \cdot \mathbf{B} . \quad (5.8)$$

For the gauge correction g-tensor shift one can write:

$$\Delta \mathbf{g}_{GC} = \frac{1}{\mu_B} \frac{\partial^2}{\partial \mathbf{B} \partial \mathbf{S}} \langle 0 | H_{GC} | 0 \rangle \Big|_{\mathbf{B}=0, \mathbf{S}=0} . \quad (5.9)$$

Here, H_{GC} denotes the last terms in Eq. 3.69

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$$H_{GC} = -\frac{\alpha^2}{4} \sum_{iI} \frac{Z_I (\mathbf{B} \times \mathbf{r}_{iO}) (\boldsymbol{\mu}_i \times \mathbf{r}_{iI})}{r_{iI}^3} + \frac{\alpha^2}{4} \sum_{i \neq j} \frac{(\mathbf{B} \times \mathbf{r}_{iO}) (\boldsymbol{\mu}_i + 2\boldsymbol{\mu}_j) \times \mathbf{r}_{ij}}{r_{ij}^3}. \quad (5.10)$$

For the evaluation of the spin-orbit contribution to the g-tensor shift, in addition to knowing the ground state of the system, $|0\rangle$, the knowledge of the excited states, $|n\rangle$, is also needed, since for this contribution second order perturbation theory should be employed. One can write the spin-orbit g-tensor shift as:

$$\Delta \mathbf{g}_{SO} = \frac{1}{\mu_B} \frac{\partial^2}{\partial \mathbf{B} \partial \mathbf{S}} \langle \langle H_{SO}; H_{OZ} \rangle \rangle_0 \Big|_{\mathbf{B}=0, \mathbf{S}=0}, \quad (5.11)$$

where use has been made of the linear response function:

$$\langle \langle H_{SO}; H_{OZ} \rangle \rangle_0 = \sum_{n \neq 0} \frac{\langle 0 | H_{SO} | n \rangle \langle n | H_{OZ} | 0 \rangle + \langle 0 | H_{OZ} | n \rangle \langle n | H_{SO} | 0 \rangle}{E_0 - E_n}. \quad (5.12)$$

In the above equations the Hamiltonian, H_{SO} denotes the last two sums that appear in the spin-orbit interaction Hamiltonian in Eq. 3.67 :

$$H_{SO} = -\frac{\alpha^2}{2} \sum_{iI} \frac{Z_I \boldsymbol{\mu}_i \cdot \mathbf{l}_{iI}}{r_{iI}^3} + \frac{\alpha^2}{2} \sum_{i \neq j} \frac{(\boldsymbol{\mu}_i + 2\boldsymbol{\mu}_j) \cdot \mathbf{l}_{ij}}{r_{ij}^3}, \quad (5.13)$$

while the orbital Zeeman Hamiltonian, H_{OZ} , is given by the first term in the Zeeman Hamiltonian in Eq. 3.66 :

$$H_{OZ} = \frac{1}{2} \sum_i \mathbf{B} \cdot \mathbf{l}_{iO}. \quad (5.14)$$

However, when calculating the spin-orbit contribution to the g-tensor shift, one should pay attention especially when dealing with the two-electron operators which are involved in the second term of Eq. 5.13. Attention is required also for the gauge correction contribution, since the second term in the H_{GC} Hamiltonian expressed in Eq. 5.10 involves also two-electron operators. However, in this case the two-electron spin-orbit gauge correction is neglected since it gives a negligible small contribution to the total g-tensor shift. Since density functional theory is, in essence, a one-electron theory, the two-electron operators are usually substituted either by an effective single-particle operator, either by a full two-body spin-orbit operator which is evaluated using the Kohn-Sham orbitals. Among the first options, one can mention the scaled one-electron spin-orbit (SC-SO) method or the atomic mean field spin-orbit (AMFI) operator [69]. Moreover, as pointed out by Kaupp *et al.* one needs to properly account for the spin contamination issues that arise in unrestricted Kohn-Sham approaches [70].

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In this respect, the restricted-unrestricted Kohn-Sham formalism developed by Rinkevicius *et al.* [71] can be employed, as well as the extension in which solvent effects are accounted for using a molecular mechanics approach [72].

5.2 Hyperfine coupling constants

The hyperfine term in the spin Hamiltonian:

$$H_{\text{hyperfine}} = \mathbf{S}\mathbf{A}\mathbf{I}_N , \quad (5.15)$$

governs the interaction between the unpaired electron spin, \mathbf{S} , and the nuclear spin, \mathbf{I}_N , through the hyperfine coupling tensor, \mathbf{A} (not to be confused with the vector potential for which the same notation is used). If nuclei with spin $\mathbf{I}_N \neq 0$ are present in the near surroundings of the unpaired electron of a molecule, further splittings of the spectral lines appear in an EPR experiment, thus, by measuring the hyperfine coupling tensor one gains valuable insight into the local environment of the unpaired electron. A theoretical evaluation of the hyperfine tensor can be made, in accordance with Eq. 5.15, (similar as with the electronic g-tensor case) as a second derivative of the energy with respect to the electronic and nuclear spins:

$$\mathbf{A}_N = \left. \frac{\partial^2 E}{\partial \mathbf{S} \partial \mathbf{I}_N} \right|_{\mathbf{S}=0, \mathbf{I}_N=0} . \quad (5.16)$$

Up to second order in the fine structure constant, α , one can evaluate the hyperfine coupling tensor, \mathbf{A}_N , as expectation values of the corresponding terms from the Breit-Pauli Hamiltonian on the unperturbed ground state wave function, $|0\rangle$. Employing the spin-dipole operator one has:

$$\mathbf{A}_N^{SD} = \left. \frac{\partial^2}{\partial \mathbf{S} \partial \mathbf{I}_N} \langle 0 | H_{SD} | 0 \rangle \right|_{\mathbf{S}=0, \mathbf{I}_N=0} , \quad (5.17)$$

while for the Fermi-contact operator one can write:

$$\mathbf{A}_N^{FC} = \left. \frac{\partial^2}{\partial \mathbf{S} \partial \mathbf{I}_N} \langle 0 | H_{FC} | 0 \rangle \right|_{\mathbf{S}=0, \mathbf{I}_N=0} . \quad (5.18)$$

Here, the spin-dipole and Fermi-contact operators are the first and the second terms that arise in the second sum of the spin-spin Hamiltonian (see. Eq. 3.68). More specifically:

$$H_{SD} = \alpha^2 \sum_{iI} \left(\frac{r_{iI}^2 \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_I - 3(\boldsymbol{\mu}_i \cdot \mathbf{r}_{iI})(\mathbf{r}_{iI} \cdot \boldsymbol{\mu}_I)}{r_{iI}^5} \right) , \quad (5.19)$$

$$H_{FC} = \alpha^2 \sum_{iI} \left(-\frac{8\pi}{3} \delta(\mathbf{r}_{iI}) \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_I \right) . \quad (5.20)$$

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The total hyperfine coupling tensor can be expressed as a sum between the two contributions:

$$\mathbf{A}_N = \mathbf{A}_N^{SD} + \mathbf{A}_N^{FC} , \quad (5.21)$$

where the classical-like dipole-dipole interaction between the magnetic moments that correspond to the electron and nucleus respectively is described through the symmetric traceless tensor \mathbf{A}_N^{SD} , while the Fermi contact interaction between the same entities is described through the diagonal tensor \mathbf{A}_N^{FC} . In EPR experiments performed in solution at room temperature, due to the randomness that characterizes the thermal motion and the orientation of the paramagnetic spins, the spin-dipole contribution simply averages out. Thus, the only contribution to the total hyperfine coupling that remains is the Fermi contact one. Consequently, one can write:

$$A_N^{iso} = \frac{1}{3} Tr(\mathbf{A}_N) . \quad (5.22)$$

Although the expressions leading to the hyperfine coupling constant are rather simple, two important aspects related to the evaluation of the property within the density functional theory (DFT) framework should be noted: (i) one need an accurate description of the spin polarization effects, especially in the vicinity of the nuclei whose spin, $\mathbf{I}_N \neq 0$, and (ii) one needs to properly account for the electron correlation. As pointed out by Neese [18], DFT methods which are based on the unrestricted Kohn-Sham formalism are much more suitable for treating large systems when compared with *ab initio* methods. However, unrestricted Kohn-Sham approaches suffer from the spin contamination problem, and a way to overcome this is to employ a spin-restricted Kohn-Sham formalism. In turn, this approach has the drawback of not properly accounting for the spin polarization effects. The solution to these problems comes with the Kohn-Sham restricted-unrestricted approach developed by Rinkevicius *et al.* [73] and the subsequent extension which can account for solvent effects in a discrete manner [66].

Chapter 6

Summary and outlook

This thesis is devoted to the calculation of EPR spin Hamiltonian parameters of various spin labels in different environments, with the help of state-of-the-art quantum chemical techniques, and collects all the results that are connected with this field, obtained during the author's PhD studies, between Nov 2010 - Mar 2013. In these projects, in the framework of density functional response theory, electronic g-tensors and hyperfine coupling constants were calculated using the relevant Breit-Pauli Hamiltonian terms as perturbation operators.

In *paper I*, the effect of embedding a spin label into a double-stranded deoxyribonucleic acid (DNA) on the EPR parameters of the spin-label is investigated. The proposed approach consists of building a model structure that would capture the important embedding effects without being too large, so that calculation would become prohibitive due to the computational cost. Such a model consists of the rigid spin label ζ hydrogen bonded to guanine (see Fig. 6.1) stacked between two guanine-cytosine units. It is found that both stacking and hydrogen bonding effects have an almost negligible impact on the EPR parameters of the rigid spin label. This represents an important result since the distance measurements experiments involving this spin label embedded into DNA are based on the empirical assumption that the EPR spin Hamiltonian parameters of the spin label are unaffected by the environment in which it is embedded.

Papers II and *III* are the result of an extensive study in which the encapsulation influence on the EPR spin Hamiltonian parameters of a spin label enclosed in a hydrophobic cage is addressed (see Fig. 6.2). Two different approaches are presented. In *paper II* a systematic study of the dependence of the spectroscopic parameters on the hydrogen bonding topologies that occur upon encapsulation is performed. The main differences that arise between the EPR parameters of solvated free nitroxides and solvated nitroxides enclosed in hydrophobic cavities are mainly attributed to the hydrogen bonding topology that is changed in upon encapsulation when compared to the free solvated form. It is found that the magnitude of the NO bond length and the $ONCC'$ improper dihedral angle

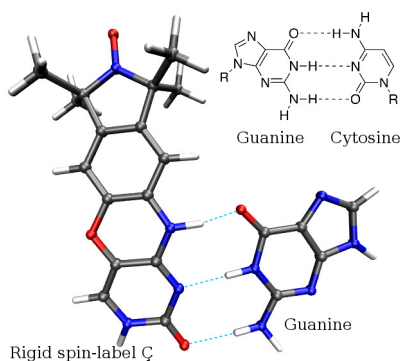


Figure 6.1: Model structure of the guanine \cdots rigid spin label unit, compared to the guanine-cytosine base pair of DNA.

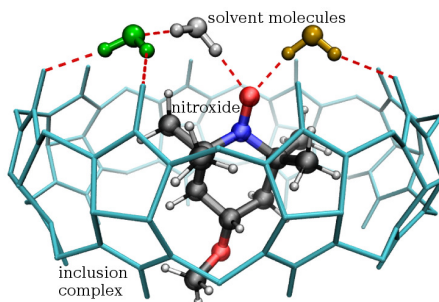


Figure 6.2: A sample snapshot taken from the molecular dynamics simulation of 4M spin label enclosed in the hydrophobic cavity of cucurbit[8]-uril performed in water solution, showing a particular hydrogen bonding pattern.

that characterize the structural properties of the R_2NO^\cdot moiety of nitroxide spin labels is highly influenced by the hydrogen bonding patterns that occur upon encapsulation. On the other hand, the structural parameters that describe the R_2NO^\cdot moiety govern the magnitude of the spectroscopic properties, namely the electronic g -tensor as well as the nitrogen isotropic hyperfine coupling constant.

In *paper III* an alternative analysis is presented, which is based on a "interaction mechanism" approach, that provides a "dynamically averaged" picture of the interactions between the solute and the solvent, which are governing the magnitude of the spectroscopic parameters. It is found that four main contributions to the encapsulation shifts arise, and they are subsequently discussed in term of their physical origin. The contributions to the encapsulation shift are due to: (i) internal dynamics of the R_2NO^\cdot moiety, (ii) interaction with the water molecules, (iii) interaction with the inclusion complex, (iv) changes in

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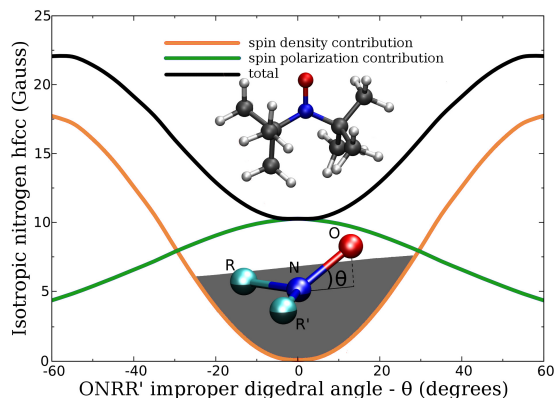


Figure 6.3: Structure - property relationship in di-tert-butyl nitroxide, showing the dependence of the spin polarization and spin density contributions to the nitrogen isotropic hyperfine coupling constant on the improper dihedral angle θ . Results obtained with the DFT/MM method, at the B3LYP/Huz-IIIsu3 level of theory.

hydrogen bond strength due to the interaction between solvent molecules and the inclusion complex. Moreover, a good agreement with experimental data is achieved for the nitrogen hyperfine coupling constant. For the electronic g-tensor the differences between the theoretical predictions and experiment may be traced in the differences between the environmental conditions in the molecular dynamics simulations vs. the ones encountered in real experiments.

Lastly, *paper IV* represents an extension of the density functional restricted-unrestricted formalism to incorporate environmental effects through a quantum mechanical/molecular mechanics approach. This extension, which is targeted at evaluating hyperfine coupling constants, has been incorporated in the DALTON [74] quantum chemistry program. The environment is represented in a discrete manner, allowing for a granular description of the polarization and electrostatic interactions between the quantum and classical regions. With this technique, it is possible to disentangle the spin polarization and spin density contributions to the hyperfine coupling constants in terms of the molecular structure, as well as on the solvent environment. This extension allows the study of larger systems without the need of including the solvent molecules into the quantum region, which would make calculations prohibitive, regarding computational costs. This significantly increases the applicability of DFT/MM to such systems, provided that polarizable force fields exist for the description of the environment molecules. Moreover, the method provides good results for the benchmark test case consisting of the di-tert-butyl nitroxide solvated in water (see. Fig. 6.3).

Moreover, it is important to stress that several simplifying theoretical mod-

els have been employed along the way, which make the predicted EPR parameters rather approximate and by no means exact. The first simplifying model employed is related to the Foldy-Wouthuysen transformation of the Dirac and Breit Hamiltonians which uncouple the electron states from the positron states, which cannot be exactly performed in the presence of electric fields. Then, the quantum electrodynamics (QED) effects are completely neglected throughout this work. One should keep in mind that the free electron g-factor predicted by the Dirac theory is exactly 2, while the QED correction is as big as 2319 ppm, in excellent agreement with experimental data. So far, there are no theoretical studies regarding the QED correction to the electronic g-tensor of free radicals, let alone radicals in various environments. The next simplifying models are related to the general many-body problem treatment. These refer to the density functional theory method, which is exact in principle, but approximate in practice since the exact exchange-correlation functional is yet unknown, as well as to the QM/MM formalism in which the environment is classically described. This list of theoretical simplifications mentioned above is by no means complete, and although several assumptions are made, the predicted EPR parameters are in a good accordance with experimental data. In summary, the projects presented in this thesis offer an example of successful usage of theoretical models and techniques for the investigation of EPR parameters of various spin-labels enclosed in different complex environments. In this way, beside the microscopic understanding of the mechanisms that govern the EPR parameters of spin-labels in such environments, these theoretical studies can also be useful to experimentalists, aiding them in the interpretation of the EPR spectra.

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