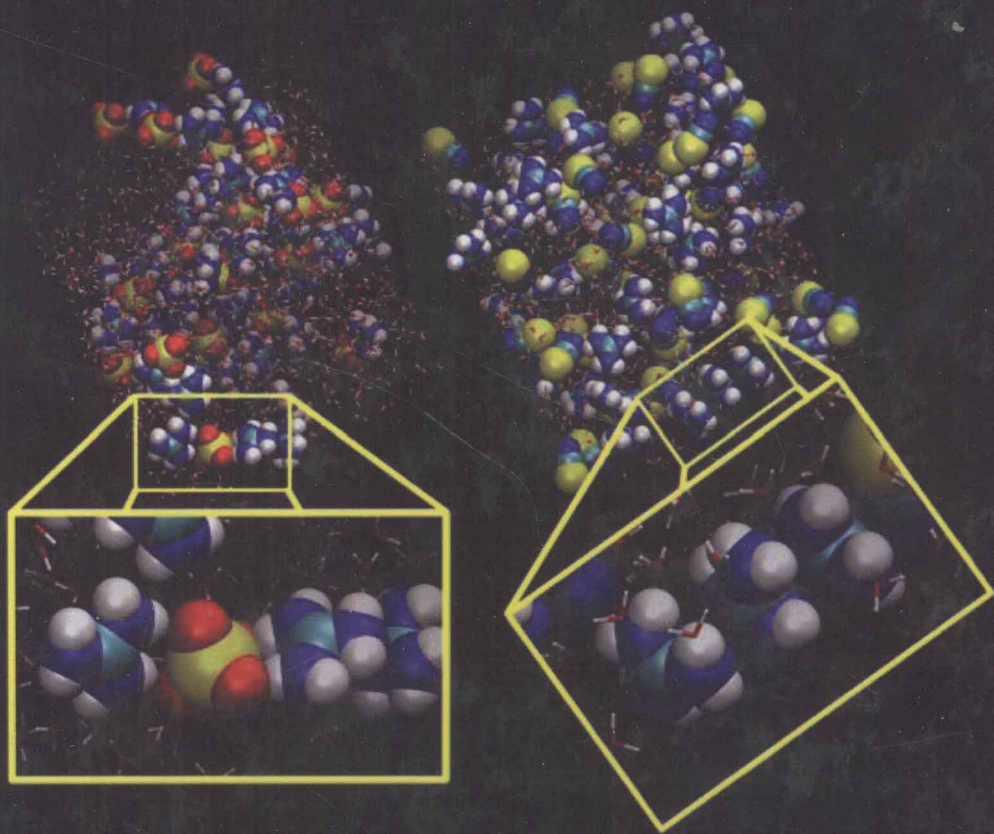


Edited by Kevin J Naidoo, John Brady, Martin J Field, Jiali Gao and Michael Hann

# Modelling Molecular Structure and Reactivity in Biological Systems



# **Modelling Molecular Structure and Reactivity in Biological Systems**

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# Modelling Molecular Structure and Reactivity in Biological Systems

## Preface

In 2005 more than 400 computational chemists and biophysicists met at the 7<sup>th</sup> triennial conference of the World Association of Theoretical and Computational Chemists (WATOC 2005) in Cape Town, South Africa. Half of the 120 invited papers describing the state of the art in computational chemistry had a special focus on applications in biology. While much is now known about the molecular functioning of proteins in cells compared with the previous ten years the elucidation of structure and corresponding function of just one class of biomolecules i.e., proteins is phenomenal. However only about one tenth of the proteins that the genome expresses has so far had its three dimensional structure determined and this figure become even smaller when the complexity of the multiple protein interactions that likely exist is taken into consideration. The complexity is further compounded by the incredible variety of mechanisms that proteins express as a result of their individual three dimensional structures. This is where computational chemistry can help to fill the gaps in our understanding and enable meaningful comments on the structure and reactivity of carbohydrates, lipids and proteins, here collectively referred to as biomolecules, to be made.

In this volume we present a thematic selection of papers lead by a review from Martin Quack followed by reports on cutting edge research in *Molecular Conformation and Electronic Structure of Biomolecules*. The state of the art in elucidating the tertiary structure of proteins and saccharides as pioneered in the laboratories of Valarie Dagget, Axel Brunger and John Brady forms part of a compendium of original papers introducing this book. This leads into an accompanying set of manuscripts laying out the landscape of modelling and current computational methods being developed to investigate *Chemical Reactivity in Biological Surroundings*. Here the spectrum of research from Ursula Rothlisberger's applications of Car-Parrinello quantum dynamics to the more pervasive QM/MD methods as reviewed by Jill Gready is covered.

Finally no text would be complete without an exposition of the coal face biological applications of computational methods which is currently being undertaken in the pharmaceutical industry. The leading industrial groups present their work and perspectives of the use of modelling *Toward Drug Discovery* with all of these contributions placed into context by Hugo Kubinyi's review of database driven methods. Computational chemistry is now a vital and integrated part of the drug discovery process both for helping to interpret experimental data. It is equally important and increasing viable for making predictions that help inform on the choices to be made in terms of which compounds to make next. As the challenges of making more cost effective drugs for the developed and developing worlds become ever more demanding, the computational chemist has a unique role to play in helping to understand what molecules we should and should not make for research purposes.

Kevin J. Naidoo, Martin Field and Michael Hann

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# **Molecular Conformation and Electronic Structure of Biomolecules**



# ELECTROWEAK QUANTUM CHEMISTRY AND THE DYNAMICS OF PARITY VIOLATION IN CHIRAL MOLECULES

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## 1 INTRODUCTION

In the introduction to his famous paper “Quantum Mechanics of Many Electron Systems” Paul Adrien Maurice Dirac wrote one of the most cited sentences in quantum chemistry <sup>1</sup>:

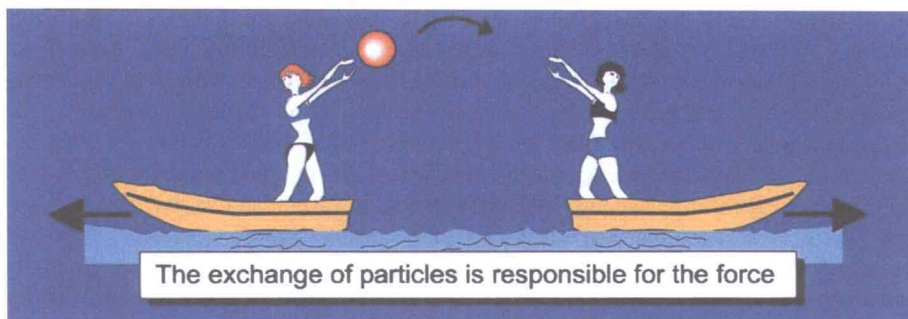
“The underlying physical laws for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble. It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to an explanation of complex atomic systems without too much computation”.

It is remarkable that the second part of this statement, which forms a reasonable starting point for modern, approximate numerical quantum chemistry and computational chemistry is only rarely cited. The more frequently cited first sentence with the strong statement about understanding “the whole of chemistry” and the small restriction “the difficulty is only”, which claims that the quantum physics of the first half of the 20th century contains all basic knowledge about chemistry, is the one that seems to be liked by many theoretical chemists and physicists. It turns out, however, that this statement is incorrect. There is at least one important part of chemistry, namely stereochemistry and molecular chirality, which can be understood properly only when including the parity violating weak nuclear force in our quantum chemical theory in the framework of what we have termed “electroweak quantum chemistry” <sup>2,3</sup>, completely and fundamentally unknown at the time of Dirac’s statement <sup>1</sup>.

Figure 1 summarizes the modern view of the origin of the fundamental interactions as publicized on the website of a large accelerator facility (CERN <sup>4</sup>) According to this view, the electromagnetic force, which is included in the “Dirac-like” ordinary quantum chemistry, leads to the Coulomb repulsion, say, between two electrons in a molecule by exchange of virtual photons. In the picture the two electrons exchanging photons are compared to the ladies on two boats throwing a ball. If we do not see the exchange of the ball, we will observe only the motion of the boats resulting from the transfer of momentum in

throwing the ball, and we could interpret this as resulting from a repulsive “force” between the two ladies on the boats. Similarly, we interpret the motion of the electrons resulting from “throwing photons as field particles” as arising from the Coulomb law, which forms the basis of ordinary quantum chemistry. The Coulomb force with the  $1/r$  potential energy law is of long range. The other forces arise similarly. The strong force with very short range (0.1 to 1 fm) mediated by the gluons is important in nuclear physics but has only indirect influence in chemistry by providing the structures of the nuclei, which enter as parameters in chemistry, but there is otherwise usually no need to retain the strong force explicitly in chemistry. The weak force, on the other hand, is mediated by the  $W^\pm$  and  $Z^0$  Bosons of very high mass (80 to 90 Daltons, of the order of the mass of a bromine nucleus!) and short lifetime (0.26 yoctoseconds =  $0.26 \times 10^{-24}$  s).

The Forces in Nature			
Type	Intensity of Forces (Decreasing Order)	Binding Particle (Field Quantum)	Important in
Strong Nuclear Force	$\sim 1$	Gluons (no mass)	Atomic Nucleus
Electro-Magnetic Force	$\sim 10^{-3}$	Photons (no mass)	Atoms and Molecules
Weak Nuclear Force	$\sim 10^{-5}$	Bosons Z, W+, W-, (heavy)	Radioactive $\beta$ -Decay, Chiral Molecules
Gravitation	$\sim 10^{-38}$	Gravitons (?)	Sun and Planets etc.



CERN AC\_Z04\_V25/B/1992

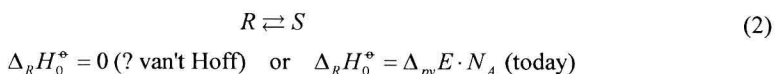
**Figure 1** Forces in the standard model of particle physics (SMPP) and important effects. This is taken from the CERN website ref. 4, but the importance of the weak interaction for chiral molecules has been added here from our work (by permission after ref. 4).

This force is thus very weak and of very short range ( $< 0.1$  fm) and one might therefore think that similar to the even weaker gravitational force (mediated by the still hypothetical graviton of spin 2) it should not contribute significantly to the forces between the particles in molecules (nuclei and electrons). Indeed, the weak force, because of its short range, becomes effective in molecules, when the electrons penetrate the nucleus, and then it leads only to a very small perturbation on the molecular dynamics, which ordinarily might be neglected completely.

It turns out, however, that because of the different symmetry groups of the electromagnetic and the electroweak hamiltonians there arises a fundamentally important, new aspect in the dynamics of chiral molecules, which we therefore have added to the figure from CERN, where this was not originally included, in our Fig. 1. Indeed the electromagnetic hamiltonian commutes with the space inversion or parity operator  $\hat{P}$

$$\hat{P}\hat{H} = \hat{H}\hat{P} \quad (1)$$

which leads to the consequence that in chiral molecules the delocalized energy eigenstates  $\chi_+$  and  $\chi_-$  have a well defined parity and the localized handed states  $\lambda$  and  $\rho$  of chiral molecules have exactly the same energy by symmetry (see section 2 for details). Therefore one can also say that the reaction enthalpy  $\Delta_R H_0^\circ$  for the stereomutation reaction (2) between R and S enantiomers of a chiral molecule would be exactly zero by symmetry ( $\Delta_R H_0^\circ \equiv 0$ ) a fact originally noted already by van't Hoff<sup>5</sup>



Today, we know, that the electroweak hamiltonian does not commute with  $\hat{P}$

$$\hat{P}\hat{H}_{ew} \neq \hat{H}_{ew}\hat{P} \quad (3)$$

and therefore parity is violated leading to a small but nonzero parity violating energy difference  $\Delta_{pv} E$  between enantiomers and thus  $\Delta_R H_0^\circ \neq 0$  (for example about  $10^{-11}$  J mol<sup>-1</sup> for a molecule like CHFCIBr<sup>6</sup>). We shall discuss in section 2 in more detail, under which circumstances such small effects lead to observable results dominating the quantum dynamics of chiral molecules.

This symmetry violation in chiral molecules is, indeed, the key concept, which leads to an interesting interaction between high energy physics and molecular physics and chemistry, indeed also biochemistry<sup>7,8</sup>. It results in the following at first perhaps surprising three statements:

- (1) The fundamentally new physics arising from the discovery of parity violation<sup>9-12</sup> and the consequent electroweak theory in the Standard Model of Particle Physics (SMPP)<sup>13-17</sup> leads to the prediction of fundamental new effects in the dynamics of chiral molecules and thus in the realm of chemistry .

- (2) Molecular parity violation as encoded in Eqs. (2), (3) has possibly (but not necessarily) important consequences for the evolution of biomolecular homochirality in the evolution of life<sup>7, 8, 18</sup>.
- (3) Possible experiments on molecular parity violation open a new window to look at fundamental aspects of the standard model of high energy physics, and thus molecular physics might contribute to our understanding of the fundamental laws relevant to high energy physics. Indeed, going beyond parity violation and the standard model, molecular chirality may provide a new look at time reversal symmetry and its violation, in fact the nature of time<sup>8</sup>.

It should thus be clear that electroweak quantum chemistry has interesting lessons to tell. A brief history of electroweak quantum chemistry is quickly told. After the discovery of parity violation in 1956/57<sup>9-12</sup> it took about a decade until the possible consequences for chemistry and biology were pointed out by Yamagata in 1966.<sup>18</sup> While his numerical estimates were wrong by many orders of magnitude (as also a later estimate<sup>19</sup>) and even some of his qualitative reasonings were flawed (see<sup>8</sup>), the link of parity violation in high energy physics and the molecular physics of chirality was thus established and repeatedly discussed qualitatively in the 1970s.<sup>20-27</sup>

The first quantitative calculations on molecular parity violation were carried out following the work of Hegström, Rein and Sandars<sup>28, 29</sup> and Mason and Tranter<sup>30-32</sup> in the 1980s.<sup>30-52</sup> Some far reaching conclusions about consequences for biomolecular homochirality were drawn from some of these early calculations but we know now, that none of these early calculations prior to 1995 can be relied on (nor can one retain their conclusions), as they were wrong even by orders of magnitude.

Indeed, in 1995 we carefully reinvestigated the calculations of parity violating energies in molecules and discovered, surprising to many at the time, that an improved theoretical treatment leads to an increase of calculated parity violating energies by about two orders of magnitude in the benchmark molecules  $\text{H}_2\text{O}_2$  and  $\text{H}_2\text{S}_2$ .<sup>2, 3</sup> This discovery triggered substantial further theoretical<sup>6-8, 53-67</sup> and experimental activity<sup>68-79</sup> and the numerical results were rather quickly confirmed in independent calculations from several research groups as summarized in table 1. While the earlier overoptimistic conclusions on the selection of biomolecular homochirality had to be revised<sup>8</sup>, our work has led to a completely new and much more optimistic outlook on the possibility of doing successful spectroscopic experiments, which are now underway in our own group and others<sup>68-77</sup>. Although no successful experiment has as yet been reported, one may now expect such results in the relatively near future.

The outline of the remainder of this review is as follows:

We shall start in section 2 by a discussion of fundamental symmetries of physics leading us to the conceptual foundations of various types of symmetry breaking. We shall discuss the related opinions or “communities of belief” for the physical-chemical dynamics of chirality, for the selection of biomolecular homochirality and for irreversibility, which are conceptually closely related because of the relationship between parity symmetry  $P$  and time reversal symmetry  $T$ . We shall then introduce the foundations of electroweak quantum chemistry in section 3, allowing us to calculate  $\Delta_{PV}E$  in chiral molecules. This will lead us to the concepts for current experiments in section 4. We shall conclude in section 5 with an outlook on the role of stereochemistry for future experiments on the foundations of

the CPT symmetry and the ultimate nature of irreversibility. In part of this we follow an earlier review (in German<sup>80</sup>, see also refs. 7, 8, 81-83. We draw also attention to recent reviews<sup>84, 85</sup> as well as to ref. 3 and an earlier review<sup>86</sup> with many further references (see also<sup>87, 88</sup>). We do not aim to be encyclopedic here but rather to provide a conceptual summary.

**Table 1** Parity-violating energy differences  $\Delta_{pv}H_0^* = \Delta, H_0^*(M) - \Delta, H_0^*(P)$  for  $H_2O_2$ ,  $H_2S_2$  and  $Cl_2S_2$  at the geometries of the *P* and *M* enantiomers indicated (close to but not exactly equilibrium geometries, chosen for intercomparison of different results). The geometry parameters used were:  $r_{OO} = 149$  pm,  $r_{OH} = 97$  pm,  $\alpha_{OOH} = 100^\circ$ ,  $\tau_{HOOH} = 90^\circ$  for  $H_2O_2$ ,  $r_{SS} = 205,5$  pm,  $r_{SH} = 135.2$  pm,  $\alpha_{SSH} = 92^\circ$ ,  $\tau_{HSSH} = 92^\circ$  for  $H_2S_2$ , and  $r_{SS} = 194.7$  pm,  $r_{SCl} = 205.2$  pm,  $\alpha_{SSCl} = 107.55^\circ$ ,  $\tau_{ClSSCl} = 85.12^\circ$  for  $Cl_2S_2$  (see also ref. 8 and references cited therein).

Molecule	Method	References	$\Delta_{pv}H_0^*$ [ $10^{-12}$ J mol <sup>-1</sup> ]
H <sub>2</sub> O <sub>2</sub>	SDE-RHF 6-31G	32	-0.0036
	CIS-RHF 6-31G	2, 3, 54, 89	-0.60
	TDA 6-31G	56, 57	-0.84
	DHF	58	-0.44
	CASSF-LR/cc-pVTZ	55	-0.41
H <sub>2</sub> S <sub>2</sub>	SDE-RHF 6-31G	32	0.24
	TDA 4.31G	56, 57 (scaled 75%, ref. 54)	14.4
	CIS-RHF 6-31G	3, 54, 89	22.5
	MC-LR RPA/aug-cc-pVTZ	59	22.4
	DHF	58	33.5
Cl <sub>2</sub> S <sub>2</sub>	MC-LR RPA/aug-cc-pVTZ	60	-15.4

## 2 FUNDAMENTAL SYMMETRIES OF PHYSICS AND THE VIOLATION OF PARITY AND TIME REVERSAL SYMMETRY IN MOLECULES

### 2.1 Fundamental Symmetries in Molecular Physics

We shall address here the fundamental symmetries of physics and how they can be investigated by molecular physics, in particular molecular spectroscopy.<sup>87, 88</sup> The following symmetry operations leave a molecular hamiltonian invariant within the framework of traditional quantum chemical dynamics including only the electromagnetic interaction (see refs. 80, 81, 90, 91, for example).

- (1) Translation in space
- (2) Translation in time
- (3) Rotation in space
- (4) Inversion of all particle coordinates at the origin (parity operation  $P$  or  $E^*$ )
- (5) "Time reversal" or the reversal of all particle momenta and spins (operation  $T$  for time reversal)
- (6) Permutation of indices of identical particles (for instance nuclei and electrons).
- (7) The replacement of all particles by their corresponding antiparticles (operation  $C$  for "charge conjugation", for instance replacing electrons by positrons and protons by antiprotons etc.).

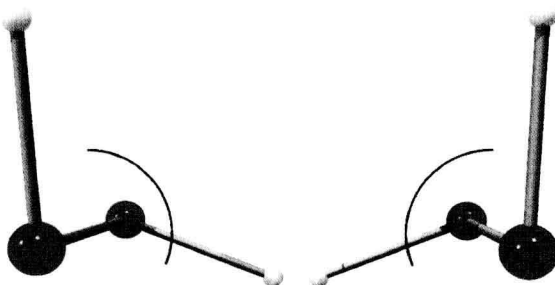
These symmetry operations form the symmetry group of the molecular hamiltonian. It is well known following the early work of Emmy Noether that in connection to an exact symmetry we have a corresponding exact conservation law. For instance (1) leads to momentum conservation, (2) leads to energy conservation, (3) to angular momentum conservation and (4) to parity conservation, that is conservation of the quantum number parity which describes the symmetry (even or odd, positive or negative) of the wavefunction under reflection at the origin. Another interesting observation is that an exact symmetry and conservation law leads to a fundamentally non-observable property of nature (see the discussion in refs. 8, 80, 92). For instance  $P$  corresponds to the fundamentally non observable property of the left-handedness or right-handedness of space. That implies that it would be fundamentally impossible to say what is a left handed or right handed coordinate system or an R or S enantiomeric molecular structure, only the opposition of left and right would have a meaning. It would correspondingly be impossible to communicate by a coded message (without sending a chiral example) to a distant civilization that we are made of S (or L)-aminoacids and not of their R (or D) enantiomers. This impossibility is removed, if the exact symmetry is invalid, "broken de lege" as we shall see. We know from nuclear and high energy physics that  $P$ ,  $C$ , and  $T$  are individually all violated, as is also the combination  $CP$ . Only the combined operation  $CPT$  remains an exact symmetry in the current "standard model".<sup>87, 88, 90-97</sup> Parity violation is in fact abundant in a variety of contexts in nuclear and atomic physics,<sup>10-12, 98, 99</sup>  $CP$  violation was originally observed in the K-meson decays only<sup>100</sup>, but is now also found in the B-Meson system<sup>97</sup> and direct  $T$ -violation has been established in 1995 after it had already been inferred from the earlier  $CP$  violation experiments.<sup>101</sup> We have speculated on several occasions that in principle all the discrete symmetries might be violated ultimately in molecular physics (see refs. 80-83, 87, 102, 103, where also some tests for symmetry violations are cited). We shall however, now usefully discuss first in more detail the



fundamental concepts of symmetry violations and symmetry breakings, starting out with the easy to grasp concepts for parity violation.

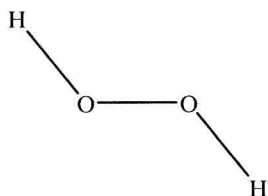
## 2.2 Concepts of Symmetry breaking spontaneous, de facto, de lege in relation to molecular chirality

The three concepts of symmetry breaking should be carefully distinguished<sup>7</sup> and we shall illustrate this with a chiral molecular example,  $\text{H}_2\text{O}_2$  (Fig. 2). This molecule is non-planar, bent, in its equilibrium geometry and an accurate full dimensional potential hypersurface has been formulated for its reaction dynamics.<sup>104</sup>



**Figure 2** *The  $\text{H}_2\text{O}_2$  molecule in its enantiomeric mirror image forms at the equilibrium structure (by permission from ref. 80). The angle between the two planes indicated is  $\alpha$ .*

In a simplified fashion the stereomutation reaction (2) interconverting the two enantiomers can be considered as a one dimensional torsional internal rotation about an angle  $\alpha$  indicated in the figure. One has barriers to this motion, a low one in the planar trans form



$$E_{\text{trans}} = 4.3 \text{ kJ mol}^{-1} (361 \text{ cm}^{-1}) \quad (4)$$