ESF report on the CECAM workshop "*Spin states in biochemistry and inorganic chemistry*"

Organisers: Marcel Swart and Mikael Johansson

Place: ZCAM Centre at the University of Zaragoza, Spain

Date: September 18 to 21, 2012

1. Summary

The electrons surrounding the nuclei of all matter around and within us can be in two different states, denoted the electron spin. This effect, although being purely quantum-chemical, has profound implications for real-world, large-scale systems like, for example, living tissue. In most cases, electrons of different spin pair up, effectively cancelling the spin-effect. In some cases, however, electrons prefer not to pair up, which leads to an excess of one type of electrons in a system. Depending on the exact conditions and surroundings, the number of these unpaired electrons can vary, leading to different spin-states not only for the individual electrons, but for much larger molecular species. In many cases, the spin-state has been found to be a key factor governing the behaviour of the system. Elucidating the role and effect of different spin states on the properties of a system, even deciding which spin-state occurs naturally, is presently one of the most challenging endeavours both from an experimental and theoretical point-of-view.

One of the goals of the workshop was to discuss the present state-of-the art for methodologies used to both probe and predict the spin states of various biochemical and inorganic systems. Leading experts within the field, both experimental and theoretical, were invited to, and did, participate. In addition to well-established experts on spin effects, the workshop delegates included many young researchers at the early stages of their career. The admixture of varying levels of experience on the topic for its own part helped to liven up and invigorate the discussions during the workshop.

In addition to via presentations and discussions establish how far quantum theoretical theory and experimental methodologies have advanced to date, an important part of the meeting was to discuss future directions and refinements on the methods used to investigate systems where the electron spin is of importance. Importantly, a significant part of the discussion involved strategies of how to aid future developments by the means of international collaboration.

2. Description of the scientific content of and discussion at the event

A day-by-day summary of the presentations and related discussions.

Day 1

After a welcome speech by the ZCAM director **Michel Mareschal**, the conference took off with a presentation by **Marcel Swart** (University of Girona/ICREA, Spain) on the origins of the workshop. The motivation for organising the meeting was followed by a brief presentation on Swart's own effort within the framework of density functional theory to develop and assess the reliability of methods for predicting spin-state energies. The SSB-D functional was shown to work very well in this respect. **Kasper Kepp** (Technical University of Denmark, Denmark) followed, discussing methodological considerations for state-of-the-art accurate calculations of enthalpies or free energies, with a particular focus on spin cross-over. Physical effects and ingredients in density functionals, their systematic errors, and approaches to deal with these errors were presented. **Daniel Escudero** (Max-Planck-Institut für Kohlenforschung, Germany) and **Mariusz Radoń** (Jagiellonian University, Poland) presented recent work employing correlated wave function methods for spin states. Two different approaches were discussed, with Escudero concentrating on the multi-configurational approach (*e.g.*, RASPT2) and Radoń presenting highly correlated, single-reference based methodology (*e.g.,* CCSD(T)). The general discussion after the first batch of presentations took off well, highlighting the inherent problems of DFT; while some critical voices and concerns of stagnation in the further development of DFT were heard, the recent advances with DFT were found to be promising. For wave-function methods, taking both the important aspects of correlation into account simultaneously is still prohibitively expensive. The conclusion was that when MR methods, which capture the non-dynamical, static correlation, and higher order coupled cluster theory, which captures dynamic correlation agree, the predictions are reliable; when the two approaches disagree, identifying the source of error is still anything but straightforward.

The second session of the first day continued on the topic of spin crossover. **Rob Deeth** (University of Warwick, UK) discussed classical molecular mechanics and dynamics simulations. With standard force fields electrons do not directly enter the description, and thus the different behaviour of different spin states is not very well accounted for. An extension to molecular mechanics, where two explicit terms dealing with the *d*-electron effects necessary to treat spin crossover for transition metals, was presented. Preliminary results are promising. **Coen de Graaf** (Universitat Rovira i Virgili, Spain) presented an example of light-induced spin crossover by combining accurate electronic structure calculations and time-dependent approaches to calculate intersystem crossing rates. By nature of being non-standard and novel methods, both talks of the last session of the first day incited a good discussion on their future applicabilites.

Day 2

Victor Guallar (Barcelona Supercomputing Centre, Spain) started off the second day by presenting methodologies developed in their group which enable following how the unpaired spin density propagates along different paths during electron transfer, with an emphasis on enzymatic processes. **Robert Scheidt** (University of Notre Dame, USA) showed how Mössbauer spectroscopy combined with other experimental techniques now have established that all high-spin iron(II) porphyrinates are *not* alike, but instead segregated into two classes, which could be important for biological processes. An example of where quantum chemical theory played a crucial role in establishing the correct mechanism, structure, and spin state of a biologically highly important system was highlighted by **Per Siegbahn** (Stockholm University, Sweden); the water oxidation catalyst in photosystem II contains four paramagnetic manganese centres, and a successful modelling of this centre is a prime example of the mature stage of quantum chemical modelling of spin states.

Alexandra Carvalho (University of Girona, Spain) discussed the detrimental effects of reactive oxygen species in our bodies, and presented molecular dynamics simulations of complex II embedded within a lipid membrane. In order to reliably model the system, new, system-specific parameters for the embedded iron-sulphur clusters were shown to be of crucial importance. The power of the interplay between theory and experimental spectroscopy was demonstrated in the talk by **Oliver Krahe** (Max-Planck Institute for Chemical Energy Conversion, Germany). **Shengfa Ye** (Max-Planck Institute for Chemical Energy Conversion, Germany) continued on the topic of combining the individual strengths of experimental and theoretical approaches in a case-study on elucidation of the reaction mechanism of nonheme iron enzymes. Spin-state changes in thermal reactions were thoroughly discussed by **Jeremy Harvey** (University of Bristol, UK). The talks during this second session of the day incited a lively discussion, where especially the importance of combining state-of-the-art theoretical methods with experiment was brought up.

The third session of the day concentrated on C—H bond activation. **Paola Belanzoni** (University of Perugia, Italy) gave a detailed analysis of the orbital interactions behind efficient catalysis of C—H bond oxidation in inorganic complexes. **Lawrence Que, Jr.** (University of Minnesota, USA) gave an intriguing overview of the synthesis and experimental characterisation of oxoiron(IV) complexes of both intermediate (S=1) and high-spin (S=2) character. Modelling aspects of biomimetic hydroxylation of C—H bonds were discussed by **Puneet Gupta** (Goethe-University, Germany), a theme further discussed by **Prokopis Andrikopoulos** (University of Lyon, France) in his presentation on *in silico* design of efficient catalysts for alkane oxidation.

Kallol Ray (Humboldt-Universität zu Berlin, Germany) showed recent results on trapping a transient copper–tosylnitrene species, which allowed for a thorough experimental characterisation of its controversial electronic structure. **Sam de Visser** discussed biomimetic cysteine dioxygenase model complexes and compared their electronic properties and reactivities with enzymatic systems.

The various successful combinations of experimental and theoretical methods presented during the day gave rise to lively discussions and exchange of ideas on how to further science by

increased collaboration between disciplines. This discussion was continued in an even less formal setting during the conference dinner which ended the official programme of the second day.

Day 3

Martin Kaupp (Technische Universität Berlin, Germany) started the day off with a detailed exploration of the difficulties within contemporary DFT for describing spin states and spin density distributions, as well as novel methods and approaches for solving or circumventing the problems. The topic was further elaborated on by **Markus Reiher** (ETH Zürich, Switzerland), who also presented accurate *ab initio* spin density within the density-matrix renormalization group (DMRG) formalism. **Rongzhen Liao** (Max-Planck-Institut für Kohlenforschung, Germany) showed how a combination of quantum mechanics and molecular mechanics (QM/MM) was used to show that the oxidation state of iron is crucial for the enzymatic activity of aldoxime dehydratase. The ensuing discussion welcomed the newly developed methods to the repertoire of quantum chemical modelling. An intense discussion, revisiting the topics and methods from day one as well, showed that using several different approaches with the same ultimate goal, reliable theoretical modelling of spin states, is important; the complementary insights provided by different approaches are crucial.

The power of mutations for elucidating electronic structure and function of proteins was demonstrated in the talk by **Kara Bren** (University of Rochester, USA). Employing, among other methods, NMR, ESR, and resonance Raman spectrosopies, the spin states and densities in cytochromes *c*, and their dependence on the degree of haem ruffling was explored. **Dage Sundholm** (University of Helsinki, Finland) gave an overview of the gauge-including magnetically induced currents (GIMIC) approach, discussing examples of how different spin components give rise to electronic currents in molecules under the influence of a magnetic field. **Eckard Münck** (Carnegie Mellon University, USA) presented Mössbauer, EPR and DFT studies of high-valent diiron TPA complexes, and showed how careful control of the spin state can increase activity of C—H bond cleaving a thousand fold. Again, the discussion after the session managed to bring the relations between experimental and theoretical approaches in tune.

Cecilia Sánchez-Hanke (Brookhaven National Laboratory, USA) gave an overview of the impressive capabilities of the new synchrotron beamline at the National Synchrotron Light Source (NSLS), discussing possible novel uses of the machine for elucidating spin states, extending an invitation to perform experiments never performed before. **Ulf Ryde** (Lund University, Sweden) presented a theoretical study on models of [Ni, Fe]-hydrogenase, employing several theoretical approaches, including DFT, CASPT2/RASPT2, and coupled cluster approaches, providing a good summary on the strengths and shortcomings of the methods, continuing the debate of the topic during the workshop. **Lucian Constantin** (Istituto Italiano di Tecnologia, Italy) showed how a spin-dependent correction to standard density functionals helps to improve their description of atomization energies of molecules and solids. Another case-study showing the power of the combined QM/MM methodology was presented by **Julianna Oláh** (Budapest University of Technology and Economics, Hungary). A good discussion on how to best combine the latest developments in experimental and theoretical methodology and machinery ended the session.

The need for accurate treatment of multiple spin states was convincingly exemplified by **Lubomír Rulíšek** (Institute of Organic Chemistry and Biochemistry AS CR, Czech Republic). This need

was further cemented by **Kristine Pierloot** (University of Leuven, Belgium) in her presentation utilising multiconfigurational perturbation theory for uncovering the details of NO binding to transition metal centres. The last discussion session of the day was diverse, continuing in the bus.

Day 4

Miquel Costas (University of Girona, Spain) started the final day with presenting impressive synthetic efforts for studying biologically relevant oxidation catalysis with non-heme Fe complexes with N-based scaffolds. **Kazunari Yoshizawa** (Kyushu University, Japan) continued on the topic of spin crossover effects, emphasizing their importance in enzymatic and catalytic reactions and analysing the underlying mechanisms using quantum chemical calculations and orbital interaction analyses. Dinitrogen functionalisation utilising the flexibility of the Fe—B bond was discussed by **Marc-Etienne Moret** (University of Utrecht, The Netherlands).

Different, spin-dependent pathways in nitrene insertion reactions were presented by **W. M. Chamil Sameera** (Institute of Chemical Research of Catalonia, Spain), in a combination of theoretical and experimental efforts. The last presentation of the workshop was given by **Pablo Campomanes** (Ecole Polytechnique Fédérale Lausanne, Switzerland), and represented an exemplary case-study where the combination of high-level *ab initio* calculations, dynamic effects *via* QM/MM simulations, and high-field EPR spectroscopy lead to an unambiguous assignment of the zero-field splitting parameters for the Mn(II) centres in oxalate decarboxylase.

The meeting was wrapped up in a lively discussion on the present best-practices for employing theoretical modelling, strategies for enhancing the two-way interplay between experiment and theory, and concrete suggestions on how to use the insights of the workshop in the future.

3. Assessment of the results and impact of the event on the future direction of the field

The initial goal of the workshop to probe the present state-of-the-art in spin state modelling and experimental characterisation was achieved very satisfactorily. It became clear that there is still much to do with respect to method development before the extremely complex problem of spin states can be generally solved in a black-box manner. At the same time, development was found to be rapid and diverse, with many novel ideas being put into practice. The workshop served as a very good introduction to many new methods, disseminating not only their existence, but also their promising features to a large audience. The highly international composition of the workshop delegates ensures that the new ideas will get exposure to a broad audience within the field.

The performance of more established modelling methods was also thoroughly discussed, and shown to, in many cases, to be able to provide much insight into problems involving spin states. Thus, already with existing and readily available techniques, important properties of systems where the electron spin is important *can* be probed. During the meeting, the limitations of older methods were clearly identified. While this naturally means that new, more accurate avenues have to be explored, the discussion also helped identify the cases where less accurate methods are perfectly adequate for gaining relevant scientific insights.

Another highly successful aspect of the meeting was its ability to bring experimentalists and theoreticians closer. The vivid interplay during the discussion session helped both points-of-view in gaining a mutual understanding of the limitations and strengths of methods available to the communities studying molecules *in vitro* and *in silico*. Crucially, the discussions brought into light new opportunities and ideas on how to tackle specific and more general problems and unanswered questions by the means of collaboration. The discussion sessions managed to bring up topics that within a specific discipline could be considered, say, common knowledge, but for specialists in another, even if closely related field, came as a revelation. Breaking down the scientific language barrier between fields on many occasions during the meeting furthered the understanding and facilitated future collaborative projects; learning how your own expertise, in combination with that of others in a maybe only remotely familiar field, could lead to interesting insights was exciting.

A practical follow-up to the meeting is to establish and maintain a database of compounds and systems with known spin states and spin-related properties. Such a centralised database presently does not exist. During the final discussion of the workshop, the usefulness of such a database was universally agreed upon. How to precisely implement it, and the decision process of what kind of data exactly the database should include divided the delegates to a degree, as expected. The details of the database will be, and are being, worked out, of course.

All-in-all, the delegates seemed to enjoy the meeting and its scientific content.

4. Final programme of the meeting

Day 1 – Tuesday, September 18, 2012

Session Ia – Chairperson: Mikael Johansson

- 15:00 to 15:30 – Welcome
- 15:30 to 16:00 - **Marcel Swart**
  Origins of Workshop
- 16:00 to 16:30 - **Kasper P. Kepp**
  Consistent Descriptions of Spin-Crossover in Inorganic Chemistry
- 16:30 to 16:45 - **Daniel Escudero**
  RASPT2/MM Studies on the Spin State Energetics of Cpd I
- 16:45 to 17:00 - **Mariusz Radoń**
  Spin State Energetics of Heme-Related Models From DFT and *ab initio* Calculations
- 17:00 to 17:15 – Discussion
- 17:15 to 17:45 - Coffee Break

Session Ib – Chairperson: Sam de Visser

- 17:45 to 18:15 - **Rob Deeth**
  Molecular Discovery and Spin Crossover
- 18:15 to 18:45 - **Coen de Graaf**
  Ultrafast Deactivation Mechanism of the Excited Singlet in the Light Induced Spin Crossover of $[Fe(bipy)_3]^{2+}$
- 18:45 to 19:00 – Discussion

Day 2 – Wednesday, September 19, 2012 (morning)

Session IIa – Chair: Kara Bren

- 9:00 to 9:30 – **Victor Guallar**
  QM/MM Methods: Following Electrons in Complex System

- 9:30 to 10:00 - **W. Robert Scheidt**
  All High-Spin (*S* = 2) Iron(II) Porphyrinates are NOT Alike

- 10:00 to 10:30 - **Per E. M. Siegbahn**
  Spin States and Mechanisms for Natural Water Oxidation

- 10:30 to 11:00 – Discussion

- 11:00 to 11:30 - Coffee Break

Session IIb – Chair: Paola Belanzoni

- 11:30 to 11:45 - **Alexandra T. P. Carvalho**
  Molecular Dynamics of Complex II Within a Lipid Membrane: Parameterization of the Iron-Sulfur Clusters

- 11:45 to 12:00 - **Oliver Krahe**
  Interplay of Theory and Spectroscopy: Study of an Fe^{V}-Nitride Complex and its Photolytic Formation

- 12:00 to 12:30 - **Shengfa Ye**
  Elucidation of the Reaction Mechanism of Nonheme Iron Enzymes by a Combined Theoretical and Experimental Approach

- 12:30 to 13:00 - **Jeremy Harvey**
  Spin-State Changes in Thermal Reactions: What Can We Learn from Computational Chemistry?

- 13:00 to 13:30 – Discussion

Lunch

13:30 to 15:30 – Lunch

Day 2 – Wednesday, September 19, 2012 (afternoon)

Session IIIa – Chair: Rob Deeth

- 15:30 to 16:00 - **Paola Belanzoni**
  How to Make the Iron-Oxo Group an Effective Catalyst in the Oxidation of C–H Bonds and Water

- 16:00 to 16:30 - **Lawrence Que, Jr.**
  Spin State Effects on C–H Bond Cleavage by High-Valent Iron-Oxo Complexes

- 16:30 to 16:45 - **Puneet Gupta**
  Biomimetic Hydroxylation of Non-Activated C–H Bonds in a Bis-(μ-Oxo)Dicopper Complex: An Evaluation of DFT for Mechanistic Studies

- 16:45 to 17:00 - **Prokopis Andrikopoulos**
  Oxidation of Alkanes: In Silico Catalyst Design

- 17:00 to 17:15 – Discussion

- 17:15 to 17:45 - Coffee Break

Session IIIb – Chair: Kasper Kepp

- 17:45 to 18:15 - **Kallol Ray**
  Lewis-Acid Trapping of an Elusive Copper-Tosylnitrene Intermediate Using Scandium Triflate

- 18:15 to 18:45 - **Sam de Visser**
  Cysteine Dioxygenase: Enzymatic Reaction Mechanism and Biomimetic Models

- 18:45 to 19:00 – Discussion

Conference dinner

- 21:00 to 23:30 - Social Dinner (Restaurante La Bastilla, C/ Coso 177)

Day 3 – Thursday, September 20, 2012 (morning)

Session IVa – Chair: Lubomír Rulíšek

- 9:00 to 9:30 - **Martin Kaupp**
  Challenges and Means to Obtain Correct Spin-Density Distributions by DFT

- 9:30 to 10:00 - **Markus Reiher**
  Spin States, Spin Density and Local Spin in DFT

- 10:00 to 10:30 - **Rongzhen Liao**
  Why is the Oxidation State of Iron Crucial for the Activity of Heme-Dependent Aldoxime Dehydratase? A QM/MM Study

- 10:30 to 11:00 – Discussion

- 11:00 to 11:30 - Coffee Break

Session IVb – Chair: Marc-Etienne Moret

- 11:30 to 12:00 - **Kara Bren**
  The Influence of Heme Conformation and Second-Sphere Interactions on Spin State and Spin Density Distribution in Cytochromes *c*

- 12:00 to 12:30 - **Dage Sundholm**
  The Gauge Including Magnetically Induced Current Method

- 12:30 to 13:00 - **Eckard Münck**
  Mössbauer, EPR and DFT Studies of High-Valent Diiron TPA Complexes: Spin Transitions at an Fe(IV)-Oxo Site Induced by Superexchange Interactions

  13:00 to 13:30 – Discussion

Lunch

13:30 to 15:30 – Lunch

Day 3 – Thursday, September 20, 2012 (afternoon)

Session Va – Chair: Coen de Graaf

- 15:30 to 16:00 - **Cecilia Sánchez-Hanke**
  Magnetic Circular Dichroism and Other Synchrotron Techniques Sensitive to Spin States

- 16:00 to 16:30 - **Ulf Ryde**
  Accurate Calculations of Geometry and Spin-Splitting Energies for Active-Site Models of [Ni, Fe] Hydrogenase

- 16:30 to 16:45 - **Lucian Constantin**
  Improving Atomization Energies of Molecules and Solids with a Spin-Dependent Gradient Correction from One-Electron Densities Paradigms

- 16:45 to 17:00 - **Julianna Oláh**
  The Peculiar Role of the Iron-Oxo Species in the Catalytic Cycle of the Human Aromatase Enzyme

- 17:00 to 17:15 – Discussion

- 17:15 to 17:45 - Coffee Break

Session Vb – Chair: Markus Reiher

- 17:45 to 18:15 - **Lubomír Rulíšek**
  Calculations of Spectroscopic Parameters of Open-Shell Bioinorganic Systems: Need for Accurate Treatment of Multiple Spin States

- 18:15 to 18:45 – **Kristine Pierloot**
  Coordination of NO to Metal Heme and Heme-Related Systems Studied with Multiconfigurational Perturbation Theory

- 18:45 to 19:00 – Discussion

Day 4 – Friday, September 21, 2012

Session VIa – Chair: Kallol Ray

- 9:00 to 9:30 - **Miquel Costas**
  Biologically Relevant Oxidation Catalysis with Non-Heme Fe Complexes with N-Based Scaffolds that Provide Strong Ligand Fields

- 9:30 to 10:00 - **Kazunari Yoshizawa**
  Spin-Crossover Phenomena in Electronic Properties and Chemical Reactions Mediated by Transition Metals

- 10:00 to 10:30 - **Marc-Etienne Moret**
  Dinitrogen Functionalization at Iron Metallaboratranes

- 10:30 to 11:00 – Discussion

- 11:00 to 11:30 - Coffee Break

Session VIb– Chair: Ulf Ryde

- 11:30 to 11:45 – **W. M. Chamil Sameera**
  Nitrene Insertion Reactions: Concomitant Involvement of the Singlet and Triplet Pathways

- 11:45 to 12:00 - **Pablo Campomanes**
  Assignment of Zero-Field Splitting Parameters for the Mn(II) Centers in Oxalate Decarboxylase

- 12:00 to 13:00 - General Discussion and Conclusion

Lunch

13:15 to 14:15 – Lunch

Departure

14:15 to 14:45 – Departure, with bus to RENFE train station, then hotel