European Cooperation in the field of Scientific and Technical Research
- COST -

Brussels, 22 November 2013

COST 050/13

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action CM1305: Explicit Control Over Spin-states in Technology and Biochemistry (ECOSTBio)

Delegations will find attached the Memorandum of Understanding for COST Action CM1305 as approved by the COST Committee of Senior Officials (CSO) at its 188th meeting on 14 November 2013

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as

COST Action CM1305
EXPLICIT CONTROL OVER SPIN-STATES IN TECHNOLOGY AND BIOCHEMISTRY (ECOSTBIO)

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4114/13 "COST Action Management" and document COST 4112/13 "Rules for Participation in and Implementation of COST Activities" , or in any new document amending or replacing them, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to establish a European network of researchers dedicated to the understanding and application of spin-states in technological and biological applications.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 64 million in 2013 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of section *2. Changes to a COST Action* in the document COST 4114/13.

A. ABSTRACT

It has long been recognized that metal spin states play a central role in the reactivity of important biomolecules, in industrial catalysis and in spin crossover compounds. The latter offer many exciting possibilities for novel, switchable materials with applications in computer storage and display devices. Elucidating the role and effect of different spin states on the properties of a system is presently one of the most challenging endeavours both from an experimental and theoretical point-of-view.

This ECOSTBio Action will create a network of both experimental and theoretical research groups that will tackle a diversity of chemical problems where spin is an important factor. This will be achieved by the joint creation of a SPINSTATE database of systems with known spin states and spin-related properties. This freely accessible database will be of great benefit for the scientific community at large, and will lead to scientific and technological advances. Based on it, explicit control of spin states of transition-metal compounds will be exerted through rational design of ligand coordination. The interactions of theorists and experimentalists will create a synergy, helping theoreticians to validate their models and experimentalists to improve the performances of novel materials with desired properties.

Keywords: Spin-states, computational chemistry, metal-oxo complexes, spin-crossover compounds

B. BACKGROUND

B.1 General background

The current Action is a follow-up on a recent ESF/CECAM-workshop organized in Zaragoza (Sept. 2012), where both experimentalists and theoreticians came together to discuss the importance of spin states in biochemistry and inorganic chemistry. The workshop was highlighted in *Nature Chemistry* ("Discussion of an open problem", *Nature Chemistry* 2013, *5*, 7-9), which gives a good introduction to the background of the Action:

"Quantum mechanics rears its head in many places and one of them is inorganic chemistry, where the electronic spin associated with unpaired electrons has a profound influence. Molecules with different numbers of unpaired electrons, hence with different spin states, have distinct geometric structures, energetic properties and reactivity. Complexes of redox-active transition metal complexes can exist in many different spin states, and this plays an important role in inorganic chemistry and, because of the prevalence of transition metals in living systems, in bioinorganic

chemistry. These themes provided the focus for the recent ESF/CECAM workshop on 'Spin States in Biochemistry and Inorganic Chemistry'. The aim of the workshop was to assess the role of spin state in such reactions, and the way in which theoretical chemistry can be used to characterize the properties and reactivity of open-shell transition metal compounds, as well as to estimate relative energies among possible spin states. Discussion in the meeting addressed both theoretical and experimental studies and covered a diversity of chemical problems where spin is an important factor."

A highly successful aspect of the Zaragoza meeting was its ability to bring experimentalists and theoreticians closer. The vivid interplay during the discussion sessions 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 to 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, which 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. It was exciting to see how someone's expertise, in combination with that of others in a maybe only remotely familiar field, could lead to interesting insights.

One of the main recommendations from the Zaragoza meeting was 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 by both experimental and theoretical scientists.

The main purpose of the ECOSTBio Action is to establish a European network of experts working in the European Research Area (ERA) on spin states, to build a proper research environment and providing tools (SPINSTATE database) for the sharing and integration of complementary expertise and results from research as already funded by national, regional and European programs. Based on this, COST appears to be the ideal mechanism for providing specific support to this Action.

B.2 Current state of knowledge

Spin states play an important role in enzymatic reactions, in metal-oxo complexes, in spin crossover compounds and there exists even spin-state catalysis where (with one and the same compound)

different reactions take place for different spin states. Heme-containing proteins perform a wide range of functions including electron transfer, oxygen transfer and storage, gas sensing, gene regulation and catalysis. In the case of catalysis, the active complex often involves a metal-oxo (M=O) species, as is e.g. the case in horse radish peroxidase, catalase and cytochrome P450. The family of P450s serves two broad functional roles: within catabolic pathways they initiate the breakdown of environmental compounds, either for use as food or as means of detoxification. These P450 enzymes are responsible for the phase I metabolism of approximately 75% of known pharmaceuticals. Thus, the P450s have received considerable attention from pharmacologists, toxicologists, biochemists, and chemists since their discovery. The prototypical and most studied example of this family is P450cam which shows an intriguing catalytic cycle that includes a number of spin flips. The catalytic mechanism of these enzymes is often poorly understood, in particular regarding the spin-state and the effect this may have on the functioning of the enzymes. An experimental study at cryogenic temperatures in 2000 hinted at the existence of a metal-oxo as the active species in this cycle, which was confirmed in 2010 for a thermophilic P450 from *Sulfolobus acidocaldarius*.

Also non-heme proteins use high-valent oxoiron(IV) and formally oxoiron(V) species to couple the activation of dioxygen to the oxidation of their substrates. In most cases, an oxygen atom is inserted into an unactivated C–H bond of the substrate; for example, in hydroxylation reactions. However, many other reactions, including halogenation, desaturation, cyclization, epoxidation and decarboxylation, are also known to involve oxoiron species. Additionally, superoxidized metal centers with (valence) isoelectronic imido and nitrido ligands, as well as ‘surface nitrides’, have also been implicated as key intermediates in the nitrogen atom transfer reactions, the biological synthesis of ammonia by the nitrogenase enzyme and the industrial Haber-Bosch process. The generation of well-described model compounds can provide vital insights into the mechanism of such biological and chemical oxidation reactions. Consequently, considerable effort has been made by synthetic chemists to prepare viable models for the putative reaction intermediates in the catalytic cycles of O_2 and N_2 activating enzymes (as e.g. done in COST Action CM1003, “Biological oxidation reactions – mechanisms and design of new catalysts”). Surprisingly, whereas the enzymatic species are usually high-spin (quintet), most of the biomimetic complexes have intermediate spin, which affects their reactivity patterns. Computational chemistry has contributed essential insight into properties of these reactive intermediates and their mechanisms, thus leading to fruitful experimental-theoretical interplay.

Complexes of most transition metal ions can support multiple magnetic states. The most common manifestation is in the six-coordinate complexes of the first-row transition metals with four to seven

d electrons. One of two possible spin states occurs: high spin (HS) with a maximal number of unpaired electrons or low spin (LS) with fewer (or no) unpaired electrons (low spin). Under favourable circumstances, the HS and LS states are close enough in energy such that an external perturbation like heat or pressure can induce a spin-state change or spin crossover (SCO). SCO compounds can thus act as single-molecule switches/sensors. The in silico design of new spin crossover (SCO) and Light-Induced Excited Spin State Trapped (LIESST) materials is a new area, with great interest for molecular electronics, data storage, etc. Since the discovery of new transition-metal complexes with potential for either SCO or LIESST would require conformational averaging and molecular dynamics for any candidate, the use of quantum-mechanics is prohibitive. Methodologies such as Ligand-Field Molecular Mechanics or Ligand-Field Density Functional Theory may be viable alternatives, but their predictions for spin-state preferences need to be fine-tuned, for instance by comparison with reference data from the SPINSTATE database as developed in this Action.

In order to help understand the subtleties with spin-state properties and explore the missing steps in reaction mechanism that occur too fast for experiments to follow, theoretical chemistry can play an important role. However, theory is not without its own problems.

B.3 Reasons for the Action

Modelling of spin states (by either quantum-chemistry or biomimetic complexes) has historically proven to be particularly difficult. 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. Experimentally, it has proven difficult to be able to tune the spin state of biomimetic complexes, while for theory at present the situation is such that it is advisable to always include the results from a number of different quantum-chemical methods, to ensure the results are consistent. In practice, when large molecular systems are of interest, the density functional theory (DFT) approach is the only viable alternative. There are, however, many different functionals that are proposed by different research groups (B3LYP*, TPSSh, OPBE/OLYP, SSB-D, M06-L, B3LYP, B2PLYP, …), without a clear consensus on which should be used (and why). One of the aims of this Action will be to get together important players in the field to work together and end this unfortunate situation in a joint effort. The focus of the Action will not be limited only to theory; many of the assumptions about spin-state preferences are based on experimental data, which may not be unambiguous in each and every case (in which case the SPINSTATE database will be very helpful). For instance, different complications

may occur in the experiments, such as dimerization, ligand exchange, or disproportionation, so that the system studied theoretically does not correspond to the one for which experimental data are observed. Likewise, there may be metal impurities present in the sample that might interfere with the observation of magnetic moments. Therefore, the creation of the SPINSTATE database through the ECOSTBio Action is expected to have a long-lasting impact on the fields of bioinorganic chemistry, inorganic chemistry, biology and technology as it will deliver a wealth of reference data with spin-state properties of a wide range of transition-metal complexes. This will be of great benefit for the scientific community at large, as it will lead to scientific and technological advances. Moreover, the ECOSTBio Action will boost the training of young scientists by supporting their mobility among ECOSTBio participants.

Research in Europe on spin-states in biochemistry and (bio)inorganic chemistry is at the moment strong, but a bit fragmented. The creation of the ECOSTBio Action will be a way forward to tackle the current situation and enhance European research capabilities, for instance through the SPINSTATE database and contributions to it from both experimental and computational data by the network of experts in the ECOSTBio Action. This European framework will allow the participating research groups to stay ahead of the competition in the USA and Asia. The ECOSTBio Action aims at rational design of transition-metal compounds with spin crossover properties (e.g. off-on switch), and biomimetic models with specific (pre-determined) spin states. Based on the outcome of benchmark studies on spin-state properties of transition-metal complexes, new computational methods will be designed and developed (and benchmarked against the reference data in the SPINSTATE database). A broad palette of ligands will be explored and included in the database, from which the most promising candidates will be selected and enhanced for spin crossover properties and specific spin-states in biomimetic models. The database will comprise complexes for iron, manganese, cobalt, nickel, copper (among others) in different oxidation states and with different coordinations (trigonal, tetragonal, trigonal bipyramidal) around the metal ions.

The characterization of these transition-metal complexes and enzymes, especially transient intermediates, is not trivial. The determination of oxidation and spin state cannot be achieved by an experimental or computational technique alone, but needs a combined approach of both experimental (Electron Paramagnetic Resonance (EPR), UV-Vis, Mössbauer, Xray Absorption Spectroscopy (XAS)) and computational (DFT, Molecular Dynamics, complete active space perturbation theory (CASPT2), coupled cluster with singles, doubles and perturbative triples (CCSD(T))) techniques. This has been shown recently for the spin and oxidation state of a Sc^{3+}-capped iron-oxygen complex, characterization of the missing (hidden carbon) atom in the FeMoco cofactor, or oxidation and spin state of molybdenum in the latter. For these reasons, a combined

experimental/theoretical approach is needed for which the creation of a network of experts through the ECOSTBio Action is highly desirable.

B.4 Complementarity with other research programmes

There are a number of national or pan-European efforts that separately touch on some aspects of the research in the Action (e.g. bioinorganic chemistry); however, there is apparently no pan-European program that integrates spin-states aspects in the combined experimental and computational way that the ECOSTBio Action will do. Moreover, the creation of the SPINSTATE database is an innovation that is specific for the ECOSTBio Action. Once the Action has been firmly established, it may be the source of early-stage training programs and integrated projects.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The main objective of the Action is to establish a European network of researchers dedicated to the understanding and application of spin-states in technological and biological applications. This will lead to the creation of the SPINSTATE database that is expected to have a long-lasting impact on the fields of bioinorganic chemistry, inorganic chemistry, biology and technology as it will deliver a wealth of reference data with spin-state properties of a wide range of transition-metal complexes. This will also be relevant for the field of life sciences, materials science, and chemoinformatics, and hence may become important for pharmaceutical companies as well.

C.2 Objectives

These are the objectives of the Action:

1. setting up a SPINSTATE database with well-characterized transition-metal complexes with known spin ground-state, providing both experimental (e.g. magnetic moment, Mössbauer data, X-ray structures, UV-Vis spectra, EPR parameters) and computational data (e.g. ‘relaxed’ structures, spin-state energies, spectroscopic parameters);
2. design and development of new computational methods;
3. obtaining benchmark computational studies on spin-state properties of transition-metal complexes to be included in the database, for providing reliable reference data to compare new methods with;

4. explicit control of spin states of transition-metal compounds through rational design of ligand coordination.

Although the following objectives of the Action are listed as secondary, they do give strong support to the main objectives of the Action:

- encourage multidisciplinary activities within the ECOSTBio Action and with neighbouring disciplines;
- increase the level of understanding of the Action's scientific issues;
- dissemination of the Action's results and raising awareness to target groups and end users (see section C.5);
- sharing of know-how and facilitating training possibilities to Early Stage Researchers.

Deliverables of the ECOSTBio Action will be:

- creation of an online and freely accessible SPINSTATE database with well-characterized transition-metal compounds, their structures and spectroscopic properties;
- definition of suitable computational methodologies for the proper description of spin-state properties of transition-metal compounds;
- training facilities and formation of young experimental and theoretical scientists through courses, participation in research activities.

C.3 How networking within the Action will yield the objectives

The participants of this COST Action provide manpower, laboratory instruments and facilities, practical experience and research grants to pursue the scientific objectives of the Action. The COST Action will be focused on enhancing the potential of each participating research team through:

- sharing of know-how and learning possibilities for Early Stage Researchers through Short-Term Scientific Missions (STSMs)
- workshops aimed at training of (and mainly organized by) young and Early Stage Researchers (Master and PhD students, post-docs)
- annual Working Group (WG) meetings and Management Committee (MC) meetings
- International Meetings dedicated to spin states in biochemistry, inorganic chemistry and technology
- dissemination of results obtained in the Action to stakeholders, target groups and end users (section C.5)

The participation of Early Stage Researchers and efforts to enhance their capabilities will follow the guidelines as set out in the Early Stage Researchers Strategy document (COST 295/09).

C.4 Potential impact of the Action

As outlined in Section B3, the results of the Action will constitute fundamental knowledge that will benefit the scientific community as a whole, and will lead to the creation of the freely accessible SPINSTATE database. The scientists involved in the Action will benefit from the establishing of new links and broadening of their research perspectives and the strengthening of this particular research area within Europe and relative to the rest of the world. In particular, the young scientists will benefit from a multidisciplinary training that cannot be offered to them outside of the framework of the Action.
The results obtained may find applications in chemical synthesis (including pharma), technology (spin crossover) and biochemical industry. The involvement of stakeholders and end-users (see section C.5) will be targeted through dissemination and "advertisement" of the Action and its applications, where the Dissemination Manager will play an active role. The results and their potential application will be presented at the International Meetings to which stakeholders and end-users will be invited.

C.5 Target groups/end users

The immediate end users of the results obtained within the Action will be academic scientists and industrial development scientists. The creation of the SPINSTATE database and rational design of ligand coordination will open up the results to a broad field of: computational chemists and biochemists, material scientists, biotechnological and innovative materials small and medium enterprises (SMEs), biophysicists, bioinorganic chemists, and pharmaceutical companies. Other COST Actions (such as CM1003, "Biological oxidation reactions ─ mechanisms and design of new catalysts") may benefit from this Action as well, both through the access to the database and through the knowledge obtained in this Action of how the spin-state of transition-metal complexes may be fine-tuned. Moreover, due to the combined theoretical and experimental approach and the dissemination of its results the COST Action will also reach regional and national policy makers involved in setting priorities for R&D funding, and the general public interested in the social impact of the COST Action's scientific focus.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The ECOSTBio Action aims at rational design of transition-metal compounds with spin crossover properties (e.g. off-on switch), biomimetic models and enzymatic reactivity with specific (pre-determined) spin states. Based on the outcome of benchmark studies on spin-state properties of transition-metal complexes, new computational methods will be designed and developed (and benchmarked against the reference data in the SPINSTATE database). A broad palette of ligands will be explored and included in the database, from which the most promising candidates will be selected and enhanced for spin crossover properties and specific spin-states in biomimetic models. The database will comprise complexes for iron, manganese, cobalt, nickel (among others) in different oxidation states and with different coordinations (trigonal, tetragonal, trigonal bipyramidal) of ligands.

SPINSTATE database

Whenever available, or appropriate, the following information will be provided in each record: 1) molecular formula and total charge of the compound; 2) spin state of the compound, and clear description on which data this assignment has been made; 3) structural formula of the compound (in figure form); 4) physical state of the compound to which the data refer; 5) counter-ion and solvent, if any; 6) spectroscopic properties (raw data will be included if available in e.g. figure form); 7) main experimental method which afforded the exposed data; 8) Cartesian coordinates of the geometry optimized structures with quantum-chemical (QC) methods like Density Functional Theory (DFT), multi-reference (MR-MP2) or multi-configuration (CASPT2) methods; 9) spin state energy splittings and computational spectroscopic data obtained with a variety of QC methods: DFT, multi-reference, multi-configuration, coupled cluster; 10) technical details of equipment used (experiment) and computational setup; 11) comments and additional information. Apart from adding data obtained from the literature, the primary aim of the SPINSTATE database is to collect data obtained in the Action, and make these available to the scientific community (after publication of the results in scientific journals and/or patents).

Although the SPINSTATE database is conceived to be a comprehensive reference for the data concerning spin states of the important transition metal compounds, it will inevitably possess gaps, and will be continuously updated by participating groups of the ECOSTBio Action. An effort to list all the available information, both experimental and computational, of the spin state energetics regarding transition metal compounds, no matter the source or the experimental technique or the type of the model Hamiltonian, will unite all members of the ECOSTBio Action. They will work

together, using online information exchange (e-mail, Skype, etc.) to integrate their activities and to make the data in the SPINSTATE database widely accessible through a dedicated portal on the Action website.

Based on the combination of experimental and computational data for a variety of transition metal complexes within the SPINSTATE database, new computational methods will be developed (e.g. new DFT functionals or improved Ligand-Field Molecular Mechanics methods), whose results will be benchmarked against the data in the SPINSTATE database.

The relationships established during the Action lifetime will continue beyond the end of the Action, and is expected to be embodied subsequently in new projects and initiatives.

Enzymatic spin states

Many enzymes have transition metal cofactors, and the species present during catalytic turnover are known to exist in a broad variety of spin states and more generally, bonding states. Both experiment and computation have been extensively used to probe the structure and electronic structure of key intermediates for large numbers of enzymes based on iron, nickel, copper, vanadium, and molybdenum cofactors. It has been shown that many reaction steps during catalysis are strongly affected by the spin state of the metal centre, e.g. in oxidation by non-heme iron oxidation catalysts, or in 'rebound' steps as involved e.g. in oxidation by cytochrome P450 enzymes or by copper-based peptidylglycine α-hydroxylating monooxygenase (PHM). Again, computation and experiment have shown in some cases that changes in spin state must occur during the catalytic cycle of some metalloenzymes. The identity of ground states is defined by the nature of the metal centre, by the nature of the atoms it is bonded to in a particular type of reactive intermediate (e.g. the oxo group in many important bioinorganic species), by the ancillary ligands (e.g. water molecules or amino acid side-chain functional groups), and perhaps also by structural (entatic) and electrostatic effects from the surrounding protein. Given the importance of spin state in metalloenzymes, these factors must have been the object of considerable evolutionary pressure.

Although there is extensive knowledge about spin states in individual intermediates in individual proteins, there is less knowledge about general trends in bioinorganic chemistry, and the present Action will aim to provide a vast increase in such understanding. This will be done by surveying what is known from experiment and theory about the spin state of as many metal centres as possible in a large number of metalloenzymes. Also, a major attempt will be made to assess the role of the broader protein environment, beyond the first ligand sphere, in defining spin state properties.

This work will be tightly integrated with the work on the SPINSTATE database, and on biomimetic complexes and reactivity.

Spin crossover

In the solid state, thermal SCO may be gradual or abrupt, show hysteresis, be a single process or proceed through a series of steps. SCO may also be controlled spectroscopically. In light induced excited spin state trapping (LIESST), the system can be laser-pumped into the meta-stable higher spin state which can have a virtually indefinite lifetime. Laser light of a different frequency can then be used to return the system to its ground state.

Unsurprisingly, this range of SCO behaviour offers many exciting possibilities for display, memory and sensor devices. However, the discovery of SCO materials is rooted in serendipity. The required HS-LS energy balance is very subtle and it is extremely experimentally challenging to decide how to modify a particular system in order to bring it into the SCO regime. Experiment generally accesses only one spin state. In contrast, both spin states can be computed and so there is a clear and pressing role for theory. Modelling offers a real opportunity to optimise existing compounds and, more significantly, discover brand new SCO compounds.

However, the first-principles calculation of spin state energies is not straightforward and the discovery process involves screening a huge number of possible systems. Europe has a substantial lead in both areas.

The goals of the SCO Working Group (WG) are:

- Understand the detailed nature of cooperativity. Hysteresis is critical to SCO but the intimate nature of cooperativity is not understood at the atomic level.
- Explore novel metal-ligand combinations for new SCO species.

Both require an intimate interaction with experimentalists. In particular, it is important to establish the synthesisability of the systems generated by computation plus, ultimately, the actual systems need to be prepared and their magnetic and spectroscopic properties established. There will be a close, synergic interaction between theory and experiment since the realisation of novel SCO materials is certain to require an iterative approach.

Biomimetic spin states

The catalytic mechanisms of processes involving high-valent metal-oxo and imido cores (section B.2) are not well understood, in particular regarding the spin state of the high-valent intermediates and the effect this may have on their reactivity. Oxoiron(IV) cores can exist in either quintet or triplet ground states. Density functional theory calculations predict that the quintet oxo-iron(IV) species is more reactive toward C–H bond activation than its corresponding triplet partner; however, the available experimental data on model complexes suggest that both spin multiplicities display comparable reactivities. The DFT predicted higher reactivity of the S=2 oxoiron(IV) cores has often been attributed to the enhanced exchange interaction upon approaching the transition state (TS) on the quintet surface, which flattens the potential energy surface (PES) and hence lowers the

barrier of the S=2 state as compared to the S=1 state. This exchange-enhanced reactivity principle (EER) also predicts that Fe^{IV} with d^4 has maximal EER advantage in S=2 with four unpaired electrons; complexes with d^n configurations where n>4 should therefore experience low reactivity due to exchange depletion. In sharp contrast to the predictions of EER, however, rare examples of the isolated oxometal complexes of the late transitions metals like cobalt and nickel are often found to be much more reactive as compared to the corresponding S=2 oxoiron(IV) complexes.

Iron imido complexes have been characterized in four oxidation states spanning a range of spin states (Fe^{II}, S=0; Fe^{III}, S=1/2, 1, 3/2; Fe^{IV}, S=1; Fe^{V}, S=1/2). The easy accessibility of the different spin states in iron-imido chemistry raises an interesting question whether the two-state reactivity (TSR) or multi-state reactivity (MSR) scenarios are prevalent, which describe the simultaneous reactivity of many states. However, a systematic reactivity comparison (both theoretical and experimental) between the different iron-imido complexes involving different iron-spin and oxidation states is lacking in the literature. Notably, TSR and MSR are believed to prevail during the hydrogen atom abstraction reaction mediated by an oxoiron(IV) porphyrin radical cation (Compound-I) intermediate in cytochrome P450. Interestingly, in a recently trapped copper(II)-imidyl radical intermediate during the copper-catalyzed amination of C-H bonds, the S=0 and S=1 states are shown to be almost degenerate. Hence, TSR can also be prevalent during copper mediated amination and aziridination reactions.

As evident from the above discussion, the role of spin states on the reactivity of high valent metal-oxo and imido cores, which are proposed as reactive intermediates in a number of biological and chemical oxidation reactions, is presently not well understood. Accordingly, the major objectives of the biomimetic WG will be:

a) Explicit control of spin states of high-valent metal-oxo or imido compounds through rational design of ligand coordination: the spin states of the transition metal complexes featuring metal-ligand multiple bonds can be derived from simple ligand-field theory considerations. While the ligand-field strength of the metal-ligand multiple bond is inherent, the use of weak-field ancillary ligands or employing lower coordination numbers may permit high-spin configurations to be obtainable. Strong-field ligands or higher coordination numbers, on the other hand, will stabilize lower spin states. This approach has been most heavily employed in the high-valent Fe-oxo chemistry, and will now be extended to include oxo and imido complexes of the other transition metals like manganese, cobalt, nickel and copper in different spin states by employing different coordination geometries (trigonal, tetragonal, and trigonal bipyramidal). Particular efforts will be dedicated towards the synthesis of oxo-iron(IV) complexes in the elusive S=0 spin state by utilizing seven coordinate approximate pentagonal type ligand fields. Various spectroscopic methods like

UV–visible, Nuclear Magnetic Resonance, EPR, Resonance Raman (rRaman), Mössbauer, and Extended X–ray Absorption Fine Structure (EXAFS) spectroscopic techniques will be used to unambiguously assign the electronic structure (in particular the spin state) of the synthesized high valent intermediates. The spectroscopic data and corresponding DFT characterization will be added to the SPINSTATE database.

b) Establishment of spin state vs reactivity correlation: the metal oxo and imido complexes of well-defined spin states, generated during the course of this COST Action, will then be tested for their ability to oxidize organic substrates containing C-H bonds. Kinetic studies will provide rate constants and isotope effects that permit evaluation of possible mechanisms. DFT computations will be used to generate reaction trajectories, which will also provide insights into reactivity, in particular, with respect to the contributions of different spin states in the reaction. Extensive collaboration will also be carried out with the WG dealing with spin crossover compounds. The most promising candidates will be tested for their ability to activate dioxygen and dinitrogen to generate high-valent intermediates. So, temperature dependent reactivity studies will be carried out for compounds exhibiting spin crossovers. Whether more than one spin-state also contributes to dioxygen or dinitrogen activation is a particularly intriguing question, which will be studied in detail in this COST Action.

D.2 Scientific work plan methods and means

The ECOSTBio Action is organized in four Working Groups, in which the first one (SPINSTATE database) plays a central role. The Action involves researchers from different disciplines, leading to a constant stimulus for exchange of ideas and expertise in an interdisciplinary approach, both within the Action, with the scientific community at large, and within the four WGs:

- *WG1: SPINSTATE database* – Creation of an online and freely accessible SPINSTATE database with well-characterized transition-metal complexes with known spin ground-state, filling it with and providing both experimental and computational data. In this WG, computational chemists and spectroscopists will collaborate closely with the other WGs to characterize the metal complexes.
- *WG2: Enzymatic spin states* – Obtain profound understanding of interplay of spin state and reactivity in metal-containing enzymes and how this can be tuned to increase selectivity and/or catalytic activity.
- *WG3: Spin crossover* – Understand the detailed nature of cooperativity in SCO and explore novel metal-ligand combinations for new SCO species.

- *WG4: Biomimetic spin states* – Explicit control of spin states of high-valent metal-oxo or imido compounds through rational design of ligand coordination around the metal and establishment of the correlation between spin state and reactivity.

The COST Action will provide an open and flexible framework making it possible for research groups that have not participated in its preparation stage to join it afterwards.

E. ORGANISATION

E.1 Coordination and organisation

The funding for carrying the research comes from regional, national and international projects of the participating groups. The organization of the Action and its management will be in agreement with the COST Action regulations and procedures. In particular, the Management Committee (MC) of the Action will assume responsibility for:

1. organization of workshops and start of the activity of the COST Action
2. monitoring of the progress of the scientific activities, including the organization of internal or external milestone reviews
3. coordination of joint activities and meetings, and stimulation of (new) collaborations
4. exploration of the possibilities for participation and exchange of information with EU-specific programmes
5. promotion of activities for young researchers, both via STSMs and via specific workshops for younger researchers

Furthermore, the MC will appoint Leaders for the four Working Groups (see section E.2), a STSM Manager, a Website/Database Manager, and a Dissemination Manager. The STSM Manager will arrange the STSMs in consultation with the specific scientists involved and the relevant WG Leader(s). The Website/Database Manager will be responsible for the establishment and continuous updating of a website for the Action, plus the establishment and maintenance of the online and freely accessible SPINSTATE database. The Dissemination Manager will coordinate the dissemination activities, “advertise” the COST Action, provide interested people and organisations with the necessary information and will be responsible for interacting with and recruiting new research groups interested in joining the COST Action. The MC Chair will report to the MC about the progress and achievements made by them.

Specific research activities and coordination of research within the Working Groups will be the responsibility of the four Working Groups (see section E.2) and their Leaders.

Scientific milestones are mentioned in Section D. Organizational milestones include:

1. formation of WGs and start of scientific activity within the framework of the WGs
2. commencement of STSMs
3. website implementation (M3), which will publish reports of all official meetings, scientific reports of all STSM grantees and material for workshops aimed at younger researchers
4. establishment of SPINSTATE database (M6), which will contain well-characterized transition-metal compounds, their structures and spectroscopic properties
5. annual report of research activities, papers published, contributions to workshops and meetings and STSM grantees (M12, M24, M36, M48)
6. organization of two international meetings dedicated to spin states in biochemistry, inorganic chemistry and technology (M21-22, M45-46)
7. reviews and assessment of activity of the Action (M24, M48)

E.2 Working Groups

The Action is organised in four Working Groups (for a detailed scientific description see section D.2), each of which will be led by a Working Group Leader (who will be appointed by the MC). The WG Leaders will be responsible for:

1. setting and monitoring WG milestones
2. coordinating WG contributions to the website and SPINSTATE database
3. interacting with the Dissemination Manager to promote and publish WG activity and results, both within and outside of the Action
4. coordinating the WG meetings (at least one a year)
5. communication with the STSM Manager for arranging the STSMs within the WG
6. report to the MC about progress being made in the WG
7. participate in internal/external evaluation (M24, M48) of the COST Action

E.3 Liaison and interaction with other research programmes

There does not appear to be another international research activity working on the same topic. In particular, there is no international research framework focusing on the control and application of spin-states in technology and biochemistry. The focus on spin-states of biomimetic complexes means that fruitful interactions with COST Action CM1003 (“Biological oxidation reactions ─ mechanisms and design of new catalysts”) may be expected, both through exchange of information

and results and also the possibility of joint meetings with this Action will be explored. It should be noted that the focus of the current Action is on the explicit control of spin-states, and not "merely" on catalysts.
The MC will also establish interactions with large-scale Research Infrastructures within Integrated Infrastructure Initiatives (I3) and the future Horizon 2020 programme if during the course of the ECOSTBio Action it deems this necessary. The Dissemination Manager will be in contact with active members of these infrastructures for exchanging information and details of the respective projects.

E.4 Gender balance and involvement of early-stage researchers

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.
As outlined above (Section E.1), the involvement of Early Stage Researchers will be promoted via Short-Term Scientific Missions as well as workshops that are specifically targeted on (and to a large extent organized by) young researchers. The STSMs are crucial for scientific exchange and collaboration between the individual research groups, and provide a scientific glue within the Working Groups and the Action. Moreover, both the STSMs and workshops will enable the Early Stage Researchers to enhance their capacities by acquiring additional expertise from other research groups, in line with the Early Stage Researchers Strategy document (COST 295/09).

F. TIMETABLE

The duration of the COST Action ECOSTBio will be four years. The Action will proceed as indicated in the following timetable:

Year 1	M0	MC Nomination
	M1	MC meeting for designation of the Action Chair (AC) and Vice-Chair (VC), the Working Group Leaders, the STSM Manager, Website Manager and Dissemination Manager
	M3-4	Website publication, including page with call for STSM applications
	M6	Establishment of SPINSTATE database
	M6	MC meeting, coinciding with WG meetings
	M6-12	STSM

Year 2	M1-3	WG meetings
	M1-12	STSM
	M8-10	MC meeting, mid-term evaluation of the Action; International meeting open to general scientific public and workshop for (and organized by) young researchers will be held in conjunction with MC meeting
Year 3	M1-3	WG meetings
	M1-12	STSM
	M8-10	MC meeting; workshop for (and organized by) young researchers will be held in conjunction with MC meeting
Year 4	M1-3	WG meetings
	M1-12	STSM
	M9-10	Closing MC meeting, final assessment of the Action and Final Report; International meeting open to general scientific public and workshop for (and organized by) young researchers will be held in conjunction with MC meeting

Deliverables expected for each WG:

• A mid-year (progress) and an annual (scientific) report, to be sent to the MC. The first reports will ideally contain a state-of-the-art of the main subjects of interest, as well as a global European roadmap for R&D, market, potential partners, etc.

• Contribution to the Action website by editing a specific webpage

• In collaboration with the MC: organisation of at least one dedicated event (Workshop, Training School for early-stage researchers, scientific conferences). Short-Term Scientific Missions will be organized through the duration of the Action

• Scientific publications

• Proposition of concrete projects (at least one) at the end of the Action, involving partners issued from the different WGs

Interactions between the four WGs will be strongly encouraged by the MC. Anyway, a joint meeting will be organised once per year by the MC.

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, CH, CZ, DE, DK, ES, FR, HU, IE, IT, NL, NO, PL, RS, SE, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 64 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

The primary audience for the dissemination of results is research scientists in chemistry, biochemistry, biophysics, life sciences and materials science, including industrial scientists in chemical industry and technology. The results will also be amenable to popular science lectures, web information and articles aiming at a more general public, politicians, funding bodies and lobbyists to aid in implementation of the applications and guide the setting of priorities for R&D funding.

H.2 What?

The results of the research activities will be documented and disseminated via (i) scientific papers, reviews and conference contributions (target audience: the scientific community) (ii) the Action website (targeting both the scientific community, the general public, politicians and funding bodies) (iii) Ph.D. and M.Sc. theses (target: the scientific community) (iv) press releases and highlights via the home institutions of the researchers involved in the Action (targeting the general public, politicians and funding bodies) (v) workshops and symposia (primarily targeting the scientific community), (vi) patents (where applicable), and finally (vii) social networks like Twitter, Facebook, YouTube, Slideshare, and Wikipedia to promote the visibility of the ECOSTBio Action and increase the level of understanding of the Action's scientific issues.

H.3 How?

The publication of scientific papers, reviews, conference contributions will be highlighted on the Action website. Popular science papers, reports of all official meetings, scientific reports of all STSM grantees and material for workshops aimed at younger researchers will be published on the Action website. Conference contributions based on material and results from the ECOSTBio will be made available through Slideshare, and will be made accessible on the Action website. Copies of PhD and Master Theses will be circulated within the participating groups of the Action, and if it does not violate copyright, will be made available for download on the website. In general, workshops and symposia will be open to the general scientific public and members of funding bodies (if so desired) and will be arranged in conjunction with larger meetings in order to reach a

maximum audience. The strategy for dissemination of results will be evaluated as a part of the yearly assessment of progress within the Action, and as a part of the mid-term evaluation process.