Evaluation of the Research and Professional Activity of the Institutes of the Czech Academy of Sciences (CAS) for the period 2010–2014

Final Report on the Evaluation of the Institute

Name of the Institute: Institute of Organic Chemistry and Biochemistry (IOCB)

Fields, in which the Institute registered its teams:

Chemical sciences

Observer representing the Academy Council of the CAS: Jiri Ctyroky
Observer representing the Institute: Moravcova/Fusek

Commission No. 4: Chemical sciences
Chair: Dr Habil, Academician Christian Amatore

Date(s) of the visit of the Institute: November 30 - December 4, 2015
Programme of the visit of the Institute: see attached Minutes from the visit

Evaluated research teams (in order of IOCB written report):

- **Vaclav Kasicka - Electromigration Methods**
- **Pavel Hobza - Quantum Chemical Calculations on Model Complexes**
- **Pavel Jungwirth - Computational Chemistry**
- **Lubomir Rulisek - Theoretical Bioinorganic Chemistry**
- **Combined Junior groups of medicinal chemistry**
- **Josef Michl - Organic Synthesis**
- **Petr Beier - Organic Chemistry of Fluorine, Phosphorus, Sulfur and Silicon**
- **Ivo Stary - Helical Aromatics, Functional π-Electron Systems**
- **Petr Bour - Biomolecular Spectroscopy**
- **Michal Hocek - Bioorganic and Medicinal Chemistry of Nucleic Acids**
- **Ivan Rosenberg - Phosphonate Nucleotides and Oligonucleotides**
- **Ullrich Jahn - Chemistry of Natural Products**

A. Evaluation of the Institute as a whole

1. Introduction

The scientific mission of IOCB entails several important experimental (methodology, syntheses) and theoretical domains of chemical and biological processes, especially in chemical biology and medicinal chemistry which are investigated with a specific focus on the reactions considered at the molecular level.

The researches performed are very fundamental and curiosity-driven, but there is also a strong record, and an increasing interest, in the applied outcomes, particularly, in drug design and development. This is perfectly illustrated by the important patent asset, hence, the financial revenues that IOCB have been judiciously used to sustain its researches, engage a high degree risk, and construct and restore its buildings.

A significant part of the researches are focused on the identification and characterization of potential targets and biologically active compounds for therapeutic use against human and veterinary diseases. This includes not only the design, synthesis, and testing of new ligands and inhibitors, but also the characterization of their metabolism, their mechanisms of action, and relationships between structure and activity.

The accent put on biologically-oriented-chemistry investigations involves studies of various natural systems and models, the use of small molecules or biomacromolecules in order to map and control biological processes, the syntheses of artificial ‘bioanalogues’ and observation of their performance, etc. This relies heavily on the fundamental know-how developed in the various scientific avenues developed by the Teams of the Institute (e.g., organic synthesis, design of new materials, structural biology, catalysis, physicochemical and analytical methods, and computational and theoretical chemistry) thanks to their own research interests. As such, the Institute constantly benefits from a leading task-force of chemists that it has been gathering to successfully explore these different areas with a high degree of competence.

Most of the Institute members have very good national and international reputations and visibility, in part due to their own scientific value but also partially thanks to the high financial income linked to the commercial success of Prof. A. Holý’s compounds and the collaboration with Gilead Sciences, Inc., that will represent more than 80% of

its financial income up to 2017. It is notable, that the Institute has been able to use this high patent financial asset with high profitability. This financial income has allowed the Institute not only for renovating its infrastructures (and build new ones) and equipment parks, but also to introduce a great flexibility in its scientific structure comprising six different types of groups (Distinguished Chairs, Senior, Junior, Research-Service, Service and Targeted), mostly led by internationally recognized scientists (incl. several foreign group leaders recruited as based on regular international calls). It is noteworthy, that new appointments and promotions are examined on a regular basis following rigorous peer-review evaluations (performed by IAB) of existing groups and of new junior groups (tenure-track system). This has allowed tailoring a very good age-structure distribution with many young scientists (12 junior group leaders, 75 post-doctoral fellows and 120 supervised Ph.D. students).

The high number of students show the interest of the many teaching actions delivered in several surrounding universities by the Institute members. This corresponding “integration” with universities is properly reinforced by an extended network of collaborations (e.g., Charles University, University of Chemical Technology, Palacký University, South-Bohemian University and many institutes of Academy of Sciences of the Czech Republic).

2. Strengths and opportunities

The bibliographic record of the Institute is impressive (ca 250-300 papers published per year; however, when considered in relation with the high number of personnel in the Institute, this figure becomes quantitatively rather modest). The importance of the Institute publication output should thus better be appreciated on qualitative grounds, e.g., in view of the many papers published in the most prestigious journals (*Nature*, *Science*, *PNAS*, *JACS*, *Angew*. *Chem*.). The excellent international impact of the Institute is also evidenced by the awarding of ERC Advanced Grants to two of its scientists in 2009 and 2010.

Over the years, the institute has known how to build and develop a wide and exceptional instrumental park that provides state-of-the-art instrumental facilities (NMR, MS, various other spectroscopies, massive computer systems, etc.) to its members and to the research community, with many important resources and services necessary for the many cutting-edge researches. These facilities are hosted in a modern or modernized set of buildings (campus

refurbished in 2016) that now hosts modern laboratories used by the researchers. Of high interest in this respect is also the library of compounds that assembles and preserves a unique collection of novel molecules prepared in the Institute. This enables in-house facile screening with respect to cytostatic and antiviral activities. Finally, the Committee has appreciated the presence of a platform (IOCB-TTO) facilitating a transfer of results from basic science to practical applications and internal spin-offs.

The end in 2017 of the current resources based on patent royalties creates some concern, but according to the information delivered by the Institute Director, Gilead Sciences, Inc., has agreed to provide the Institute with a 1.5 M$/year grant without control on the scientific use of this money. However, this will still be a small fraction of what is available today.

3. Weaknesses and threats

As said above, the end of the royalties on which the Institute heavily relies for pursuing its researches creates a big concern. Although the 1.5 M$/year grant allocated by Gilead Sciences, Inc. should make this rupture less critical, the high running costs of the present campus and its instrumental parks may far exceed what is feasible based on this grant and traditional fundings.

The flat structure of the Institute in which ca. 40 group leaders depend directly on the Director of the Institute creates a potential risk. This does not seem to be a problem today owing to the exceptional management ensured by the present Director, but may become a serious one if his successor has not the same scientific discernments and managerial qualities.

4. Recommendations

The research plans presented by the Director during the on-site visit and in the written documents appear adequate to pursue the excellent quality of the Institute research output as well as the ensuing high training level for its students. However, this implies that the financial resources of the Institute remain high.

5. Detailed evaluations

Owing to the large range of chemical, biochemical, biological and theoretical research fields covered in the Institute, the detailed evaluations are provided at the occasion of those of the teams.

Important Caveat

The Commission recognizes that it unfortunately missed a proper scientific and cultural expertise to assess the medicinal aspects and constraints of the researches performed in the groups of Drs. Hocek, Rosenberg and Janeba.

The Chair of the Commission informed the CAS Administration about this lack of specific expertise before the onset of the Phase II but, unfortunately, this could not be remedied.

Consequently, our expertises should be viewed as only addressing the organic synthetic and methodological aspects of the works and that the Commission recommends that CAS gets access to the most recent copies of the recent evaluations performed by the internal International Advisory Board of IOCB to have a more complete evaluation of these groups.

Finally, it is noted that the evaluations of the different teams has been performed by different experts of the Committee. Though the Committee as a whole has been discussing them in a closed session and therefore shares them, the style used by each relevant expert obeys the style and format that he uses for evaluations performed elsewhere. Nonetheless, all the points that CAS needed to be evaluated are answered in each individual report. The fact that the style of evaluations (in particular, not always respecting the CAS template) differs from team to team does not have particular meaning.

B. Evaluation of the individual teams

Evaluation of the Team: Vaclav Kasicka - Electromigration Methods

1. Introduction

This team's exclusive orientation has been in the development of various electrophoretic methods, particularly capillary electrophoresis (CE) in its various forms and modes of operation: capillary zone electrophoresis, isotachophoresis, isoelectric focusing, electrokinetic chromatography, affinity CE and capillary electrochromatography. Over the years, the team has established international recognition as a leading group in an important segment of analytical separation science. It has kept a respectable productivity, as evidenced by the number of scientific outputs. The team publishes mainly in the specialized journals of the field and participates regularly at the national and international meetings and symposia on separation science. During this period of evaluation, the team has completed construction of a home-made instrument with a "nearly universal utility", featuring a multi-detection setup and versatility of switching between different CE modes. Depending on different application needs, UV-absorbance, native fluorescence or solute conductance can be measured. While this team regularly contributes to various methodological aspects of the CE field, it is also clearly responsive to different analytical needs of the Institute as a whole, in whichever ways CE can be used for advancing biochemical and synthetic efforts. The applications of different CE techniques have thus been used in the traditionally important areas of proteins and biologically active peptides analyzes. Both quantitative analysis and physicochemical characterization by CE can be accomplished. The team has thoroughly investigated various buffer systems to enhance performance of various CE forms in characterization of different analytes (peptides, proteins, and various smaller molecules of interest) and their complexation behavior. In collaboration with other groups in the Institute, CE was also successfully applied in the area of synthetic nucleotides and nucleosides and new functional organic molecules. The developed skills in chiral separations through CE-based techniques have been particularly evident in the studies of newly synthesized organic molecules, such as helicenes, and pharmaceutically important acyclic nucleoside phosphonates. Besides their key analytical role in the institutional collaboration, the team is also interactive with other

scientists in the CAS Institute of Physiology, University of Montpellier (France), University of Madrid (Spain), and the Institute of Macromolecular Chemistry (Prague). As a highly respected scientist, the team leader represents the institution at the national and international meetings in his field. He also regularly serves as an advisor to the academic institutions in Prague and the organization of scientific meetings.

2. Strengths and Opportunities

The scientific capabilities of this team are an important asset to the Institute. Capillary electrophoresis and its related techniques will likely continue to provide an important niche among modern analytical methods as well as a valuable tool to investigate a solution behavior of biological polymers. A combination with mass spectrometry (MS) into a truly effective CE-MS is on the horizon. An acquisition of the “right” type of MS instrument will be a critical step as the technology in this area rapidly evolves. The proposed instrumentation (in future plans) is a logical extension of the activities of this team. The capabilities to analyze complex mixtures will undoubtedly be enhanced in future. The capabilities to study biomolecular complexation behavior through affinity CE are also valuable to the overall goals of the Institute. As new synthesized molecules become available, the CE-based technologies developed by this team are likely to attract more collaborative activities.

3. Weaknesses and Threats

The research team is relatively small and smaller than it was in 2010. Given the proposed research into the next period, what is actually the optimum size of the group? The publication record of this group is quite respectable. It counts the development of new versions of CE techniques, numerous collaborative papers according to the institutional needs and some invited minireviews. Future activities will be strongly influenced by the requests from other teams to use CE technologies. The involvement of graduate students seems relatively low.

4. Recommendations

This team is a valuable resource for the Institute and its share of internal collaborations with other scientists should be encouraged.

5. Detailed Evaluations

While the primary role of this team appears to be facilitating the use of advanced CE

techniques to solve the analytical problems and physicochemical characterization of compounds isolated from natural sources and those synthesized by other teams in the Institute, a systematic development of new CE capabilities is a notable accomplishment in itself. The quality of results obtained in both categories appears genuinely high, with the majority of publications with reasonable impact factors. The quality and quantity are at least satisfactory. There are some publications with multiple authors. There is some involvement of students with this team. The research is societally relevant due to the involvement in characterization of newly synthesized chemicals including important pharmaceutical candidates with antiviral and anticancer activities. The group leader is a well-known scientist at the national and international levels. The team has sufficient plans for future research to sustain a healthy balance between the development of enabling tools and their applications.

Evaluation of the Team: Pavel Hobza - Quantum Chemical Calculations on Model Complexes

1. Introduction

The leader of the Quantum Chemical Calculations on Model Complexes professor Pavel Hobza is a recognized senior scientist. His main research topic concerns intermolecular interactions.

Quantum chemistry elaborates new theories, then new computational algorithms based on them, and finally offers the computational tools to the community, which uses them to enlarge our knowledge about molecules. Pavel Hobza's main achievements belong to the latter part, although contrary to other researchers, Hobza looks at chemistry in a rather broad perspective. The group is not interested in the "case by case" studies (as it is often the rule elsewhere). Rather, the laboratory is searching for general phenomena of importance in general chemistry. As the first example may serve the ubiquitous and all important hydrogen bond X-H···Y. It is in this team that was first noticed that the red-shift of the X-H vibration cannot serve as the proof for hydrogen bond formation (as was commonly assumed before). Hobza and co-workers have proven that a blue-shift is also possible in hydrogen bond formation. This was unexpected, but turned out to be true. Another example of searching for new chemical phenomena is what is known as the halogen bond, discovered by the group as well. It turned out that an unexpected bridge X=O···Y- (Y denotes a halogen atom, so two negatively charged atoms, O and Y, bind themselves) can be formed due to the so-called 'sigma hole interaction' discovered by the group. They have shown that the 'sigma hole interaction' has an electrostatic character.

The above results have been obtained by using sophisticated computational tools offered by contemporary quantum chemistry in the form of ab initio programs (based on first principles). The ambition of the Hobza team goes, however, to much larger molecules, for which such calculations are not possible so far. In such a seemingly hopeless situation they decided to improve the existing semiempirical approach (also based on first principles of quantum chemistry but replacing necessary integrals by some empirical data). To this end, the team assumed (approximation) that interaction of large molecules represents a sum of interactions of their "standard fragments".

The improvement relies on a semiempirical approach, but involve careful parametrizations of the integrals able to reproduce the ab initio results for each fragment-fragment interaction. This success made the computation of interactions in large molecules easier and more “exact”, and lead to a “library of fragment-fragment” interactions that virtually covers the whole Mendeleev table.

2. Strengths and opportunities

Among quantum chemistry laboratories all over the world, the Hobza’s group is exceptional in heading towards computationally derived and/or grounded generalizations valid for all chemistry. This is a very important and nice feature, which naturally creates a strong interaction of this theoretical group with experimental chemists. This fact together with the clarity of presentation of the publications (about 30 papers published in 2014) and the generality of the approach result in a huge number of citations the group has collected so far. It is noted that a fraction of these citations are related to the use of the “molecular fragments interaction” databases published by the team.

Though no specific information was provided, creating such a large research group is not possible without an extensive and good teaching.

Besides the calculations that are focused on particular systems and serve to elucidate them, the team is engaged in the in characterization of some novel type of bonding interactions as improper blue shifting, H-bonding, dihydrogen bonding, halogen bonding, stacking, dispersion-bonding, etc. The team is internationally widely known. Hobza and coworkers are the authors of highly cited articles. For example, his article with Havlas about blue-shifting hydrogen bonds (their own concept and evidence) in *Chem. Rev. 2000* has 1305 citations to date. Several other articles – the tenth one in the citation order has some 500 citations - have similar number of citations (they usually pertain either to methodological achievements or to important biologically related systems).

Pavel Hobza is thus the most cited scientist in Czech chemistry (if not in the whole Czech science) and this provides him a very good international reputation.

3. Weaknesses and threats

No doubt, such a treatment of intermolecular interactions as introduced by the team represents the state-of-the-art level. Nevertheless, we are sure they know that their

approach is still limited to relatively small systems (even if they are proteins). There is an even more important limitation though. It was not mentioned by the leader that what the team does at the beginning is freezing the conformation of a large molecule (like e.g., a protein). In such a way, they focus on a guess of the structure to be calculated, whereas billions of other conformations are ignored. This is of course involves a statistically-validated static approach since no dynamics is included. Finally, it seems to us that the continuous solvent model used by the team is unable to take into account the all-important hydrophobic effect, which comes mainly from the water hydrogen bond lattice.

4. Recommendations

Full linearization of computational scaling is important, as is parallelization of computations. This is however rather going to larger and larger systems. The team is aware that the search for new interactions is important, which means a kind of their systematization and elucidation of their role. One may suggest attacking theoretically supramolecular problems. The team is already going in this direction; an example is their investigation of “cucurbit complexes”, supramolecules with the largest binding energy found to date. There are plenty of fascinating supramolecular phenomena to investigate in this direction.

Evaluation of the Team: Pavel Jungwirth - Computational Chemistry

1. Introduction

Quantum mechanics describes chemistry to a very good accuracy, There are currently several commercial and non-commercial programs which might do this job. The problem is that the computational effort increases extremely fast for larger and larger systems. This is the reason, why, to study such systems, some drastic simplification of the quantum methods is necessary. For systems with thousands of atoms (as it is the case for those investigated by this group) the only practical method of choice is molecular dynamics. This method applies simply the classical Newtonian dynamics to the nuclei based on force fields, while the electrons of the system "disappear". Their role is however recovered by the electronic energy, which represents the potential energy of the force fields mentioned above that control the motion of the nuclei. In practice, this electronic energy is usually approximated by using local force fields, which basically represent a molecule through a "spring-and-balls" model whose physical characteristics are determined based on some educated guess (with some help of quantum mechanics).

Molecular dynamics (MD) can be used to analyze many phenomena and many structures in chemistry, except chemical reactions (unless some special treatment is applied). This still means, however, that many structural problems may be investigated for large systems, sometimes fascinating ones, where nobody may know a priori how the system might behave.

2. Strengths and opportunities

The group is very large, having 21 people. They collaborate with more than a dozen of foreign laboratories.

The group uses computers as virtual experimental equipment (common approach). Their key problem is to select important and general phenomena to be investigated and to cast them into feasible computational targets. In this respect, the Team is highly successful and has investigated many of such systems, thus reaching to a series of surprising (but entirely rational when considered afterwards) results that have captured the attention of many chemists. One may cite several examples.

One work published in 2015 in *Nature Chemistry* finally explained why alkali metals explode when dropped into water. It turned out, contrary to common expectations,

that this features a kind of Coulombic explosion of the metal cations. In a more common (but still important) investigation published in 2015 in *JACS,* the group could determine the first ionization potentials of the nucleic bases (using a combined theoretical and experimental approach). In another recent paper (2014), the team proved that even electrically neutral markers have a non-zero electrophoretic mobility – a quite general and useful concept. Another article in 2014, published in *J. Phys. Chem. (B),* was aiming at elucidating the orientational distribution of a fluorescence dye in a model phospholipid membrane. In the *J. Phys. Chem. Letters 2012* publication, a detailed study of a structure related to the hydrated electron is reported, following a *J. Phys. Chem. (B) 2010* publication from the team that established how a hydrogen atom is created in water from a hydrated proton and a hydrated electron. A very unexpected result was that, in this reaction, the proton moves but not the electron. In 2009, the group also established another unexpected effect: the guanidinium cations forming arginine side chains tend to pair in water despite the obvious Coulomb repulsion between them.

The papers of the group are highly cited in the international literature. For example a review "*Specific ion effects at the air/water interface*" by P, Jungwirth and D.J. Tobias in *Chem. Rev., 2006* scored nearly 800 citations. The tenth paper in the group citation order has 166 citations.

3. Weaknesses and threats

No apparent weaknesses could be spotted by now. However, the method has some evident drawbacks due to the necessity of using adequate force-fields, a fact that must be handled with special care since this ultimately determines the validity of the outcomes. This means that some independent checking is always necessary, though this was not sufficiently stressed in the group Leader's presentation.

4. Recommendations

The group research plans are entirely reasonable in view of its expertise and past successes. Supramolecular systems may offer interesting issues introducing a new dimension in their research achievements. Similarly, out-of-equilibrium processes may provide another type of interesting challenges.

Evaluation of the Team: Lubomir Rulisek - Theoretical Bioinorganic Chemistry

1. Introduction

The group research is essentially based on Density Functional Theory (DFT). DFT is a quantum-mechanical approach, which is based on the electronic density distribution in a molecule (rather than on its wave function). The method has a lot of practical versions which depend on the formulation of what is known as exchange-correlation energy and remains a matter of educated guess. This characteristics also pertains to the DFT/B3LYP method which belongs to the so called hybrid versions of DFT, and involves empirically-guided adjustment of the exchange-correlation energy.

The team is almost uniquely focused on performing molecular computations by using codes available in the community. Since such computations are not feasible for real enzyme molecules, it assumes that what matters is only the enzymatic pocket and that, hopefully, can be simplified. This simplification is performed by careful integration of local structural effects. For example, the exact location and orientation of amino acid side chains provide specific coordination sites to ions like Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, etc., and modulate their reactivity.

In another project, the four-electron reduction of dioxygen to two water molecules was investigated by quantum mechanics coupled with molecular mechanics (QM/MM method) and shown to involve a trinuclear copper cluster.

The Team is also performing development of theoretical methods for improving QM/MM. Its computations are performed on a computer cluster of 150 nodes.

2. Strengths and opportunities

The team is engaged in a high-level science and international collaboration (mainly with USA, Sweden, Germany) providing a international impact and an excellent visibility world-wide.

Forty papers in five years, six being published in 2014 mostly in well recognized journals (one *JACS*, two *Chem. Eur. J*.). These publications are very often well cited in the international literature (e.g., the most frequently cited one has 237 citations and the tenth in the citation order scores about 40).

The Team is presently training two Ph.D. students, which is reasonable for three staff persons in the group.

3. Weaknesses and threats

The task of the Team is at the same time important and very difficult. One of the difficulties is that the original protein molecules are too large to be considered as a whole, so the research outcomes highly depend on the correctness of the assumptions made in describing the effect of the chemical environment surrounding the reactive cores. This is especially in view of the “so-called” multiple minima problem that is practically unsurmountable for molecules of large sizes.

A second one relates to the problem of the quasidegeneracy of electronic levels of transition metal ions. DFT methods are then used here in a situation of near degeneracy of electronic states, while they are designed, in principle, for electronic ground states.

These difficulties are general in theoretical approaches and are not particularly related to this group. However, they impose that compromises have to be established with care since they condition the ultimate quality of the results. These are recalled here only to show the limits of the group approaches though, as does the community, the Committee recognizes that important results have been brought by this Team.

4. Recommendations

The Committee agrees with the Team Leader in considering that some of the above complications (§3) are under proper control (e.g., when removing peripheral moieties of a protein molecule). However, it may be useful for the team to consider what the isolobal analogy introduced by Roald Hoffmann, or the Valence Bond concept and methods developed by Sason Shaik may bring to their computations. Indeed, the latter method has proven to be highly successful in finally resolving similar theoretical issues in cytochrome P_{450} that the former QM/MM methods could not treat or predict (e.g., the origin of the experimentally observed “rebound mechanism” that was theoretically interpreted and shown to critically depends on spins-interactions).

Evaluation of the Team: Combined Junior groups of medicinal chemistry

Important Caveat

The Commission recognizes that it unfortunately missed a proper scientific and cultural expertise to assess the medicinal aspects and constraints of the researches performed in the groups of Drs. Hocek, Rosenberg and Janeba.

The Chair of the Commission informed the CAS Administration about this lack of specific expertise before the onset of the Phase II but, unfortunately, this could not be remedied.

Consequently, our expertises should be viewed as only addressing the organic synthetic and methodological aspects of the works and that the Commission recommends that CAS gets access to the most recent copies of the recent evaluations performed by the internal International Advisory Board of IOCB to have a more complete evaluation of these groups.

1. Introduction

This presentation, performed by Dr. Janeba, summarized the research outputs of three research groups, i.e., that of the presenter and those the groups of Drs. Krecmerova and Nencka.

The Director's presentation led the Committee to understand that the Leaders of the "Junior Groups" are involved in a local "tenure track" system through which their permanence in the Institute and their possible promotion is evaluated by a specific Board in the Institute with the help of the Institute Advisory Board. Hence, the Committee did not felt that it was its task to interfere with this internal "mechanism" by performing an evaluation similar to those made for the other groups of the Institute. As such, the Committee decided to provide only brief general comments. For the same reason, the Committee decided not to make recommendations, though these are self-evident through the comments in §2 and §3.

The young groups are evidently working productively (as seen by their publication record). They selected biochemical targets having simultaneously scientific interest and importance. However, their approaches in the area of synthetic organic and medicinal chemistry are not particularly innovative. This may be due to the intention

of achieving as fast as possible selected goals rather than taking risks in exploring new but challenging methodologies that may be more effective and probe new reactivities. However, these “facile solutions” may at long create a strong contrast with the challenging approaches that make the international visibility of the best established groups of the Institute. This may point out to the fact that the Leaders of the Junior Groups feel that a too heavy pressure is applied on them to reach rapidly an international reputation. This was not explicitly stated by any of the Team members but could be implicitly inferred.

Also, there is a significant overlap among the three groups, which detracts from their possible international impact and will certainly create a problem upon evaluation of individual successes at the end of the tenure track processes.

Finally, it was surprising to observe that the repartition of the students between the three groups was very far from even, although the Committee understood from the Director’s presentation that the Junior Group Leaders were finding equal treatment. This may create an off-balance competition between them.

2. Strengths and opportunities

The three groups have evidently a strong background in synthetic and medicinal chemistry that they may use with profit owing to the modern conditions and equipment (including the Institute screening platform) offered to them by the Institute.

From Dr. Janeba’s presentation, the Committee understood that the three Leaders had an extensive set of international collaborations.

The Junior Group has apparently developed a few unique ‘hit compounds’. This is an important factor for their future research outcomes.

3. Weaknesses and threats

It is not clear to the Committee how the Junior Teams can fulfill their financial needs. This appears highly critical.

From Dr. Janeba’s presentation, it results that the Junior Teams would benefit from added collaborations in translational preclinical research, however, it is not clear what prevents establishing such collaborations.

Evaluation of the Team: Josef Michl - Organic Synthesis

1. Introduction

The Michl group is one of the most well-known groups at the IOCB and one of leading groups worldwide in the area of physical organic chemistry.

The group has an international composition and is excellently funded. The group Leader has an exceptional world-wide visibility.

Presently, the group is interested in four major areas/projects: assembly of dipolar molecular rotors, alkylation of Au surfaces, singlet fission, and other projects.

Although the Committee agrees with the ERC Jury that the “molecular rotor” project is intellectually highly fascinating, the potential impact of this chemistry is not entirely clear to the Committee experts. The point made that molecular motors have to be in close interactions (with a nanoporous matrixes or between themselves in LB monolayers) to develop macroscopic features is interesting, though it is often disregarded in many laboratories that focus on isolated molecular motors.

The observation that gold surfaces can be alkylated with organostanannes is highly interesting and should be pursued further for its many potential applications. Indeed, reactions on metal surfaces involving strong covalent anchoring groups (i.e., beyond classical sulfur-SAMs) are very rare, so this is an interesting discovery that may enlarge the possibilities for construction of (bio)sensors and supported catalysts. The Committee has noted with pleasure that the scope of this new grafting procedure is already the subject of investigation in the group.

The singlet fission solar cell is an interesting idea that has been carefully analyzed from a theoretical point of view.

2. SWOT analysis

No significant SWOT analysis could be provided by the Committee. Indeed, all members have been impressed by the continuous scientific achievement of the group Leader and by his inexhaustible talent for discovering/promoting new exceptional entries. However, as stated by Dr. Michl himself, this creates simultaneously a threat on the permanence of the group.

Evaluation of the Team: Petr Beier - Organic Chemistry of Fluorine, Phosphorus, Sulfur and Silicon

1. Introduction

The main research area of the Beier group is the organic chemistry of fluorine, in particular, the preparation of reagents for fluoroalkyl transfer reactions and the study of hypervalent sulfur fluorides.

Organofluorine chemistry is a very actively studied field at the present time, and there are several very productive international groups to compete with. This competition can only be successful if one can offer innovative and widely usable chemistry in this area. This is clearly the case with the Beier group. The PI and his group have developed several approaches for fluoroalkyl transfers, using, for example, fluorinated phosphonates as the reagents of choice. These allow the preparation of fluorinated polyfunctional products (nitro compounds, esters, olefins) which can be employed for further transformations. On the other hand, polyfluorinated reagents have been synthesized with the help of sulfur reagents.

A particularly useful development for the preparation of (functionalized) fluorinated organic compounds has been in the area of hypervalent sulfur fluorides. The —SF_5 substituent which is typical for these derivatives confers to the products not only a high electronegativity (and high dipole character) but also stability and lipophilicity. Many hypervalent sulfur fluorides are therefore useful as liquid crystals, in polymer applications, as ionic liquids, and agrochemicals, to name but a few. There is hence a broad spectrum of applications of these fluorine compounds for the solution of practical problems.

The Team has also developed various routes for the use of these derivatives in e.g. synthesis of novel aromatic compounds, in particular, the derivatization of SF_5–containing nitrobenzenes. This innovative methodology provides substituted aromatics which are not available by classical approaches.

Since the Beier group has prepared hundreds of organic fluorine derivatives, it has also engaged in the study of their physical properties (solubility, miscibility etc.). These studies are largely carried out in co-operative projects, but they are of interest and add to the visibility of the Team through their outcomes.

The international visibility of the Beier group is very good and, accordingly, it has

been able to develop an important network of international collaborations.

Most of the research outcomes have been reported in very good international journals. However, publications in the top chemistry journals, i.e., in *JACS* or *Angew. Chem.*, are still lacking.

2. Strength and opportunities

Beyond the dynamic group Leader, the group integrates young and ostensibly highly motivated scientists.

The Team has a good productivity though, as noted above, publications in major journals are still lacking.

The very nature of the group researches should create opportunities to industrial collaborations.

3. Weaknesses and treats

As stated above, an effort towards reaching publications in top-ranked chemical journals is a necessary step to increase the group international status beyond the strict “fluorine community”.

Evaluation of the Team: Ivo Starý - Helical Aromatics, Functional π-Electron Systems

1. Introduction

The Starý group is interested in the preparation of novel π-systems, either helical and distorted or flat ones. Its many achievements in this delicate field have provided the Team with an excellent worldwide reputation among this community and beyond. This is clearly evidenced by their publications record, as well as through the Team's contributions to symposia and conferences.

Beyond the intellectual fascination for their structures, these highly unsaturated sterically constrained chiral molecules are of interest in material science, structural chemistry, and stereochemistry. Possible applications are seen in the fields of catalysis (new, configurationally stable, chiral catalysts) and aromatic chemistry (designed preparation of novel aromatic compounds with interesting π-electron structure).

So far, the Starý group is largely known for its imaginative contributions to helicene chemistry. Helicenes, whether all-carbon systems or heteroaromatic representatives, have been known for some time, but their study has long been restricted because of their poor availability. The Starý group has changed this in recent years by inventing novel and highly creative routes to these compounds.

Within the carbocyclic series, the methods developed by the group have led to new helical molecules that could not be prepared by conventional methods. The generality, hence the importance, of the approach developed by the Starý group is also demonstrated by the recent synthesis of laterally and axially extended helicenes. Recently, the Starý group has started joint projects with surface and material scientists, e.g., for the investigation of charge and spin transport phenomena in these systems, or functionalization of nanoparticles. Further developments of these projects are strongly encouraged.

2. Strength and opportunities

Altogether, the studies of the Starý group demonstrate very nicely how complex aromatic compounds with interesting (and so far largely neglected) properties can be prepared by basic research methods and then move towards practical applications. The preparation of novel aromatics is an important and very actively studied field for

which many new results can be expected based on controlled chirality, even many not foreseen presently. The Starý group plays a prominent role in the front row of this field worldwide, and his methodologies would help exploring such applications.

3. Weaknesses and treats

None have been identified (see however §4).

4. Recommendations

The fact that the Team has unraveled efficient methodologies for accessing a wide range of helical aromatics, which is fine. However, this has simultaneously opened a strong competition worldwide, including with physical laboratories. Hence, establishing strong and fruitful collaborations with established groups of physicists and engineers is clearly a major concern.

Evaluation of the Team: Petr Bouř - Biomolecular Spectroscopy

It must be pointed out that no Committee member was able to evaluate this field with the highest scientific expertise required. Indeed, after the Chair informed CAS about this problem before the on-site evaluation, CAS appointed Professor Vladimir Baumruk, but he had to declare a conflict of interest concerning this Team (common publications and grants). Hence, after interrogating the Committee members, the Chair allowed Professor Baumruk to remain seated in the session during Professor Petr Bouř's presentation and the ensuing discussions with the Committee, provided that he remained silent and did not contribute to the writing of this evaluation. Though, after the following evaluation was written and accepted the Chair sought Professor Baumruk's general opinion to ensure that no erroneous comment was made due to the lack of sound expertise of the other Committee members.

This group was established in 2007 and was able to gather several experienced scientists around its Leader. Its research program is vast and ambitious, being aimed to unravel the structures, properties and interactions of molecules and biomolecules through original methodological combinations between spectroscopic and theoretical methods, with the ultimate goal of changing their function to exploit them. Based on the publication record of the Team and the on-site presentation it was apparent to most of the Committee members that these excellent works are pushing the field forward.

These certainly form an impressive series of goals, especially when considering that such original approaches may give access (using rather simple spectroscopies, e.g., using chiral vibrational optical activity) to difficultly accessible structural information unless one resorts to much more expensive instrumentation. This was shown to be achievable because of the Team strengths in chiroptical spectroscopy both on experimental and theoretical grounds. For example, it seems to the Committee that one of the key strategies developed in the group is their tensor transfer technique that enables the simulation of spectra of rather large molecules (e.g., proteins).

Based on the research output of the group as evidenced by the number (124) and quality of its publications (e.g., *Nature Chemistry* in 2015), its number of supervised or co-supervised students (3 BSc, 2 MSc and 5 Ph.D.s) or of theses defended (3 MSc and 3 Ph.D.s), it is clear that the group is performing extremely well.

Although, the works performed in the Team could not be analyzed with the proper scientific level, most of the Committee members have been impressed by what has been achieved.

Evaluation of the Team: Michal Hocek - Bioorganic and Medicinal Chemistry of Nucleic Acids

Important Caveat

The Commission recognizes that it unfortunately missed a proper scientific and cultural expertise to assess the medicinal aspects and constraints of the researches performed in the groups of Drs. Hocek, Rosenberg and Janeba.

The Chair of the Commission informed the CAS Administration about this lack of specific expertise before the onset of the Phase II but, unfortunately, this could not be remedied.

Consequently, our expertises should be viewed as only addressing the organic synthetic and methodological aspects of the works and that the Commission recommends that CAS gets access to the most recent copies of the recent evaluations performed by the internal International Advisory Board of IOCB to have a more complete evaluation of these groups.

1. Introduction

The Hocek group works in four areas: synthetic methodology, medicinal chemistry, synthesis of C-nucleotides, and functional nucleic acids for chemical biology. The molecular targets are certainly of high interest in biology and for potential medical applications. Though, none seems to be a specific prerogative of this group and are widely developed elsewhere.

Many of the preparative methods applied are standard routes. This is particularly true in the area of the development of synthetic methodologies. The routes used for the modification of nucleo-bases, for example, are all standard in modern synthetic chemistry (metal-mediated cross-coupling reactions, C-H activation).

2. Strength and opportunities

The teaching and students' supervision intensity is among the largest ones observed by this Committee over all the CAS chemical Institutes evaluated. This involves not only the group scientists but also the graduate students and the post-doctoral fellows; 15 Ph.D. students have defended their theses during the evaluated period.

The group has very good grant support and has good cooperative projects with other academic and industrial groups, which points out to the practical importance of its researches even if the methodological aspects are rather common.

3. Weaknesses and treats

The group is highly productive on quantitative grounds, but several of its works are published in middle-ranked journals (though it is noted with satisfaction that a significant fraction of these works are published in top two-quartiles journals). Furthermore, it seems that most of the citations to its works originate from self-citations (ca. 38%).

Finally, it is noted with dissatisfaction that the group leader during the on-site presentation used a high hype-style and disregarded presenting a self-SWOT analysis. These were the matter of serious concern to several members of the Committee.

Evaluation of the Team: Ivan Rosenberg - Phosphonate Nucleotides and Oligonucleotides

Important Caveat

The Commission recognizes that it unfortunately missed a proper scientific and cultural expertise to assess the medicinal aspects and constraints of the researches performed in the groups of Drs. Hocek, Rosenberg and Janeba.

The Chair of the Commission informed the CAS Administration about this lack of specific expertise before the onset of the Phase II but, unfortunately, this could not be remedied.

Consequently, our expertises should be viewed as only addressing the organic synthetic and methodological aspects of the works and that the Commission recommends that CAS gets access to the most recent copies of the recent evaluations performed by the internal International Advisory Board of IOCB to have a more complete evaluation of these groups.

1. Introduction

This group self-declared mission is to increase knowledge in the chemistry, biochemistry, and biology of phosphonate nucleotides and oligonucleotides analogs, with strong aspects towards applications. This involves two main fields. One investigates nucleoside phosphonic acids with different structures as potential inhibitors of enzymes involved in nucleosides, nucleotides, and nucleic acids metabolism. The second one develops syntheses of sugar phosphonate backbone-modified oligonucleotides in deoxyribo- and ribo-series to create new types of biologically active oligonucleotide analogs (viz., antisense oligonucleotides, siRNAs, and CpG motif-containing oligonucleotides).

35 publications have been produced over the reference period but several of them are published in medium- to low-ranked journals (though it is noted with satisfaction that another fraction of these works are published in top two-quartiles journals). Since the competitors in the fields investigated by this Team are generally publishing in top-ranked journals, this is symptomatic of the fact that the impressive goals announced by the Team may not be leading to scientifically impressive results in its hands, but

have rather an interest for applicative purposes.

In fact, the experts in the Committee considered that the works involve rather routine nucleotide syntheses. This seems to be a type of work that could be better carried out in an industrial setting. Its presence in an Institute that otherwise gather several groups with the highest research achievements is somewhat surprising.

Finally, the group has supervised 2 BSc, 1 MSc and 4 Ph.D. students while 1 BSC and 1 Ph.D. student defended their theses.

Evaluation of the Team: Ullrich Jahn - Chemistry of Natural Products

1. Introduction

The Jahn's group important and excellent research activity concerns two important fields of organic chemistry, electron transfer and free-radical chemistry, as well as their mutual concerted or sequential interdependence with ultimate scopes aimed towards synthetic methodology, catalysis and total synthesis.

Reactions taking place in a concerted fashion or via intermediates such as radicals or carbocations have been employed in organic synthesis very often – but the combination of these methods in a one-step/one-pot approach has not been usually successful before the many achievements performed in this scope in the Jahn group.

Similarly, the concept of "traceless oxidative catalysis" introduced by the Jahn group seems to be a very promising approach for the one-pot syntheses of organic rings from the coupling of easily available olefins.

His novel approaches to synthesis has led to the preparation of a large number of important natural products, among them prostaglandins and other lipid metabolites, antiviral compounds, many important pheromones (a recent field of study, for the Jahn group, illustrated here by the important example of the preparation of stylopsal), steroid derivatives which could be important for neuroprotection, and more.

For the development of synthetic organic chemistry, the recently discovered photochemical amination of acyclic and cyclic ethers may also become of significant interest, a process which has not only been used in a photoredox catalytic version but also in combination with C-C coupling processes, thus leading to a plethora of multi-functionalized reaction products (amino ketones, amino nitriles, etc.).

Other area of research in which the Jahn group is building up a reputation is the design of new organosuperbases. Superbases such as the so-called Schwesinger bases are, in principle, very important for organic synthesis since they could be used to generate important carbanions without the use of metal organic reagents (such as the Grignard reagents or the organolithium compounds). However, to become important in organosynthesis, these bases must be readily available. This is exactly what the Jahn's group has provided to the community, and hence a widespread use of these new reagents is expected without any doubt.

The growths in research output, its number of co-workers and of important topics successfully investigated have impressively increased during the period evaluated here. The age distribution of the group provides a guarantee of development for the group, as is also evidenced by the steady flux between supervised and co-supervised students (2 MSc, 2 Ph.D.) and defended theses (2 MSc, 2 Ph.D.).

It is very likely that, based on the exceptional dynamism of the group Leader and of his experienced co-workers, this impressive series of successes will continue during the 2015-2019 period.

2. Strength and opportunities

The Jahn group presents excellent results in the development of novel concepts, in natural product synthesis and in the development of novel reagents.

All of this is cutting-edge research that is strong enough to compete on the international level.

3. Weaknesses and treats

None was identified.

4. Recommendations

The Committee has no other recommendation than encouraging the Jahn group to continue to develop its creative researches as it is apparent in the Team’s research plans.

The new developments towards neurosteroids already under way are excellent. The same is true for polycyclic Indole alkaloids, or for the combination of dual single- and two-electron catalysis.

Date: December 30, 2015

Commission Chair: Dr Habil, Academician Christian Amatore