Estonian Higher Education Accreditation Center

Evaluation of Estonian Research in Organic and Bioorganic Chemistry and Biochemistry

Institutes evaluated:

Institutes of Chemical Physics and Organic Chemistry,

Tartu University

Institute of Chemistry,

Tallinn Technical University

Laboratory of Bioorganic Chemistry,

National Institute of Chemical Physics and Biophysics

Department of Biochemistry and Biophysics

Institute of Experimental Biology

Estonian Agricultural University

Visit dates:

January 28 - February 2, 2001

Expert team:

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Part I

General Overview

Introduction

The evaluation team consisted of Prof. Matti Saraste (European Molecular Biology Laboratory, Heidelberg), Prof. Ari Koskinen (Helsinki University of Technology) and Prof. Jorma Mattinen (Åbo Akademi University).

The organizer for the evaluation was the Estonian Higher Education Accreditation Center (EHEAC). The evaluation was carried out by an examination of documents and a series of visits, interviews and consultations with research staff and students over the period January 29 - February 2, 2001. Each evaluator had received the self-assessment reports of the National Institute of Chemical Physics and Biophysics, the Institute of Chemistry at the Tallinn Technical University, Institutes of Chemical Physics and Organic Chemistry of Tartu University, and the Department of Biochemistry and Biophysics of the Institute

of Experimental Biology at the Estonian Agricultural University. Additional material was provided by the evaluated institutes, laboratories, research groups and individual scientists during the visit. The self-evaluation reports were generally well prepared and informative. However, some projects were grouped together in an artificial fashion including parts, which were already dormant.

The visits started with a general introduction on the organization, financing and main research topics given by the institute directors. The team leaders then gave presentations on their work. We discussed matters related to the ongoing research with individual team leaders, and took the opportunity to meet the graduate students. These discussions and meetings gained us a good understanding of the current research activities. Sets of relevant recent publications that were provided for the Team greatly assisted the evaluation.

Approach to the evaluation

The evaluators were asked to

1) judge the activities of research and development institutions and the research topics implemented by them to ensure the state funding for internationally recognized research and development;

2) identify deficiencies in the activities of research and development institutions;

3) give recommendations on the development concerning research and development and research areas to the state of Estonia.

The Team was given the following material: A working schedule, principles and criteria for evaluation of the research institutions, and self-evaluation reports created by the institutions. The Team arrived on January 28, 2001, in Tallinn and was shortly briefed by Dr. Tiit Laasberg on the remit and practical arrangements.

Each institute was evaluated using the following criteria on a four-point scale (excellent, good, satisfactory, unsatisfactory):

1) the novelty of the results of research and development;

2) the quality of research and development;

3) the strategy and perspective of research;

4) the competence of research groups and their capability for development;

5) success in applying for funds and grants;

6) national and international co-operation;

7) the implementation opportunities for the research results and their importance for the Estonian society;

8) the correspondence of research and development to the international level.

Additionally, we also emphasize the quality of research in relation to material and financial resources available. Consideration has also been given to the organization of post-graduate studies (levels and numbers of M.Sc. and Ph.D. students). Our discussions with students were very enlightening in this respect.

Part II

General Comments

General remarks on and recommendations for Estonian science organization and funding

The evaluation Team got an overview of the present state of organization and conduct of Estonian science, research and development. We were also introduced to the funding system in Estonia. The Team understands that the Estonian scientific system has undergone a tremendous change during the past decade. In this report, our focus is clearly on the further development of the Estonian scientific atmosphere and research community. We hope that our criticism is understood in this context, as we want to be constructive.

At the outset, we want to emphasize that only continued long-term financial support can create a general atmosphere that is able to incubate novel scientific ideas and research themes, and support coherent research groups. Presently, the funding of the research is achieved through an elaborate system, which is not transparent to an outsider. The maze-like management of research funding is also seemingly confusing to the Estonian scientists. For instance, the Ph.D. students are funded partly as 'Ph.D. students' and partly as 'researchers'. Outside Estonia, the Ph.D. students regularly are involved in both teaching and research as part of their curricula.

Students were generally content with the supervision they receive. However, for some students the problem setting and curriculum towards their degree seemed to be rather unclear. Therefore, we recommend that a Graduate School system is rapidly established in Estonia. The graduate school system should include curricula for the students as well as financing and regular evaluation of the postgraduate studies.

The improvement of graduate teaching and post-doctoral studies would help to make the research staff more juvenile. At the moment, the age structure of the evaluated institutions is not optimal. The proportion of senior staff is too high. It is worrying that in some institutes the average age of the staff is over 45 years, and the staff lacks younger scientists who would overtake the activities in the future.

We also recommend that Ph.D. graduates are actively encouraged to spend a post-doctoral training period abroad, followed by a possibility to return to Estonia to establish their own research initiatives.

The organizational 'independence' of the research facilities from the universities provides a rather bizarre surrounding for the growing generations of Ph.D. students. We strongly feel that the links between universities and research institutes should be strengthened so that all curricular activities, including post graduate research, is conducted under the auspices of universities.

We feel that the innovation infrastructure already has reached a stage, where industrial applications are arising from academic research. However, the applications too easily leak out of the country. A good case to point is the novel fluorescence spectroscopy that is developed by an Estonian research group (Dr. Peet Kask). The application of these methods is completely carried out by a German company mainly outside Estonia. For the creation of new industrial activities, a strong University system in close physical connections to a Science Park, further augmented by a well-organized graduate school system, would support future technology transfer activities more efficiently.

Part III

Evaluation of institutes and research groups

Institutes of Chemical Physics and Organic Chemistry

Faculty of Physics and Chemistry, University of Tartu

General overview

The Institute of Chemical Physics is headed by Prof. Ilmar Koppel. The Institute has two additional professors, and a fourth Chair that is currently vacant. The Faculty has additionally 4-5 Associate Professors. Furthermore, the ICP has 1 lecturer, 15 researchers, and 10 technical staff. Student enrolment in the ICP is 22 Ph.D. students and 13 M.Sc. students. The evaluation team considers that the ratio between M.Sc. and Ph.D.

students is too biased. During the past five years, 10 Ph.D. theses have been examined in the Institute.

The Institute of Organic Chemistry is headed by Prof. Ants Tuulmets. The reformation of the University has resulted in a very small Institute that has in addition to the Chair only 1 Associate Professor, 1.5 positions for teaching assistants, and 2 researchers, and further 3.5 positions for infrastructural support. Recent funding for the Institute has been at a very low level, but has slightly improved this year.

Evaluation of the Institutes and recommendations

Institute of Chemical Physics (Ilmar Koppel)

The four Chairs at the Institute of Chemical Physics are Analytical Chemistry, Bioorganic Chemistry, Theoretical Chemistry and Chemical Physics. We have evaluated Bioorganic Chemistry and part of Analytical Chemistry (Prof. Koppel). The structure of the two Institutes is probably the results of the historical past. This historical aspect did not become entirely clear during our visit. However, in our view it does not make sense to separate one chemistry Chair, that of Organic Chemistry, from the rest of the Chairs.

The infrastructure of the Institute requires strong improvement as soon as possible. The laboratories should be renovated, and there is a clear need for upgrading the instrumentation.

The Institute has been active both in publishing research results and in educating new PhD's during the past five years. We had discussions with all professors including Mati Karelson who we do not evaluate. It is obvious that collaboration between Chairs and research groups is on a good level. We also discussed a number of topics with the Ph.D. students in the absence of their supervisors. This meeting revealed that there seems to be a good atmosphere in the Institute, and we did not find any problems between the supervisors and the students.

Institute of Organic Chemistry (Ants Tuulmets)

The activities of the Institute are presently very low indeed. Presumably due to insufficient past funding and isolation from the other laboratories, the laboratory facilities and the current working routines are seriously outdated. Rapid restoration of activities would be needed. For the future, we recommend that the Institute performs a thorough self-evaluation of the research themes and target setting, and defines a clear strategy for itself. In our view, it would make much sense to merge this Institute with the other chemistry Chairs. However, it is highly important for the future development of Estonian chemistry that also Tartu University retains strong Organic Chemistry component beyond the retirement of Prof. Tuulmets.

Evaluation of the specific research themes

Laboratory of Analytical Chemistry, Institute of Chemical Physics (Ilmar Koppel, Peeter Burk, Ivo Leito)

Prof. Ilmar Koppel is working on several different topics. The Team has evaluated only one, his research on acid-base equilibria in the gas phase, and in solution. The group consists of one professor, three associate professors, two researchers and three Ph.D. students. The Koppel group has recently published a number of high quality papers in leading chemistry journals. The evaluation Team has noticed the high publishing activity of this group as well as the good profile of the track record.

The group produces solid high quality data that have great importance for synthetic and reaction mechanistic work in general. These results have been notified among chemists, and the articles published by the group will most probably attract a number of citations. However, the novelty of this kind of work is not high. We also paid attention to the low number of Ph.D. students in this research group. On the other hand, the performance of the two young Associate Professors Peeter Burk and Ivo Leito is a very promising, and we expect that their research will be an important component of the Institute in the future. We rank this project as **good**.

Laboratory of Bioorganic Chemistry (Jaak Järv, Ago Rinken)

In the Institute of Chemical Physics, Prof. Jaak Järv is the head of a research group studying the interaction of enzymes and receptors with their substrates and ligands. In the former field, Järv's group is working on protein kinases from mammals and plants. One particular interest of the group has been mapping of the target phosphorylation sites of serine/threonine and tyrosine kinases. This work has been carried out using analysis of observed target sequences as a guide leading to consensus patterns. An interesting paper on the statistical analysis of sequence patterns that specify protein kinase activities was published in 1998, but has not yet lead to further systematic experimental analysis. Computational activities in the group, such as the collaborative work with Prof. Mati Karelson on modelling of peptide conformations, could lead to important future developments of true biocomputing activity in Tartu.

The receptor studies have been rather diverse but recently focused on the P2Y purine receptors. These studies largely rely on the synthesis of adenosine derivatives that is carried out by Mart Loog in the Laboratory of Bioorganic Chemistry. The receptor studies are expanded by Ago Rinken and his students to address problems related to downstream signalling in different cell types.

Overall, the research in both areas suffers from the lack of a clear focus. Too many systems are studied at the same time. Stronger focus and in-depth studies would be needed to transform published work into a substantial contribution in understanding kinase action or receptor-mediated cell signalling. The current publication profile mostly consisting of short letters is very low. On the other hand, Jaak Järv's group has been very

active as regards education of Ph.D. students. The team has several long-term collaborative links to abroad as well as to Estonian Institutes, and it has also been relatively successful in obtaining funding. Better focus on key biochemical issues using the tradition of organic synthesis along with modern methods such as combinatorial screens and computational analyses could improve the work of this currently **good** group into the nearly excellent category.

Institute of Organic Chemistry (Ants Tuulmets)

The Institute consists of the remnants of the previous Department of Organic Chemistry, after the major reformation of the University of Tartu. This is evident from the current number of personnel in the Institute, and therefore also in the activity and productivity of the Institute. Psychologically, the downgrading of the activities seems to have had a deleterious effect on the general atmosphere. The head of the Institute is approaching retirement, and much of the future progress must thus rely on the younger staff. It is questionable whether only one person (Uno Mäeorg) alone can re-vitalize the research in the Institute. The laboratory facilities (including basic synthetic laboratory glassware and equipment) are critically out of date and would need rapid renovation. Of the current five research themes (Grignard reagent solvation, ester aminolysis, sonochemistry, hydrazine chemistry and alkyne isomerisation), the studies on Grignard reagent solvation and its applications for instance in modulation of reactivity is definitely of timely value, also internationally. The other four projects should be considered as secondary since those are either in areas of very high competition with large groups, or research topics that have a poor chance for dramatic new findings.

Due to the above-mentioned infrastructural problems, we rate this group as **unsatisfactory**. We strongly recommend that the status of the group should be carefully considered: it should be either rapidly strengthened, or incorporated into the Institute of Chemical Physics. The latter solution would still require upgrading of the facilities and modus operandi.

Institute of Chemistry, Tallinn University of Technology

General overview

We evaluated the Organic and Bioorganic Chemistry and Biochemistry section of the Institute. These entail altogether about 35 personnel, out of whom 26 were listed as researchers. The operations are currently located in two separate buildings, but will move to a single unit soon. The space is quite adequate (approx 20 m^2 of laboratory space per

scientist). We note with pleasure that the renovation will also touch issues such as services (air ventilation, water and gases).

The three laboratories have altogether 11 Ph.D. students, the Laboratory of Organic Chemistry being the largest one. The groups have active collaboration both nationally and internationally.

Evaluation and recommendations for the Institute of Chemistry

The facilities are adequate, but rapid renovation and upgrading would be needed in some cases. For example, the Institute has only a 90 MHz NMR instrument, and access to higher fields at the National Institute of Chemical Physics and Biophysics. However, for any serious attempt to reach the international high standards in synthetic organic chemistry, routine access to modern NMR facilities (at least 200 MHz instrument capable of 2D work) is absolutely mandatory.

The research in the evaluated laboratories is very well organized, with clearly defined projects. The students are very well motivated and content with their working environments.

Evaluation of the specific research themes

Department of Organic Synthesis and Technology (Margus Lopp)

The leading thought and the red thread in all ongoing projects at the Department are synthesis and especially asymmetric synthesis. Although the group of Prof. Margus Lopp has several different projects going on, the team appears to work as one, and communication between team members works well. The department is currently rapidly developing. The ongoing changes in the infrastructure explain the relatively low number of papers. On the other hand, the team we met was very enthusiastic and juvenile. There are six ongoing Ph.D. thesis projects.

The synthetic work of the Lopp group is highly relevant and very innovative. Chiral synthesis is one of the most central and demanding themes within organic chemistry.

Professor Lopp’s group should be ranked as good according its performance up to date. However, the future prospects of this group are excellent. The spirit in the team is enthusiastic, and the renovation of the laboratory space that is at the group's disposal will be finished in the near future. The evaluation team takes this into account and ranks Margus Lopp’s team as **excellent.**

We encourage the team to undertake even more demanding synthetic targets. This would also provide a natural ground for collaboration within the Institute and with external colleagues. We also recommend a closer collaboration with the NMR laboratory at

National Institute of Chemical Physics and Biophysics so that the trained Ph.D. students from the Department could operate NMR instruments by themselves.

Department of Bioorganic Chemistry (Nigulas Samel)

Nigulas Samel and his group are working on the biosynthesis of prostaglandins. These studies are based on previous tradition on mechanistic aspects of prostaglandin synthesis that was established by Dr Ülo Lille in the Department. A novel, fresh angle to this problem has been created by shifting the biological aspect of this project to a study on the prostaglandin synthesis in invertebrates. Prostaglandins are abundant in corals, and the Samel group has organized a vigorous project focusing in the analysis of prostaglandins and their biosynthesis in these organisms. This innovative decision has led to a series of excellent recent publications.

The research group has shown that similarly to the vertebrate situation, cyclooxygenase is a key enzyme in the biosynthetic pathway leading to prostaglandins in corals. The group has also identified a novel peroxidase-lipoxygenase fusion protein in the Caribbean Sea coral *Plexaura homomalla*. The latter discovery that was made together with the collaborating group of Alan Brash (Vanderbilt University) was published in *Science* in 1997.

The Samel group is able to combine expertise in organic chemistry with creative use of biochemical systems and state-of-the-art molecular biology methods. The group has established an active and functional collaboration to be able to use such a multi-disciplinary approach. Recent publications of the Samel group fully meet the international standards. We rate its performance as **excellent**. Further phylogenetic analysis of the biosynthetic pathways of prostaglandins in different organisms using the accumulating genomic databases as guides may be helpful for the further success of this research.

Biocatalytic, stereochemical synthesis (Omar Parve)

This research group is clearly undergoing a change of generations. Dr. Lille, an internationally established and respected scientist, is handing over the baton to a younger colleague. The research is centered on lipase catalysis, especially as applied to prostanoid synthesis. This makes potentially an attractive environment for collaboration with the other teams in the Institute, and such collaboration could provide completely novel ideas to be explored. The group is also interested in modelling approaches for both lipase catalysis and NMR interpretation (i.e. assignment of absolute configuration). Spreading scarce resources over a wide range of interest is always problematic.

We rate this group scientifically as **good** and suggest that the team would concentrate on the primary project until a critical mass is reached for expansion. Further, a clearer problem setting is necessary to focus the research in order to attract international recognition. The field itself is certainly of high visibility.

Laboratory of Bioorganic Chemistry, National Institute of Chemical Physics and Biophysics

General overview

Laboratory of Bioorganic Chemistry is one of the four laboratories of the National Institute of Chemical Physics and Biophysics and it is headed by Dr. Jüri Siigur. The laboratory staff consists of nine persons of whom six are on the Ph.D. level and three have a M.Sc. degree. The laboratory has access to the facilities that are the best we have seen in Estonia. All instrumentation is located in the Laboratory of Bioorganic Chemistry. However, the NICPB is constructed in such a way that all groups in principle can use its entire infrastructure. The facilities have adequate, state-of-art instrumentation for molecular biology, cell culture, mass-spectrometry and NMR. To have access to specialized techniques, In addition, researchers in the Laboratory have access to specialized techniques through international collaboration. This collaboration has, however, led in some cases to the situation where Estonian scientists act as sub-contractors for projects that are mainly conducted elsewhere.

Evaluation and recommendations for the Laboratory of Bioorganic Chemistry

Despite the small size of the laboratory, there are three on-Going research projects. We recommend a clear focusing of research in order to avoid the spearing of the scarce resources.

Evaluation of the specific research themes *(Jüri Siigur, Tõnu Kesvatera, Aivar Lõokene)*

Proteinases of snake venom (Jüri Siigur)

Jüri Siigur has a long-term interest to study the haemostatic coagulants and anti-coagulants that can be isolated from snake venoms. A particular effort is focused on proteinolytic enzymes present in the venom of *Vipera lebetina*. His group has isolated a zinc-metalloproteinase called lebetase, and studied its properties in detail. These studies have revealed that there are several isoenzymes of lebetase with distinct properties. Lebetase is a fibrinolytic enzyme. The *V. lebetina* venom also contains another proteinolytic entity that activates factor V. This hemorrhagic proteinase has been preliminarily characterized by the Siigur group.

Jüri Siigur's research plans include ideas to engineer a fibrinolytic proteinase (lebetase) into an activator of blood-clotting factor (factor V activator). This is an ambitious plan that may require further structural studies on the two enzymes. The group has, however, very good laboratory facilities at its disposal in the NICPB. These should indeed encourage more ambitious research than is conducted in the Siigur group currently. This group has largely continued its traditional approaches and avoided new innovative areas. A possible avenue into novel discoveries would be the completion of the screening of cDNA library constructed from a snake venom gland. Sequencing of cDNA clones has already suggested the presence of disintegrins in the venom. Their study in the context of angiogenesis in cancer tissues, as planned by Jüri Siigur, could be such a possible new direction. Taken the weak publication record and lack of innovation into account, we rank Jüri Siigur's research **satisfactory**.

Molecular forces in structure and function of calbindin (Tõnu Kesvatera)

The project is aimed at better understanding of the pH dependence of calcium binding for the title protein. The pK_a values for all ionisable groups of the protein have been successfully determined by NMR titration. A theoretical (computational) model has also been developed. The project has relied heavily on collaboration with Lund University, Sweden. The scientific work itself has been conducted according to high standards, but the originality of the problem and justifications of its conduct here rather than at Lund are somewhat dubious. We rate the project as **satisfactory**.

Lipoprotein lipase (Aivar Lõokene)

This work depends strongly on the collaboration with Prof. Olivecrona (Umeå University) that has started during the post-doctoral studies of Aivar Lõokene in the Swedish laboratory. The enzymatic studies are complemented by mapping of the substrate binding regions on the lipase molecule, and by investigations between lipase and heparin sulfate on the cell surface. It seems to us that the current work does not match the quality of Lõokene's previous research activity in the Olivecrona laboratory. Therefore, we think that it may not be wise to continue this work in a highly competitive area as a subscriber to a project running more effectively elsewhere. For these reasons, we rank the lipase project at the NICPB as **satisfactory**.

Department of Biochemistry and Biophysics, Institute of Experimental Biology at the Estonian Agricultural University

General overview of the Department

The Department is situated in the Harku campus of the Estonian Agricultural University. It is physically separated from the cluster chemistry laboratories at the Mustamae campus in Tallinn. The research activities are carried out by three teams. Dr. Peet Kask develops new spectroscopic methods based on fluorescence, Dr. Ergo Raukas studies structural

aspects of DNA, and the Head of Department, Prof. Aavo Aaviksaar works on biophysical enzymology. These three themes have little internal links but derive from the previous research traditions of the leading scientists. Even the possible applications of fluorescent methods developed in the Department are not yet used to study the biochemical problems.

The scientific isolation of the Department was obvious to us. This research community is simply too small to be sustainable in the future. It needs to develop stronger coherence with the biology groups in Harku, or join the other related biochemical and/or biophysical activities elsewhere in Estonia.

Evaluation of the specific research themes

Peet Kask and his team develop novel methods for imaging and spectroscopy that are based on fluorescence correlation spectroscopy. The group has recently developed two-dimensional fluorescence intensity distribution analysis (2D-FIDA) and a related multiple distributions analysis (FIMDA). These methods can be used in monitoring molecular recognition in a versatile manner. Peet Kask has an ongoing active collaboration with a company in Germany (EVOTEC Biosystems, Hamburg). This joint enterprise aims at the development of high throughput screening strategies for protein-ligand interactions. The Kask group in Harku is financially dependent on the financing received through this collaboration.

Peet Kask's research is innovative and productive, and speaks for a strong expertise in physics. His team has published several solid papers on the novel methods in high-quality international journal. We rank his research performance as **good.** Our recommendation is that it is important to secure the financial support of Peet Kask and his team for the future. The results of the Kask group could also be used by Estonian enterprises better.

Apart of Peet Kask's activity, the research at the Department is very old-fashioned and does not fulfill the criteria of modern biochemistry or biophysics. Therefore, we have to give the ranking **unsatisfactory** as regards the overall performance of the Department.

Part IV

Final Remarks

Finally, the Team wants to point out three issues

First, the average age among Estonian scientists is rather high. There will unavoidably be a generation change in the near future. On the other hand, the number of possible candidates for professorships in science among younger generation appears to be rather low at the moment. Consequently, there is a clear need to increase the resources for educating a new generation of scientists. This should be kept seriously in mind when planning the future science policy in Estonia.

Secondly, and following from the first point, the Team strongly recommends that a Graduate School system should be rapidly constructed in the country. This system should include well-planned curricula for the students including participation in international summer schools and courses. The management of the Graduate School system should include proper financial resources to support students as well as the teaching universities. A regular evaluation of the postgraduate studies must also be included in the new system. Specifically we recommend that

- the graduate students should receive monthly fellowships that adequately support their needs and prevent brain drain from the universities and research institutions at this stage

- the graduate students should receive organized supervision, participate in departmental seminars and have access to international teaching courses and summer schools.

- the curriculum of Ph.D.'s in chemistry and biochemistry should aim for graduation at the age below 30.

Thirdly, the past organization of higher education and scientific research in Estonia is still visible. Due to this historical background, the universities and independent research institutes are still separated. We consider that this situation leads to serious waste of limited recourses. It also hampers the access of university students to modern science and research culture during the early years of university studies. We think that it would be highly advantageous to concentrate all scientific research and higher education to the universities. A consequence of this would be that University of Tallinn is created as a conglomerate of the universities and research institutions that already exist in the city. We warmly support this idea.

Tallinn, March 12, 2001

Matti Saraste (chairman) Ari Koskinen Jorma Mattinen