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Physical Methods for Molecular and Biomolecular Structure and Dynamics

Spring Meeting 2003 of the Swiss Chemical Society (SCS)

24/25 March 2003, at ETH Zürich

A Symposium in Honour of the Contributions to Science of Prof. Richard R. Ernst and Prof. Jack D. Dunitz, jointly organized by the Laboratory for Physical Chemistry and the Laboratory for Organic Chemistry together with the Division Chemical Research (DCR) of the Swiss Chemical Society (SCS)

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By 24 March 2003 spring had finally arrived and the spring meeting of the Swiss Chemical Society had come to Zürich. This was the first time that a spring meeting of our society had been jointly organized by the two laboratories for Physical Chemistry and for Organic Chemistry of the ETH, in honor of two distinguished emeriti, *Richard R. Ernst and Jack D. Dunitz*, with an interdisciplinary symposium under the auspices of the Division Chemical Research (DCR) of the Swiss Chemical Society (SCS). A little calculation quickly shows that 2003 is a particularly appropriate year given the years 1923 of the birth of *Jack D. Dunitz* and 1933 of *Richard R. Ernst*, providing for a 150 years' anniversary, thus anticipating the 150 years of ETHZ in 2005 (and bypassing those of EPFL, presumably).

To start with, ***André Merbach*** (Fig. 1) opened the meeting with the traditional Ceremony of awarding prizes and honors (see also *Chimia* **2003**, *57*, 298). This year the important Sandmeyer Prize (SFr. 20'000.-) went to a team from Sulzer Chemtech, whereas the Dr. Max Lüthi medal (SFr. 1000.-) for an outstanding diploma thesis went to Benoît Dubray (Fribourg). As a further high point of the ceremony André Merbach awarded the honorary membership of the Society to the two Swiss Chemistry Nobel Prize winners of the ETH Zürich, Richard R. Ernst and Kurt Wüthrich (see Fig. 2, showing Richard R. Ernst still bearing injuries from an accident but bravely holding out during the meeting including even his own lecture). This ceremony was concluded by a long lasting and enthusiastic acclamation by an audience which more than overfilled the largest lecture hall in the new Chemistry building of ETH Zürich on the Hönggerberg site.

The scientific session then started with ***Kurt Wüthrich's*** lecture on 'NMR in Structural and Functional Proteomics', which included many historical recollections from the early times on NMR and the Ernst – Wüthrich collaboration in the years 1976–1988. He showed the list of joint projects of 1979 (still kept in original form by Richard R. Ernst) and referred to their common habit of always extending their lectures beyond speaker's time ("Richard, because he has always so much to tell and Kurt, because he speaks so slowly …", see Fig. 3). He mentioned the enormous task presented by protein structure determination from hemoglobin to cytochrome c and how he tackled it starting in 1969 at the Bell Labs and finally solving it many years later. He mentioned the difficulties of publishing with *FEBS Letters* (at the time of the earlier editor, a problem which was solved when Georgio Semenza took over as editor) and the enormous technical developments (NOESY, SECSY, TROSY …) necessary for solving protein structures, culminating in membrane proteins. For well-known reasons many of the scientific aspects of the

Meeting report prepared by K. Albert Keppler, S. Albert, M. Gottselig, M. Hippler, H. Hollenstein, L. Oeltjen, M. Quack*, G. Seyfang, A. Sieben, J. Stohner and M. Willeke

*Correspondence: Prof. M. Quack
Laboratorium für Physikalische Chemie
ETH Zürich Hönggerberg HCI
CH-8093 Zürich
Tel.: +41 1 632 44 21
Fax: +41 1 632 10 21
E-Mail: Martin@Quack.CH

Fig. 1. SCS President André Merbach (right) at the opening ceremony with three members of the Sulzer Chemtech team (Peter Moritz, Kurt Breu, Claudia von Scala), receiving the Sandmeyer prize

Fig. 2. President Merbach congratulating the two new honorary members of the Swiss Chemical Society, the two Chemistry Nobel Prize winners Kurt Wüthrich (left, 2002 Prize) and Richard R. Ernst (middle, 1991 Prize)

Fig. 3. Kurt Wüthrich lecturing

Fig. 4. Bob Griffin after his lecture in discussion with Richard R. Ernst

lecture can be found nicely summarized in print (K. Wüthrich, Nobel lecture, *Angew. Chem., Int. Ed.* **2003**; see also R.R. Ernst, Nobel lecture, *Angew. Chem., Int. Ed.* **1992**).

The second lecture was given by ***Bob Griffin*** (Fig. 4) from MIT on 'Structural Studies of Membrane and Amyloid Proteins with Dipolar Recoupling and Dynamic Nuclear Polarization'. He addressed MLF structure, TTR, amyloid fibrils, and bacteriorhodopsin as well as the prion proteins in general. He also went into some detail of the technical advances necessary for studying such complex systems. In particular, dynamic nuclear polarization and the use of BWOs and powerful gyrotrons as mm-wave and microwave sources proved useful here.

The first talk in the afternoon session chaired by *Beat Meier* (Fig. 5) was given by ***Horst Kessler*** (Fig. 6) from the TU München with the title 'NMR Investigations of Large Biomolecular Complexes'. He started out with some very general remarks on the ubiquitous symmetries (found in the symbols ETH, TUM and MUT, some themes of Bach's in the art of the fugue …) and the violations of such symmetries, the investigations of which have found a long and still lasting interest in research at ETH Zürich both in the laboratories for Organic and for Physical Chemistry. After mentioning his paper together with Richard R. Ernst in 1983 (on symmetries in pulse sequences) he turned to p53, the molecule of the year, of relevance for 50% of all human cancers. He discussed its X-ray crystal and NMR structure determinations, using palindromic sequences, and extended then his discussion to p63 and p73 as a superfamily of transcription factors. He addressed the question of protein folding, where later in the discussion he expressed his opinion that we are still very far from understanding. His extended contributions on aspartic pro-

Fig. 5. Beat Meier introducing Horst Kessler's lecture

Fig. 6. Horst Kessler lecturing

tease dimerization were also addressed and later on in the discussion period Richard R. Ernst pointed to the importance of evolutionary considerations for aspartic protease. All in all this was a lecture particularly stimulating some lively interest and discussion among the audience.

In the following lecture entitled 'Two Dimensional Solid State NMR Spectroscopy: From Richard R. Ernst's Ideas to Elucidation of Supramolecular Systems' ***Hans W. Spiess*** (Fig. 7, Max-Planck-Institut für Polymerforschung, Mainz) referred to the central importance of carefully chosen building blocks in advanced synthesis and self-assembly in biological systems. Their organization is crucial for their ability to perform functions such as transport of ions and charges, selective absorption of materials, molecular recognition, or acting as mechanical nano devices. Despite being highly ordered on a local scale, the generated systems often do not crystallize and their structures cannot be determined by conventional X-ray crystallography. Even more challenging is to unravel the dynamics of these systems over a wide range of time scales. H.W. Spiess pointed out that two-dimensional NMR spectroscopy offers unique possibilities in this area. The developments he presented are based on the combination of two seminal ideas of Richard R. Ernst: 2D exchange spectroscopy allows the investigation of slow motions in the range above one millisecond, and 2D correlation allows the determination of geometry without model assumptions. Application of these methods in soft matter research provided unprecedented insight into collective dynamics of macromolecules and the collective building blocks of columnar liquid crystals. Moreover, they led to new concepts of the structure of non-crystalline systems on the nanoscale. Recently developed high-resolution solid-state ^{1}H-NMR techniques provide structural and dynamical information of complex supramolecular systems requiring only a small amount of as-synthesized samples. These techniques combine fast 'Magic Angle Spinning' and 'Double-Quantum' NMR spectroscopy making use of homonuclear and heteronuclear dipole–dipole couplings involving protons. Hans W. Spiess described in detail three examples where these techniques have provided new important insight: hydrogen-bonded structures in the solid state and their relation to proton conductivity, columnar stacking of discotics and their relation to photoconductivity and polymers adsorbed at colloids and hydrogen bonding in self-assembled monolayers.

Fig. 7. Hans W. Spiess thinking about a question during his lecture

Ad Bax (Fig. 8, National Institute of Health, Bethesda) gave an instructive talk with the title 'Weak Alignment Provides New Opportunities in NMR Studies of Biomolecules'. He started his lecture by explaining that biomolecular structure determination by NMR to date has relied in almost all cases on local parameters, such as NOEs and J couplings. Then he explained that the direct measurement of dipolar couplings in weakly aligned macromolecules allows information to be accessed on the orientation of individual internuclear vectors relative to the molecular alignment tensor. These vectors have also an intrinsic global character and can constrain the relative orientation of parts of the structure, which are not connected by NOEs. He stressed that this is particularly useful in the study of non-globular and multimeric structures. He went on with an illustration that dipolar couplings can be measured with very high relative accuracy, which provides a precise monitoring of the local structure. He stated that in general the higher the resolution of the reference structure, the better the agreement between the measured dipolar couplings and the protein structure. He explained this on the example of protein G, where an excellent agreement was observed between the structure determined from the ^{13}C–^{1}H dipolar coupling measurements and the corresponding X-ray structure. He amplified that this agreement can be further improved if the X-ray structure is

Fig. 8. Ad Bax in action

refined by one-bond dipolar couplings, using backbone $^{13}C'$–$^{13}C^{\alpha}$ and $^{13}C'$–N dipolar couplings. He then briefly discussed that this procedure provides precise information on the position of the amide protons, which in turn allows to figure out how far amide protons can fall outside the C'–N–C^{α} plane. As Ad Bax mentioned, the question of what causes the deviation of the peptide bond from planarity – C–N twist or pyramidalization? – is an old one, addressed, for instance by F.K. Winkler and J.D. Dunitz (*J. Mol. Biol.* **1971,** *59*, 169) and answered as both being important.

During the question period R.R. Ernst stated that he had two events in his life when he thought that he is out of business. One of this events, R.R. Ernst carried on, was "as the young Ad Bax sat in my office asking all these questions going deeply into my secrets…".

The first day of the symposium was closed by the lecture of ***Richard R. Ernst*** (Fig. 9, ETH Zürich) entitled 'NMR and Beyond'. As the chairman *Arthur Schweiger* (Fig. 10) had introduced Richard R. Ernst's methods as being capable of measuring the content (and quality?) of a closed wine bottle, Richard Ernst was quick in pointing out that "you should leave the bottle unopened, particularly if you are a woman", by showing pictures of two human brains (male and female) after extensive alcohol abuse, as one application of NMR. R.R. Ernst first discussed the development of nuclear magnetic resonance (NMR) as a method which is useful in everyday life and state-of-the-art research. It was established as a powerful tool next to X-ray crystallography. Whereas X-ray techniques are suitable to determine the structure of a sample, NMR is able to reveal its dynamics. Three different branches of NMR are at the center of attention at the moment, the methodological development in the field of materials science, the application frontiers in biological NMR, and the interpretation of results in medical and functional magnetic resonance imaging (MRI). He stressed the recent role of NMR-imaging in understanding brain function.

Fig. 10. Arthur Schweiger as session chairman

After the scientific part of his talk R.R. Ernst turned to the social responsibilities of human beings in general and of scientists in particular. In a time of belief in an almost unlimited potential for problem-solving, suspected limited natural resources, an unbroken trust in the free market, an increasing gap between the rich and the poor, a loss of accepted ethical standards, and the world dominance by a single super-power, questions about the obligations of academia and the social responsibility also of its members arise. Can maximizing shareholder value replace social responsibility? Even in research the question about motives may be asked. Is it the aim to be number one in your field, the race for a Noble prize, or the satisfaction of your personal curiosity in the scientific ivory tower? Or should it not be the sense of responsibility for solving major global problems and an altruistic drive to help? An accepted first principle of science is absolute honesty. Although it should apply not only to science, but also to politics, for example, it seems clearly less accepted there, as the prime goal seems to be getting reelected in a democracy – independent of the means used in this goal. This gives a special responsibility to scientists who do not depend upon reelection, who have the right of free speech, who have received a high-level education, who, indeed, work in science's ivory tower. It should be an obligation for them to state their opinions also on ethics, moral, and their ideas for a beneficial future for all people. Social responsibility demands it. We as scientists must speak out. He was himself an example for this by clearly expressing his opinion on the enormous importance international agreements and organizations have as invaluable instruments in shaping world politics for the better, and the destructive effects the current policy of the Bush administration has precisely on these international instruments. But he in the end insisted in addressing scientists in the first place by quoting Rabelais "Science sans conscience n'est que la ruine de l'âme".

This speech – and RRE's well known opinions – provided the occasion for Ad Bax to transmit another honor to Richard R. Ernst at the following speakers' dinner, sent from the informal American peace club, no money involved, just a T-shirt (Fig. 11), which Richard immediately set out to wear. The dinner – for those who attended – turned out to be a most refreshing event in the Zunfthaus zur Zimmerleuten, where many fond memories of Jack's and Richard's were revived.

Fig. 9. Richard R. Ernst lecturing (sitting because he is still hurt after an accident)

Fig. 11. Richard R. Ernst holding the T-shirt that he received from Ad Bax during dinner

The following day of the meeting started with a session chaired by *François Diederich* (Fig. 12) and was centered around crystallography and structure of crystals. ***Michael McBride*** (Fig. 13, Yale University) talked about 'Studying the 'Mechanism' of Crystal Growth & Dissolution by Atomic Force Microscopy'. He reported recent results on crystal growth and dissolution of benzoin, that stem from his particular interest in a new kind of rational organic synthesis, the goal of which is to assemble not molecules from atoms, but crystals from molecules. In his attempt to understand crystallization he cited Wilhelm Ostwald (*Z. Phys. Chem.* **1897**, *22*, 289) in thinking about energy, but whenever possible considered the energy associated with individual molecules and the detailed stereochemical structure of their environments. He showed direct observational evidence (of course in a two-dimensional sense) taken from atomic force microscopy in real time and with nanometer resolution, that enabled him to tackle some very important questions: How big is the critical nucleus (*i.e.* the metastable crystal that neither grows nor dissolves) and what determines its critical size? What determines the rate of ledge motion?

He demonstrated that one can learn about crystal growth by studying crystal dissolution, and provided a new explanation why growth is not just the opposite of dissolution and *vice versa.* He described a particularly interesting series of experiments on simultaneous growth and dissolution in a two-component crystal (racemic benzoin in water with 5% n-PrOH containing (*S*)-benzoin). He showed for the latter system and concluded that in general adjusting the solution ratio of the components

Fig. 13. Michael McBride lecturing

in a mixed crystal (*e.g.* a racemate) allows one to determine the directionality of growth (or dissolution) in a centric crystal, identify (or specify) surface molecules and create (or delete) layers one at a time. These possibilities render such a system very interesting for the atomic force microscopic investigation of crystal growth and surface dynamics. He convincingly demonstrated that such direct observational results "will be indispensable in transforming the venerable art of crystal growth into a science".

Hans-Beat Bürgi (Fig. 14, University of Bern) started his lecture on 'Exploring Molecules in the Solid State: Order, Disorder, Statics and Dynamics' with a short review on the enormous progress made in diffraction techniques since the time Jack D. Dunitz did his first investigations in this exciting field. He passed from a typical working environment as it might have been in Jack D. Dunitz's laboratory in 1948, then went on to the year 1968, when the first laboratory computers became available, and ending with an environment in current use, where laptops and highly automatic computer-controlled procedures in combination with equipment for temperature- and time-dependent measurements are standard. He emphasized the need for high-quality control in order to eliminate erroneous structures and mis-assignments when using these automated new techniques.

The second part of the talk was concerned with the problem of determining real structures from measured atomic displacement parameters (ADPs). Benzene was taken as an example. The question whether benzene in the solid state is hexagonal or whether one has to deal with a centro-symmetric superposition of hexatriene structures is anything but trivial and may be answered only after careful examination of temperature-dependent and temperature-independent contributions to the ADPs. A further exciting field concerns the investigation of excited state structures by time-resolved X-ray diffraction in combination with laser excitation. Finally, Bürgi gave an outlook on future developments, going in the direction of exploring structures of disordered materials, of 3-dimensional reconstruction of the structure of nanosized specimens from over-sampled X-ray diffraction patterns, high-resolution 3D X-ray diffraction microscopy and other new imaging techniques.

The next speaker was ***Angelo Gavezzotti*** (Fig. 15, University of Milan) with the theme 'The Calculation of Intermolecular Forces from Molecular Electron Densities'. The fast and reliable calculation of intermolecular potentials is a frontier research interest with strong influence on such diverse fields as biomolecular energetics, materials design, or polymorph prediction for pharmaceutical compounds. He described a new method, called SCDS (semi-classical density sums)-Pixel (A. Gavezzotti, *J. Phys. Chem.* **2003**, *B107*, 2344), whereby a molecule is represented by some 10,000 pixels of its electron density, calculated by ordinary quantum chemical methods at the MP2 level. The method then allows within that pixel representation the calculation of electrostatic and polarization energies between two or many such electron density distributions in dimers, molecular clusters or crystals, by summation over all electrostatic interactions represented by classical formulae; the evaluation of dispersion energies by a sum of terms approximated by lo-

Fig. 12. François Diederich introducing as chairman the second day

Fig. 14. Hans-Beat Bürgi during his lecture

cal distributed polarizabilities; and the calculation of repulsion energies assumed to be proportional to the overlap between densities. He demonstrated that interaction energies in molecular dimers, from the water dimer to the guanine–cytosine Watson-Crick base pair, are well described, both in absolute terms as well as for the partitioning between the various energy contributions. He further showed that enthalpies of sublimation of many organic crystals are reasonably well reproduced. Computing times are as short as a few minutes for a complete crystal structure calculation and only a few seconds for a dimer calculation. In the end of the talk A. Gavezzotti stated that the SCDS-Pixel method shows promise as an intermediate between atom–atom force fields, since such calculations are becoming increasingly outdated, and full quantum chemical methods which cost a lot of computing time and are well known for problems when trying to properly include electron correlation.

Fig. 15. Angelo Gavezotti giving a skeptical look to a questioner

After lunch there was a short interlude with President ***André Merbach*** leading the general assembly of the Swiss Chemical Society.

Then the chair was taken by *Dieter Seebach* (Fig. 16) for the next scientific session. In the exciting lecture presented by ***Laurence Barron*** (Fig. 17, University of Glasgow) on 'Structure and Behaviour of Proteins, Nucleic Acids and Viruses from Raman Optical Activity' we gained new insight into nonregular structures of proteins, structures of nucleic acid and even viruses by Raman scattering spectroscopy of optically active biomolecules. Raman optical activity spectroscopy is becoming a valuable tool to investigate structure and action of large chiral biomolecules.

Fig. 16. Dieter Seebach as chairman introducing Laurence Barron

Fig. 17. Laurence Barron during his lecture

Raman spectroscopy provides vibrational spectra *via* the inelastic scattering of light, which can be analyzed with a spectrograph. When polarized light interacts with a chiral molecule, left- and right-handed enantiomers respond differently to the polarized incident light. A tiny difference between the scattered intensity of left- and right-circularly polarized light is measured as a function of light frequency. Raman optical activity (ROA) has first been observed experimentally by Barron *et al.* in 1973 (*J. Am. Chem. Soc.* **1973**, *95*, 603–605). Since the sign and magnitude of a vibrational ROA band depends on molecular geometry including handedness, a sign change is observed for spectral structures when switching from left-handed to right-handed enantiomers. Thus, ROA is very well suited for the determination of absolute configurations of chiral molecules, when combined with sufficiently accurate *ab initio* calculations. This has been demonstrated for small molecules like CHBrClF, where the absolute configuration has been determined to be *R*(–)-CHBrClF using ROA. ROA is also an efficient tool for routine measurements of biomolecules in aqueous solutions. It is sensitive to chiral elements in biomolecular structures and thus provides information on structure and dynamics in solution. Vibrational bands originating from backbone protein or peptide structure dominate ROA spectra and are indicative of solution conformational structure. Raman optical activity is complementary to NMR and X-ray crystallography techniques (Barron *et al.*, *Prog. Biophys. Mol. Biol.* **2000**, *73*, 1–49). An extensive field of research focuses on human diseases caused by partial unfolding of proteins resulting in self-association and tissue deposition among which prion encephalopathies (BSE, Creutzfeld-Jakob), Parkinson's and Alzheimer's diseases have a strong impact on human society. Since Kidd reported the first electron microscope picture of Alzheimer neurofibrillary tangles in 1963 much has been learned about molecular implications of AD. For viruses the structural information delivered by NMR or X-ray diffraction is very limited to coat proteins and not the nucleic acid core. In contrast, ROA can provide information on protein as well as on nucleic acid structures. This has been demonstrated for the tobacco mosaic virus and the cowpea mosaic virus (E.W. Blanch *et al., J. Gen. Virology* **2002,** 2593–2600).

The most stimulating talk given by ***Lia Addadi*** (Fig. 18, Weizmann Inst. Rehovot), 'Taking Advantage of Disorder: Amorphous Calcium Carbonate and its Roles in Biomineralization' discussed the building of skeletal material from stable amorphous calcium carbonate (ACC) and from transient amorphous calcium carbonate.

Research on biomineralization involves the study of mineralized materials built by organisms. These materials have evolved over more than 500 millions years to fulfill widely varying functions, including scaffolding, protection, food grinding and navigation in the earth's magnetic field. Nature had the advantage of time and evolution in the enormous playground of the world, to test, optimize, discard, or preserve not only

the materials, but also concepts and strategies in material design. As a result, high levels of sophistication and control characterize the design of many biogenic materials at all levels, from Angstroms to millimeters, which are composite materials built of minerals and biological macromolecules. To understand the strategies and mechanisms active in biomineralization, Lia Addadi and her group are studying the various components of the mineralized tissues, the interface between them, their properties and relations of structure to function.

Fig. 18. Lia Addadi lecturing

One of the most interesting issues in biomineralization is that of controlling the shape of skeletal parts. The mineral is solid and often crystalline. Crystals tend to grow preferentially along defined directions determined by molecular interactions within the lattice, and they terminate with sharply defined faces. Yet organisms in all kingdoms achieve control of shape routinely, building objects with convoluted shapes at length scales ranging from fractions of millimeters all the way to centimeters and more.

In general there are three solutions to the shape problem. These are building the object out of an amorphous mineral, out of a single crystal, or from polycrystalline assemblies. Each has its own advantages and difficulties. The talk concentrated on the use of amorphous calcium carbonate (ACC), either as the major final component of the skeletal material, or as a transient phase that is instrumental in determining the properties of the final product.

In order to understand how this occurs, one must characterize structurally the amorphous phase of calcium carbonate, and try to understand how it is stabilized. Lia Addadi's group studied three examples of stable ACC coming from very different species: an ascidian (chordates), a lobster (crustacean) and a plant (Y. Levi-Kalisman, S. Raz, S. Weiner, L. Addadi, I. Sagi, *Adv. Funct. Mat.* **2002**, *12*(1), 43–48). The composition is amorphous calcium carbonate, *i.e.* none of these minerals show sharp reflections in X-ray or electron scattering experiments. They all contain protein, in approximate amounts of 0.05 weight%. The macromolecules alone are able to stabilize the amorphous phase *in vitro*.

Fascinating questions come to mind: what information does the microenvironment of mineral deposition contain to encode the fate of the mineral phase to be formed? How 'amorphous' is amorphous calcium carbonate or, for that matter, any amorphous mineral?

The group also looked at a second strategy widely used by organisms, which consists of building a skeletal element from a single crystal. In the sea urchin larval spicule, as in the mature sea urchin spine and test, the final product of mineralization is one single crystal of calcite.

The results of Addadi's group lead to a number of conclusions and hypotheses, as follows: i) Formation of such complicated single crystals as in the sea urchin cannot be achieved by uncontrolled nucleation or crystal growth. The sea urchin 'chooses' to stabilize transiently ACC and then transform it in a slow controlled manner into calcite, where desired, when desired. A similar process appears to be active in the formation of the polycrystalline mollusk larval shells. ii) Transient ACC may thus have encoded structural information about the final crystalline product. iii) The use of ACC as a transient phase may be a common strategy to control the formation of crystalline phases. iv) Amorphous calcium carbonate may well be much more abundant than so far suspected in biomineralization. v) ACC is not one mineral but a family of minerals with very different structural characteristics. Finally, the study of amorphous 'structures' may teach fundamental lessons on crystallization.

After the short coffee break, *Renato Zenobi* (Fig. 19) took over as chairman and 'Mechanistic View of Protein Synthesis and trans-Translation' was the title of an impressive lecture given by ***Nenad Ban*** (Fig. 20, ETH Zürich). The ribosome, consisting of a larger and a smaller sub-unit, is the site of messenger-directed protein synthesis, the final stage in the expression of genetic information from RNA. Both recent and ongoing investigations of the structure and function of the ribosome, as they pertain to the process of protein synthesis, were discussed.

Fig. 19. Renato Zenobi chairing the last session

Fig. 20. Nenad Ban's lecture

Determination of the structure of the large ribosomal unit required a combination of X-ray crystallographic methods and improvement of the procedures used at that time: the object of interest was approximately five times larger than previously solved structures. The speaker was part of the team that solved the structure of the large ribosomal sub-unit in 2000.

If genetic information is to be expressed correctly and translated in the protein sequence accurately by the ribosomes, it is vital that the mRNA involved be complete. If the mRNAs are truncated, this leads to the synthesis of defective proteins, and the jamming of the ribosomes involved when they reach the end of information provided by the truncated mRNA molecule. A hybrid transfer-messenger RNA mole-

cule, tmRNA, unjams the ribosome and then designates the flawed proteins for degradation. The speaker and his research group have successfully determined the structure of the tRNA-type part of tmRNA in complex with small protein B, and proposed a model for the binding of tmRNA on the ribosome. Certain antibiotics, for example erythromycin, can inhibit the function of the ribosome by binding inside the tunnel through the ribosome and inhibiting the passage of the peptides. Another interesting discussion point was the action of the toxic agent ricin on the sarcin/ricin loop: by cleaving a single bond, ricin inhibits the delivery of tRNA to the active site.

The final session of the symposium was closed by a thoughtful talk by ***Jack D. Dunitz*** (Fig. 21, ETH Zürich) entitled 'Looking backwards, glancing sideways' (see also J.D. Dunitz, in 'Essays in Contemporary Chemistry', Eds. G. Quinkert, M.V. Kisakürek, VHCA, Zürich, **2002**). He added to the possible motives of scientists doing science ("perhaps we just like playing a game …not very serious") remembering the early days of X-ray crystallography. He then started his lecture by showing to the audience how much effort one had to spend in the 1940s for the determination of a crystal structure without all the technology developed over the last 60 years. He now focused on a still open question, which had interested him since his PhD time, the 'anomalous isotope effect in some hydrogen bonds'. J.D. Dunitz explained that such an effect was first noted in the 1930s, based on the observations that in some hydrogen bonds the O...O distances expand when the hydrogen is replaced by deuterium (Ubbelohde). He pointed out that several theoretical explanations had been proposed from Nordman and Lipscomb or Singh and Wood among others but after more than 60 years the phenomenon is still not completely understood. He illustrated this with the examples of oxalic acid dihydrate, acetylene dicarboxylic acid dihydrate and potassium hydrogen maleate. He mentioned that in the latter case the short, symmetric (or nearly symmetric) hydrogen bond has also "had a long career as an unsolved problem and seems to be still a matter for further studies". He reported an attempt in the literature to fit a one-dimensional potential function in such a way that it could reproduce the experimental observations. However, the resulting potential energy curve has a rather unphysical shape. Therefore it seems clear for him that one has to include more than one degree of freedom in the model to explain this effect. Then he switched to a related problem, which is also still unsolved: the few known cases of isotopic polymorphism, where substitution of a deuteron by a proton leads to a change in crystal structure. He illustrated this by showing the different crystal structures of trifluoroacetic acid tetrahydrate and the corresponding deuterated compound. In some systems intermolecular proton transfer between the two hydrogen-bonded partners occurs in the crystalline state as the temperature is changed. He demonstrated this on the example of 4-methylpyridine-pentachlorophenol, where at low temperature a N–H...O bond has been found, whereas for higher temperatures a N...H–O bond has been observed.

The symposium was closed by *Martin Quack* as chairman of the Division Chemical Research of the Swiss Chemical Society (Fig. 22). He thanked again Richard R. Ernst and Jack D. Dunitz for providing the opportunity for this exceptional spring meeting, the speakers, who provided us with superb lectures, his fellow chairmen, in particular François Diederich from the Laboratory for Organic Chemistry, the Swiss Chemical Society as represented by André Merbach, Markus Straub, and Roland Wenger, who provided also some very substantial help, the Quack research group for much work in helping to organize the event and the ETH (SEP and industry sponsors (Fig. 23)), who helped in financing beyond the sponsorship by the Society. Last, but not least, the success of the meeting was made by a large, interested and stimulating audience, thanks to them all.

Fig. 21. Jack D. Dunitz giving the last lecture of the Spring meeting 2003

Fig. 22. Martin Quack who introduced and closed the meeting as chairman of the Division Chemical Research

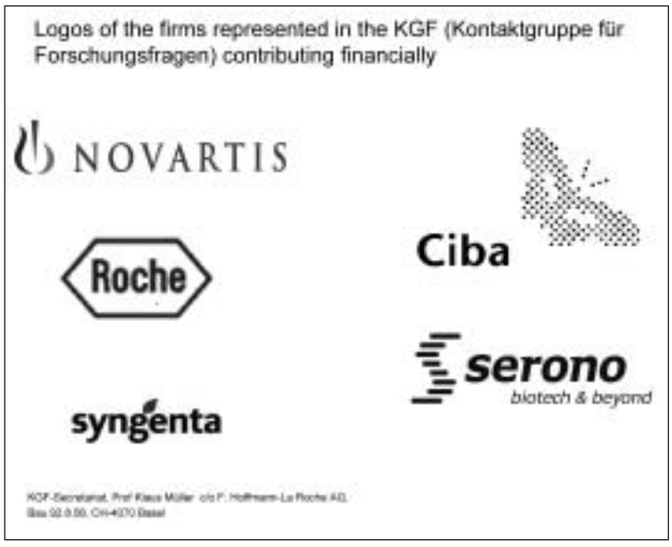

Fig. 23. Logos