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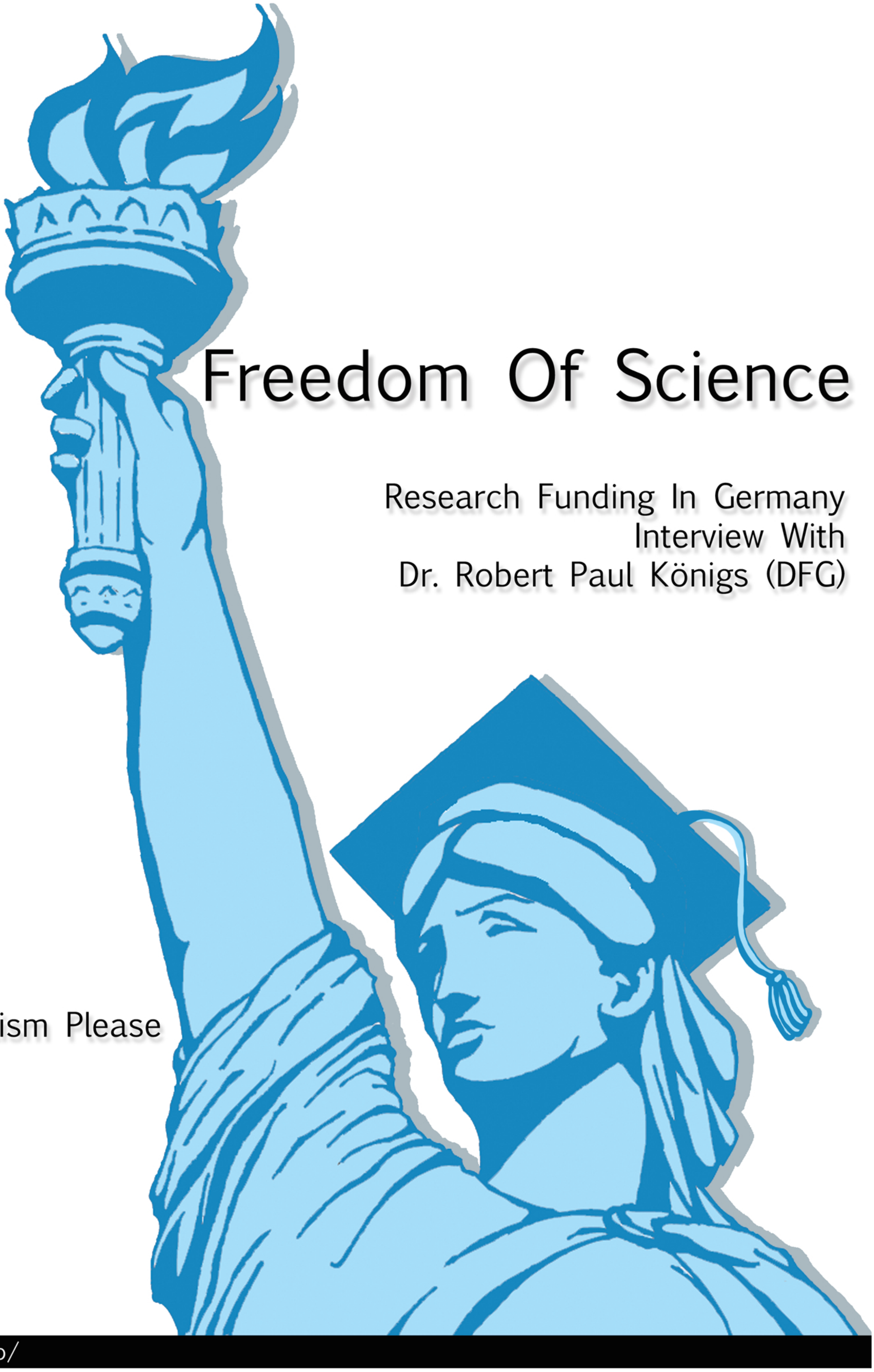
JUNQ

Journal of Unsolved Questions



Open Questions:
Is Calcite Chiral?

How Do Pseudouridine
Synthases Work?

Freedom Of Science

Research Funding In Germany
Interview With
Dr. Robert Paul Königs (DFG)

Article:
Predicting Half Metallic
Ferromagnets
- A Little Bit More Realism Please

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Preface

Editorial Note

Dear Reader,

The freedom of scientific inquiry is a societal good worthy of being highly valued and protected. And especially today it is. As I am writing this editorial note, the sun is blazing outside on a hot summer day, and I am experiencing quite vividly some of the freedom I enjoy as a scientist: in delighting contrast to someone working, say, in an upscale business firm, I do not have to adhere to any rigid dress-code or work time schedule and I can decide for myself when and where I will be working on what. So right now I am at home, with open windows, no shoes, a cool drink, and I just decided that right now I could take the time and write something for JUnQ. There you go: academic freedom.

But let's try and be serious. At first glance, most of you will not question the initial statement, I assume. And indeed: If our aim and societal mandate as scientists is to produce genuine and independent knowledge – or even find "truth" (as some actually think they can) – it is obviously crucial that we enjoy freedom, liberties on various different levels. I see mainly two: (1) The "freedom to" do scientific research, in the sense of being (en)able(d) to dispose of the appropriate means and resources such as time, money and equipment. (2) The "freedom of/from" interference, censorship, or even repression by other parties, for example if our research should entail conclusions that do not go in accordance with popular (or some ideological) belief or knowledge. The freedom of science appears to be a tricky thing. With this issue of JUnQ, we try to shed some light on the different meanings and values freedom carries with respect to science as a whole, disciplines or the individual researcher.

Most international legal systems include regulations to provide and protect freedom for academia in these two respects. In Germany, academic freedom is granted as a fundamental right by article 5 (par. 3) of the constitution: "Art and science, research and teaching are free." With this regulation, the state protects the scientific community mainly from governmental intervention and takes on the responsibility to establish universities and enable research. Over the last years, the understanding of what the "freedom of science" is or how it is to be fostered has undergone some changes. A good example is the "Freedom of Science Initiative" launched by the German government in 2008. Its aim is to grant non-university research institutions more freedom in the form of flexibility when allocating their funds, which in turn shall promote their effectiveness. The so-called "Wissenschaftsfreiheitsgesetz" (Academic Freedom Act) of 2012 permits research institutions the acquisition of third party funding to attract or hold high-level researchers, and facilitates the acquisition of shares in external companies. Naturally, these new liberties come with a new and increased set of individual responsibilities for research institutions such as monitoring and auditing procedures.[1] So far, so good. However, this newly won freedom also seems to bring along the displacement of traditional forms of scientific self-regulation in research institutions by market principles like competitive constraints, opening up academic structures more to external (economic) parties and their demands and affecting the internal structure of scientific institutions (mainly by strengthening the management level). This is where the individual active researcher and her individual freedom of choice comes to mind, and one has to wonder whether it is her who gains freedom in the process or the institution, its directing board, or high prestige "flagship researchers", respectively.

The recourse to means from third party funding has always been a part of the German academic system. Over time however, third party funding has gone from an "extra" to a vital resource for scientific research, at public universities as well. This has been subject to a lot of controversy, with critics sensing a potential threat to the integrity of scientific inquiry and a severe infringement to the individual researcher's independence in choosing subjects or questions to study: The amount of third party funding acquired alone can influence a scientific career. The German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) is the largest and most important funding agency in the country. To find out about the impact this logic of funding may have on the freedom of academic research, Thomas Jagau talked to Dr. Robert Paul Königs, DFG's head of the department of scientific affairs (pp. XVIII).

But scientific research not only depends on monetary resources, of course. As mentioned above, intellectual freedom from ideologically motivated censorship is just as important – the freedom to ask questions, even if they are not en vogue; the freedom to publish answers that are not popular. Dependence on paradigms and disciplinary trends but also the influence of non-scientific doctrines can restrict research. How this can affect entire disciplines is demonstrated by chemist and chemistry historian Klaus Röker (pp. XXI). He shows how scientific knowledge is always embed-

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[1] http://www.bmbf.de/en/12268.php (last access 20.06.2013)

ded in the intellectual and social context of its time and how it is determined by political, socio-economic or religious influences.

On the micro level of things, and from the perspective of individual scientists, freedom is first and foremost an object of desire. It is particularly young scholars who often find themselves in a complex net of dependencies – from their supervisors, scholarship providers, the next (and next, and next) fixed-term and part-time contract, and the like. Hence, ever higher degrees of independence in doing their research is what most scientists strive for. This kind of freedom increases with seniority and merit, from students to graduates, to doctors, professors, and so on. Since in academia, the only one forcing you to go on is yourself – are we left with the paradoxical (or tragic?) situation that acquiring greater amounts of freedom requires increasing willingness to engage in self-exploitation? Is freedom something we should maybe consider stop striving for? This is just polemic, of course. Putting a different spin on our cover topic, philosopher Ingo Gerhartz shows that asking this question anyway may indeed be heuristically useful. In his essay, he regards "Freedom as a Problem" that could possibly prevent us from gaining any knowledge at all (pp. XVII). JUnQ's David Huesmann turns to secondary uses of scientifically generated knowledge that is intended for peaceful applications, but may in the wrong hands have disastrous impacts (think of nuclear technology). He also asks whether there should be limits to scientific freedom when it comes to the possibility of such dual use (pp. XXIII).

Along with our "magazine" section you will of course also find the latest articles on null result research and open questions we received, at the core – and heart – of this issue. It is these contributions that exemplify the idea behind JUnQ: Making use of your freedom as a scientist to publish the results you produced by doing good academic work and making them accessible for fellow researchers – even if they do not fit current paradigmatic views or common expectations. We would like to thank all contributors for being a part of is idea and extend an invitation to you to send us your "failed" science for the next issue of JUnQ. We are looking forward to it.

I wish you an enjoyable read

—Tobias Boll

Freedom as a Problem

Ingo Werner Gerhartz[2] is a doctoral candidate at the department of philosophy in Mainz and a member of the Gutenberg Academy since 2013. He obtained his M.A. of philosophy and hellenistic studies at Johannes-Gutenberg University in 2008. His research focuses on the concept of guilt in classical greek tragedy, myth and practical philosophy.

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Philosophy, one might argue, primarily concerns itself with unsolved questions. Out of these, the question of freedom has certainly proven to be one of the most difficult. This is not so much owed to a lack of empirical data or it being such a lofty endeavor of academic interest that it eludes rational solution. Rather, we will see that by nature of its subject, the very act of asking the question itself creates the difficulties it struggles to overcome.

Nevertheless, we have to ask, because freedom is such an integral part of our everyday life. Not a single conscious choice – be it trivial, political or personal – could be made that does not rely on it as a presumption at least. Without it, we would not even be held accountable for our actions before a court, since judgment regarding moral and legal responsibility is passed based on whether or not we had a choice and if it really was ours to make. In our western culture, freedom is held aloft as one of our greatest values. Where it is suppressed or neglected, we passionately strive to reclaim it and go to great lengths to defend it.

Perhaps this is why the meaning of the words "freedom" or "liberty" is generally defined in negatory terms: the absence of compulsion or restraint, self-legislation (autonomy) as opposed to slavery, independence from outside forces. Positive definitions of what freedom is seem to pale in comparison to the assertions of what it is not.

No wonder then, from an historical perspective, that freedom first became a problem around the time when the notion of a universe governed by a singular abstract principle (logos or "reason") was formulated by philosophers of the ancient greek Stoa, reducing human decision to compliance with a predetermined fate (synkatathesis). Fueled by more recent discoveries in neurosciences, the ongoing modern debate of free will versus various forms of causal determinism[2] still revolves intimately around these same basic concepts.

Today, we face a multitude of arguments for or against the compatibility of freedom (and thus moral obligation) with deterministic positions in science, probably best known for its expression as "Laplace's demon":[2] an omniscient intelligence able to comprehend all past and future states of the universe only by analyzing the data of the present. While there are theories that assume less strict forms of causality, or even propose the existence of absolute indetermination, these do not touch the intrinsic problem of freedom at all.

The more we learn to understand ourselves and the universe around us, the more connections we find that seem to defy this sense of liberty. How can we be free if we are subject to genetic predetermination or are the products of our upbringing? The persistent recurrence of this conundrum indicates that the answer to it might not lie with what we are or what we cannot do, but how we perceive it – it is a matter of human understanding.

Whether we examine a chemical process, the logic of an argument or a piece of art, a good part of the effort to systematically interpret and explain it is to identify a set of factors or causes of which the presented phenomenon is an effect. We cannot be said to understand anything otherwise, which is why this relation, commonly referred to as "causality", is part of what makes knowledge of objects in general possible in the first place. It is an *a priori* (meaning before and independent of all experience) "category of the faculty of understanding",[3] as eighteenth-century philosopher Immanuel Kant put it.

We can easily see how this applies to the scientific method of investigation in particular. Science seeks to explain natural phenomena by putting forward hypotheses and testing them through observation and experiment to ensure intersubjective verifiability. A theory that fails to establish a causal relationship cannot make any predictions (whether false or correct) and thus must be considered conjecture at best. While this is not really a bias, but simply the way scientific understanding works, it does create a problem:

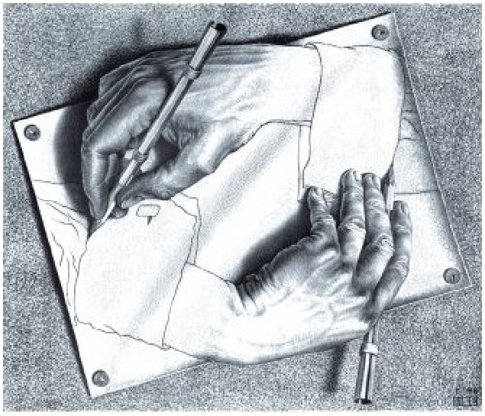

Figure 1: **Freehand drawing?** "Zeichnende Hände" by M. C. Escher ©M. C. Escher Heirs c/o Cordon Art - Baarn, Holland

Unfortunately, the same holds true when we try to understand ourselves. If freedom is the absence of a determining cause, but understanding is achieved by means of establishing causality, things we understand can never be free and things that are free can never be truly understood. Mutually

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[2] i.e. "the idea that every event is necessitated by antecedent events and conditions together with the laws of nature".[1]

exclusive, understanding freedom would seem an exercise in futility.

But is this really the freedom we seek? Dismissing any kind of determination, we would also have to include our own motives and personality, leaving nothing but pure, random chance. Having no effect whatsoever on the outcome, our decisions would merely happen to us and we would not be the authors of our actions. Obviously, this absolute freedom isn't freedom at all. A positive definition would have to allow us to be our own masters.

"Freedom is slavery",[4] George Orwell might say. But can there be a freedom that is not only compatible with causal determination, but in fact only possible because of it? At long last, a narrow path to solve this problem might lie between the alleged antipodes: a reflexive freedom that is the determination by oneself. After all is said and done, we can always choose to either consent or object – and consequently configure that which configures us in turn, expanding what limits us, nurturing what sustains us.

In doing so, we practice freedom – one such as Escher's hands drawing each other illustrate – a relation where there is no distinction between active agent and passive object, where each part is simultaneously being determined and determining that which determines it. There is no moral dichotomy either, as we are responsible for everything caused by us and even have to stand in for our decisions by suffering the consequences directly. If we had no choice, it's our own fault, because it is up to us to render them possible.

Of course, this requires us to first understand who we are, what we want (and sometimes: what we rather should want), as well as the many determinants we are subject to. The extent to which we are able to do this is the extent of our freedom, or in other words: knowledge makes us free.

Now, what does this say about liberty in academics, where knowledge is produced on a daily basis? Most of all, it should encourage us to go out and actively seek out freedom ourselves instead of waiting for it to be granted to us. This opens up a new means to interact with the various obstacles we encounter along the way, too – treating them not as hindrances, but as opportunities for personal growth. By learning how they affect us, we comprehend our own position in relation to them and can use this knowledge to change the rules of the game. After all, freedom indeed is what we make of it.

—Ingo Gerhartz

[1] Hoefer, Carl *"Causal Determinism" In Zalta*, Edward N. (ed.): The Stanford Encyclopedia of Philosophy (Spring 2010 edition)

[2] Laplace, Pierre Simon *A Philosophical Essay on Probabilities* London 1902 [1814], p. 4.

[3] Kant, Immanuel *Critique of pure Reason* translated and edited by Paul Guyer and Allen W. Wood. Cambridge Univ. Press 1998, A80/B106.

[4] Orwell, George *1984 - a novel. Signet Classic*, New York 2010 [1950], p. 4.

Research Funding in Germany

Interview with Dr. Robert Paul Königs[1]

Every research project begins with an idea. But for an idea to be put into practice another resource is generally required, which is scarce: money. While the allocation of money to research takes place in different ways, it is probably fair to say that research funding organizations play a crucial and ever-growing role in this regard.

In Germany, the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), a membership association under private law with its members being mainly universities, is the most important organization of this kind. We talked to Dr. Robert Paul Königs, head of the department of scientific affairs at the DFG, about the role of third-party funds for science and the humanities, the characteristics of the German funding system, and the principles of DFG funding.

JUnQ: The DFG is the largest research funding organization in Germany. What share of scientists in Germany is applying to the DFG? Is third-party funding indispensable?

Königs: A competition for funding based on scientific criteria is an efficient way to allocate scarce resources in the interest of the best research. So, yes, third-party funding is an essential factor in maintaining a first-class research base. However, it can only work in this way if there is sufficient basic funding at universities, e.g., to test new ideas, prepare projects, and tide over funding gaps. We estimate that more

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than 60% of all researchers apply for DFG funding. There is a gradient from the life sciences to the humanities, but it is not as steep as one might expect.

JUnQ: Over the past decades, the level of regular funding has been steadily reduced at German universities. Third-party funds were icing on the cake, but are now considered an indispensable pillar for most research.

Königs: This is correct. The pressure on researchers to apply for third-party funding is further increased by the fact that many universities make the size of third-party funding a parameter in allocating internal funds and salary decisions.

JUnQ: How does the impact of this change differ for different scientific fields?

Königs: The effect is notable particularly in those disciplines, in which many researchers were able to work without much additional funding, e.g., the humanities.

JUnQ: Does the increasing relevance of third-party funds imply that the funding agencies guide science more and more?

Königs: Sadly, this is a real danger. An agency worth its salt will, however, ensure that there is always room for non-programmatic research.

JUnQ: There is an astonishing variety of DFG funding programs. Other funding institutions offer further programs and scholarships. As a young researcher, I am overwhelmed, if not confused by this variety. How do I find the program that suits my needs?

Königs: First, consult our website, especially the part on Research Careers. Second, call the program director responsible for your field of research – also on our website – and ask for advice. It helps to be specific about your needs. And finally, ask an experienced colleague.

JUnQ: How came the variety of DFG programs into being?

Königs: The DFG's portfolio has developed steadily since 1951 with each new program corresponding to a specific need. Some programs were so successful that they stayed, long after the particular need had disappeared (e.g., the Heisenberg program, installed in 1977 in anticipation of a large impending retirement wave). Some were imitated (the Emmy Noether Program has many similarities with ERC Starting Grants) and thus are not as singular as they were at their inception. Some have been ended. By and large, we feel we can give good reasons for upholding each of our programs.

JUnQ: The DFG provides ample and very detailed instructions on the requirements a proposal has to meet. There are even people who offer seminars on how to set up a DFG proposal. Is it a science on its own to prepare a scientific proposal?

Königs: Not a science, but perhaps a skill. The DFG grants considerable sums of taxpayers' money and it has a responsibility to ensure that taxpayers' concerns are observed in doing so. This ranges from what the money is spent on (only on research-related costs, e.g., not on heating, rent, or Ferraris) and whether laws and regulations are observed (e.g., concerning experiments on humans or benefit sharing in biodiversity research) to pay scales for employees involved in the projects. The proposal is a sensible time and place to check this, which is why we require the corresponding information at this stage.

A second aspect is that each proposal enters a competition for scarce funds and must be evaluated by other researchers whose time is valuable, too. Standardization ensures that the playing field is level and that the reviewers know where in a proposal they have to look for a specific piece of information. They must also be able to determine whether the funds requested are adequately calculated.

This said: We are determined to fund good projects, not just well-written proposals (even though the two are quite well correlated) and we try hard to "keep things as simple as possible – but not simpler", to quote Albert Einstein. We have almost completed a modularization of the proposals in all our programs and we have also managed to reduce restrictive specifications on the funds granted.

JUnQ: When an applicant submits a proposal, he or she uses the forms provided by the DFG, structures the proposal as suggested by the DFG, and assigns it to a subject area predefined by the DFG. One could worry that this influences the way we think about science and that it promotes conformism. How does the DFG cope with these issues?

Königs: I do not share this concern. The apparent complexity in proposal writing is one of form, not content. The seeming limitations are those of the project format. We do expect researchers seeking our funding to be able to formulate their idea, to put it in the context of research already done, to explain how they have prepared the project, and how they will set about investigating. This is reasonable and generic and in no way pre-structures scientific investigation. A lot of the thinking, perhaps in a more unstructured mode, will have to be done beforehand.

Also, proposals have not become more uniform in terms of content over the past decades. We have, however, the impression that increasing competition is honing the proposal-writing skills across many disciplines.

JUnQ: What about a scientific idea that questions the boundaries between scientific fields? Will a proposal that fits into the established structures not have an inherent advantage in the review process?

Königs: The DFG is very much aware of this problem. We believe we are equipped to deal with it in several ways. Since we are responsible for funding in all areas of research, we do not have to ask whether any proposal would fit better with a funding agency in another area of investigation, and we have access to competent reviewers in every subject. Our procedures ensure that we consult reviewers from all fields of research relevant to a proposal, usually also with some experience in boundary-crossing research. Then, if necessary, we involve more than one disciplinary panel in assessing the proposal and its review. The final responsibility for funding decisions rests with our Grants Committee, whose members represent all disciplines. A recent survey indicates that boundary-crossing proposals as a rule do not have significantly differing success rates.

JUnQ: From an international perspective, it is rather an exception that one single institution – the DFG – is in charge of funding all disciplines.

Königs: There is an additional dimension to this observation. In Germany, too, research funding is the task of many organizations: The Max Planck Society, the Leibniz Association, the Helmholtz Centers, the Fraunhofer Society, etc., all of which fund a wide range of fields. The division is not by discipline but by type and mode of research.

This approach is, however, not entirely exceptional. In Austria, France, and Switzerland, there are prominent examples of similar agencies. I can only speculate on the reasons for the structure in Germany. Perhaps it has to do with the German perception of "Wissenschaft", a term that has no counterpart in English, and its connotations of the indivisibility of research and scholarship.

JUnQ: What are advantages and disadvantages of the German system?

Königs: An advantage is certainly that all research across disciplinary borders can be considered without encountering institutional barriers. It broadens the scope for competition across the whole range of research, avoiding external decisions allocating funds to certain areas. Following a principle of conservation of complexity, the disadvantage is that institutional barriers arise if there is a need for concerted action – nationally or internationally – in a certain area, in which university researchers and those from the research-performing organization are involved.

JUnQ: Do all disciplines feel comfortable with the current situation? Or have there been attempts to split up the DFG or to establish separate funding agencies for certain fields?

Königs: Basically all disciplines accept the situation. The DFG also makes special efforts to respond to the research needs of individual communities, e.g., in the Förderinitiative Geisteswissenschaften (Humanities Research Funding Initiative). Sporadically, some discipline may consider going it alone, but these attempts are half-hearted at best and soon peter out.

JUnQ: A recent survey by the Institute for Research Information and Quality Assurance[3] found that an increasing share of German scientists thinks that money always accumulates in the hands of the same people. Is this impression correct?

Königs: It would be more precise to state that an increasing share of German researchers *feel* money always goes to the same people. I have too few data to give an accurate answer, but my impression is that the number of recipients of DFG grants is growing. I am also not sure I agree with the implication that giving the best researchers a larger share of funds is a bad thing.

JUnQ: At core of DFG funding are individual research grants, which can be applied for regardless of the subject. Do similar programs exist in other countries? My impression is that funding agencies in other countries spend a larger share of their money on programs with predefined subjects.

Königs: All self-respecting funding agencies have a program in responsive mode, which can, indeed, vary in size and importance. Few, perhaps, are as programmatically committed to response mode as the DFG, but this has to be seen in the context of the German funding structure, in which other actors, e.g., the Ministry of Research, put substantial funding into directed research.

JUnQ: It has sometimes been claimed that the importance of individual research grants is dwindling. Is this true? How do approval rates for individual grants compare to those in other programs?

Königs: The Individual Grants Program is still the DFG's defining program, and it is unrivaled in its openness and flexibility. With a slightly rising share of more than one third, it is the largest item in the DFG's budget. It is also very popular and the program most open to the pressures mentioned above, so that demand is outstripping supply, leading to falling approval rates over the years. Our current rate – about a third of all proposals are at least partially funded – is still high by international standards. A comparison with other programs is difficult, for instance because unlike individual grants they are evaluated in a two-stage process.

JUnQ: Are individual research grants of greater importance for certain disciplines?

Königs: Individual grants are an important source of funding for all disciplines. For different reasons it seems that physics, mathematics, and mechanical engineering rely more on collaborative programs and thus less on individual grants than other fields.

JUnQ: My perception is that funding through "special" programs like the Excellence Initiative is considered more prestigious, at least in public. Why are regular grants not as prestigious?

Königs: Big quasi-institutional grants are more visible and better news than small ones with hard-to-understand topics. As far as the public is concerned, that does not worry me. Among researchers, individual grants have high prestige; I sometimes wish university leadership would hold them in higher esteem.

—Thomas Jagau

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[3] An institute founded in 2005 by the DFG in order to explore the impact of funding programs and political actions on science and the incentives and deficits of the German scientific system.

Chemistry and Freedom – a Historical Approach

Dr. Klaus-Dieter Röker[1] received his doctoral degree in chemistry in 1974 from TU Clausthal. After his business career with Continental AG and TÜV NORD AG (Chairman of the Management Board) he followed his interest in the history of chemistry. From 2007 to 2010 he had lectureships for the history of chemistry and organic chemistry at the Stiftungsuniversität Hildesheim. 2012 he published the non-fiction book "Chemische Zeitreisen".

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Science in danger – shifting the feeding bowl for scientists. With this spectacular headline in October 2012 the internet magazine SPIEGEL ONLINE pinpointed the increasing importance of utilitarianism in research. What is it good for? According to Professor Gerd FOLKERS (*1953, professor for Pharmaceutical Chemistry) this ubiquitous question is limiting the freedom of the scientists to follow their own ideas. At a first glance a discussion on the interrelation between chemistry and freedom seems to be rather artificial. But at a second glance it might be worthwhile to reflect on. Might be that a short look into history is appropriate.

Chemistry is a rather young science. The origin is lying in the fog of history. First contours of alchemy in the antique western world are visible at the beginning of our era at the Museion, the famous center of science in Greek-Egypt Alexandria. Alchemy developed during the centuries into a hybrid consisting of mystic-mythic visions interspersed with empirical scientific knowledge. For understandable reasons this pseudo science alchemy temporarily had a bad reputation, which resulted in numerous bans during the centuries. Alchemy and later on chemistry was not independent of external influences, as are religious, ethical or political structures. Since the very beginning, alchemy was strongly affected by religion in the Christian world as well as in the Islamic sphere. The old antique conception of atoms is a typical example. Due to the unbelievably bad image of the Greek philosopher EPICURUS ($\approx$ 341 – 271 B.C.E.) in the Christian church the concept of atoms was vigorously refused until the priest and scientist Pierre GASSENDI (1592 – 1655) succeeded in achieving compatibility with Christian doctrines. It was only since the Renaissance that revolutionary masterminds like Robert BOYLE (1627 – 1691, who questioned the principles of alchemy) and Georg Ernst STAHL (1659 – 1734, who developed the phlogiston theory) prepared the long way to modern scientific chemistry and enabled Antoine Laurent de LAVOISIER (1743 – 1794, oxidation theory) and John DALTON (1766 – 1844, atomic theory) to become founders of modern chemistry. But still in the 20th century non-scientific doctrines were restricting research. In the Third Reich quantum chemistry was regarded to be Jewish and in the Soviet Union Darwin's theory was banned because of non-compatibility with communism. Even nowadays are there noticeable influences, just to mention the stem cell discussion in Germany or the influence of creationism in the U.S.

Obviously external influences are affecting the limits of free research but this is true for intrinsic constraints too. At a certain state of consolidation after controversial discussions the scientific community is agreeing on a common view on the interpretation of phenomena observed in the nature: Then a theory is generally accepted and defined as the valid state of science. According to Thomas Samuel KUHN (1922 – 1996, physicist, philosopher of science) this is a paradigm. A paradigm has a considerable inertia towards change. This behavioral pattern is making sense because it is representing something like a first hygienic filter. New ideas coming up which are not in accordance with the paradigm will be questioned, typically refused at first and combated pertinaciously until a new paradigm replaces the old one. Thinking outside the box is always a challenge and a risk for the established scientific community. Papers in scientific journals are accepted more readily when the editor and the evaluating committees are convinced that the contribution is representing the valid state of science. The scientific circumference has a strong impact on the acceptance of the challengers of existing paradigms. In the history of chemistry innumerable papers have been refused or have simply been neglected after fortunate publication. In case the scientist is not member of an established and recognized group problems increase, even more so when his scientific background is not adequate. 1875 van't HOFF (1852 – 1911, first Nobel price 1901) published his revolutionary ideas on stereochemistry as an unknown professor of a veterinary medical school in Utrecht. He was strongly attacked by the influential and famous chemist August Wilhelm KOLBE (1818 – 1884), and considered to be brazen simply by attempting to solve one of the major problems of chemistry. Van't HOFF was lucky to find a mentor in the chemical establishment. But for most of these unfortunate authors, personal freedom of science is restricted, and career and financial resources are negatively affected. Chemical history knows numerous chemists of this kind. The unlucky ones disappear from scientific life; some of them reappear as a footnote in books on the history of chemistry when a luckier one finally proves to be strong enough to overcome the paradigm. Selected examples are Samuel Shrowder PICKLES (1878 – 1962, who correctly recognized the structure of natural rubber) or Alexandre-Emile Béguyer de CHANCOURTOIS (1820 – 1886, who proposed a precursor of the periodic system of elements). But there were also strong characters like the Nobel award winners Henricus Jacobus van't HOFF (1852

– 1911, stereochemistry), Alfred WERNER (1866 – 1919, complex chemistry) and Hermann STAUDINGER (1881 – 1965, polymer chemistry) who successfully fought old paradigms and finally won their battle.

For research a very simple tool is required: money. Money sometimes seems to be a synonym for freedom. In the very first days of scientific chemistry some nobles such as Robert BOYLE, Henry CAVENDISH (1731 – 1810, discovered hydrogen), and Antoine Laurent de LAVOISIER were extremely successful. They had a decisive advantage compared to others: they were extremely rich. It was not until after the start of the 19th century that chemistry was established at universities as an independent branch of natural sciences, and only since then financial resources have become available for less privileged people. Scientific talents at a broader scale now also had the chance to receive an adequate education.

After the synthesis of Alizarin in 1868, the chemical industry started to recognize the economic value of research. In Germany a dual structure of academic and industrial chemical research interacted and collaborated intensely. A chemist who accepted the benefits of industrial wages consequently had to pay the price in form of a restricted area of applied research and consequently enjoyed less academic freedom. Even now research at university is not totally independent of financial influence as there is frequently external influence due to common projects. Universities are advised to acquire third party funds. They are gaining the financial resources for research; however they have to consider the interests of the partner. This is valid for both public funding and basic research. As Prof. Gerd FOLKERS argued there is a general interest to invest in research projects with a visible return on invest. And additionally it is not at all arbitrary for which projects you are looking for money. The experience teaches that projects are granted much simpler when the topic is in concordance with a scientific mainstream or with a current scientific fashion trend.

But with respect to one important aspect, freedom has been achieved. At the time being everyone who is fulfilling the preconditions for the study of chemistry has the chance to become chemist. Today there are rather equal numbers of male and female students. Reviewing the tables of Nobel Prize laureates you will find astonishing figures. Through today there are more than 150 male laureates but only 4 female: Marie CURIE (1867 – 1934, Nobel prize 1911 for the discovery of the elements Radium and Polonium), Irène JOLIOT-CURIE (1897 – 1956, Nobel prize 1935 for the discovery of the artificial radioactivity), Dorothy CROWFOOD HODGKIN (1910 - 1994, Nobel prize 1964 for the structure determination of vitamin B12) and Ada YONATH (*1939, Nobel prize 2009 for her studies of the ribosome). The history of the role of women in natural science is frustrating and disappointing. The famous revolutionary German reform of universities in 1810 by Wilhelm HUMBOLDT (1767 – 1835, philosopher and government official) was a catastrophe for the education of women because the reform defined the preconditions for academic studies: the examination Abitur was introduced as a qualification precondition for the universities. But the school system in Germany did not provide the Abitur for women and it became available only at the end of the 19th century. German women were systematically excluded from universities for nearly 100 years. Nevertheless, for those who were able to cope with these preconditions similar to the Abitur outside of Germany, the doctorate in Germany was possible. Outside of Germany, the situation was slightly more liberal. Through this method, in Julija Wsewolodowna LERMONTOWA (1847 – 1919) in Göttingen became the first woman with a chemical doctor degree in 1874. In 1900 the first German woman with a doctor degree in chemistry was Clara IMMERWAHR (1870 – 1915), who obtained access to the doctor examination via a complicated method. She became teacher, which was possible for women at this time. By means of this qualification she was accepted only as a visitor at University of Breslau. With that status, she passed successfully the Verbandsexamen (comparable to the diploma in chemistry). Clara IMMERWAHR was a tragic personality. She married Fritz HABER (1868 – 1934, Nobel price for Chemistry 1919). She became very depressed by her husband's activities in World War I, as well as her own disappointing scientific career. She ultimately committed suicide.

In the first half of the last century, the number of female students in chemistry still remained small. When the author studied at the end of the 1960s, just 3% of the students were female during his first semester at his university. These few brave women in the first lecture were not addressed warmly and were told "You should consider that you are blocking rare laboratory capacities for male students". The total average number of female students attending German universities at that time approximately was around 10%. Beginning in the mid 1970s university attendance by females started increasing, with approximately 30% in attendance today. In this regard gender discrimination does not exist any more at German universities.

For natural scientists, freedom is usually associated with Gibb's phase rule and the degrees of freedom. There are obviously other aspects as well.

—Dr. Klaus-Dieter Röker

More information about this subject can be found at:

[1] http://www.spiegel.de/wissenschaft/medizin/forschung-warum-der-utilitarismus-die-freiheit-der-forschung-bedroht-a-860141.html (last access 25.02.2013, 16:00h)

[2] William H. Brock, Viewegs Geschichte der Chemie, Friedrich Vieweg & Sohn, Braunschweig/Wiesbaden **1977**, ISBN 3-528-06645-8

The Limits of Freedom in Science – Dual Use Research

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Science has always been about breaking boundaries, but can scientists go too far? Are there boundaries that scientist should not overstep? And if so who defines these boundaries? A critical area is so called dual use research that is aimed at civilian and peaceful applications, but has also potential uses in war and terrorism. The most prominent example is possibly nuclear technology, which can be used to construct nuclear power plants on the one hand and weapons of mass destruction on the other. But also everyday technologies like the global positioning system (GPS) are problematic. Here they help me to navigate my car through an unknown city, but in crisis regions the same technology is used to effectively guide missiles that kill people. Research on dual use topics is often controversial and in the end it boils down to the questions: Is the (potential) benefit greater than the risk? And where does the freedom of researchers end?

A clear example, where a product for civil use was misused for the mass murder of people, is the infamous Zyklon B – a mixture that can release highly toxic hydrogen cyanide gas. Its original use was pest control in ships and factories, but in World War II it was used – alongside carbon monoxide – in German concentration camps to murder the Jewish inmates. Around 1000 people were locked up in one gas chamber at once with Zyklon B, which released its deadly gas after the addition of water, leaving the inmates to fight for their lives – a fight they could not win.

Sure, I can condemn the discovery of Zyklon B in hindsight, but only because I know of its extreme misuse. Its original use as a pesticide helped a lot of people by protecting food and other goods from pests.

Much more recent examples for dual use research – where we do not yet know if they will be misused – come from the field of biotechnology. The NSABB (National Science Advisory Board for Biosecurity, USA) has identified seven categories of research that they call "dual use research of concern", noting that this research needs to be under close observation:[1]

1. Enhancing of the harmful consequences of a biological agent or toxin.
2. Disrupting of immunity or the effectiveness of an immunization without clinical and/or agricultural justification.
3. Conferring to a biological agent or toxin, resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin, or facilitating their ability to evade detection methodologies.
4. Increasing the stability, transmissibility, or the ability to disseminate a biological agent or toxin.
5. Altering the host range or tropism of a biological agent or toxin.
6. Enhancing the susceptibility of a host population.
7. Generating a novel pathogenic agent or toxin, or reconstitute an eradicated or extinct biological agent.

In the last years an example of point 5 – the creation of a mutated bird flu virus, which can be transmitted between mammals by the group of Ron Fouchier – has been under controversial discussion. The question is: Why would scientists create such a virus and should this research be allowed at all?

Avian flu – or more specifically A/H5N1 – has been around for a long time. Local outbreaks of low pathogenic A/H5N1 have been reported as early as 1959 in Scotland. But it was not until 2005 that a highly pathogenic strain spread over Asia and Eastern Europe followed by Western Europe and Africa in 2006. With tens of millions of birds killed by the virus and hundreds of millions killed by farmers to prevent its spread, scientific interest in the virus rose.

The controversial work of Ron Fouchiers group was first presented on a conference in September 2011 and in November of the same year it was no longer only discussed in scientific circles. The discussion had reached the public with headlines like "Alarm as Dutch lab creates highly contagious killer flu"[2] and so it was not surprising people were concerned about the research to say the least. In response to this public fear, 40 scientists signed a moratorium to pause A/H5N1 research in January 2012. This moratorium was initially intended to last 60 days and give the scientific community, as well as the public, time to evaluate risks and benefits of the research, but as the debate intensified it was extended indefinitely. In June 2012 the results of the A/H5N1 research (obtained before the moratorium) were published with all details, accompanied by critical as well as supporting voices.[3] In January 2013 the moratorium was ended and bird flu research continues since then.

Now how do I feel about this research? Mammals can already be infected with H5N1 and there are 360 confirmed deaths associated with the virus. But until now the virus lacks the capacity to be transmitted between humans. However, the researchers showed that a few mutations – that could occur in nature – can enable infections between mammals. The researches argue, that we can take countermeasure like the creation of vaccines only if we have this infectious virus. Of course I want to be prepared as good as possible for a virus like that, but do I want to *create* a threat to fight it? What if the virus falls into the wrong hands or somehow gets out of the laboratories?

This illustrates the dilemma of dual use research quite clearly: Results from this type of research can be used for good in the right hands, but can bring great destruction in the wrong ones. This is problematic for the researchers, not because they might aim for a destructive application of their results – most of them do not – but because once the knowledge is there, it is no longer up to them how it is used by others.

It is clear that this kind of research has to be monitored and controlled, and the public debate caused a stronger focus of policy makers in the US and the EU on the issue.

For example the US Department of Health and Human Services (HHS) proposed a policy specifically aimed at "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products or technology that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, material or national security." But is dual use research always unwanted?

Of course not: Funding agencies like the US Defense Advanced Research Projects Agency (DRAPA) specifically fund military research, whose results might never the less be used for civilian purposes – like better prosthetic limbs. Dual use always goes both ways. Recently there has been a push by the US senate to reform the way NSF (National Science Foundation) proposals are reviewed focused especially on the *application* of science. This could lead to a stronger focus on the use for military purposes.

Many questions remain: What is allowed in science? Who should decide what research is beneficial for society or not? Should science, which is not in the best interest of society, be censored and forbidden? How do we make proper risk/benefit assessments for something completely new?

History has seen much controversial research and it is often impossible to predict how new inventions will affect our life for better or for worse. As scientists who insist on our freedom, we of course have to take our responsibilities very serious and make sure – the best we can – that our work benefits society.

The best way to achieve this goal is to set up very clear rules of what is ethically acceptable and what is not. We need to make sure that resources are distributed accordingly and that these rules are followed. In controversial situations we might need time to think about what our results imply for society. In these cases a research time-out and even (temporal) (self-) censorship might give us time to look at our research from different angles.

But are we not robbing us of our own precious freedom in this way? Well not really, we are only taking the freedom from those who do not adhere to ethical standards. In my opinion, freedom is a very valuable asset, but the freedom of scientists ends where their discoveries cause harm to others.

—David Huesmann

Read more:

[1] http://oba.od.nih.gov/biosecurity/biosecurity_documents.html
[2] http://www.independent.co.uk/news/science/alarm-as-dutch-lab-creates-highly-contagious-killer-flu-6279474.html
[3] S. Herfst, E. J. A. Schrauwen, M. Linster, S. Chutinimitkul, E. de Wit, V. J. Munster, E. M. Sorrell, T. M. Bestebroer, D. F. Burke, D. J. Smith, G. F. Rimmelzwaan, A. D. M. E. Osterhaus, R. A. M., *Science* **2012**, *336*, 1534–1541.

Questions of the Week

The Journal of Unsolved Question presents a "Question of the Week" on its homepage every week. Set up and formulated by the members of the editorial board, the main purpose of the "Question of the Week" consists in intriguing the reader by presenting topics of ongoing research. "Questions of the Week" published so far cover a wide variety of scientific fields, but share the feature to be of certain importance to several disciplines.
In the following, we present selected "Questions of the Week" from the last six months.

Sweet Dreams are Made of This.

by Stefan Kuhn

Dreaming is a natural part of sleeping. Every time we sleep, we dream, even though sometimes we may not remember what that dream was about or that we dreamt at all. This raises the question what the purpose of dreaming is and why we dream at all. There are many theories on this topic giving different purposes, such as learning reinforcement or rehearsing threat perception. After all, it cannot be said, which theory will prove as right, thus leaving the question why we dream unanswered.

Read more:

[1] http://www.scientificamerican.com/article.cfm?id=tetris-dreams

[2] A. Revonsuo, *Behav. Brain. Sci.* **2000**, *23*, 793–1121.

Do Clocks Influence our Actions?

by David Huesmann

Well, the answer to this question seems to be pretty obvious. Of course they do! Mine tells me when to get up in the morning, when to go to work, and so on until it tells me to go to bed again. But is there maybe a more subtle way they influence our decisions.

Pocketwatch.[1]

Clockwise and counter clockwise – there is no argument about which way is which. That is because all clocks (with some notable historical exceptions like the astronomical clock in the Münster Cathedral) describe a right-handed circle. The reason for this is that the clock's predecessor, the sundial, was invented in the northern hemisphere, where the shadow on the sundial moves in a semi-circle from left to right.
A study now suggests that the motion of the hands of a watch might influence us more than we thought. The authors hypothesized, that clockwise motion is associated with the future, making a person more open to new experiences, while counter clockwise movement is associated with the past leading to more conservative choices. Further, clockwise movement is often associated with progression towards a tools purpose, like starting a car or turning up the volume. In two experiments participants were manually performing rotational movements. The participants of the clockwise group described new symbols as more pleasant and described themselves as more open. Similar results were also observed when participants only watched a rotating square. Even when people, who thought they were participating in a different experiment, were asked to choose sweets as a reward, they preferred more (un)usual flavors depending on which way they could rotate the plate on which the sweets were served. It is noteworthy that this effect did not depend on the handedness of the participants.

The question remains: Is the openness to new things really due to our perception of clockwise movements bringing us to the future? Or is it something more primal build into our brains and animals will behave in a similar manner? And finally, once all clocks are digital, will they give us our free will back?

Read more:

[1] S. Topolinski, P. Sparenberg, *Soc. Psychol. Person. Sci.* **2011**, *3*, 308–314.

[2] http://www.psychologytoday.com/blog/unique-everybody-else/201211/turning-the-wheels-the-mind

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[1] The image was uploaded by Roger McLassus to http://upload.wikimedia.org/wikipedia/commons/7/7c/Pocket_watch_with_chain.jpg

What is the Best Way to Eat Candy?

by Stephan Köhler

> "Science and everyday life cannot and should not be separated."
>
> – Rosalind Franklin

While Franklin was talking in a much broader way about the use of science to further human wellbeing, science can also be applied to the smaller problems of everyday life. Sometimes even to problems that no one even suggested need a scientific explanation at all. Effects like the spilling of coffee[1] or the crumpling of sheets.[2] Things that everybody can relate to.

Girl eating candy.[2]

To sustain the mental effort of solving such puzzling problems the scientists need energy. If the scientists in question have a sweet tooth this energy can conveniently be provided by the sugar contained in candies and so it was only a matter of time until the next everyday effect found its way into a scientific journal: The process of eating candy.

In a recent paper by Windisch *et al.* the question of how candies dissolve is addressed for the first time.[3] A simple model for the dissolution of a spherical candy is proposed. This model represents the condition of moving the candy gently in your mouth without applying too much pressure. In this case the spherical shape of the candy is preserved and the lifetime of the candy is extended. You can enjoy your candy longer.

This happens because a sphere has the best volume to surface ratio and the surface area is what limits the dissolution under these conditions. The larger the surface area, the faster the candy will dissolve. Accordingly, if you break the candy with your teeth the bits will dissolve much faster. It is of course a matter of personal taste if one prefers to have the sugar rush from dissolving the candy in a short period of time or the slow sweetness from a gradually vanishing candy.

The study did not include any specific chemical effects and one can surely think of more than the two ways presented to eat candies. Additionally, candies come in many forms besides homogeneous spheres. So there are many more variables to consider until the optimal candy eating strategy for each person is found. But to quote the authors:[3] "[. . .] the best thing to do when eating a candy is to forget about these considerations, since they draw your attention away from what candies are made for – enjoyment."

Read more:

[1] H. Mayer, R. Krechetnikov, *Phys. Rev. E* **2012**,*85*, 046117.
[2] E. Cerda, L. Mahadevan, *Phys. Rev. Lett.* **1998**, *80*, 2358–2361.
[3] A. Windisch, H. Windisch, A. Popescu, *Phys. Educ.* **2013**, *48*, 221–229.

Why Does the Mass of the International Prototype Kilogram Change Over Time?

by Andreas Neidlinger

There are seven basic units of measure defined by the système international d'unités. They are called SI units and every other measuring unit is derived from them. Those seven units are:

- Temperature in Kelvin (K)
- Time in seconds (s)
- Length in meter (m)
- Mass in kilogram (kg)
- Luminous intensity in candela (cd)
- Amount of substance in mole (mol)
- Electric current in ampere (A)

Those units need to be defined in a very universal and easy way so that each and every person on the planet uses for example the same length for a meter, the same amount of time for a second, or the same mass for one kilogram. But how can you do that? For instance "The metre is the length of the path travelled by light in vacuum during a time interval of 1/299,792,458 of a second" as the International System of Units tells us. That puts us in need of a definition of the second, which is "(. . .) the duration of 9,192,631,770 periods of the radiation corresponding to the transition between the two hyperfine levels of the ground state of the caesium 133 atom."[1] Very cryptic, but I am sure the persons who made this definition knew what they were doing.

Anyhow, if we take a look at the kilogram, we find something peculiar, namely "The kilogram is the unit of mass; it is equal to the mass of the international prototype of the kilogram." This tells us that the actual definition of the kilogram might change over time, since it is defined by a physical object rather than by a process or concept, which is unaffected by its surroundings. There is one kilogram pro-

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[2] The image was uploaded by Kyle Flood to http://upload.wikimedia.org/wikipedia/commons/2/2d/GirlWithLollipop.jpg

totype plus six sister kilograms which were created in 1889 of a platinum iridium alloy. They sit in an air conditioned vault close to Paris and the prototype is to the day the definition of mass. Since it is very “dangerous” for our definition to rely on a single physical object, stored in a single place, 40 other kilograms were made. They did not have the exact same weight, but the offsets were recorded. To make sure that the mass – and so our definition – does not change over time, those other kilograms were taken to locations around the globe to average potential external influences, and furthermore to be used as national kilogram standard for the different countries.

When those kilograms were brought together about 50 years later to check their masses, it was found out that despite identical storage conditions and identical material of the kilogram cylinders, their masses had changed in respect to the kilogram prototype. Not even the sister kilograms stored together with the prototype kept their masses. The process behind that is not clear and more or less a matter of speculation. That, in fact, is a big problem, because several other basic SI units depend on the kilogram, not to mention other non-basic units.

Since it is certain that something needed to be done about the problem of the changing definition of the kilogram, the Avogadro Project was brought to life. Its aim is the definition of the kilogram by the Avogadro constant ($\mathrm{N_A}$) using a perfect sphere of pure silicon-28. After producing said perfect sphere of single crystal, isotopicsally pure silicon-28, its diameter can be used for accurate calculation of the Avogadro constant, allowing the definition of the kilogram in the next step.

In the end, the question about the changing masses of platinum iridium alloy cylinders remains open. But it is great to see that one can “solve” it by changing the subject.

Read more:

[1] http://www.bipm.org/fr/si/si_brochure/general.html

[2] http://www.ptb.de/cms/de/publikationen/zeitschriften/ptb-news/ptb-news-20103/das-neue-kilogramm-kommt-naeher.html

[3] http://www.youtube.com/watch?v=ZMByI4s-D-Y

What Is the Best Time For the Annual Spaghetti Harvest?

by Stefan Kuhn

Probably every spaghetti farmer knows, that the most anxious time for the annual spaghetti harvest is at the end of March, since all over Europe severe frost can impair the flavor of the spaghetti. In case you wonder if this is not just a joke . . . you are right! The documentary of the BBC about the annual spaghetti harvest is indeed a joke, in fact it’s an April Fools’ joke. It was the first April Fools’ joke on television and was broadcasted in 1957. Since everyone is familiar with the tradition of playing jokes on friends or colleagues at the first of April, the question comes up, where this tradition has its origins and if the first April Fools’ joke is known.

In Grimms Deutschem Wörterbuch from 1854 a definition of the word April Fool, “Aprillsnarr”, can be found. There is also evidence for the expression “to play an April Fools’ joke on someone” even earlier. It can be found the first time in 1618 in Bavaria, Germany, but it is believed, that the tradition dates even further back.

There are a lot of speculations about the origin of the April Fools’ joke tradition, but many are believed to be unlikely. For instance the changeful weather in April serves as an attempt to explain the origin, but the tradition is also known in regions where the weather in April is stable. A more possible explanation is a story about Henry IV who received a letter from a sixteen year old girl, inviting him to a rendezvous, but when arriving at the meeting place the royal household as well as his wife appeared, expressing their gratitude that he accepted the invitation to the ball.

Quite a likely explanation describes the April Fools’ joke as a spring tradition, where the April Fool represents the powerless winter, with whom the advancing summer can do whatever he pleases. The present-day April Fools’ joke could be a variation of this. Another quite reasonable, though completely different attempt to explain is to associate the first of April with a religious fatal day. The first of April is believed to be the birthdate of Judas and it was obvious, that the day the man who betrayed Jesus was born must be a fatal day. It then became common to play jokes on people on that same day to avoid more harm.

A lot more religious aspects as well as likely or unlikely explanations for the April Fools joke can be found, but hard evidence for one of them is still clearly missing.

Read more:

[1] http://news.bbc.co.uk/onthisday/hi/dates/stories/ april/1/newsid_2819000/2819261.stm

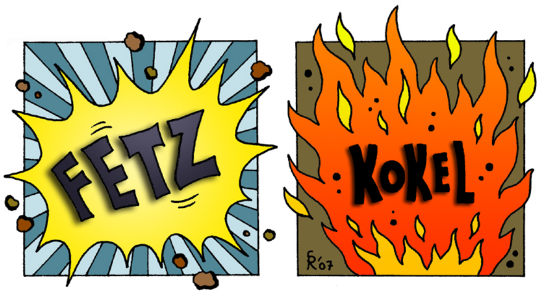
[2] http://www.religioeses-brauchtum.de/sommer/aprilscherz.html

[3] J. Grimm, W. Grimm *Deutsches Woerterbuch*, Bd. 1, Leipzig 1854.

What Is the Origin of Onomatopoeia?

by Stefan Kuhn

The first question to ask here is: What is onomatopoeia? I am sure that everyone has heard. To me it is best known from my childhood, for example from Batman movies: bam, smack, pow, crunch. The longer I think about it, the more examples come to mind, for instance in pop art, internet forums, different comic books such as Donald Duck or even in songs. Have you heard of papa-oom-mow-mow from the Rivingtons? Hence, onomatopoeia is the imitation of natural sounds. You might wonder why all those common examples can be found in a newer period of time, and so do I. So where does onomatopoeia come from?



Onomatopeic expressions.[3]

Onomatopoeia can be found in a lot of different fields. It is very widespread in the aforementioned comic speech, as a rather new development, or in child's speech, especially when it comes to animal sounds. Comic speech often uses onomatopoeia, for instance sigh, clap, squeak, but those are rather classified as a subgroup, which find their origin themselves in onomatopoeia. However, animal sounds have had a great influence on the onomatopoeic word formation. Here it is interesting to note, that this process is relatively independent of the language, for instance the cockcrow is in English cock-a-doodle-doo, in Spanish quiquiriqui and in German kikeriki.

In literature, onomatopoeias are used as stylistic devices, such as metaphors. They emphasize parts or intensify certain expressions, such as the alliteration. Therefore, not only single onomatopoeias are used, but connections of several words and even other stylistic devices are employed. An example for this is a verse by Ovid, where he emphasizes the croaking of frogs: quamvis sint sub aqua, sub aqua maledicere temptant. Even without translation one can imagine the sound, frogs make.

There are even more traces for onomatopoeia that reach even further back in time so the question remains: Where lies the true origin of onomatopoeia? Did a man in primitive times, when seeing an animal, imitate the sound of that animal in a way so that it, centuries after him, became an expression that we use today? And furthermore: How was it possible to associate that sound of nature with an articulated sound?

Read more:

[1] K. Buehler, *Sprachtheorie: die Darstellungsfunktion der Sprache*. Jena: Fischer, 1934.

[2] F. Mauthner, *Onomatopoeie der Betonung*. (http://www.textlog.de/31299.html)

[3] F. Mauthner, *Onomatopoeie der Etymologie*. (http://www.textlog.de/31298.html)

Why Do We Use the Decimal and Not the Duodecimal System?

by Robert Lindner

In fact, we use both systems. I surely don't have to explain the use of the decimal system. However, the use of the duodecimal system, i.e. counting to the base of 12, is hidden in our everyday life. When we are measuring or expressing time intervals, we do so by dividing 1 h by 60 to obtain minutes. For further accuracy we divide the minute again by 60 and call it a second. This division by 60 is in fact based on the duodecimal system, e.g. 5*12=60. If we want to measure time intervals below 1 second, we switch back to the decimal system.

The origin of the decimal system is due to the ten fingers, that each human has. But the numbers 12 and 60 are also present on our hands. If we use our thumb to count the single digits of all four of the remaining fingers, we can count to 12. After that we can use one finger of the other hand to indicate that we've already counted to 12 once. If we proceed in this manner, we can count up to 12 digits * 5 fingers, which sums up to 60.

During the french revolution, the supporters of the decimal system set the base for todays SI-unit system. Some purists among them even used decimal clocks and weeks consisting of 10 days.

Nowadays, nearly worldwide the decimal system is used. However, there are quite a few people that support the usage of the duodecimal system, as the number of divisors for 12 is higher, than for 10. 12 has 1,2,3,4,6 and 12 as divisors, whereas 10 only has 1,2,5 and 10. They propose that, when changing to the duodecimal system, mathematics would remain the same, but everyday applications would be easier. One third would not be expressed as 0.3333, but as a convenient 0.4.

Read more:

[1] http://www.dozenal.org

[2] G.Ifrah, *Universalgeschichte der Zahlen*, Cologne: Glb Parkland, 1998.

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[3] The image was uploaded by Simon Rehbach to http://upload.wikimedia.org/wikipedia/commons/7/72/Onomatop%C3%B6ie.jpg

What Are the Costs of Ecosystem Services?

by Stephan Köhler

In recent years it became clear that humans have a significant impact on our planet. The publicly most discussed topics in this regard are climate change and conservation, two topics that are not independent, e.g. forests act as carbon sinks but become more vulnerable to pests in a warmer climate. Together with increased land use by humans more and more habitat for native species is lost. In addition a globalized economy frequently introduces invasive species that compete with the native species. These effects combined lead to extinction rates that are currently estimated to be orders of magnitude higher than the background rate.[1]

Flower with Bee.[4]

To counter this global extinction event many efforts have been taken to save species. But the question always arises why one should bother to do so. The answers are varied and range from ethical reasons (other species have the right to live) to economical considerations (some plant might hold the next "cure for cancer"). Even if one has come to the conclusion that the extinction of species should be averted it is not clear what policies would be effective in doing that. In a free market economy it might seem best to use economic incentives to create a demand for sustainably managed landscapes.

One way to use arguments from economics to justify conservation efforts are ecosystem services, a term popularized by a 2005 United Nations report.[2] Ecosystem services describe the processes that nature provides to human societies for free. For example plants provide oxygen, filter water and stabilize the ground using their roots, and provide shade. Another, more prominent example, are bees pollinating crops.

Calculating how much it would cost to replace these services gives an economic incentive to preserve functioning ecosystems. As ecosystems can function best if as many of their original species as possible survive the preservation of individual ecosystem services can save many species.[3]

The study of ecosystem services does not only highlight the economic importance and the biodiversity gain but it also demonstrates how dependent humans are on their environment.

While the cost of single ecosystems services can be calculated,[4] it is difficult to estimate what the costs would be on a larger scale. It is also not clear if an artificial replacement for all such services could be implemented in practice. The question of how much it would cost to replace a destroyed ecosystem is thus still open.

Read more:

[1] H. M. Pereira, P. W. Leadley, V. Proença, R. Alkemade, J. P. W. Scharlemann, J. F. Fernandez-Manjarrés, M. B. Araújo, P. Balvanera, R. Biggs, W. W. L. Cheung, L. Chini, H. D. Cooper, E. L. Gilman, S. Guénette, G. C. Hurtt, H. P. Huntington, G. M. Mace, T. Oberdorff, C. Revenga, P. Rodrigues, R. J. Scholes, U. R. Sumaila, M. Walpole, *Science* **2010**, *330*, 1496–1501.

[2] www.millenniumassessment.org

[3] G. M. Mace, K. Norris, A. H. Fitter, *Trends Ecol. Evol.* **2012**, *27*, 19–26.

[4] G. Chichilnisky, G. Heal,*Nature* **1998**, *391*, 629–630.

What is the origin of dwarf beeches?

by Thomas Jagau

In Southern Sweden ("vresboken"), Denmark ("vrange boge"), Northern Germany ("Suentelbuche"), and France ("fau de Verzy"), we find a rare cultivar of the European beech, the so-called dwarf beech. These trees are characterized by twisted and contorted branches with pendulous ends. Dwarf beeches grow more in width than in height and rarely reach a height of more than 15 m. Until the 19th century, dwarf beech forests existed at several places, but were cleared as the wood could not be used economically. Today, only about a thousand isolated specimens are left in Europe. Various ideas exist about the origin of dwarf beeches. In the old days, they were considered enchanted or tainted by the devil. Later on, it has been tried to draw a connection to soil condition, microclimate, and even radioactive ground water. Modern science has established that the growth form of dwarf beeches is an inherited defect and rooted in a genetic mutation. However, many details are still unknown, especially the clustered occurrence remains a mystery.

Read more:

[1] http://www.dfwr.de/download/DFWR_beech_forests.pdf

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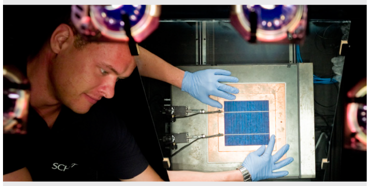
[4] The image was uploaded by user Dinkum to http://commons.wikimedia.org/wiki/File:Abeille_au_travail_-_jardin_des_iris.JPG

Graduate School Materials Science in Mainz - Germany



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The Graduate School of Excellence "MAterials Science IN MainZ" (MAINZ) offers innovative scientific, technical and complementary PhD training combined with excellent research in materials science. MAINZ bridges previously disjoint fields of materials research. This allows MAINZ members to develop a common language, to foster interdisciplinary transfer of knowledge, and to gain insight into systems traditionally seen as separate.

Scientists from Johannes Gutenberg University Mainz, the Max Planck Institute for Polymer Research (MPI-P) and the University of Kaiserslautern (TUKL) have joined to form MAINZ. MAINZ has been selected as one of the few PhD programmes in the interdisciplinary area of Chemistry, Physics and Biology as part of the Excellence Initiative.

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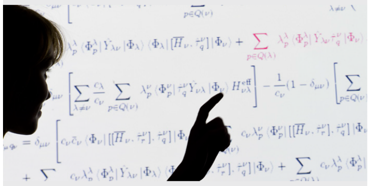

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Articles

Predicting Half Metallic Ferromagnets – A Little Bit More Realism Please

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In this paper we critically examine recent claims about half metallic ferromagnetism in open p-shell systems. Odd valence electron compounds like CaAs have been predicted to show a 100 % spin polarization at the Fermi level, if they can be grown in the zincblende structure. It has furthermore been argued that this should be possible under special conditions. We will give several arguments against this claim based on concepts from chemistry and density functional calculations.

1 Introduction

Ever since half metallic ferromagnets (HMFs) have been theoretically discovered by de Groot[1] in the half Heusler compound MnNiSb, HMFs have been a widely studied topic in condensed matter physics and material sciences. A HMF is a ferromagnet with an extremely high spin polarization[2] and can occur in many structure types such as Heusler compounds, perovskites and other transition metal oxides such as CrO_2. One of the unique features of a HMF is a 100 % spin polarization at the Fermi level, making HMFs ideal candidates for spintronic devices, e.g. in combination with MgO tunnel junctions. Semiconducting relatives are the precondition for half metallic ferromagnetism because a gap in one spin direction is necessary to achieve the desired 100 % spin polarization.[3] The underlying physical mechanism for this effect is large intra-atomic exchange in some magnetic Heusler compounds, leading to an electronic structure sketched in Fig. 1a). Manganese for example acquires a large magnetic moment in an octahedral environment and carries a formal d^4 configuration which has been explained by Kübler and coworkers.[4] The magnetic moment is in agreement with the Slater-Pauling rule, which allows the prediction of new HMFs by simply counting the valence electrons.[3] Half metallic ferromagnets with a high curie temperature would have a huge impact on spintronics, but up to now only some Heusler compounds come near to the desired performance.

Basically all HMFs are based on transition metal d-shell compounds, but recently more and more people have started to investigate p-shell magnetism in odd electron compounds such as CaAs in the zincblende and other simple binary structures such as the rock salt (NaCl) or wurtzite structure, which are not the thermodynamically stable structures. The general claim is that it should be possible to stabilize compounds such as CaAs in those structures as metastable materials under certain conditions. Open p-shell systems are known as radicals in chemistry, which usually are not stable, with some exceptions such as in extended π-electron systems. What they find are compounds that show half metallic ferromagnetism, if they crystallized in structures with tetrahedral coordination (see Ref. [5] and references therein).

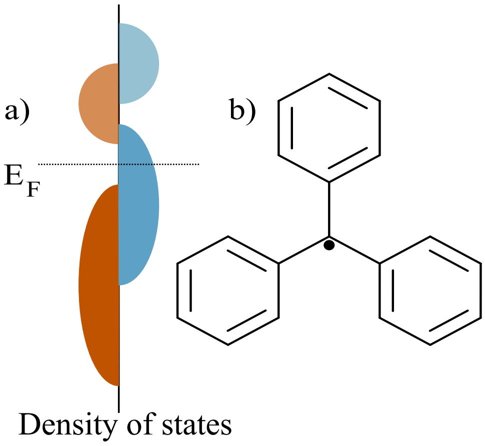

Figure 1: **a)** Schematic DOS of a HMF. **b)** Triphenylmethyl radical.

2 Outline

In this letter we want to question the feasibility of p-shell magnetism of binary compounds in zincblende structures,

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especially the existence of metastable systems. We will discuss our thoughts on this topic by choosing CaAs as an example, because here the actual occurring crystal structure is well known. This letter does not claim to be a complete treatise on the topic (a more sophisticated analysis will be published elsewhere). We rather want to introduce the reader to our arguments based on chemical intuition supported by density-functional theory (DFT) calculations. It is important to stress that the mere purpose of our calculations in this paper is just to illustrate ideas. They should not be taken as a proof that the claims are wrong. Rather, they are just a hint that much more work with more sophisticated methods lies ahead. To really determine if a structure is thermodynamically stable with respect to another phase, molecular dynamics calculations have to be performed.

3 Discussion

CaAs crystallizes in a layered hexagonal structure. The layers consist of buckled CaAs hexagons resembling a structure related to cyclohexane. Another striking feature is the existence of As_2 dimers at the edges of the unit cell, as can be seen in Fig. 2d). CaAs can be understood in the context of Zintl compounds. In general, stable compounds tend to have a formal closed shell configuration, which can be accomplished by different types of bonding in solid state compounds, alternatively metals are formed. We will now argue against these claims and show that the half metallic ferromagnetic structures should be unstable with respect to the naturally occurring structure using ideas from chemistry and DFT calculations.

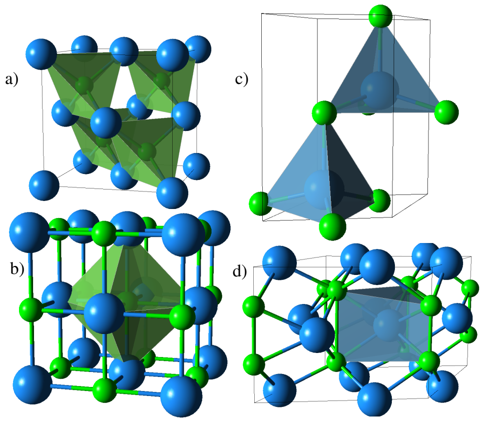

Figure 2: Unit cells of a) zincblende, b) NaCl, c) wurtzite, and d) the real hexagonal structure. Notice the different types of coordination.

CaAs is a 7 valence electron compound. Because of the difference in electronegativity of Ca and As, we could think of this compound as consisting of Ca^{2+} and As^{2-}. In this configuration, As^{2-} has a single unpaired electron and can be described as a radical which would contribute to paramagnetic behavior.

In chemistry, radicals are usually not considered to be stable, i.e. there will be many side reactions that will destroy the radical state, e.g., reaction with O_2. Despite this, we know several circumstances in which stable radicals exist.

- Magnetic compounds, such as in d- or f-electron systems.
- Delocalization of the radical, as known from aromatic organic molecules such as the triphenylmethyl radical in Fig. 1b).
- Kinetic stabilization, i.e. steric effects prevent the radical from reacting with other molecules.[2]

How can we achieve such a stabilization in our solid state problem? Delocalization occurs when conjugated π-orbitals overlap and thus the Hamiltonian matrix elements should be large. Since the hopping parameter t within the tight-binding approximation is proportional to these matrix elements, while the bandwidth is proportional to t, we would expect to see a large bandwidth in the band structure for the radical state of As, indicating delocalization. Another possibility is the formation of a covalent bond between two radical partners resulting in a closed shell electronic structure. These things are well known to chemists and rely on very simple but accurate concepts such as the Zintl concept. A stable structure should now either show a large bandwidth of the valence band or should have As-As bonding interaction within its structure.

All calculations have been performed with the WIEN2k code using the PBE-GGA functional.[6] The lattice constants have been relaxed, as well as the internal coordinates of single atoms, if not constrained by symmetry. We calculated total energies, the density of states for both spin channels as well as a spin polarized band structure for CaAs in hypothetical zincblende, wurtzite and NaCl structure and compared them to the electronic structure of the real compound. The plane wave cut-off parameter $R_{MT}K_{MAX}$ was set to 7 and the Brillouin zone was sampled by 4000 k-points. It turns out that the buckled hexagonal structure with the dimers is much lower in energy per formula unit compared to all other structures (Tab. 1). In zincblende and wurtzite structures, tetrahedral sp^3 bonding plays the most important role and interestingly half metallic ferromagnetism exists in this structures. The band structure for the zincblende calculations shows the typical gap in the minority spin channel and a constant shift of energy for the majority spin channel. Taking a look at the density of states we can immediately see the occupation difference of both spin directions, leading to a magnetic moment of 1 μ_b per unit cell for both tetrahedral structures. The small differences in the density of states can be attributed to the lower symmetry in the wurtzite structure compared to the zincblende compound. Coming back to our previous considerations, we can neither find a large bandwidth in the valence band, nor covalent As-As bonds in these structures. On the contrary, the bandwidth for the valence band (the radical band) in the

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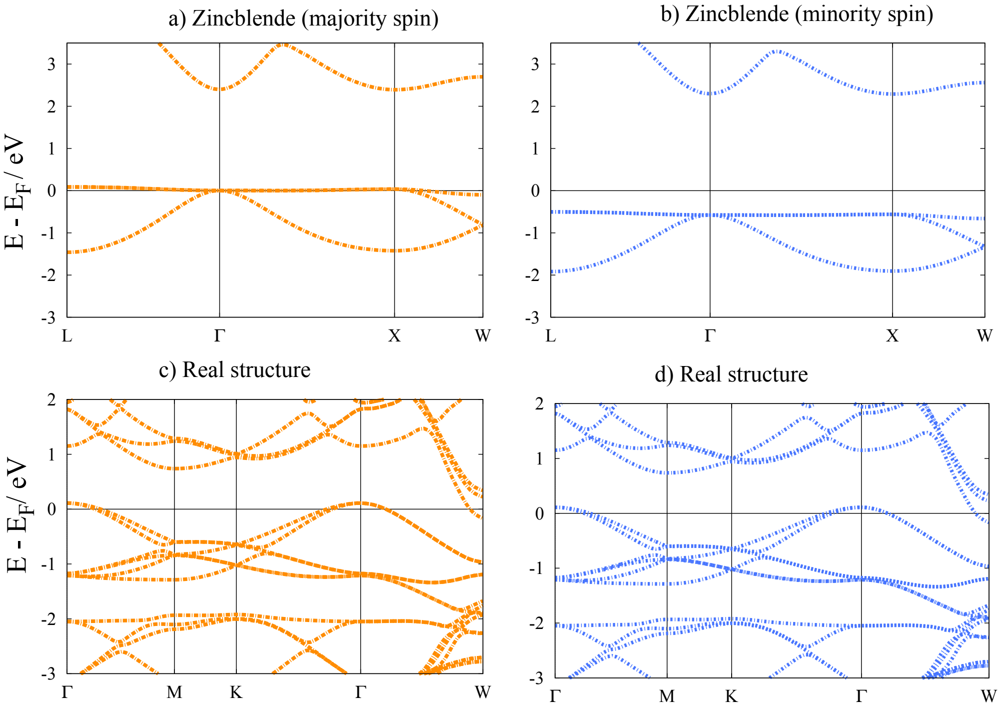
[2] Even under ultra high vacuum conditions, many organic radicals still react with remaining traces of hydrogen (or other molecules) in their environment resulting in lifetimes in the order of milliseconds if not stabilized by kinetic control.

zincblende structure is very small (0.16 eV), which can be attributed to a very localized state.

Going away from the tetrahedral structures we find a much lower spin polarization for CaAs in the NaCl structure, which can be attributed to the higher octahedral symmetry and coordination number. A very interesting fact is the high polarization of the low lying s bands, which is in agreement with non-directed bonding. The band structure shows a large bandwidth (1.9 eV) of the valence band, which explains the much smaller energy difference to the experimentally observed structure. One reason for the non-realization of the NaCl structure must be traced back to the fact that a bonding As-As interaction is not present in this structure, because of the high coordination number, which does not favor covalent bonding in contrast to ionic interactions.

Table 1: Energies per formula unit (FU) for CaAs in different structures.

Structure	E_{FU} / Ry	E^{struc}_{FU} - E^{real}_{FU} / kJ mol^{-1}
Zincblende	-5883.031913	148.0
Wurtzite	-5883.038164	139.8
NaCl	-5883.097351	62.1
Real structure	-5883.144661	0


a) Zincblende (majority spin)

b) Zincblende (minority spin)

c) Real structure

d) Real structure

Figure 3: Band structures of CaAs in zincblende, and in the real structure.

In the real structure now both ways of stabilizing the radical character of this compound are present. Not only do we have dispersive bands at the Fermi level, but we can also observe As_2 dimers within the structure and due to the lower symmetry, two crystallographically different As positions exist in this structure, which can be seen in the tilt of the trigonal prism as shown in Fig. 2d).

A further indicator for this stability can be found in the density of states (DOS), since the DOS of the stable structure shows a minimum at the Fermi level, to which in contrast all other structures show a maximum, indicating an electronic destabilization of the structures.

Next to this very basic discussion, further remarks on the level of theory have to be pointed out. Usually, localized states are not treated correctly within LDA/GGA calculations and related methods, so more correlation effects have to be taken into account, which for instance can be observed in Rb_4O_6.[7] In this compound, open shell hyperoxide O_2^- anions coexist with O_2^{2-} peroxide anions, the former having an unpaired electron. Regular methods such as LDA predict a metallic ground state. Only more sophisticated methods such as hybrid functionals yield a magnetically frustrated ground state in agreement with experiment, which shows the importance of electronic correlation in open p-shell systems. Returning back to our simple example, this observation has an important consequence, since all calculations so far have been performed with methods that do not treat correlation effects very well and might give the wrong ground state. Thus, in order to verify that the predicted compounds really show the desired property, a careful investigation of all possible structures and magnetic configurations together with more exact methods is mandatory as already mentioned in the outline.

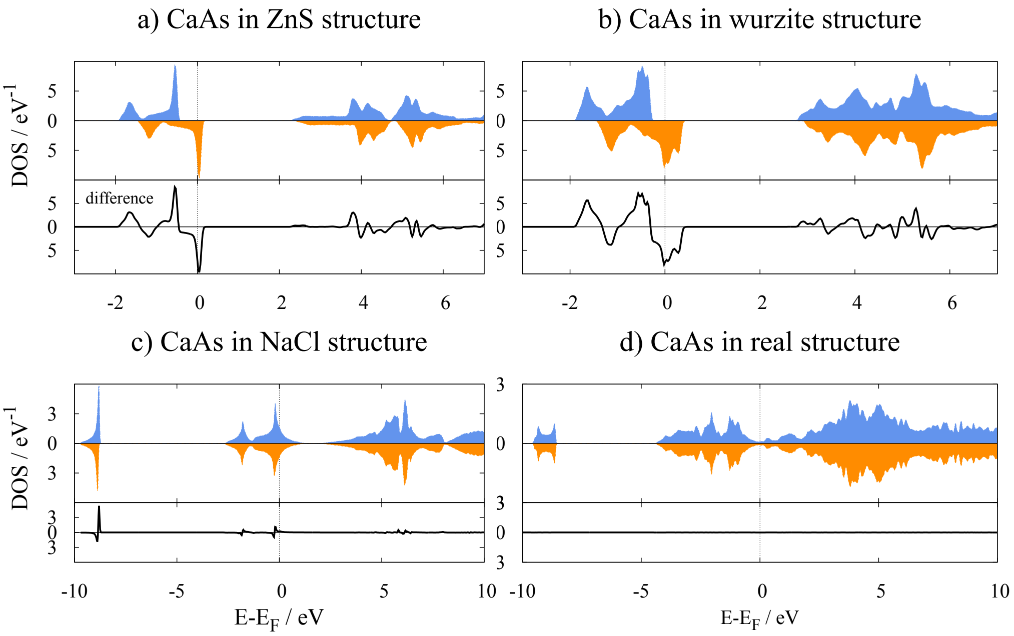


Figure 4: Density of states per formula unit for CaAs in zincblende, wurtzite, NaCl, and the actually occurring structure.

4 Summary and Conclusions

We will now quickly summarize our observations:

- Radicals are usually not stable with respect to further side reactions, if not stabilized by kinetic control or delocalization.
- Hallmarks of such stabilization could be dispersive bands with a large bandwidth at the Fermi level, but none of the proposed alternative structures shows this, except for the NaCl structure.
- Arguing with the Zintl concept, one would also expect the formation of dimers within a stable structure, which only occurs in the real structure.
- Inclusion of correlation effects will most likely result in a different ground state (see Rb_4O_6).

We hope we could convince the reader that chemical intuition can help to identify unrealistic predictions with the support of computational methods. Despite the interesting emergence of magnetism in tetrahedral structures, such claims should only be made with emphasis on the theoretical implications (i.e. the mechanism). Actually claiming that unrealistic structures can eventually be grown is not only wrong, but will also cause confusion within the community. There is nothing wrong with calculating things that do not exist (this is what theory is for), but it should always be pointed out very clearly.

Without a careful optimization of the structure and taking into account electron correlation, a naive scientist could thus predict an endless number of new half metallic ferromagnets, just by combining elements with an odd number of electrons per unit cell.

In conclusion and in the spirit of Roald Hoffmann's paper on the prediction of new molecules,[8] we thus demand more care and realism when predicting new materials. Please!

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Open Questions

How Do Pseudouridine Synthases Work?

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In the central dogma of molecular biology DNA (deoxynucleic acid) is transcribed into RNA (ribonucleic acid) which in turn makes the protein. 60 years after the creation of this dogma, however, it is clear that RNA is much more than the transient copy of DNA. A special subgroup of RNA molecules also transfers the aminoacids to the protein making machinery, thereby requiring a delicate balance of conformational uniformity and flexibility. In addition, RNA carries out many regulatory functions and is, in particular, the catalytic component of the proteinmaking machinery of the ribosome. It is understood today that RNA has to be heavily and specifically modified to carry out all these complex functions: The four building blocks known at the beginning of RNA research (adenosine, cytidine, guanosine, and uridine) are extended to 160 to date, numbers growing. Pseudouridine (Ψ), the so called 'fifth nucleoside', is a *C-C*-glycosidic isomer of uridine and is as abundant as the four canonical bases. While its function is only partly understood, the mechanism of its formation by the action of enzymes called Ψ-synthases, is even more nebulous. This article sums up information obtained by using the mechanistic probe 5-fluorouridine (5FU) on Ψ-synthases: Three mechanisms were proposed to date of which none is solidly proven or disproven. Recent results show, however, that 5-fluorouridine may not form a reaction intermediate of usual Ψ-formation, as expected, but may react by a totally different mechanism. Could new mechanistic probes and simulations help to elucidate the mechanism of these marvelous enzymes?

1 Introduction

Today, more than a decade after the completion of the human genome project, a considerable acceleration of research in the life sciences can be attributed to this achievement.[1] However, the real challenge is still ahead: How is our genetic code actually put to use, which portions are important? And particularly: Are there dynamics in the usage of the genetic code, are portions switched on or off? At the beginning of nucleic acid chemistry this question appeared to be an easy one: Only four DNA (deoxynucleic acid) building blocks, called nucleotides, seemed to exist.[2] Now, almost sixty years later, this is not true anymore, since derivatives of cytidine were found to expand the base canon to seven building blocks and opened the field of epigenetics.[3] Epigenetics describes mechanisms that regulate gene activity, thereby affecting a cell's fate and the development of a whole organism without actual alteration of the genetic code. Instead of changing the genetic code epigenetics determines which portions of the genetic code are used and which are not. Consequently, the mechanisms of epigenetics are thought to be of paramount importance in diseases.[4]

To render the field of epigenetics even more complex gene regulation does not stop on the DNA level. Following the central dogma of molecular biology DNA is to be transcribed into messenger RNA (ribonucleic acid, mRNA), a rather transient active copy, which is translated into proteins by using transfer RNAs (tRNA) as adaptors. Therefore, an obvious way to alter or stop protein expression is via RNA modification. In fact, RNA alone can have catalytic properties,[5] which led to a hypothesis of an RNA world, predating the protein world.[6] Consequently, the joining of amino acids to form proteins is catalyzed by the RNA component of the ribosome, called ribosomal RNA (rRNA).[7] In the past decade the search for metabolite sensing and catalytically active RNA has intensified.[8] Apart from this long non-coding RNAs, small nucleolar RNAs (snoRNAs)

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and many others carry out important regulatory duties in gene regulation.[9]

That RNA combines all these properties makes it more alike to proteins than to DNA. As in proteins catalytic properties as well as specificity are provided by a complex, finely tuned tertiary structure of the specific molecule. RNA can access this additional structural regime which is blocked to DNA, since it carries an additional 2'-OH moiety at the sugar. This moiety organizes RNA into another helix form than DNA and provides an additional hydrogen bond donor, thereby creating the basis for numerous complex tertiary structural motives.[10, 11] Another fundamental difference of RNA from DNA is that RNA does not consist of only four or even seven building blocks, as DNA does, but of at least about 160 building blocks (several new ones are discovered every year).[12] This diversity is generated by chemical alterations of the four basic RNA building blocks, which are called modifications. Modifications are not to be confused with mutations. Mutations are the result of harmful environmental effects, like exposure to radiation or UV light: Here, one basic building block is exchanged with another or even deleted.

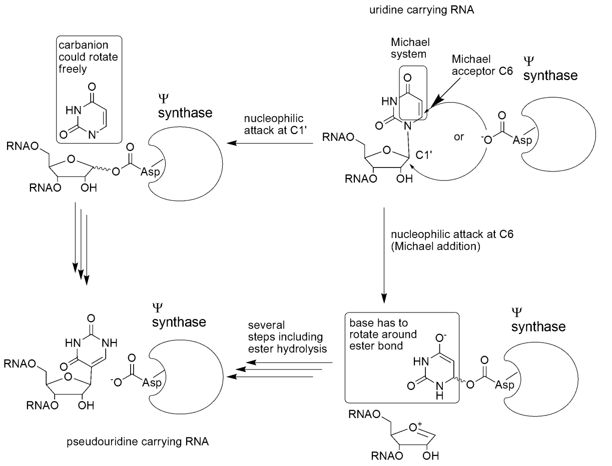

Figure 1: Presumably pseudouridine is formed by a nucleophilic attack of the catalytic aspartate (Asp) of a Ψ-synthase on a uridine residue inside an RNA sequence. The attack on the uridine carrying RNA can either occur at the C1' of the sugar (upper left) or at the C6 of the ribose, thereby following a Michael addition (lower right).

Modifications, on the other hand, are useful and they are introduced on purpose at specific positions using specialized enzymes. The complex network of mutual modulation that these modifications create is best understood in the context of tRNA, where many of them meet on a relatively short stretch of nucleotides, but even for the 'easy' subject of tRNA many questions remain unanswered.[13] The most abundant modification of RNA is pseudouridine (Ψ), a *C*-*C*-glycosidic isomer of uridine. This base, being as abundant as the four canonical bases, is thought to stabilize RNA structure by providing one additional hydrogen bond donor and by intensifying base stacking.[14] Pseudouridine is especially abundant in tRNA,[13] but is also found in rRNA[15] and snRNAs (small nuclear RNAs).[16] A quite fascinating ability of Ψ is that it converts stop codons on messenger RNA into sense codons, thereby increasing protein diversity by the generation of longer proteins.[17] The actual effect of Ψ may be best understood in tRNA, where it plays multiple, counteracting roles: It stabilizes the anticodon loop[18] and acts in fine tuning of a modification network that corrects the balance between stability and flexibility.[19, 20]

Introduction of Ψ into tRNA seems to enable mesophiles (organisms living at non-extreme temperatures) to adapt to high temperatures,[21] while it enables thermophiles (organisms living at very high temperatures) to adapt to low temperatures.[22]

2 Ambiguous results

Matching the diversity of their substrates, six enzyme families of pseudouridine synthases (Ψ-synthases) exist that introduce one or several Ψs in a sequence specific manner into RNA sequences of tens to thousands of nucleotides. Surprisingly this modification can be introduced without the use of cofactors, meaning also without an external source of energy to fuel the reaction.[23] But which chemical mechanism do these marvelous enzymes apply?

From sequence alignment and mutational studies it is established that the catalytically active residue in Ψ-synthases has to be an aspartate (Asp), which may act as the nucleophile, facilitating the cleavage of the *N*-glycosidic bond, which is followed by base rotation and reformation of a *C*-*C*-glycosidic bond (see Fig. 1).[23] To achieve *N*-glycosidic bond cleavage two different scenarios would suffice: The aspartate could either attack the Michael acceptor C6 at the base in a Michael addition or the aspartate could attack the C1' of the ribose (see Fig. 1).

Initial studies of the reaction mechanism used the probe 5-fluorouridine (5FU). Here the hydrogen at position 5 of the base is substituted by fluorine. Utilization of this probe resulted in the formation of a rearranged product with a non-saturated ring, since the fluorine could not be subtracted as F^+ (see Fig. 2). That the product of 5FU carried a hydroxyl group at the former C6 was, without further proof, interpreted as indication for a Michael addition like mechanism (see Fig. 2).[24]

That some complexes of Ψ-synthases and 5FU carrying substrates were extremely stable and could only be disrupted by heating[24, 25, 26] was attributed to a covalent bond connecting the catalytic aspartate to the pyrimidine ring (like Fig. 1 lower right), thereby indicating a Michael addition like mechanism. However, in the numerous cocrystal structures available, this covalent bond could not be observed.[25, 27–29] It was assumed that the bond was either cleaved by slow hydrolysis during crystallization or cleavage occurred due to the high energy input during the X-ray diffraction measurement.

To further investigate, whether the hydroxyl group at position 6 of the product of 5FU conversion originated from ester hydrolysis of a Michael addition like intermediate, ^{18}Olabeling studies were performed. A 5FU-RNA-Ψ-synthase complex was heat disrupted in ^{18}O-water with the expectation to obtain an ^{18}O-labeled protein. The experiments yielded an ^{18}O-carrying RNA, thereby excluding that the hydration was caused by ester hydrolysis (see Fig. 2).[26, 30] As the authors point out this observation does not disproof the Michael addition like mechanism.

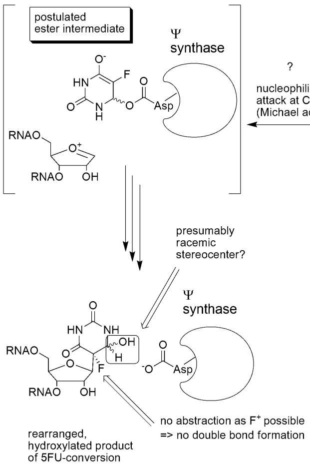

Figure 2: Use of the mechanistic probe 5FU (upper right) led to the formation of a rearranged, hydrated product (lower left). This product was classified as reaction intermediate of Ψ generation: One of the last reaction steps, proton abstraction at the new *C-C*-glycosidic bond was not possible due to the fluorine modification. The occurrence of a hydroxyl group was interpreted as proof of a Michael addition like mechanism, the intermediate of such a mechanism is shown in brackets in the upper left. That the product showed two peaks in HPLC analyses was attributed, without further proof, to a racemic stereocenter (see lower left).[24]

From HPLC analyses it was deduced that the Ψ-synthases called TruA and TruB generate two products from 5FU-substrates. This was, without further proof, attributed to the formation of two stereoisomers of the hydrated product (see Fig. 2 lower left).[24] To clarify the identity of these products for the Ψ-synthase TruB, extensive NMR studies were performed recently by Miracco and Mueller.[31] NMR studies are relatively rare in RNA research, since research usually takes place in the lower microgram regime, which is far below the NMR's limit of detection.

The surprising result of these NMR studies was: While the major product is the isomer observed in the crystals, the minor product is not isomerized at C6, the hydration site of the pyrimidine ring, but at the C2' of the sugar, generating an *arabino* isomer (see Fig. 3b)). Miracco and Mueller point out that since no evidence for *arabino* pseudouridine from action on uridine substrates was obtained so far, their study provides first evidence that the mechanistic probe, 5FU, which was used in all these studies, might use another reaction pathway than the native substrate, uridine.[31]

Based on their observation of an *arabino* isomer, Miracco and Mueller proposed a so called acylal mechanism for 5FU conversion, where the aspartate attacks the ribose (see Fig. 3b)). The main product generated from the acylal intermediate would be the *ribo* isomer. The *arabino* isomer may be formed due to the decreased nucleophilicity of the 5FU anion compared to the uridine anion: Action of the aspartate as base would allow the formation of a glycal intermediate, which could be reprotonated by the aspartate at C2' to yield either isomer.

For Ψ-to-U conversion Miracco and Mueller propose a different mechanism to account for the lack of *arabino* product (see Fig. 3a)): Here the aspartate acts first as a base, generating the glycal intermediate. Because of the higher nucleophilicity of the uridine anion the nucleophilic attack and reprotonation of C2' by the aspartate occur in concerted fashion, giving rise to only one product, the *ribo* isomer.

Miracco and Mueller conclude that the action of the active site aspartate as an acid during the reprotonation step strongly disfavors a Michael addition like mechanism, since the aspartate would be unable to act as an acid, if it is covalently bound to the substrate. This conclusion, however, is still based on the assumption that the mechanistic probe 5FU does not change the chemistry of the reaction. If the nature of a reaction mechanism is only accessible by using mechanistic probes, an influence of the probe can never be completely excluded. Miracco and Mueller assume that 5FU only increases the lifetime of the glycal intermediate without changing the fundamental chemistry. This hypothesis is reasonable, but remains, as long as there is no evidence of a glycal intermediate during U-to-Ψ conversion, an unverified hypothesis. Consequently, Miracco and Mueller announced in their study to be trying to prove a glycal intermediate in uridine conversion,[31] a project which was not published to date.

3 Conclusion and new perspectives

One can conclude that Ψ-synthases are marvelous enzymes, since they convert an *N*-glycosidic bond into a *C-C*-glycosidic bond without the use of cofactors. The chemical mechanism they use for this conversion, however, could not be revealed unambiguously within 15 years of research. To make matters worse it was shown recently that the mechanistic probe, 5FU, which was used during all mechanistic studies, is converted not into one, but into two products. This observation gave rise to the question, whether the chemistry of the mechanistic probe is really identical to the chemistry of the natural substrate. To further clarify the subject, new mechanistic probes for Ψ-synthases are needed. 5FU seems to be of no use, since it may react differently than uridine and since the probe was unable to distinguish two possible mechanisms. Furthermore, it is known for some time that 5FU does not inhibit all Ψ-synthases, which argues against the assumption that the product of 5FU-RNA-Ψ-synthase action is an intermediate analogue and therefore tighter bound.[32]

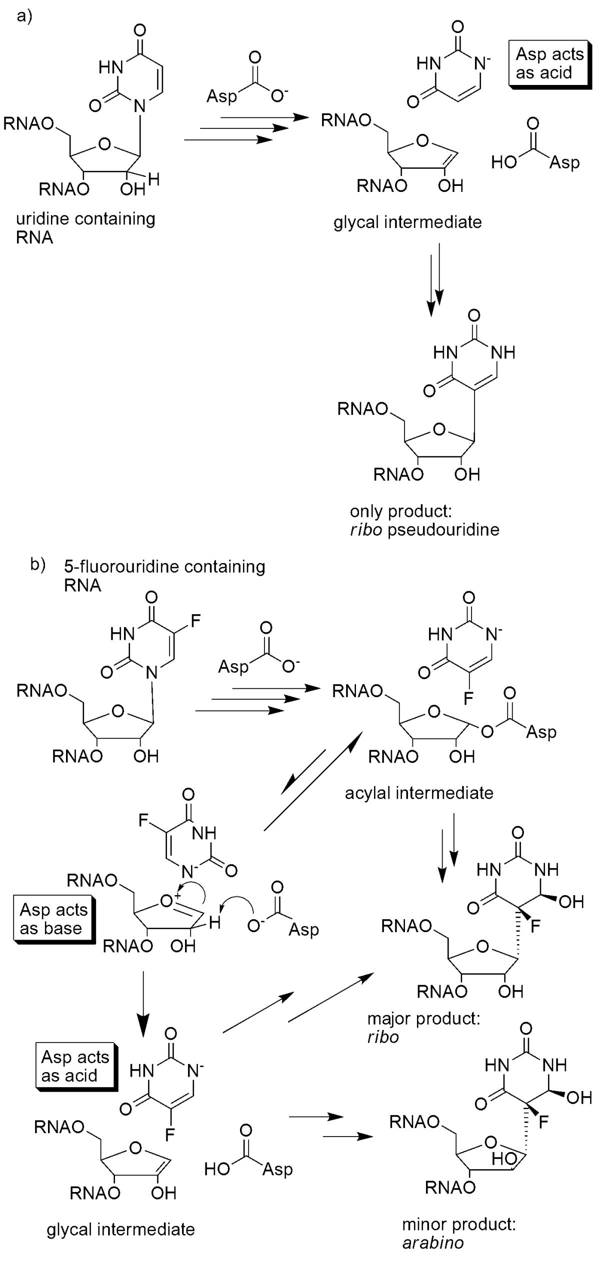

Figure 3: **a)** Glycal mechanism for U-to-Ψ conversion: Concomitant or after glycosidic bond cleavage the catalytic aspartate deprotonates the C2'-position, leading to the formation of a glycal intermediate. **b)** The reaction of 5FU with Ψ-synthases may occur via an acylal intermediate, which is in equilibrium with the glycal intermediate. Due to the decreased nucleophilicity of the 5FU anion both, an *arabino* and a *ribo* product may arise from the glycal intermediate (derived from [31]).

To answer the question how Ψ-synthases work, one has to answer the following question first: What could a new mechanistic probe look like? In spite of some considerable effort to elucidate the enzyme's mechanism this is, surprisingly, a question unasked so far. Since an attempt to trap an enzyme intermediate complex was unsuccessful, one could try to abolish reaction pathways instead. This could be achieved by altering the electron densities at base or ribose, respectively, to lower their electrophilictiy.

Another route could be opened by quantum mechanics / molecular mechanics (QM/MM) calculations:[33] Here the actual enzymatic reaction and the key residues involved are modeled by QM. Since QM methods can only address relatively small systems the parts of protein and RNA substrate that are not directly involved in the reaction have to be modeled by another approach called MM. If such a model could be tuned on the 18 nucleotide long minimal substrate RNA in complex with the Ψ-synthase with about 400 amino acids (depending on the enzyme family) the enzymatic reaction could be carried out *in-silico*. Such an experiment would help to elucidate the most likely reaction mechanism by directly assessing the stability of the respective intermediates. Since enzyme product complexes with 5FU-carrying RNAs are known[25, 24, 27–29, 33] there is the chance that a large part of the protein and many RNA residues could be excluded from the quantum mechanical part of such calculations. Still it remains a demanding task, which may explain why such an approach is missing until now.

4 References

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Is Calcite $(10\bar{1}4)$ a Chiral Surface?

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1 Introduction

Calcium carbonate ($CaCO_3$) is one of the most abundant simple salts in nature. It is found in the shells of molluscs such as slugs or sea shells, where it combines with organic molecules to materials with remarkable properties named biominerals.[1] To understand, imitate, and control the formation process of these biominerals, they have been the focus in a vast number of recent studies.[1,5] Most interestingly, calcium carbonate has been discussed being related to the homochirality of life.[2] This aspect became evident in studies, where the adsorption of amino acids has been demonstrated not only to be enantiospecific,[15] but also to influence enantiospecific the macroscopic growth.[28,41] Although it is established that the bulk-truncated structure of the most stable calcite $(10\bar{1}4)$ surface is achiral due to a glide plane symmetry,[14] the existence of a chiral surface structure has been claimed from studying the phase selection of calcium carbonate.[41] As this finding violates the bulk-truncated symmetry properties, it has been discussed controversially, eventually resulting in a correction of the previous statement.[22,24] Here, we briefly revisit the symmetry properties of the calcite $(10\bar{1}4)$ surface, unambiguously concluding that the bulk-truncated surface is achiral. Furthermore, we present clear evidence that one surface property, the already observed, so-called row-pairing reconstruction,[23,29,30,32,34,36,39] can violate the remaining symmetry element and would, thus, create a chiral surface. We critically analyze the existence of this row-pairing reconstruction and give arguments for and against its existence. Based on AFM experiments, we describe a strategy to identify the enantiomers and, furthermore, show that the enantiomer does not change from terrace to terrace on the surface. However, due to the given ambiguity on the existence of the row-pairing reconstruction, the question whether the calcite $(10\bar{1}4)$ surface is chiral remains open.

2 Calcite Bulk and $(1\,0\,\bar{1}\,4)$ Surface Properties

Calcite, the most stable polymorph of calcium carbonate, crystallizes in a trigonal crystal system (rhombohedral holohedral $\bar{3}2/m$).[33] It belongs to the symmetry group $R\bar{3}c$ and the crystal structure is usually described by a hexagonal *structural* unit cell.[33] In this coordinate system, the most stable cleavage plane is denoted as the $(10\bar{1}4)$ surface. This surface has been investigated at a fundamental level by both, experimental[8,9,12,16–18,23,25,27,29,32,34,36–39] and theoretical[6,10,11,20,35,42] methods.

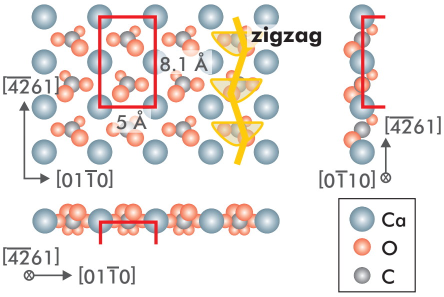

Figure 1: Bulk-truncated calcite surface in top- and side views. The (1×1) unit cell is depicted by a solid red rectangle, while the zigzag of the topmost oxygen atoms is indicated by a yellow line. The tilt of the carbonate groups is visualized by yellow triangles.

The bulk-truncated structure of the calcite $(10\bar{1}4)$ surface has a rectangular unit cell with dimensions $4.99 \times 8.10\,\text{Å}^2$. The unit cell vectors $\vec{a}$ and $\vec{b}$ are oriented along the $[01\bar{1}0]$ and $[\overline{42}61]$ crystallographic directions, respectively. The surface unit cell contains two carbonate (CO_3) groups and two calcium atoms as depicted in Fig. 1. In the bulk-truncated model, each carbonate group is rotated by an angle of $44.63°$ with respect to the surface plane such that one of the three oxygen atoms protrudes the plane, one lies in the plane, and one is beneath the plane spanned by carbon and calcium atoms. Determining either the $[42\overline{61}]$ orientation or the tilt direction of the carbonate groups bears equivalent information. In the following, we abstract the tilt of the carbonate groups by yellow triangles. In the bulk-truncated structure, the carbon atoms of the carbonate groups are perfectly centered between two calcium atoms, both along the $[01\bar{1}0]$ and the $[\overline{42}61]$ direction. However, the two carbonate groups inside one surface unit cell are rotated with respect to each other, the topmost oxygen atoms thus point either to the left or right. Following the position of these protruding oxygen atoms, a zigzag line becomes apparent as indicated in yellow in Fig. 1.
Early atomic force microscopy (AFM) and low-energy elec-

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tron diffraction (LEED) experiments have indicated the existence of two surface reconstructions. One reconstruction is known as the "row-pairing reconstruction", while the other has been identified as a (2×1) reconstruction.[2] While the (2×1) reconstruction has now been observed with different techniques[20,30,35–39] and can, thus, be accepted as a real surface property, the row-pairing reconstruction has so far only been evident using atomic force microscopy techniques.

An overview over literature studies giving clear or no evidence for the row-pairing reconstruction is given in Tab.1. The reconstruction has been observed in several studies using contact AFM (C-AFM) in liquid environment[23,29,32,39] as well as under ambient conditions.[39] Further indications for this reconstruction have been given by non-contact AFM (NC-AFM) measurements in water[34] and under ultra-high vacuum (UHV) conditions.[30,36] On the contrary, to the best of our knowledge, its existence has not been found with X-ray methods such as X-ray scattering (XRS) in liquid[8,12] and grazing incidence X-ray diffraction (GIXRD) under ambient conditions.[25] In the latter studies,[8,12,25] the conservation of the *pg* symmetry has been investigated and related to the (2×1) reconstruction. From our understanding – as we will show in the next Section 3 – a *pg* symmetry violation points towards the existence of the row-pairing reconstruction, while the (2×1) reconstruction would conserve the *pg* symmetry. Thus, we interpret the data such that an existence of the row-pairing reconstruction has not been found, leaving the question open whether this is due to its non-existence or due to experimental challenges for its detection.

	liquid	ambient	vacuum
C-AFM	✓[23, 29, 32, 39]	✓[39]	
NC-AFM	✓[34]		✓[30, 36]
XRS	✗[8, 12, 25]		
GIXRD		✗[25]	

Table 1: Literature survey on the observation of the row-pairing reconstruction using different experimental techniques (rows) in different environments (columns). ✓: The row-pairing reconstruction has been observed, ✗: The reconstruction has not been revealed in the cited references.

In AFM data, the row-pairing has usually been evident as a height modulation along the $[\overline{42}61]$ surface direction, where one row of carbonate groups is imaged higher ("brighter") than the other (see Tab.1 and Fig. 2(b,c)). The most complete picture on imaging the $(10\bar{1}4)$ surface has recently been drawn using the AFM in the non-contact mode under UHV conditions, where ten different contrast modes have been observed experimentally.[30] The contrast mode assignment made here is based on the classification that has been presented previously.[30] Similar contrast modes have very recently also been found on a related material, namely the dolomite $(10\bar{1}4)$ surface.[19] Typical NC-AFM images presenting the zig-zag, the row-pairing reconstruction, and both effects combined are presented in Fig. 2. In the topography image 2 (c), each second species along the $[\overline{42}61]$ direction is imaged higher and at the same time, a zigzag of the bright species is revealed.

However, the row-pairing is a reconstruction *within* the surface unit cell. The orientation of each carbonate group to the tip is different, opening the possibility for a different interaction of a scanning probe tip with the two different carbonate groups. We will show later that the imaging-relevant part of the tip has to be chiral to cause an apparent row-pairing reconstruction. A tip-induced artifact arising from these different interactions with the carbonate groups cannot be ruled out in general. This statement even holds true for scanning probe tips that resolve single point defects – which is usually accounted for by a tip with a most sharp apex. However, as clearly evident in Fig. 2 (c), even under these conditions, the row-pairing reconstruction is apparent.

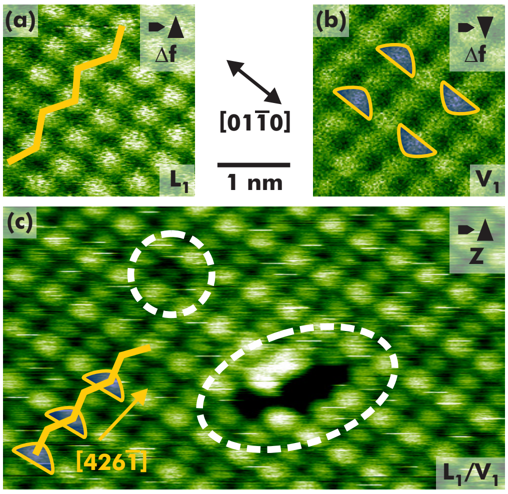

Figure 2: Atomic-resolution imaging on calcite (raw data). **a)** Contrast mode $\mathbf{L_1}$ presenting the zig-zag. **b)** Contrast mode $\mathbf{V_1}$ showing the row-pairing reconstruction as a modulation along the $[\overline{42}61]$ substrate direction. Two triangle orientations are possible if the absolute sample orientation is not known.[21] (c) Combination of these two contrast modes. A most sharp AFM tip is demonstrated by the imaged surface defects. The enantiomer identification discussed later is included in (c).

3 Symmetry and Chirality of the $(1\,0\,\bar{1}\,4)$ Calcite Surface

The $(10\bar{1}4)$ surface belongs to the plane symmetry group *pg*,[14,22] which contains glide reflections as the only symmetry element. A glide reflection is a combination of a reflection with respect to a given line and a translation along that line.[7] For $CaCO_3(10\bar{1}4)$, only one glide reflection axis oriented along the $[\overline{42}61]$ substrate direction with a

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[2] We will show later that the row-pairing changes the symmetry of the surface. Thus, it has to be accounted as a reconstruction and not as a surface relaxation.

shift of $b/2$ is found. This isomorphism is depicted in Fig.3. It should be noted that this isomorphism is still existent even if the surface undergoes a (2×1) reconstruction as the surface unit cell simply doubles along the $[01\bar{1}0]$direction. As the glide reflection axis is a symmetry element of the second kind, the $CaCO_3(10\bar{1}4)$ is thus an *achiral* surface according to the IUPAC definition.[26]

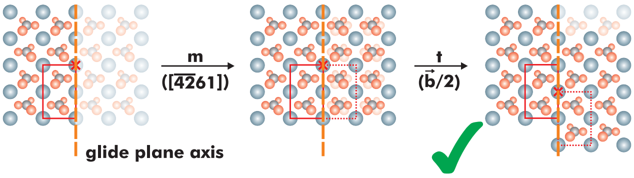

Figure 3: Glide reflection symmetry on the $CaCO_3(10\bar{1}4)$ surface. The initial configuration is mirrored along the glide axis (in orange) and translated by $b/2$ along the glide axis. The result of these symmetry operations is isomorph to the initial structure.

Interestingly, the *pg* symmetry can be violated when considering the row-pairing reconstruction. As the microscopic details of this reconstruction are still unclear, we only assume that the two carbonate groups within the surface unit cell are different. Physically, the difference could be a rotation of the CO_3 groups as proposed by Jin *et al.*[18] or any other structural or electronic reconfiguration. In our illustrated models, we simply color one row in blue. As shown in Fig. 4, the glide reflection is clearly no longer an isomorphism for the row-pairing reconstructed $(10\bar{1}4)$ surface as the position and orientation of the blue-colored carbonate groups is different after the symmetry operation compared to the initial structure. As, additionally, no other symmetry operations of the second kind are found for this reconstructed surface, the $CaCO_3(10\bar{1}4)$ is now a *chiral* surface. The two enantiomers named 1 and 2 are depicted in Fig. 4.

Three properties have to be considered when defining and identifying the enantiomers: The tilt of the carbonate group, the orientation of the topmost oxygen atom, and the “color”, which is the microscopic difference between the two carbonate groups. Neglecting the color property, both groups are identical in accordance with the glide plane symmetry presented in Fig. 3. We can abstract these properties by a triangle and the zigzag line as depicted in Fig. 4. The triangle marks the orientation of only the blue carbonate group (which can be assigned to the “bright” imaged row in the AFM experiments) and the zigzag follows the topmost oxygen positions. In this abstraction, the two enantiomers are easily distinguished by the direction of the yellow zigzag line leaving the triangle – which is either pointing left or right.

The identification of the different enantiomers is possible using the NC-AFM technique when the surface is imaged in a suitable contrast mode[30] and when the absolute crystal orientation, which is equivalent to the carbonate tilt orientation, is known.[21] Both are accessible for the calcite $(10\bar{1}4)$ surface. The row-pairing reconstruction and the zigzag have to be resolved simultaneously to meet the first condition, which is the case in modes $\mathbf{V_1}$, $\mathbf{L_3}$, and $\mathbf{L_1}$ according to the proposed contrast classification scheme.[30] The latter requirement is fulfilled as the absolute sample orientation can be determined by both, macroscopic and microscopic strategies.[21]

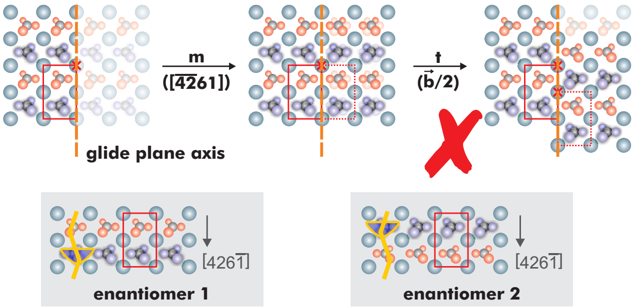

Figure 4: Glide reflection symmetry violation for the $CaCO_3(10\bar{1}4)$ surface with row-pairing: the glide reflection is no longer an isomorphism for the surface structure, rendering the calcite $(10\bar{1}4)$ surface a chiral surface. Two enantiomers 1 and 2 are found. The row-pairing is here simply visualized by a blue colored row.

Fig. 2 depicts atomically resolved NC-AFM images acquired on the calcite $(10\bar{1}4)$ surface. In Fig. 2 (c), a sharp AFM tip is assumed as single surface defects are resolved (marked by white circles). The row-pairing reconstruction is revealed along the $[\bar{4}261]$ direction as a modulation of the imaged atomic height. Additionally, the zigzag is faintly resolved as indicated by a yellow line. By determining the absolute sample orientation,[21] we can unambiguously determine the tilt direction of the carbonate groups as indicated by the yellow triangles in (c). To identify the enantiomer, we assign the row imaged “bright” as the “blue” row in Fig. 4 and can, thus, identify enantiomer 2 within this image.

4 Results and Discussion

The existence, origin and microscopic manifestation of the row-pairing reconstruction is not yet clarified. Especially, this reconstruction has so far only been observed using variants of the atomic force microscope, but these techniques have not unambiguously shown the existence of both enantiomers so far. Kristensen *et al.*[20] have analyzed the surface relaxation near surface step and kink sites by means of numerical modeling with the aim to investigate the (2×1) reconstruction. We speculate that a similiar step-edge induced formation of the row-pairing reconstruction could be possible, especially as kinks on step edges constitute chiral centers, possibly leading to the enantiomer formation.

To follow this speculation, we acquired NC-AFM data on different surface terraces next to each other. Care was taken not to induce any tip modification during this experiment to maintain the same contrast mode. The area of interest is depicted in Fig. 5 (a). The line profile in (b) reveals step heights around 3 Å, which agrees well with the height of a calcite monomolecular layer of 3.0 Å. It should be noted that four layers with a total height of 12.1 Å span a single bulk unit cell.

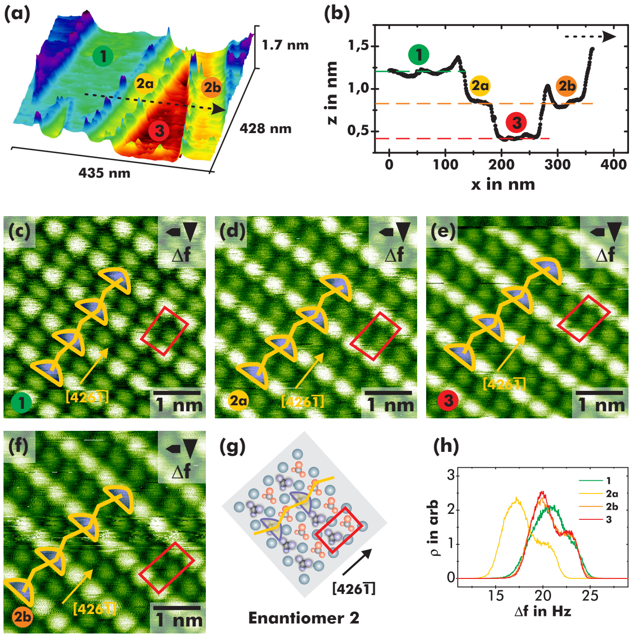

Figure 5: Identifying the surface enantiomer on different terraces. **a)** Three-dimensional representation of the relevant area, the investigated terraces are indicated by numbers 1, 2a, 2b, and 3. **b)** Line profile extracted from **a)**. **c)** to **f)** Terraces imaged at the atomic level. In all NC-AFM images, the orientation of the carbonate groups, the zigzag, and the row-pairing is indicated, unambiguously identifying enantiomer 2 for all images. The corresponding surface model is given in **g)**. The frequency shift distribution for each image can be seen in **h)**.

Atomic-resolution imaging was possible on three different terraces at four different positions named 1, 2a, 2b and 3 in Fig. 5. These terraces span 3/4 of the whole bulk unit cell. Before moving to the respective terrace, the tip was retracted from the surface to avoid any tip modification, especially upon crossing the step edges. After the tip relocation step, the tip was reapproached to the same tip-sample distance by adjusting nearly the same frequency shift set-point as indicated in Fig. 5 (h). Uncontrolled tip-sample movement due to piezo creep and thermal drift was measured and compensated after each tip relocation using a home-built atom-tracking system.[31]

All data are frequency shift images acquired in a quasi constant-height mode. All data in Fig. 5 show a combined $\mathbf{V_1/L_1}$ contrast mode, which allows for the enantiomer identification. Furthermore, the sample orientation has been identified[21] with the directions indicated. We find that in all images the surface enantiomer is type 2, thus, we do not find evidence for a step-induced enantiomer formation within this experiment.

5 Conclusions

In this work, we discussed the relation between a possible chirality of the calcite $(10\bar{1}4)$ surface and the row-pairing reconstruction. We demonstrate that this reconstruction can turn the $(10\bar{1}4)$ bulk-truncated achiral surface into a chiral one. Using NC-AFM, we present a strategy for identifying the surface enantiomer. Furthermore, we used this identification strategy to investigate the influence of step edges and terrace sites on the enantiomer formation. From our high-resolution NC-AFM data, where on each of three adjacent terraces the same enantiomer was found, we can conclude that the surface enantiomers do not generally alternate on consecutive calcite layers.

However, the row-pairing reconstruction has exclusively been observed by atomic force microscopy. By using scanning probe microscopy methods, a tip-induced artifact leading to the observed row-pairing contrast cannot be ruled out. Specifically, the chiral center could be a tip, which is chiral at the relevant imaging part. Thus, an independent evidence obtained with a complementary technique is necessary for answering the open question, whether calcite $(10\bar{1}4)$ is chiral or not.

Acknowledgments

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Methods

All experimental results shown herein were acquired with an AFM[4] operated in the non-contact (NC) frequency modulation (FM) mode.[3] With this technique, an atomically sharp tip mounted to the end of a cantilever is raster-scanned above a surface, while the interaction force between the tip and the sample is measured at every raster point. In the FM mode, this force measurement is realized by tracking the resonance frequency of an oscillated cantilever using a phase-locked loop detection scheme. The frequency shift $\Delta f = f - f_0$, which is the difference between the current frequency f and the resonance frequency f_0 of the freely oscillating cantilever, is the main measurement signal and related to the tip-sample forces.[13] All experiments were performed under UHV conditions (base pressure better than 1×10^{-10} mbar) using an Omicron Nanotechnology (Taunusstein, Germany) VT AFM 25 operated at room temperature. An easyPLL Plus from Nanosurf (Liestal, Switzerland) is used for oscillation excitation and frequency detection. Doped Si tips from Nanoworld (Neuchâtel, Switzerland) were excited to amplitudes around 15 nm at resonance frequencies around

300 kHz. The tips were sputtered by Ar^+ ions prior to usage to remove contaminants and the oxide layer. Calcite samples from Korth Kristalle (Altenholz (Kiel), Germany) were mechanically cut to the desired sample holder size and freshly prepared by in-situ cleaving[40] and annealing before the NC-AFM experiments.

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