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What Matters?

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The inexorable force of chemical synthesis to create matter with entirely new properties has profoundly changed the world—and arguably so—largely for the better. Developed societies embrace the service that chemistry can provide, while otherwise cultivating a certain chemophobia (certainly in Europe). Many reasons are to be blamed for this somewhat schizophrenic attitude, including some severe mistakes on our own side. Another issue is the difficulty of conveying the beauty of our science to the general public. Organic chemistry uses a notation that only an adept scholar is able to understand. Mathematics and music face a similar challenge: as a result, the fruits of these disciplines are subject to mass consumption too, but real appreciation is scarce and, maybe, even declining as a consequence of changing priorities in the education system. One may complain about this situation, but we are well advised to keep touch with a broad audience. Neither ignorance nor skepticism form a sound basis for sustained public support for science in general and chemistry in particular. In fact, dwindling financial resources are an increasingly serious menace for basic research in many countries.

In times when money is tight, topics that do not promise any short-term revenues often have a hard time to get funded. The political expectations often take the form of top-down agendas that predetermine what scientists have to be interested in if they want to survive within their system. Neither can I convince myself that such "five-year plans" are the best response to the challenges that modern society is facing, nor do I believe that they correspond particularly well to the very nature of the chemical sciences. Let me give you a few examples that I consider reasonably representative.

It is fair to say that the organometallic chemistry of palladium, an exceedingly rare and expensive metal, has had a tremendous impact on our quality of life. Not only a panoply of important drugs, but also agrochemicals, liquid crystals, and even sun protecting agents, are made through palladium catalysis, with massive annual sales. Interestingly, this success story can be traced back to some pretty basic and curiosity-driven investigations. One of the key contributions was made by Tsuji and coworkers, who reacted malonate anions with stoichiometric(!) amounts of allylpalladium complexes to form mixtures(!) of products that can be made much more readily otherwise. Although definitely not practical, this result has fundamentally changed our understanding of organometallic chemistry because it proved that organopalladium species are electrophiles rather than nucleophiles (as essentially all other organometallic species known at the time). In similarly pioneering studies, Heck investigated the reactivity of organomercury(!) compounds in the presence of palladium salts. Incidentally, the author was working in industry at the time. Would any of these research projects get funded under today's circumstances? In a climate favoring investigations of practical relevance, such proposals might well cause Homeric laughter. Hence, everybody who has to take a drug compound made by cross-coupling partly owes his or her health the liberty of the funding agencies forty years ago—not to speak of the wealth that this chemistry has ultimately created in return to the start-up investment of money. "*This was sometime a paradox, but now the time gives it proof*" (*Hamlet*).

In this context, I also kindly ask you to re-read the original publication on biaryl formation through what later became famous as the Suzuki coupling. Would you have predicted then that this paper will change the world and finally lead its author to Stockholm? Olefin metathesis is yet another formidable case; only after a "lag period" of about three decades of pretty basic organometallic research was the avalanche set off. Finally, I can't help but reiterate the story of Karl Ziegler, former director of my own institute. As a young man he discovered that benzylpotassium reagents add to stilbene. This somewhat exotic result, however, actually denotes the first recorded case of a carbometalation reaction and, as such, Ziegler's first step on his path to polyethylene which took no less than three more decades from there on.

Of course, I appreciate that only very few innovations gain such relevance. At the meta-level however, these examples showcase that innovation eventually wins over trendiness, quality over political agendas, originality over mass production, curiosity over determinism, reliability over mannerism. Whereas glamour asks for immediate reward, innovation means sustained success.

If you ever tried to chase a complex natural product yourself, you may have experienced how challenging, labor intense, expensive, and even frustrating

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total synthesis can be. If that raises doubts about the relevance of the field altogether, I kindly ask you to take a minute before ruling the final judgment. Many people tend to forget that natural products made by total synthesis are today on sale in any convenience store. Take, for instance, vitamin C, whose de novo synthesis was originally developed in an academic environment. It uses a renewable starting material, is protecting-group free, and entirely catalysis-based; comprising heterogenous, homogeneous, and biocatalytic steps. This wonderful piece of academic research of the greatest practical beauty. It provides a striking illustration of the fact that natural product synthesis is not just an intellectual game to satisfy autistic academicians, but can prove effective and economically viable on a scale greater than 100000 tons per year.

Likewise, the vast majority of drug compounds on the market continue to be made by multistep routes. The anticancer agent Halaven is made on scale by a sequence comprising more than 60(!) steps. What was the time frame to make this project successful? Is total synthesis really obsolete? Is the answer the same if one has to resort to such a drug?

Yet, science must not be mistaken for a slot machine where you put one dime in and get two dimes back. We need to emphasize in public that some of the biggest triumphs of our discipline are to be credited to projects that were strictly devoid of any practical meaning. There is obviously no need to synthesize glucose, as it is the most abundant organic molecule on earth. Its structure elucidation and conquest by Emil Fischer, however, rigorously proved the then still controversial concept of the tetrahedral coordination geometry about carbon to be correct. At the same time, this monumental accomplishment heralded the age of stereoselective synthesis. Several decades later, a totally different approach to the hexoses by Sharpless and Masamune became an eye-opener again, thus illustrating the awesome power of strictly catalyst-controlled asymmetric synthesis.

The glucose case is by no means the only synthesis project of the highest intellectual caliber but devoid of any immediate economic implications. The Woodward–Hoffmann rules and Corey's concept of retrosynthesis also come to mind: in either case, inspiration was provided by targets (vitamin B_{12}, longifolene) whose total synthesis nobody could ever justify by utilitarian arguments. I sincerely hope that our funding institutions are still prepared to support projects that don't even pretend to cure cancer.

Some may object that I talk about a glorious past. I gather that even fellow chemists pretend that the time of the great discoveries in "hardcore" chemistry is coming to an end and that chemical synthesis is increasingly obsolete. "*In chemistry, everything has been discovered. Well, not everything, but lots of it.*"[1] Others linked total synthesis to "macho" behavior.[2] Yet others proclaimed that "*one can imagine producing nearly any organic molecule—even those that are not produced naturally—in an engineered microorganism*", not without emphasizing that "*synthetic biology has many advantages over chemical synthesis*".[3]

Although I admit to be biased, I can't see that these arguments are particularly sound; in any case, they are not in line with my personal experiences: since my graduation in the late 1980s, I witnessed how catalytic C–C and C–X cross coupling fundamentally changed the way molecules are stitched together; I saw acyclic stereocontrol taking reign; I experienced the avalanche of interest in asymmetric catalysis as well as the triumph of metathesis once metal carbenes had been taught chemoselectivity; since then, the implementation of parallel synthesis has profoundly changed the practice of medicinal chemistry; the use of small organic molecules as catalysts has evolved from singularities to textbook knowledge; likewise, N-heterocyclic carbenes were known then but basically irrelevant; C–H activation played hardly any role thirty years ago but now forms a real "hot spot"; the same is true for π-acid catalysis. I simply can't see that the time of chemical discovery is coming to an end; rather the ability of the synthesis and catalysis community to innovate seems as strong as ever.

Synthetic biology without doubt is a fascinating field that stimulates natural product chemistry and challenges traditional synthesis; sure enough, it will provide the better solution in certain cases.[3] I am neither envious of its success nor am I afraid that it makes chemical innovation obsolete. I suppose that mankind will need synthetic chemistry as well as synthetic biology (which can indeed be considered a branch of chemistry) to solve the many challenges it is facing. Rather than spending time on "religious warfare" within the community, we should lobby together for adequate support for the best science.

As the new Chairman of the Editorial Board of *Angewandte Chemie* I will do my very best to foster this process in a dialogue with the editorial office and the scientific community at large. *Angewandte Chemie* has and always will have a liberal policy that is based on quality rather than fashion; after all, scientific publishing is a part of science itself.

[1] E. L. Winnacker, *Chemistry World*, May **2007**, p. 13.
[2] a) R. F. Service, *Science* **1999**, *285*, 184; b) C. Djerassi, *Science* **1999**, *285*, 835.
[3] J. D. Keasling, *Nature* **2012**, *492*, 188.