“It’s starting to spit!” exclaimed Fritz Haber one afternoon in the laboratory of Physical Chemistry at the University of Karlsruhe sometime in the middle of the year 1909. He was greatly excited, realizing his achievement to synthesize ammonia from its elements nitrogen and hydrogen for the very first time! “This was a moment of glory not only for Haber but also for mankind and human history,” acknowledged Professor Athanassios Giannis from the University of Leipzig (Germany).

The credit for the industrial production of ammonia (more than 100 megatons per year) belongs, however, to Carl Bosch (Figure 1), an expert in high-pressure technology, and Alwin Mittasch, an expert in catalyst development, both working at BASF (Germany). F. Haber and C. Bosch were each awarded the Nobel Prize in Chemistry, in 1918 and 1931, respectively. “It is estimated that the number of humans supported per hectare of arable land has increased from 1.9 to 4.3 persons between 1908 and 2008,1 which was made possible mainly because of Haber–Bosch ammonia production,” said Professor Giannis, who added: “It is calculated that every second nitrogen atom in our body stems from the Haber–Bosch process! It is also estimated that 40% of the world’s population at the end of the twentieth century was dependent on fertilizer inputs to produce food. Nitrogen fertilizers were responsible for feeding 44% of the world’s population in 2008. That means the lives of about half of the human race are made possible by the Haber–Bosch process!! ‘Bread out of air’ is a German term used to describe these facts.”

Ammonia is used not only for the production of fertilizers but also for the synthesis of drugs, dyes, fibres and a lot more. “Unfortunately, there is a dark side to ammonia: it is used in the production of explosives. The Haber–Bosch process is directly linked to about 150 million deaths in the last century,” said Professor Giannis.

During the years 1998 – 2002 Athanassios Giannis was Professor of Organic Chemistry at the University of Karlsruhe (Germany). About that period, he recalled: “I had the opportunity every day to see the (in the meantime roasted) high-pressure steel reactor for the production of ammonia via the

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**Figure 1** Carl Bosch (1874–1940)

**Figure 2** First page of Bosch’s PhD work
Haber process, displayed at the beginning of the Fritz-Haber-Weg on the university campus. By a curious quirk of fate, I moved to the University of Leipzig (Germany) in 2002, where Carl Bosch had performed his PhD work under the supervision of Johannes Wislicenus. He continued: “Last year I had a discussion with my colleague Professor Lothar Beyer, a retired Professor of Inorganic Chemistry who is deeply interested in historical aspects of the University of Leipzig. He is presently preparing the second volume of the book “Vom Doktoranden zum bedeutenden Chemiker”, Passage Verlag Leipzig, with Dr. Lothar Hennig, and in this context they asked me to help with the re-evaluation of Carl Bosch’s PhD work.”

In his thesis entitled “Über die Kondensation von Dinatriumacetondicarbonsäurediethylester mit Bromacetophenon” (undertaken in Leipzig between 1896–1898, Figures 2 and 3), Bosch envisaged the synthesis of a derivative of heptamethylene (a cycloheptane derivative). These efforts were related to the work of F. S. Kipping and W. H. Perkin, but the young student realized that the reaction did not yield the expected product. In fact he isolated a derivative having the formula $C_{25}H_{24}O_6$ and proposed three different structures 1–3 with a preference for 2 (Figure 5). Professor Giannis said: “I was glad to meet Toni Smeilus, a smart undergraduate student who was very enthusiastic to participate in these studies. He performed the reaction and from the yellow-colored mixture (Figure 4) he isolated a main product.” Professor Giannis continued: “Subsequently, and using modern analytical methods (high-resolution mass spectrometry, NMR) as well as X-ray
crystal-structure analysis (Figure 4) we were able to identify the structure of Bosch’s product: It was the highly functionalized cyclopentenone with structural formula 4 (Figure 5). This reaction is generally applicable and further similar cyclopentenone derivatives were synthesized. From the mixture of the original reaction, traces of derivative 5 (mixture of isomers) were also isolated."

This method enables access to highly functionalized cyclopentenone derivatives, which occur in several bioactive natural products, as for example, in cyanthiwigin diterpenoids, aflatoxins, manamone, cantabrenoates, or in other anti-proliferative agents like rocaglamide and silvestrol. Finally, a merger of Hünlich base 3 and Bosch product 4 was successfully performed to obtain derivative 6. Professor Giannis remarked: “By the way, Hünlich was also a PhD student at our university about 100 years ago.”

Professor Giannis said: “In summary, Bosch made a mistake concerning the structure of his derivative. However, he did not have the analytical tools we now routinely use. Using these tools we were able to elucidate the structure of the unknown derivative and simultaneously open the way for the synthesis of compounds containing a highly functionalized cyclopentenone moiety. Bosch’s mistake, combined with our curiosity, disclosed new organic compounds that can serve the organic chemist working in the area of natural product synthesis.”

The syntheses in this work were performed by Toni Smeilus, with NMR studies by Dr. Hennig. Professor Sieler was responsible for the X-ray crystal-structure analysis and Professor Beyer rediscovered Bosch’s PhD work. Professor Giannis concluded: “I only had the pleasure to wait in my office for the nice and exciting results!”

REFERENCES


Figure 5 For details see text
About the authors

Lothar Hennig was born in Eilenburg (Germany) in 1953 and obtained his PhD in 1981 at the University of Leipzig. Since 1992 he has been the Laboratory Head of Spectroscopy within the Institute of Organic Chemistry. The main topic of his work is the structure determination of organic compounds, especially by NMR methods. He is author and co-author of more than 160 papers and collaborates with numerous national and international institutions.

Joachim Sieler was born in Markranstädt (Germany) and obtained his PhD at the University of Leipzig in 1966. He established X-ray crystal-structure analysis at the Faculty of Chemistry and is author and co-author of 216 papers in the field of solid-state and structural chemistry.

Toni Smeilus was born in Leipzig (Germany) in 1990. He received his Bachelor of Science in chemistry from the University of Leipzig in 2013 and is currently performing research under the supervision of Professor A. Giannis at the same university as a postgraduate student. His research concerns, among other topics, the synthesis of C-nor-D-homosteroids.

Athanassios Giannis is a chemist and physician. He was born in Greece in 1954 and studied chemistry from 1972–1980 and medicine from 1978–1987 at the University of Bonn (Germany). He completed his PhD in 1986 with Konrad Sandhoff and habilitated in 1992 at the University of Bonn in organic chemistry and biochemistry. From 1998–2002 he was Full Professor of Organic Chemistry and Natural Products Chemistry at the University of Karlsruhe (Germany). Since 2002 he has been a Full Professor of Organic Chemistry and Natural Products Chemistry at the University of Leipzig. His area of research is biological- and medicinal-oriented organic chemistry.

Lothar Beyer is Professor Emeritus of Inorganic Chemistry at the University of Leipzig (Germany). He was born in 1936 in Oberwiesenthal (Germany), studied chemistry and obtained his PhD in 1965 under the supervision of Eberhard Hoyer at the University of Leipzig. He was Visiting Professor at the Chemistry Department of the University Montevideo (Uruguay) from 1970–1972 and Professor of Chemistry at the Technical University of Leipzig from 1982–1993. He was appointed as a C4-Professor at the University of Leipzig in 1993 and became Director of the Institute of Inorganic Chemistry. His research is focused on coordination and bioinorganic chemistry with sulfur ligands, the history of chemistry and the relations between chemistry and art. He has published several textbooks in inorganic chemistry and various books about the history of chemistry. He received Doctor honoris causa of the San Marcos University Lima (Peru) in 2000.

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From left to right: Prof. L. Beyer, Dr. L. Hennig, Prof. J. Sieler, Prof. A. Giannis, T. Smeilus