Special topic

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Peaks and more

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Abstract: After an engagement in analytical chemistry during 50 years, I am looking back to my scientific carreer. To some extent it is based on my successful textbook in high-performance liquid chromatography. However, too much contemplation of one's own contributions to science is boring, and it is necessary to look ahead to the future challenges in chemistry, namely to cope with the threats of climate change. And there is another topic which was and is most important in my life: mountain climbing. Its physical and maybe also mental top was to reach the summit of Mount Everest in May 2007.

Keywords: analytical sciences; chirality; chromatography; Distinguished Women in Chemistry and Chemical Engineering; HPLC textbook; measurement uncertainty; mountain climbing; peak capacity; peak overlap.

Looking back

Fifty years ago, my professional occupation with chemistry started. In 1968, as a 17-year-old, I began an apprenticeship in Bern (Switzerland) at the Swiss laboratories for drug control, by then the *Interkantonale Kontrollstelle für Heilmittel*, now *Swissmedic*. Since we were analysing drug formulations, this education led me to analytical chemistry, a field I never left although I learnt also preparative (organic) synthesis. After this 3-year apprenticeship I studied chemistry and chemical engineering at the *Technikum Burgdorf* for another 3 years; the *Technikum* is now called *University of Applied Sciences*, and the diploma degree is a Bachelor of Science. Later I got a job at the University of Bern, *Institute of Organic Chemistry* (now *Department of Chemistry and Biochemistry*) in the field of separation science, mainly high-performance liquid chromatography (HPLC), which was a very young technique in 1976.

Although not being part of my duties, this job offered the chance to take time by the forelock, namely the possibility to publish scientific papers. My first two papers in English as a single author were about preparative HPLC [1] and HPLC theory "for the practitioner", i.e. a hands-on discussion of the parameters which can easily be obtained from a chromatogram [2]. This latter paper was an incredible success; I got more than 600 postcards from all over the world (there was no internet yet) demanding a reprint. And this second paper was somewhat typical of me: It was a product of thinking and logic and not of experimental work. I need to confess that I was always more a thinker than an experimenter; a single-working person instead of a group leader who inspires her collaborators. Maybe this is the reason why I never became a professor. This fact was not for the worse: Less professional duties allowed to spend more time for my second passion besides science – mountaineering.

Then there was another opportunity during my appointment at the University of Bern. After some years of observing the students and how they were engaged in their PhD work, I realized that I could strive for my own PhD. Since my appointment was not more than a 65 % job, I continued working but passed also some exams, wrote a master thesis (about enantioselective HPLC), and finally wrote a PhD thesis (about preparative HPLC). In 1989 I had completed all this and went to Israel (Weizmann Institute of Science, Rehovot) and to the USA (University of Delaware, Newark, DE) for post-doctoral studies. After my return to the University of

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Bern, I was again an employee of the Department of Chemistry and Biochemistry until 1997 when my appointment came to an end. However, in 1995 I could achieve the *Habilitation* and became *Privatdozentin* with the formal right to teach at the University. In all these years, HPLC was my main scientific interest.

From 1997 to 2015 when I reached the age of retirement I worked at *Empa Materials Science and Technology* in St. Gallen (Switzerland) with a focus on measurement uncertainty in analytical chemistry. Although I was no longer a university employee, I continued teaching at the Department of Chemistry and Biochemistry (HPLC, chromatographic analysis, and measurement uncertainty) until 2014.

I am very grateful for my broad education in chemistry. The studies included a lot of mathematics, physics and biology, opening a comprehensive view on many aspects of our world: What is the composition of wood, of blood, of a transistor? Why is chlorine an extremely aggressive gas while helium is inert? How tiny are the atoms and of which kind is their influence on the properties of the elements? Why is there a limited number of elements, and is it really limited? Which molecules act as greenhouse gases and why? How small is man compared to Earth, and how small is Earth compared to the universe?

Writing a book

When I began to use HPLC, a certain textbook was the top reference: Snyder and Kirkland's *Modern Liquid Chromatography* [3]. In addition, there was a book by Engelhardt in German [4]. The technique began to find its way into the analytical laboratories, and in 1977 I was asked by the Bernese association of laboratory technicians to give an educational course about HPLC. They not only wanted oral instructions but also a written text. Therefore I prepared a manuscript in German; its first version was printed chapter by chapter in the journal

Fig. 1: The first German edition (1979), the version printed in the *Schweizerische Laboratoriums-Zeitschrift* (1978–1980), and the fifth English edition (2010) of *Practical High-Performance Liquid Chromatography*.

of the association, the *Schweizerische Laboratoriums-Zeitschrift*, between September 1978 and February 1980. After edition, this text appeared as a book in 1979 [5] which was dedicated to my late husband Otto Meyer. In a process of continuous improvement and extension, its tenth edition appeared in 2009 [6]. Nine years after the first German edition, Wiley in England realized that there is a successful book about HPLC and published it in English; its fifth edition appeared in 2010 [7]. Figure 1 shows the evolution of this HPLC textbook.

I suppose that it was this book which led to the IUPAC award *Distiguished Woman in Chemistry/Chemical Engineering* in 2017. Of the German editions, more than 20 000 copies were sold, of the English ones more than 10 000 copies.

This book shaped my scientific carreer and was keeping me busy for more than 30 years. In fact, it is not really customary to publish an influential book by the age of 28. The work still makes me proud and happy because it helped many people to do proper HPLC analyses. Its success was probably based on its hands-on approach with many problems and answers. It was *practical* although I presented a lot of theory. With any analytical technique, only the comprehension of its background and theory leads to its proper use and to correct results. The text of the book could be understood by laboratory technicians as well as by chemists with a doctoral degree.

In addition to this basic textbook I also created a "picture book" which demonstrates what can go wrong in liquid chromatography: *Pitfalls and Errors of HPLC in Pictures* [8]. Both the German and English versions were published in three editions between 1996 and 2013, always improved and expanded. Instead of teaching the readers "you must not do this or that" in a theoretical manner, this book shows with real examples how a chromatogram looks like if a mistake occurred during sample preparation or the chromatographic process.

Chromatography

During my "HPLC carreer" at the University of Bern I did a lot of column packing, from the analytical scale with 3.2 mm inner diameter to 21 mm preparative columns. Indeed, my first scientific paper, written in German, was about how to pack HPLC columns [9]. The topic was new by then and the choice of commercial products was very limited, making the self-packing of columns a real alternative. In our laboratory, we used mostly the 3.2 mm columns for analytical tasks. I could never understand why 4.6 mm columns were (and still are) so popular; they need the double volume of mobile phase (producing the double volume of waste solvent) than the smaller columns [2].

One of my important tasks during this time was the preparative HPLC separation of mixtures from organic synthesis, prepared by the master and PhD students in the course of their research [1]. As a logical consequence, *Preparative HPLC as an Aid in Organic Synthesis* was the title of my fist poster ever, shown at the 1984 liquid chromatography symposium in New York.

During my post-doctoral work in the field of dating of fossils by amino acid racemization [10], I began to wonder about the accuracy of analytical results obtained from overlapping chromatographic peaks. If a sample consists of many compounds of interest, e.g. of amino acids in both enantiomeric forms, it is very demanding to obtain a chromatogram with fully resolved peaks. What about the quantitation of overlapping peaks? This question looks trivial, but up to the early nineties this problem was rarely mentioned, and if, the opinions published were not consistent. I love simple questions – why ponder on difficult problems if there is no answer to the simple ones? As expected, but indeed new, the answers were rather simple, too, see Fig. 2: If overlapping peaks are symmetric (Gaussian) and of equal size, there is no area error by integration. If they are or non-equal size, the smaller one is too small, the large too large, irrespective of their order. If overlapping peaks are tailed (the usual case), the area of the first one is too small, the second one is too large [11]. The case of "rider peaks", i.e. of a small peak sitting on the tailing edge of a much larger one, is a topic of itself [12, 13].

To avoid such errors, all peaks to be quantified should be fully separated in a chromatogram. This problems leads to the question of the statistical distribution of peaks [14]. Although they are eluted in accordance to the physico-chemical properties of the analytes, the stationary phase, and the mobile phase, in many cases their elution pattern looks statstical for the observer. Analysts must cope with statistical peak overlap, and their weapon is a high peak capacity of their separation system [15]. The peak capacity is the number of peaks which can be resolved from each other with resolution 1.0 which is a bit less than baseline separation.

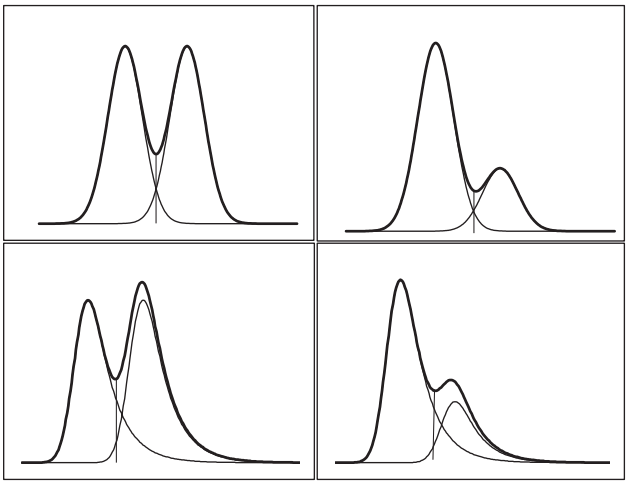

Fig. 2: Integration errors when overlapped chromatographic peaks are separated by a vertical drop. Top left: Both peaks are integrated correctly because they are of equal size and symmetrical. Top right: The area of the small peak is too small, irrespective of the elution order. Bottom: In the case of tailing, the area of the second peak is too large.

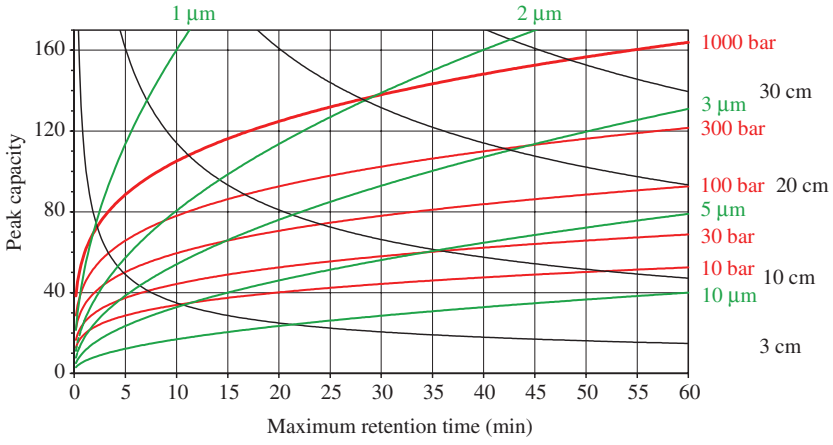

Fig. 3: How many peaks can be resolved with resolution 1.0 within a given time at optimum van Deemter velocity of the mobile phase in isocratic mode? Example: If the system allows to work at a pressure of 1000 bar (in red) and if the separation time must not be longer than 30 min, a column of 20 cm length (in black), packed with a 2 µm stationary phase (in green) of the reversed-phase type yields a peak capacity of approx. 140, see the highest intersection of the red, black, and green lines in the graph. The maximum peak capacity of 160 is obtained with 1000 bar, a column with a length of more than 30 cm, a stationary phase of 2.5 µm, and an elution time of 1 h. The eluent has a viscosity of 1.2 mPa s.

The task is very demanding and expensive, as can be seen in Fig. 3 which shows a typical HPLC case, namely isocratic separations in the reversed-phase mode. As a matter of course, peak capacity is higher in gradient separations but this mode increases the performance of the system shown in Fig. 3 to not more than 400 resolved peaks (linear gradient form 10 % to 100 % B solvent). If the sample mixture consists of, e.g. 100 compounds which must be resolved, a peak capacity of 400 is ridiculously small.

Chirality

Many macroscopic objects of our world are chiral – think of finger gloves. It is funny to discover chirality in daily life: books (a book in Arabic is handled in a different way than a book in English); shirts (the buttons

are placed on different sides for men's and women's shirts, this goes back to the old times when men were armed with a sword); snowboards (the binding is mounted *regular* or *goofy*, depending on the preference of the user); and cars of any type, see Fig. 4, to name but a few.

Molecules can be chiral, too, and the two forms may differ markedly in their properties, e.g. as a drug. In the early eighties, several research groups began to synthesize and study HPLC packing materials with a chiral bonded phase on silica, which offered one of several possibilities for the liquid chromatographic separation of enantiomers [16]. Also the group of Professor Hans Arm at the Institute of Organic Chemistry, University of Bern, was involved in this research [17].

I was always fascinated by the phenomenon of chirality and its influence on the properties of molecules and other objects. After a lot of thinking I came up to a truly hands-on representation of the so-called *three-point interaction rule* by Dalgliesh [18]: For enantioselective recognition, three attractive interaction points or two attractive and one repulsive points are needed for a chiral selector being able to discriminate between the enantiomers. My friend Maya Rais, a graphic designer, created the illustrations as shown in Fig. 5 [19]. Professor Vadim Davankov of the *Academy of Sciences*, Moscow, was fascinated and proposed a follow-up paper, again illustrated by Rais [20]. These two papers were by far the most beautiful ones of my scientific carreer.

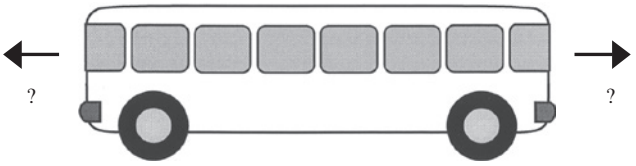

Fig. 4: In which direction is the bus driving? Go to the next bus station and compare real vehicles and the drawing. The answer depends on the country you live; e.g. it differs in the United Kingdom from continental Europe.

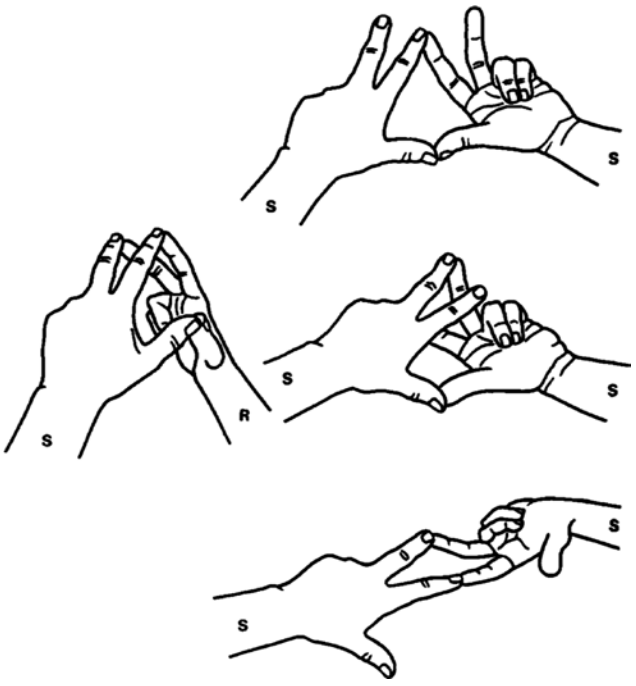

Fig. 5: With three interaction points between selector and selectand, enantioselective discrimination is possible, as in the case between a left (S) and a right (R) hand. With two left hands, only two interactions are possible [19]. Transferred to molecules, the RS complex is more stable than the SS complex. In chromatography (and in this very case), the S enatiomer would be eluted first.

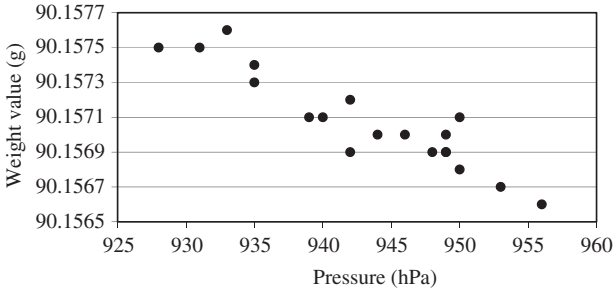

Fig. 6: Dependence of the weight value (the "mass") of an empty and open 50 mL Pyrex glass bottle with density 2230 kg/m³ from the atmospheric pressure measured in St. Gallen, Switzerland, over the span of 6 months. The experiments were performed in an air-conditioned laboratory of 23 °C and 50 % relative humidity. The balance displayed a resolution of 0.01 mg but the values were rounded to 0.1 mg.

Measurement uncertainty

In 1998 I got a job at Empa because by then, this research institute was running a program about measurement uncertainty, in analytical chemistry. Luckily for me, they needed a specialist in chromatography. Indeed, it was the perfect match because I was also interested in errors and uncertainties which may happen in chromatographic analyses.

Any measurement in science is subject to uncertainty; repeating the measurement will yield a deviating result if the resolution of the measuring process or instrument is adequate. A comprehensive guide about measurement uncertainty in analytical chemistry is published by Eurachem/Citac [21].

In many chemical analyses, the sample preparation is the step which carries the highest weight to the total uncertainty, in both aspects – systematic deviation (as recovery) and random variation (measured as standard deviation of the result). The uncertainty of an analytical reference standard can be in the 1 % range [22]. For highly precise analyses it is necessary to look also at the detail. An autosampler can be the source of imprecision [23]. A signal (a chromatographic peak or any other representation of a measurement) with low signal-to-noise ratio suffers from this disturbance, resulting in poor repeatability [24]. Weighing, i.e. the determination of a mass, can be highly precise [25]; however, air buoyancy can corrupt the weighing result of an object with low density [26]. This fact is often overlooked. The weight value (the number on the balance display) of a glass bottle depends on the local variations of the atmospheric pressure. If all other parameters of the air density (mainly its temperature and humidity) are constant, the weight value can fluctuate in the 10^{-5} range, see Fig. 6, an order of magnitude which can easily be detected with analytical balances. When organic liquids are weighed, this effect is in the per mil range.

Measurement uncertainty data should be a mandatory part of any analytical result. In most cases, it is not necessary and even unwanted to keep it as low as possible. A very low uncertainty must be paid dearly, making the analysis expensive. If the legal upper concentration of a pesticide in drinking water is, e.g. 0.1 µg/L, a simple analytical method with a relative uncertainty of 10 % can be used as long as the measured value is always at the 0.01 µg/L level. On the other hand, if one wants to know if the copper concentration in a certain ore is high enough for profitable mining, the uncertainty should be in the per mil range.

The *Highlights of Analytical Sciences in Switzerland*

The *Swiss Chemical Society* (SCS) consits of several Divisions. When I became a committee member of the *Division of Analytical Sciences* in 2006 (by then the *Division of Analytical Chemistry*), I was asked to write a regular column about analytical topics in the SCS journal *Chimia*. But analytical chemistry is too big a subject to be overlooked by a single person. Therefore I decided to let the involved scientists describe their work by them-

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Highlights of Analytical Sciences in Switzerland

Division of Analytical Sciences
A Division of the Swiss Chemical Society

^{1}H High-resolution Magic-Angle-Spinning NMR Spectroscopy to Determine Phosphate Sugars in Biological Tissues and Cell Cultures

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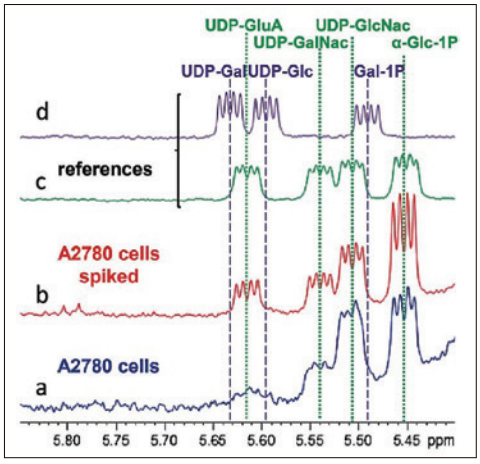
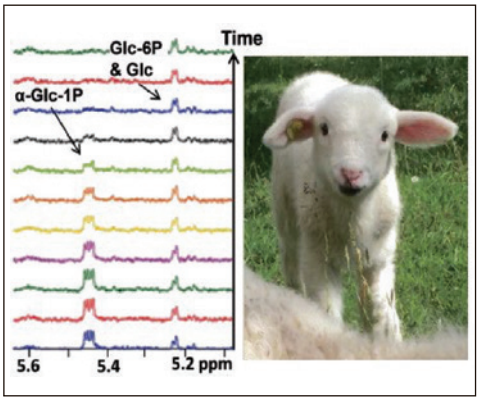
Keywords: Glucose phosphates · ^{1}H HR-MAS NMR · Nucleotide sugars · UDP-X

Nucleotide sugars, mainly those containing uridine diphosphate (UDP-X), are key players in glycosylation processes. Glucose phosphates (Glc-1P and Glc-6P) are intermediate metabolites of the glycogen cycle and as such important for storage and transfer of energy. Tissue biopsies and cells can be metabolically characterized by high-resolution magic-angle-spinning (HR-MAS) NMR. Temporal metabolite changes can be monitored by this technique, thus enabling metabolic pathway activities to be followed. ^{1}H HR-MAS NMR allows these phosphate sugars to be assessed qualitatively and quantitatively as a minimally invasive analytical tool, preserving the cell and biopsy integrity, as no extraction or separation steps are required.



Cell NMR spectra spiked with different phosphate sugars, confirming the presence of UDP-GluA, UDP-GalNAc, UDP-GlcNAc and α-Glc-1P. Reprinted with permission from Springer, Diserens *et al.*



Sheep cardiac muscle NMR spectra acquired over 3.5 h after biopsy, showing the evolution of the α-Glc-1P content.

Anomeric sugar protons bound to phosphate show the typical doublet of doublet resonances between 5.4 and 5.7 ppm. Due to similar patterns and only slight chemical shift differences of those peaks originating from different sugar phosphates, a correct assignment can be challenging. Therefore, the metabolite assignment was supported by spiking experiments.

The results of our study clearly demonstrated that sugar phosphates can be determined quickly and non-destructively in living cells and in biopsies by HR-MAS, including their quantitative estimation, without extraction processes. Considering the importance of phosphate sugars in cell metabolism for nucleic acid synthesis, HR-MAS measurements may prove valuable. Different phosphate sugars could be clearly separated from each other. In skeletal and cardiac muscle, the presence of α-Glc-1P and Glc-6P could be unambiguously assigned. The α-Glc-1P kinetics proves exemplarily the possibility of monitoring metabolic processes dynamically by ^{1}H HR-MAS NMR. As suggested by the kinetic analysis, the initial α-Glc-1P increase and subsequent decrease may be due to glycogen breakdown, followed by enzymatic conversion into Glc-6P and finally Glc through phosphoglucomutase. **^{1}H HR-MAS NMR allows the assessment of phosphate sugars contained *e.g.* in cells and skeletal and cardiac muscle biopsies, and facilitates the study of their kinetics for monitoring metabolic pathways.**

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Reference

G. Diserens, M. Vermathen, I. Gjuroski, S. Eggimann, C. Precht, C. Boesch, P. Vermathen, *Anal. Bioanal. Chem.* **2016**, *408*, 5651.

Can you show us your analytical highlight?
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Fig. 7: An example of the *Highlights of Analytical Sciences in Switzerland* in the journal *Chimia* [27]. With permission from the Swiss Chemical Society and from Dr. G. Diserens.

selves. I created the one-page *Highlights of Analytical Sciences in Switzerland* with a focus more on interesting applications than on fundamental research. They should be interesting reading for every chemist irrespective of his or her specific field of work. An example is presented in Fig. 7 [27]; it is the first one which appeared after the IUPAC *Distinguished Women* award ceremony in São Paulo on July 9, 2017. By the end of 2018, a total of 136 *Highlights* were published, one in every of the ten *Chimia* issues per year. The *Highlights* represent a

truly unique type of scientific communication. They can be downloaded free of charge from https://chimia.ch (look for *Columns*).

Mountains, the real peaks

Science, as important as it was and is for me, is not my only passion. An inexplicably strong one are the mountains and mountaineering. In the course of decades, I could climb almost all 4000-meter summits of the Alps (Aiguille Blanche de Peuterey, Aiguille Verte, and Barre des Ecrins are missing) and over 1000 other different peaks higher than 2000 meters. My personal list of mountain peaks also includes the *Seven Summits*, the highest peaks on all the seven continents with Mount Everest as the top which cannot be topped. We, a group of five (including two sherpas), reached the summit on May 16, 2007 at 4 a.m. which means that we were sitting there in darkness and fog. Nevertheless, the climb during the night was less strenuous than expected, and the descent offered spectacular views, see Fig 8.

This exploit was not predetermined. My parents were hikers but not mountaineers with rope, ice-axe, and crampons. And when I was 23 years old, I learnt that I suffered from a heart defect at the aortic valve which could become life-threatening in my fifties or even earlier. Nevertheless, I was not limited in my climbing activities until age 46, but then the moment came when I told my doctor that it was time for heart surgery. A mechanical aortic valve was implanted. Of the Seven Summits, I had climbed Kilimanjaro and Carstensz Pyramid before this surgery, and Elbrus, Aconcagua, Denali, Mount Vinson, and Mount Everest after it. For decades, Everest was out of my focus, but after I had been successful on six of the prestigeous summits I tried also the highest one. It was not easy, and only the fifth attempt brought me to the top of it. When looking at my medical condition, this story is a really uncommon one; it was the reason that I wrote my memoirs [28].

Why mountaineering? To me, the answer is still not obvious, and it is complex. Climbing a mountain, especially one which is new to me, is a demanding task both physically and mentally. On this view, it is a perfect parallel dimension to the mental and laboratory work in science. If you want to learn self-dependent

Fig. 8: Coming back from the summit of Mount Everest to the highest camp on the North side, located at an altitude of 8300 m. Everything up there is aslope!

climbing, you need to conquer fear, to improve your technical skills, including orientation, to endure exertion, to develop complete trust in your partner, and to judge difficult and dangerous situations correctly. In my case, a hidden motif could be that mountaineering is completely useless, while I was always striving for useful insight in science. An obvious but thrilling motif is the ever new and inspiring experience of incredibly grandiose and beautiful landscapes in many places of our world.

Looking ahead

In the future, we will need all the mental power of mankind to cope with the huge challenges which threat life and peace on Earth. Of course, I invite all young people to study chemistry or the other natural sciences. But we need also brilliant lawyers, journalists, teachers, medical doctors – as well as musicians, professional fine artists, poets, and actors. During your professional and private carreer, do not forget to be yourself, but not to be selfish. Be honest and follow your decent goals. Do not invest your working power and intelligence in something which may harm other people or Nature. Do not run after money but after knowledge.

Maybe go to politics. There are by far not enough elected members of parliaments with a sound background in natural sciences. Unfortunately many of these members lack knowledge of physical, chemical, or biological processes. Therefore the threat by climate change is undervalued; the urgent measures are not taken and necessary laws are not enacted. Personally, I am an elected member of the city parliament of St. Gallen since 2015 for the Green Party. My role model in local politics is Jacques Dubochet, winner of the Nobel Prize in chemistry in 2017, who is an elected member of the city parliament of Morges, a town located at the Swiss shore of lake Geneva.

The times when chemists invented poison gas or chemical weapons must be over. In contrast to such dark activities, it is a real satisfaction to create new drugs, to control the quality of food or consumer goods, or to detect new (bio-)chemical relations in Nature. And there is a really great and important challenge for chemists: To use carbon dioxide, gathered from air, as the general carbon source for organic synthesis instead of oil.

Article note: A special collection of invited papers by recipients of the IUPAC Distinguished Women in Chemistry and Chemical Engineering Awards.

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