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# Becoming a Crystallographer

Martin Egli [1]

"What do you want to be when you grow up?" is a common question posed to children, and answers such as firefighter, policeman, athlete, doctor, or teacher are probably just as common. Some, like Oliver Sacks, recall an early fascination with metals, the periodic table, and chemical reactions that planted the seeds for the later pursuit of the natural sciences or medicine (neurology in his case). We are familiar with memories of chemists that include their first chemistry set, followed by complaints by parents over strange smells and close calls due to particularly exothermic reactions. For others, including myself, a future in research remained more obscure until a later period in adolescence or perhaps even the undergraduate years. Rather than seeking out a field, the field finds you. In actuality, teachers and mentors with expertise in and enthusiasm for a field exert a force that charts a path toward scientific research throughout life. Here, I stress the importance of terrific teachers and mentors from high school onwards to the undergraduate, Ph.D., and postdoc years for setting me on a track (and on occasion preventing me from derailing) to research in structural chemistry and molecular mechanism using crystallography as the main tool.

***Keywords***: Biography; Chemical Bond; Diffraction; DNA; ETH Zürich; Mentor; MIT; Modeling; RNA; Stereochemistry, Training, X-ray.



## INTRODUCTION

Now that I am approaching an age that was thought of as old in our youth, the sad news of the death of teachers, mentors, academic advisors, and more senior friends and colleagues in science reaches one with an unfortunate regularity. Remembrances and celebrations of their lives and achievements recount their upbringing, training, mentors, struggles, growth as scientists, and the legacy they leave in the form of their published work and scientific offspring.

In September of 2021, we honored Robert "Bob" Letsinger (1921–2014), the "father of synthetic DNA chemistry" at a centennial symposium as part of the annual meeting of the Oligonucleotide Therapeutic Society (OTS)[1]. The life and work of Nadrian "Ned" Seeman (1945–2021), the founder of DNA nanotechnology and origami, was celebrated at a memorial in New York City in February 2022 and in an entire issue of the *Biophysical Journal*[2,3]. In an obituary that appeared in *Nature*, Philip Ball described how a high school biology teacher sparked Ned's passion for science, which led him to chemistry, crystallography, and eventually using DNA to engineer self-assembling 3D structures, the latter inspired by an Escher woodcut[4]. Mano Manoharan, a close friend and collaborator of mine, organized a 1-day meeting in December 2022 to celebrate the centennial of Har Gobind Khorana (1922–2011), a pioneer of the chemical synthesis of nucleic acids and Nobelist for the discovery of the genetic code. The gathering brought together advisees, co-workers, collaborators and friends, and present-day users of DNA and RNA synthesis to share stories of this great man's unlikely journey from a small village in Punjab (India) inhabited by some 100 people, across three continents and on to the pinnacle of scientific achievement. The tenacity of the young Gobind to visit and learn from the best is of particular note, among them Vladimir Prelog (1906–1998), during a short stint at ETH Zürich (ETHZ) in 1948/1949, where

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he also learned German to better grasp the original literature, and later Alexander R. Todd in Cambridge, UK[5]. Jack D. Dunitz (1923–2021), my mentor and Ph.D. advisor at ETHZ together with Vladimir Prelog, published many reminiscences about his formative years and the various stages of scientific life[6], among them an article about "famous friends" that appeared after his death[7]. One interesting aspect about the research direction that Jack pursued throughout his career was that he decided to focus on chemical crystallography, X-ray analysis, and the structure of organic molecules (the title of his well-known textbook[8]). Cyclobutane ("bent bonds")[9] and ferrocene ("molecular sandwich")[10] are among the earliest structures he determined. Thus, despite being among the very first to inspect the DNA model built by Watson and Crick and having trained and worked with the founders of molecular biology and prominent crystallographers that pioneered structural biology, like Dorothy Hodgkin, Linus Pauling, and the Elder Bragg, he never ventured into protein crystallography and macromolecular structure-function studies.

Reading and hearing about the life, work, and education of these and many other researchers and how encounters with teachers and mentors affected their future endeavors, inevitably made me think of my own path toward research, the initial choice of field, and the people that influenced that choice. This brief essay, written in gratitude to important teachers and mentors for their guidance, trust, and help, revisits several stations from before high school to the postdoctoral years that led me to structure and function research in chemistry and biochemistry.

## Early steps

I grew up in a small village adjacent to the Rhine Falls in the North of Switzerland. My father was a mechanical engineer in the packaging machine division of Swiss Industrial Corporation (SIG) in Neuhausen. This city had attracted manufacturing since the mid-nineteenth century, mainly because of its proximity to the Rhine and abundant hydropower. Thus, Neuhausen became the cradle of the European aluminum industry when Héroult and companions began producing aluminum bronze in 1888. My father had started his career at the Büchi Syndicate established in Winterthur by Alfred Büchi, the inventor of turbocharging, but decided to use his talents to design machinery to package and preserve foodstuffs. The proximity of our house to the factory allowed him to get there on foot and back and forth across the railroad bridge over the Rhine.

The Swiss education system had many idiosyncrasies and differed between cantons (states) and even neighboring communities. One example concerned the school calendar, specifically the start of classes either in the spring as in some cantons or in the fall. At the time SIG moved its packaging branch to the new Beringen site, cantons had not yet found common ground regarding the start and end of the school year. Moving the family to Beringen meant a short walk to work for my father once again. However, this benefit came with the drawback that our old and new homes were situated in different cantons and that—despite the distance of fewer than 10 miles—the school year was now messed up. Moreover, the Alemannic dialects spoken in the Swiss-German cantons display strong regional differences. With regards to dialects, one episode made a big enough impression on me that I still remember it after some 55 years. In the new school, the second-grade teacher made me stand in front of the class and say a few words and then sternly explained to the assembly that I did not speak like them, that is, properly. The belittling left me with mixed feelings about educators in my primary school years: important and to be respected, but not always of sound judgment. In any case, I never adopted the local dialect.

A prominent citizen of Beringen who briefly taught at the local school was the botanist and hydrobiologist Otto Jaag, who was later appointed as a professor at ETHZ and director of the Swiss Federal Institute for Aquatic Science and Technology (EAWAG)[11]. However, the Swiss school system had erected a few hurdles before one could advance to the high school and later the university stage. The first of these was an exam at the end of primary school that divided pupils into those who would potentially go on to high school after two more years of secondary school and others who would eventually graduate after nine school years and then pursue an apprenticeship. To qualify for high school, the former group had to pass an entrance exam. One problem with a system that set the tracks so early was that it precluded many from attending school for 12 years and go on to college. Finishing a high school degree was not a goal in and of itself but was meant to prepare the student for pursuing a university degree. Thus, only some 25% of all students make up that category in Switzerland. The legendary baseball player Yogi Berra once joked that "when you come to a fork in the road, take it." If only the school system had been that forgiving! Still, with some twists and turns and assistance from my parents, I survived the lower and middle school years more or less unscathed.

Two more experiences stayed with me from those early years. My mother being fluent in French and Italian, which are official languages in Switzerland. Learning languages has only benefits and is central to effective communication. The other was accompanying my father on visits to the factory on weekends, when he would check whether any new orders had come in and walking past new machinery that was being assembled or tested in large light-drenched halls. Looking back, these were initial lessons in form and function: Objects such as biscuits, butter, chewing gum, coffee, chocolate,

teabags, and so forth, being reliably and tightly packed in 3D space by mechanical ingenuity.

### High school: Kanti Schaffhausen

I entered Kanti Schaffhausen in 1976. The school is located on the Emmersberg, and its athletic field lies adjacent to the Munot fortress (Figure 1). The earliest presence of a castle at that site goes back to 1379. From its top, one has a great view over the city and the Rhine. Schaffhausen is a small canton and there is only one high school. Albert Einstein (1879–1955) spent a few months in the city of Schaffhausen in 1901/1902 after obtaining his diploma from ETHZ and before entering graduate school[12]. By all accounts, it was not a happy period in Einstein's life: He faced an uncertain future, and employment was hard to come by. His lodgings were above the Restaurant Cardinal and Einstein was tasked with tutoring struggling high school students at a private school located at Fulachstrasse 22. Both locations can be reached from the high school on foot, and a recent visit confirmed that the buildings appear unchanged; nothing reminds of the famous visitor in a different era. Two Kanti alumni I met years later are Gerhard Geier, who taught general chemistry at ETHZ, and Ulrich K. Laemmli, professor emeritus at the University of Geneva. Biochemists and molecular biologists will recognize the latter's name; his paper on the improved polyacrylamide gel electrophoretic separation of proteins using the SDS-containing "Laemmli buffer" has garnered some 300,000 citations!

I really started liking school and studies upon entering the Kanti. The quality of the teachers was one reason for my motivation as were the diversity of topics and the broadened horizon. If I had any regrets about my interactions with the teachers (or professors, as many had earned a doctorate in their field), it would be the failure to express my appreciation for their dedication and expertise during the five and a half years spent there. I did get a chance later to tell Albert Burkhardt "Bubu", our chemistry teacher, who postponed his retirement and shepherded us toward the finals. I met him for many years during visits to Schaffhausen in Cafés at the Vordergasse that he frequented on a daily basis. Bubu is the reason I decided to study chemistry. Beyond chemistry as a science, he had a special flair for discussing the historic context and social, health, and cultural impacts of chemistry. He was passionate in his insistence to not confuse the science of chemistry and the cultural obligation to enlighten students about it with the potential of chemistry in an industrial setting to both benefit and endanger life. The Seveso disaster at the Icmesa chemical plant near Milan (Italy) in 1976 was a case in point, and Bubu rightly argued that chemistry was not to blame, but rather the operators of the facility, technical glitches, lax safety, or a host of other potential issues. After all,

*Figure 1. Kanti Schaffhausen (background) and the Munot fortress (foreground). Still frame from the drone video https://www.youtube.com/watch?v=OJXDqcgR9KE.*

as Vladimir Prelog explained many years later in an interview with ZDF German TV, nobody blames mechanics when two trains collide although mechanics is inevitably involved in the accident[14].

Chemistry, physics, and biology all came with demonstrations during classes as well as lab courses. Bubu's faithful assistant in chemistry was Mr. Herrmann, who made all the practical work possible, tweaked the experiments, prepared the chemicals, and prevented many a mishap. Jost Schwendener (biology) was a gifted teacher and experimenter and delivered his lectures with a dry humor and dressed in a crisp white lab coat. Kurt Schweingruber in physics sported the same attire but also had the habit of chewing on a short Stumpen (Swiss cigar) during class. The one demonstration in physics that I remember like it happened yesterday was Huygens's principle and diffraction on a single slit or slits using a grating and a ruby laser and measuring and later calculating the resultant intensity maximum and auxiliary maxima and minima. Schweingruber cautioned beforehand that this could all end at the local forest cemetery, accompanied by somber tunes. No such thing happened!

Manfred Trächsel taught geography and geology and took us on excursions to the Randen mountain range, which is located predominantly in the canton of Schaffhausen and between the Jura and the Swabian Jura. On another occasion, we visited the Hegau volcanoes, and for a brief period, I was tempted to study earth sciences and geophysics. Switzerland offers a rich playground to the geologist not least thanks to the Alps. At the time, I also read the inspiring book on modern earth sciences "Restless Earth" by British science writer Nigel Calder[15]. In it, he compressed the earth's geomorphology, 4.6 billion years, into the life of a 46-year-old person.

Together with algebra and geometry that were instructed by Oskar Müller, two additional classes, "Darstellende Geometrie" (descriptive geometry) and "Technisches Zeichen" (technical drawing), proved to be of much use later in crystallography. The Kanti math teacher Roland Stärk had written the definitive book on the former subject[16], concerned with representing 3D objects in two dimensions by employing a set of procedures. Important in engineering, design, architecture, and the arts, paper, pencil, and ink pen have now all been replaced by CAD/CAE, and I doubt high school students are exposed to it anymore these days. The art teacher Rudolf Härdi also instructed technical drawing, a skill that came in handy for producing schematic illustrations of molecular complexes in subsequent years. The Kanti time coincided with the introduction of pocket calculators, and we put aside the slide ruler that we had relied on initially. Similar to the Apple and PC camps, the class was divided into users of Hewlett-Packard and Texas Instruments calculators.

I graduated from Kanti Schaffhausen in 1980 and headed to ETHZ to study chemistry, well equipped to handle the coming challenges.

### Mineralogy and crystallography, Walter M. Meier

At ETHZ, the first- and second-year curricula in the Department of Chemistry featured no elective courses. Lectures and exercises filled the mornings, and the afternoons were spent in the laboratory. The classes in the first year included general chemistry, analysis, linear algebra, physics, computer science, and mineralogy/crystallography. Besides the rigid core curriculum of 40 hours of lectures and practical lab per week, student evaluations at ETHZ also differed significantly from the typical midterm and final exams in each semester or quarter at a United States university. There was just one cumulative exam, the first "Vordiplom" (pre-diploma) after the freshman year. In Chemistry, the second "Vordiplom" could be tackled after the fifth semester at the earliest. And unlike in the United States, where exams are completed before students leave the campus for vacations, these examinations at ETHZ were normally taken in the middle of the long summer break.

The mineralogy–crystallography class was given by Walter M. Meier (1926–2009) at the Institute of Crystallography and Petrography (Figure 2a). According to Grimmer[17], courses named "general mineralogy," were compulsory for chemists during their first three semesters since the 1930s. Crystallography has a long and rich tradition in Switzerland[17]. The field developed from mineralogy in the 17th century, initiated by the discovery of regularities in the forms of crystals and anisotropies of their physical properties. Thus, the term "Crystallographia" was introduced 300 years ago by the Swiss physician and scientist M. A. Cappeller[18]. The first crystallographic dissertation in Switzerland was submitted by J. H. Hottinger to the Collegium Carolinium (predecessor of the University of Zürich, UZH) in 1698[19]! The development of the mathematical classification of three-fold periodic structures dates to the 19th century and comprised the derivation of the 7 crystal systems, 14 lattice types, 32 crystal classes, and the 230 types of space groups[20]. Important figures in physics and crystallography in Zürich in the early years included Max von Laue, who was professor at UZH between 1912 and 1914. His predecessor there was Peter Debye, who became Professor at ETHZ in 1920 along with Paul Scherrer; the Debye–Scherrer powder diffraction camera is named after the two scientists.

Walter Meier, who also held a professorship at UZH, introduced us to the classification of symmetry and symmetry elements. Many are aware of symmetry all around us and in everyday objects. For an entertaining and illuminating introduction to the topic, I refer the reader to the excellent book by Jack Dunitz and Edgar Heilbronner on *Reflections on Symmetry in Chemistry....and Elsewhere*[21]. The central role

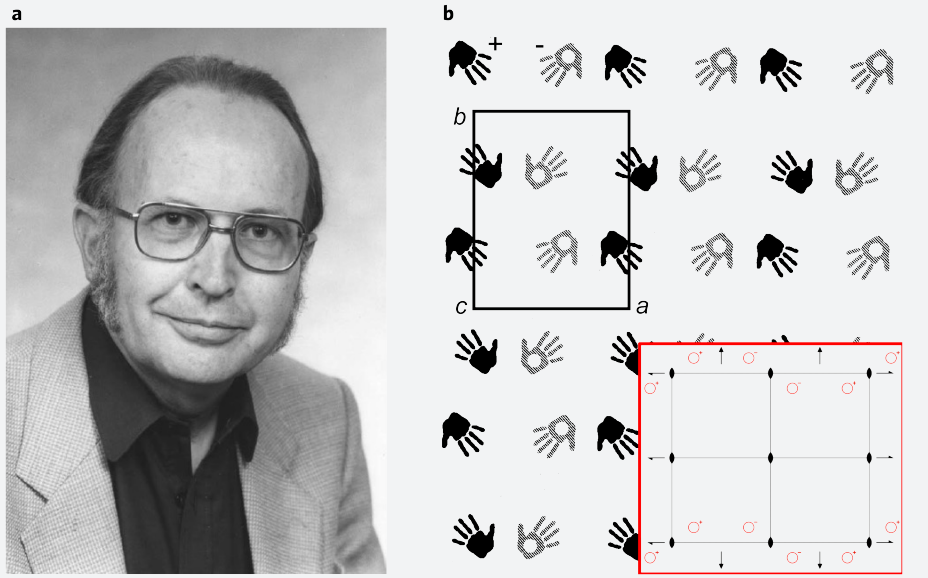


*Figure 2. (a) Walter M. Meier. (b) An example of a simple 2D pattern of left hands representing the orthorhombic space group $P2_122$ No. 17. A coin indicates that the palm of the hand is oriented upwards (otherwise it is oriented downwards). Also indicated is the unit cell with the directions of the a-, b-, and c-axes. The inset depicts the space group diagram as listed in the International Tables.*

of symmetry in Escher's work, who forged his own way to the symmetrical partitioning of 2D and 3D space has been explored by MacGillavry[22]. Walter Meier's research focused on zeolites and metal phases and the initial lectures included a discussion of the crystal lattices of metals and numerous inorganic materials, principles of packing, the definition of the unit cell, Bravais lattices, crystal systems, point groups using both the Schönflies and Hermann–Mauguin notations, space groups, and crystallographic symmetry elements. In short, the class provided a solid footing in symmetry as a foundational concept in crystallography.

I remember that many of my fellow students were somewhat bored with all the definitions and classifications that they considered lacking in relevance for chemistry. Perhaps they could not see the crystal for all the unit cells? I for one was hooked and fascinated by the realization that symmetry could be systematized and had a mathematical underpinning (i.e., group theory). Meier's use of patterns of hands and feet to illustrate space group symmetry was particularly helpful in this context (Figure 2b)[23]. Above all, it was clear that crystallography constituted the most important technique for deriving accurate valence geometry parameters, that is, bond lengths and angles. If metals and inorganic materials could be studied in all this detail, so too could organic molecules and biopolymers and their conformations, as long as one could trap them in a crystal. Indeed, the Cambridge Structural Database (CSD) constitutes the largest repository for crystal structures of small molecule compounds, with over a million structures deposited and curated. The Cambridge Crystallographic Data Center (CCDC) was established in 1965 by Olga Kennard (1924–2023)[24].

The lecture "Chemical Bond" by Hans Primas (1928–2014)[25] in the third semester shone a very different light on the interaction between atoms than the ball-and-stick impression conveyed by models of crystallographic lattices, neatly displayed in glass cabinets along the hallways in the mineralogy institute. It provided an entry into the complex relationship between quantum mechanics and chemistry, bordering on the philosophical. For most of us, the real-world challenges posed by the mathematical concepts placed theoretical chemistry somewhat out of reach. However, we generally appreciated that Primas aimed at a reconciliation between the more familiar classical view of chemical bonding derived from, say, crystallography (interatomic distances) and exemplified by model building sets, and spectroscopy-derived quantal properties.

With symmetry and symmetry rules being of such central importance in crystal lattices, it can be tempting to apply these principles to the conformations adopted by single molecules[26]. However, the rigid convention of only two-fold,

three-fold, four-fold, and six-fold rotational symmetries in crystals does not apply to, say, the helical conformation of peptides. Linus Pauling escaped that straightjacket when he built the model of the α-helix with 3.6 amino acids per turn[27]. Similarly, the B-form DNA and A-form RNA double helices have 10 and 11 base pairs per turn, respectively[28]. Whereas crystals can feature left- or right-handed screw axes, the α-helix is exclusively right-handed. DNA and RNA helices have no left-handed counterparts either. Thus, phosphate groups in left-handed Z-DNA cannot be traced with a smooth B-spline curve. At the time the author became familiar with the structure of crystals and crystallographic symmetry, the discovery of quasicrystals by Shechtman[29] and the presence of 5-fold, 10-fold, or 12-fold, and so on, rotational symmetries in such solids were still on the horizon.

### Chemical crystallography, Max Dobler and Walter Petter

In the third year, I enrolled in the chemical crystallography class taught by Max Dobler (1937–2019; Organic Chemistry, Figure 3a) and Walter Petter (Institute for Mineralogy and Petrography), who made an excellent team. I was the only student in the practical X-ray course that accompanied the lectures, and this turned out to be a rather lucky constellation. The class covered a wide array of topics, including model building using among other tools acrylic spheres and acetone[30]. No doubt this has gone out of fashion given ubiquitous computer access and modeling software. Thus, we assembled cubic and hexagonal close-packed structures to visualize the types of holes in such arrangements and various others, including structures with lattice defects. One innovation was the use of the Apple II computer for practical exercises using software written in the Pascal programming language that had been designed by Niklaus Wirth (ETHZ). Max Dobler wrote all the software for the purpose of the class to immediately put theory into practice. Test data could be processed and Fourier transformation, convolution, Patterson function, electron density maps, Harker sections, and least-squares refinements computed by students on their Apple II desktop machines.

The practicum was handled by Walter Petter, and as I was the only student, I benefited from one-on-one tutoring on all aspects of small molecule crystallography for a year. I learned to work with precession and Weissenberg cameras using the lab manual "Röntgenographische Einkristallmethoden." An illustration from the manual on how to record a so-called (X-ray reflection) cone axis image is depicted in Figure 3b. Walter Petter assigned reading materials from the International Tables for Crystallography[31] and diverse textbooks, and we would then discuss the papers in long sessions. He had an encyclopedic knowledge of crystallography and seemed to have read the International Tables from front to back. Interestingly, long before the IUCr published the series, Paul Niggli, later Professor of crystallography at ETHZ, wrote a predecessor of the tables[32]. During this time, I also received valuable lessons in X-ray crystal structure analysis from scientific coworkers at the Laboratory for Organic Chemistry and the Institute for Mineralogy and Petrography, among them Paul Seiler, Bernd Schweizer, and Volker Gramlich. Walter Petter taught me how to collect X-ray data with

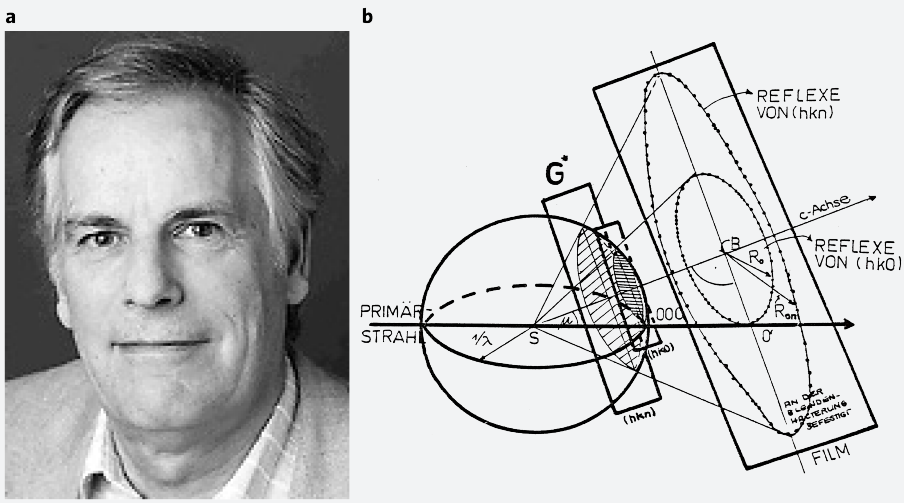


*Figure 3. (a) Max Dobler. (b) Diagram depicting the recording of a cone axis image on a precession camera, with incident beam, Ewald sphere, reciprocal space layers, and the particular position of the film.*

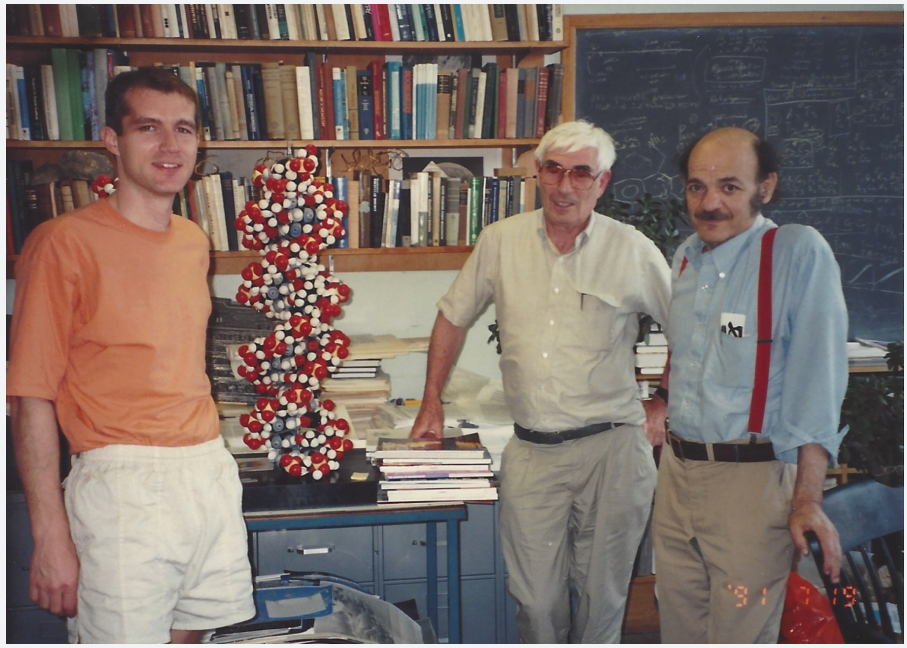

*Figure 4. The author with Jack Dunitz (middle) and Alexander Rich (right) at MIT in 1991.*



crystals of organic molecules, initially on a Picker single crystal diffractometer. I remember that he had a sweet tooth: every time a new structure got solved one was expected to bring a cake. At the rate structures are being determined now, we would all suffer from diabetes!

### Jack Dunitz

I first encountered Jack Dunitz (Figure 4) in an upper-level organic chemistry course in which he lectured on current topics in structural chemistry. On this occasion, he discussed anisotropic Gaussian displacement parameters that are obtained from crystal structure analyses and can yield insights into molecular or atomic group mean-square libration amplitudes[33]. At a basic level, this was instructive because it served as a reminder that crystals are not mere "chemical graveyards," a derisive statement ascribed to the famous ETHZ organic chemist and Nobel laureate Leopold Ružička (1887–1976). Thus, molecules "boxed into" unit cells can retain significant freedom of movement. From that point onwards, the criticism frequently leveled at crystallography as being irrelevant for the situation in solution, and the lattice essentially acting as a tyrant forcing conformational artifacts, seemed to me less concerning. Every scientific problem requires an optimal approach. If diffraction is the only viable technique to gain insight into the question at hand, be it molecular conformation or intermolecular interactions, worries about the potentially limiting role of the crystal lattice will take a back seat.

During the final semester and as part of my diploma thesis, I determined several crystal structures in the Dunitz lab. The research group was quite small and consisted of more senior coworkers who held permanent positions and postdoctoral fellows. In addition, there was a regular flow of academic visitors who gave seminars or spent sabbatical stays. Others included former coworkers who had stayed in the lab's orbit over the years. Joining the research group was like being accepted into a family, without the restraints that word sometimes implies. One example were the shared lunches, even open to a student taking the first steps in independent research. They were not a ritual but offered both food and food for thought. Any topic could be discussed at the table in a small room located in the chemistry tower overlooking Zürich and the lake. Oftentimes, these gatherings provided the first contact with a new area of research. On other occasions, the time together was spent with minutiae, linguistic riddles, historic figures, technological advances, music, and much more. I was not just becoming a crystallographer but getting schooled in the cultural meaning and importance of science, the casual exchange of information and its importance for advancing scientifically, and ultimately scientific communication in general. Beyond

mental fitness, regular tennis matches with Jack helped us maintain our physical fitness. They were fun and the ride to and from the court offered more opportunities for bouncing off ideas and getting advice.

One recurring theme was hydrogen bonding (H-bonding) and the strengths of specific H-bonds, for example, those of the C–H···O type. At the time, the crystal structure analysis by Seiler, Dunitz, and collaborators of a tricyclic orthoamide trihydrate had fortuitously revealed an eclipsed arrangement of a $C_{sp}{}^3$–$CH_3$ bond[34]. Interestingly, each hydrogen of the methyl group pointed at an adjacent water molecule, with an H···O distance of 2.67 Å and a C–H···O angle of 170°. This highly unusual arrangement was not seen in the crystal structure of the anhydrous material, where the methyl group adopted the normal staggered orientation. This allowed the team to correlate the structural observations, that is, H-bonds between methyl groups and water, with the energetics of eclipsed and staggered methyls using semiempirical calculations. The outcome was a significantly higher than expected stabilization of ca. 1.8 kcal/mol afforded by each of the three C–H···O H-bonds. Beyond the surprising strength of an H-bond involving a methyl group, the work offered a cautionary tale in terms of treating the conformational regularities of aliphatic portions of molecules in nonaqueous environments versus embedded in a matrix of water molecules as one and the same. It is just one example that demonstrated Dunitz's unmatched ability to synthesize structural, geometric, and thermodynamic data (often aided by calculations at various levels of theory) in order to arrive at fundamental insights that quite often changed a previously held view. Such structure correlations were a recurring theme throughout his academic career at ETHZ[35].

The structures determined in my diploma work concerned *N*,*N*-dimethyl-8-nitro-1-naphthaleneamine in seven crystalline environments[36] and chiral poly((9,9')-spirobifluorene) crown ethers[37]. The manuscripts reporting the results became my first publications. The seven independent conformations observed for the naphthalene scaffold with two reactive groups attached at the 1 and 8 positions offer another example of structure correlation. The dimethylamino and nitro moieties adopted a variety of relative orientations that were related by conrotatory motions about the two exocyclic C–N bonds. The lone pair of the amino N-atom was directed toward the nitro N-atom, whereby the latter was slightly pyramidalized toward the amino group. Further, the data provided evidence that the nitro group was a weaker through-space electron acceptor than a carboxylic ester, which stands in contrast to their through-bond electron acceptor propensities.

The crown ether project bore some relation to earlier studies of medium-sized (carbon-) ring compounds carried out in the laboratories of Dunitz and Prelog. It also offered an opportunity to try and simulate computationally the conformations of much larger rings. Sampling constituted a considerable hurdle, and conformationally changing the ring required severing a bond to allow one to alter the values of torsion angles in the opened ring. This was followed by energy minimization using a home-made force field that included a ring closure step. "Anybody can make a force field for alkanes!" (JDD quotation)[38]—true, but this was a bit more complicated. Needless to say—I was not a great programmer and instead became an avid user of crystallographic software rather than their creator. I remain a big fan of molecular modeling to quickly simulate the interactions between macromolecules, such as new designs of chemically modified nucleic acids and enzymes[39,40].

Attention to detail is another valuable lesson learned during the "Dunitz years." I always sought advice from Jack in matters of intricate structural observations later in my career. One such study involved lone pair···π interactions first observed in the structure of left-handed Z-DNA; he communicated the manuscript reporting these to the *Proceedings of the National Academy of Sciences USA*[41]. A follow-up paper reviewing the occurrence of such interactions in DNA and RNA and correlating geometry and stability remains my most cited publication[42]. When I visited Jack after publishing a paper on the detailed water structure around RNA while at Northwestern University, he greeted me with "your best paper yet!". Another overlapping interest in later years concerned organic fluorine, now ubiquitous in newly approved small molecule drugs. Jack wrote with authority about its near inability to act as an H-bond acceptor despite the record electronegativity[43]. In fact, this work became his most cited publication. Thus, fluorine constitutes an exception to the rule, the odd man out[44]. However, every exception comes with an exception; there are cases where H-bonds involving fluorine clearly exert a stabilizing influence[45]. Still, I heed Jack's advice to not necessarily interpret a short contact as stabilizing—it can mean nothing or quite the opposite.

Jack valued accuracy in crystallography[46] and language[47,48]. Writing a paper was a lengthy back and forth with many revisions and re-revisions. To the young recruit, it seemed puzzling and tedious at first. In hindsight, I am enormously grateful for his patience and advice—I leave it to the reader to decide whether his coaching was successful in my case.

Following the diploma work, Jack proposed to study first-order phase transitions in organic crystals as a possible Ph.D. project. I gave it some thought as only relatively few inroads had been made into the area of research. It also offered the prospect of applying crystallography, thermodynamic tools as well as computational modeling and theory. However, it was highly specialized and did not involve chemical synthesis,

which was of considerable appeal. Jack revisited the topic of phase transitions in crystals a few years before his death and lamented the lack of progress in the field[49].

### Vladimir Prelog

The crown ether project provided an in-person introduction to Vladimir Prelog, a name that chemistry students inevitably come across when they hear about the Cahn–Ingold–Prelog (CIP) priority rules to unequivocally name molecular stereoisomers. Prelog had retired some years before, but still occupied a small library and an office adjacent to the Dunitz and Dobler laboratories. This was a somewhat unusual arrangement as the title of Professor Emeritus did not exist at ETHZ at the time and faculty were expected to leave the department following retirement. Prelog also shared a lab in an adjacent building that housed research groups in the Laboratory for Organic Chemistry. This allowed him to pursue active research, the practical aspects of which he entrusted to several organic chemists that had joined over the years while on leave from PLIVA Pharmaceutical Company (Zagreb, Croatia). In the mid-1980s, this research was carried out by Miljenko Dumić, who was later succeeded by Miće Kovačević.

The research directed at chiral poly((9,9')-spirobifluorene) crown ethers became part of Prelog's "Alterswerk" and was concerned with so-called host–guest interactions. This subject was of considerable interest in supramolecular chemistry and had been initiated by Donald Cram in the preceding decade[50]. In this particular case, the hosts were chiral and capable of discriminating between enantiomeric guests such as α-aminoalcohols (e.g., ephedrine) and α-amino acids. In energetic terms, the discrimination between the two enantiomers was small ($\Delta\Delta G < 1$ kcal/mol). However, attached to a resin, such hosts opened the possibility to chromatographically separate the stereoisomers of a potential pharmacophore readily and cheaply. I liked this topic as it afforded the opportunity to combine synthetic chemistry, physical–chemical approaches, X-ray crystallography, and molecular modeling. The two latter approaches were needed to shed light on the origins of the enantiomeric discrimination.

Hence, I became a graduate student with three advisors, Jack Dunitz, Max Dobler, and Vladimir Prelog, and trying to master stereochemistry, synthesis, chemical crystallography, and molecular modeling. There was a considerable age gap between me and the advisors, particularly in the case of Vladimir Prelog. Our relationship in many ways resembled that of the medieval concept of master and apprentice. As in painting watching and experiencing the master in contemporary science could be steppingstones to new styles, techniques, and subjects. There are many important benefits to older advisors, but the three most obvious are experience, perspective, and wisdom. Imagine daily encounters with a master of the trade (Figure 5) whose life spans almost the entire 20th century European history and evolution of

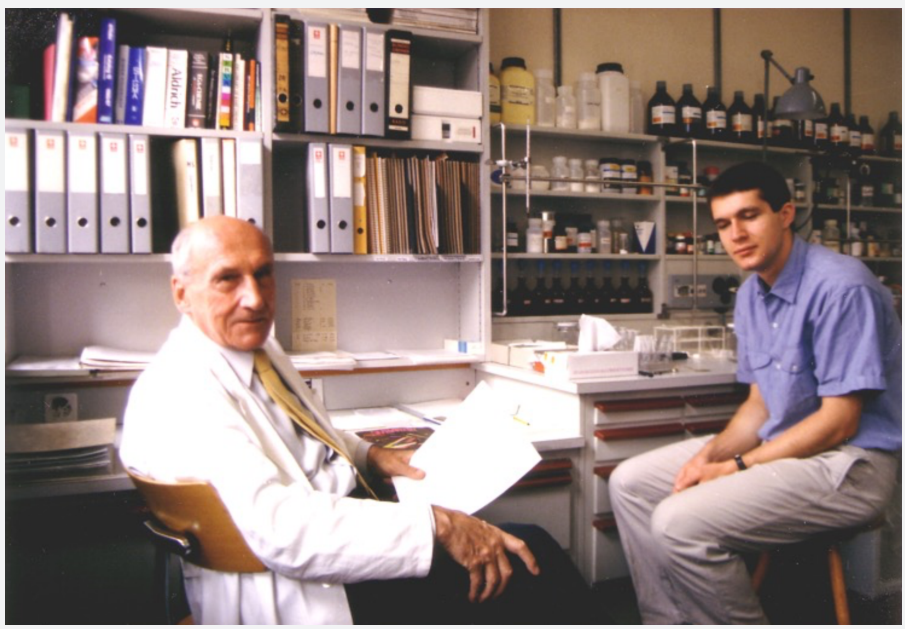

*Figure 5. The author with Vladimir Prelog at ETHZ in 1987.*

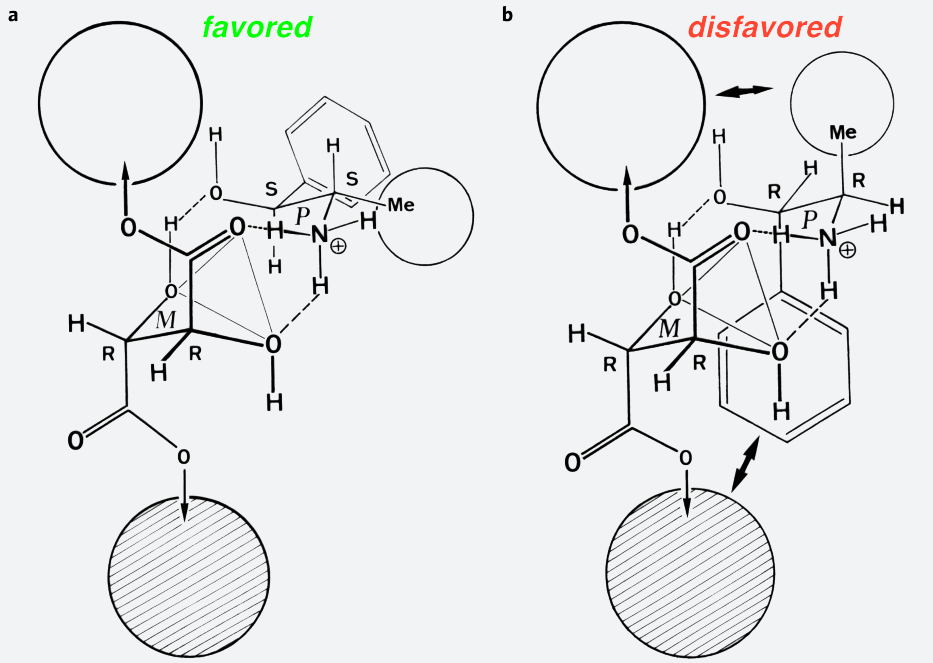


*Figure 6. Tartaric acid diesters as simple hosts for enantioselective discrimination of α-aminoalcohol guests. In the diamond lattice models of the guest (a) favored and (b) disfavored by the host, alcohol moieties and methyl groups are indicated by circles, and H-bonds are dashed lines. Arrows point to steric conflicts.*



chemistry[51]. As a small boy, Prelog was standing in the crowd that lined the avenue in Sarajevo taken by Archduke Franz Ferdinand's carriage before his assassination that day, an event that led to World War I.

The poly((9,9')-spirobifluorene) crown ethers were aesthetically pleasing and effective at separating enantiomers—Prelog referred to the largest one characterized by a 104-membered ring and eight (9,9')-spirobifluorene moieties[37] as the "Maria Callas of crown ethers." However, synthesizing and purifying them was challenging and expensive, motivating the search for simpler hosts that could discriminate between enantiomeric guests. This led us to the diesters of tartaric acid, a classic among optically active or chiral molecules that took center stage in the discovery of molecular chirality by Pasteur some 140 years prior. Indeed, tartaric acid diesters could discriminate between the enantiomers of α-aminoalcohols, α-amino acid esters, and 1,2-diamines. The (*R*,*R*)-tartaric acid diester of (1*R*, 2*S*, 5*R*)-menthol bound to erythro-[(1*R*,2*S*), (1*S*,2*R*)] or threo-[(1*R*,2*R*), (1*S*,2*S*)] norephedrine pairs set a record with a ΔΔG of up to 0.43 kcal/mol between diastereoisomeric complexes (Figure 6). Models of the complexes were consistent with the Ogston postulate[52], which stipulates that for enantioselectivity to be achieved, the components of complexes are bound at three analogous sites (three oxygens of tartaric acid situated close to each other and forming a "chiral triangle," Figure 6). The ability to rationalize the observed enantioselective discriminations as resulting from steric factors that differed between guest enantiomers, both tethered to the host via three H-bonds, validated the usefulness of the diamond lattice as a simple structural tool for approximating the relative stability of complexes (Figure 6). In stereochemistry, diamond lattice sectors are useful for ordering hypothetical structures or groups of structures, a concept used by Speakman as early as 1941[53], before the introduction of conformational analysis. Albert Eschenmoser referred to the diamond lattice as the "poor man's computer"[54].

The crystallographic efforts in the project were, of course, directed at the structures of the constituents of the complexes and the complexes themselves. In due time, such crystal structures data were produced. Prelog was often urged to "play with models" to glean insight into stability and selectivity before quantitative data became available. He had a deep fascination with the spatial forms of molecules. As Jack Dunitz pointed out, "Stereochemistry is not so much a branch of chemistry as a way of looking at the science"[55]. Thus, it is explicitly concerned with molecular shape. Experimental structural data combined with calculations

provide definitive answers, but the judicious use of models with input from empirical stereoelectronic and steric rules and chemical intuition is very powerful. Trying to grow crystals of a particular molecule irrespective of its size can be very frustrating, but Prelog was never tiring of providing technical advice and encouragement. At no time did I perceive these interactions as being pushed. Years later, I found that H. Gobind Khorana experienced the same support and approval some 40 years earlier when he spent a year in the laboratory of Vladimir Prelog[5]. The expectation to be updated daily on progress or setbacks was a sign of encouragement and interest rather than doubt or distrust. Emerging issues were dealt with swiftly; before I could make my way to his office on some days, Prelog would often appear in the doorframe of the lab, cheerfully announcing that "when Moses doesn't come to the mountain, the mountain comes to Moses!".

Prelog kept a cassette tape player in his office and meetings were accompanied by background music. He was particularly fond of Dvořák's chamber music—the "Dumky" piano trio was a favorite—and Borodin, a Romantic composer and chemist. From stereochemistry, synthesis, separation, and crystallization, the discussions would drift to history, public figures, his native Yugoslavia, life's lessons, and anecdotes. There was an endless flow of the latter—Prelog has been referred to as a "master entertainer of the anecdote"[56]. These were delivered with a gleam in his eye and a perfectly timed punchline. Many times, his humor was self-deprecatory, as when he recounted walking to the Chemiebar (cafeteria) and encountering a gaggle of students in the hallway. He inquired whether they knew who he was, and when they replied in the negative, he informed them that he was Professor Prelog. Oh, they replied, we came across your name in class but thought you were dead. The conversations oftentimes had a deeper meaning and contained lessons by the accomplished teacher and researcher Prelog. However, as the title of his autobiography, "My 132 Semesters of Chemistry Studies," suggests, he thought of himself as a lifelong learner and student[51].

During the three and a half years in graduate school, I was supported by a stipend from the Scholarship Fund of the Swiss Chemical Industry. The stipend did not cover travel or conference attendance. Prelog was generous with advice and time, and his generosity also extended to financial matters. I attended a German Chemical Society meeting in Hamburg where he gave a presentation, and he paid out of pocket for all my expenses. We took the train together to attend a meeting at the University of Basel for Tadeus Reichstein's 90th birthday, where he held the laudatio honoring his friend (Prelog never owned a car and relied on public transport throughout his life). Tadeus Reichstein (1897–1996) was awarded the Nobel Prize in physiology or medicine in 1950 for his work on the isolation of cortisone. In 1933, while at ETHZ, he invented the synthesis for ascorbic acid (vitamin C) and the principal industrial process to produce vitamin C still carries his name[57].

I would like to leave the reader with two quotes by Vladimir Prelog that provide an excellent roadmap for research and life. In an article in 1985, he said of the natural products: "They are the result of the development of the living world spanning 3 billion years and have survived evolutionary selection over a long time. I am convinced that they always contain a message and that it is our task to decipher this message"[58]. When asked by Frank Elstner in an interview with ZDF German TV in 1988 what message he would like to give us, Prelog responded: "I would tell everyone to try to find out where their weaknesses are, where their strengths are, they should get to know themselves, that's very important and not very easy. It's easier to say 'do this' than actually do it. And when one knows one's good qualities, one should use them to be useful to the community in which one lives. So, I paraphrase John Kennedy who said: 'Ask not what your country does for you, ask what you can do for your country'. That's very good. I just didn't say 'country', that seems too political, and I didn't say 'humanity', that seems too dramatic. So I just use 'community you live in'. It can be big or small, depending on your capacity or your charisma. It can be the whole world, it can be a family, but do something useful for the others. The others mostly appreciate it. And that will make you happier"[14].

### Alexander Rich

Near the end of my graduate work, Jack Dunitz suggested that I join Alexander Rich's laboratory at MIT to learn biology. Indeed, my knowledge of biology—or shall we say molecular biology—was extremely poor. Apart from bioorganic chemistry or natural products courses there was nothing biological on offer for chemistry students. Chemistry and biochemistry were physically separated on the main campus of ETHZ, and molecular biology was located on the new campus at the outskirts of town. And so, I drove with Jack to Zürich airport to meet Alex and his wife Jane, who were in transit on a trip to Israel later that day. Three months later, I arrived in Cambridge (MA) with a suitcase that also contained a few books on nucleic acid structure, genes, and cloning and started my adventures with Alex in the Department of Biology (Figure 4).

Alex had created a unique environment in his research group where one could take on pretty much any project of one's choice and then run with it. There were no specific directives or demands; what was needed were motivation and initiative. Those who waited for guidance and detailed instructions were sorely disappointed. Alex would appear late in the day, no doubt having poured over papers in his library at home, read some more, contemplate, spend time

on the phone, let it all percolate, and out tumbled intriguing questions and ideas. The door to his office was always open, and he was generous with his time and always encouraging. I don't remember him ever being in a bad mood or dismissive. Despite the enormous freedom members of the lab were granted, the scientific approach was never chaotic, and the new results were produced efficiently and published at an amazing rate. What I took away from my 3 years in Alex's lab was a deep appreciation for his style of pursuing science. Any attempt to recreate this environment and trying to emulate his approach in one's own future research would likely be doomed.

A few words about that environment. At the time I joined the lab, there were some 20 postdocs working on two floors in adjacent buildings. Nowadays, we talk a lot about interdisciplinary research, team science spanning various disciplines, hybrid or integrated approaches, and so forth. Alex's lab had all that decades ago, and the backgrounds of scientists were as diverse as their origins. Fields such as biology, biochemistry, chemistry, crystallography, computer science, engineering, genetics, pharmacology, physics, and many more were all represented. The best thing about this was that one could pick the brains of all these people, learn techniques hands-on, start to see a problem from a very different angle, and often glean an answer by doing so that wasn't apparent from the get-go.

It isn't hard to understand how such an environment fosters creative thinking, breeds teamwork, and learning from each other. Thus, it paved the road to breakthroughs such as the crystal structure of transfer RNA and a host of DNA crystal structures, among them those of complexes with important antibiotics and anticancer drugs, and of course the discovery of the left-handed Z-DNA at atomic resolution[59]. Naturally, the focus was not just on DNA and RNA structure and function, but their interactions with proteins and enzymes were of intense interest early on. The sequence-specific recognition of duplex DNA by proteins offers a case in point. The proposed recognition of base pairs in the major and minor grooves by particular amino acid side chains years before the first structures of protein-DNA complexes emerged was brilliant[3].

At MIT, I did get schooled in biology and become familiar with molecular biology tools. Solid foundations laid by years of training in small molecule crystallography at ETHZ facilitated the transition to macromolecular crystallography in Alex Rich's research group. The techniques to grow crystals of oligonucleotides were pioneered there. The first projects included the crystal structure of cyclic GpGp, a cellulose synthase inhibitor that later turned out to act as an RNA riboswitch regulator[60]. Here, the quality of the data mattered, and improving the crystals allowed phasing by direct methods. Familiarity with the interpretation of Patterson functions helped in the rapid manual solution of the structure of the complex between an oligonucleotide and the Upjohn experimental cancer drug nogalamycin[61]. Structures of hybrids between DNA and RNA[62] and all-RNA structures[63] became more common as the chemical synthesis of RNA advanced. Above all, the time at MIT stands at the beginning of three decades of my work on the 3D structures of native and chemically modified nucleic acids[39,40] and xeno nucleic acids[64].

I am grateful for everything I learned with regards to the chemistry and biology of nucleic acids from Alex Rich and his teammates. During the last 30 years, macromolecular X-ray crystallography and structural biology have undergone dramatic changes that include all aspects, beginning with protein and nucleic acid production and purification, crystallization, data collection and processing to phasing, structure refinement, model visualization and validation. Suffice it to mention multiBac expression system, fusion proteins and affinity chromatography, automated solid phase synthesizers, sparse matrix screens, crystallization robotics, nanobodies, cryoprotection, X-ray synchrotrons, shutterless data collection, pixel array detectors, single-wavelength anomalous dispersion, simulated annealing, Bayesian approaches, small angle scattering, neutron spallation sources, cryo electron microscopy, microcrystal electron diffraction[65], learned potentials, and artificial intelligence[66].

What hasn't changed is that a solid training in crystallography, symmetry relationships, and stereochemistry is crucial to advancing our understanding of molecular structure, function, and mechanism. I want to end this section with just one example structure to illustrate this point. It does not concern the biggest molecule by a long stretch or a multi-protein assembly with complex functional properties. Nevertheless, it took me and my coworkers over a decade to crack the crystal structure of Eschenmoser's homo-DNA[67,68]. Key steps to the solution included a good grasp of oligonucleotide synthesis and purification, intricate knowledge of symmetry principles, and thinking completely outside the box as far as phasing approaches were concerned. Identifying symmetry and interpreting its meaning was also a key factor in the race to build the correct model of the DNA double helix 70 years ago[69].

## Human–Scientist–Crystallographer

I had the good fortune to learn crystallography, symmetry, stereochemistry, and structural biology from the best. The famous cellist Yo-Yo Ma often recounts that the equally famous cellist Pao Casals thought of himself as a human being first, a musician second, and a cellist third[70]. I believe this would also apply to Jack Dunitz, Vladimir Prelog, and Alexander Rich. They were humans first, scientists second, and (fill in the respective discipline) third. The meaning and impact

of their teachings and research go far beyond the specific discipline they chose to pursue. In all my interactions with them, the most important lesson was to use knowledge and insight not in isolation but for a higher purpose. Science and music are not the same, but like music, scientific discovery entails beauty and can elicit deep satisfaction and a feeling of happiness.

Nowadays, many universities don't offer an X-ray crystallography course. There are virtually no faculty appointments anymore in chemical crystallography. Worse, most chemistry departments don't maintain a structure determination service, and operating an in-house X-ray instrument is considered unnecessary. A majority of graduate students I encounter in biochemistry have no idea of symmetry and symmetry elements; I expect the situation is similar in chemistry. Crystallography still thrives in structural biology research, and X-ray synchrotrons around the world are undergoing a next-generation upgrade. Still, despite having engaged in structural biology projects and structure and function studies of circadian clock proteins, kinases, polymerases, and a range of other enzymes, I consider myself a chemist and chemical—or perhaps biochemical—crystallographer. I appreciate Linus Pauling's philosophy of chemistry's supremacy over biology in this regard. He offered this piece of advice to his postdoc Alexander Rich at the time: "Do the chemistry first, and look for biological ramifications, if any, later"[71].

Finally, I would like to reiterate why crystallography is so attractive and unusual among the natural sciences in the words of Jack Dunitz: ". . . if crystallography has an uncertain future it has a great past and it still possesses the rare intellectual charm of relating to the three basic sciences, physics, chemistry and mathematics, as well as to the decorative arts. It should not be taught or studied in a too restrictive, introspective manner"[72].

## CONFLICT OF INTEREST

Martin Egli declares that he has no conflict of interest relating to the content of this article.

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