Asymmetry in Chemical Structures and in Life: My Last two Articles

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(in cooperation with Meghan Banach)

Asymmetry in chemical structures has followed me all my life. I decided to study chemistry when I was 15 years old. At the Oberschule in Baden we had an excellent chemistry teacher whose specialty was the gas laws of chemistry. Under his inspiring influence, together with that of the history/geography and French teachers, I decided to attend the University, in my case the University of Vienna, and study chemistry. I should remind today’s readers that a student had to decide at the age of 10, to attend and complete the University with a doctoral degree. Deviations from this program were not impossible, but very difficult and the options limited. The top 10% of the students in each class received special mention, equivalent to what we would call the dean’s list today.

I completed the undergraduate program in chemistry in 2 ½ years; I then prepared for the qualifying examination and with its success began graduate work for my PhD. There was no degree given prior to the doctoral degree.

When I started thinking of my thesis and how to select a “dissertation father“ it had become obvious that I would like to become an organic chemist and try to work for the Head of the Institute, Professor Ernst Spaeth at the Chemical Institute of the University of Vienna and also the President of the Academy of Sciences of Austria.

Unfortunately, on his return trip home from a visit with his daughter in Sweden, Spaeth in 1946, only 60 years old, suffered a fatal hearth attack.

The next in line in organic chemistry at the II. Chemical Institute was Friedrich Galinovsky. All the students of Spaeth were placed under his guidance and completed their PhD with him.
Galinovsky had at that time two female graduate students of his own: Erika Stern, who later became his wife and Hilde Mullay. When I applied to him in 1947, he was delighted to take me. At this time there was no financial obligation for him, the Institute supplied the laboratory space and chemicals. Both were available in abundance. So I became his senior graduate student at the II. Chemical Institute of the University of Vienna, he was a docent with the title (but not the position) of an Associate Professor. Galinovsky was responsible for one of the laboratory courses of the Institute: Quantitative Inorganic Chemistry, a 6 day lasting course. The laboratory was open daily (6 days) from 8 a.m. to 6 p.m from Monday to Saturday.

Most Professors of the II. Chemical Institute worked on alkaloids, Spaeth, Galinovsky mad Gruber. Kratzl did not work on alkaloids but cellulose, lignin and lignin derived products, but still on chiral products (with chiral carbon atoms).

After I had formally joined Galinovsky’s group, Galinovsky told to me one day: that when he was younger (he was 40 at that time), he had worked a little bit on steroids. Steroids were quite fashionable at that time. For example, the famous Prelog synthesis, the Ruzicka side chain oxidation of sterines, that gave in 3% yield), andosterones and the Reichstein discovery of cortisone.

Galinovsky had 2 kg of cholesterol from the Quinoin Co. in Budapest (which dissolved during the war, but was later reassembled as “Synthex Co.” in Mexico with George Rosenkranz – a student of Ruzicka - (later a renowned professional bridge player) and developer the birth control pill as one of the leaders.

Back to Galinovsky and 1947 in Vienna. Galinovsky said to me: Let’s try to synthesize provitamine D₂, also called 7-dehydrocholesterol. We can brominate cholesteryl acetate with the just discovered new reagent N-Bromosuccinimide
and, should the bromination be successful in the right position, namely the 7 position of cholesterol, we can dehydrobrominate.

Under the conditions that we used, it was a total failure – but we did isolate 5, 7 cholestadienol-3. – only 6,8 cholestadienol-3, only to find out that this work had been done 3 years earlier by a Dutch chemist, Wiberg. In 1947, we did not have the up-to-date literature available. In the wartime and early post wartime Western literature had not become available at the II. Chemical Institute of the University of Vienna.

However, something good came out of this period. Galinovsky said one day, it must have been in late 1947: My friend Christiani has separated cholestanol (5-hydrogen in trans position) from coprostanol (5-hydrogen in cis position)) by Tswett chromatography. Why don’t you try to separate the 3α from the 3-beta hydroxysteroids the same way? Take cholesterol and epi-cholesterol, cholestanol and epi-cholestanol, coprostanol and epi-coprostaol and see if you can separate the epimers. And it worked.

I had to learn to synthesize the sterols. In the post war period there was no laboratory that synthesized exotic chemicals in quantities required (and paid for) as we do today. You had to synthesize your own products from basic chemicals. The Meerwein-Ponndorf synthesis of the corresponding 3-ketones gave a mixture of about 1/3 epi and normal steroid alcohols, the epi alcohol was also called α, today most probably axial, and the 3β-hydroxysteroid, today the 3-hydroxy group in equatorial position. I had to learn to separate and purify the individual “sterins”.

Chromatography with petroleum ether (on aluminum oxide carrier) took out the hydrocarbon by-products, the epi-compound came out with benzene and the
regular β product could be obtained by extraction of the remaining aluminum oxide chromatographic carrier with ether.

The chromatographic separation of epi-meric sterin alcohols resulted in my first scientific paper and I was then barely 20 years old. But it also introduced me to the chirality of the 3- hydroxy group on a chiral carbon atom and the stereochemistry of *Chiral Carbon Atoms*.

So I was familiar with the chiral carbon atom. Later, 30 years later, I became acquainted with Prof. Michalski, Director of the Institute of Chemistry of the Polish Academy in Lodz. He was an expert in phosphorous chemistry, one of the subjects was the investigation of the *chiral phosphonium cation*. He had been a student in Cambridge, UK and had worked with Lord Todd of nucleic acid fame.

This is my story and experience with the chiral atom, carbon or phosphorous. There exists another asymmetry in organic molecules, an asymmetry which I learned to appreciate much later. This asymmetry in organic molecules is caused by restricted rotation around a major bond. I was also exposed to this type of asymmetry by accident. During the post war years at the II. Institute at the University of Vienna, several professors were involved in the synthesis of alkaloids. Most frequently, the synthesis, if successful, ended up in the preparation of the racemate of the desired compound, for example the alkaloid, and the racemate had to be separated into the antipodes using optically active (chiral) acids. Most commonly, tartaric acid was used as the acid to separate these basic nitrogen compounds as their salts. But what if the salt did not crystallize?

This happened sometimes. In this case, another acid had to be used, one example was 2.2’-dinitro-6,6’-diphenic acid. The biphenyl structure had two substituent groups, a nitro and a carboxylic acid group on each of the phenyl
rings, of the biphenyl structure. They were too bulky and prevented the rotation of the major link between the two phenyl rings. *Macromolecular Asymmetry.* Hilde Mullay, the graduate student in Galinovsky’s group, was assigned to synthesize the antipode of this acid and I had to assist her because I needed some of this 2,2’-dinitro,6,6’-diphenic acid for the separations of my own alkaloid (isopelletierine) in the future. In this way I learned that molecular asymmetry was not only caused by a chiral atom with 4 different substituents, but could also be caused by restricted rotation. I needed this knowledge in a more sophisticated form 20 years later.

In the early 60’s I worked for Du Pont and had to worry about my future and to accomplish the requirements of the needs of the company, not my personal scientific interests. I had discovered the aldehyde polymerization of higher aldehydes and Corradini of the Natta group had determined the structure. I had to give the polyaldehyde work up because it could not be commercialized. However, my luck and a short membership in a small Super-Exploratory Research Group at Du Pont brought me to the Central Research Department of DuPont at the Experimental Station. I proposed and was allowed to work on the polymerization of trichloroacetaldehyde, choral.

With intense determination I succeeded polymerizing chloral into any kind of shape of polychloral by initiating chloral above the ceiling temperature and polymerizing the initiated chloral by cooling into any shape desired. Among the successful initiators was cholesterol oxide, made from cholesterol and butyl lithium. You can clearly see the influence of my thesis work, the knowledge of the stereochemistry of the 3-sterin alcohols.

We are now in 1963 and I had been regularly attending the Gordon Conference on Polymers at Colby College in New London, New Hampshire. At this Conference, Piero Pino, whom I had met previously 2 years before, at the
Moretonhampstead Conference, presented an unusual research result and came up with a very preliminary proposition to explain the results. His group had studied the polymerization of chiral 3-methylpentene and had found (reason later) that the polymer obtained had an optical rotation, substantially larger than what was expected from the monomer, which had a rotation of 15°. Discussions of polymer physic chemists at the conference based on Pino’s proposal came to the conclusion that some portions, maybe several units aligned and realigned in helical form of the polymer in solution and this helicity contributed to the increased optical rotation. We have later concluded, in cooperation with Pino, that indeed these polymers crystallized essentially as does polypropylene but the optical purity of the monomer caused the formation of the helical structure based on polypropylene. And the polymer rotation consisted of the rotation of the monomer (~15°) and additional 150° of rotation based on the helicity of the 3/1 helix of the polypropylene based unit.

Pino’s optical activity measurements of the solid powder of poly(3-methylpentane) were not fully substantiated. Together with Pino’s group, we later refined the techniques of solid-state measurements of polymer (and other optically active) powders and found Pino’s early measurements of his isotactic polyolefin substantially correct.

I was fortunate that I had a brilliant student, L. Steven Corley, who not only accepted my assignment to clear up most of the polychloral stability problems but he also demonstrated that the polymer could be made in optical active form by initiating the polymerization with a chiral alkoxide initiator (cholesteroxide) but also with an initiator with a chiral counter ion. He used the chiral phosphonium salt, with a chiral phosphorous atom, provided by Prof Michalski in Lodz.

At the 1978 Polymer Gordon Conference I declared that we had made chirally pure polychloral, based on molecular Asymmetry. Prof Francesco Ciardelli
corrected me in the discussion and reminded me that the proper nomenclature should be *Macromolecular Asymmetry*. which was quite correct and we have used this nomenclature ever since.

Polychloral is a polymer that is stereochemically and conformationally structurally pure. When subjected to chiral initiation and polymerization it can be optically active based on macromolecular asymmetry.

This was the story by the end of the 1980’s. Then we became interested in chiral crystallization. We found that chiral crystallization is a phenomenon of the solid state. We found that certain salts can be crystallized, when properly nucleated (initiated) to give chirally pure crystals. We could estimate the size of the crystal necessary, for the chirality of the crystallization. We could also relate the crystallization with the polymerization, i.e. of chloral to stereospecific and conformationally specific polymer. (only isotactic, but no atactic polymer exists).

We have published this paper with all its possible ramifications, but also another paper that has as its ultimate conclusion the proposal to encourage investigations to prepare chiral isotactic polypropylene though chiral nucleation and chiral crystallization.

**Zvonimir Janovic, Ante Jukic and Otto Vogl, Spacer groups in macromolecular structures, POLIMERI 31, 1:14-21 (2010)**

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Spacer groups in macromolecular structures

Abstract
Spacer groups are often an essential part of polymer structures, particularly functional polymers. Many physical, chemical and biological properties depend strongly on their size. They provide flexibility and functionality in high molecular polymers. They also provide accessibility of functional groups, crystallization of side chains, separation of groups from the main chain for efficient chemical reactions and other characteristics. They can be found in natural polymers where flexible spacer groups provide essential links for the stability of polypeptide structures. In our research work we have studied the effects of flexible side chains for side chain crystallization and flexible side groups for reactivity on synthetic polymers, particularly poly(vinyl chloride), poly(vinylidene fluoride), poly(vinylidene chloride) and poly(vinyl chloride) which are used in practical applications. Ultimately, we have shown that in the presence of a monomer these groups prevent polymerization. In this paper we are trying to show, on a few demonstrative examples, the importance of spacer groups in macromolecular structures.

KEY WORDS:
functional polymers
poly(vinyl chloride)
poly(vinylidene fluoride)
poly(ethylene oxide)
polymer structure
polyethylene
poly(vinylidene chloride)
functional groups

Kључне речи:
функционални полимери
поли(vinyl chloride)
poli(ethylene oxide)
pолимерна структура
полиетефилен
функционални групи

Razmalkne skupine u strukturi makromolekuła
Sažetak

Introduction
Polymers with functional groups are of great interest, because they impart specific chemical, spectroscopic and mechanical polymer properties. Many have been synthesized where the active groups are liquid crystals, catalysts for chemical reactions or hydrogenations. Polymers UV absorbers, antioxidants, polymers with photo-, thermo- and electro-active as well as biologically active groups have also been prepared. Such polymers may include homopolymers and copolymers, polymers of various additional characteristics: specific solubility, insolubility of even completely insoluble materials, they also include: oligomers or polymers of low, medium and high molecular, or specially designed molecular weights or molecular weight distributions. Functional polymers have been prepared in order to modify such basic chemical and physical properties as glass transition temperature, melting point, solubility, crystallinity and other fundamental properties, which depend directly upon these requirements, polarity and interaction of functional groups. It has been estimated that polymers in the health and food industry and for the production and preservation of energy, will be the main thrust of the research development in polymer science over the next decade. As polymer engineering, polymer physics and polymer chemistry, respectively, were important in the development of polymer science in each of the preceding decades. In this discussion examples of spacer groups influence on properties of some typical functional polymers based mostly on our own research activities are presented. Spacer group reversibility of accessibility of functional groups, crystallization of side chains, separation of groups from the main chain for efficient chemical reactions and other characteristics. They can be found in natural polymers where flexible spacer groups provide essential links for the structure configuration and stability of polypeptide structures. There has been tremendous attention paid to the influence of the kind and size of spacer groups. The reactivity of a functional group may be low when it is directly attached to the main chain, which may be a result of steric hindrance by the polymer backbone and neighboring side groups. Vogl and others described the effect of spacer groups in different
Cover
Spacial modeling of the "oligo-crystallization" of NaClO₃ led to "isotactic" linear crystallization involving helical propagation. It seems to require unequal sizes of the cations and anions, which, by branching propagation leads to 3D chiral crystallization. For more information, see the article by O. Vogl on page 1299.

Highlight
Chiral Crystallization and the Origin of Chiral Life on Earth 1299
O. Vogl
Evidence of chiral emergence by a combination of chiral crystallization, formation of helical polymers with preferred structure based on macromolecular asymmetry inspired ideas and rules for the origin of chiral life. These investigations needed the understanding of the requirements for chiral crystallization, for the stereochemistry of the initial formation of helical polymers, the measurement of optical activity of solids, and their coordination with the fundamentals of chirality. Spacial modeling of the "oligo-crystallization" of NaClO₃ led to "isotactic" linear crystallization involving helical propagation that requires unequal sizes of the cations and anions, which by branching propagation leads to 3D chiral crystallization. Published online 11 January 2011.

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Chiral Crystallization and the Origin of Chiral Life on Earth

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ABSTRACT: The creation of chirality on Earth and the development of chiral life have been discussed in this highlight. Convincing evidence for the introduction of chirality on Earth is still fragmentary. We believe that by a combination of chiral crystallization and formation of helical polymers with preferred chiral conformational structure is the key to this question. This concept of macroscopic chirality has inspired ideas and resulted in possible rules for how chiral life as we know it could have been introduced. These investigations needed the understanding of the requirements for chiral crystallization, for the stereochemistry of the initial formation of helical polymers, the measurements of optical activity of solids and their coordination with the fundamentals of chirality. Spacial modeling of the “oligocrystallization” of sodium chloride led to the conception of “isotactic” linear crystallization, which involves helical propagation. It seems to require unequal sizes of the cations and anions, which, by branching propagation leads to three-dimensional chiral crystal formation. Linear “isotactic” propagation of crystallization seems to be equivalent to stereo and conformational specific polymerization. One and a half turns of the helix seems to be required for stereo- and conformational specificity, that is, between the pentamer and hexamer in chloral polymerization (11/3 or nearly 4/1 helix) and between trimer and tetramer for the sodium chloride crystal (2/1 helix). © 2010 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 000: 000-000, 2010

KEYWORDS: chiral; crystallization; life on Earth; macromolecular asymmetry; mineral; polychloral sodium chloride

Otto Vogl is Professor Emeritus of the University of Massachusetts and the Herman Mark Professor Emeritus of the Polytechnic University. He was and is a leading personality in polymer science, in original and innovative research, teaching, and publishing. He was very active in polymer-related societies in the United States and abroad and a proponent of globalization of polymer science. Vogl’s research interest involved to a great extent in “chirality.” His early work involved work involving the chiral carbon, then molecular asymmetry, and later macro-molecular asymmetry (helicity) and the single helix. Ultimately, he became interested in chiral crystallization (see also http://works.bepress.com/otto_vogl/).

INTRODUCTION Our planet Earth was formed about 4.5 billion years ago. It seems that it initially had a molten surface that solidified and crystallized 4.0 billion years ago. As the Earth cooled over the next few hundred million years, water began to condense.1

As early as 3.5 billion years ago, some life existed, as demonstrated by recent fossil discoveries. In “Early Life: Nature, Distribution, and Evolution,” Frances Westall2 has made a detailed review of the trace of signatures of life in the early rock records, explaining how life could have or has evolved 3.5-3 billion years ago. But, to have life as we know it today required the introduction of chirality on Earth. We believe that chirality was introduced 4-3.8 billion years ago either during the solidification process of the Earth’s surface, possibly under high temperatures and pressures, or later in aqueous environment of the Earth’s oceans.

Most of our Earth consists of inorganic minerals, inorganic macromolecules, while our living world is made up of organic macromolecules.3,4 When the earth was born four billion years ago, it was an Earth of inorganic material, mostly crystalline in nature. Some of these inorganic macrostructures might have contained inherent asymmetry in their fundamental structures. As water condensed on earth, some of the materials, water soluble salts ‘leached out’ of the original surface, allowing chemistry to develop in aqueous systems. Therefore, it is also possible that chiral chemistry was born in aqueous solutions. Either way, some of the conditions that existed on the young Earth, allowed for the