

Extroverted Confusion – Linus Pauling, Melvin Calvin and Porphyrin Isomers**

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Dedicated to Professor Emanuel Vogel

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No other modern era chemist has influenced chemistry and molecular biology as much as Professor Linus Pauling (1901–1994) (Fig. 1).^[1] In a career spanning seven decades he worked and made important contributions in all areas of chemistry including physical, structural, analytical, inorganic, and organic chemistry, as well as biochemistry. While always being interested in the structure and bonding of molecules, he worked on genetics, evolution, hematology, immunology, brain research, biomedicine and nutritional therapy, too. In addition, his charismatic and dynamic personality also made him a humanitarian par excellence. He remains the only person to have been awarded two unshared Nobel Prizes, the 1954 Nobel Prize in Chemistry and the 1962 Nobel Peace Prize.

His contributions are well known and with respect to porphyrin related work he is probably best remembered for his ground breaking concept of the "molecular disease" based on studies on sickle cell anemia.^[2,3] However, he made contributions to basic porphyrin chemistry as well. Most are derived from his longstanding interest in the coordination geometry of iron porphyrins, an area of research we today call the core geometry of porphyrins.^[4] His studies on the magnetic properties of hemes are beautifully described in his timeless classic "The Nature of the Chemical Bond".^[5] He initiated early studies into the absorption spectra of porphyrins,^[6] worked himself on the electronic structure and ligation properties of hemes^[7] and predicted the structural changes that occur

upon oxygen binding.^[8] This later led to the concept of conformational changes upon axial ligand binding in porphyrins.^[8,9] Ultimately, this can be considered as the precursor to newer studies on the modulation of cofactor interactions through conformational control.^[10]

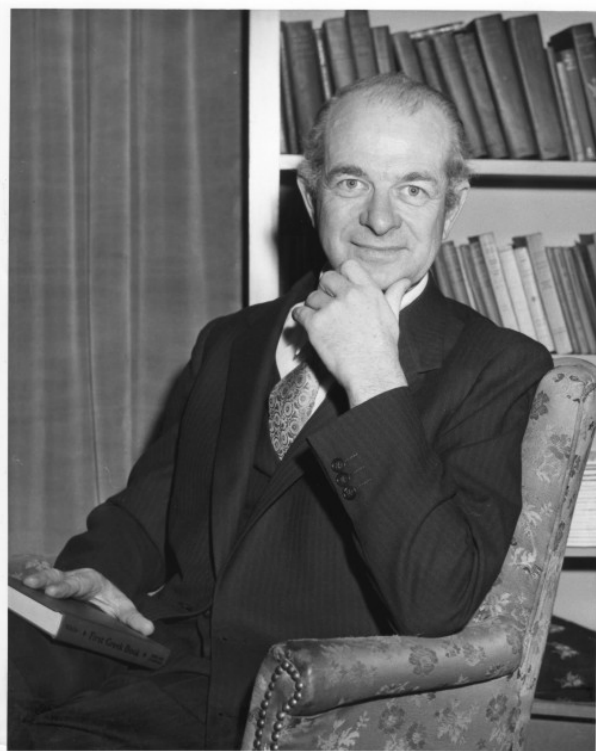


Figure 1. Professor Linus Pauling in 1950.^[1]

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His impact was felt in other areas of porphyrin chemistry as well. To name only two examples, in the early thirties he was the Ph.D. advisor of James L. Hoard (1905-1993) who became the pioneer in small molecule porphyrin crystal structure analysis.^[11] Likewise,

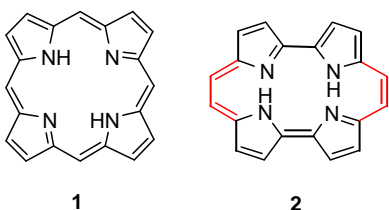
Hans Kuhn was a post doctoral fellow of his in the Forties of the last century.^[12] On a lighter side, he even made predictions about good sources for porphyrins and suggested the giant angworms in Australia as an alternative to blood.^[13]



Matthias Senge, born in Silbach, Germany (1961), studied chemistry in Freiburg, Amherst, Marburg, and Lincoln and graduated from the Philipps Universität Marburg in 1986. After a Ph.D. thesis in plant biochemistry with Horst Senger in Marburg (1989) and a postdoctoral fellowship with Kevin M. Smith at UC Davis, he moved to the Freie Universität Berlin and received his

habilitation in Organic Chemistry in 1996. From 1996 on, he was a Heisenberg fellow at the Freie Universität Berlin and UC Davis and held visiting professorships at Greifswald and Potsdam. In 2002 he was appointed Professor of Organic Chemistry at the Universität Potsdam and since 2005 holds the Chair of Organic Chemistry at Trinity College Dublin. He was the recipient of fellowships from the Studienstiftung des Deutschen Volkes and the Deutsche Forschungsgemeinschaft; from 2005-2009 he was a Science Foundation Ireland Research Professor. His main interests are synthetic organic chemistry, the chemistry and biochemistry of tetrapyrroles and coordination compounds, photobiology and photomedicine, structural chemistry, history, and medicinal and bioorganic chemistry.

He also appears to have been actively thinking about the fundamental structure of porphyrins **1** as well. While doing some unrelated library research on the history of photomedicine, I became aware of the laboratory notebooks of Linus Pauling. His research notebooks, held in the special collections section of the Oregon State University in Corvallis,^[14,15] show several entries dealing with porphyrins that span his career.



In addition to matters relating to hemoglobin these include correspondence with colleagues on the fundamental nature of porphyrins, studies on metal insertion, and spectroscopic studies. However, an intriguing one relates to one of the more significant advances in porphyrin chemistry which was made much later in 1994. Entries in his notebook from June 1944 relate to the bond structure and isomers of porphyrins. This field was pioneered by Emanuel Vogel^[16] and is exemplified by the synthesis of the C-skeleton isomer porphycene **2**.^[17] In the past two decades this developed into a whole new area of tetrapyrrole research on expanded, contracted and isomeric porphyrins, as they were so aptly named in the title of a book by Sessler and Weghorn.^[18]

June 1944 was a month of significant historical events. The world was locked in the cauldron of The Second World War and people focused more on a desperate struggle for survival than on basic science. Allied Forces were set to attack "Fortress Europe" on D-day, in the pacific theater the US Marines were poised to land on

Saipan in the Mariana islands, the Japanese forces were about to retreat back into Burma after the battle of Imphal-Kohima, and on the Eastern front Operation Bagration would lead to the destruction of Army Group Center, setting the path for the advance of the Red Army.

During the war years, Pauling offered his services to his government and worked on explosives (one even called Linusite), missile propellants, oxygen monitoring in submarines, did research on synthetic blood plasma for battlefield transfusions, and was active in the recommendation of post war research funding, ultimately resulting in the foundation of the NSF (National Science Foundation). For his services he was awarded the Presidential Medal for Merit by President Harry Truman in 1948.^[19]

Still, he never lost his passion for basic science. Two days before the start of Operation Overlord and the landing in Normandy, Professor Pauling was thinking about the bond structure and isomeric forms of porphyrins. As shown in Figure 2 he appears to have been mainly interested in the electronic structure of porphyrin isomers. His research notebook entries of that day illustrate his thoughts on what he called the "determination of numbers of unexcited electronic structures for porphyrin".

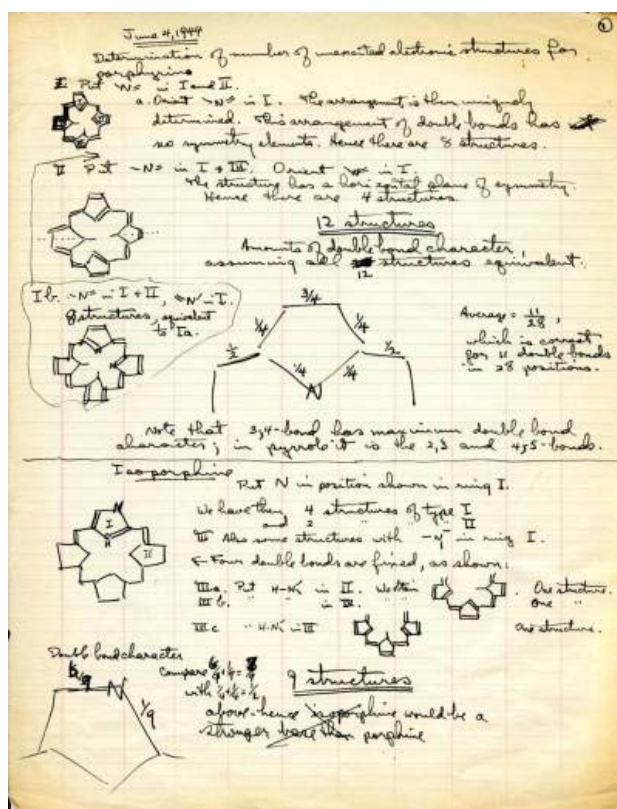
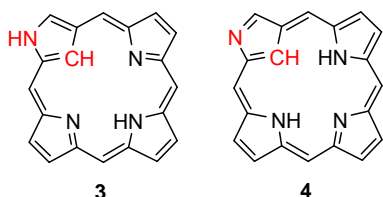


Figure 2. A page from the June 4, 1944 entries in Linus Pauling's notebook. © Ava Helen and Linus Pauling Papers, Oregon State University Special Collections.

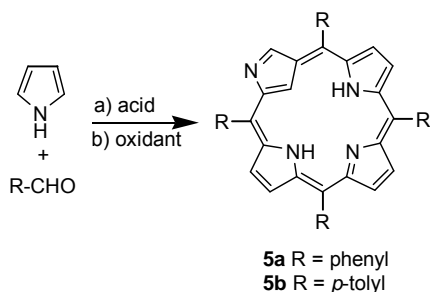
The entries in his notebook describe his attempt to predict the stability of porphine and its isomers with "extroverted" pyrrole rings depending on the double bond arrangement and the number of possible structures that can be drawn. He termed this class of compounds "isoporphine". In effect he determined the number of

possible resonance structures with 11 double bonds that can be drawn for each type of system to assess their stability. Starting with porphine, he analyzed systems with one, two, three and four extroverted pyrrole rings, i.e. with a pyrrole nitrogen atom being located on the *outside* of the porphyrin macrocycle instead of in the core.^[20]

Following the IUPAC nomenclature for porphyrins,^[21] today we call the porphyrin isomer **3** with one extroverted pyrrole ring 2-aza-21-carbaporphyrin (or its tautomeric form **4**). However, this compound is better known by the colloquial term "*N-confused porphyrin*".^[22] It was first discovered in 1993 and described in two seminal publications by Furuta *et al.* and Latos-Grażyński and coworkers in early 1994.^[23]



Both groups found the N-confused porphyrins (**5a** and **5b**) serendipitously as side products in the acid-catalyzed Rothmund condensation²⁴ of pyrrole and benz-^[23a] or *p*-tolylaldehyde^[23b] in yields of 4-7 % (Scheme 1). The main product was the standard porphyrin. Mechanistically, they are formed first by inversion of a pyrrole ring and then followed by fusion. Subsequently, improved pyrrole condensation methods and [3+1] or [2+2] condensations were developed, allowing for in-depth studies of these systems.^[25,26]



Scheme 1. Serendipitous synthesis of N-confused porphyrin.

Based on his analysis of the electronic structures Pauling noted that the N-confused porphyrins with one and two confused (extroverted) pyrrole rings would be stable. For systems with three confused pyrrole rings he stated that "*all the isomers with three extroverted rings might exist – but they would be unstable*" while porphyrins with four confused pyrrole rings are "*impossible*".^[27] So far this analysis has been born out by the experimental results. A computational analysis of 95 isomers of porphine and N-confused porphyrins indicates that the stability of the systems decreases with the number of confused pyrrole rings in agreement with Pauling's notes.^[28]

However, Pauling was not the only one, nor was he the first, to have made early suggestions about the structure of basic porphyrin isomers. In fact, as pointed out by Latos-Grażyński,^[29] Prof. Melvin Calvin (1911-1997) from the University of California at Berkeley

appears to be the first one to formulate a porphyrin isomer of type **3** in a publication. Like Pauling, he served his country during the war years and worked for the National Defense Research Council. For two years he worked on the Manhattan Project and developed a process of oxygen purification from air. Calvin later came to renown for the pioneering use of radioactive isotopes to unravel biosynthetic pathways. For his identification of the biosynthetic steps involved in carbon dioxide assimilation during photosynthesis (the Benson-Calvin-Bassham cycle) he was awarded the Nobel Prize in Chemistry in 1961.^[30,31]

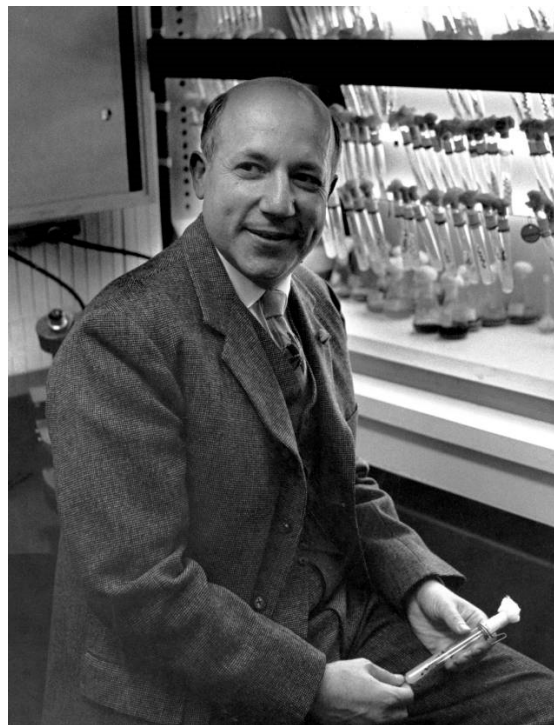


Figure 3. Professor Melvin Calvin. © Ernest Orlando Lawrence Berkeley National Laboratory.^[32]

In 1943 Calvin and his graduate student, Sam Aronoff (1915-2010), published a paper entitled "The porphyrin-like products of the reaction of pyrrole with benzaldehyde".^[33] They performed a Rothmund-type condensation reaction between pyrrole and benzaldehyde (similar to the reactions later used by Furuta and Latos-Grażyński, Scheme 1) and analyzed the products. Based on absorption spectra, acid numbers, crystal morphology and elemental analysis (more or less the same analytical methods in use since the works of Willstätter) they identified six different forms of condensation products but were unable to assign the structures of the various fractions. Based on intuition, they suggested a range of putative compounds that might have been formed.

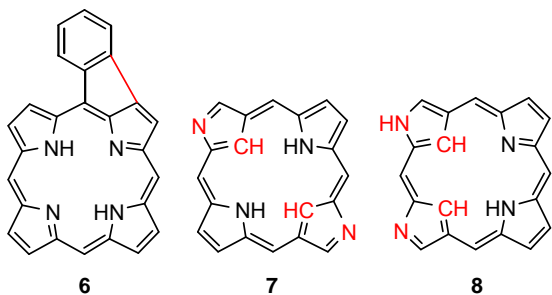
The structures suggested included various *N-H* tautomers of porphyrin and a few rather unusual structures akin to the initial (incorrect) structure proposed by Hans Fischer. Notably, they also formulated several porphyrin isomers with one or two inverted pyrrole rings. Close to the current nomenclature, they named these compounds "carboporphyrins". While they did not include valence bonds in their structures, the basic structure and arrangement of core hydrogen atoms is identical to Pauling's structures and those later identified for N-confused porphyrins. Thus, in formal terms they

were the first to suggest the formation of core modified porphyrin isomers.

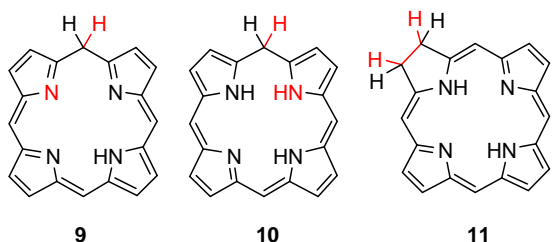
Note, that they also proposed a structure **6** with a direct meso-*m*-phenyl C–C linkage. An example of such a compound was prepared in 2004 by Fox and Boyle through intramolecular Pd(0) catalyzed coupling of *o*-iodinated meso phenyl porphyrins.^[34] It is one of the now many meso- β fused or annulated porphyrin compounds.^[35]

I was unable to ascertain whether Pauling was aware of Calvin's studies. Both knew each other, met several times, and exchanged infrequently letters on other matters. No specific reference was made to Calvin's paper in the relevant notebook entries or anywhere in his correspondence or Calvin's autobiography.^[36] The fact that Pauling used the term isoporphine while Aronoff and Calvin used carboporphyrin might indicate that Pauling was unaware of these studies.

Numerous papers have by now been published on systems with one extroverted ring and the two tautomeric forms (**3** and **4**) have clearly been identified.^[37] Likewise, several examples for N-confused porphyrins with two extroverted pyrrole rings have been reported.^[38] Pauling also compared the structures obtained for either the pyroline rings or the extroverted pyrrole rings being located in neighboring or opposing quadrants of the molecule and indicated that both can exist. Indeed, derivatives with electron withdrawing meso substituents of both the "trans" **7**^[38c] and "cis" **8**^[38a] form have been synthesized.



Pauling also compared the N-H tautomeric forms of porphine, "isoporphine" and other derivatives.^[39] While he made no notes on the relative stability of the N-H tautomers of porphine, he clearly seems to have assumed the existence of both.^[40] It should be noted that Pauling's term "isoporphine" (isoporphyrin) in this day and age is used for a different type of porphyrin compound. Isoporphyrin is used for the tautomeric form of porphyrin **9** which has interrupted macrocycle conjugation due to a saturated meso carbon atom. It was first proposed by R. B. Woodward in the 1960's based on his groundbreaking observations about phlorin **10** as a nonaromatic, isomeric form of chlorin (dihydroporphyrins) **11**.^[41,42]



Since the landmark discovery by the groups of Furuta and Latos-Grażyński research on N-confused porphyrins and related compounds has burgeoned into a field with more than 400 publications.^[43] Next to synthetic studies areas of current interest included the metal coordination chemistry due to the ability of these systems to form carbon-metal bonds, their anion sensing abilities, and their utility as photosensitizers, to name only a few. The whole field of macrocycle modified porphyrins has evolved to include isomeric expanded systems,^[44] heteroatom substituted and carbaporphyrins,^[45] Möbius aromatics,^[46] cyclic oligopyrroles,^[18] calixpyrins and -pyrroles,^[47] and more. Even the chemical interconversion, i.e. macrocycle "metamorphosis", has been reported for several of these species.^[29b,48] A topical example is the transformation of N-confused porphyrins to N-fused porphyrins.^[49]

None of this could have been foreseen by Pauling, Calvin or Aronoff in the 1940s. The analytical methods and spectroscopic techniques available at that time made a detailed structural assignment of isomeric compounds impossible. Yet, the porphyrins with extroverted pyrrole rings are clearly the N-confused porphyrins of today. Thus, while pyrroles might be extroverted or porphyrins can get confused, they clearly were not. Like so many other examples in their research career, the fact that they correctly assumed the existence and stability of N-confused porphyrins 50 years before their actual synthesis and experimental characterization clearly illustrates the chemical intuition of these remarkable scientists.

Neither Pauling, Calvin or Aronoff appear to have come back to their early studies on porphyrin isomers. Pauling focused on aspects of structural and molecular biology, became involved in issues of nuclear testing and world peace, and later in his life was active in nutritional research. Calvin was the founder of the Laboratory of Chemical Biodynamics, in a sense the first interdisciplinary bioorganic chemistry research team. He was also an Associate Director of the Berkeley Radiation Laboratory, worked on coordination compounds and catalysis, identified the crucial role of chlorophylls, studied the chemical evolution of life, and became a pioneer of plants as alternative energy sources.^[50] To foster interdisciplinary cooperation he was also one of the first to plan an open space research laboratory, now so much in favor with science administrators. Samuel Aronoff, who died in February 2010 in his home town of Corvallis (Pauling's Alma Mater), went on to publish widely on plant physiology, build up the Department of Biochemistry at Iowa State University in Ames, was Dean of Graduate Studies at Boston College, and ended his career as the Dean of Science of the new Simon Fraser University in Vancouver. Much of this has faded into history, but as shown, their work on the porphyrin isomers easily bridges and interconnects 70 years of advances in porphyrin research.

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Entry for the Table of Contents

Layout 1:

Porphyrin Isomers

Mathias O. Senge*

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Extroverted Confusion – Linus Pauling,
Melvin Calvin and Porphyrin Isomers



Porphyrins may be confused, but not Linus Pauling or Melvin Calvin. Calvin proposed "carboporphyrins" in 1943 and, unbeknownst to contemporary science, Pauling analyzed the existence and stability of such fundamental porphyrin isomers in 1944. What he called "isoporphyrins" with "extroverted pyrrole rings", nowadays called N-confused porphyrins or 2-aza-21-carbaporphyrins, were discovered 50 years later in 1994 by Furuta *et al.* and Latos-Grażyński and coworkers and opened a whole new area of heteroatom substituted tetra- and oligopyrrole research.