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

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cofactors · history of chemistry · Pauling, Linus · macrocycles · porphyrinoids

Dedicated to Professor Emanuel Vogel

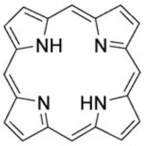
No other chemist of the modern era has influenced chemistry and molecular biology as much as Linus Pauling (1901–1994; Figure 1).[1] In a career spanning seven decades he worked and contributed to all areas of chemistry including physical, analytical, inorganic, and organic chemistry, as well as structural chemistry biochemistry. His main interests were the structure and bonding of molecules, but he worked on genetics, evolution, hematology, immunology, brain research, biomedicine, and nutritional therapy, as well. In addition, his charismatic and dynamic personality made him a humanitarian par excellance. He is the only person to have been awarded two unshared Nobel Prizes: the 1954 Nobel Prize in Chemistry and the 1962 Nobel Peace Prize.

Figure 1. Linus Pauling in 1950.[1]

His contributions are well known and with respect to porphyrin-related work he is probably best remembered for his groundbreaking concept of "molecular diseases" 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 today called 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 on the electronic structure and ligation properties of hemes,[7] and predicted the structural changes that occur upon the binding of oxygen.[8] This later led to the concept of conformational changes in porphyrins upon the binding of axial ligands.[8,9] Ultimately, this can be considered the precursor to more recent studies on the modulation of cofactor interactions through conformational control.[10]

His impact was felt in other areas of porphyrin chemistry as well. To name only two examples, in the early 1930s he was the PhD advisor of James L. Hoard (1905–1993), who later pioneered porphyrin crystal structure analysis.[11] Hans Kuhn was also a postdoctoral fellow in the Pauling group in the 1940s.[12] On a lighter side, he made predictions about good sources for porphyrins and suggested the giant angleworms in Australia as an alternative to blood.[13]

He also appears to have been 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



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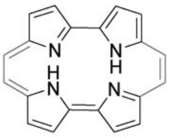

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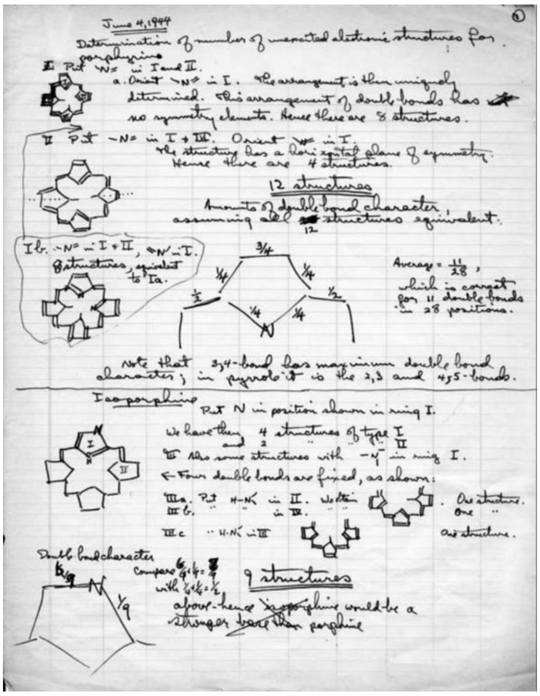
Linus Pauling. His research notebooks, held in the special collections section of the Oregon State University in Corvallis,[14,15] show several entries on porphyrins that span his career. In addition to matters relating to hemoglobin these include correspondence with colleagues on the fundamental nature of porphyrins, studies on metal insertion, and spectroscopic studies. However, an intriguing entry 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 bonding structure and isomers of porphyrins. This field was explored in experimental work by Emanuel Vogel[16] and is exemplified by the synthesis of the C-skeleton isomer porphycene (**2**).[17] In the past two decades this work has 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 in the throes of The Second World War and people were more focused on the desperate struggle for survival then on basic science. The Allied Forces were set to attack "Fortress Europe" on D-day; in the Pacific theater the U.S. 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 the Soviet Operation Bagration would lead to the destruction of German 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 organization of research funding after the war, 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, Pauling was thinking about the bonding 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*".



June 4, 1944

①

Determination of number of unexcited electronic structures for porphyrins.

I Put -N= in I and II.

a. Orient -N= in I. The arrangement is then uniquely determined. This arrangement of double bonds has no symmetry elements. Hence there are 8 structures.

II Put -N= in I + III. Orient -N= in I. The structure has a horizontal plane of symmetry. Hence there are 4 structures.

12 structures

Amounts of double bond character, assuming all 12 structures equivalent.

Ib. -N= in I + II, =N' in I. 8 structures, equivalent to Ia.

Average = $\frac{11}{28}$, which is correct for 11 double bonds in 28 positions.

Note that 3,4-bond has maximum double bond character; in pyrrole it is the 2,3 and 4,5-bonds.

Isoporphine

Put N in position shown in ring I.

We have then 4 structures of type I
and 2 " " " II

III Also some structures with $-\overset{-}{N}-$ in ring I.

← Four double bonds are fixed, as shown:

IIIa. Put H-N< in II. We obtain One structure.
IIIb. " " in IV. " " One "
IIIc " H-N< in III One structure.

Double bond character

Compare $\frac{6}{9}+\frac{1}{9}=\frac{7}{9}$
with $\frac{1}{4}+\frac{1}{4}=\frac{1}{2}$

9 structures

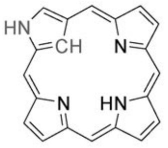
above – hence ~~isoporphine~~ would be a stronger ~~base~~ than porphine

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.

Mathias Senge studied chemistry in Freiburg, Amherst, Marburg, and Lincoln and graduated from the Philipps Universität Marburg in 1986. After a PhD thesis with Horst Senger in Marburg (1989) and a postdoctoral fellowship with Kevin M. Smith at UC Davis, he moved to the FU Berlin and received his habilitation in Organic Chemistry in 1996. From 1996 on, he was a Heisenberg fellow at the FU Berlin and UC Davis, and was a visiting professor at Greifswald and Potsdam. In 2002 he was appointed Professor of Organic Chemistry at the Universität Potsdam and since 2005 has held the Chair of Organic Chemistry at Trinity College Dublin. From 2005–2009 he was a Science Foundation Ireland Research Professor.

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 "isoporphines". 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, that is, 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 (as well as its tautomeric form **4**) 2-aza-21-carbaporphyrin. 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 co-workers in early



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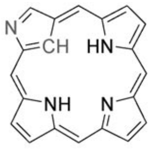

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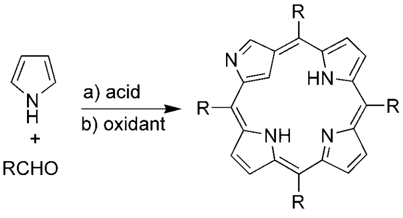
1994.[23] Both groups found the N-confused porphyrins **5a** and **5b** serendipitously as side products in the acid-catalyzed Rothemund condensation[24] of pyrrole and benz-[23a] or *p*-tolylaldehyde[23b] in yields of 4–7% (Scheme 1). The main product was the standard porphyrin. Mechanistically, the isomers are formed by inversion of a pyrrole ring followed by macrocyclization. Subsequently, improved methods for pyrrole condensation and [3+1] and [2+2] condensations were developed, allowing for in-depth studies of these systems.[25,26]



5a: R = phenyl
5b: R = *p*-tolyl

Scheme 1. Serendipitous synthesis of N-confused porphyrins.

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 predictions.[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 and Stępień,[29] Melvin Calvin (1911–1997; Figure 3) from the University of California at Berkeley appears to be the first 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. Calvin later achieved 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]

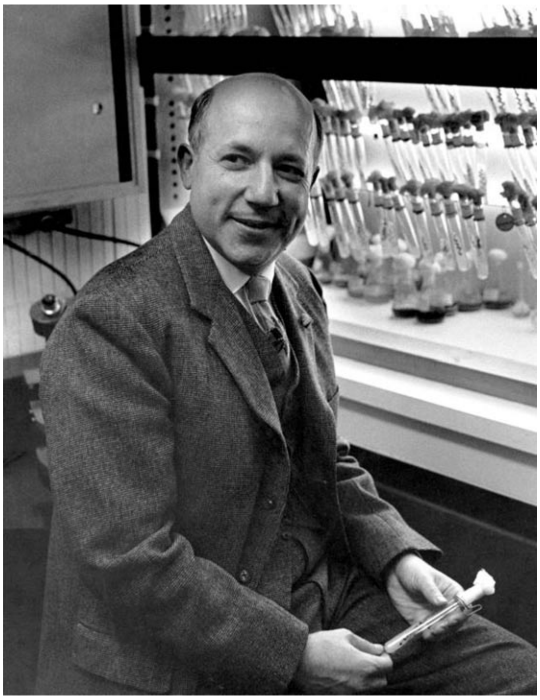


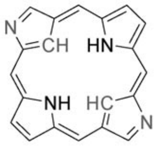
Figure 3. Melvin Calvin. Ernest Orlando Lawrence Berkeley National Laboratory.[32]

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 Rothemund-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 Willstätter's time) they identified six different condensation products but were unable to assign the structures. 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, which they named "carboporphyrins", similar to the current nomenclature. 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 Calvin and Aronoff were the first to suggest the formation of core-modified porphyrin isomers. Note, that they also proposed a structure with a direct C–C linkage between the pyrrole 3-position and the *ortho* position of an attached phenyl group. An example of such a compound was prepared in 2004 by Fox and Boyle through intramolecular Pd^0-catalyzed coupling of *ortho*-iodinated meso-phenylporphyrins.[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. They knew each other, had met several times, and exchanged letters infrequently on other matters. No specific reference was made to Calvin's paper in Pauling's notebook entries or anywhere in his correspondence or in Calvin's autobiography.[36] The fact that Pauling used the term isoporphine while Aronoff and Calvin called these compounds carboporphyrins might indicate that Pauling was unaware of these studies.

Since then, numerous papers have been published on systems with one extroverted ring and the tautomeric forms **3** and **4** have clearly been identified.[37] Likewise, several examples of N-confused porphyrins with two extroverted pyrrole rings have been reported.[38] Pauling also compared the structures in which either the pyrrolenine rings or the extroverted pyrrole rings are 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*" **6**[38c] and "*cis*" **7**[38a] forms have been synthesized.



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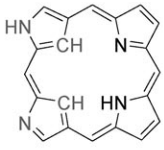

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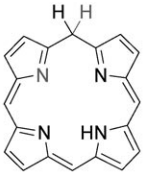
Pauling also compared the N–H tautomeric forms of porphine, "isophorphine", and other derivatives.[39] While he made no notes on the relative stability of the N–H tautomers of porphine, he seems to have assumed the existence of both.[40] It should be noted that Pauling's term "isoporphine" (isoporphyrin) is used for a different type of porphyrin compound nowadays. Isoporphyrin is used for the tautomeric form of porphyrin **8** in which the conjugation in the macrocycles is interrupted by a saturated meso carbon atom. This compound was first proposed by R. B. Woodward in the 1960s based on his groundbreaking observations of phlorin (**9**) as a nonaromatic, isomeric form of chlorins (dihydroporphyrins) **10**.[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] Current research includes, besides synthesis, the metal coordination chemistry of these systems (since they can form carbon–metal bonds, their anion-sensing abilities, and their utility as photosensitizers. The whole field of macrocycle-modified porphyrins has evolved to include isomeric expanded systems,[44] heteroatom-substituted and carbaporphyrins,[45] Möbius arenes,[46] cyclic oligopyrroles,[18] calixphyrins and -pyrroles,[47] and more. Even the chemical interconversion, that is, 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]



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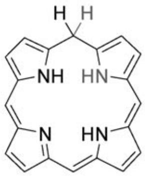

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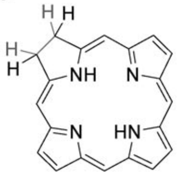

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None of this could have been foreseen by Pauling, Calvin, and Aronoff in the 1940s. The analytical methods and spectroscopic techniques available at that time made a detailed structural assignment of isomeric compounds impossible. Yet the porphyrins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

None of the three appears to have returned 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, Oregon (the location of Pauling's alma mater, Oregon State University), went on to publish widely on plant physiology, build up the Department of Biochemistry at Iowa State University in Ames, served as the Dean of Graduate Studies at Boston College, and ended his career as the Dean of Science of the new Simon Fraser University in Vancouver, British Columbia. Much of this has faded into history, nevertheless, the work of Pauling, Calvin, and Aronoff on porphyrin isomers easily bridges and interconnects 70 years of advances in porphyrin research.

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