The Story of Vitamin B_{12}: Discovery, Structural Elucidation, and Total Synthesis

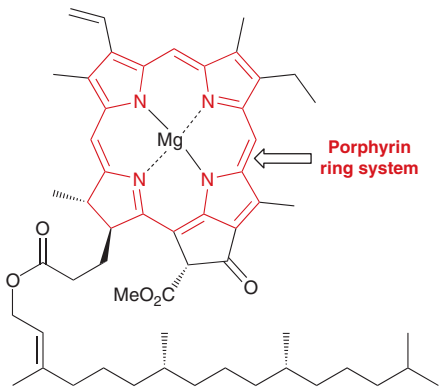
Through many years of research, a team of scientists discovered a pink-colored "vital" component in liver extracts that was eventually isolated and identified as vitamin B_{12}. If a person is anemic because their body has trouble absorbing the vitamin, they may need B_{12} shots.

The story of vitamin B_{12} began in 1926 when Harvard physicians William Murphy and George Minot recognized that anemia, a disease caused by a low concentration of red blood cells, could be prevented in most patients by eating a half-pound of liver every day. This finding earned the researchers a portion of the 1934 Nobel Prize in Medicine. It also sparked a race to extract the compounds in liver and isolate the component capable of treating "pernicious anemia" (an autoimmune disorder so named because of its harmful, and often deadly, effects). Karl Folkers and other scientists at the Merck Chemical Company had already been working on the isolation and synthesis of B vitamins, so they joined the pursuit to identify the mystery component (or components). One challenge to the research was a lack of animal models, so studies had to rely on identifying human subjects who had the relatively rare disease and were willing to volunteer for medical research. This problem was solved by Mary Shorb, a microbiologist at the University of Maryland who had worked at the US Department of Agriculture. Dr. Shorb identified a method to evaluate the potency of liver extracts by measuring their ability to promote the growth of a bacterium used to make yogurt (such testing methods are called *bacteriological assays*). In subsequent research funded by Merck, Shorb and Folkers discovered that the liver extracts with the most promising bioassay results had a pink color. The pink color was explained in 1947, when a team led by Dr. Folkers and Ed Rickes successfully isolated and purified the "vital" component as small, red, needle-shaped crystals. In 1948, the Merck researchers reported that anemia patients responded favorably to treatment with the compound in a clinical setting, and they named the previously elusive "anti-pernicious anemia factor" vitamin B_{12}.

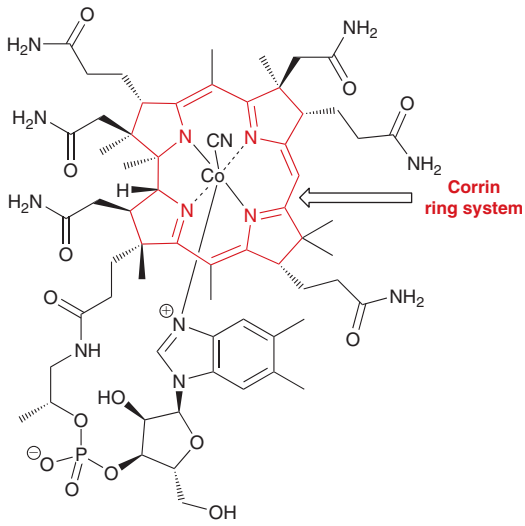
Next, research efforts were focused on determining the structure of vitamin B_{12}. Some structural features were initially elucidated by the Merck team, but the complete structure was successfully determined in 1956 by Dorothy Crowfoot Hodgkin (Oxford University) using X-ray crystallography. She found that the structure of vitamin B_{12} is built upon a corrin ring system, which is similar to the

porphyrin ring system present in chlorophyll, the green pigment that plants use for photosynthesis (see below).

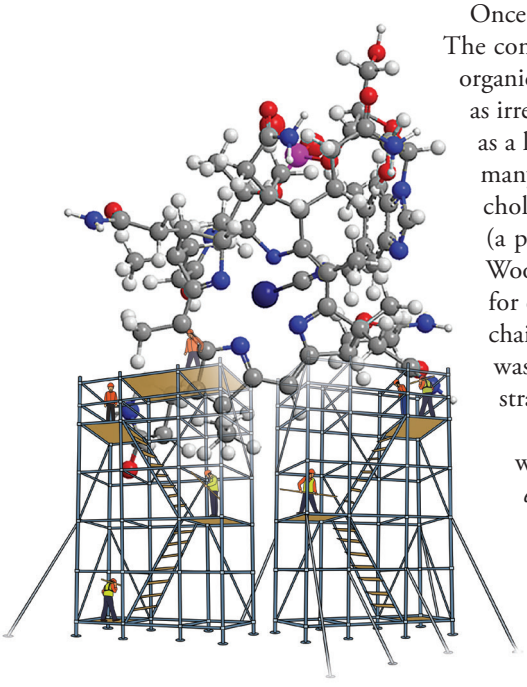
Chlorophyll *a*



Vitamin B_{12}



Much like the porphyrin ring system in chlorophyll, the corrin ring system of vitamin B_{12} is also comprised of four heterocycles (rings containing an atom other than carbon, such as nitrogen) joined together in a large ring called a macrocycle. However, the corrin ring system of vitamin B_{12} is constructed around a central cobalt atom instead of the magnesium of chlorophyll, and vitamin B_{12} contains many more chiral centers than chlorophyll. The determination of the vitamin B_{12} structure pushed the boundaries of X-ray crystallography, which until then had never been used to elucidate such a complex structure. Vitamin B_{12} has 181 atoms, and it took eight years to map! Hodgkin was a pioneer in the field of X-ray crystallography and throughout her career she identified the structures of many important biochemical compounds. For her efforts, Dr. Hodgkin was awarded the 1964 Nobel Prize in Chemistry (thus becoming the third woman to earn this award).



Once the structure of vitamin B_{12} was determined, the stage was set for its total synthesis. The complexity of vitamin B_{12} represented the greatest challenge of the time to synthetic organic chemists, and a couple of talented synthetic organic chemists viewed the challenge as irresistible. Robert B. Woodward (Harvard University) had already established himself as a leading player in the field of organic chemistry with his successful total synthesis of many important natural products, including quinine (used in the treatment of malaria), cholesterol and cortisone (steroids that will be discussed in Section 26.6), strychnine (a poison), and chlorophyll. With these impressive accomplishments under his belt, Woodward eagerly embraced the challenge of vitamin B_{12}. He began working on methods for constructing the corrin ring system as well as the stereochemically demanding side chain. Meanwhile, Albert Eschenmoser (at the university ETH in Zurich, Switzerland) was also working on a synthesis of the vitamin, but with a different macrocyclization strategy to construct the corrin ring system.

Woodward and Eschenmoser each faced a number of obstacles, so a partnership was forged in 1965 to tackle the problem together. *It is interesting to note that even highly accomplished scientists struggle and often find success by teaming up with partners—1965 was the same year that Woodward was awarded the Nobel Prize in Chemistry for his contributions to the field of synthetic organic chemistry!* Woodward and Eschenmoser continued to work together for another seven years, often spending an entire year optimizing the conditions for an individual step. The intense effort, which involved nearly 100 graduate students working for a

decade, would ultimately be rewarded. Woodward's team completed the assembly of the side chain, and the two groups combined the best methods and practices that were developed while working on the construction of the corrin system. The pieces were finally joined together, and the synthesis was completed to produce vitamin B_{12} in 1972. This landmark event represents one of the greatest achievements in the history of synthetic organic chemistry, and it supported the belief that organic chemists could prepare any compound, regardless of complexity, if given enough time.

During his journey toward the total synthesis of vitamin B_{12}, Woodward encountered a class of reactions that were known to proceed with unexplained stereochemical outcomes. Together with his colleague Roald Hoffmann, he developed a theory and a set of rules that would successfully explain the stereochemical outcomes of an entire area of organic chemistry called pericyclic reactions. This class of reactions will be covered in Chapter 16. The development of these "Woodward-Hoffmann" rules led to a Nobel Prize in 1981, for which Woodward would have been a co-recipient had he not died two years earlier.

The story of vitamin B_{12} is a wonderful example of how organic chemistry progresses. During the total synthesis of a structurally complex compound, there is inevitably a point at which the planned route fails, requiring a creative method for circumventing the obstacle. In this way, new ideas and techniques are constantly being developed. Unexpected experimental results can certainly be frustrating, but to the observant scientist they sometimes represent the discovery of a new reaction—thus creating opportunities for new lines of research, or perhaps giving birth to entirely new fields of chemistry! In the decades since the total synthesis of vitamin B_{12}, thousands of synthetic targets, most of them biologically active compounds, have been constructed. New techniques, reagents, and principles constantly emerge from these endeavors. With time, synthetic targets are getting more and more complex, and the leaders in the field of organic chemistry are constantly pushing the boundaries of synthetic organic chemistry, a discipline that continues to evolve on a daily basis.

"If I have seen further, it is by standing on the shoulders of Giants" Isaac Newton, 1675