Profile of William S. Knowles

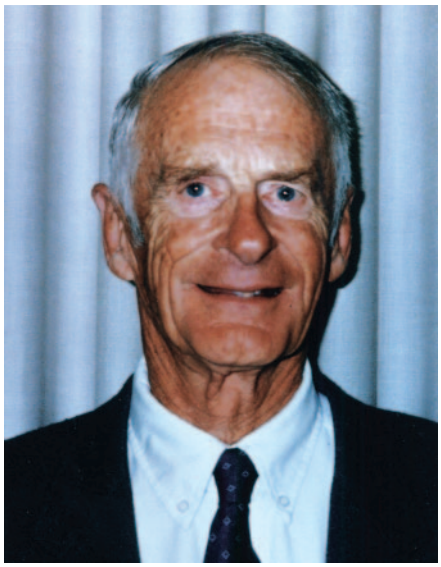
For every left hand, there is a matching right hand, and for every L-isomer, a D-isomer. So goes the mirror-image rule of chirality. Most molecules in nature exist in either of two chiral enantiomers, forms that mirror each other in structure. In chemistry, chiral molecules are important because one enantiomer of a given compound may be biologically active, whereas its mirror-image enantiomer is inactive. For example, the common amino acid alanine has two chiral forms—*S*-alanine and *R*-alanine—but only *S*-alanine is prevalent in proteins.

Enriching only the bioactive chiral forms of a compound has been a major focus among chemists for decades, and William S. Knowles is one of the founding pioneers of the field of chiral chemistry. Retired after more than 40 years at Monsanto (St. Louis, MO), Knowles was elected to the National Academy of Sciences (NAS) in 2004. Together with Ryoji Noyori and K. Barry Sharpless, Knowles was awarded the Nobel Prize in Chemistry in 2001 for his lifetime of trailblazing work in catalytic asymmetric synthesis, specifically in the area of hydrogenation (1, 2). Catalytic asymmetric synthesis is an enzyme-like process that can rapidly produce an excess of one chiral compound form, a process with numerous practical applications, such as production of industrial biomaterials and pharmaceuticals.

New England Chemistry

Born in 1917 in Taunton, MA, Knowles grew up in nearby New Bedford where his family was involved in business and maritime activities. He attended boarding school at Berkshire School (Sheffield, MA) in western Massachusetts and excelled in mathematics and science. "I was terrible at athletics and never made a team but quite easily led my class in academics," says Knowles in his Nobel Prize autobiography. Studying in the Northeast provided Knowles with "a good lesson in New England thrift," he says. "To get free ice for our physics experiments, we had to wait until it snowed."

Although admitted to Harvard University (Cambridge, MA) at 17 years of age, Knowles was advised against attending at that point because of being "too young socially to go to college." Thus he spent a second senior year at another boarding school, Phillips Academy Andover (Andover, MA). At Andover, Knowles took his first chemistry class, taught by Bushy Graham, and became "fascinated by the subject." Says



William S. Knowles

Knowles, "I remember [Graham] trying to explain Avogadro's number and his discussion of the dangers of hydrogen and oxygen." At the end of the year at Andover, Knowles entered a competitive examination and won his first academic award, a $50 Boylston prize in chemistry.

Knowles entered Harvard the following year, majoring in chemistry with a focus on mathematics. "The one who got me into chemistry in the first place was Louis Fieser at Harvard," says Knowles, who became interested in organic chemistry in one of Fieser's classes. "I was headed to . . . physical chemistry because of my proclivity for math, but [Fieser] turned me in another direction." From that point on, organic chemistry became Knowles's lifelong research passion.

Drafted into Industry

After receiving his A.B. from Harvard in 1939, Knowles began doctoral studies at Columbia University (New York) under Robert Elderfield. Knowles' doctoral thesis focused on the synthesis of simple analogs of cardiac aglycones and testing of their cardiac activity (3, 4). "I was sort of a steroid chemist," he says. Knowles's Ph.D. thesis focused on the synthesis of analogs of digitalis (digoxin), a drug used in cardiovascular therapy. He received his doctorate in synthetic organic chemistry in 1942.

Knowles' academic career as a synthetic organic chemist was short-lived, however, and a professional one took its place as World War II began and scientists were utilized by the government. "New York was an exciting place to be in those war years, [but] my draft board forced Columbia to push me out sooner" than normal, recalls Knowles. "In those days, industry would hire any chemist that could breathe." Thus, in 1942, Knowles began working at the Thomas and Hochwalt laboratories, part of Monsanto, in Dayton, OH. He described his work at that time as "pretty mundane" as he performed chemical tasks such as synthesizing pure hexamethylenetetramine for making the explosive cyclonite.

Knowles was transferred in 1944 to Monsanto in St. Louis to work on plasticizers and intermediates. He worked on a variety of projects over the next several years, including the manufacture of benzyl benzoate as a mite repellent for soldiers' clothing; the production of dichloro-diphenyl-trichloroethane (DDT), which began in earnest after the war; and the synthesis of vanillin, which was abandoned after lignin was found as a means to produce this flavor. The work with vanillin at Monsanto eventually led to the commercial production of the amino acid L-3,4-dihydroxyphenylalanine (L-DOPA), which is used to treat Parkinson's disease.

Knowles also cites the total synthesis of cortisone during these early years of his career as one of his most important and "glamorous" research projects. He began this work in 1950 under Robert B. Woodward. Knowles was able to simplify Woodward's 50-step cortisone synthesis process to 36 steps. "I got involved in [steroid synthesis] early at Monsanto because of the fact that . . . I was the only one they hired who had a steroid background," he says. "They immediately picked that off my resume and put me on that project." Monsanto was interested in cortisone because it looked to be "the general cure for everything . . . arthritis, common cold, whatnot," says Knowles. "It really looked like a real bonanza."

He returned to Harvard in 1951 for a 9-month-long, company-sponsored postdoctoral stint with Woodward. "The experience working with the 'great man' is one I'll never forget," says Knowles in his Nobel autobiography. "We would spend an hour or more scribbling chemical structures on the menu or placemats. His phenomenal memory was beyond anything I'd ever seen." Knowles continued to study the total synthesis of cortisone, as well as its active bicyclic

This is a Profile of an elected member of the National Academy of Sciences.

© 2005 by The National Academy of Sciences of the USA

Downloaded by guest on November 15, 2019

intermediates, throughout the 1950s (5–9). "Nothing came of the effort" to commercialize Woodward's total synthesis of steroids, says Knowles, "but it did leave me with an interest in steroid chemistry as an inactive observer."

Kinetics of Efficiency

At the end of the 1950s, Knowles turned back to his old mathematics roots and became involved with kinetic studies, mostly for making simple aromatic molecules (10–12). He cites this research work as some of his most noteworthy because of the value it provided for Monsanto and the chemical industry. From these kinetic studies, Knowles and colleagues were able to reduce reaction cycles dramatically and increase production by as much as 2-fold, all with the same equipment, and thus benefit the industry.

"I grew up in a heyday of the chemical processing industry," says Knowles. "The whole industry was hungry for chemicals, with a tremendous push to get more out with the equipment you happened to have." Conducting research in an industry setting was more readily accomplished during these times. "I think it was probably a little easier back then because we hadn't reached the law of diminishing returns" on industrial processes and revenues, he says. "The research paid off."

Nowadays, however, rates of diminishing returns can be seen in the biochemical industries. For example, pharmaceutical and biotechnology companies continue to spend billions of dollars on research and development of new therapeutic compounds, but only a minority of resulting drug products offsets those costs. "I suppose it's happening in pharmaceuticals," says Knowles. "They're getting a great push now, but eventually it'll be harder and harder and harder to come up with blockbuster drugs. I don't know where they'll go from there."

Asymmetry in Earnest

In the mid-1960s, Knowles's asymmetric synthesis research began in earnest, work that one day would earn him the Nobel Prize. "I was always interested in stereochemistry since my first year of organic chemistry," he says, "but I never did much about it until I worked on Woodward's total synthesis of steroids, where, of course, stereochemistry was of central importance." In the synthesis process, Knowles was bothered by the fact that he would "essentially throw away half of our starting material when the first asymmetric center was generated."

At that time, if chiral compounds were needed, they were obtained either by biochemical methods or from racemic mixtures followed by laborious and expensive resolution steps. Knowles found that although racemic mixtures for amino acids without the unwanted D-isomer could readily be made, the costs and complexity of these techniques were high and could not compete with biochemical processes, where the desired L-isomer could be obtained directly.

But Knowles saw a solution, albeit a potentially difficult one. "What was needed was a catalyst, which would make the desired isomer directly like an enzyme," says Knowles. Such a catalyst would not require "nature's 100% yields" because "presumably Nature has to be quantitative, since, unlike the chemist, she does not have the ability to purify between steps."

On winning the Nobel, "I didn't really expect it would happen to me . . . but that probably made it doubly sweet."

Two research findings in the mid-1960s made Knowles believe such a catalyst would be attainable. First, G. Wilkinson's group discovered chloro-*tris*(triphenylphosphine)rhodium [$RhCl(PPh_3)_3$], which could act as a soluble hydrogenation catalyst for unhindered olefins at rates comparable with well known heterogeneous counterparts (13). Second, Horner and Mislow separately reported methods for preparing optically active phosphines (14, 15).

Based on this knowledge, in 1968, Knowles and his group strategized to replace the triphenylphosphine in Wilkinson's rhodium catalyst with a chiral phosphine and hydrogenate a prochiral olefin (1). Their first hydrogenations gave only 15% enzymatic efficiency, and subsequent phosphine modifications to the molecule increased efficiency to 28–32%. Continued modifications resulted in the creation of methylphenyl-*o*-anisylphosphine (PAMP), with 58% efficiency. Finally, when the phenyl group in PAMP was modified to a more hindered cyclohexyl to give methylcyclohexyl-*o*-anisylphosphine (CAMP), the efficiency jumped to 88%. This breakthrough was the first time that enzyme-like selectivity had been achieved with a man-made catalyst, and Knowles and his colleagues were thrilled.

Industrial Chemistry

Just when Knowles and his group discovered CAMP, another seemingly unrelated development would soon impact his research—the discovery that L-DOPA was useful in treating Parkinson's disease. This finding created a sudden demand for this rare amino acid. Furthermore, unbeknownst to Knowles, Monsanto was already custom-manufacturing a racemic intermediate starting with vanillin, which Hoffman–Laroche was resolving and deblocking to L-DOPA. The process, which used the Erlenmeyer Az-lactone synthesis (16), involved a hydrogenation step with a symmetric catalyst. In principle, all that was required to make L-DOPA directly without laborious resolution was to substitute the symmetric catalyst with the new asymmetric catalyst.

Knowles thus saw an application for his asymmetric catalytic process. L-DOPA "offered a golden opportunity for us to commercialize this burgeoning technology," he says. "We were able to add our catalyst to get the L-enantiomer." With CAMP in hand and found to work equally well in the L-DOPA precursor, Knowles and his group used their asymmetric hydrogenation technology for the commercial production of L-DOPA. Later, the 80–88% efficiency of their chiral catalysis process using CAMP was further improved to 95% using DiPAMP, a dimerized form of PAMP (2). The commercial L-DOPA process was quickly converted to utilize DiPAMP, which also happened to be easier to make than CAMP. Thus Knowles's overarching contribution to asymmetric catalysis was established with the invention of the first industrial process to chirally synthesize an important compound.

Nobel Surprise

Knowles's catalytic asymmetric synthesis research spanned the 1970s and 1980s, and, in 1986, he retired from Monsanto and served in a consulting capacity for 5 more years. "I was always interested in finding more efficient ways to make chemicals," he says. Fifteen years after retiring, the Nobel Prize committee recognized this sentiment by awarding Knowles the Nobel Prize in Chemistry. Half of the prize was shared by Knowles and Ryoji Noyori, with the other half awarded to Barry Sharpless.

"Knowles did it all," says Sharpless, W. M. Keck Professor of Chemistry at The Scripps Research Institute (La Jolla, CA) and an NAS member elected in 1985. "Bill Knowles showed us we could do it, and the rest of us came along and did it," he says about catalytic asymmetric reactions. Whereas Knowles

Downloaded by guest on November 15, 2019

and Noyori received their share of the Nobel Prize for their work on chirally catalyzed hydrogenation reactions, Sharpless received his prize share for research on chirally catalyzed oxygenation reactions. Paraphrasing esteemed chemist and NAS member Jack Halpern of the University of Chicago, who has also contributed major knowledge in catalytic hydrogenation, Sharpless says, "The monopoly that nature had on this kind of trick was broken." Thanks to the work of Knowles and others, specific and efficient man-made processes were now possible.

"This achievement convinced the academic/industrial community of the power of chemical asymmetric synthesis," states Noyori, Professor of Chemistry at Nagoya University (Nagoya, Japan) and President of RIKEN (The Institute of Physical and Chemical Research; Saitama, Japan). A foreign associate of the NAS elected in 2003, Noyori explains that a host of important biological chiral compounds are now accessible by purely chemical means. Knowles "demonstrated the significance of basic research by pioneering homogenous asymmetric hydrogenation," he says.

"What I think is so cool about Knowles is that he's such a gentleman," says Sharpless, "and he came out of nowhere, actually. He was surprised, I think," to win the Nobel Prize. Knowles agrees. "It came out of the blue to me," he says. "I didn't really expect it would happen to me . . . but that probably made it doubly sweet."

One clue Knowles received that he might win the Nobel Prize came in the spring of 2001, when he received a call from organic chemist Per Ahlberg in Sweden. Ahlberg claimed to be writing a review article of Knowles's field for a local publication. He promised to send Knowles a reprint. In fact, however, this "review article" turned out to be information for the Nobel committee. After winning the prize, Knowles recalls Ahlberg saying, "I hope you're not going to wait for that reprint!" Muses Knowles, "His job was I think to more or less establish that I was alive and kicking."

Knowles specifically points out that a fourth chemical researcher, Henri Kagan, deserves recognition for his contributions to the field of catalytic asymmetric synthesis. Emeritus Professor of Université Paris-Sud (University of Paris-South, Orsay, France) and founder of the university's Laboratoire de Synthèse Asymétrique (Asymmetric Synthesis Laboratory, Orsay, France), Kagan made similar discoveries in asymmetric synthesis about 6 months after Knowles. Although, in a way, "Kagan got left out of the act," says Knowles, he points out that Kagan received the Wolf Prize for Chemistry in January 2001, alongside Noyori and Sharpless. Awarded by the Wolf Foundation in Israel, the Wolf Prize is often considered the most prestigious award in chemistry after the Nobel.

As to why he was chosen to receive the Nobel Prize, Knowles believes it was because he created an immediately applicable "invention" with his large-scale chiral synthesis production process for L-DOPA. "That was the difference," he says. According to Knowles, what impressed the Nobel committee probably had more to do with inventing something immediately applicable and with life sciences relevance, despite the fact that they usually do not give prizes to industry. "This was not a laboratory curiosity," he says, pointing out that the technique was used within 6 months to establish a 50-gallon production process. "That was unusually fast for a brand-new invention," and this is what caught the attention of the Swedish academy, in Knowles's opinion.

Green Chemistry

Well into retirement, Knowles ponders the future of chemistry. Peering forward, he foresees his field entering the realm of "green chemistry." Green chemistry focuses on making industrial and biological chemicals safer for the environment and public with far fewer byproducts. To achieve this goal of less wasteful chemical production, catalytic chiral synthesis will likely play a critical role. "Green chemistry is really copying nature a little bit," says Knowles. "It's going to require mostly catalytic chemistry to do this. We've got to have better catalysts."

Finding ways to compete with nature has driven much of Knowles's research career. "We happened to find a way" with catalytic asymmetric synthesis "and that's why we got some recognition," he says. "The problem with nature's catalysts is . . . you don't have any versatility. It's very specific for what nature designed it to do. That's all it does." Returning to the words of Halpern, however, Knowles's catalytic chiral achievements "broke nature's monopoly" and indeed found a way to outdo nature. Despite these accomplishments, Knowles says, "Nature's still the best chemist."

Oliver Yun, *Science Writer*

1. Knowles, W. S. & Sabacky, M. J. (1968) *Chem. Commun.*, 1445–1446.
2. Knowles, W. S. (1983) *Acc. Chem. Res.* **16,** 106–112.
3. Knowles, W. S., Kuck, J. A. & Elderfield, R. C. (1942) *J. Org. Chem.* **7,** 374–382.
4. Knowles, W. S., Fried, J. & Elderfield, R. C. (1942) *J. Org. Chem.* **7,** 383–388.
5. Barkley, L. B., Farrar, M. W., Knowles, W. S. & Raffelson, H. (1953) *J. Am. Chem. Soc.* **75,** 4110–4111.
6. Barkley, L. B., Farrar, M. W., Knowles, W. S., Raffelson, H. & Thompson, Q. E. (1954) *J. Am. Chem. Soc.* **76,** 5014–5016.
7. Barkley, L. B., Farrar, M. W., Knowles, W. S. & Raffelson, H. (1954) *J. Am. Chem. Soc.* **76,** 5017–5019.
8. Barkley, L. B., Knowles, W. S., Raffelson, H. & Thompson, Q. E. (1956) *J. Am. Chem. Soc.* **78,** 4111–4116.
9. Knowles, W. S. & Thompson, Q. E. (1957) *J. Am. Chem. Soc.* **79,** 3212–3218.
10. Knowles, W. S. & Thompson, Q. E. (1959) *Chem. Ind. (London)*, 121.
11. Knowles, W. S. & Thompson, Q. E. (1960) *J. Org. Chem.* **25,** 1031–1033.
12. Alt, G. H. & Knowles, W. S. (1960) *J. Org. Chem.* **25,** 2047–2048.
13. Osborn, J. A., Jardine, F. H., Young, J. F. & Wilkinson, G. (1966) *J. Chem. Soc.*, 1711–1732.
14. Gallagher, N. J. & Jenkins, I. D. (1968) in *Topics in Stereochemistry*, eds. Allinger, L. & Eliel, E. L. (Wiley, New York), Vol. 3, Chapter 1.
15. McEwen, W. E. (1965) in *Topics in Phosphorus Chemistry*, eds. Grayson, M. & Griffith, E. J. (Interscience, New York), Vol. 2, Chapter 1.
16. Allen, C. F. H. & VanAllan, J. A. (1944) *Org. Syntheses* **24,** 1.

Downloaded by guest on November 15, 2019