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Friedrich Wöhler (1800–1882), on the Bicentennial of His Birth

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Abstract: The life and contributions to various areas of chemistry of German chemist Friedrich Wöhler (1800–1882) are briefly sketched. His serendipitous synthesis of urea from ammonium cyanate in 1828, which is dealt with in some detail, challenged the vitalistic theory that organic compounds can be produced only by living organisms and led to today's synthetic chemical industry and its host of products that we take for granted.

Introduction

The year 2000 marks the bicentennial of the birth of one of the 19th century's most versatile and important chemists, renowned for his synthesis of urea from inorganic components, his collaboration with lifelong friend Justus von Liebig (1803–1873) to produce an article on the benzoyl radical that exerted a profound influence on organic chemistry, and his research on a wide range of subjects in a number of areas of chemistry.

Wöhler's Early Years

Friedrich Wöhler (Figures 1 and 2) was born on July 31, 1800, in the village of Eschersheim, near Frankfurt am Main in the grand duchy of Hesse in western Germany, where three generations of his family had been equerries (*Stallmeister*) to the Elector of that duchy [1–7]. August Anton Wöhler, his father, was equerry to the Electoral Prince and later Elector Wilhelm II, while Anna Katharina Wöhler (née Schröder), his mother, was the daughter of the headmaster of a first-grade classical school (*Gymnasialdirektor*) in nearby Hanau. The father later left Hesse, becoming a farmer, court official, and then prominent citizen in Frankfurt, where young Friedrich attended high school (*Gymnasium)* from 1814 to 1820, supplementing his school work with chemical experiments and mineral collecting, which was encouraged by Johann Jacob Casimir Buch (1778–1851), a physician and member of the Natural Science Society.

Wöhler then spent a year as a medical student at his father's alma mater, the Universität Marburg. He turned his living quarters into a laboratory where he worked on thiocyanic acid and other cyanide compounds, which, through Dr. Buch's sponsorship, resulted in his first publication [8]. Here he described for the first time the behavior on heating of mercury(II) thiocyanate, $Hg(SCN)_2$, known to chemists and chemistry students as the basis of Pharaoh's serpents, from the voluminous, wriggling ash produced by its combustion.

Wöhler then left Marburg for the Universität Heidelberg to study under Leopold Gmelin (1788–1853) (Figure 3), of *Gmelins Handbuch der anorganischen Chemie* fame, who became his favorite teacher and most benevolent advisor and friend during his stay at the university. However, Gmelin considered attendance at his lectures to be unnecessary for the fledgling but already experienced student, and, *mirabile dictu*, Wöhler, who so enriched our science with his many discoveries, never heard any formal chemistry lectures. Yet, perhaps more importantly, he worked in Gmelin's laboratory and benefited greatly from his personal contact with him. Here Wöhler began his experiments with cyanic acid (HOCN), describing its formation from the action of cyanogen on barite ($BaSO_4$), a harbinger [9] of his later, famous urea synthesis [10].

Another factor leading Wöhler to his urea synthesis was the influence of Friedrich Tiedemann (1781–1861), who at the time was involved in chemical–physiological studies with Gmelin and who aroused in Wöhler an interest in physiology. The medical faculty offered a prize for a study of the transformation of materials in urine, and Wöhler carried out a large number of experiments, mostly on dogs, but sometimes on himself. He won the prize and could have used the work for his dissertation, but he preferred to have it published in Tiedemann's *Zeitschrift* [11].

On September 2, 1823 Wöhler passed his examination by the faculty and received his degree of Doctor of Medicine, Surgery, and Obstetrics (*Doktor der Medizin, Chirurgie und Geburtshilfe) insigni cum laude*, but Gmelin had earlier advised him to abandon medicine and to devote himself to chemistry. It was then customary for German chemists to go abroad for advanced training. Encouraged by Gmelin and by the complimentary mention of his first publications in Berzelius' *Annual Reports* (*Jahres-Berichte*) [12], even before graduating, on July 17, 1823 Wöhler wrote to the Swedish chemist, the most famous and influential of the day, asking to work in his laboratory. Wöhler received an almost immediate, favorable, and friendly reply in a letter of August 1, 1823:

> Whoever has studied chemistry under Herr Leopold Gmelin's direction will certainly find very little to learn with me. In spite of this I will not deny myself the happy opportunity to become acquainted with you personally and will therefore gladly and heartily accept you as my fellow worker (*Arbeits-Camerade*) [13a].

Wöhler's Year with Berzelius

In October 1823 Wöhler departed for Stockholm to work with Jöns Jacob Berzelius (1779–1848) (Figures 4–6), the

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Figure 1. Young Friedrich Wöhler (1800–1882), a sketch from reference 13.

Figure 2. Friedrich Wöhler (1800–1882) at an advanced age, a sketch from reference 4.

Figure 3. First-day cover, issued July 14, 1988 to commemorate the 200th anniversary of Leopold Gmelin's birth. Scott Catalogue No. 1560, Germany. The 80-pfennig stamp shows his portrait, and the postmark bears the formulas $CrCl_2$ and $ZnCrO_4$ as well as chromium's system number in his famous *Handbuch*, from reference 94, p 62 (Courtesy, Foil A. Miller).

Figure 4. Jöns Jacob Berzelius (1779–1848), a sketch made at the age of 44, in 1823 when young Friedrich Wöhler studied with him in Stockholm.

Figure 5. Three stamps honoring Jöns Jacob Berzelius (1779–1848). With symbols of the elements, for many of which he determined the atomic weights, \$1.10, issued on September 9, 1987. Scott Catalogue No. 1536, Grenada, from reference 94, p 33 (left). Seated in the laboratory, 1.70 kronor, issued on September 6, 1979 to commemorate the 200th anniversary of his birth. Scott Catalogue No. 1293, Sweden, from reference 94, p 33 (center). 10 öre, issued on June 2, 1939. Scott Catalogue No. 297, Sweden, from reference 94, p 130 (right) (Courtesy, Foil A. Miller).

Figure 6. Jöns Jacob Berzelius (1779–1848), a 1970 caricature by William B. Jensen titled "The Fond Dictator." Berzelius was the ultimate arbiter of chemical matters during the early 19th century. In 1818 he was knighted by Swedish King Karl XIV Johann (Jean-Baptiste-Jules Bernadotte, Marshal of France under Napoléon) in connection with his coronation. In 1835, when the 56-year-old chemist married the 24-year-old daughter of a cabinet minister, the king made him a baron, hence the decorations in the caricature (Courtesy, Oesper Collection, University of Cincinnati).

foremost chemist of the time, and the ultimate authority and arbiter on matters chemical [14–19]. Berzelius was then at the height of his career. He was a liberal, vital, and revolutionary force in chemistry, whereas in his later years he became a scientific conservative who was eventually disregarded by mainstream chemists. Although many of the leading chemists of the first half of the 19th century worked with Berzelius both before and after him, Wöhler was extremely lucky to be the only chemist working in Berzelius' private laboratory at the time.

Berzelius was then at work on his studies of silicon, boron, and fluorine compounds, and Wöhler was able to observe the Master at first hand in all these investigations, and assimilate his ingenious techniques and methods in difficult preparative chemistry and mineral and organic analysis. Berzelius did not give systematic instruction to his disciples, but he encouraged them to choose their own projects and welcomed questions and discussions on these investigations. Wöhler resumed his work on cyanogen and cyanic acid, which resulted in publications in both Swedish and German [20], to which we will have occasion to refer in our discussion of his urea synthesis. By the action of ammonia on cyanogen he observed, along with ammonium oxalate, colorless, radiant crystals of urea, which he did not recognize at the time:

$$2NH_3 + (CN)_2 + H_2O \rightarrow NH_4OCN + NH_4CN$$

$$NH_4OCN \rightarrow O{=}C(NH_2)_2$$

Wöhler was able to attend regularly Berzelius' lectures at Karolinska Institutet in Kungsholm. He also took the opportunity during his stay in Sweden to collect numerous Swedish minerals on geological–mineralogical trips to southern Sweden, Uppsala, and Dannemora, and near the end of his life he humorously recalled these influential educational experiences [21]. Together with Berzelius, Wilhelm Hisinger (1766–1852), Johann August Arfvedson (1792–1841), and Carl Retzius (1798–1833), he visited the island of Utö (which my wife and I visited in 1983—GBK), the site of the minerals petalite ($LiAl(Si_2O_5)_2$ or $Li_2O{\bullet}Al_2O_3{\bullet}8SiO_2$) and spodumene ($LiAl(SiO_3)_2$ or $Li_2O{\bullet}Al_2O_3$), from which Arfvedson had isolated lithium in 1817. He also made the acquaintance of a number of leading scientists. For example, on a trip to Denmark he also met British chemist Sir Humphry Davy (1779–1829), discoverer of the alkali metals, and Danish physicist Hans Christian Ørsted (1777–1851) (Figure 7), discoverer of electromagnetism.

Although Wöhler spent less than a year in Stockholm, Berzelius influenced the entire course of his future career, and like his mentor, Wöhler became a versatile chemist and made important contributions to both inorganic and organic chemistry. The two became lifelong friends, and their voluminous correspondence has been collected and published [13].

Wöhler kept many portraits of Berzelius and Liebig, his two best friends, in his study. Shortly before his death, on parting with a friend, he gave him a small wrapped box saying, "Keep it in remembrance of me. Do not open it until you are on the train." The box was found to contain a platinum spoon with a note, "A present from Berzelius; he used this spoon many years in his researches."

Wöhler took advantage of the long Nordic winter evenings to learn Swedish in order to translate into German Berzelius' articles for the *Annalen,* and the *Introduction to the Mineralogical Geography of Sweden* of Berzelius' friend, Hisinger. Furthermore, for more than two decades he translated Berzelius' authoritative and often controversial *Årsberättelse* (*Annual Reports*) [12] from Swedish into German. Because Berzelius depended on accurate and rapid translation to disseminate his work throughout Europe, his grateful pupil translated three editions of his famous text, *Lärbok i Kemien* [22].

First Academic Position

On September 17, 1824 Wöhler bade Berzelius farewell and returned to Germany, reaching his parents' home in Frankfurt on October 31. Although he intended to prepare a *Habilitationsschrift* (a paper embodying the results of original research required to receive the *venia legendi* or *venia docendi*—the privilege of lecturing at a university) the following summer at the Universität Heidelberg, he soon found employment in Berlin. In March 1825 Wöhler succeeded Heinrich Rose (1795–1864) as a teacher of chemistry and mineralogy at the newly founded Municipal Trade School (*städtische Gewerbeschule*), initially for one year on "mutual approval" at a salary of 400 thalers and a free apartment. The school was not a university, and in addition to his regular lectures, he was required to give chemistry lectures on certain evenings during the winter to manufacturers and businessmen. Wöhler was appointed Professor by royal decree in 1828, the year of his urea synthesis [10].

In Berlin Wöhler now possessed his own laboratory, and he began research on a number of projects. He had already prepared tungsten oxide during his Stockholm stay. He now applied the method to prepare chromium(III) oxide by igniting a mixture of potassium dichromate and ammonium chloride:

$$2NH_4Cl + K_2Cr_2O_7 \rightarrow Cr_2O_3 + 2KCl + N_2 + 4H_2O$$

Chemical educators will readily recognize Wöhler's preparation as a variation of the ignition of ammonium dichromate—the popular chemical volcano demonstration of a striking redox reaction:

$$(NH_4)_2Cr_2O_7 \rightarrow Cr_2O_3 + N_2 + 4H_2O$$

In 1824 Berzelius had prepared amorphous silicon by heating metallic potassium in an atmosphere of silicon(IV) fluoride, SiF_4 [23]. In a similar reaction in 1827 Wöhler used potassium to reduce anhydrous aluminum chloride to prepare impure metallic aluminum [24] (Figure 8), an improvement on Ørsted's earlier preparation [25]. Wöhler's tacit assumption of priority for the preparation has been challenged [26]. However, Wöhler was the first to describe the properties of this metal, which until the electrolytic processes (1887) of Charles Martin Hall (1863–1914) and Paul-Louis-Toussaint Héroult (1863–1914) was a rare and expensive element. In 1845 Wöhler succeeded in melting powdered aluminum into a coherent metallic mass.

In 1854 French chemist Henri Étienne Sainte-Claire Deville (1818–1881), who honored Wöhler as the discoverer of aluminum, used Wöhler's method to produce the first pure

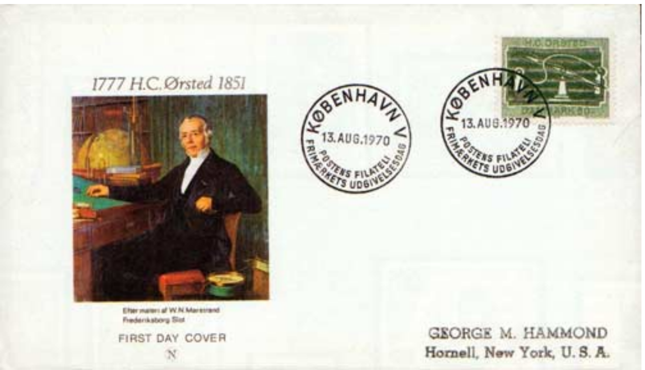

Figure 7. First-day cover honoring Hans Christian Ørsted (1777–1851), painting by W. N. Marstrand, 80-öre stamp with apparatus consisting of electric wire and magnetic needle, issued on August 13, 1970. Scott Catalogue No. 470, Denmark, from reference 94, p 44 (Courtesy, Foil A. Miller).

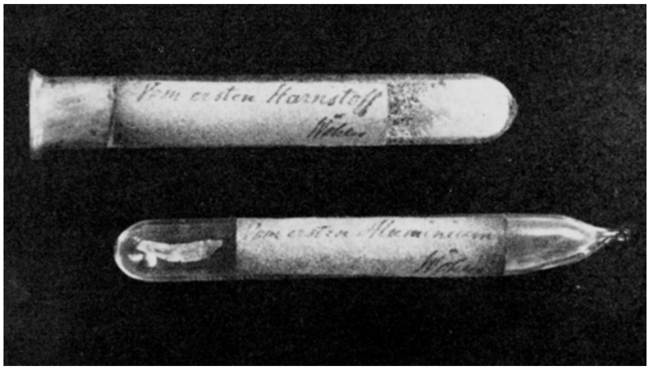

Figure 8. Close-up of samples of Wöhler's original syntheses labeled in his own handwriting with his signature. Urea, 1828 (top); Aluminum, 1827 (bottom). Preserved in the Deutsches Museum, Munich, from *J. Chem. Educ.* **1950**, *27*, 162 (Courtesy, *Journal of Chemical Education* and Dr. Otto Krätz, Deutsches Museum).

Figure 9. The aluminum medal with Napoléon III's image that the French Emperor presented to Wöhler along with the Cross of the Legion of Honor in 1854 as thanks for his discovery of aluminum in 1827 (center). Under the Emperor the manufacture of aluminum jewelry flourished in Paris. On the right is an aluminum brooch that Wöhler acquired in Paris for the wife of a friendly Göttingen anatomist. On the left is a sealed tube labeled in Wöhler's hand containing the sample of his original synthetic urea (1828) (Courtesy, Dr. Otto Krätz, Deutsches Museum).

metal. From the first bar of aluminum that he had obtained, Deville had a medal cast with a portrait of French Emperor Napoléon III (1808–1873) on one side and Wöhler's name and the date 1827 on the other [4].

During the seven years that Napoléon was imprisoned in the Ham fortress, which he called the "University of Ham," he worked in a small private laboratory where he learned considerable chemistry, especially electrochemistry. When aluminum had became a common metal, Napoléon III honored him for his discovery [27] (Figure 9). Other medals and plaques bearing Wöhler's portrait were cast, e.g., an aluminum plaque with Wöhler's portrait was presented to Professor Frank B. Dains (1869–1948) of the University of Kansas by Howard M. Elsey of the Westinghouse Research Laboratory, East Pittsburgh, Pennsylvania [28] (Figure 10). Wöhler also prepared metallic beryllium and what he thought was yttrium, by the reduction of their anhydrous chlorides and found them to be metals similar to aluminum [29].

Isomerism and the Wöhler-Liebig Friendship

The names of Friedrich Wöhler and Justus von Liebig (1803–1873) [30–34] (Figures 11–13) are as inextricably linked as that famous Damon-and-Pythias chemical duo—the Norwegian brothers-in-law Cato Maximilian Guldberg (1836–1902) [35] and Peter Waage (1833–1900) [36] of mass-action fame [37]. As Liebig wrote to Wöhler on December 31, 1871:

> Even after we are dead and our bodies long returned to dust, the ties which united us in life will keep our memory green, as an instance—not very frequent—of two men who wrought and strove in the same field without envy or ill feeling, and who continued in the closest friendship throughout [38].

Their relationship may have involved the attraction of opposites. According to Wöhler, "The two of us, Liebig and myself, have talents of unequal types, which in cooperation complement each other and allow achievements" [39]. Wöhler was calm and modest, and he possessed a dry sense of humor, while Liebig was choleric, contentious, and prone to indulge in polemics, which he did repeatedly in his position as Editor of the *Annalen*. Wöhler preferred to avoid disputes and rarely made enemies. Time after time he advised his friend to do likewise, but to no avail.

Like most chemists of the time, both friends, especially Wöhler, were heavy smokers. Wöhler once told a nonsmoking colleague, "There are examples of nonsmokers who also became bearable chemists; however, this occurs only rarely" [4].

Their acquaintanceship resulted from Wöhler's early work on the cyanates, which, as we have seen, he discovered in 1822 [9] and analyzed in 1824 [20]. The composition that Wöhler had found for silver cyanate (AgOCN) was the same as that obtained for the explosive compound silver fulminate (*Knallsilber*, AgONC) by Liebig [40], then Professor Extraordinarius at the Universität Giessen (Figure 14) [41]. Joseph-Louis Gay-Lussac (1778–1850) stated that if Wöhler's analysis was correct, and the fulminate and cyanate had the same composition, "it would be necessary, in order to explain their differences [in properties], to admit a different manner of combination between their elements" [42]. After a few additional preparations and analyses by both Liebig and Wöhler, the two agreed that the compounds indeed had the same composition—a conclusion not startling to us today but unprecedented at the time.

In 1830, the year in which the two friends (in October) abandoned the formal *Sie* in favor of the more intimate *Du*,

Figure 10. Wöhler plaque cast in aluminum, presented to Frank B. Dains by Howard M. Elsey, from reference 28 (Courtesy, *Journal of Chemical Education*).

Figure 11. Justus von Liebig (1803–1873), from *The Illustrated London News*, May 3, 1873.

Figure 12. Two stamps bearing the portrait of Justus von Liebig (1803–1873). 5-pfennig stamp, issued on July 18, 1978. Scott Catalogue No. 1926, Germany (DDR). Wheat and retort with the symbols for nitrogen, phosphorus, and potassium, the three most important elements in agricultural chemistry, a field in which Liebig was a leading authority, from reference 94, p 186. (left). 30-pfennig stamp, issued on May 12, 1953. Scott Catalogue No. 695, Germany, from reference 94, p 35 (right) (Courtesy, Foil A. Miller).

Figure 13. Justus von Liebig (1803–1873), a 1970 caricature by William B. Jensen titled "*Annalen.*" Liebig was the longtime editor of *Liebigs Annalen*. The picture of an alembic with cilia toward which Liebig is pointing refers to a satirical article by him in his *Annalen* ridiculing Louis Pasteur's theory that fermentation is caused by microorganisms (See de Mayo, P.; Stoessl, A.; Usselman, M. The Liebig/Wöhler Satire on Fermentation. *J. Chem. Educ.* **1990**, *67*, 552–553) (Courtesy, Oesper Collection, University of Cincinnati).

Figure 14. Joseph Louis Gay-Lussac (1778–1850), 10 + 3-franc stamp, issued on June 2, 1951. Scott Catalogue No. B260, France, from reference 94, p 35 (Courtesy, Foil A. Miller).

Berzelius reported on Wöhler's and Liebig's results [43] and first used the term "isomeric bodies" (*isomeriska kroppar*) to refer to different compounds with the same composition, citing the case of tartaric and racemic acids [44]. In the same volume of the journal, he stated that compounds of the same composition can have different properties, and he called the phenomenon "isomerism" from the Greek *ίσομερής,* composed of equal parts) [45]. He cited five examples: cyanic and fulminic acids; phosphoric and metaphosphoric acids (he disregarded the water content of these acids); the two varieties of stannic acid, one produced by the action of nitric acid on tin and the other produced by the action of alkali on tin(IV) chloride; tartaric and racemic acids; and ammonium cyanate and urea. The last case arose from Wöhler's most celebrated work of not only his tenure in Berlin but also of his entire career.

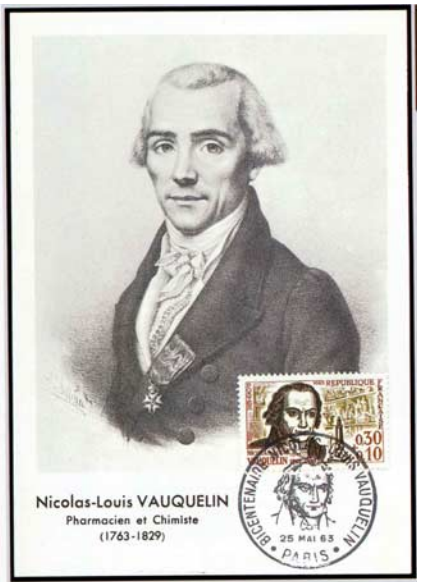

Figure 15. Maximum card commemorating the 200th anniversary of the birthday of Nicolas-Louis Vauquelin, pharmacist and chemist (1763–1829), 30 + 10-centime stamp, issued on May 25, 1963. Scott Catalogue No. B372, France, from reference 94, p 16 (Courtesy, Foil A. Miller).

The Artificial Synthesis of Urea

As we have already seen, Wöhler had synthesized urea in 1824 in Berzelius' Stockholm laboratory [20] but had failed to recognize this. But before him, other chemists had achieved the feat, also failing to recognize the fact. For example, in 1811 English army surgeon John Davy (1790–1868), Sir Humphry's younger brother, had synthesized it by the action of phosgene (which he was the first to discover) on ammonia [46]:

$$COCl_2 + 2NH_3 \rightarrow O{=}C(NH_2)_2 + 2HCl$$

and in 1818 French chemist Nicolas-Louis Vauquelin (1763–1829) (Figure 15) could not have avoided producing it by Wöhler's method [47]. Rather than detracting from Wöhler's achievement, perhaps these earlier syntheses and failures to recognize urea, make his success more remarkable [48].

Wöhler was no innovator or revolutionary. His genius lay not in theory but in his observational skills. In a letter of 1863 to Liebig he objectively evaluated his strengths and weaknesses as a chemist:

> My imagination is rather active. But in thinking I am very slow. No one is less made to be a critic than I. The organ for philosophical thought I lack completely as that for mathematics. Only for observing do I possess, or at least I believe I do, a passable arrangement in my brain. A kind of instinct that allows me to become aware of relations among data may well be connected with it [49].

Wöhler's serendipitous synthesis of urea from ammonium cyanate, published in 1828 as a four-page article in *Poggendorff's Annalen* [10], challenged the vitalistic theory that organic compounds can be produced only by living organisms (Figures 16–19). Despite his numerous other multifaceted contributions, it remains his main claim to fame and has exerted the greatest influence on chemistry in particular and science in general [49, 50]. Although at the time he was not completely aware of all the ramifications of his discovery, Wöhler was well aware that it was most unusual. In a letter dated February 22, 1828 Wöhler excitedly told Berzelius:

> I can no longer, as it were, hold back my chemical urine; and I have to let out that I can make urea without needing a kidney, or even of an animal, whether of man or dog: the ammonium salt of cyanic acid (*cyansäures Ammoniak*) is urea. Perhaps you can remember the experiments that I performed in those happy days when I was still working with you, when I found that whenever one tried to combine cyanic acid with ammonia a white crystalline solid appeared that behaved like neither cyanic acid nor ammonia…. I took this up as a subject that would fit into a short time interval, a small undertaking that would quickly be completed and—thank God—would not require a single weighing
>
> The supposed ammonium cyanate was easily obtained by reacting lead cyanate with ammonia solution…. Four-sided right-angled prisms, beautifully crystalline, were obtained. When these were treated with acids, no cyanic acid was liberated, and with alkali, no trace of ammonia. But with nitric acid lustrous flakes of an easily crystallized compound, strongly acidic in character, were formed; I was disposed to accept this as a new acid because when it was heated, neither nitrous nor nitric acid was evolved, but a great deal of ammonia. Then I found that if it were saturated with alkali, the so-called ammonium cyanate reappeared; and this could be extracted with alcohol. Now, quite suddenly I had it! All that was needed was to compare urea from urine with this urea from a cyanate [13b].

A Simple but Classic Experiment

Wöhler's synthesis of urea belongs to a small group of classic experiments that have radically changed our view of the world, opened up new paths of research, and yet are simple enough to be duplicated by the average undergraduate student. In fact, to commemorate the sesquicentennial of Wöhler's 1828 synthesis in 1978, we modified it to produce a reproducible experiment for the undergraduate laboratory (SHC was a sophomore student at the time) [51].

Wöhler's directions are minimal; his entire article is less than 800 words long. Like Wöhler, we too prepared ammonium cyanate solutions "by the decomposition of cyanate of silver with sal ammoniac [ammonium chloride] solution:

$$AgOCN + NH_4^+ + Cl^- \rightarrow NH_4^+ + OCN^- + AgCl\downarrow$$

or of cyanate of lead by aqueous ammonia" [10b]:

$$Pb(OCN)_2 + 2NH_3 + H_2O \rightarrow PbO + 2NH_4^+ + 2OCN^-$$

and heated them to dryness to produce urea:

$$NH_4OCN \rightarrow O{=}C(NH_2)_2$$

However, unlike Wöhler, we also used cation- and anion-exchange resins, substances unavailable to Wöhler, of course, to obtain ammonium cyanate solutions, and we synthesized

Figure 16. Friedrich Wöhler (1800–1882), a 1970 caricature by William B. Jensen titled "In the Beginning there was a Dog Kidney," superimposed on the first page of Wöhler's urea article (reference 10a) (Courtesy, Oesper Collection, University of Cincinnati).

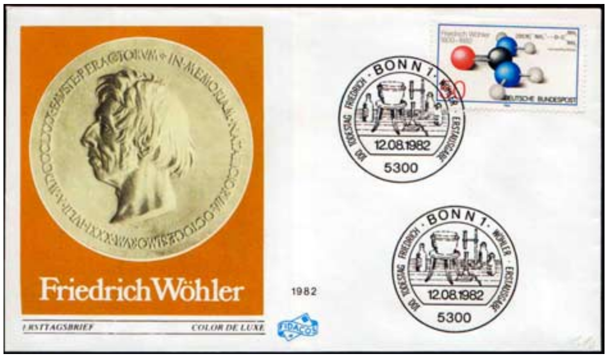

Figure 17. First-day cover, issued August 12, 1982 to commemorate the 100th anniversary of Friedrich Wöhler's death. Scott Catalogue No. 1379, Germany. The 50-pfennig stamp shows a molecular model of urea and the equation for its formation from ammonium cyanate. The medal with Wöhler's profile was cast to honor his 80th birthday, July 31, 1882, from reference 94, p 62 (Courtesy, Foil A. Miller).

Figure 18. George B. Kauffman at the entrance of the Deutsches Museum in Munich, one of the world's most famous museums, where Wöhler's original samples of urea and aluminum are preserved, June 9, 1964. Photograph by Ingeborg Kauffman.

FRIEDRICH WÖHLER
BEOBACHTETE 1828 IM LABORATORIUM
DIE BILDUNG VON
SYNTHETISCHEM HARNSTOFF
AUS ANORGANISCHEN ROHSTOFFEN.
SEINE HARNSTOFFSYNTHESE ERWIES DIE
MÖGLICHKEIT, AUCH SOLCHE STOFFE
AUFZUBAUEN, DIE MAN BIS DAHIN NUR
ALS PRODUKTE LEBENDER ORGANISMEN
ANGESEHEN HATTE. HUNDERTTAUSENDE VON
ORGANISCHEN STOFFEN WURDEN SEITDEM
ERFORSCHT UND MEHRERE TAUSENDE
INDUSTRIELL HERGESTELLT

Figure 19. Plaque and original sample of Wöhler's synthetic urea, Deutsches Museum, June 9, 1964. The plaque reads, "Friedrich Wöhler observed in 1828 in the laboratory the formation of synthetic urea from inorganic raw materials. His urea synthesis proved the possibility of also synthesizing such materials, which until then had been regarded only as products of living organisms. Hundreds of thousands of organic materials have been discovered since then, and several thousand have been prepared industrially." Photograph by George B. Kauffman.

urea directly by evaporating to dryness a solution of potassium cyanate and ammonium sulfate and extracting the urea with ethanol, thus giving new twists to an old classic. Like Wöhler, we demonstrated that the "colorless, clear crystals often more than an inch long in the form of slender four-sided, dull-pointed prisms" [10b] did not give the characteristic reactions of an ammonium salt or of a cyanate salt. It did not liberate ammonia on treatment with bases:

$$NH_4^+ + OH^- \rightarrow NH_3 + H_2O$$

or react with acids to form unstable cyanic acid, which isomerizes to isocyanic acid, which hydrolyzes to liberate carbon dioxide and ammonia:

$$HN{=}C{=}O + H_2O \rightarrow [H_2NCOOH] \rightarrow CO_2 + NH_3$$

and it did not precipitate insoluble cyanates with silver or lead salts. However, a concentrated solution of the product reacted with one acid—nitric acid—to produce "at once a precipitate of glistening scales" [10b] (urea nitrate):

$$(H_2N)_2C{=}O + H^+ + NO_3^- \rightarrow [(H_2N)_2C{=}OH]NO_3$$

a notable exception to the general chemistry rule that all nitrates are soluble. Wöhler—and we—then carried out the same comparative tests on completely pure urea isolated from urine. This clinched the case: As he wrote to Berzelius, "the ammonium salt of cyanic acid is urea" [13b].

Unlike Wöhler, we added a number of additional confirmatory tests on and reactions of urea and thiourea, for "few other organic compounds, if indeed any, reflect more closely the development of organic chemistry from its earliest beginnings than does urea" [52]. In addition to our macroscale version of Wöhler's synthesis, others have developed a microscale version [53]. As we expressed it, whether students perform the macro- or microscale version, they "should gain the satisfaction of having duplicated a classic experiment and should emerge from this experience with a greater appreciation for the experimental and observational skills of a master scientist" [51].

Wöhler compared the elemental composition and relative number of atoms of nitrogen, carbon, hydrogen, and oxygen obtained by William Prout (1785–1850), of Prout's hypothesis fame, a decade earlier in his analysis of urea [54], with the theoretical values calculated for ammonium cyanate and found them to agree. He modestly concluded his article:

> I refrain from all the considerations which so naturally offer themselves, particularly those bearing upon the composition relations of organic substances, upon the like elementary and quantitative composition of compounds of very different properties, as for example, fulminic acid [HONC] and cyanic acid [HOCN], a liquid hydrocarbon [butylene, C_4H_8] and olefiant gas [ethylene, C_2H_4]. The deduction of a general law awaits further experiment on several similar cases [10b].

Appraisals of the Urea Synthesis

In his textbook Berzelius characterized Wöhler's synthesis as follows:

> Wöhler has made the very remarkable discovery that urea can be artificially formed by treating freshly precipitated silver cyanate with a solution of ammonium chloride. This silver salt is converted into silver chloride and urea is obtained instead of ammonium cyanate which should be formed. Urea is also formed when lead cyanate is treated with ammonium hydroxide [55].

He also seemed to attach more importance to Wöhler's work as an example of isomerism, of which few cases were known at the time, than to the synthesis itself:

> This is a very remarkable transformation. We are here dealing with a substance having exactly the same composition as a salt. Yet it is no salt, for it is not decomposed by bases, acids, or salts, as it should be if it were a salt. On the contrary, it has all the properties of an organic compound atom [molecule] of the first order and combines partly with acids and partly with bases. This is an example, therefore, that shows how compounds, containing the same relative number of atoms of the elements, can differ in their chemical properties, because of the different relation of the simple atoms to one another in a compound atom.

Although he did not consider the formation of urea as a synthesis from its elements [48], Berzelius referred to Wöhler's synthesis in his *Annual Report* for the year 1830:

> Beyond all question one of the most unexpected and therefore most interesting discoveries in the field of animal chemistry is the artificial production of urea. This discovery was made by Wöhler who found that the treatment of silver cyanate with ammonium chloride solution, or of lead cyanate with ammonium hydroxide, led to the formation not of ammonium cyanate but of a crystalline substance which in all its properties differed in no wise from pure urea, and which therefore *is urea* [56].

Others also sang the praises of Wöhler's work. For example, according to his friend Liebig:

> The extraordinary and to some extent inexplicable production of urea without the assistance of the vital functions, for which we are indebted to Wöhler, must be considered one of the discoveries with which a new era in science has commenced [57].

In his 1882 obituary of Wöhler, August Wilhelm von Hofmann (1818–1892) eulogized the work to an exaggerated degree:

> The synthesis of urea is in the true sense of the word an epoch-making discovery. With it was opened to investigation a new field of which chemists did not hesitate to take possession. The present generation, which daily reaps rich harvest on this field conquered for it by Wöhler, can transport itself only with difficulty to those remote times when the formation of an organic compound in the body of the plant or animal seemed to be brought about in a mysterious manner by the vital force, and it is able therefore hardly to realize the sensation produced upon their minds by the building up of urea from its elements.… [it] removed at a single blow the artificial barrier which had been raised between organic and inorganic chemistry [3].

In his obituary of Wöhler American chemist Ira Remsen (1846–1927), who served as President of the American Chemical Society in 1902, made a statement with which certainly no one can disagree:

> It would be difficult to exaggerate the importance of this discovery. That a substance like urea, which up to that time had only been met with as a product of processes which take place in the animal body, should be formed in the laboratory out of inorganic compounds appeared to chemists then to be little less than a miracle. Today such facts are among the commonest of chemistry. The many brilliant syntheses of well-known and valuable organic compounds, which have been made during the past twenty years, are results of this discovery of Wöhler [58].

Significance of Wöhler's Synthesis

Articles discussing the significance of Wöhler's urea synthesis by chemists and historians of chemistry and of science have persisted from Wöhler's time to the present [48–50, 59–69] and are likely to continue in the future. Its significance has been considered to be threefold [51]. First, urea was regarded "as the first organic compound artificially produced" (Liebig) from inorganic substances, and thus "the natural barrier which until then separated the organic from inorganic compounds had fallen, and a classification of chemical compounds into organic and inorganic in the earlier sense had no natural basis" (Hermann Kolbe). Wöhler's synthesis demonstrated that a vital force (*vis vitalis,* or what French philosopher Henri Bergson was later to call *élan vital*) is not necessary for the production of organic substances, and it therefore encouraged other chemists to attempt the synthesis of organic compounds. Second, Wöhler's production of urea represents the first synthesis of an organic compound in the sense as used by Kolbe, i.e., from its elements [70]. Third, Wöhler's synthesis provided another example of the idea that compounds with different properties can have the same composition, at a time when very few cases of isomerism were known. In this case, the first of its kind, the isomerism was between an organic compound and an inorganic salt [71].

Although some historians and chemists have attacked the first and second of these roles of Wöhler's synthesis, they have never questioned the third. In fact, with regard to the first point, despite his reputation for having driven vitalism out of organic chemistry, Wöhler, like his mentor Berzelius, remained a vitalist [64, 65]. Just as Joseph Priestley (1733–1804), a confirmed phlogistonist, contributed to the eventual downfall of the phlogiston theory, so Wöhler, a lifelong vitalist, contributed to the overthrow of vitalism [65].

Statements hailing the synthesis as dismantling at one stroke the supposed wall of separation between organic and inorganic chemistry and converting what Wöhler told Berzelius was "the dark forest of organic chemistry" [13c] into the fruitful, systematic science that it is today are obviously oversimplifications. As is often the case in science, e.g., with Avogadro's hypothesis, more than a half-century elapsed before all the implications of Wöhler's discovery were fully realized. Although it did not immediately sound the death knell for the doctrine of vitalism, there is no doubt that it led inexorably to the gigantic, international, synthetic organic chemical industry and to innumerable syntheses of artificial dyes, plastics, fibers, pharmaceuticals, and a host of other products emanating daily from today's industrial laboratories. Without it the experiments of Nobel chemistry laureate Harold C. Urey and Stanley Miller on the synthesis of amino acids, the building blocks of life, from a possible primordial atmosphere of methane, ammonia, hydrogen, and water with the aid of electric sparks [72–74] would have been unthinkable. Indeed, as John H. Brooke has written, "with respect to the significance of Wöhler's preparation, the last word has not been spoken" [67].

Later Life

Wöhler was only 27 years old at the time of his urea synthesis, which we have just examined in detail, and the major part of his life lay before him. During the summer of 1829, he visited Frankfurt, Wiesbaden, and Kassel. In the last city he and his cousin, Franziska Wöhler, the 18-year-old daughter of his father's brother, a Privy Justice Councilor, became engaged, and on June 1, 1830 they married. The couple had two children—a boy, August, who grew up to be a farmer who managed his grandfather's farm at Rödelheim near Frankfurt, and a girl, Sophie [7]. In 1831 a cholera outbreak in Berlin caused Wöhler to send his wife and young son to stay with her parents in Kassel. He soon followed her and became Professor at the new *Gewerbeschule* in Kassel, where he served from 1831 to 1836. Franziska died in June 1832, soon after Sophie's birth, and in order to distract him from his grief, Liebig invited him to Giessen to collaborate with him on what became their celebrated work on benzaldehyde.

In February 1834 Wöhler became engaged to Julie Pfeiffer, a banker's daughter and a friend of his late wife. The couple married on July 16, 1834 and had three daughters [7]. In April 1836 he accomplished his lifetime goal—to occupy a chair at a prominent German university. He succeeded Friedrich Stromeyer (1776–1835) as Professor of Chemistry and Pharmacy at the Universität Göttingen, founded in 1736 by George II (1683–1760), King of England and Elector of Hanover (1727–1760) (Figure 20). After 1839 he worked primarily on inorganic chemistry.

For the rest of his life he remained at Göttingen, where it is estimated that 8200 students, many of them foreigners, including Americans, many of whom became prominent and several of whom became Presidents of the American Chemical Society [75, 76], passed through his laboratory during the period 1846–1866 alone [7]. His famous German students and co-workers include Hermann Kolbe (1818–1884), Georg Städeler (1821–1871), Johann Anton Geuther (1833–1889), Rudolf Fittig (1833–1910), Hans Hübner (1837–1884), who succeeded his teacher at Göttingen, Friedrich Conrad Beilstein (1838–1906), and Bernhard Tollens (1841–1918) [7].

Wöhler was a popular and dedicated teacher. In a letter to Wöhler, Liebig paid tribute to his didactic ability. After Wöhler had asked Liebig to provide a space in his laboratory for one of Wöhler's students, Liebig wrote, "Those are rather stupid fellows, who go from Göttingen to Giessen for the sake of chemistry, like going from a horse to a donkey" [4, 7].

Books and Editorial Work

Wöhler authored several textbooks. His *Foundation of Chemistry* [77] was published in two volumes—Volume I, on inorganic chemistry, which first appeared in 1833, and Volume II, on organic chemistry, which first appeared in 1840. The first volume went through 15 editions, the last appearing in 1877, and was translated into Danish, Dutch, French, Norwegian, Swedish, Russian, and English. The second volume went through 13 editions, the last appearing in 1882, and was similarly translated.

Wöhler's *Examples for Practice in Analytical Chemistry* [78], a little book from which several generations of chemists learned the art of analysis, appeared in 1849. The first editions appeared anonymously. On April 26, 1849 Wöhler modestly and humorously wrote to Liebig:

> I send you herewith some selenium slime and vanadium-containing ore. For the simplest way to work on these, you will find recipes in the enclosed cook book, which I recently smeared together. It is designed for my laboratory students and is to serve the purpose of sparing me the enormous boredom of having to preach one and the same thing a thousand times [4].

On May 5, 1853 Wöhler wrote to Liebig in a similar vein:

> I have entirely rewritten the little book [now titled *Practical Exercises in Analytical Chemistry* [79]]. It is again to appear without my name, for after all, everybody can write such a book [4].

Together with Liebig and Poggendorff, Wöhler edited the first six volumes of the massive *Dictionary of Pure and Applied Chemistry*, which began publication in 1842 in irregular installments [80]. Since its founding in 1832, Wöhler had published most of his articles in Liebig's *Annalen der Pharmacie*. In 1838 he became its coeditor, and his name, which appeared on almost 200 volumes, first appeared on the title page of Volume 27 (1838), and he was a member of the editorial board until his death. On October 18, 1838 he wrote to Liebig:

> For the *Annals of Pharmacy* you must, in the future, introduce the title, *Annals of Chemistry and Pharmacy*. The present title certainly does not fit our uric acid investigation, for example, at all. The publisher will have no objections, and the number of subscribers will only increase [4].

The new title began to appear with Volume 33 in 1840; it was later changed to *Liebigs Annalen der Chemie* in 1874.

Figure 20. Wöhler's laboratory in Göttingen, from reference 38.

Inorganic Contributions

Wöhler's contributions to inorganic and organic chemistry are so numerous and multifaceted that here we can only mention a few of the highlights.

Wöhler prepared phosphorus by heating bone black (calcium phosphate and carbon) with sand, later the basis for an industrial process, carried out in an electric furnace [81]. While in Kassel, the large amounts of industrial materials—*Kobaltspeise, Arsennickel* (nickel arsenide), etc.—that had accumulated at the Hessian bluing works of Schwarzenfels led Wöhler to work on the technical production of nickel [82]. Together with several friends, he established a nickel factory, which produced thousands of pounds of the metal annually. He thought that nickel could be used in coins, but his idea was not accepted [4].

With Heinrich Buff (1805–1878) he discovered the spontaneously flammable silicon hydride, silane (SiH_4, the silicon analogue of CH_4, methane), and organosilicon compounds [83]. Of the former he wrote to Liebig on June 25, 1863: "I am becoming more and more convinced that it is constituted in the manner of organic substances in which the carbon is replaced by silicon" [4].

Wöhler prepared calcium carbide by heating an alloy of calcium and zinc with carbon, and he prepared acetylene from it by reaction with water [84]:

$$CaC_2 + 2H_2O \rightarrow C_2H_2 + Ca(OH)_2$$

thus laying the cornerstone for the later developing carbide industry and autogenous welding.

In electrochemistry Wöhler constructed new galvanic elements for batteries. Johann Christian Poggendorff (1796–1877) had modified the cell invented by William Robert Grove (1811–1896), consisting of zinc in dilute sulfuric acid and platinum in concentrated nitric acid, by replacing the expensive platinum with iron. Wöhler substituted iron for zinc and constructed an inexpensive battery consisting of iron in dilute sulfuric acid and iron in concentrated nitric acid that delivered a strong current [4].

Wöhler's lifelong interest in geological samples led him to publish a book on mineral analyses [85], and 50 articles on minerals, meteorites, and their analysis. He also observed the passivity of meteoric iron to oxidation.

Organic Contributions

In their first joint collaboration Liebig and Wöhler isolated mellitic acid (*Honigsteinsäure*, benzenehexacarboxylic acid, $C_6(COOH)_6$) and some of its salts from a sample sent by Heinrich Rose of the honey-yellow honeystone (*Honigstein*, mellite, hydrous aluminum mellate, $AlC_{12}O_{12}•18H_2O$), a mineral of the rare class of salts of organic acids [86].

Wöhler also investigated picric acid, then known as carbazotic acid. Because of its explosive properties, he thought that it might contain nitric acid. He was able to produce nitric acid from it by the action of manganese dioxide, sulfuric acid, and barium sulfate [87].

In 1832 Wöhler, together with Liebig, published an article on oil of bitter almonds (benzaldehyde, C_6H_5CHO) [88], which took the first significant step in finding order in the bewildering complexity of organic chemistry. They began this classic paper on what they called the "benzöyl radical," C_6H_5CO (they derived the suffix from the Greek $\upsilon\lambda\eta$, material or matter) with the following sentence:

> If in the dark region of organic nature we perceive a point of light, promising an entrance through which we may perhaps reach the right path to the exploration and recognition of this region, we shall have reason to congratulate ourselves, even when we realize the illimitable extent of our objective [88].

In their article Wöhler and Liebig presented clearly for the first time the idea that a group of atoms can remain intact throughout a series of chemical reactions and function as a unit—a radical, an idea which they borrowed from inorganic chemistry. They prepared and characterized a number of derivatives: benzyl alcohol, $C_6H_5CH_2OH$; benzoic acid, C_6H_5COOH; benzoyl chloride, C_6H_5COCl; benzoyl bromide, C_6H_5COBr; benzoyl iodide, C_6H_5COI; benzoyl sulfide, $(C_6H_5CO)_2S$; benzoyl cyanide, C_6H_5COCN; benzamide, $C_6H_5CONH_2$; and ethyl benzoate, $C_6H_5COOC_2H_5$. As Liebig wrote in 1837 to French chemist Jean Baptiste André Dumas (1800–1884):

> In mineral [inorganic] chemistry the radicals are simple; in organic chemistry the radicals are compound; that is all the difference. The laws of combination and of reaction are otherwise the same in these two branches of chemistry [49].

This idea that the radicals of organic chemistry could be considered the equivalents of the atoms of inorganic chemistry led eventually to the concept of valency.

As we have seen, in 1828 Wöhler had won a prize for an essay on the conversion of substances taken orally and excreted in the urine [11]. He and Liebig collaborated on an investigation of uric acid (2,6,8-trihydroxypurine, $C_5H_4N_4O_3$), which was then obtainable only from snake excrement. The two oxidized and reduced uric acid and its derivatives, and in their 100-page article, the last of their major joint studies, they described the preparation and analysis of 14 new compounds [89]. Wöhler's work with Liebig on the action of hydrochloric acid on amygdalin ($C_{20}H_{27}NO_{11}$), the first example of a glycoside, led him to postulate that amygdalin contains oil of bitter almonds, hydrocyanic acid, and sugar as constituents [90].

Wöhler discovered quinhydrone ($C_6H_4O_2•C_6H_4(OH)_2$), the compound of hydroquinone (p-$C_6H_4(OH)_2$) and quinone

($OC{=}(CH{=}CH)_2{=}CO$), and he established the relationship between the two [91]. He worked on narcotine (β-gnoscopine, $C_{22}H_{23}NO_7$) [92], an alkaloid found in opium, and its decomposition products, and his study of another alkaloid—cocaine (benzoylmethylecgonine, $C_{17}H_{21}NO_4$) [93]—led to the discovery of a new alkaloid, ecgonine tropinecarboxylic acid, $C_9H_{15}NO_3$).

Wöhler's Legacy

Wöhler was an honorary member of various academies of science and scientific societies around the world, and he received numerous scientific honors. For example, he was elected an honorary member of the Royal Society in 1854, and he received the Copley Medal, the society's highest award in 1872. From 1864 he was a foreign associate of the Institut de France and an officer of the Legion of Honor. Yet nothing pleased him more than the celebrations organized by his students on the occasions of his 60th, 70th, and 80th birthdays as well as on the 50th anniversary (1878) of his urea synthesis [3, 48].

Wöhler was tall, slender, and delicate in build, and not suited for prolonged exertions. Thus he suffered from frequent colds and other illnesses to which chemists in inadequately ventilated laboratories of that day were subject. He was neither ambitious nor possessive, and he was content with the various circumstances of his positions at Berlin, Kassel, and Göttingen. Shy and reserved as he was, he avoided acting as a speaker at festivities and congresses. After Liebig's death in 1873, Wöhler rarely left Göttingen. Although he still wished to contribute to the advance of chemistry, he lacked the strength, the memory, and the ideas to do so. Finally he was forced to partially give up his lectures and laboratory teaching. Until the end, however, he conducted the business of the Göttinger Societät der Wissenschaften, whose secretary he had been since 1859.

Although by the age of forty Wöhler had published only about a fourth of his papers, none of his later ones were as important as his earlier contributions. During his later years he was no longer able to follow the advances in chemistry, especially organic chemistry, to the development of which he had contributed so much. Organic chemistry had become so repugnant to him that as early as October 1859 he had written, "Organic chemistry is truly enough to drive one to despair if one reads various articles" [7]. He found especially displeasing the new "tasteless, barbaric names, with which things are named" [7].

In the autumn of 1882 the aged *Geheimrat* was suddenly stricken with dysentery. At 10 A.M. on September 23, 1882 he died quickly and peacefully in Göttingen. In accordance with his wishes, no monument marks his grave—only a simple stone bearing his name [3]. However, his numerous students and friends erected a statue of him in Göttingen, where he had worked faithfully for 45 years.

Wöhler's urea synthesis alone would have assured him of immortality in the annals of chemistry. But furthermore, largely due to the contributions of Wöhler, in collaboration with Liebig, within his lifetime the field of organic chemistry, which he had once characterized as a "jungle" [7] had been transformed into a systematic, orderly, and fruitful branch of our science. Yet he preferred to work in inorganic chemistry, to which he also made numerous significant contributions—an unusual display of versatility in our current age of narrow specialization. His profound influence on chemistry continued beyond his death through the contributions of his many students.

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