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Historic review

Frederick Challenger, 1887–1983: chemist and biochemist

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Frederick Challenger (1887–1983) lived a long life as a chemist and biochemist. He received a PhD for work with O. Wallach at the University of Göttingen in 1912 and a DSc from the University of Birmingham in 1920. After positions at Birmingham, UK, and Manchester, UK, he became Professor of Organic Chemistry at the University of Leeds, UK, in 1930, remaining as Head of the Department until 1953, when he retired as Emeritus Professor. He continued with scientific activity, publishing his final paper in 1978. Much of his work concerned the biological methylation of metalloids such as arsenic, selenium, and tellurium. He determined precise chemical structures for the methylated products and he established a role for adenosylmethionine in the process. An important finding was that the sulfonium compound, $(CH_3)_2-S^+-CH_2-CH_2-COO^-$, was present in several algae and on decomposition led to production of dimethylsulfide. This sulfonium compound was the first of this class to be found in a plant. He had many other wide-ranging interests, including the organic chemistry of compounds of bismuth and thallium.

KEYWORDS: trimethylarsine; dimethyl selenide; dimethyl telluride; biological methylation; terpene chemistry; fungal metabolites; chemistry and biochemistry of sulfur compounds

EDUCATION AND PROFESSIONAL CAREER

In a long life, Frederick Challenger, 1887–1983 (Fig. 1), achieved an impressive career in organic chemistry and biochemistry, with many publications to his credit. He began publishing in 1910, and in 1978, at age 91, sent a written introductory paper to an American Chemical Society Symposium—a publication record covering almost seven decades.

Early studies, BSc and PhD degrees

This remarkable individual, the son of the Reverend S. C. Challenger, was born in Halifax, Yorkshire, on 15 December 1887. That year was also notable as the 50th year of the reign of Queen Victoria—the Jubilee Year. Following study at the Commercial and Mathematical School, at Mansfield, Nottinghamshire, he became a student at Ashville College, Harrogate, Yorkshire, in 1900 at age 13. He remained there for 4 years obtaining a Certificate of Matriculation from London University. This college, founded in 1877 by the Methodist Church, is now an independent co-educational day and boarding school, proud of its traditions but committed to progress. A major function of the college was and is to prepare students for entrance to a university.

For a student with high academic achievement the usual goal early in the 20th century would have been admission to a university such as Cambridge, Oxford, London or Edinburgh. Challenger followed a very different path. From 1904 to 1907 he was a student at the small Derby Technical College. Derby, a town in the English Midlands about 130 miles north of London, had no claim to academic fame or excellence in the sciences. The town was a manufacturing center with many industries, including the 'Royal Crown Derby' porcelain factory, and was also a major railroad center for the Midland Railway. Rolls-Royce had a factory there as early as 1908. The Technical College, originally Derby Municipal Technical College, had been enlarged with new

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Figure 1. This thoughtful portrait of Frederick Challenger was made available by Special Collections, Leeds University Library, and it is published with their permission. The authors are grateful to the University Archivist at Leeds for assistance and to C. D. W. Sheppard for publication permission.

buildings in 1899 just prior to Challenger's admission. To a major extent, it provided courses for the more ambitious of those working in the various industries.

Derby Technical College was not a degree-granting organization, but students took examinations administered by London University and thus obtained an 'external' degree (e.g. BSc) from London. This external degree program with affiliated institutions had originated in 1858 and was discontinued in 1973. To take the Honours Degree, students had first to sit the 'Pass Examination', selecting three of eleven prescribed subjects (pure mathematics, applied mathematics, astronomy, experimental physics, chemistry, geology, botany, zoology, physiology, psychology, or logic and methodology). Candidates were warned to expect questions testing their knowledge of German or French. Finally, the student took a minimum of six papers in his/her selected branch of science, including a practical examination and an essay paper, as well as a subsidiary paper in another related subject. Challenger received what must have been a disappointing third-class Honours in Chemistry. The system had not changed very much when one of us (RB) followed Challenger's tracks in 1943. Derby Technical College has now been subsumed into the University of Derby; a single-subject program in chemistry is no longer offered.

It is not clear why Challenger followed this course; perhaps there was a financial difficulty—the Technical College would certainly have been less expensive than a more prestigious university. The Derby years had one permanent result. Challenger formed a long-lasting friendship with the Head of the Chemistry Department, Andrew Jamieson Walker. Walker was acknowledged in Challenger's PhD thesis[1] (see later) as follows: 'Herrn Dr Andrew Jamieson Walker, Derby, England, in Dankbarkeit für seine langjährige dauernde, freundliche Liebenswürdigkeit sowie wertvolle wissenschaftliche Unterstützung, gewidmet'. (Dedicated in gratitude to Herrn Dr Andrew Jamieson Walker, Derby, England, for his friendly kindness of many years duration, as also for valuable scientific support.) Many years later, in 1935, Challenger was to write an obituary for Walker.[2]

In December, 1907, Challenger went to see the well known Professor Frederick Stanley Kipping (1863–1949) about a research scholarship, valued at £50 per annum, that had been advertised at the nearby University College of Nottingham (later, upgraded to the University of Nottingham).[3,4] Although this particular scholarship was awarded to someone else, Kipping made alternate arrangements for Challenger to work in his department (initially, £25 for 6 months). University records indicate that he studied 'Prac. Chemistry' 1907–08, and that by 1908–09 he was undertaking research with the aid of a Science Research Scholarship. At this time he received a Board of Education Certificate in Practical Organic Chemistry in the Institute of Chemistry (later, the Royal Institute of Chemistry) and became an Associate of University College, Nottingham. University College was certainly not than one of the most prestigious institutions in the UK. However, at that time, Kipping was head of an excellent Chemistry Department. In 1910, Challenger was the recipient of an '1851 Exhibition Scholarship', which made possible his thesis work in Germany. These scholarships were one of the legacies from the Great Exhibition of 1851 when the Crystal Palace was constructed. Among Exhibition Awardees were 11 future Nobel Prize winners.[5]

Challenger has acknowledged his 'deep indebtedness' to Kipping. Kipping had worked with von Baeyer and developed exacting laboratory methods using simple, basic equipment (beakers, test tubes, flasks, etc.). Even when shaking machines were available, von Baeyer preferred glass stirring rods.[6] Kipping (along with Perkin and Cohen) brought much of the scientific spirit of von Baeyer's laboratory in Münich to Britain. Kipping had actually been a research student with Perkin when the latter was Privatdozent in von Baeyer's group. These individuals had an important influence on the development of chemistry in the United Kingdom. Since von Baeyer had written a DPhil dissertation on work done in Kekulé's private laboratory, Challenger had a remarkable chemical 'genealogy': Liebig; Kekulé; von Baeyer; Perkin and Kipping; Challenger.

Another thread in Challenger's chemical heritage came by way of his thesis advisor, Otto Wallach. Wallach (1847–1931) had worked briefly with individuals such as Fittig, Hofmann, Kekulé, Wöhler and Hübner (with whom he obtained a doctoral degree). He was a pioneer in the study of terpenes, receiving the Nobel Prize in Chemistry in 1910. He had been appointed at the University of Göttingen (more accurately, Georg-August-Universität Göttingen) in 1889 and was also Director of the Chemical Institute there. Challenger studied in Göttingen from 1910 to 1912. Interestingly, in a biography at the end of his thesis, he found it necessary to state that 'Ich, Frederick Challenger, evangelischer Konfession. . .'.[1]

Challenger's PhD thesis was titled 'Abwandlungsprodukte der Thujaketonsäure' (Degradation Products from Thujaketonic Acid). We have found no evidence of publications listing Wallach and Challenger as coauthors. However, in two lengthy papers with only Wallach listed as author, there are mentions of Challenger. The paper, 'Abhandlung CV. Zur Kenntnis der Terpene und der ätherischen Öle',[7] contains a section headed 'V. Versuche in der Thujonreihe' (Ref. 7, pp. 81–86). It carries the notation 'Mitbearbeitet von *Frederik (sic) Challenger*'. This section contains much of the material in Challenger's thesis and is concerned with various transformations of thujaketone (e.g. to thujaketonic acids, dihydrothujaketone, dihydrothujaketol) and the reduction of β-thujaketonic acid to *i*-δ-acetyl-β-isopropylvalerianic acid (i.e. [±]-3-isopropyl-6-oxo-heptanoic acid). Similarly, a second Wallach paper[8] in the same series contains a section, 'II. Über 1,3-Isopropylcyclopentanon', with the previously listed notation and misspelling of Frederik. This was also work described in Challenger's thesis—the conversion of 1,3-isopropylcyclopentanone to the corresponding alcohol and dehydration of the latter to a mix of two isopropylcyclopentenes, C_9H_{16}.

This rather indirect and somewhat demeaning citation style was apparently not an uncommon practice in the major departments of chemistry in Germany at that time. For instance, von Baeyer, who published over 300 papers, might add the name of a coworker to 'a section of a set of papers published together with a lengthy introductory section under his own authorship' (Ref. 6, p. 139). In the case of Villiger (known for the eponymous Baeyer–Villiger oxidation) there were 28 papers with both men as coauthors but 15 others with only an acknowledgment to Villiger. In today's world, when some papers may carry the names of dozens of investigators, this practice seems surprising. Thirty years later in Challenger's career, he included by way of modern practice a junior author in the author list for a paper—which would be listed in bibliographies with all three authors—in the following way: 'By Frederick Challenger, Phillip Taylor, and (in part) Bernard Taylor'.

Documentation for his 'Promotion' at Göttingen shows that Challenger underwent oral examinations in chemistry, physics and 'agricultural bacteriology' (Landwirtschaftliche Bakteriologie), the latter administered by Alfred Koch (not one of the many brothers of Robert Koch). Koch, 1853–1922, had originally studied botany and in 1886 was appointed as Privatdozent in Botany at the Plant Physiology Institute in Göttingen.[9,10] He had interests in nitrogen fixation and metabolism in plants and bacteria and fermentation in general; many of his papers were abstracted in Chemical Abstracts (from 1907 to 1926). By 1901, he had become Director of a new school for Agricultural Bacteriology in Göttingen. Although there are apparently no publications authored by Koch and Challenger, Challenger appears to have studied with him. In his written communication for the American Chemical Society Symposium on Organometals and Organometalloids (1978), Challenger stated 'It was not solely an interest in organo-metallic compounds that led to our work on the arsenical Gosio-gas but an equally keen attraction, microbiological chemistry, of which I gained some rudimentary knowledge in the laboratory of Professor Alfred Koch in Göttingen (1910–1912) and maintained in Manchester'.[11] One would like to know more about this association, but the above summary is all that we have located.

Professional appointments, Birmingham, Manchester, Leeds

At some time in 1912, Challenger responded to an advertisement from the University of Birmingham. University of Birmingham Council Minute no. 4534, 14 December 1912, reads as follows: 'Resolved that Mr Fredk Challenger BSc, be and is hereby appointed Assistant Lecturer & Demonstrator in the Chemical Department. . .'. At that time, Percy Faraday Frankland (1858–1946) held the Chair in Chemistry at that university. Percy Frankland was the younger son of Sir Edward Frankland (1825–99), a very distinguished chemist.[12] Sir Edward had discovered the first organometallic compound, diethyl zinc, and was a co-discoverer of helium; in addition, he had made significant contributions to valency and bond theory and to organic synthesis. In 1868, he had been appointed to a Royal Commission on river pollution and made many contributions to the subjects of water analysis, contamination and purification. Percy Frankland had studied at the Royal School of Mines and, working with Wislicenus, had obtained a PhD at Würzburg University. He worked for a time with his father on water analysis, having become interested in microorganisms present in water. Unfortunately, there was a falling out between them, and in 1888 Percy Frankland became Professor at University College, Dundee. Together with his wife, the former Grace Toynbee, Frankland published a number of papers in microbiology and an 1894 text on aquatic microorganisms.[13] It has been claimed that Percy Frankland is actually the inventor of the Petri dish.[14] Percy Frankland first went to Mason College, Birmingham, in 1894 and was at Birmingham University from 1900 to 1910; he was Dean of Science there from 1913 to 1919.

Challenger was promoted to Lecturer in 1915, and his stipend was increased from £150 to £250. Although aged 27 in 1914, he apparently did not serve in the military during World War I. He became Acting Head of the Department of

Chemistry at the beginning of 1919, when Frankland resigned. In turn, Challenger resigned from his Birmingham position in October 1920. In July of that year, he had presented a thesis, 'Organic derivatives of silicon. Pt. 13 (and 8 other parts)' to his university and was awarded the degree of Doctor of Science.

He next became Senior Lecturer in Chemistry at the University of Manchester, the appointment dating from 29 September 1920. His initial stipend was £550 per annum 'rising according to scale'. Soon after his arrival in Manchester, Challenger married Esther Yates in 1922. The couple had two daughters. Mrs Challenger died in 1969. After the 1920 appointment, he remained at Manchester as Senior Lecturer for 10 years before resigning in consequence of his appointment at the University of Leeds. At a meeting of the Council of the University of Manchester on 23 July 1930 it was 'Resolved:

(i) That the resignation be accepted as from the date mentioned.
(ii) That Dr Challenger be congratulated on his appointment and thanked for his service to the University'.

When Challenger joined the University of Manchester, H. B. Dixon was the Sir Samuel Hall Professor of Chemistry but he retired in 1922 soon after Challenger's arrival.[15] Arthur Lapworth, who had been Professor of Organic Chemistry since 1913, was appointed to fill the vacancy. He also became Head of the Department. Lapworth was a distinguished organic chemist, credited with initiating attempts to clarify and interpret reaction mechanisms. He had become acquainted with Robert Robinson (1886–1975) in about 1909 in Manchester, and together they developed an electronic theory of organic reactions. Robinson was to become the major organic chemist in the UK, receiving the Nobel Prize in Chemistry (1947). Lapworth's move was deliberate—it left the Chair of Organic Chemistry vacant and Robinson was appointed to that position in 1923. Challenger thus found himself under the influence of these two very distinguished chemists.

There is a curious connection between Lapworth and Kipping. In 1887, W. H. Perkin Jr married Mina Holland; subsequently, Kipping married her sister, Lily, and Lapworth the third sister, Kathleen. These three sisters thus married organic chemists who all achieved the distinction of Fellowship of the Royal Society.

In August of 1930, it was formally announced that the Council of the University of Leeds had elected Dr F. Challenger 'to the chair of organic chemistry shortly to be vacated by Prof. C. K Ingold'.[16] Thus, his journey finally ended at the University of Leeds, where he made his scientific home for the next 23 years. He was 43 years old. His journey is atypical, always involving study or positions in the Midlands (Derby, Nottingham, Birmingham) or the North of England (Manchester, Leeds). Possibly as a Yorkshireman he felt more at home in those cities. He never ventured into the south of England and had no experiences at Cambridge, Oxford or London. In fact, the most southerly point in his journey was the 8 years spent in Birmingham.

Challenger has written a history of the Chemistry Department at Leeds[17] and a brief account will be given here. It begins with the establishment of the Yorkshire College of Science in 1874, when T. E. Thorpe became the first Professor of Chemistry. Thorpe had worked in Germany with Bunsen and Kekulé. There were two other professors, one for experimental physics and mathematics, the other for geology and mining. New buildings to replace the earlier structures were started in 1877, the college then being renamed as The Yorkshire College. Thorpe resigned in 1885, being replaced by A. Smithells. At that time there was no Chair in Organic Chemistry. To remedy this situation, J. B. Cohen was appointed as Assistant Lecturer, becoming Professor in 1904. On his retirement, in 1924, C. K. Ingold had been appointed.

RESEARCH ACHIEVEMENTS

The work for which Challenger will be long remembered centers on methylation reactions in biology. More specifically, he was concerned with the ability of microorganisms to methylate metalloid elements such as arsenic, selenium and tellurium, with the formation of volatile products. He defined the structures of the volatile materials, the conditions under which they were produced, and the actual chemical mechanisms for methylation. This work began after his appointment at Leeds, the first publication coming in 1933.[18] His interest in this topic continued even beyond his retirement in 1953.[19] The origin of this interest is not entirely clear. However, in 1931 there had been a celebrated case of arsenic poisoning involving two children in the Forest of Dean. Arsenic had been found to be present in both wallpaper and plaster and the County Analyst had 'found definite traces of arsenic being given off in gaseous form from the wall that was affected by mould...'. Challenger cites this work in his seminal review on biological methylation.[20] Perhaps, after the Forest of Dean case, he recalled that 'Gosio Gas' (see later) was allegedly diethyl arsine and decided to reinvestigate.

The work on metalloid methylation was also influenced by two practical experiences. The first was the study of organometallic compounds that he began in work with Kipping (Nottingham) and continued in Birmingham. The second came from an interest in microorganisms and their metabolism. This was initiated by the association with Alfred Koch at Göttingen (see above), and was stimulated by experimental work on the biosynthesis of some fungal acids at Manchester. There may have been a further connection, since it is likely that Challenger, at Birmingham, would have discussed Edward Frankland's work on organometallics with Percy Frankland, who was himself interested in microbiology. These important formative influences will be described in some detail; also, an account of his overall achievements in the area of biomethylation will be given. Challenger and his

associates also worked in many other areas; some of this work will be discussed under appropriate headings when several, related papers exist. Inevitably, the account will be incomplete. One difficulty is that we could not locate a definitive listing of Challenger's publications.

Organometallic compounds such as trimethylarsine have one general characteristic: unpleasant odors. Challenger's laboratories were located across the street from neighbors selling perishable foodstuffs. It has been stated that 'The noisome character of the by-products of some of these operations, together with their affectionately clinging nature, at one time made the department highly unpopular with its neighbours. . .'.[19] Interestingly, R. W. Whytlaw-Gray, who held the Chair of Chemistry at Leeds from 1923 to 1945, had studied the interaction of tellurium hexafluoride with tellurium in an alumina vessel at 200 °C. This reaction produced tellurium tetrafluoride. Whytlaw-Gray's students suffered from the characteristic 'garlic breath' formed by biomethylation after ingestion of tellurium compounds.[17] The odor is due to dimethyl telluride.

Chiral derivatives of silicon and phosphorus—Nottingham

The chemical strand of his biomethylation interest began in his work with F. S. Kipping at University College, Nottingham. At the beginning of the 19th century, there was considerable interest in the possibility that elements other than carbon might yield compounds that could be separated into enantiomorphous forms. An early example involved the 'asymmetric' nitrogen atom. Le Bel resolved methyl ethyl propyl isobutyl ammonium chloride into two enantiomers. Another atom of interest was silicon. Although Kipping had resolved one silicon compound, he had been unable to resolve benzyl ethyl methyl propyl silane (then termed 'silicane'). Challenger converted dibenzyl ethyl propyl silane to a dibenzyl ethyl propyl monosulfonic acid; resolution of the latter was achieved via a brucine salt (several other bases that were examined as resolving agents did not achieve resolution—see later). Proving that resolution had occurred required much effort, the difficulties being compounded by the low levels of optical rotation.[21,22]

In other work, Challenger and Kipping investigated the chirality of a phosphorus compound. Although (±)-phenyl-β-naphthyl hydrogen phosphate, $O{=}P(OC_6H_5)(OC_{10}H_7){-}OH$, could not be resolved by salt formation with chiral bases, the corresponding acid chloride reacted with (−)-menthylamine to give a mixture of two amides with the structure $O{=}P(OC_6H_5)(OC_{10}H_7){-}NH{-}C_{10}H_{19}$. One of the diastereoisomeric amides was sparingly soluble and was easily isolated in a pure state. The more soluble form was obtained in a slightly impure state. Hence the chirality of a phosphorus atom was confirmed;[23] earlier, other workers had resolved $O{=}P(CH_3)(C_2H_5)(C_6H_5)$.

In long reviews of the life and work of Kipping,[3,4] Challenger has provided a vivid picture of work in the Nottingham laboratory. When Challenger began work there in January 1908, 'new research students were required to prepare (±)-methylhydrindamine starting from ethylbenzylmethylacetoacetate. During this preliminary initiation or very shortly thereafter I first heard addressed to me, the words so familiar to all of Kipping's students—''you started out with 50 grams of ester, you now show me 5 grams of this stuff. Where's it all gone to?'' There was often no answer'.

Only after months of work by Challenger trying to resolve dibenzyl ethyl propyl monosulfonic acid with various chiral bases, and at a time when Kipping was ready to abandon the project was brucine investigated on the last 1 g of sulfonic acid. Although in May 1909 success appeared to be at hand, it was not until the end of November of that year that sufficient amounts of the two brucine salts could be prepared for more detailed investigation. Challenger has described in emotional terms how the sparingly soluble brucine salt was converted to a levorotatory sodium salt with specific rotation of about −1.0°. When Kipping was informed he replied 'You know what I think', implying possible contamination by brucine itself. However, this was not the case. The sodium salt of the soluble brucine salt was next found by Challenger to have a slight dextrorotation, with another worker confirming the direction of rotation. 'Kipping was informed by telephone—with careful suppression of any natural exuberance. ''Well''—pause—''We shall be able to get on now''. Nothing more! Two years hard labour—two years in which I, in common with others, had only been sustained by the words quoted by Seton Merriman in one of his novels, then so much the vogue—''He who has lost all hope has also lost all fear''. Two such years— during which at times the sight of the *Journal of the Chemical Society* was almost a pain, so remote did success and possible publication appear—might have warranted slightly warmer congratulations. But the Master had trained us well. We did not expect much'.

The following morning, Kipping himself used the polarimeter to confirm the most welcome observation. He noted a slight turbidity in the solution and used the occasion to continue the student's education. 'The sooner you learn that you can't take a rotation in a turbid solution the better' he remarked. Challenger says that work with Kipping was no easy thing. 'He believed with Jeremiah that ''it is good for a man that he bear the yoke in his youth''.'

Organic derivatives of bismuth, etc.—Birmingham and Manchester

In 1914, Challenger published the first of six papers under the general title of organo-derivatives of bismuth resulting from work carried out in Birmingham. These papers were primarily descriptions of the preparation and properties of tertiary aromatic bismuthines (Ar_3Bi), together with many halogen, cyano and thiocyano derivatives.[24] Much later, in 1934, he wrote a long paper on organic derivatives of bismuth and thallium.[25] A lengthy 1926 paper from Manchester involved the introduction of the selenocyano group into aromatic compounds using some selenium and tellurium

compounds.[26] For example, triphenylbismuthine reacted with cyanogen triselenide to form phenylselenocyanate and diphenylselenocyanobismuthine:

$$BiPh_3 + Se(SeCN)_2 \rightarrow BiPh_2{-}SeCN + PhSeCN + Se \quad (Ph = C_6H_5) \quad (1)$$

Triphenylstibine dichloride gave triphenylstibine hydroxyselenocyanate, $SbPh_3(OH){-}SeCN$ or possibly the corresponding oxide. In experiments involving tellurium, triphenylbismuthine reacted with tellurium dicyanide to form diphenylcyanobismuthine, $BiPh_2{-}CN$, and unstable phenyltellurocyanide, PhTeCN (decomposing to diphenyl ditelluride). This work is of interest in view of Challenger's later experiments on the fungal biomethylation of selenium and tellurium.

Fungal metabolism—Manchester

Challenger carried out a number of studies of fungal metabolism in Manchester, often in collaboration with T. K. Walker. This work was notable since it marked the beginning of the process by which he grew into biochemical research. As already noted, he had first become interested in microbial chemistry through his acquaintance with Alfred Koch, although apparently not doing any research. Now in Manchester, he became reacquainted with microbial chemistry and it was this development that eventually led him to the topic of biomethylation at Leeds.

One aspect of the Manchester work was concerned with the formation of the familiar acids, citric, lactic, malic and oxalic, by *Aspergillus niger*.[27–30] A number of experimentally observed conversions carried out by this fungus suggested the following metabolic pathway:

Glucose → gluconic acid → saccharic acid
→ $\beta\gamma$-diketoadipicacid → citric acid
→ acetonedicarboxylic acid → malonic + acetic acids
→ acetic acid (2 mol) → glycollic acid
→ glyoxylic acid → oxalic acid

However, as J. W. Foster has noted, 'The history of citric acid metabolism in fungi is strewn with theories purporting to be the biochemical mechanism of the origin of this substance from hexose sugars'.[31] The above pathway was one such theory. The details of the 'citric acid cycle' only emerged much later from work on mammalian biochemistry; however, the fundamental reaction of oxaloacetic acid and acetic acid (actually in an activated form) had been proposed for fungal citric acid formation much earlier in a classic paper by Raistrick and Clark.[32] Challenger also published some general accounts of the alcohol fermentation[33] and other technical processes involving microorganisms.[34]

Another fungal metabolite investigated by Challenger and Walker was the γ-pyrone, kojic acid. This compound had originally been discovered on fermentation of rice and carbohydrates by *Aspergillus oryzae*, but it was also known to be formed by other fungi and from a variety of substrates. The main biochemical question was whether glucose (i.e. in the pyranose form, D-glucopyranose) was directly converted to kojic acid without being split into smaller molecules (as suggested by structural considerations) or whether formation of, for instance, C_2 and/or C_3 compounds took place followed by resynthesis to the pyrone structure. Challenger studied kojic acid formation from pentoses and dihydroxyacetone and believed that the direct conversion of the pyranose ring of glucose to the pyrone ring of kojic acid did not take place.[35,36] Much later, and now at Leeds, Barnard and Challenger[37] investigated kojic acid production from ethanol; the cultures also produced acetaldehyde. Soon after this work, Arnstein and Bentley,[38] using [1-^{14}C]-D-glucose, were able to show the direct dehydration and oxidation of glucose to kojic acid and to account by reasonable biochemical mechanisms for its synthesis from compounds with fewer than six carbon atoms.

Studies of biomethylation—Leeds

As far as Frederick Challenger's scientific legacy is concerned, the work he directed in the early 1930s will probably be considered the most significant over the long term. Beginning in the fall of 1931, Challenger and his colleagues first determined the structure of Gosio gas (see below).[18] Their methods—used in this and much subsequent work—involved sterile air purged through bread-containing flasks with cultures of a fungus, *Scopulariopsis brevicaulis*. The cultures were amended with sterile solutions of arsenic-containing compounds (concentrations on the order of 10 mM) and allowed to grow for days or weeks. The exiting gas was continuously bubbled into a solution of mercury(II) chloride in dilute HCl (Biginelli's solution), capturing a derivative of the unknown as a precipitate. Their methods of chemical identification of the precipitate were those common to organic chemists of the early 20th century and would become a mainstay of their efforts over the next 20 to 25 years to identify volatile metalloid-containing metabolites: (1) comparison of the isolated derivatives' melting points with those of known compounds; (2) identification of further reactions of the derivative with various reagents; and (3) examination of other physical attributes, chemical reactivity, or even the characteristic odors of the volatile unknowns.[18,20] A summary of over a decade of these experiments and exhaustive review of the biomethylation literature—with citations stretching back to the 18th century—was published by Challenger in a landmark review in *Chemical Reviews* in 1945, but the writing of some sections of that summary was begun as early as 1939.[20] Two other general reviews of biomethylation were published in 1951 and 1955.[39,40] One of Challenger's coworkers was initially referred to as 'Miss C. Higginbottom' and later 'Dr Higginbottom'; another as 'Mr. P. T. Charlton' and yet another as 'Miss V. K. Wilson, M.Sc.' Apparently, Dr

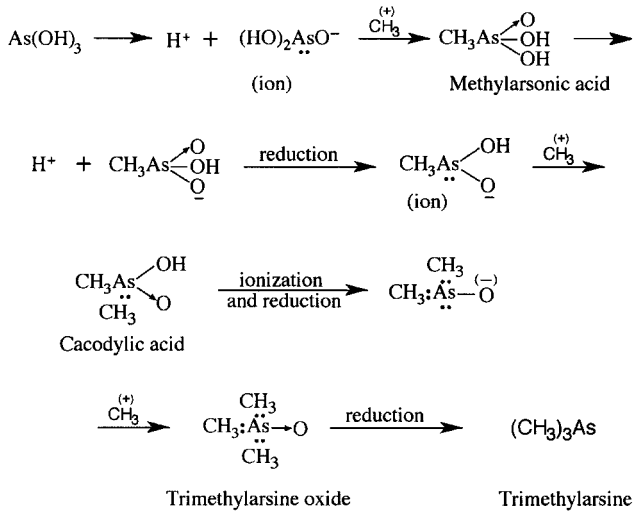
Frederick Challenger was respecting of social titles and was also keen to update them as they changed. Another colleague, initially (Miss) Simpson later became Dr Whitaker.

The seminal work on biomethylation was published in the *Journal of the Chemical Society (London)* as the first (part I) in a series of Challenger's papers in that and other journals entitled in part 'The Formation of Organo-metalloidal Compounds by Microorganisms. Part . . .' in 1933[18] up to part VII in 1939.[41] In several cases, there were slight variations on this title. A revised title, 'Studies on Biological Methylation', began to be used in part VIII in 1942[42] to indicate more clearly the scope of the investigation. The final member of this series was published 25 years later, in 1957,[43] after Challenger's formal retirement.

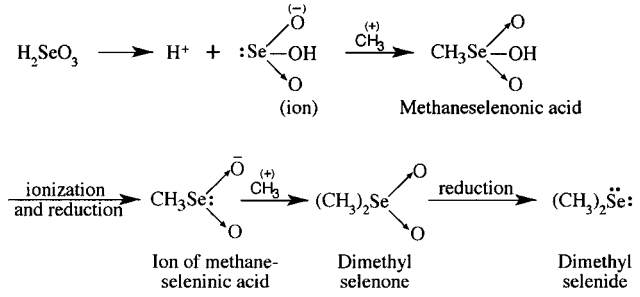
A very important result was the determination of the structure of the so-called Gosio gas. This volatile arsenic compound was shown to be formed by growth of various fungi on inorganic arsenic compounds in early work by the Italian physician, Bartolomeo Gosio.[44] Formation of the volatile gas in damp rooms containing wallpaper with arsenical pigments was a significant public health problem in the 19th century. The fungus *S. brevicaulis* was particularly active in arsenic volatilization. Although Gosio had some evidence that his gas was diethylarsine, the careful work by the 'Leeds School' corrected the structure to that of trimethylarsine, $(CH_3)_3As$.

Beginning in the 1930s, these analytical techniques were also applied to the determination of dimethyl selenide produced by the mold *S. brevicaulis*[45] and *Penicillium notatum*[46] and dimethyl telluride.[41] Much later they were extended to the tentative identification of trimethyl antimony[47] as captured from these same two organisms. Amendments involved oxyanion-containing salts of the metalloids of interest. Moreover, extensive chemical investigations of potassium alkaneselenonates and other alkyl selenium derivatives were carried out.[48] Also of chemical interest was the structure of diallyl disulfide; evidence indicated that it was most likely $(CH_2{=}CH{-}CH_2{-}S)_2$.[49]

As Challenger has noted, 'when we found that Gosio-gas was pure trimethylarsine, we were suddenly ejected from our small corner and pitchforked directly into the growing field of Transmethylation, then in the early stages of its development in animals by the fundamental work of Vincent du Vigneaud'.[11] Challenger had considered materials such as formaldehyde, choline and betaine as possible methyl donors for *S. brevicaulis* and other organisms.[50,51] However, it emerged that methionine, especially as its sulfonium derivative, *S*-adenosyl-methionine (SAM), had a critical role. Today, SAM is known as a near-universal methyl group donor.[52] Before this recognition, the Leeds School had proposed that a positive methyl group, CH_3^+, could be used for arsenic methylation, and in 1954 was able to show that the methyl group of methionine was transferred during fungal biomethylation.[53] Attempts to obtain enzymatic synthesis of trimethylarsine using press juice or acetone-dried mycelium of *S. brevicaulis* were not successful.[54]



Scheme 1. The Challenger mechanism for biomethylation of arsenic. The mechanism is shown in its original form. A more modern interpretation is available.[55]



Scheme 2. The Challenger mechanism for biomethylation of selenium. As with arsenic (Scheme 1) the mechanism is shown in its original form. A more modern interpretation is available.[62]

One of the most important contributions described in the 1945 review was the proposed mechanism for biomethylation for arsenic and selenium, and by analogy, tellurium. Now known as the Challenger mechanism, these sequences of chemical steps involving alternating methylation and reductions (see Schemes 1 and 2) were based on the research of the Leeds School.[20] It is now clear that the CH_3^+ group, originally proposed as the methylating agent, is derived from SAM. These chemical mechanisms, proposed almost 60 years ago, have provided a framework for understanding biomethylation to the present day.[55]

Challenger and his colleagues also investigated reactions leading to the methylation of sulfur compounds, showing the fission of both disulfide and monosulfide links. Also of importance was a proposed mechanism for the formation of dimethyl sulfide by an alga. This compound, produced by many living organisms, has an important role in the environment.[56] Addition of inorganic forms of sulfur to the usual bread cultures of *S. brevicaulis* did not lead to formation

of dimethyl sulfide. However, dialkyl sulfides, R–S–S–R (R varying from CH_3 to C_5H_{11}), were converted to alkanethiols, R–SH (adsorbed by mercuric cyanide), and methyl alkyl sulfides, R–S–CH_3 (adsorbed by mercuric chloride). This fission of the disulfide link appeared to be a general reaction, but it was not determined whether it was reductive or hydrolytic. The source of the methyl groups was not investigated.[57,58]

Fission of a monosulfide link was explored in the interaction of DL-methionine with bread cultures of *S. brevicaulis*.[59] Both CH_3–SH and $(CH_3)_2S$ were formed. Similarly, alkyl cysteines, R–S–CH_2–$CH(NH_2)$–COOH, reacted in the same way forming R–SH and R–S–CH_3 (R varying from CH_3 to C_3H_7). *S. brevicaulis* was also shown to methylate the thiols C_2H_5–SH and C_3H_7–SH.[20] Very much later, in a case of severe human liver necrosis, a strong odor was observed in breath (foetor hepaticus) and in urine.[60] The odor was due to dimethyl sulfide, probably derived from the high level of methionine in the patient's blood.

In 1948, Challenger and Simpson (later Dr Whitaker) made the important observation that the red, marine alga *Polysiphonia fastigiata* contained 2-carboxyethyldimethylsulfonium chloride, $[(CH_3)_2S^+–CH_2–CH_2–COOH]Cl^-$, a compound also described as β-propiothetin.[61] This was the first example of a sulfonium compound to be found in a plant. Some green algae also contained this material.[39] Decomposition of this sulfonium compound yielded dimethyl sulfide; this odorous material was released when the algae were exposed to air. When the algal sulfonium compound was added to cultures of *S. brevicaulis*, only a low yield of dimethyl sulfide was obtained. With the bromide salt and *P. notatum* cultures, however, dimethyl sulfide was formed in 36% yield.[39] In addition, both fungi converted $[(C_2H_5)_2S^+–CH_2–COOH]Br^-$ to diethyl sulfide in 25% yield. These results indicated that there was likely to be an enzymatic mechanism for fission of sulfonium salts. This suggestion has been confirmed in recent experiments.[62]

The characteristic odor of human urine following ingestion of asparagus was found to be due to dimethyl sulfide.[40,63] The precursor was again a sulfonium compound, this time a sulfonium salt of *S*-methylmethionine, $(CH_3)_2S^+–CH_2–CH_2–CH(NH_2)–COOH$. Dog urine, when treated with alkali, yields volatile sulfur products. Although early evidence suggested the presence of diethyl sulfide, the Leeds School demonstrated that the volatile material was a mixture of methyl *n*-propyl sulfide with a small amount of methyl *n*-butyl sulfide. The presumed precursor sulfonium compounds could not be identified.[63]

Volatile organo-sulfur compounds from onions were investigated in Challenger's work of 1948 with the gas-trapping methods so productive in his fungal research of that past decade. The presence of allyl sulfides and various alkylated thiols[64] was detected, presaging similar, but more sophisticated, reports 50 years later using gas chromatography and mass spectrometry.

It is appropriate to end this section by noting that another post-retirement project for Challenger was the writing of a text (1959) on the chemistry and biochemistry of organic compounds of sulfur.[65]

FURTHER RESEARCH

Terpene chemistry, PhD thesis—Göttingen

A brief description of this work[1] has already been given. In essence, it was part of Wallach's investigation of the structural characteristics of the terpenes. Although Challenger apparently made no further experimental contributions to terpene chemistry, in 1928 he wrote the paper 'The Investigation of Essential Oils'.[66] This review concerned Wallach's research up to that particular time.

Sulfur compounds in shales, petroleums, etc., dyestuffs—Manchester

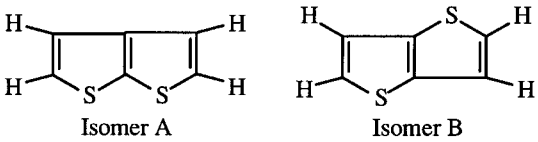
Challenger published several papers dealing with the sulfur compounds found in materials such as Kimmeridge shale oil, petroleum, and mineral oils. Thiophen, thiophen derivatives and multiple-ring thiophens were prominent components, along with CS_2, alkyl sulfides, and polymethylenesulfides.[67–69] A somewhat uncharacteristic effort was a book on the chemistry, manufacture and application of dyestuffs and coal-tar products, co-authored with three other individuals.[70]

Heterocyclic sulfur compounds—Leeds

A solid bicyclic form of thiophen, $C_6H_4S_2$, termed a thiophthen, was formed by reaction of acetylene with boiling sulfur at 440 °C.[71] Its structure was determined (see Scheme 3, isomer A). A low melting-point isomer formed in the same way was shown to be isomer B (Scheme 3). It underwent Friedel–crafts acetylation at the α position to the sulfur atom.[72] In other work, thiophen derivatives were found to undergo electrophilic substitution at the α position. Thiophen reacted with ethylmagnesium iodide at 160–170 °C. On subsequent carbonation of the product, likely 2- thienylmagnesium iodide, thiophen-2-carboxylic acid was obtained.[73]

Methionine–cystine relationship in mental retardation

Long after his 1953 retirement Challenger published two reviews involving the biochemistry of damaged amino acid



Scheme 3. Thiophthen isomers. Isomer A is a liquid (m.p. 6.5 °C) at room temperature and isomer B is a solid (m.p. 56 °C).

metabolic cycles in humans.[74,75] The sulfide sulfur in methionine is normally converted to thiol sulfur in homocysteine in the so-called, trans-sulfuration cycle. In fact, the methionine–homocysteine cycling acts as a detoxification mechanism to prevent the build up of either one.[76] In conjunction with cystathionine synthetase and vitamin B_6, cystathionine ($HOOCCH(NH_2)-CH_2-CH_2-S-CH_2-CH(NH_2)COOH$) is produced, ultimately leading to cysteine, cystine, and sulfate. An abnormality in a small number of patients with mental disorders and neural tumors, so-called cystathioninuria, has more recently been divided into deficiencies in cystathionine synthase, 5, 10-methylene THF reductase deficiency, or B_{12} deficiency.[77] Urinary excretions of mixtures of the disulfides of cysteine and homocysteine (homocystinuria) had also been reported, and homocystinuria is now the more common term used. After Challenger's then recent speculation on the biological occurrence of isethionic acid, $HOSO_2CH_2CH_2OH$,[78] in the later review[75] he noted that isethionic acid had been determined in plasma and commented on its possible importance in the metabolism of sulfur-containing amino acids of the trans-sulfuration pathway.

The last paper(s)

As far as we can tell, the last scientific publication of Frederick Challenger's life was a contribution to an American Chemical Society (ACS) Symposium *Organometals and Organometalloids: Occurrence and Fate in the Environment* in 1978.[11] His introductory paper on the symposium's topic, submitted at the age of 91, was entitled 'Biosynthesis of Organometallic and Organometalloidal Compounds'. This work was a thorough review on biomethylation of arsenic, selenium, and antimony and it touched on mercury, lead and cadmium, including comments on research presented in the symposium itself. It included 75 bibliographic references and an additional symposium comment (added '*in absentia*') on the methylation of arsenic, including further reference to scientific literature of just the year before. He was clearly and impressively active even at this late stage of his long life.

In 1987, in the centennial year of his birth Dr Peter Craig—at De Montfort University (then Leicester Polytechnic), Leicester, UK—and Professor Frank Glockling—University of Oxford, UK—co-hosted a conference sponsored by the Royal Society of Chemistry 'commemorating the centenary of the birth of Professor Frederick Challenger. . .'.[79] This gathering once again celebrated Challenger's pioneering work in the biomethylation of metalloids and opened with an introduction that mirrored the earlier ACS Symposium introduction, which could have been authored by Challenger himself.

PROFESSIONAL AND ADMINISTRATIVE ACTIVITIES

Challenger brought to his department at Leeds a needed period of stability and growth. He encouraged staff members to pursue independent lines of research and was scrupulously fair in the allocation of resources.[19] Perhaps influenced by his time with Wallach, his department did not harness all effort to a single end, and a great variety of work was carried out in addition to his own concerns (e.g. kinetics and mechanisms of organic reactions, preparation of estrogenic, anti-tubercular and anti-malarial compounds, end-group determination in peptides and proteins). He 'will always be remembered in the Department of Chemistry for the warm human interest which he displayed in everything connected with it'.[19] In lectures, he considered not only the hard facts but also the personalities of the researchers. He made much effort to secure portraits of well-known chemists to be shown as lantern slides. Not only tenacious in what he believed to be right, he was equally tenacious in obtaining funding and facilities. He would urge his case patiently and continuously until he received a letter from a university administrator saying, in effect, 'You win'. Wightman, who was writing on the occasion of Challenger's retirement, referred to 'the spirit of happy co-operation which has pervaded his department for twenty three years'.[19]

In professional activities, he was much concerned with the affairs of the Institute of Chemistry (later, the Royal Institute of Chemistry, and still later, merging with the Chemical Society, London, to form the Royal Society of Chemistry). He served several terms as a Council Member and from 1949 to 1951 was Vice President of the Institute. In the Chemical Society, he was a Council Member from 1934 to 1937.

Epilogue

Although his career initially followed a somewhat unconventional route, and although he never worked in a center such as Cambridge, London or Oxford, Challenger established a very well-regarded and productive school at the University of Leeds. He has been described as 'one of the few scientists who have the foresight to select research topics which blossom into major fields of discovery and research'.[80] His work on biomethylation did indeed open up a major research field; however, it was not fully appreciated at the time it was carried out, and it was only acclaimed at a later date. Moreover, 'Professor Challenger was a pioneer investigator working on ''environmental chemistry'' a generation before that expression was coined'.[80] Reviewing his life, one gains the impression that he was a dedicated scientist, concerned for his students and colleagues, but with little interest in self-promotion. It is sad that, despite his many achievements, he did not attain the honor of Fellowship of the Royal Society, perhaps as a result of his innate modesty.

In his nine full decades of life, he lived through two World Wars and saw the enormous changes wrought by technology. When he was born in 1887 the horse was still the major energy source, since the automobile was largely experimental until about 1910. Alexander Graham Bell had patented a telephone system in 1876–77, 10 years before his birth. In chemistry, the tetravalence of carbon was postulated by Kekulé in 1857 and the foundations of stereochemistry were only laid down by van't Hoff and Le Bel in 1874. When he was less than 10 years

old, the electron was discovered by J. J. Thompson. When he died, atomic bombs had been used, and the world was totally transformed.

During his life, Challenger was listed by *Who's Who*. At his death (12 February 1983) he received obituary notices in *The Times* (17 February 1983), *The Yorkshire Post* and in the University of Leeds Review.[80] His death was also noted by the Royal Society of Chemistry.[81] He is said to have remained in full possession of his faculties to the end. A few days before his death, he had written a letter to a friend referring to his favorite relaxations, railways and walking.

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