BIOGRAPHICAL MEMOIRS

Charles Wayne Rees CBE. 15 October 1927 — 21 September 2006

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Biogr. Mems Fell. R. Soc. 2015 61, 351-378, published 19 August 2015
originally published online August 19, 2015

Supplementary data

"Data Supplement"
http://rsbm.royalsocietypublishing.org/content/suppl/2015/08/18/rsbm.2015.0023.DC1

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CHARLES WAYNE REES CBE
15 October 1927 — 21 September 2006
Charles Rees was an eminent organic chemist. He specialized in the area of heterocyclic chemistry—the study of rings made up of carbon, nitrogen, oxygen and sulphur atoms—an important subject given that many medicines, agrochemicals, dyes and reprographic materials, as well as a very large number of naturally occurring compounds, including the DNA bases, the building blocks of life itself, are heterocyclic molecules. His scientific work was dominated by two overarching themes: reactive intermediates, in particular neutral, electron-deficient species such as carbenes, nitrenes and arynes, and unusual ring systems, particularly strained rings and novel aromatic systems, including those rich in sulphur and nitrogen atoms. Born in 1927, he was educated at Farnham Grammar School, then spent three years at the Royal Aircraft Establishment, before going to University College Southampton (later Southampton University) (BSc 1950, PhD 1953). After a postdoctoral period, he was appointed assistant lecturer at Birkbeck College, London, in 1955, before moving to a lectureship at King’s College, London, and subsequently to chairs at the University of Leicester (1965), the University of Liverpool (1969) and Imperial College, London (1978). He was elected to the Royal Society in 1974 and appointed CBE in 1995. He died in London in 2006.

Early life and education

Charles Rees was born in Egypt on 15 October 1927, the second of three children of Percival Charles Rees and Daisy Alice (née Beck). Percival Rees was a career soldier who served as a Corporal in the Royal Field Artillery during World War I and in 1927 was serving in the British Army in Egypt, where he remained until 1929. Percival left the army in 1934 with the rank of Regimental Quarter Master Sergeant. He then had various jobs before obtaining a clerical position at the Military Academy, Sandhurst. On return to the UK from Egypt the family lived
in quarters at Keogh Barracks in Mytchett, Surrey. Charles attended Ash Vale primary school, where he passed his 11-plus examination, and in 1939 he entered Farnham Grammar School. While at Farnham, aged 15 years, his mother died. Charles often spoke about his younger brother, John (born in 1936), and his elder sister, Daisy (1924–2007), who looked after him and made up for this tragic loss.

At school, in addition to his academic achievements, Charles was prominent in several activities in his house (Childe House), where he was an active sportsman representing his house in athletics, cross country running, boxing and rifle shooting. He was an excellent boxer, winning his weight in 1942, and reached the final again in 1944 only to be defeated. The report stated that his opponent ‘used his enormous advantage in reach to very good effect, and Rees was shaken by a number of straight lefts. Rees tried hard but was unable to get many punches home.’ Charles was also part of a strong house rifle shooting team, but success at cross country running was more elusive, with 40th place in the annual school run in 1942 being his best achievement. Academically, Charles was awarded a Form Prize for ‘Good Work’ every year, and on leaving school he was awarded the William Stroud Prize for ‘Services to the School’. Rees was not the only eminent chemist to attend Farnham Grammar School: in the early 1900s two distinguished physical chemists, James Kendall (FRS 1927) and Eric (later Sir Eric) Rideal (FRS 1930), were contemporaries at the school. Later, as Rees entered school in 1939, another organic chemist, Ernest Braude, was leaving. Coincidentally, Braude went on to be appointed to the Chair of Organic Chemistry at Imperial College, London, in 1955 before committing suicide in 1956—the same chair that Rees was to succeed to some two decades later in 1978.

On leaving school in 1944 Rees spent three years as a laboratory technician at the Royal Aircraft Establishment, Farnborough, Surrey. Here he was exposed to modern science and he enrolled himself in evening classes (night school) to continue his education. This led to his becoming the first member of his family to attend university, gaining a place at University College Southampton (later Southampton University). After graduating in 1950 with a BSc (University of London External Degree), he remained in Southampton to undertake postgraduate research with Norman B. Chapman, later Professor of Organic Chemistry at the University of Hull (1956–82), studying the reactions of chloropyridines and chloropyrimidines with nucleophiles; this resulted in his first publication (1)*. He obtained his PhD in 1953 (also a University of London External Degree), in the same year as he was married to Patricia (Tricia) Mary Francis. They had met in Southampton, where Tricia was an undergraduate reading English, Latin and history.

A postgraduate contemporary at Southampton was Brain Capon, later also Rees’s colleague at Leicester (1965–68). In 1965 Capon and Rees were the founding co-editors, along with John Perkins, of the new series Organic reaction mechanisms, now in its 49th annual volume, a task they undertook for seven further volumes. Outside the laboratory, both Capon and Rees became keen opera lovers, something they ‘inherited’ from their PhD mentor, Norman Chapman.

On leaving Southampton, Rees started postdoctoral work with Professor Adrian Albert, the foundation Professor of Medical Chemistry at the School of Medical Research, in the Australian National University. As no laboratories were yet available in Canberra, Albert launched his department in hired facilities in London; Rees therefore started his postdoctoral

* Numbers in this form refer to the bibliography at the end of the text.
work in surroundings somewhat less exotic than Canberra, in the Euston Road. There he worked with Albert on antimicrobial compounds, publishing six papers, including one on the binding of tetracycline antibiotics to metal cations (2), that, interestingly, remains Rees’s most cited paper.

**Birkbeck College, London, 1955–57**

In 1955 Rees was appointed as an assistant lecturer at Birkbeck College, University of London, in the same year that Derek (later Sir Derek) Barton FRS left Birkbeck to take up the Regius Chair at the University of Glasgow. Clearly, Rees made an immediate impression at Birkbeck. Writing in the ‘Lives remembered’ section of *The Times* after the publication of Rees’s obituary, Dr D. P. Moody (no relation to the present author) remembers: ‘I was the senior student demonstrator in chemistry at Birkbeck College on the day an apparition in a bow-tie started as assistant lecturer. It fell to me to introduce Charles Rees to the joys of teaching. … Charles slotted in immediately.’

Rees’s interest in heterocyclic chemistry started during his postgraduate and postdoctoral studies and continued at Birkbeck. Apart from a brief foray into carbocyclic ring systems during the 1980s (*q.v.*), heterocycles remained at the heart of his research career. Having said that, one remnant from Rees’s Birkbeck days was a collaboration with W. G. Overend on the oxidation of carbohydrates with bromine. Notwithstanding his status as an assistant lecturer, Charles was able to recruit his first two PhD students at Birkbeck, Mohammed Habib and Thomas Emerson. Both worked on heterocyclic *N*-oxides, and subsequently moved with Rees when he left for King’s College.

**King’s College, London, 1957–65**

After just two years at Birkbeck College, Rees was appointed to a lectureship at King’s College, London, and made the short journey from Malet Street to the Strand in 1957. He spent a productive eight years at King’s and was promoted to Reader in 1963. During this time, the organic chemistry group at King’s, under the leadership of the Daniell Professor, Donald H. Hey FRS, was an impressive group of scientists, many of whom were subsequently appointed to chairs and elected to the Royal Society, including Gareth Williams, Bernard Henbest, Leslie Crombie (FRS 1973), John (now Sir John) Cadogan (FRS 1976), John Perkins and Charles Stirling (FRS 1986). Like Hey himself, several of these colleagues at King’s were Welshmen, and an apocryphal story has it that Charles was only appointed because Hey thought that with a name like Rees, he, too, was from Wales!

Sir John Cadogan remembers:

In 1956 I had just become a lecturer at King’s. Shortly afterwards Hey decided he needed a lecturer in heterocyclic chemistry and I was delighted to learn that Charles would be applying. I was not at all surprised that he was successful, my only part in it was when Hey told me of his decision but asked me whether I thought Charles would ‘fit in’. It was easy to say yes—and fit in he did. He had a delightful, warm personality, was an excellent lecturer, popular with the students and staff and an enthusiastic researcher. We went on to share a laboratory and office for 5 years while lunching daily on tins of soup and Lyons bread rolls until I left. Unburdened by any
administrative chores, they were very happy days with never a cross word between us then and indeed for the 55 years we knew each other.

Hey was very helpful to his two young lecturers. He provided one or two research students for our sole supervision and desired us to co-supervise others with him. Charles was busy with his heterocyclic N-oxides, and helping Hey with reactions of aryldiazonium salts (the Pschorr reaction). There is no doubt that he made a big difference in these latter studies, bringing his flair for mechanistic aspects to bear. Remember, these were the early days of organic reaction ‘mechanisms’. His generation of an intermediate dehydroaromatic compound (an aryne) in the synthesis of an unexpected product that turned up in one of the Pschorr reactions was quite brilliant. This was the start of his subsequent excellent work on reactive intermediates.

Meantime, I was occupied with free radical reactions and organophosphorus chemistry, well away from Charles’s interests, but nevertheless we spent much fruitful time talking about each other’s chemical conundrums and they did sometimes coincide. For example one of my reactions of diazonium entities had most anomalously, and seemingly unbelievably, thrown up what I was sure was an aryne. His challenging and penetrating questions gave me confidence to go ahead in publishing this extraordinary observation. Indeed, this perception of the mechanisms of organic reactions was one of his great strengths. Another was his command of the literature.

In the shared Rees and Cadogan office there was plenty of banter and friendly rivalry. Legend has it that they used to eagerly await the publication of the Chemical Society’s Annual Reports so they could look in the index to see who had the most citations. With Crombie, who arrived in 1958, they introduced postgraduate problem classes, hitherto unknown at King’s, and after they went their separate ways, Rees and Cadogan remained lifelong friends.

Just as at Birkbeck, Charles made an immediate impression at King’s. Students remember his friendly personality, his infectious enthusiasm for his subject, which in those days apparently even extended to carbohydrate chemistry, and, of course, the ever-present red bow-tie. On one occasion, the whole undergraduate class adorned itself with similar red bow-ties, and upon entering the lecture theatre, Charles was momentarily speechless, before continuing in his inimitable style: ‘I see we have a full house. Splendid, well done.’ His undergraduate lectures are remembered as relaxed and informal, often with an exchange of lively banter, a direct contrast to the much more formal style teaching that was prevalent in the 1960s.

Rees’s research in heterocyclic chemistry flourished at King’s, and he attracted a group of talented co-workers, most notably Tom Gilchrist and Dick Storr, both of whom followed him to Leicester and Liverpool and who were highly influential collaborators for more than 15 years. Although Rees published several collaborative papers with Donald Hey, mainly on the reactions of aryldiazonium salts, it was his work on reactive intermediates that was beginning to attract attention. These included studies of heterocyclic N-oxides, the ring expansion reactions of indoles with dihalocarbenes and the start of his work on the oxidations of N-amino compounds that culminated in the brilliantly conceived generation of 1,2-didehydrobenzene (benzyne) (5).

It was during the time at King’s that Charles and Tricia’s three sons were born: David (1958), George (1959) and Michael (1961); coincidentally, David also subsequently studied chemistry at Southampton University (1976–79). The first family home was in New Malden, Surrey, and Rees’s PhD students recall being invited to the house for dinner, something that was unusual in the 1960s. Charles and Tricia’s hospitality towards PhD students remained a feature of his academic career.
Charles Wayne Rees

University of Leicester, 1965–69

In 1965 Rees was appointed to the Chair of Organic Chemistry at Leicester University, then a relatively small chemistry department. Some of the King’s postgraduates and postdoctoral researchers moved with Rees, including Dick Storr and Colin Campbell, and Tom Gilchrist joined a year later after a postdoctoral period in Khartoum. Studies on reactive intermediates and on N-amino compounds continued apace in Leicester, with Bob Atkinson, a new postdoctoral worker, making a major contribution. Highlights included the addition of a nitrene intermediate to acetylenes to generate, for the first time, a reactive, antiaromatic, three-membered ring nitrogen compound, a 1H-azirine (9), and the generation of benzocyclopropenone (11). In some ways, Rees’s work on reactive intermediates was ahead of its time, and as early as 1968 he and Tom Gilchrist were attempting to make stable transition-metal complexes of benzyne (8). It was also during the time in Leicester that Rees and Gilchrist co-authored the excellent monograph *Carbenes, nitrenes and arynes* (73), published in 1969. Although Rees’s time in Leicester was prolific in terms of publications, it was quite short, and after the departure of Alan Battersby FRS to Cambridge in 1969, Rees moved to the University of Liverpool.

University of Liverpool, 1969–78

Rees took up the second Chair of Organic Chemistry in Liverpool in 1969, moving to a department with a strong research reputation in biological molecules such as porphyrins and peptides under the leadership of the Heath Harrison Professor, George Kenner FRS. Rees was subsequently appointed to the Heath Harrison Chair after Kenner’s tragic death in 1978. Interestingly, at the time of Rees’s appointment, Organic Chemistry was a completely separate department from Inorganic, Physical and Industrial Chemistry in Liverpool, occupying opposite ends of the building with very little interaction between them. Dick Storr moved from Leicester in 1969, and Tom Gilchrist followed a year later, ensuring a continuation of their fruitful collaborations. In 1974 Rees’s contributions to chemistry were recognized by his election to the Royal Society.

Rees’s decade in Liverpool was extremely productive and about 40 co-workers—PhD students (including the present author), postdoctoral researchers and academic visitors—passed through his laboratories during this period. These included some colleagues who went on to senior positions in the UK pharmaceutical industry, such as John Dixon (Fisons/Astra/AstraZeneca), Mike Williams (Pfizer) and Frank King (Beechams/SmithKlineBeecham/GlaxoSmithKline). Research continued to focus on unusual ring systems and reactive intermediates. Rees was particularly interested in the extrusion of dinitrogen from heterocyclic rings, often employing the technique of flash vacuum pyrolysis, and used this to great effect. Thus, with Dick Storr he was able to access the elusive azacyclobutadiene ring system (18), another highly reactive, antiaromatic ring compound whose structure was of much interest to theoreticians at the time. The Liverpool group was able to isolate the ring system at low temperature and intercept it in chemical reactions. He also continued to explore the generation and reactions of reactive nitrene intermediates, including the photochemical cleavage of S,N-ylides (sulphimides) (20), thereby starting the interest in sulphur–nitrogen chemistry that was to occupy his later career (see below). The last piece of work from the Liverpool era was the
generation of a completely new aromatic ring system, a carbocyclic, tricyclic [10]-annulene (25), and although this represented a departure from heterocyclic chemistry, as will be explained later, the project was firmly rooted in the chemistry of nitrogen heterocycles.

With a larger research group in Liverpool, Charles was always able to engender a fantastic spirit within the group, often aided and abetted by his wife, Tricia. The annual bonfire parties on Formby beach, the summer picnics in north Wales, and the generous entertainment at the Rees family home in West Kirby on the Wirral Peninsula will be recalled by many. He also worked extremely hard and did much to maintain the high profile of organic chemistry at Liverpool. He was always thinking about chemistry, and after each weekend or trip to a conference he would return with pages of ideas—occasionally overwhelming for inexperienced PhD students. Thankfully, Tom Gilchrist and Dick Storr were on hand with valuable advice, and students were able to prioritize the really good ideas (of which there were many).

IMPERIAL COLLEGE, LONDON, 1978–2006

In 1978 Sir Derek Barton left Imperial College, London, to take up the directorship of the Institut de Chimie des Substances Naturelles at Gif-sur-Yvette, France. Charles Rees was appointed to the vacant Hofmann Chair, thereby returning to the University of London, where he had started his academic career some 23 years earlier, and also following on from Derek Barton for the second time in his career. He remained at Imperial College for the remainder of his career, officially retiring in 1993, but continuing to work as hard as ever as an emeritus professor.

The chemistry that had started to blossom in Liverpool continued to thrive in London. One of the early projects was the exploitation of his discovery, towards the end of his Liverpool days, of an entirely new aromatic system—tricyclic [10]-annulenes—reflecting Charles’s love of new ring systems (26). In the 1980s Charles, who by this time had been joined by the present author as a young lecturer, extensively investigated the use of nitrene intermediates in the synthesis of heterocyclic compounds. The simple thermal decomposition of azidocinnamates to give, via reactive intermediates (vinyl nitrenes and azirines), important heterocycles such as indoles in high yield has since become standard methodology. The indole ring is an important constituent of many natural products, neurotransmitters and synthetic drugs. Possibly against his instincts, Charles was persuaded by the present author that this reaction could be used to great effect in the synthesis of biologically important naturally occurring compounds. The 1983 synthesis of coenzyme PQQ using this methodology (28) was followed by routes to other natural products—including phosphodiesterase inhibitors (36)—and culminated in a formal synthesis of the potent anticancer agent CC-1065 in which all six heterocyclic ring nitrogen atoms were incorporated by nitrene cyclizations (51). The main scientific feature of Charles’s later years at Imperial was the work on heterocyclic systems rich in sulphur and nitrogen. This work, from its beginnings in the early 1980s that involved the reaction of tetrasulphur tetranitride (S₄N₄) with organic substrates (30), an area that Barton himself had previously dabbled in, uncovered a number of totally new heterocyclic ring systems (40). Charles’s incisive mind brought a fresh new approach to an area of organic chemistry that was once regarded as the province of inorganic chemists.

Some 80 co-workers and academic visitors passed through the Rees laboratories in the 15-year period 1978–93 and made major contributions to his research programmes. It was the
research group that organized a celebration to mark his 60th birthday on 15 October 1987, an afternoon scientific symposium and a dinner attended by more than 70 colleagues and former co-workers. Needless to say, Charles was in top form and delivered a brilliant after-dinner speech. The same date is also remembered as the night that a hurricane struck the southeast of England, and those of us who staggered home after an excellent dinner recall that it did seem a bit breezy! Similar celebrations were held five years later, when the Royal Society of Chemistry organized a symposium in honour of Charles’s 65th birthday. The fact that this one-day meeting was attended by more than 350 people attests to Charles’s standing in the chemical community.

Charles’s official retirement in 1993 made little difference to his research output. As emeritus professor he continued his work on sulphur–nitrogen-containing ring systems, and a further 100 publications emerged over the next decade. Much of this work was performed in collaboration with French and Russian groups, whose leaders had spent time at Imperial College and then continued the projects in their own laboratories.

**Scientific work**

Charles Rees’s scientific work was rooted in heterocyclic chemistry—the study of rings made up of carbon, nitrogen, oxygen and sulphur atoms—a subject of immense importance given that many medicines, agrochemicals, dyes and reprographic materials, as well as a very large number of naturally occurring compounds, including the DNA bases, are heterocyclic molecules. His curiosity-driven approach, based on a sound understanding of reaction mechanisms, was evident throughout his career. The early work on reactive intermediates was followed by detailed studies of nitrenes and the unusual ring systems that resulted from their reactions. This led to the application of such reactions in the synthesis of biologically active natural products, and, unexpectedly, to a new class of carbocyclic aromatic compounds. The final chapter in Rees’s scientific work was an extended study of sulphur–nitrogen compounds that led to the discovery of several novel aromatic ring systems.

*The early days—reactive intermediates: carbenes, nitrenes and aryynes*

Charles Rees’s scientific work was dominated by two overarching themes: (i) reactive intermediates, in particular neutral, electron-deficient species such as carbenes, nitrenes and aryynes, and (ii) unusual ring systems, particularly strained rings and novel aromatic systems.

His interest in reactive intermediates started with his first PhD student at King’s College. The reaction of dichlorocarbene with pyrroles and indoles was known, but Rees and Smithen were able to correct an earlier misunderstanding of the reaction. Specifically they showed that in the reaction of dichlorocarbene with 2,3-dimethylindole 1, the ring expansion product 4 was formed directly from the initial dichlorocarbene adduct 3 and not from the 3-dichloromethylindolenine 2 (scheme 1) (4).

Rees’s interest in aryne intermediates arose out of collaborative work with Donald Hey on the decomposition of aryldiazonium salts, in which it was suspected that an aryne intermediate might be involved. Indeed, Rees was able to confirm the structure of an unusual spiro-dienone product in one such reaction using an aryne-based route; this was one of the first uses of an aryne intermediate in synthesis. Thus, both of the isomeric bromides 5 and 6 were converted into the spirocyclic dienone lactam 7 via the same benzyne intermediate (scheme 2) (3).
However, it was his brilliantly conceived oxidation of 1-aminobenzotriazole 8 leading to benzyne that attracted worldwide attention. Under these conditions, benzyne is generated in high yield, by fragmentation of the nitrene, with the loss of two molecules of dinitrogen, and rapidly dimerizes to biphenylene (5). Rees also showed that the Diels–Alder reaction of benzyne with E,E-hexa-2,4-diene was stereospecific (scheme 3) (10).

Rees and Gilchrist also attempted to intercept benzyne as a transition-metal complex, but all attempts to isolate a Pt(0) complex failed (15). Extending the methodology, Rees and Storr were able to generate 1,8-didehydronaphthalene 10, a meta-benzyne, by the oxidation of 1-aminonaphthotriazine 9 in benzene (scheme 4). In the absence of an added trap, fluoranthene was formed by reaction with the benzene solvent (12). However, it was the electronic structure of 10 that attracted much interest from theoreticians, including Roald
Hoffmann (ForMemRS 1984). The aryne is much more reactive than benzyne and can lead to the formation of radical abstraction products. The 1,2-addition to Z- and E-1,2-dichloroethene was stereospecific, suggesting that the intermediate had a singlet diradical structure (13).

### N-Aminonitrenes and small rings

The key to the successful generation of aryne intermediates was the oxidation of N-amino compounds to give aminonitrenes that rapidly fragmented by the loss of dinitrogen, as in the formation of benzyne from 8. Other nitrenes did not fragment, but they could be intercepted in addition reactions; the main substrates for such reactions were N-aminobenzoxazolone 11 and N-aminophthalimide 12. It is noted, in passing, that subsequent work by Atkinson, a former Rees postdoctoral researcher, has suggested that the true intermediate in these lead tetraacetate oxidations of N-amino compounds is an unstable N-acetoxyamino species rather than a free nitrene, but this does not detract from Rees’s early contributions to this field.

Oxidations of N-amino compounds 11 and 12 using lead tetraacetate in the presence of alkenes gave the corresponding aziridines 13 in good yield. The reactions were more than 95% stereospecific when Z- and E-but-2-enes were used, suggesting that they proceeded via cycloadditions of singlet aminonitrenes (scheme 5) (6, 14).

The nitrenes could also be trapped by reaction with dimethylsulphoxide to give sulphoximines 14 (scheme 5) (17), which could be used to regenerate the nitrenes upon irradiation. When oxidation of the N-amino compounds was performed in the presence of 1,3-dienes, 1,2-addition occurred to give vinylaziridines 15 (6). Subsequently, Rees was the first to report the rearrangement of such vinylaziridines to pyrrolines 16 upon heating (scheme 6) (7).

Additions of nitrenes to alkynes should in principle lead to the formation of 1H-azirines, but the reaction had never been observed because of the antiaromatic nature of such three-membered rings. Rees was the first to describe the addition of the N-aminonitrene from N-aminophthalimide 12 to alkynes to give 1H-azirines 17 that underwent spontaneous rearrangement to the 2H-isomers (9, 19). Thus, oxidation of 12 in the presence of hex-3-yne gave the 2H-azirine 18 (scheme 7).
The third type of \(N\)-aminonitrenes investigated by Rees and co-workers were those that underwent rearrangement rather than fragmentation or addition reactions. For example, oxidation of both 1-amino and 2-amino indazoles 19 and 20 resulted in the almost quantitative formation of benzo-1,2,3-triazines 21 (scheme 8) (16).

Concurrent with the work on azirines, Rees was also interested in other small, highly strained rings such as benzocyclopropenone 24. This molecule, suggested as an intermediate in the thermal fragmentation of phthalic anhydride, was of interest because of its possible homo-aromatic character. Again, the route relied on the oxidation of an \(N\)-amino compound, benzotriazinone, to give a fragmenting \(N\)-aminonitrene. Both 6-substituted and 7-substituted benzotriazinones 22 and 23 led to the same intermediate that underwent nucleophilic ring opening in both directions (scheme 9) (11).

Another reactive ring system to be generated for the first time in the Rees laboratory was azete, a nitrogen analogue of the antiaromatic cyclobutadiene. The molecule was stabilized by the presence of an additional benzene ring and was generated by vapour-phase flash vacuum pyrolysis of 4-phenylbenzo-1,2,3-triazine 25, itself prepared by a nitrene route (scheme 8), in which any reactive species were immediately trapped on a cold (−80 °C) surface. When the pyrolysis was conducted at above 500 °C, only biphenylene and benzonitrile were isolated (scheme 10). At lower temperatures (420–450 °C), a red solid, 2-phenylbenzazete 26, was isolated on the cold surface. On warming, the azete dimerized...
but could be intercepted in cycloaddition reactions (scheme 10) (18). Subsequently it was found that the fragmentation of 4-arylbenzotriazines could also be conducted under photochemical conditions (21).

**Nitrene cyclizations**

In continuation of earlier work using sulphoximines as nitrene precursors (scheme 5), Rees and colleagues investigated sulphimides, nitrogen–sulphur ylides, as alternative nitrene precursors. In work performed by the present author, \(N\)-arylimidoyl sulphimides 27 were found to give benzimidazoles 29 upon irradiation (scheme 11) (20), presumably via the corresponding imidoylnitrene 28. Upon heating above 150 °C, the sulphimides 27 gave, in addition to benzimidazoles 29, quinazolines 30 that incorporated one carbon from the \(S\)-methyl group. Needless to say, such a mechanistic puzzle intrigued Rees and it was not long before a plausible mechanism emerged (scheme 11).

Some years later, Rees became interested in cyclic sulphimides as examples of the rare azathiabenzenes. The first examples were reported in the thiophene series whereby heating the azide 31 in toluene delivered the desired cyclic ylide 32 as orange-red crystals (scheme 12) (42). X-ray crystallography confirmed the cyclic ylide structure rather than a delocalized azathiabenzene. On heating further, these reactive ring systems rearranged by a \([1,4]\)-shift to carbon to give the fused thiazines 33 (scheme 12) (27, 43). This theme of unusual sulphur–nitrogen rings would eventually dominate Rees’s later research career.
After the successful synthesis of benzimidazoles 29 from sulphimides 27, Rees posed the question of what would happen if the cyclization of the nitrene intermediate were blocked by a methyl group. The experiments were duly performed and gave a highly unusual product, the cyclopentapyrimidine 35 in which the benzene ring had somehow contracted to a five-membered ring. Again, Rees and Tom Gilchrist were quick on the draw with a plausible mechanism (scheme 13) (23). The key to the mechanism was the intermediacy of the 3aH-benzimidazole 34, formed by nitrene cyclization, followed by a series of [1,5]-sigmatropic shifts.

Although the yields of cyclopentapyrimidine 35 were modest, the reaction focused Rees’s attention on intermediates such as the 3aH-benzimidazole 34 in which the conjugated system is interrupted by an sp³-carbon at the ring junction position. Following on from the interesting results obtained from the generation and reactions of imidoylnitrenes 28 (schemes 11 and 13), an obvious question was to address the corresponding vinylnitrenes 37. It was already known from the literature that nitrenes 37 could be generated by solution thermolysis of readily available azidocinnamates 36, and in the absence of interfering substituents these readily cyclized to indoles 38 (scheme 14). Rees’s first contribution in this area was to introduce ortho-methyl blocking groups to emulate the earlier reactions of blocked imidoylnitrenes.
Charles Wayne Rees

However, the vinylnitrenes \(R=2,4,6\)-trimethyl) behaved differently and inserted into the methyl group to give, after aerial oxidation, isoquinoline \(39\) (scheme 14) \((22, 34)\).

The natural products excursion

Similar azidocinnamates to those described above were employed in an alternative isoquinoline synthesis whereby an \textit{ortho}-acyl group \(40\) participated in an intramolecular aza-Wittig reaction (scheme 15a) \((48)\). The reaction was subsequently used in a synthesis of the alkaloid siamine \(43\). Thus, the azidocinnamate \(41\) underwent clean cyclization upon treatment with triethyl phosphite, leading to the isoquinoline \(42\) (94%), which was then converted into siamine (scheme 15b) \((49)\).

As noted above, unfettered vinylnitrenes usually cyclize to give indoles in good yield (scheme 14). This conversion was used to good effect by Rees in a synthesis of coenzyme PQQ \(46\) (scheme 16) \((28)\). Azidocinnamate \(44\), readily prepared from the corresponding benzaldehyde, cyclized with a loss of nitrogen upon heating in xylene to give the indole \(45\), which was subsequently converted into coenzyme PQQ.

This successful route to an important natural product was an early indicator of the utility of reactive intermediates such as nitrenes, carbenes and arynes in the synthesis of complex target molecules, a topic that is still of interest today. Further examples followed from the Rees laboratory, including syntheses of the phosphodiesterase inhibitors PDE-I and PDE-II, and a formal synthesis of the potent antitumour agent CC-1065. The syntheses of PDE-I \(51\) and PDE-II \(52\) began with a nitrene cyclization to give indole \(48\) in quantitative yield from azide \(47\). Conversion of the bromide \(48\) into azide \(49\) in five steps set the stage for a second nitrene cyclization in 97% yield (scheme 17). Pyrroloindole \(50\) was subsequently converted into PDE-I and PDE-II \((36)\).

The syntheses of pyrroloindoles PDE-I and PDE-II paved the way for a formal synthesis of the more complex natural product CC-1065. First, the left-hand pyrroloindole \(57\) was prepared,
again using two nitrene cyclizations. Vinyl azide 53 was prepared from the corresponding acetophenone and underwent nitrene cyclization to give indole 54 after N-protection. Conversion of the bromide 54 into azide 55 was followed by a second nitrene cyclization to give pyrroloindole 56, which was subsequently converted into the cyclopropapyrroloindole 57 (scheme 18) (41). With all three pyrroloindole fragments available by nitrene cyclization, a formal synthesis of CC-1065 followed (51).
New aromatic systems: \([10\text{-}\text{annulenes}]\)

The cyclization of ortho-blocked imidoylnitrenes to give the 3a\(H\)-benzimidazole 34 (scheme 13) prompted Rees to investigate the all-carbon analogue, the 3a\(H\)-indene ring system, with the conjugated system interrupted by a methyl group at the ring junction. The synthesis of this reactive tetratria started with the reductive alkylation of 1-indanone to give diene 58, converted into the trienone 59 (scheme 19). Enolization followed by \(O\)-alkylation or \(O\)-silylation gave the unstable 3a\(H\)-indene 60. The 3a\(H\)-indene 60 readily underwent an extended \([8+2]\)-cycloaddition with dimethyl acetylenedicarboxylate to give adduct 61. Likewise, addition of the ketene equivalent, 2-chloroacryloyl chloride, followed by further transformations, gave the tricyclic ketone 62 (scheme 19) (24).

However, the main interest in this chemistry lay not in the interrupted conjugated system 60 but in the subsequent reactions of its cycloadducts 61 and 62. It was quickly realized that the elimination of methanol from adduct 61 would result in a tricyclic system with a fully conjugated periphery. This reaction proved straightforward in practice, and the resulting cyclopent[cd]indene 63 was formed in good yield (scheme 20). Its NMR spectrum was fully consistent with a diamagnetic ring current with the central methyl group having an upfield signal at \(\delta -1.34\). Hence, a new aromatic system, a tricyclic [10]-annulene, was born (25, 29).

The unsubstituted [10]-annulene 64 was readily obtained from the diester 63 by reduction to the dialdehyde and double decarbonylation. Alternatively, annulene 64 could also be prepared from the ketone cycloadduct 62 (26, 31).

With the parent ring system 64 in hand, the chemical properties of this new aromatic system could be evaluated. Annulene 64 is rapidly hydrogenated to give the fully saturated hydrocarbon 65, the ease of reduction of an aromatic system probably reflecting the ring strain in the tricyclic annulene. On heating, annulene 64 underwent rearrangement by a [1,5]-sigmatropic shift of the methyl group to give the isomer 66. On reaction with electrophiles, the annulene 64 undergoes classical aromatic electrophilic substitution reactions, and although nitration gave a mixture of all four possible mononitro compounds, acetylation and formylation were much more selective (scheme 20) (32).

Over the next five years several other novel tricyclic [10]-annulenes emerged from the Rees laboratory (scheme 21). These included the keto–enol derivatives 67 and 68 with the 2-isomer 67 existing entirely in the keto-form and the 5-isomer 68 entirely as the phenol (37). Different substituents were introduced into the central 7b-position, including ethyl 69a, isopropyl 69b, and...
and benzyl $69c$ (38, 39). Finally the benzo-fused derivative $70$ and the quinone $71$ were also prepared (33), thereby adding to the range of novel aromatic 10π-systems to study.

New aromatic systems: S,N-rings

The later part of Rees’s scientific career was dominated by another series of novel aromatic systems, but of a very different nature, namely those that are rich in nitrogen and sulphur atoms (scheme 22). Initiated by curiosity-driven research on the reactions of tetrasulphur tetrinitride ($S_4N_4$), Rees and Daley reinvestigated the reaction of $S_4N_4$ with dimethyl acetylenedicarboxylate. Two new products were obtained and were shown by X-ray crystallography to be the novel ring systems $72$ and $73$, trithiadiazepines and trithiatriazepines (30, 44). Similar reaction with diphenylacetylene and phenylacetylene gave further novel S,N-ring systems $74$ and $75$ respectively and ushered in a complete new area of research (45).

Further reactions of organic molecules with $S_4N_4$ followed, giving rise to other unusual S,N-ring systems (scheme 23). Thus reaction with phenyl vinyl sulphoxide, an ethyne equivalent, gave the tetrathiatetra-azulene $76$ (35), and reaction with highly electron-deficient
alkynes gave trithiadiazepines 77 in good yield (50). Reaction with diazoalkenes gave another new ring system, the trithiadiazines 78 (52).

After the serendipitous formation of such unusual ring systems in the reactions of $S_4N_4$, there next followed a more rational approach. The parent trithiadiazepine 79 could be prepared from bis(trimethylsilyl) sulphurdiimide, $(TMS)_2N=S=N(TMS)_2$ by reaction with bis-sulphenyl chlorides (scheme 24) (46).

With larger quantities of trithiadiazepines available, a more detailed study of their chemistry could follow. The parent ring system 79 underwent standard electrophilic aromatic substitution to give monobromo (or dibromo) 80a and nitro 80b compounds (46, 47). The thallium derivative 80c could also be generated and converted into the iodide, nitrile and carboxylate 80d–f. The bromide 80a underwent facile displacement with amines to give the corresponding amino compounds in good yield (scheme 25) (53). The reaction probably proceeds via the corresponding aryne that can be intercepted in Diels–Alder reactions with furans (54).

The next phase of Rees’s research in the S,N arena involved a detailed study of the reactions of organic substrates with sulphur reagents, starting with the so-called Appel salt (4,5-dichloro-1,2,3-dithiazolium chloride, 81). Much of this later work was performed after Rees’s official retirement, and in collaboration with the group of Thierry Besson in La Rochelle, France, and Oleg Rakitin in Moscow. The salt 81 reacted readily with anilines to give the iminodithiazoles 82 in excellent yield. Heating of 82 resulted in the loss of S and HCl to give the 2-cyanobenzothiazole 83 (scheme 26) (56, 58, 64).
The final chapter involved the reaction of organic compounds with two inorganic reagents—disulphur dichloride (sulphur monochloride; $S_2Cl_2$) and triathiazyl trichloride ($N_3S_3Cl_3$)—that uncovered some extraordinary reactivity. Thus, reaction of indenone oxime with $S_2Cl_2$ gave the dithiazole 84 (scheme 27) (55). Cyclopentanone oxime gave the dithiazole 85, a deep violet 10π-pseudoazulene, whereas extension of the reaction to the bis-oxime 86 gave the cyanoethyl dithiazole 87 and remarkably the pentathiepin 88 (scheme 27) (67).

In the course of the above work, another remarkable result was discovered in the reaction of $S_2Cl_2$ with diisopropylethylamine (Hünig’s base), which gave the bis(dithiolo) thiazine 89 (scheme 28) (57, 66). In this process all 14 isopropyl C–H bonds have been replaced by 10 C–S bonds.

When the reaction was repeated with $N$-isopropyl pyrrolidine, two unexpected products were formed, both of which contained pentathiepin rings. A similar reaction proceeds with $N$-methylpyrrole to give the pentathiepin 90, whereas $N$-methylindole delivers pentathiepin 91 (scheme 29) (71). In another series of astonishing transformations, Rees found that a pentathiepin, the thieno derivative 92, results from the reaction of $S_2Cl_2$ triethylamine, together with the heptathiocane 93 (scheme 29) (70). When treated with triphenylphosphine and dimethyl acetylenedicarboxylate, pentathiepins 90 and 91 are converted into 1,4-dithiins 94 and 95 (scheme 29) (72).
Trithiazyl trichloride 96, a stable moisture-sensitive solid, is known to be in thermal equilibrium with the monomer N≡SCl, and its reactions with organic substrates are often complex. However, Rees was able to show that reactions with furans proceeded smoothly to give isothiazoles 98, possibly via an initial Diels–Alder adduct 97 of the monomer (scheme 30) (59, 60, 68). N-Arylpyrroles behave similarly to give the corresponding isothiazole 99, although N-methylpyrrole gives the unusual tricyclic bis-thiadiazole 100 (scheme 30) (63).

Further reactions of trithiazyl trichloride 96 followed. Reactions with alkenes or alkynes gave 1,2,5-thiadiazoles 101 (61), and with 1,3-dienes to give a range of products including bis-thiadiazole 102 and fused thiazines such as 103 and 104 (scheme 31) (65).

Finally, reaction of 96 with activated methylene compounds gave thiadiazoles 105 (62). Oximes of cyclic ketones, in contrast, gave bis-thiadiazoles 106 (scheme 32) (69).

The highly unusual S,N-containing products resulting from the above reactions often seemed extremely puzzling. As ever, Charles Rees rose to the challenge and was able to rationalize such reactions with insightful mechanistic understanding.
Charles Rees was more than just a distinguished researcher. He was generous with his time and served the scientific community in many ways: he was the President of the Royal Society of Chemistry (RSC) from July 1992 for two years, also serving on its Council and many boards and committees. He was President of the Perkin Division of the RSC and President of the Chemistry Section of the British Association for the Advancement of Science. He also served on the Council of the Royal Society (1977–78) and on several of its committees, including the Rutherford Memorial Committee (1980–86), the Guest Research Fellowship Committee (1983–86), Science in Developing Countries (1989–93), the Physical Sciences Awards Committee (1996–97) and the Wolfson Research Merit Awards Committee (2001–06). In addition, he co-edited three leading reference works with Alan Katritzky FRS, *Comprehensive heterocyclic chemistry I* and *II* (1984 and 1996) (74, 76), and *Comprehensive organic functional group transformations* (1995) (75).

He was also much in demand as a consultant, and in later years as an expert witness in patent cases. His first industrial consultancy started in 1964 at Smith Kline and French (SK&F)
in Welwyn Garden City, and later at their process chemistry site in Tonbridge, in an association that lasted many years. Colleagues from SK&F remember that Charles was always very lively, analytical and thought-provoking, always had something to contribute, and was great value as a consultant. Unusually, he liked to wander around the offices and laboratories to spend time with individual chemists, particularly the younger ones, whom he would encourage with his usual good humour. He also worked with Kodak for many years, where he is remembered as their most popular consultant. According to one Kodak source,

bench chemists vied for time to see him, to talk about problems we may be encountering in our research work, or just to discuss our work in general. He was a very personable and likeable man with an old world charm and charisma rarely found these days. He was always very helpful wherever he could make suggestions that would solve our problems and his chemical memory and recall of literature references was really astonishing.

The achievements listed above say nothing about the man. Not only was he an outstanding scientist, he was a great friend and colleague to many. Sir John Cadogan writes:

In 1951, as students we both held Exhibitions from the British Association for the Advancement of Science which paid our expenses and gave us £10 in hand to attend the Annual Meeting in Edinburgh when the young Prince Philip was that year’s president. The big event for us 10 or so Exhibitioners was the opportunity to be presented to the Prince. A downside was that we needed a dinner jacket that in my case cost £20 from the 50 Shilling Tailors. Although we did actually exchange thoughts about Chemistry, mostly we had a good time driven by his most amusing personality and his wicked sense of humour that persisted and grew throughout his life.

Although subsequently we departed to other universities (in the mid-1960s), we remained in close personal and chemical touch sharing many a platform at conferences, particularly at three Gordon Research Conferences and many meetings of the Royal Society of Chemistry Heterocyclic Group at Grasmere. His lectures and after-dinner speeches at the latter meetings were simply excellent and often hilarious. At these meetings he was first on his feet to comment on and solve mechanistic teasers thrown up by other speakers.

We came close together again on my appointment as Visiting Professor at Imperial College and for 10 years before his death, I occupied an office just across the corridor from his after his so-called ‘retirement’, which is not a good description because he never stopped his research and industrial consultancies, where he was much in demand to the very end. In this respect he believed his role was to break new ground not to bend his own research to short term industrial problems or to conform to a directed programme. Today’s dangerous emphasis on ‘impact’ horrified him. Rather he preferred to use his knowledge derived from undirected, blue sky research to throw light on the problems in industry and medicine. In the latter respect, for example, he was a valued consultant at Smith Kline and French [see above] during the development of the first anti-ulcer drug Cimetidine, which, typically with tongue in cheek, he was fond of saying that this was a bit of organic chemistry which saved the NHS countless millions by putting large numbers of ulcer surgeons out of work.

Throughout his academic career, Charles Rees was ably supported by his wife of over 50 years, Tricia; their kindness and generous hospitality to all, particularly to young PhD students, was appreciated and remembered by dozens of researchers. The tradition of group picnics continued in London, although the venues were mostly city parks rather than the more spectacular surrounds of north Wales. Visiting scientists were entertained at their London home, and each year before the January one-day meeting on heterocyclic chemistry Charles would host a champagne reception. Tricia, who for many years was a voluntary guide at London’s Victoria and Albert Museum, still lives in their house in London and often sees their
During his career Charles Rees mentored about 150 young scientists, comprising about 100 PhD students and 50 postdoctoral researchers and visiting scientists. He was a source of inspiration to these young people and instilled in them a desire to pursue curiosity-driven research rather than follow fashion. He would have been truly appalled by the modern attempts to ‘manage’ research by so-called priority areas. He also encouraged his co-workers to think broadly and deeply about their scientific problems. This approach was apparent not only from regular meetings in the laboratory but also in the weekly evening group meetings during which his enthusiasm and optimism were inevitably transmitted to students. He was an irrepressible source of ideas during such meetings, although it has to be said that not quite all of the ideas withstood the closer scrutiny of the following morning. The development of young scientists under Charles’s mentoring was truly impressive. He was always willing to give everybody a chance and was able to take students from less conventional academic backgrounds and convert them into first-class researchers. Former students and colleagues all speak of his positive effect on their careers, and of his infectious enthusiasm. He was a ‘tremendously helpful and supportive supervisor. He seemed to know instinctively when I needed help or advice, or when I could be left alone to find my way through a problem.’ Others recall his unrestrained delight when presented with those ‘oh, so beautiful crystals,’ and the fact that ‘he did not see chemical impossibilities or poor students. He saw only more fun in exploring chemical opportunities and encouraging students to do better.’

Charles Rees was an exceptional person with enormous charm. He had great enthusiasm not only for his subject but also for life in general. He enjoyed music, particularly opera, and was fond of good food and wine. He was also a great raconteur with a razor-sharp wit. Nobody who attended a scientific conference at which he delivered the after-dinner speech will ever forget him. His speeches at the biennial Lakeland International Conference on Heterocyclic Chemistry held in Grasmere were legendary, although his ever-so-slightly irreverent sense of humour may have left the non-native English speakers somewhat bemused. In recognition of his many contributions to the Grasmere Conference a special lectureship was established, formalized in 2008 by the Royal Society of Chemistry’s biennial Charles Rees Award.

All who crossed Charles’s path will remember his enormous charm, his wise advice and his conviviality as a teacher, research mentor, colleague and friend. Many of us count ourselves extremely fortunate to have been associated with him.

**Awards and Honours**

1974 Royal Society of Chemistry Tilden Medal and Lectureship  
Elected Fellow of the Royal Society  
1980 Royal Society of Chemistry Award in Heterocyclic Chemistry  
1981 President, Perkin Division, Royal Society of Chemistry  
1984 Royal Society of Chemistry Pedler Medal and Lectureship  
1992 President, Royal Society of Chemistry  
1994 Honorary DSc, University of Leicester  
1995 International Award in Heterocyclic Chemistry  
CBE in the New Years Honours List
Charles Wayne Rees

1999  Fellowship of King’s College London
2000  Honorary DSc, University of Sunderland.

ACKNOWLEDGEMENTS

I acknowledge several former students and colleagues of Charles Rees for their help in preparing this memoir: Sir John Cadogan FRS, Roger Edgell and Cyril Trust (Old Farnhamians Association), Carey Smithen and John Leonard (King’s College), Tom Gilechrist (King’s College, Leicester, Liverpool), Anthony Roe and Robin Ganellin FRS (Smith Kline & French) and Mike Crawley (Kodak). I am particularly grateful to Charles’s son David Rees for his invaluable help, and also to Gerry Pattenden FRS for helpful comments on the manuscript.

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