

## Reflections on the Life and Works of Sir John W. ('Kappa') Cornforth

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It is true to say that Sir John and Lady Rita Cornforth need no introduction to those familiar with chemistry, and particularly with Australian chemistry, where they occupy a unique position in our chemical heritage.

We know they studied together at the University of Sydney, before they travelled to England in 1939. We know they enjoyed a unique partnership for 70 years. We know many honours were bestowed upon them, particularly to Sir John – whom most of us know simply as 'Kappa' (Fig. 1). However, perhaps what we don't know so well is what Kappa thought about their chemistry.

Luckily, for Kappa's 75th birthday, Bernard Golding inspired Kappa, and many of his colleagues and friends, to write about the Cornforth publications and these were duly published as 'Selected Research Papers with Commentaries'.<sup>[1]</sup> Some of these papers and commentaries I share with you now.

### Early Years

Regarding 'Research on Indoles'<sup>[2]</sup>, Kappa writes in a typically brief and factual manner: 'This is the only paper in which Rita appears under her maiden name. Gordon Hughes and Francis Lions were lecturers at Sydney, both interested in heterocyclic chemistry. Rita did the work with the hydrindones, I did the coumaranone.' David Black added that this paper came out of work during their Honours year, that it was an extension of the Fischer indole synthesis, and that many years later, polycyclic indoles are still actively sought because of their potential for DNA intercalation.

I was lucky to meet Frank Lions in his later years, and remember well the Honours lecture he gave us on 'Hard and Soft Acids and Bases'. Hughes died before I came to Sydney, but I knew the partnership he had with Ern Ritchie. Knowing Lions and Ritchie, and assuming Hughes was similar, I doubt that Rita and Kappa could possibly have had more dedicated mentors. The atmosphere at Sydney was full of enthusiasm, of dedicated and inspiring teachers; the Cornforths could hardly have had a better start. Indeed, over 50 years later I was fortunate to have



**Fig. 1.** John W. Cornforth with a picture of Robert Robinson on the occasion of his Liversidge lecture at the University of Sydney, 15 May 1985. He is known to have said 'Robinson was an argumentative person...and I have known the same thing to be said about myself!' Photo by Damon Ridley.



*Having graduated from The University of Sydney (Ph.D., B.Sc. Hons Class I, and University Medal), Damon Ridley was a Research Fellow in Oxford, before taking up a Lectureship in Chemistry at Imperial College, London. He returned to The University of Sydney in 1972, where he worked for the next 30 years. During this time, he made contributions in many areas: he was Pro-Dean of the Faculty of Science, Chair of the Organic Division of the Royal Australian Chemical Institute, the recipient of an Excellence in Teaching Award, and author of over 150 publications, as well as Captain of the University First XI. Damon is also well known for his work on chemical information retrieval. From 2003 to 2012, he was Head of the Department of Chemistry at Silverbrook Research, which was then Australia's largest private research company. During this period, he was the author of over 50 US patents. During 1978–1979, he was on study leave at the University of Sussex with Professor Sir John Cornforth, with whom he established a lifelong friendship.*

Table 1. Titles of CPS Reports<sup>[6]</sup>

CPS Report	Title
#57	Attempted Synthesis of Penillic Acid. New Syntheses of Iminazoles and Oxazoles
#58	2-Hydroxymethylene-5-propyloxazolone and its Condensation with Penicillamine
#59	4-Hydroxymethylene-2- <i>n</i> -amyloxazolone and its Condensation with Penicillamine. Possible Synthesis in Small Yield of Dihydropenicillin-I or a Stereoisomeride
#69	$\beta,\beta$ -Diethoxyalanine
#100	Further Studies in the Degradation of Penicillin
#423	Oxazoles and Related Topics
#492	Preparation of 2- <i>n</i> -amyl-5-chloro-oxazole-4-aldehyde and its Condensation with Penicillamine
#647, #684, #689	Interim Report from the Dyson Perrins Laboratory and the Sir William Dunn School of Pathology
#691	The Preparation of 2- <i>n</i> -Heptyl-4-methoxymethylene-5-oxazolone and its Condensation with D-Penicillamine

Kappa show me his collection of medals. When he came to showing me his University Medal, Kappa said: 'And here is the first Medal I received. It is one of which I am most proud. It also reminds me very fondly of my days as a student at The University of Sydney.'

One of the earliest Oxford papers, 'Nuclear Methylation of Phenols by Means of Methanolic Sodium Hydroxide'<sup>[3]</sup>, is noteworthy for several reasons.

First, methanolic sodium hydroxide would not be an obvious reagent for methylation of phenols, and indeed in the first paragraph of the article there is a comment: 'Fission into  $\text{Me}^+$ ,  $\text{O}^-$ , and  $\text{Na}^+$ , which might explain the result, appears highly improbable.' (Of course Kappa solved the mystery – first, oxidation of methanol to formaldehyde, followed by reduction of the hydroxymethyl intermediate formed through electrophilic substitution; simple today, but all this had to be worked out in the early 1940s.) Second, the paper was the first bearing the names of the formidable team: J. W. Cornforth, R. H. Cornforth, R. Robinson. Third, Kappa notes: 'The method proved useful to Woodward and Doering in their synthesis of quinine a few years later.' And finally (Kappa), 'This paper contains a mistaken identification which I spotted soon afterwards and which we corrected after further work.'

This last comment resonates with all who knew Kappa, who in addition to having an obsession for detail and for accuracy, also recognised that he did not always get things right. High levels of detail and accuracy were also required of others, and indeed in the 1980s with one of his Ph.D. students (Ming-Hui Du), Kappa discovered a new thermal oxazolone-pyrone rearrangement.<sup>[4]</sup> Well, perhaps, since upon the discovery Kappa reports 'on looking at the literature for any analogous case we uncovered a small portion of a large mess that I felt bound to clean up. There is no villain in this comedy, but plenty of clowns...'

Kappa was not backward in correcting poorly chosen words either. On a walk in the Blue Mountains in the 1980s, we came across a particularly attractive *Banksia ericafolia* in full bloom. I commented that it looked like a pin-cushion. Kappa proffered a more precise term: 'velcro'. We laughed, but for me it was a reminder to try always to be precise, and I further add that anyone who ever heard Kappa lecture would have admired his precise and eloquent presentation. There were relatively few words, but all were excellently chosen.

Arthur Birch, in his note on the selected paper 'The Preparation of  $\beta$ -Tetralone from  $\beta$ -Naphthol and Some Analogous Transformations',<sup>[5]</sup> wrote: 'It was the direct foundation of Cornforth's later total synthesis of steroid hormones. It became an essential ingredient in the mixture of ideas leading eventually

to the total synthesis of 19-norsteroid hormones and the oral contraceptive pills, of which Cornforth could claim to be the Great Grandfather. I register my personal gratitude, and I am sure that of synthetic organic chemists, for his lead into one of the most highly used specific synthetic organic reactions.' 'Great grandfather of the oral contraceptive pills' alone is an interesting thought, but I now wonder whether Birch considered himself the grandfather or father?

Kappa's comments on this paper? 'I was looking in the 1937 *Berichte* for something else, and happened to notice a paper by Windaus. The odd "demethylation" [of a methyl tetralone], caught my eye ... the first experiment with 2-methoxynaphthalene was done a few hours later. The potential usefulness of  $\beta$ -tetralones was already at the back of my mind: this moved it to the front!'

### Penicillin and Oxazoles

Kappa's specific contributions in Oxford during the war years on the penicillin program are published in several CPS (Committee for Penicillin Synthesis) Reports. These reports are available through the UK Government National Archives in the Bodleian Library, Oxford University, but from the Titles of Reports that contain Kappa's name we gain an idea of his contributions. Kappa and Rita are named on all the Reports in Table 1, but other names include E. P. Abraham, W. Baker, C. T. Beer, E. Chain, M. J. S. Dewar, E. Fawaz, and R. Robinson. One can only imagine what these chemists discussed at group meetings or in the laboratory, and under what conditions they worked.

In 'Selected Papers', several commentators (Jean-François Biellman, Sandy McKillop, Otto Meth-Cohn, and Chris Moody) chose 'A New Synthesis of Oxazoles and Iminazoles, Including its Application to the Synthesis of Oxazole'<sup>[7]</sup> as a crucial paper. Kappa's notes included statements: 'This procedure, the first to yield oxazole, was discovered during secret work on penicillin synthesis. It started a love affair with the oxazole.' The 'love affair' with oxazole lasted for 10 years and resulted in several publications.

### Steroid Synthesis in the Laboratory

Leslie Crombie commented on 'Experiments on the Synthesis of Substances Related to the Sterols. Part XLVIII. Synthesis of a Tricyclic Degradation Product of Cholesterol'<sup>[8]</sup>: 'Even before Rosenheim and King had proposed the now accepted steroid structure (1932), Sir Robert Robinson at Oxford had initiated work directed towards the total synthesis of cholesterol. With almost no spectroscopic aids, and many lets and hindrances

unknown to the modern synthetic researcher, such work required a chemist endowed with manipulative, observational, and interpretative skills of the highest order. Allied to this was the requirement for perseverance and determination. In John Cornforth, Robinson found a young collaborator with those qualities.'

About this work, Kappa wrote: 'After the penicillin work, I returned to the sterol synthesis, developing the tetralone preparation. We moved to the National Institute for Medical Research in October 1946 and Charles Harington, our Director who was always very good to us, allowed the collaboration with RR on sterol synthesis to continue. I did the experimental work, some of my best, in the old Hampstead building, a converted hospital, during part of 1947.'

'Observational, interpretative skills of the highest order' and 'some of my best'. Deserved? Well, you have only to look at the details in any description under the experimental section of Kappa's papers. For example, part of the *Resolution of the Hydroxy-ketone (I-A)*<sup>[8]</sup> reads:

'The residue was mixed with an equal volume of light petroleum (b.p. 40–60°), cooled to about –40°, removed from the cooling bath, and scratched. The mass soon became solid; it was taken up in boiling light petroleum (15–20 c.c.) and set aside at 0°. Next day the crystals (7.0 g; fluffy needles) were collected ...'

and then, a little later:

'The crude product was recrystallized, first from ethyl acetate-light petroleum and then from large volumes of light petroleum (b.p. 40–60°); the light petroleum solutions were concentrated to half their bulk before crystallisation was allowed to take place. In this way mixed crops of slender colourless needles and larger, slightly yellow prisms were obtained; the prisms were picked out where possible, and advantage was also taken of their slower rate of dissolution in light petroleum.'

The care and the detail with which he conducted his experiments are obvious. In 1978–79, I worked on the next bench to Kappa. He usually was in the laboratory. He would carry out his experiments with the greatest of care. A swirl of the flask here, a careful note made in his laboratory book, keen observation of the shapes of the crystals, every now and again a sniff of the flask, depth of thought. The best!

In around 10 papers, he and Robinson described solutions to all the key problems associated with cholesterol synthesis in the chemical laboratory, and a lot of this work was summed up in 'Total Synthesis of Steroids'.<sup>[9]</sup>

### Steroid Synthesis in Nature

However, Kappa pondered how nature did it, and to understand this it was first necessary to break cholesterol down, atom by atom.

On 'Studies on the Biosynthesis of Cholesterol. 4. Degradation of Rings C and D'<sup>[10]</sup> Kappa wrote: 'Irene Gore (a fellow Australian), George Popják and I shared the experimental work for this paper. The problem of taking the sterol carbon skeleton to pieces, atom by atom, was immensely stimulating with plenty of novel problems. Effectively, we proved the structure of cholesterol all over again by degradation. The determination of the absolute configuration of cholesterol<sup>[11]</sup> was a useful spin-off.'

Fast-forward some 20 years and 35 joint papers later, and there is Kappa delivering his Nobel Lecture: 'Asymmetry and Enzyme Action'.<sup>[12]</sup>

We can all look up the papers that led to this momentous award, and indeed I leave you to do just that. Instead, I share with you a couple of Kappa's insights.

On 'Studies on the Biosynthesis of Cholesterol',<sup>[13]</sup> Kappa wrote: 'I had to visit Oxford some time during 1958. Unprogrammed changes of train are an occupational hazard for deaf people travelling alone, and in due course I found myself on Swindon platform, with two hours to wait. Having nothing to read, I began to think; and before the return train arrived I had the plan for using labeled mevalonic acid, instead of labeled squalene, to solve the problem of methyl rearrangement. The ensuing work stretched us all – I never knew an experiment that needed so much innovation.'

We know Kappa had nothing to read, but did he have something to write with? If he did, then I wonder on what he wrote. Was it perhaps on the back of the train ticket? Or was the entire plan formulated and worked through mentally? If so, one can imagine the complexity of thought involved – but the synthesis of complex thoughts was something Kappa had clearly displayed at an early age in another of his passions: chess.<sup>[14]</sup>

About 'Substrate Stereochemistry in Squalene Biosynthesis',<sup>[15]</sup> Kappa wrote simply: 'We delivered this lecture jointly. It marked the first public recognition of the work.' However, Heinz Floss put it in better perspective: 'This ranks by far as my all time favourite. It not only presents a very concise and extremely readable description of a series of beautiful experiments, but it also is virtually a mini-textbook on concepts and techniques in the field of enzyme stereochemistry.'

But not everything went to plan. 'I told the story of the chiral methyl group in my Nobel Prize Lecture. But one thing seems worth adding – our first attempt to make chiral acetic acid was a failure, because we tried to go from acetophenone to acetanilide via a Beckmann rearrangement of the oxime. An extensive exchange of methyl hydrogen during the rearrangement unexpectedly destroyed the chirality.' The successful experiments are reported in 'Asymmetric Methyl Groups and the Mechanism of Malate Synthase'<sup>[16]</sup> and the significance of the discovery is explained in 'The Chiral Methyl Group – Its Biochemical Significance',<sup>[17]</sup> the failed Beckmann rearrangement remains only somewhere in Kappa's laboratory book.

### Stereochemistry and Enzymes

Synthesis, asymmetry, and enzymes pre-occupied Kappa (and Popják) for most of the 1960s and 1970s, and many publications followed. The stereochemistries of reactions involving squalene synthetase, squalene oxidocyclase, malate synthase, succinate dehydrogenase, *re*-citrate synthase, *si*-citrate synthase, ATP-citrate cyclase, isopentenyl pyrophosphate isomerase, 3-hydroxy-3-methylglutarylcoenzyme A synthase, hydroxymethylglutaryl-CoA lyase, methylglutaconyl-CoA hydratase, and acetyl-CoA carboxylase were all worked out, and used to good effect in asymmetric syntheses, particularly for isotopically labelled substances.

Kappa wrote extensively on enzymes and stereochemistry, and I had the privilege to hear and then transcribe The Ernest Ritchie Memorial Lecture (1977) titled 'Order and Disorder in Enzymic Systems' for *Chemistry in Australia*.<sup>[18]</sup>



## Synthesis of Enzymes?

In 1975, Kappa moved to the School of Chemistry and Molecular Sciences at the University of Sussex and work there resulted in a series of publications, the first of which was a non-committal ‘Unsymmetrical Biphenyl Synthesis using Copper(1) t-Butoxide’.<sup>[19]</sup> So why was Kappa making unsymmetrical biphenyls?

The concept was to make a ‘synthetic enzyme’ to catalyse the hydration of *trans*-2-butene – hopefully stereoselectively. The enzyme needed to have an acidic group in a hydrophobic cleft. Probably there needed to be a proton shuttle, and of course the catalyst needed chirality.

This was all put together into a substituted dibenzophosphole containing a phosphinic acid as the desired acid group, and with hydrophobic groups flanking the phosphinic acid. The starting points were unsymmetrical biphenyls.

Kappa had to develop new chemistry, and I volunteered to be part of the fun. The chemistry was extremely challenging, but before I describe the result, let me tell a story about potassium.

We needed large quantities of copper(1) t-butoxide which, of course, was made in an inert atmosphere from copper(1) chloride and potassium t-butoxide. And you all know where potassium t-butoxide comes from. In earlier days in Sydney, I dreaded potassium since even the smallest amount of metal always seemed to find enough atmospheric moisture to make things ‘interesting’. Now, in Sussex, we often used 1 mol of potassium at a time.

However, I now had Kappa to demonstrate how to work with potassium. He calmly distilled dioxane (that had been stored over sodium wire) into an open beaker, heated the dioxane to near boiling point and started spooning in the potassium. In a few seconds, the brownish skin on the potassium (potassium oxides and carbonates, of course) slid to the bottom of the beaker and we were left with brilliantly silver, molten potassium balls on top of the hot dioxane. These balls were allowed to cool just a little until they solidified, whereupon we spooned them into warm t-butyl alcohol.

I asked Kappa whether he had ever had a fire. ‘Never,’ he said, ‘but I remember one day years ago when Rita was weighing potassium “the old way”. Her lab coat caught on fire, and I had to employ the fire-extinguisher to douse the flames!’ Ho! Ho! Ho! – well that’s about the best I can describe the often used, extremely likeable, but quite unique Cornforth laugh.

On the last paper in the series: ‘Synthesis of Substituted Dibenzophospholes. Part 8. Synthesis and Resolution of Atropisomers of a 4,6-Diaryldibenzophosphole’,<sup>[20]</sup> Kappa wrote: ‘At the moment this paper is the last report on a piece of unfinished business. We developed methods for making these novel and complex structures which were good, but not quite good enough; so the preparation of candidate catalysts became over-laborious. We need better ways to construct a nucleus on which a large variety of enveloping groups can be tried without too much effort; so far, I have not been able to find such ways, and the best catalyst we have so far gives an unexciting acceleration of olefin hydration...’

## General Lectures

Of course, Kappa published many more articles than the few to which I have referred here, and their omission in no way reflects their lack of importance. I have merely pulled a few pearls out of a collection of gems.

Three publications (among my favourites) resulted from general lectures. They show the depth of thought and feeling which occupied Kappa’s mind, and any quick reflection on Kappa’s life and works necessarily should include them.

The first is ‘Stereochemistry of Life’.<sup>[21]</sup> Kappa summed it up better than anyone:

‘Speculation on the origins of life is a malady to which many chemists have succumbed. In this lecture I was concerned to de-mystify the chirality of life, and especially to emphasize what is still not widely appreciated: that living things during the whole of their lifetimes are continuously being broken down and built anew. It is this effect, I feel, that provides the necessary selection pressure on prebiotic synthesis: where everything is hydrolyzing, only self-replicating molecules can achieve and improve the survival not of themselves, but of their pattern.’

The second is ‘Scientists as Citizens’, which was presented at the Royal Australian Chemical Institute’s 75th Anniversary, which was published in the *Australian Journal of Chemistry*, and which this Journal has made freely available.<sup>[22]</sup> As usual, every word is carefully chosen, and there are many gems that need to be read, and re-read, to fully understand their beauty.

‘It may once have been possible for one human brain to grasp the essentials of all sciences, but not now, not ever again. Even in my own discipline, organic chemistry, I keep having to make assumptions that I have not tested.’

‘What one scientist assumes in a statement by another is that evidence about it has been recorded and can be checked, and that facts incompatible with it have been looked for and not found.’

‘Scientists do not believe; they check.’

‘If we are citizens of anything, we are citizens of the earth.’

‘Scientists are apt to overvalue the importance of new discoveries, and to underrate the extent of their own ignorance ... As citizens they cannot afford to be humble, but as scientists they must be.’

‘Scientists of different disciplines are understanding each other less and less, the search for information outside their own speciality becomes more and more laborious, and cross-fertilization of ideas becomes rarer.’

‘For the scientist, truth is seldom the sudden light that shows new order and beauty; more often, truth is the uncharted rock that sinks his ship in the dark.’

‘If you are a scientist, you realize before long that if the future is in anyone’s hands it is in yours.’

‘Scientists have these dilemmas, that their role as loyal citizens and employees, and respectable members of society, can be in conflict with their science, based as it is on free exchange and recording of information.’

The third is the Sir Robert Price Lecture, 1992, titled ‘The Trouble with Synthesis’ and which also was published in the *Australian Journal of Chemistry*, and which is freely available.<sup>[23]</sup>

‘If you boast too loudly that you can devise a synthesis of anything, those who use your work may relegate *you* to the rank of a technician. It is better to have good reasons of your own for your syntheses – reasons that others accept but do not choose.’

'It is well worth looking at the proposition that chemical synthesis is an art form, needing no justification because it permits self-expression in its creators and produces aesthetic pleasure in those who examine its products.'

As I complete this foreword, I have no idea of the papers that will be included in this special issue. However, I eagerly look forward to reading them. To each of you who contributed, I express many thanks. I also thank you scientists/readers who are also today's custodians of the wonderful field of chemistry that Kappa made so famous.

Those of us who are Australians should feel as proud of our contributions to science, as we feel lucky to be able to travel to work with others and to invite them to our country. Kappa was one of our finest examples, and strongest advocates. Right throughout his career he went out of his way to invite Australians to his laboratories, and his hospitality was superb.

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