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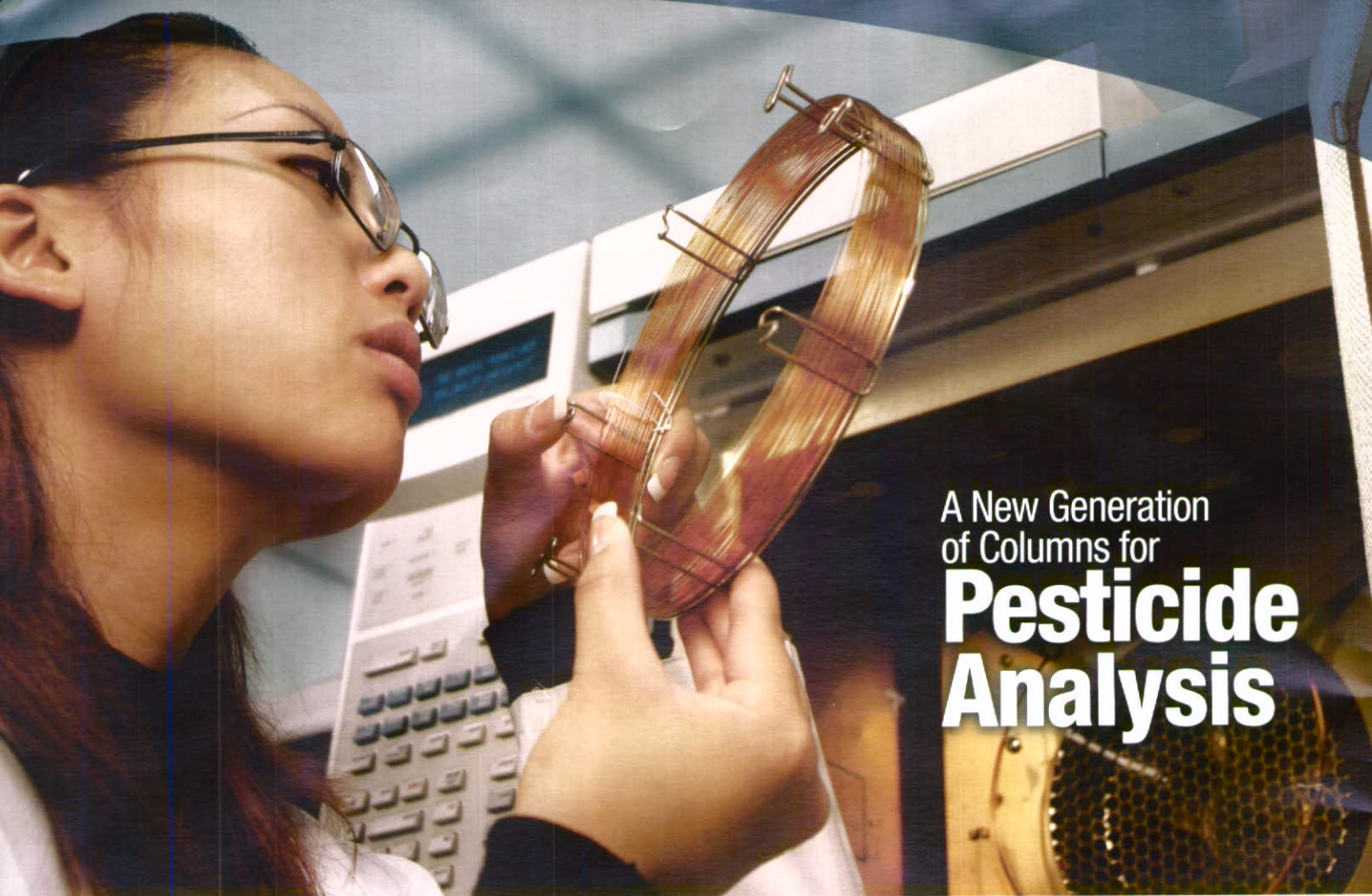
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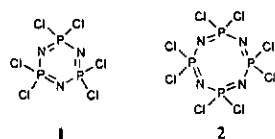
Towards Metal-Rich Molecular Scaffolds

Eric W. Ainscough, Andrew M. Brodie, Carl A. Otter

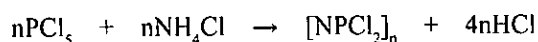
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Introduction to Cyclo- and Polyphosphazenes

Cyclophosphazenes are inorganic heterocyclic rings made up of a valence *unsaturated* skeleton containing the $[N=PR_2]$ repeat unit, where the phosphorus centre is pentavalent and tetra-coordinate, while the nitrogen is trivalent and di-coordinate. The chemistry of the series $[N=PCl_2]_n$ is best developed¹ for the cyclic trimer, $N_3P_3Cl_6$ ($n = 3$) **1** and tetramer, $N_4P_4Cl_8$ ($n = 4$) **2**, which contain six- and eight-membered rings, respectively.

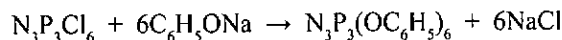


These two cyclic phosphazenes are the major products formed from PCl_5 and NH_4Cl in boiling chlorobenzene² according to the equation:

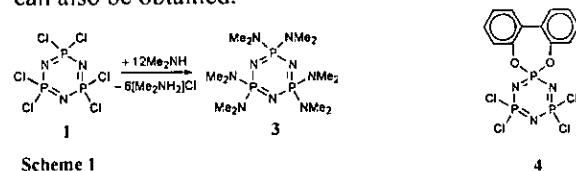


in a quite complex reaction discovered over a century ago. The first intermediate is the salt, $[Cl_3P=N=PCl_3]^+[PCl_6]^-$ and this is followed by other chain-lengthening reactions prior to ring closure. Presumably, as the solvent separates the individual molecules, chain closure to form a ring is favoured over chain growth to form a linear polyphosphazene. Extraction of the light petroleum soluble portion of the product with *c.* H_2SO_4 removes $N_3P_3Cl_6$ because of its greater basicity.

Halogen replacement reactions are the most important ways to increase the diversity of cyclophosphazenes,¹ *e.g.* reactions of $N_3P_3Cl_6$ **1** and $N_4P_4Cl_8$ **2** with Me_2NH lead to the isolation of $N_3P_3(NMe_2)_6$ **3** and $N_4P_4(NMe_2)_8$, respectively (Scheme 1). The HCl produced was removed by the addition of extra base. In a similar way, aryloxycyclophosphazenes may be obtained by use of the sodium salt of the phenol according to the equation:



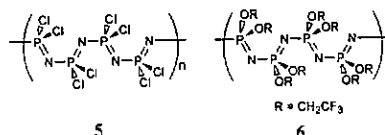
As well as obtaining the fully substituted product in this reaction, the penta-substituted derivative, $N_3P_3(OC_6H_5)_5Cl$ can also be obtained.



If a bifunctional reagent, such as biphenol,³ is used then two of the oxygen atoms will react with one phosphorus to produce a *spirocyclic* product *e.g.* **4**. Other bifunctional compounds, *e.g.* 1-aminopropanol, less commonly give

ansa products where the two ends (NH and O) are attached to two different phosphorus centres.

In the late nineteenth century, the American chemist Stokes found that heating $N_3P_3Cl_6$ to high temperature resulted in the formation of a polymeric crosslinked material $[NPCl_2]_n$ that had poor solubility in common organic solvents and was extremely sensitive to hydrolysis.⁴ This situation persisted until Allcock, Kugel and Valan,⁵ in a series of groundbreaking papers, reported the preparation of the non-crosslinked linear polymer $[NPCl_2]_n$ **5** from heating $N_3P_3Cl_6$ at 250 °C in vacuum (Fig. 1). Careful control over time, temperature, and termination of the reaction before it reached about 70% conversion to polymer were found to be important. The polymer is soluble in tetrahydrofuran when $n > 15,000$ (M_r *ca.* 1.2×10^6 ; polydispersity index > 2). It is proposed that initiation of the ring-opening polymerization occurs by a heterolytic cleavage of a P–Cl bond in $N_3P_3Cl_6$ to generate a phosphazanium ion, which may be attacked by a skeletal nitrogen of another $N_3P_3Cl_6$ causing ring-opening and chain growth. The rubbery product reacts with moisture finally to yield phosphoric acid, ammonia and hydrochloric acid. However, when organic nucleophiles replace the chlorine atoms the P=N skeleton in the product is very stable to hydrolysis. Fibre-type X-ray diffraction studies imply a regular arrangement of substituents along the chain. A so-called *cis-trans-planar* conformation **5** is preferred where steric repulsion between the substituents on the phosphorus atoms is minimized.



Substitution reactions on organic high polymers are often disappointing because of the low reactivity of the side groups, and coiling of the macromolecular chain in solution may retard these reactions relative to their small molecule counterparts. These limitations apply less to substitution reactions of poly(dichlorophosphazene). Surprisingly, even though all the chlorines may not be equal-



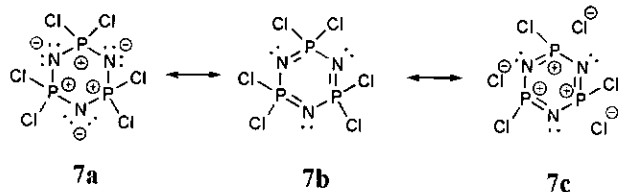
Fig. 1. The preparation of poly(dichlorophosphazene): (a) heating the trimer in vacuum, (b) removing unreacted trimer from the polymer by sublimation.

ly exposed to the nucleophiles, the reactivity of the P-Cl bond is high and macromolecular substitution reactions are usually rapid and complete. Thus it is possible to replace all 30,000 chlorine atoms on $[\text{NPCl}_2]_{15,000}$ with little evidence for cleavage of the main chain, although it can occur with some nucleophiles.⁶ Mixed-substituent polymers can be prepared by sequential reactions of the substrate polymer with two or more different nucleophiles.

A wide range of substituted derivatives are available with varying properties dependent on the nature of the groups attached to the phosphorus atoms.⁷ These include flame resistant materials, elastomers, membranes, biomaterials, hydrogels, and solid ionic conductors. As an example consider $[\text{NP}(\text{OCH}_2\text{CF}_2)_2]_n$ **6**. Opalescent flexible films of it can be produced and it remains flexible to its melting point of 242 °C; it has a low glass transition temperature of -66 °C. The polymer is more water-repellent than Teflon and has high crystallinity which can be enhanced by stretching and orientation to yield strong fibres or films.

The Electronic Structure of Cyclophosphazenes

The bonding in cyclophosphazenes is still the subject of discussion but it is recognised that these compounds are neither *unsaturated* in the sense of non-conjugated alkene species, nor are they *aromatic* like benzene.⁸ The P-N bond in cyclophosphazenes, at around 158 pm, is shorter than expected for a single bond (*ca.* 177 pm) and it tends to be similar around the ring if all the substituents on the phosphorus atoms are identical. While the six-membered rings do not deviate significantly from planarity, the eight-membered analogues can adopt a variety of conformations, *e.g.* planar, saddle, boat, or chair.⁹ Early models for the bonding in the rings used 3d orbitals on the phosphorus atom to achieve electron delocalization *via* $d\pi_p-p\pi_N$ overlap thus resulting in *islands* of electron density over the P-N-P units with nodes at the P centres. However, accurate *ab initio* molecular orbital calculations indicate that the phosphorus 3d orbitals do not play an important role⁸ and show that the P-N bond has significant ionic character as represented by **7a**, but negative hyperconjugation **7c** also plays an important role consistent with the weak cyclic delocalization that would originate from its multiple bond character.



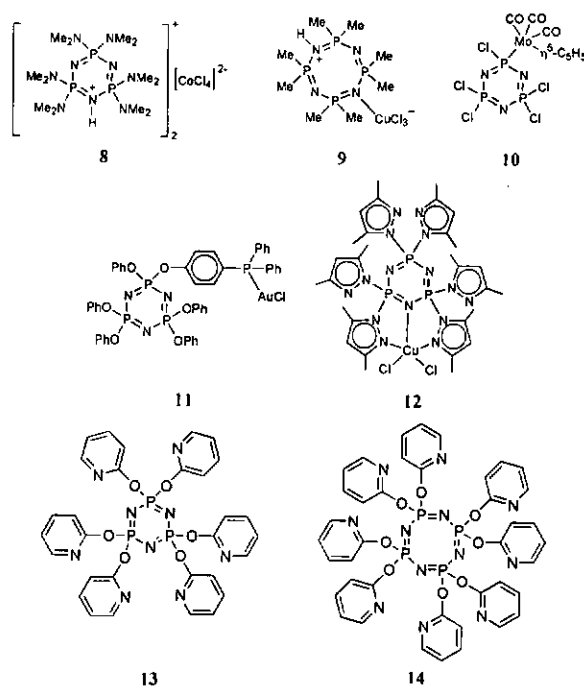
Metal Ion Binding to Cyclophosphazenes

The coordination chemistry of cyclophosphazenes is a rich area although it has been confined, in the main, to systems based on the trimeric, $\text{P}_3\text{N}_3\text{X}_6$, ring.¹⁰ The interaction of metal ions with cyclophosphazenes can be divided into four areas, namely:

- (i) Ionic salts that, strictly speaking, are not coordination compounds as the metal ion species is a counter anion to balance the charge of the phosphazene ring

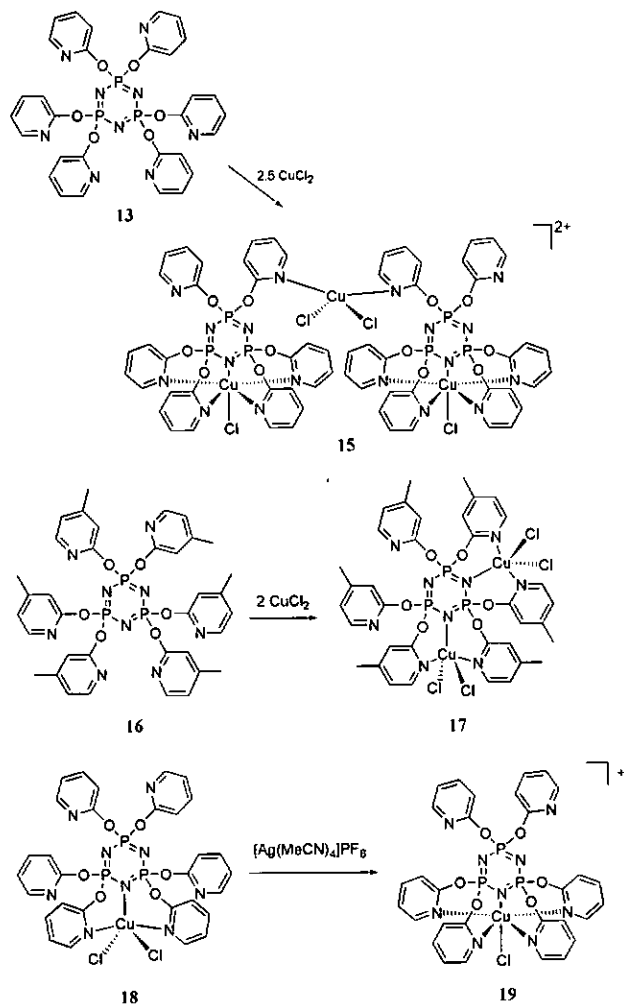
nitrogen, *e.g.* **8**.

- (ii) Coordination by the phosphazene ring nitrogens to a transition metal ion that can occur exclusively, especially if basicity is enhanced by electron releasing substituents (such as Me or NMe₂) on the phosphorus atoms, *e.g.* **9**.
- (iii) Ring phosphorus binding, obtained by nucleophilic substitution reactions involving an organometallic anion with formation of a covalent M-P bond, *e.g.* **10**, cannot occur directly since the ring phosphorus atom is formally pentavalent.
- (iv) Coordination by a pendant group bound to the phosphazene ring phosphorus accounts for the largest group of metal ion derivatives as a great variety of potential donor ligands can be readily attached to the phosphorus *via* nucleophilic substitution. Metal ion binding may be exclusively *via* a donor atom on the pendant group, *e.g.* **11** (where the pendant ligand is a phosphine), or the phosphazene ring nitrogen may also be involved as in pyrazolyl derivative **12**.



The focus of our research has been in this latter area with the preparation of cyclophosphazene ligands designed to provide binding models for metal interactions with appropriate polyphosphazenes. The facile substitution chemistry of the phosphazene PCl_2 groups has allowed us to prepare a variety of different ligand types based on the trimeric and tetrameric cyclic phosphazene platforms. Hence, the $[\text{NPCl}_2]_3$ **1** and $[\text{NPCl}_2]_4$ **2** platforms have been fully substituted with oxypyridine groups to give the ligands **13** and **14**.^{11,12} Both of the ligands **13** and **14** are multimodal and have rich metal ion coordination chemistries. The reaction of **13** with 2.5 equivalents of copper(II) chloride produces the trimetallic dicationic species **15** containing two identical complex moieties linked by a CuCl_2 bridge (Scheme 2).¹³ The formation of the complex anion $[\text{Cu}_2\text{Cl}_6]^{2-}$ accounts for the remaining uncoordinated copper chloride from the reaction. This species also forms when 2 equivalents of CuCl_2 are used in the reaction, but when the methyl-substituted analogue **16** is treated with two equivalents

of CuCl_2 the dimetallic species **17** carrying two copper atoms bound to the phosphazene ring, crystallises preferentially.¹¹ The reaction of **13** with 1 equivalent of CuCl_2 gives the complex **18** containing a five-coordinate copper centre that becomes the six-coordinate cationic complex **19** when one of the chloride ligands is abstracted with silver. Five-coordinate complexes are also observed with Co(II) , Ni(II) and Zn(II) halides, although the use of pyridinoxy arms from opposite sides of the phosphazene ring (non-geminal *trans* coordination) in the Ni(II) and Zn(II) complexes allows the metal ions to lie closer to the plane of the phosphazene ring.¹⁴



Scheme 2

When the metal atoms bind to the phosphazene ring there are small but concerted changes in the P–N bond lengths in the ring. Generally, the P–N bonds flanking the coordinated metal lengthen and the P–N bonds involving the uncoordinated ring nitrogen atoms shorten. For example, in **19** the two flanking P–N bonds are *ca.* 160 pm with other four bonds being somewhat shorter (155–159 pm). Although these differences are small, they are significant and have been observed in a wide range of cyclophosphazene metal complexes. Recently, we have carried out DFT calculations on some of our complexes and find the bond length changes can be explained in terms of the transfer of electron density from bonding P–N orbitals into a 4s orbital on the metal.¹⁵

The self-assembly of discrete dications of **15** encouraged us to examine the coordination chemistry of **18** with silver, with a view to forming supramolecular materials. When

18 is reacted with $[\text{Ag}(\text{MeCN})_4]\text{PF}_6$ a linear coordination polymer **20** forms (Fig. 2) in which an infinite chain of **13** ligands are linked together through phosphazene ring nitrogen atoms by coordination to the silver ions.¹⁶ The hexafluorophosphate counter ions reside in channels between the polymeric columns.

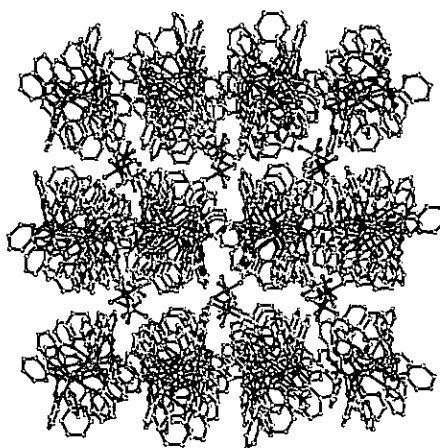
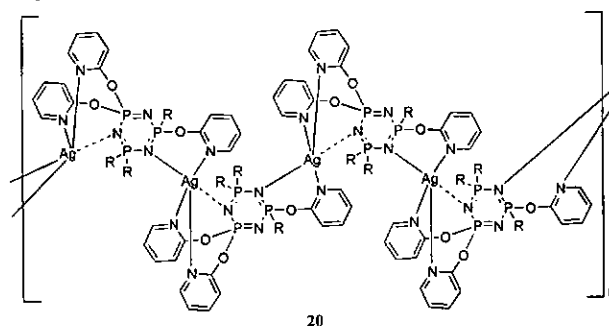
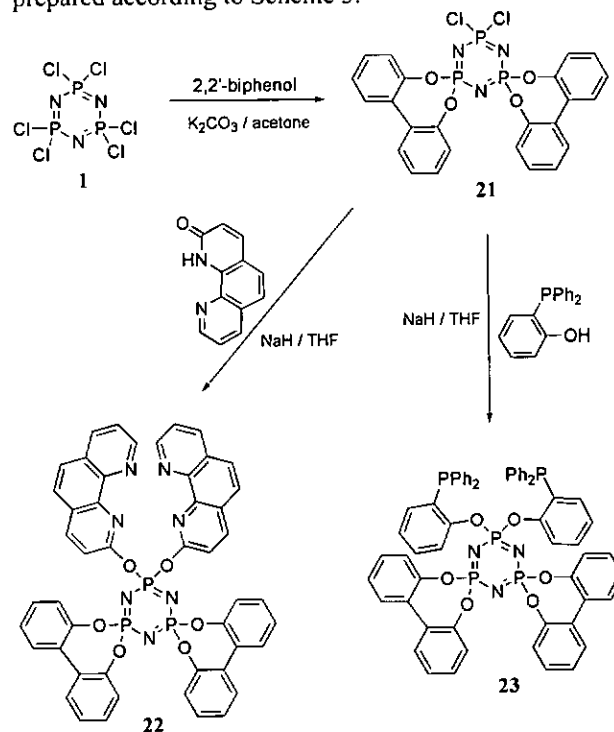


Fig. 2. Silver coordination polymers and a transverse section through the columns of **20** in the crystal structure showing the PF_6^- ions occupying intercolumnar channels.

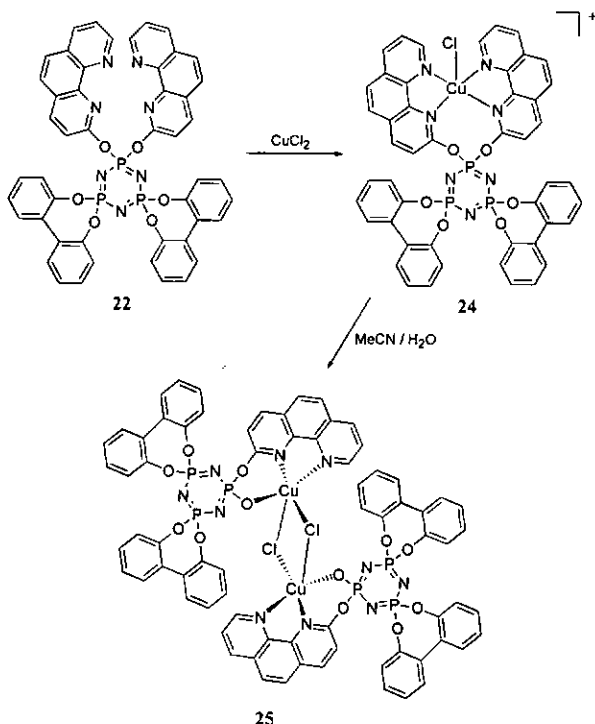


We have developed other ligand types using spirocyclic biphenol groups to block two of the phosphorus atoms in the cyclic trimer. Ligands containing 1,10-phenanthroline¹⁷ and triphenylphosphine¹⁸ derivatives have been prepared according to Scheme 3.

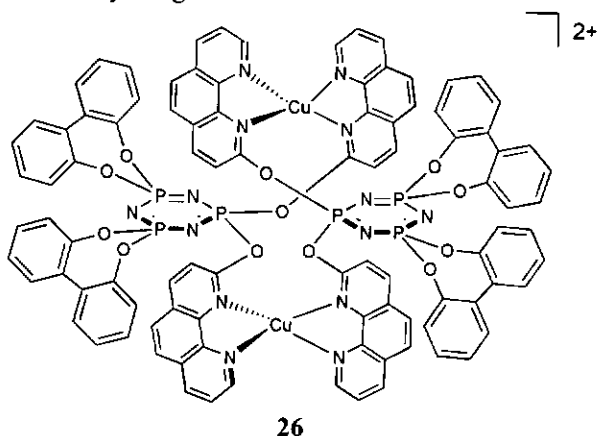


Scheme 3

The ligand **22** can bind as a tetradentate ligand through both phenanthroline ligands and we have prepared five-coordinate adducts such as **24** with copper(II) chloride (Scheme 4). The complex **24** is prone to hydrolysis and if allowed to stand in acetonitrile solution in the presence of adventitious water the complex loses a ligand arm and dimerizes to form **25**.

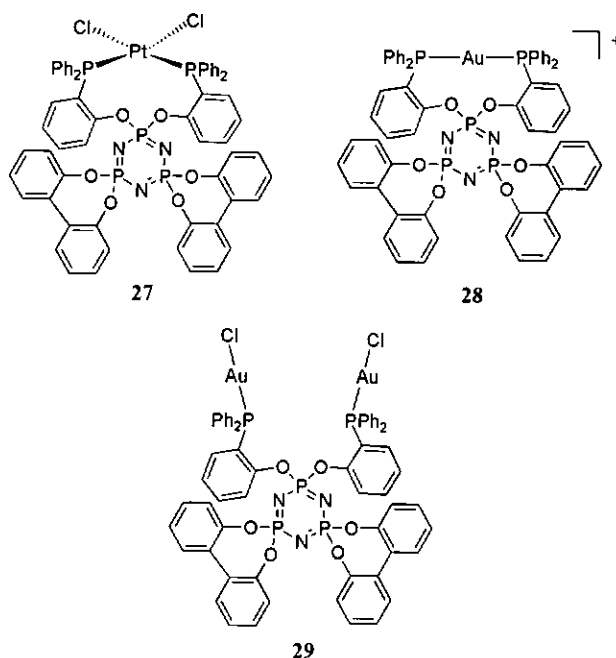


When **22** is reacted with $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ the result is the self assembly of an interesting helical dimetallic species **26**. In the solid state the complex cations form closely packed undulating sheets through various stacking interactions and intermolecular close contacts. The counterions and co-crystallised solvent molecules lie between the sheets and engage in weak H-bonding interactions that effectively bridge the sheets.



The ligand **23** represents a new diphosphine ligand that is capable of a variety of binding modes. *cis*-Bidentate coordination is observed in the platinum(II) chloride complex **27** while linear bidentate or bridging behaviour is found respectively in the gold(I) complexes **28** and **29**.

Our research on the metallo-cyclophosphazene ring compounds is now being extended to the polymeric analogues of such molecules as **13** and **23** hence allowing us to prepare metal-rich polymers.



Acknowledgements

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New Chemical Synthesis Business at NZP

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Introduction

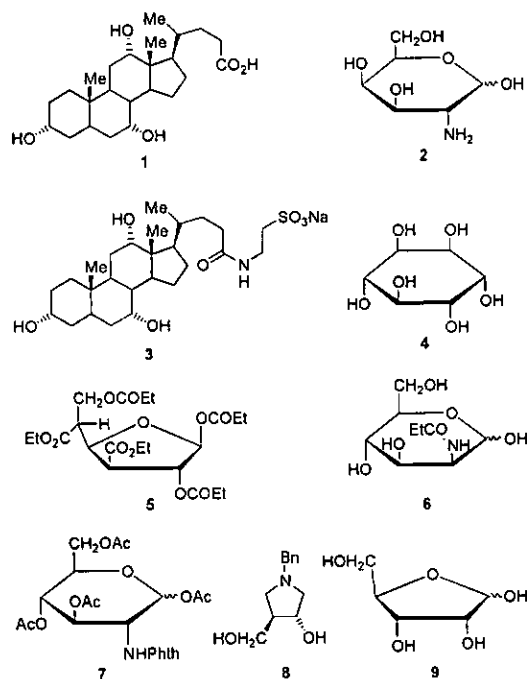
Three years ago I wrote an article for *Chemistry in New Zealand* about New Zealand Pharmaceuticals Ltd (NZP) entitled *Thirty Years On!* Time has flown since then and I am again putting fingers to keyboard to describe NZP: *three years on!*

Recall that NZP is an established, profitable company that primarily manufactures biochemicals from a variety of animal, plant, and marine sources with over 99% of its products exported. The core products are the bile acids in their various forms with the biggest seller continuing to be cholic acid **1** (Chart 1).

Bile acids and other animal-derived products, such as chondroitin sulfate, are sold to the pharmaceuticals and the dietary supplements sectors. Synthetic derivatives of the bile acids continue to interest the biotechnology and pharmaceutical world even though restrictions occur due to regulatory concerns about mammalian viruses. Derivatives are also popular in the over-the-counter (or non-prescription) pharmaceuticals and supplements sectors to ease indigestion and to treat bowel health problems.

Research into bile acids and their derivatives has been undertaken at IRL and its predecessor, Chemistry Division, DSIR. IRL continues to be our primary research provider. We are steadily diversifying from the original focus of animal-derived products by utilizing other raw materials and manufacturing technology. This report describes NZP's growing investment into one of its new business areas, chemical synthesis.

Chart 1



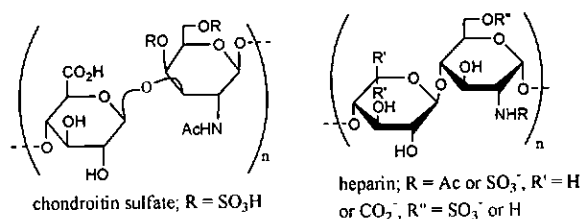
The Lure of Chemical Synthesis

The marketing and technical teams at NZP have known for some years that there is a potential limit to growth for animal-derived products and there is keen interest by the Directors and staff for NZP to continue to develop new skills and grow export receipts. However, while the technical skills and experience are very strongly focused in the extraction business, and while high quality (Good Manufacturing Practice, GMP) products are produced, the demand for animal or plant products in the pharmaceutical market remains limited. It is evident to NZP that the world is moving away from animal-derived materials whenever an opportunity to do so is confirmed. NZP also needed to move on and the biotechnology sector was perceived to hold new opportunities for the Company.

While our primary customer is a Japanese pharmaceutical company, there were clear market signals that we could also supply products to the biotechnology sector. Such products could be small molecules for fermentation and vaccine development, or materials applied to biotechnology methods and active pharmaceutical ingredients (APIs).

It was appropriate to assess what biotechnology offered. The US biotech sector was booming with proteins in heavy demand (but produced by genetically modified organisms); yet, contrary to popular perception, it was apparent that small molecules had not lost their place in the biotech world.

NZP could see opportunities to expand its carbohydrate-based materials business. It already sells several polysaccharides including heparin and chondroitin sulfate and had investigated several more (glycosaminoglycan mixtures, low molecular weight heparin, and marine polysaccharides).



Customers were seeking derivatives of these polysaccharides, especially galactosamine **2**, a derivative of chondroitin sulfate, and other monosaccharides along with several derivatives of the bile acids, e.g. taurocholic acid **3**. Needless to say, staff at NZP were well aware that one of the world's leading and largest carbohydrate research and development groups was located nearby at IRL in Lower Hutt and a good relationship had existed for a long time. Another reason for our optimism was the NZ Government commitment to biotechnology as a key sector develop-

ment area with application falling to NZ Trade and Enterprise (NZTE), a Government Department established in 2003. As a corollary, or as a fortunate coincidence, the rules concerning application of the FRST *Technology for Business Growth Fund* appeared to change; it became much more business focused.

It could be seen that expansion from the relative comfort of extraction and purification technology into a new chemical business area carried significant risks but also a good opportunity for growth in niche manufacturing. The decision to proceed was taken and a more sophisticated synthesis capability targeted. One point of caution for NZP was the knowledge that India, China and emerging Eastern European countries especially, have very strong synthesis capabilities, and that they are very active in promoting these and their low cost structure. NZP saw opportunities built around specific relationships.

Business and Technical Support from NZTE and FRST

While IRL had offered support in our traditional business areas and with polysaccharides, it was not until NZP took a close interest in IRL small molecules—the monosaccharides and their derivatives—that the NZP new business plans really took flight. Products such as *D-chiro*-inositol **4** and pentapropionyl glucofuranose **5** already had established (though irregular) sales, others were developed that remain a useful and steady business for NZP. These early leads encouraged management, and with key support from the NZ Trade and Enterprise (NZTE) client manager, Mark Turney, and his biotechnology Director, Dr Chris Boalch, NZP was encouraged to seek Government funding to match its investment in the development of synthesis business. We were strongly supported by IRL, especially by business manager, Tom Nicolle and carbohydrate science leader, Dr Richard Furneaux. This invigorated effort in co-operation was considered critical to success by our management since NZP saw that it needed IRL as its technical mentor.

The timing was also ideal for developing the NZP/IRL relationship. While NZP began to feel its way in synthesising simple carbohydrate derivatives, Furneaux and his team were establishing larger scale multi-step syntheses of APIs and GMP synthesis up to clinical trials scale in the IRL GlycoSyn facility. The IRL experience with GlycoSyn and larger scale manufacturing, and the support from NZTE, encouraged us to seek and gain a small Growth Service Fund (GSF) grant to support market investigation of carbohydrates in association with IRL. There was also support for NZP to investigate investment in a new synthesis capacity. Arguably, this grant triggered a roll on effect at NZP; the more that was learned, and the more that the sales of simple carbohydrate derivatives grew, the more interested NZP became in developing significant multi-step synthesis capability.

NZTE liked the application for a small GSF grant and invited NZP to apply for a larger one! With continuing support from IRL our application for a larger GSF grant was soon approved, and what started as a planned expan-

sion into synthesis within the pilot plant evolved into a plan to improve the pilot plant *and* build a new synthesis-enabled factory to support the burgeoning growth in sales of carbohydrates.

It was obvious to all parties that the syntheses undertaken at IRL used a quite different technology to traditional NZP business. While NZP has experience in product isolation, purification, chemical analysis, and the preparation of the documentation that GMP entails, it had much less experience in the world of synthesis despite several of its chemists having postdoctoral experience in the field. Syntheses at the 1 g scale are quite a different matter to those in the 10-100 kg range where kinetic, thermodynamic, and workup issues are paramount. The NZP scientists and technology and production teams needed additional training—and fast! Lins Kerr from FRST suggested ways of using the Technology for Business Growth (TBG) scheme for staff recruitment, training, and new technology development. A FRST-TBG contract was awarded to NZP and is proving an ideal vehicle for fast-tracking the education of staff as it ideally complements the GSF contract.

The IRL GlycoSyn facility, established by this time, was operating with a 250 L glass-lined reactor. An obvious solution to the FRST business managers was for NZP to work closely with IRL and to learn the tools of the commercial synthesis trade with carbohydrates and their derivatives as the primary commercial targets. The TBG contract is substantial and is supporting training and technical development at NZP for up to four years with help from IRL and Massey University; there exists the prospect of added support from other NZ synthesis experts. There can be no question that NZP would not have entered this business area so vigorously without the prior existence of the GlycoSyn facility and the combined support of NZTE and the FRST.

Work in Progress

Over 30 years ago, NZP began a *quiet revolution* by adding value to the waste streams of the sheep and beef meat industries. Today, it is happening again. The core products will retain a central platform for NZP business security for many years to come. However, visitors now see a new factory—with the interim name *Specialty Products Facility* (SPF)—under construction (Fig. 1) and due for completion by the end of the year. This factory is partly modelled on the GlycoSyn facility and employs the same consulting engineers used for the construction of GlycoSyn.

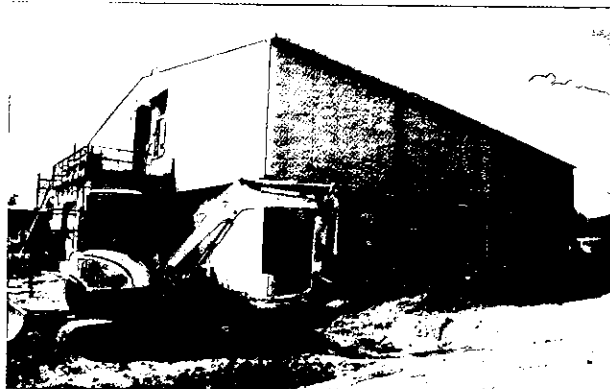


Fig. 1. The SPF under construction, September 2006.

In order to strengthen the highly complementary business functions of GlycoSyn and the SPF, IRL scientists and engineers also reviewed the SPF design to see where value could be added. While the GlycoSyn building is designed for APIs to be used for up to Phase 1 or Phase 2 clinical trials, the NZP SPF is larger. It is designed for production scale GMP manufacture of niche APIs and their intermediates. The SPF will also be able to produce plant or marine extracts that require GMP certification, e.g. botanical drugs as defined by the US FDA. The facility contains a number of suites with dedicated protective clothing change rooms, equipment, and high efficiency particulate airflow.

The NZP pilot plant schedules currently are committed to the manufacture of products that will move directly into the SPF, so from the day the SPF opens it will contribute to our revenue stream. The pilot plants will be reclaimed by the Product Development team and the backlog of products under investigation in the laboratory will quickly grow to the kg scale in the revitalised pilot plants. A new 150 L glass-lined pilot plant reactor, equipped to handle aggressive reaction conditions, is being installed to provide products at a more timely rate than that currently achievable.

While NZP is now attracting new commercial opportunities, it is well recognised that much competition exists in the world; pitfalls are expected and have been included within our commercial models. However, the united strengths of NZP and IRL will soon enable a seamless commercial opportunity (a one-stop shop) to be offered to clients. Provision will include new chemicals from designer chemical synthesis (IRL), to pilot-scale (IRL and NZP) and full-scale API manufacturing (NZP).

The Meaning of Synthesis at NZP

Among the first products to emerge from the NZP synthesis business are conjugated bile acids. Companies have requested these products from NZP ever since it started their commercial extraction. These new products are synthesised from raw materials of animal origin and, while described briefly previously,¹ they have progressed to become a steady business. Patents concerning the synthesis and use of the conjugated bile acids have been around for many years, but it is only recently that growth in the ap-

plication of the compounds has occurred. The conjugated bile acids are used as biological detergents, in drug delivery, vaccine manufacture, adjuvants, and as a component of *biorelevant gastrointestinal media to be used for the dissolution testing of drugs* as recommended by the US FDA.

Another product range is derivatives of mannosamine hydrochloride such as *N*-propanoyl- β -D-mannosamine **6** and other unnatural acylated derivatives which are undergoing intense world-wide scrutiny by research groups investigating *cell surface engineering*. These mannosamine derivatives are incorporated into cell surfaces as modified sialic acids but now with unique biological activities.²



Most products under development cannot be detailed here because of commercial sensitivities, but two representatives of the new NZP capability that are to be manufactured can be described. The first, tetraacetyl-2-deoxy-2-*N*-phthalimido- β -D-glucose **7** is a protected monosaccharide produced in two steps from glucosamine hydrochloride. It is a useful building block for a range of biologically active carbohydrate derivatives. The second, (3*R*,4*R*)-1-*N*-benzyl-3-hydroxy-4-(hydroxymethyl)pyrrolidine **8**, a patented product licensed from IRL, is prepared in nine steps from benzaldehyde! As one can guess from considering the starting material, carbohydrates are not involved, but **8** is a little like ribose **9**. It is a carbohydrate analogue intermediate in the synthesis of one of the IRL key APIs. This modern chemical synthesis is sophisticated with each step a novel synthetic exercise in itself; boranes, enzymes and other sensitive reagents are used at various stages in the process.

Yes, this is NZP's second quiet revolution!

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The 21st Australia and New Zealand Mass Spectrometry Conference (ANZSMS) – Christchurch.

The 21st Australia and New Zealand Society for Mass Spectrometry (ANZSMS) conference is to be held in Christchurch from Sunday 21 through Thursday 25 January 2007. It is the first such conference to be held in NZ for 21 years and the first ever in Christchurch.

The conference is to open with the Morrison Lecture to be delivered by Prof **Richard O'Hair** (University of Melbourne). Other plenary lecturers are Profs **John Yates** of the Scripps Research Institute, California, **Diethard Bohme** (York University, Toronto), **Mike Bowers** (UC-Santa Barbara, California) and **Carlito Lebrilla** (UC-Davis, California). In addition, there will be a great variety of contributed topics with commercial input available and awards made for the best student posters.

For those who are not current ANZSMS members details are available at: www.latrobe.edu.au/anzsms/Membership

On-line registration and full details for all are available from: www.conference.canterbury.ac.nz/anzsms21

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Entering the Dragon - Intellectual Property Rights in China

By Blair Hesp

'Man Bites Dog' was how one American journalist described the first major patent infringement action taken by a Chinese company against an American company. With a population of over 1 billion people China is potentially the single biggest marketplace in the world, but it is also regarded by many as the wild wild west of intellectual property (IP).

One of the biggest, and most publicized, concerns about intellectual property in China is the inability to enforce intellectual property rights and the lack of real deterrents when it comes to penalties. Indeed many companies would consider fines of \$US625-37,500 (maximum \$US62,500) as being a drop in the bucket when compared to the product development costs and the potential returns in the Chinese market alone. Although, it should be noted that current draft changes to Chinese patent legislation intend to raise the levels of fines to up to three-times the profits made by infringers. The resulting general perception when it comes to IP in China is "Why bother, my invention will be copied within seconds of arriving on the market and there is no meaningful enforcement of IP rights in China." While in the past this could be considered a valid point of view, it is worthwhile taking an in-depth look at the history of IP protection in China and the forces driving the current Chinese crackdown on IP infringement.

Firstly, it is not well known that the Chinese patent office only came into existence in 1984. Compare this with the Statute of Monopolies of 1623 of Great Britain (which is still referred to in the current New Zealand Patents Act 1953), and you begin to gain an understanding that intellectual property is a rather new concept to the Chinese. In addition, all inventions and ideas developed by an entity in a communist state were considered to belong to the country and were to be used to the benefit of all citizens of the state. Under this philosophy, private intellectual property rights and protection were not too long ago considered to be a truly foreign concept to the Chinese.

However, with accession to the World Trade Organisation (WTO) in 2001 and a rapidly developing economy the Chinese are awakening to the economic reality that meaningful intellectual property protection and enforcement is essential for the growth and development of China. While there may be a perception that foreign institutions are bullying China into taking this line, Chinese companies themselves are coming under the threat of counterfeiters in their own country destroying their competitive advantage and stifling growth.

Intellectual property infringement and enforcement issues are something that will be weighed up by any chemist looking to gain protection for a new compound internationally, and many will ask "Do you bother with China?" The answer is "yes". Firstly, the current state of intellectual property in China in some respects still reflects the

past, and will not truly reflect the future. For example, patents covering pharmaceutically active compounds were not patentable in China until 1992. Subsequently, many of the well known drugs developed in the 70's and 80's were made generically in China because they were never patented there. At the same time, fears of a lack of enforcement resulted in many companies choosing not to file patents in China, and this impression has certainly not been helped by the recent events surrounding the granting, revocation and reinstatement of Pfizer's Viagra™ patent in China.

Secondly, a patent lasts for 20 years. Twenty years is a long time, and if we look back to 1986 the Chinese patent office had only been open for business for two years. As China takes further measures to align with international standards it is most likely that over the next 20 years substantially more effective IP protection will be available in China. Therefore, the consequences of not obtaining IP protection in China now will most likely be amplified in the future.

Thirdly, many big pharmaceutical companies are setting up their own manufacturing capability in China to tackle this market. This is seen by many as an endorsement of the Chinese market and intellectual property regimes that are in place.

With a burgeoning middle class and impressive growth prospects, the Chinese market has become too big to ignore when it comes to IP protection, and likewise China's IP enforcement issues have become too significant for the Chinese government to ignore. Accordingly, positive developments are occurring in the Chinese IP environment, and it would be prudent for any inventor with an eye to the future to secure IP protection in China.

A reminder: if you have any queries regarding patents, or indeed any form of intellectual property, please direct them to:

Patent Proze
Baldwins
PO Box 852, Wellington
Email: email@baldwins.com



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Understanding Milk Proteins: Lactoferrin and Bone – Current Knowledge and Future Potential

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Composition of Milk

Milk is the quintessential whole food, providing not only immediate energy requirements, but also the vitamins, minerals, cofactors, growth regulators and immune-protective factors required to sustain growth and development in the neonate. Physically, milk can be considered as a colloidal multi-phase system in which the nutritional components are uniquely packaged. The generally hydrophobic casein proteins, which account for 80% of the protein complement in bovine milk, occur as micelles in which high concentrations of calcium phosphate are held in a colloidal matrix. The micelles are maintained in the aqueous phase of milk (serum) and prevented from coalescing by stereochemical hindrance and surface electrostatic repulsions. The milk fat is contained in droplets which are dispersed throughout the serum and encapsulated by the milk fat globule membrane, a complex array of protein and phospholipid. The serum contains lactose, minerals, nucleotides, small organic acids, and the remaining 20% of the milk protein complement. These proteins collectively constitute the whey protein; whey is the aqueous portion of milk remaining after precipitation of the caseins as occurs in cheese-making. Whey proteins occur in a hierarchy of abundance with the major protein, β -lactoglobulin, constituting ~50% of the total, and at the other end of the spectrum, growth factors accounting for only 0.001%.

Whey Protein and Bone Health

Whey is now generally regarded as a functional food which has measurable effects on health outcomes.¹ In particular, the effect of whey and whey components on bone has received increasing attention in recent years. Milk has traditionally been associated with bone through provision of calcium, a *sine qua non* (indispensable need) for bone growth and maintenance; in milk this is delivered through the calcium associated with the casein micelles. However, other components of milk may well contribute to skeletal growth. Whey protein fractions have been shown to have demonstrable effects on indices of bone turnover and biomechanics,² and may have therapeutic application in the treatment of bone disorders such as osteoporosis, in which bone is eroded over time producing fragile and easily fractured skeleton. Osteoporosis is a major cause of morbidity and health expenditure in ageing populations.³ Currently available therapies are limited in their ability to restore bone mass and reduce the incidence of osteoporotic fractures.⁴ Consequently, agents which are anabolic to the skeleton and which induce greater increments in bone density with greater reductions in fracture risk are being sought. In this regard we have made a novel and exciting discovery. Working through Lactopharma Consortium, a joint venture between FoRST and Fonterra aimed at revealing novel

milk bioactivities for potential pharma or nutraceutical applications, we have found that the whey protein lactoferrin is potently anabolic to bone.

Lactoferrin

Lactoferrin occurs in most mammalian milks and is isolated as a salmon-pink powder from bovine milk (Fig. 1). It is a dominant component of whey protein in human breast milk, being present at a concentration of ~2 mg/mL;⁵ in bovine milk it is considered to be a minor protein, at ~0.1 mg/mL accounting for only 1-2% of whey protein and 0.3% of total milk protein.⁶ It is also found in other biological secretions such as tears and saliva, at mucosal surfaces, and it is present in white blood cells (neutrophils). Lactoferrin is a relatively large non-haem, iron binding glycoprotein (~80 kDa) and a member of the transferrin family of iron carriers. It exists as two structurally homologous lobes, each containing two domains that form and enclose an iron-binding site (Fig. 2).⁷ In milk, the iron-binding sites are only partially saturated; the significance of which has yet to be properly understood although it is proposed that lactoferrin can act as an iron scavenger in the gut, thus protecting the tissue against the damaging oxidative activity of free iron.⁸ On the other hand, lactoferrin might well facilitate delivery of iron.⁹ Although an exact role for lactoferrin is yet to be defined, it has been associated with many diverse bioactivities (many of which are iron-independent) including modulation of growth, differentiation and embryogenesis, and in this respect can be considered as pleiotrophic. Lactoferrin is perhaps more widely known for its broad spectrum antimicrobial activity and its immune-modulating properties—hence, it is generally regarded as a natural defence protein in milk.

Effects of Lactoferrin on Bone

The actions of lactoferrin on bone were found to be surprisingly two-fold, both anabolic – serving to build bone mass, and anti-resorptive – acting to prevent bone loss. Healthy bone is maintained by being continually replaced and on average the turnover time is 8 to 10 years. The two main cell types responsible for this are the osteoclasts that break down the old bone and the osteoblasts which form new bone. Skeletal renewal is initiated by the action of the osteoclasts, multi-nucleated macrophage-derived cell-types, on the mineral phase of bone. The cells attach to bone and secrete both acid (H^+ – to dissolve the hydroxyapatite mineral) and enzymes (to break down the collagen network within the mineralized matrix). The osteoblasts then move in and lay down a new matrix. In healthy mature bone, formation keeps pace with resorption; however, in conditions such as osteoporosis the rate of resorption exceeds formation resulting in net loss of bone mass.



Fig. 1. Lactoferrin isolated from bovine milk.

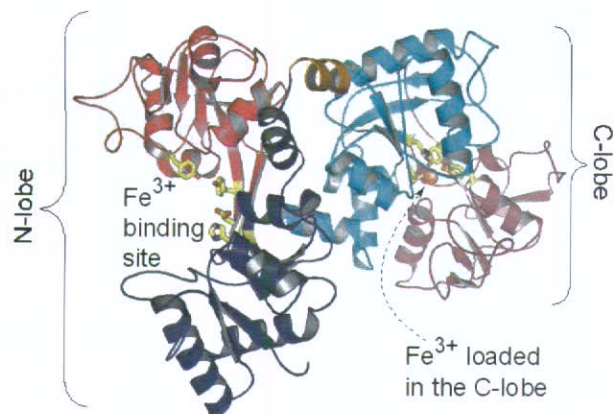


Fig. 2. X-ray crystal structure of bovine lactoferrin showing the C-lobe closed (iron loaded) and the N-lobe open and available to bind a second iron atom.

Using rat and human primary osteoblast cultures, lactoferrin was shown to have a dose-dependent and potent proliferative effect on osteoblasts at physiological concentrations ($\geq 1 \mu\text{g/mL}$).¹⁰ In this context, circulating levels of lactoferrin (predominantly neutrophil derived) range from 2–7 $\mu\text{g/mL}$ in healthy subjects, although during inflammation and sepsis this can be much higher.¹¹ Interestingly, there appeared to be no species specificity, with bovine, human, and recombinant human lactoferrin all having similar magnitude of effect over the same dose range. Furthermore, neither the degree of iron saturation nor glycosylation were critical to activity.¹² In addition to its mitogenic effect, lactoferrin was also able to stimulate differentiation of the osteoblasts. This was assessed by bone nodule formation, a process that involves bone matrix deposition and mineralization, both of which are functions of differentiated osteoblasts. Lactoferrin increased the number of nodules and the area of mineralized bone formed dose-dependently, although these effects required a higher concentration of lactoferrin than for the proliferative effect. Additionally, lactoferrin acted as a potent survival factor in osteoblasts, dramatically reducing apoptosis (programmed cell death) at concentrations similar to those causing proliferation. These effects on both proliferation and survival of osteoblasts are profound. They are far greater than those observed in response to established osteoblastic growth factors such as epidermal growth factor, TGF β , IGF1, or insulin. Thus overall, lactoferrin acts to expand the pool of early osteoblastic cells by exerting mitogenic and anti-apoptotic effects as well as driving differentiation to produce a more mature osteoblastic phenotype capable of promoting bone matrix deposition and mineralization.

These effects, collectively acting to promote bone formation, are in remarkable apposition to the ability of lactoferrin

Control Lactoferrin

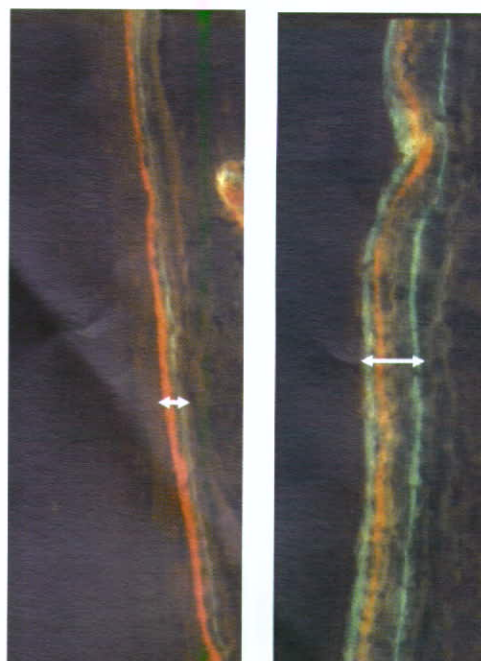


Fig. 3. Lactoferrin dramatically increases bone mass *in vivo*. Bone growth accretion is represented by the distance between arrows.

to reduce bone resorption through its effects on osteoclast development. Lactoferrin was able to dose-dependently decrease and even completely arrest the development of osteoclasts in mouse bone marrow cultures. However, lactoferrin had no effect on bone resorption by isolated mature osteoclasts, measured as the number of pits produced by these cells on bone slices. Although lactoferrin does not appear to influence the activity of mature osteoclasts, limiting the development of these is still likely to result in a profound reduction in bone resorption.

The above effects were demonstrated *in vitro*. When administered *in vivo* using a mouse skull local injection model, lactoferrin was shown to dramatically increase bone growth after only 5 daily injections (Fig. 3); moreover, the bone formed appeared normal. The potency of the effect was further attested to by increases in new bone formation observed at sites remote from the injection site. This anabolic potency suggests that lactoferrin or its analogues could be explored as therapies for osteoporosis to restore bone, as opposed to most current interventions which merely arrest further structural decline. Certainly, utility as a local agent to effect bone repair is indicated by such activity.

Mechanism of Action of Lactoferrin on Bone

We have investigated the mechanism of action of lactoferrin on osteoblasts in order to understand the physiological importance of this protein and perhaps enable more precisely targeted therapies. We have demonstrated that lactoferrin acts through a low-density lipoprotein receptor-related protein (LRP)1 or LRP2. LRP1 and LRP2 receptors are known to bind a number of different ligands and recent evidence suggests that these receptors function both as endocytic and signalling receptors.¹³ Not only was lactoferrin shown to bind to osteoblastic cells, but LRP1 and LRP2 were shown

to be expressed in these cells.¹⁴ Moreover, using confocal laser scanning microscopy and receptor blocking agents, lactoferrin was shown to be endocytosed by a mechanism involving functional LRP1 or LRP 2 receptors. Further work using specific antibodies against LRP1 as well as other cell lines (osteoblastic-like cells) that do not express LRP2 or are LRP1 null, allowed discrimination between the role of the two receptors. The proliferative effect of lactoferrin on osteoblastic cells appeared to be transduced by the LRP1 receptor, strongly suggesting that LRP1 functions as a mitogenic receptor for lactoferrin in osteoblastic cells. In fact, this was the first demonstration that LRP1 produces a cell-proliferative signal.

Although some evidence suggests that lactoferrin directly regulates gene transcription¹⁵ (in which case endocytosis and subsequent nuclear localization would be prerequisite for activity), it appears that internalization of lactoferrin is not required for activation of mitogenic signal in osteoblastic cells. Thus the endocytic function of LRP1 in this case is independent of its signalling function and binding of lactoferrin to the receptor is alone sufficient to activate the signal.

What then, are the mechanisms by which the signal is transduced to produce a response at the gene transcription level? Activation of intracellular phosphorylation cascades, such as the p42/44 mitogen activated protein kinase (MAPKs), is a common feature of proliferative signals by a variety of extracellular agents.¹⁶ Using immunoblotting techniques whereby specific cellular proteins are visualised by chromophore-linked targeted antibodies, it was shown that lactoferrin did indeed induce phosphorylation of MAPK kinase, the kinase that specifically phosphorylates and activates p42/44 MAPKs.¹⁴ Furthermore, inhibition of MAPK kinase by structurally related inhibitors reduced the mitogenic effect of lactoferrin on osteoblastic cells. LRP1 receptor blockers also inhibited MAPK kinase phosphorylation leading to the hypothesis that lactoferrin stimulates osteoblast mitogenesis through LRP1 to the p42/44 MAPK kinase pathway.

On the other hand, lactoferrin promotes survival of osteoblasts, which is determined at the nuclear level, by persuading the cell against the apoptotic pathway and toward the survival pathway; two distinct pathways with a common control point Akt (a serine/threonine protein kinase). Akt is activated by various growth and survival factors which act through cell surface receptors to induce the production of second messengers that activate phosphoinositide 3-kinase (PI3K) upstream of Akt. Lactoferrin indeed activates PI3 kinase-dependent Akt signalling in osteoblasts but, intriguingly, this effect is neither LRP1-dependent nor required for lactoferrin-induced cell survival. Thus the cell survival signal appears not to be transduced by PI3K, opening up the possibility of novel pathways for signal transduction.¹⁷

Concluding Remarks

In conclusion, lactoferrin has powerful bone anabolic as well as potent bone resorption inhibitory properties and can increase bone formation *in vivo* as shown in Fig. 4. What then is its physiological role and therapeutic potential? Lactoferrin is expressed biphasically in embryogen-

esis¹⁸ and could play a significant role in development of the foetal skeleton. It is expressed in high concentrations in human milk and given the leaky neonatal gut may act systemically to further promote neonatal bone growth. In the human adult, lactoferrin production is believed to be influenced principally by inflammatory stimuli which trigger release of the protein from the secretory granules of neutrophils.¹⁹ In inflammatory states, lactoferrin may play a role in counterbalancing the osteolytic effects of some of the cytokine mediators of the inflammatory response.²⁰ Although the exact physiological role of lactoferrin in bone growth and maintenance remains to be elucidated, there are certainly indications that lactoferrin may have use as a therapeutic agent in bone disorders, and as a local agent in bone repair. It may even be possible to influence the effect of lactoferrin on bone through its receptor. Current opinion favours the theory that orally ingested lactoferrin acts through receptors in the gut,²¹ eliciting systemic responses by induction of cytokines.²² In this case lactoferrin, which is easily extracted from cow's milk, may well have oral efficacy as a remediator in osteoporosis or other bone indications.

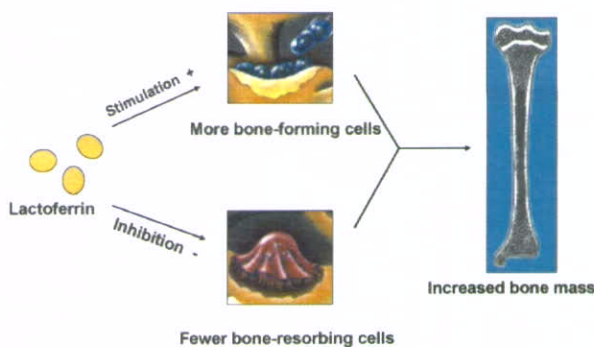


Fig. 4. Lactoferrin acts to build and preserve bone.

Acknowledgement

The authors are grateful to Geoffrey Jameson for provision of the diagram of bovine lactoferrin.

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The 2006 Nobel Prize in Chemistry

The 2006 Nobel Prize in Chemistry has been awarded to Roger D. Kornberg (Department of Structural Biology, Stanford University Medical School, California) for his fundamental studies concerning how the information stored in genes is copied, and then transferred to those parts of the cells that produce proteins.

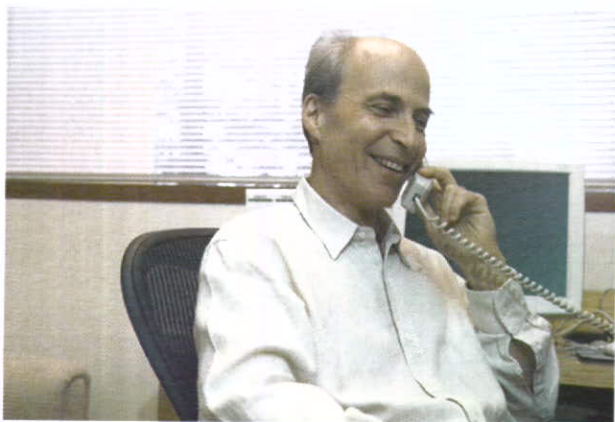


Photo Caption: 2006 Chemistry Laureate Roger Kornberg

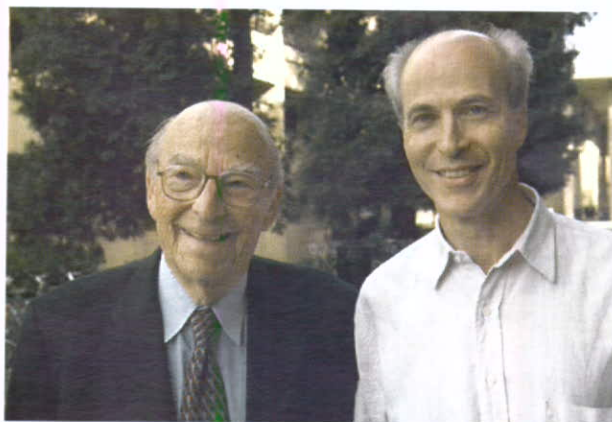


Photo Caption: Nobel Laureates Arthur Kornberg (1959 Medicine of Physiology) with son Roger (2006 Chemistry).

Synopsis

When twelve years old Roger Kornberg went to Stockholm to see his father, Arthur Kornberg, receive the 1959 Nobel Prize in Physiology or Medicine for his studies on the transfer of genetic information from one DNA-molecule to another. Kornberg senior had described the transfer of genetic information from a mother cell to its daughters. What Roger Kornberg himself has now done is to describe how the genetic information is copied from DNA into messenger-RNA.

The constant transcription of the genetic information in DNA is a central process for all living beings. The DNA-molecule itself lies protected within each cell nucleus and genetic information needs to be copied and transformed into messenger-RNA, which carries the information out into the protein-producing parts of the cells. It is the proteins that in their turn construct the organism and its function. If the transcription process is interrupted the organism soon dies as cell protein production terminates. This is what happens in cases of poisoning by certain types of toadstools, *e.g.* the death cap, where the function of an enzyme RNA-polymerase (which plays a central role in the transcription process) is blocked. Within a few days

the toxin spreads from the bowels to the liver and kidneys slowly destroying the organs. Many illnesses—cancer, heart disease, and different kinds of inflammation—are also linked to disturbances in the transcription process.

Kornberg has made breakthrough progress in the **molecular understanding of transcription** and its regulation in eukaryotic cells. His combination of advanced biochemical techniques with structural determinations has enabled the atomic level reconstruction of RNA polymerase from yeast in isolation, as well as in a number of functionally relevant complexes with template DNA, product mRNA, substrate nucleotides, and regulatory proteins.

There was a long standing preconception that the gene structure and transcriptional machinery identified in bacteria would be the same in all cells. However, we now know that in eukaryotes, such as yeast and humans, the chromosomal DNA is bound to proteins and packaged in nucleosomes and higher-order forms of chromatin not seen in bacteria. In contrast to bacteria, eukaryotic cells contain three different RNA polymerases (I-III)¹ but all the protein-coding genes are transcribed by RNA polymerase II, the main target of transcriptional regulation. During the 1970s, continued work on eukaryotic RNA

polymerases demonstrated them to be composed of multiple subunits which displayed no capacity for selective transcription of purified DNA.

Bacterial RNA polymerase consists of a four-subunit core with a variable fifth subunit called *sigma*.² The σ subunit is required for the core polymerase to recognize a promoter and to initiate transcription. The promoter is a specific sequence of nucleotides in DNA that serves as the start site for RNA synthesis. Surprisingly, no eukaryotic σ -like factors could be identified. Thus further progress in eukaryotic transcription depended upon the development of a reconstituted cell-free system. This had to be capable of promoter-specific transcription on exogenous DNA dependent upon RNA polymerase II. A human tissue culture cell extract which, together with purified RNA polymerase II, was able to specifically initiate transcription at a viral promoter was reported³ in 1979. Biochemical fractionation of this extract revealed⁴ the existence of multiple transcription factors for RNA polymerase II in 1980. These were called general transcription factors because they were involved in the transcription of virtually all genes and their characterization (TFIIB, -D, -E, -F and -H) involved many investigators.

Assisted by the five general transcription factors, RNA polymerase II in eukaryotes recognizes the start site on a gene, separates the strands of the DNA template, copies one strand into RNA (using ribonucleoside triphosphates as building blocks) and finally re-unites the two DNA strands while it translocates along the DNA. The promoter concept was originally derived from studies of transcription in prokaryotes but eukaryotic are much more extended than the prokaryotic promoters. Studies by Schaffner⁵ and Chambon⁶ and their groups led to the identification of gene-specific *enhancer* elements—DNA sequences that bind gene activator proteins which, in turn, control the transcription of specific genes.⁷

Kornberg's Contributions

Roger Kornberg entered the field of transcription while working on the structure of chromatin as a postdoctoral

at the MRC in Cambridge (UK) with Francis Crick and Aaron Klug. At that time, X-ray studies had shown that chromatin consists of repeated units with a size of around 10,000 pm. Fragmentation of chromatin with nuclease resulted in cleavage-products being multiples of a certain size.⁸ In 1974 Kornberg and Thomas⁹ reported that histones H3 and H4 form a tetramer of the type (H3)₂(H4)₂ in solution and then Kornberg proposed¹⁰ the basal unit of chromatin (the nucleosome) to be a histone octamer and 200 base pairs of DNA.

After returning to Stanford, Kornberg's main objective continued to be the understanding of transcriptional regulation in eukaryotes. Taking advantage of the versatility of Baker's yeast *Saccharomyces cerevisia* as a model, he developed an *in vitro* yeast transcription system.¹¹ It was soon apparent that the reconstituted system [containing highly purified RNA polymerase II and the five general transcription factors TFIIB, -E, -F, -H, and the TATA-binding protein (TBP)] only supported basal transcription and did not respond to the addition of gene-specific activator proteins. This observation led to the unexpected discovery and purification of *Mediator*, a multiprotein complex composed of *ca.* 20 different proteins whose role in all eukaryotes (from yeast to humans) is to transfer positive and negative signals from DNA-binding, gene-specific transcription factors to RNA polymerase II and the general transcription factors.¹²

With the isolation of Mediator, the three essential components of gene regulation and transcription in eukaryotes had been established, *viz.* the general transcription factors, Mediator, and RNA polymerase II. In bacteria, transcriptional repressors and activators directly contact RNA polymerase and affect its binding to the promoter. In eukaryotes, chromatin and Mediator constitute new layers of regulation between the gene-specific transcription factors and RNA polymerase, and provide for much greater complexity of regulation. However, even with the knowledge of all the proteins involved in eukaryotic transcription, there was still little molecular understanding of the process and all the participating polypeptides could

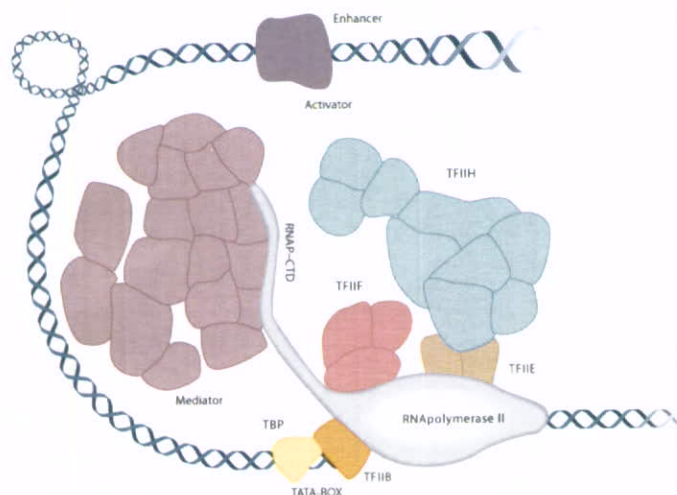


Fig. 1. A cartoon of a eukaryotic transcription initiation complex consisting of DNA, the general transcription factors TBP, TFIIB, -E, -F, -H, Mediator, RNA polymerase II, and a specific transcription factor binding to an enhancer element.

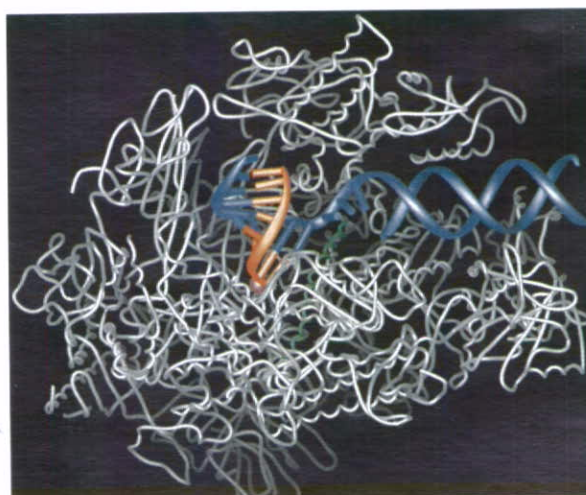


Fig. 2. Structure of an RNA polymerase II transcribing complex. The bridge helix is shown in green and the active site metal as a pink sphere. The DNA helix is colored blue while the newly synthesized RNA is in red.

merely be depicted as ball-shaped structures assembled around the promoter DNA (Fig. 1).

The structures of TBP in complex with a piece of TATA-box DNA and the ternary complex of TFIIB, TBP and DNA were solved by X-ray crystallography more than a decade ago.¹³ This provided some information about promoter recognition but very little about the rest of the transcriptional apparatus. Kornberg had realized that RNA polymerase might be the platform around which the whole eukaryotic transcription machinery is built but the large size of yeast RNA polymerase II—12 subunits—and the scarcity and instability of the purified complex made structural studies very difficult. Kornberg approached the problem using a combination of electron microscopy and X-ray crystallography and finally solved the problem after 20 years of biochemical work with protein expression and purification along with the development of a method to form 2D protein crystals on a lipid surface.¹⁴ Another important prerequisite was the establishment of the *in vitro* yeast transcription system mentioned above. The breakthrough came in 2001. In two papers in *Science*, the structure of a 10-subunit yeast RNA polymerase at 280 pm resolution was described as well as an elongating complex consisting of RNA polymerase, template DNA and product RNA.^{15,16} In the first structure, the two largest subunits lie in the center on either side of the apparent nucleic acid-binding cleft, with the many smaller subunits on the outside. The cleft is bridged by an α -helix from one of the two large subunits passing through the active site for phosphodiester bond formation and RNA chain elongation. Binding of nucleic acid in the cleft was directly demonstrated in the second structure (Fig 2). Due to the extensive homology between RNA polymerase II in yeast and the corresponding enzymes in mammalian cells, the work on yeast RNA polymerase is expected to offer an excellent model for all multi-subunit eukaryotic RNA polymerases, including those from human cells.

Subsequent publications have provided nearly a dozen new crystal structures of RNA polymerase describing different functional complexes with DNA, RNA, nucleotides or other proteins. These results have enabled a dynamic interpretation of the transcription process. The first crystal structure of an elongating complex was obtained using a DNA duplex with a long 3' overhang on one of the strands. The transcribing polymerase molecules were paused at a specific site on the template by withholding one of the four ribonucleotides. The structure represents the molecular conditions immediately after the formation of a phosphodiester bond between the 3'-end of the RNA chain and the incoming ribonucleotide *before* translocation of the DNA-RNA hybrid has occurred.¹⁶ More recently, in the crystal structure of a transcribing complex, the enzyme was combined with a 15-nucleotide DNA and a 9-nucleotide complementary RNA in the presence of a chain-terminating 3'-deoxyadenosin nucleotide. In this complex, the binding site for the incoming nucleotide is unoccupied and it represents a stage *after* translocation of the DNA-RNA hybrid.¹⁷

Conclusion

Roger Kornberg's mechanistic studies of eukaryotic transcription, provide a molecular understanding of promoter recognition, the mechanism of transcription initiation, how the DNA-RNA hybrid is translocated after the addition of a nucleotide, how the newly synthesized RNA strand is separated from the DNA template, and of the structural basis for accurate selection of an incoming ribonucleotide that is complementary to the DNA template. Furthermore, the structure of RNA polymerase II is the basis for the next generation of research to determine the precise operations of the general transcription factors and Mediator in transcriptional regulation.

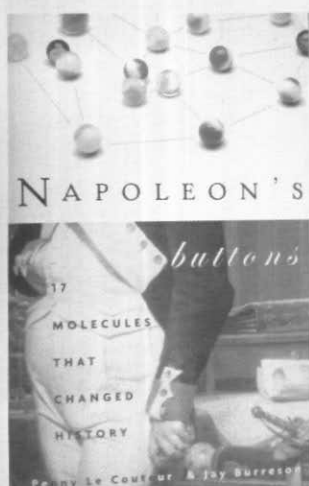
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Compiled by Editor Brian Halton from material freely available from the Nobel Foundation where further details may be found. See: www.nobel.se

Book Review: Napoleon's Buttons

By Penny Le Couteur & Jay Burreson



The title of this book is deceptive unless one reads the sub-title – *17 molecules that changed history*. The story about “Napoleon’s Buttons” is recorded in the introduction. It illustrates how often there can be a ‘chemical reason’ behind an event that changes the course of history. The tale is told of how Napoleon’s troops were defeated in Russia because the tin used to make the buttons on their great-coats disintegrated

in the low temperatures. This is a well used story among chemical educators the world over, even though historical evidence indicates the story is more likely apocryphal than fact. Despite this, it wonderfully illustrates how small changes in the underlying chemistry of substances can lead to changes in properties that have enormous consequences for individuals and ultimately, for society. In this book 17 ‘molecules’ (one could argue salt is not a molecule) that had a huge influence on society and world events are explored. In each case the history of the discovery and use of the molecules is discussed along with their world shaping influence.

The chemical industry as we know it today had its origins in the development of synthetic dyes in the 19th century. However, the influence of some particular molecules on world history goes back much further. This is apparent in the compounds chosen by the authors. They fall into two main groups; those from natural sources and those made in the laboratory. Valuable compounds from natural sources have been sought after in every age and have governed many aspects of history. For example, desire for glucose (sugar) and cellulose (cotton) drove and sustained the slave trade to the Americas from the 17th century. The desire for spices pushed forward the ‘Age of Discovery’ as new routes to India were sought to break the Venetian monopoly. Salt, silk and oleic acid (olive oil) are also noted for their influence on trade across the centuries. Vitamin C made a difference to the length of the journeys that sailors could undertake and so new worlds opened up.

The advance of the chemical industry in the past century and a half has given rise to compounds made in the laboratory or factory. Many, such as the dye, indigo and the vitamin, ascor-

bic acid are identical to those found in nature while others, like aspirin, have small variations to the natural product which gives them more useful properties. ‘Wonder drugs’ such as antibiotics, steroids, contraceptives and anesthetics are explored as are the alkaloid molecules, caffeine, morphine and nicotine. Again, small changes on the molecules that have led to new useful or controversial compounds are explored from a historical and a chemical perspective. In each case the chosen chemicals have been responsible for a key event in history or for a series of events that have transformed society.

The authors weave the stories of each compound’s discovery, use, and influence with discussions of chemical properties. They consistently make connections between chemical structures and historical episodes. Thus the book is not written in chronological order but chapters are based on connections between similar or related molecules. For example following on from the chapter on cellulose is one about nitro compounds and the link is the discovery of ‘gun cotton’ and the story of Schonberg’s exploding apron. To quote the authors ‘this book is not about the history of chemistry; rather it is about chemistry in history.’

The key to this book is the connection between chemical structures and the desirable properties of each compound. Helpful chemical structures are included in the text and the significance of any changes to the structures clearly explained. For example the position of the –OH group in the hydrocarbon chain of the molecule produced by bees helps them distinguish between a worker and a queen. A brief explanation of ‘organic chemistry’ and the structural representation of organic molecules are included in the introduction to the book. The authors cleverly minimise the complexity of some of the organic molecules by highlighting the important group under discussion and treating the rest of the molecule as something that this group hangs from.

There is much mention in current chemistry education literature of the need to make ‘real life’ connections for our students. This book is a gold mine of anecdotes, stories and everyday examples that link to many aspects of the chemistry we teach in schools and universities. As such it should be found in every school science department and school library. It is a great read for anyone with a basic understanding of chemistry and an interest in science and history. The authors have skillfully blended history, chemistry and culture in a wonderfully readable, interesting book.

Reviewed by Suzanne Boniface, Queen Margaret College

Chemistry in New Zealand Reader's Competition

We are offering readers the opportunity to win a \$100 voucher (of your choice). All you need to do is e-mail or write to us, with your name and contact details, and tell us the name of one of the advertisers who has appeared in *Chemistry in New Zealand* in 2006.

E-mail your answer to fiona@thinkdifferent.co.nz or post it to:

CiNZ Reader's Competition
PO Box 39-122
Christchurch

The competition closes 31 January 2007. The winner will be contacted before 10 February 2007 and details will be published the April issue of *Chemistry in New Zealand*.



Conference Calendar

Australian Colloid and Interface Symposium 2007, Sydney, Australia

4-8 February 2007

ACIS 2007 is the international meeting of the RACI colloid and surface science division. Themes will be:

- Spectroscopy and scattering in surface and colloid science (organisers: Jim McQuillan, NZIC & David Beattie).
- Pharmaceutical applications (organisers: Ben Boyd & Ian Larson).
- Hierarchical materials (organisers: Calum Drummond & Matt Trau).
- Surface forces, nanotribology and biological interactions (organisers: Roger Horn & Michelle Gee).
- Inorganic oxide surfaces (organisers: George Franks, Yang Gan & Jonas Addai-Mensah).
- Drops and Bubbles (organisers: Ray Dagastine & Clive Prestidge).
- Frontiers of Colloid and Interface Science (organisers: Greg Warr, Rob Atkin & Shannon Notley).

Further details available at the conference website:
www.colloid-oz.org.au or email acis@pco.com.au

AMN-3 Third International Conference on Advanced Materials and Nanotechnology, Wellington, New Zealand

11-16 February 2007

The conference will be covering the latest findings in the areas of nanotechnology and advanced materials. It will consist of two and a half days of plenary addresses from many of the best international and local researchers in these areas including Prof Sir John Pendry, and Nobel Laureates Prof Stephen Chu and Prof Sir Harry Kroto, followed by two days of more highly specialised parallel sessions. For more information see: www.macdiarmid.ac.nz/AMN3

Supramolecular Chemistry and Nanoscience - Towards Functional Nanostructures, Dunedin, New Zealand

3 March 2007

The aim of the meeting is to expose delegates to a broad range of interesting areas and approaches to functional nanoscience. Further details are available at the conference website: www.otago.ac.nz/conferences/supramolecular

8th International Symposium on Carbanion Chemistry (ISCC-8), Madison, Wisconsin, USA

6-10 June 2007

The conference will cover all aspects of carbanion chemistry (synthetic, mechanistic, structural and theoretical) as well as the chemistry of alkali and alkali earth metals. Further details are available at the conference website: www.chem.wisc.edu/iscc8

Eighth Tetrahedron Symposium, Challenges in Organic Chemistry, Berlin, Germany

27-29 June 2007

The Eighth Tetrahedron Symposium will celebrate 50 years

of *Tetrahedron* by addressing the challenges facing organic chemistry in the 21st Century. As with previous events in this series, a world-class line-up of international experts will provide a comprehensive review of the state of our current research and, more importantly, the challenges to future discovery. These plenary lectures are supplemented by poster sessions for which contributions are now invited. Many world-renowned speakers have agreed to present at the symposium, including two Nobel Laureates and thirteen past winners of the Tetrahedron Prize for Creativity in Organic Chemistry.

Sam Danishefsky, Harvard, USA; Peter B Dervan, Caltech, USA; Albert Eschenmoser, ETH Zurich, Switzerland; Bernd Giese, Basel, Switzerland; Bob Grubbs, Caltech, USA; Henri B Kagan, Paris Sud, France; Yoshito Kishi, Harvard, USA; Koji Nakanishi, Columbia, USA; K C Nicolaou, Scripps, USA; A Ian Scottk, Texas A & M, USA; Stuart L Schreiber, Harvard, USA; Dieter Seebach, ETH Zurich, Switzerland; K Barry Sharpless, Scripps, USA.

Call for Posters

The coverage of this anniversary event includes:

- Organic Synthesis
- Bioorganic Chemistry
- Organic Chemistry of Materials
- Supramolecular Chemistry

Contributions are invited for poster presentation on the conference topics. Abstracts should be submitted online at www.tetrahedron-symposium.elsevier.com by 22 January 2007. The Eight Tetrahedron Symposium is organised by Elsevier in association with *Tetrahedron*.

ChemEd07, Auckland, New Zealand

1-4 July 2007

9th Biennial Chemical Education Conference of the New Zealand Association of Science Educators. For the first time this meeting will include the annual conferences of the chemistry education sub-committees of both the New Zealand Institute of Chemistry and the Royal Australian Chemistry Institute.

This conference will be a great event and is an opportunity for teachers of chemistry at both secondary and tertiary level to be enthused by dynamic international and national speakers. Further details are available at the conference website: www.cce.auckland.ac.nz/conferences/index.cfm?S=CCE_CHEMED07

CHEMECA, Melbourne, Australia

23-26 September 2007,

Chemeca 2007 conference will interest all professionals in the chemical engineering and chemical process related sectors.

It will not only be a showcase for new knowledge but also a forum to discuss current issues. It is an excellent opportunity to share innovation. The industry and academia leaders will present their visions for the future of our profession, especially in the Australasian context. Further details are available at the conference website: www.chemeca2007.com
Christchurch

New Zealand Science Scene

Services popular

A steady flow of business has kept the staff of the University of Waikato's Mass spectrometry facility busy.

The facility was established in May 2005. At the end of July 2006 the facility launched its commercial services.

The collection of instruments in the suite includes a Bruker Daltonics Autoflex™ Spectrometer with associated Proteiner dp Digester, a MicrOTOF™ Spectrometer; high resolution electrospray ionisation-time-of-flight instrument, an LC-MS, GC-MS, ICP-MS, and SPR – Biacore® 3000 surface plasmon resonance instrument. The high resolution instrument has seen quite a lot of custom already.

The collection of instruments offers assistance for research in the fields of biotechnology, chemistry, molecular biology and particularly genomics and proteomics. It is housed in the School of Science and Engineering at the University of Waikato.

More details and pricing can be found on the following website www.mass-spec.co.nz

Classroom with a difference

Seven award winners from the Auckland Science Fair enjoyed the Liggins Institute's new Sir John Logan Campbell Classroom.



Photo Caption: Intense concentration as the students try their hands at micro-pipetting and gel electrophoresis.

The high school students from Onehunga High School, Diocesan School for Girls and St. Cuthbert's College got to spend a day conducting experiments that are not normally available at secondary school. They also observed ongoing research at The University of Auckland.

Jacqui Bay, Senior Tutor at the classroom, said "Through giving these stu-

dents first hand knowledge of scientific research, they can take the experience to make an informed decision of what they will be able to do through continued science study."

The students also got to pose some questions to the University's scientists.

The Sir John Logan Campbell Classroom offers hands on learning linking biotechnology and current scientific research techniques to biology relevant to secondary students. This free programme can be tailored to the needs of a secondary school group.

Bullet train for ideas

KAREN, a new super high-speed internet-style network, was launched in New Zealand at the beginning of September.

The network for New Zealand universities and research organisations is called Kiwi Advanced Research and Education Network or KAREN. The network will allow incredibly high amounts of data to be exchanged quickly and easily says Donald Clark, who is head of REANNZ, the organization that established KAREN. It can carry information at ten gigabits a second between researchers in New Zealand and beyond.

The KAREN network is a \$43M government investment and REANNZ has leased space on a fibre optic cable from Telstra-Clear. The fibre optic cable will carry data traffic between research and education institutions that connect to dedicated KAREN switches in each region.

Over 40 countries around the world now have Advanced Research, Education and Innovation Networks like KAREN.

Rewarding Scientists hard work

Penelope Brothers, Associate Professor of Chemistry at The University of Auckland has been named a Fulbright Senior Scholar. The award means she can spend six months at the Los Alamos National Laboratory in New Mexico.

The purpose of the Fulbright awards is to allow New Zealand researchers to undertake, for a short period, research or lectures in the USA.

Two other researchers at the University of Auckland have been recognised for their contribution to science in the Royal Society's annual awards.

Professor Bruce Baguley, from the Auckland Cancer Society Research Centre, has been awarded the Sir Charles Hercus Medal in molecular and cellular sciences and technologies. His research focuses on the discovery and development of new anticancer drugs.

Dr Mark Vickers from the Liggins Institute was awarded the Hamilton Memorial Prize. This award is to encourage researchers in the early stage of their career. Dr Vickers' research focused on the links between poor foetal nutrition and its long-term consequences particularly a predisposition towards diabetes and obesity in adult life. His research has shown this pre-programming can be reversed.

NZAS Awards

NZAS has announced its 2006 Medal recipients. Other than FNZIC David Parry (see NZIC News) the awards go to Dr Tim Haskell (Physicist, IRL) – Marsden Medal; Dr Jamin Halberstadt (Psychology, University of Otago). Research Medal, Dr Liz Carpenter, (AgResearch Hamilton) – Communicator Award.

RSNZ

The RSNZ Academy elected ten new Fellows and two Honorary Fellows at its annual meeting in November. They are Dr J R Caradus, (CEO, Grasslanz™, AgResearch), Prof H J Carmichael (Physics, Auckland University), Prof T F Cundy (Medicine, Auckland University), Prof D M Fergusson (Psychological Medicine, Otago University) Dr S L Goldson (Chief Science Strategist, AgResearch and Professional Fellow, Lincoln University), Prof P E Lobie (Associate Director, Liggins Institute, Auckland University), Prof B W Melville (Civil and Environmental Engineering, Auckland University), Dr P E H Minchin (HortResearch), Prof H W Morgan (Biological Sciences, Waikato University) and Prof M J Visser (Victoria University). The Honorary Fellows are Profs R D Bardgett (Ecology, Lancaster University) and S B H Kent.

New Zealand Institute of Chemistry

supporting chemical sciences

December News



NEW ZEALAND INSTITUTE OF CHEMISTRY

75th Anniversary – NZIC is 75 in 2007

NZIC's President for the 75th Jubilee year will be Dr Jan Wikaira, Manager of the X-ray Crystallography Laboratory at the University of Canterbury.

Awards

NZIC Awards

The NZIC NuFarm Prize is awarded to Dr **Harvey Indyk** (Senior Scientist, Fonterra Nutritionals Centre, Waitoa), the HortResearch Prize for excellence in research is awarded to Prof **Peter Steel** of the University of Canterbury, and the NZIC Chemical Education Award goes to **Denis Hogan**, also of the Canterbury Branch, for his continuing work in the education arena and especially with CHEM NZ. This latter award was presented to Denis at a private ceremony in his home on October 24th.

We are saddened by the recent news that Denis Hogan, formerly Registrar and ChemNZ editor, and one of our most respected and loved members, passed away on November 16th. A full obituary will appear in the April issue, along with a transcript of the speech Denis made upon receiving his award.

NZAS Awards

NZAS has announced its 2006

awardees. They include Prof **David Parry** (ISF, Massey University) as recipient of the **Shorland Medal** – congratulations from the NZIC.

RSNZ Awards

RSNZ has bestowed its highest honour, the **Rutherford Medal**, on Prof **Ted Baker** (Auckland University) for his protein structure work.

The RSNZ Hector Medal has been awarded to Dr **Richard Furneaux** of the Carbohydrate Group, Industrial Research Limited, for the outstanding contribution he has made to the advancement of carbohydrate chemistry and to world-wide recognition of chemistry and pharmacology in New Zealand.

The **Pickering Medal** for excellence and innovation in the practical applications of technology was awarded to Prof **Murray McEwan** (University of Canterbury).

The 2006 **Sir Charles Hercus Med-**

al in molecular and cellular sciences and technologies has been awarded to Prof **Bruce Baguley** of the Cancer Research Institute Auckland, for his contribution to the development of new cancer therapeutics.

The **Academy of RSNZ** has elected Prof **S. B. H. Kent** (Chemistry, Biochemistry and Molecular Biology, University of Chicago) as an Honorary Fellow. He is a world leader in biological chemistry with research focused on understanding the chemical basis of protein function, particularly enzyme catalysis, and to design and build protein molecules with novel properties. He is a Board Member of the Functional Genomics Centre at Victoria University and an Adjunct Professor in Biological Sciences at Auckland University. He has provided training and advice on recent technology that is underpinning interdisciplinary research in Auckland on the development of vaccines to treat cancer.

NZIC News

2007 Executive

The NZIC 2007 Executive consists of Dr Jan Wikaira (President), Prof Bill Henderson (1-VP), Prof John Spencer (2-VP), Richard Rendle (Hon. Gen. Secretary) and Dr Colin Freeman (Treasurer).

Chemical Education Award Renamed

Council is delighted to announce that the chemical education award has been renamed, with permission, in honour of Denis Hogan former editor of CHEM NZ and NZIC Regis-

trar from 1961-1988. From 2007 it will be known as **The Denis Hogan Chemical Education Award**.

New Fellows

Council offers congratulations to the following members who were elected to the Fellowship at its September meeting:

Alistair Bingham, **David Williams** (Auckland); **Mike Boland**, **Grant Boston** (Manawatu); **Ian Brown**, **Graham Caygill**, **Patrick Holland**, **Max Kennedy**, **Kate McGrath**, **Keith Morgan**, **Sarah Russell**, and **James Waters** (Wellington)

Chemical Education Trust

The CET, established in 1987, supports NZ chemical education in the widest possible sense. Its three trustees are required to be former NZIC Presidents appointed by Council. Currently these are Pat Holland (Cawthron Institute), Alastair MacGibbon (Fonterra) and Andrew Brodie (Massey University). Each year the Trust calls for applications for funding and this year grants totaling \$3395 were made to **Burnside High School** (Christchurch – for tungsten and magnesium cylinders to illustrate density), **Hillmorton High School** (Christchurch – for

upgraded of Crocodilia Chemistry software), *Middleton Grange School* (Christchurch – for a balance), *Nelson College* (Nelson – for syrettes for titrations), *Taradale High School* (Hawke's Bay – for molecular models), *Te Awamutu College* (Te Awamutu – for pH meters), *Villa Maria College* (Christchurch – for the RSC publications package).

The *NZIC Chemical Education Specialist Group* was awarded a \$500 grant-in-aid to Suzanne Boniface to attend the 19th International Conference in Chemical Education in Seoul. Although this grant sets a precedent it is permitted under the Trust rules. Suzanne was asked by Council to reactivate the *Chemical Education Specialist Group* and the application was seen in this light. However, any future application for funding from a teacher to attend a conference must come with strong support from the *Chemical Education Specialist Group*.

The income of the CET comes from the interest on invested capital and donations and this year it has received just over \$2000 from NZIC members who have generously supported chemical education in this way. Donors should note that the Trust has been reinstated as a Charitable Trust thereby allowing a tax rebate on a donation.

BRANCH NEWS

AUCKLAND

The Branch hosted A/Prof *Keith Gordon* for his Presidential Address entitled *New Electroactive Materials for Application in OLEDs and Solar Cells* to about 40 members on September 21. Al Nielson has resigned as Treasurer due to other commitments and Gordon Miskelly has taken over; he is now Secretary/Treasurer.

Chemistry Department - AU

The Department has hosted a number of notable seminars in the recent past, including inaugural professorial lecturers by two of its own staff. August saw Prof *Terry Collins* (Carnegie Mellon University) discuss *Designing Green Catalytic Oxidation Processes*. Terry is a graduate of the Department and has had a long-term collabora-

tion with A/Prof James Wright. There was then had an interesting juxtaposition of molecular model-builders: Prof *Peter Stang* (University of Utah) spoke on *Nanoscale Molecular Architecture*, and Prof *Len Lindoy* (Sydney University) followed a week later with *New Discrete and Framework Molecular Structures Formed by Metal-Ion Directed Self Assembly*.

September 6 *Jim Metson* gave an Inaugural Professorial lecture *Photons and Factories – Applications of Surface Science to the Light Metals* following his October 2005 promotion in recognition of his outstanding service and achievements in the field of light metals research. Jim leads a multi-university research programme looking to transform the NZ light metals industry. Jim is also Head of Department, Associate Director of the University Light Metals Research Centre, and chairs the Government-established Research Infrastructure Advisory Group – a very busy man! The second Inaugural of the month was from Prof *Laurie Melton*. His lecture, *Gastrophiles and Crapulence: Sugars and Roughage*, covered many years of his research on the structure of plant cell walls and the contribution these make to the experience of eating and nutrition, as well as their role in keeping plants upright. Laurie is the Head of the successful Food Science Programme that encompasses undergraduate and graduate programmes. He is also a member of the NZ Food Safety Authority Academy of Experts and the IUPAC Committee of Chemistry and the Environment.

Other occasions of note included the re-launch of the Centre for Molecular Biodiscovery as the Maurice Wilkins Centre for Molecular Biodiscovery, with an official function attended by Trevor Mallard. The function included a visit through the Brimble laboratories—Margaret is a Principal Investigator with the Centre. The *Roper/Wright* group had one of its osmium complexes appear on the cover of a recent issue of *Organometallics*. The issue editorial gave a synopsis of Warren's substantial contribution to organometallic chemistry and the current work. The editorial preceded a major review article by Warren and

James on the chemistry of ruthenium and osmium complexes. The University Courses and Careers Day, held in September, saw thousands of final-year high-school students visiting the campus to hear lectures (Chemistry, Medicinal Chemistry, and Food Science included) and watch demonstrations.

The Department's first indoor soccer tournament was held in late August. There was a very wide participation, that included some young-at-heart staff, with no major injuries but a few sore bodies; participants agreed this event should be repeated. Finally, the annual Oktoberfest was held on Friday October 13. Aably organized and catered by Tilo Soehnel and Kathrin Wichmann, the event was preceded by an introduction to postgraduate studies and research for final year undergraduates.

CANTERBURY

Dr *Barbara Thomson* spoke at the October Branch meeting, held jointly with the Canterbury Branch of The New Zealand Institute of Food Science and Technology, on Too Much Salt, but Not Enough Iodine. For over 75 years nutritional advice has helped ensure the food we eat avoids deficiency states and reduce the risk of chronic disease. Of particular interest in the NZ diet are sodium and iodine. Too much salt may lead to high blood pressure, a risk factor for heart disease. Iodine is an integral component of thyroid hormones required for normal growth and development, energy production, and oxygen consumption. Iodine deficiency is the world's greatest single cause of preventable brain damage and mental retardation. The seminar addressed iodine and sodium intakes assessed from NZ Total Diet Studies, the main contributing foods, and public health initiatives to reverse iodine deficiencies and ensure future generations are internationally competitive for rugby world cup challenges and Nobel Prize nominations! The last meeting of the year will be a Christmas afternoon tea and AGM. Students receiving travel awards to attend the NZIC conference will also give short presentations.

Chemistry Department - UC**Prizes and Awards**

As noted above, the NZIC Chemical Education Prize went to **Denis Hogan**, an Adjunct Senior Fellow and long-time friend and affiliate of the Department. Denis has been involved with CHEM NZ since its inception and resurrecting it when it came back to Christchurch in 1989; he has been Editor and Convener of the Editorial Committee ever since. Along with the late Alan Wooff, he worked on adapting DSIR analytical methods to make them useful for high school laboratory exercises. Congratulations Denis on this well-deserved mark of recognition. Congratulations also to Prof **Peter Steel** who received the NZIC HortResearch Prize for excellence in research at the RSNZ Awards Dinner in November.

Alison Downard is one of the Principal Investigators in a research collaboration awarded \$725,000 over three years in the latest Marsden funding round. The grant is to explore a new approach to communicating with cells using embedded nanostructures by *wiring up* living yeast and mammalian cells with nanowires. Alison and coworkers aim to extract detailed, real-time information on cellular functions and provide new methods for using cellular processes. The potential applications for this research include biosensors, biofuel cells, and synthetic-biological electronic components, and it may offer insights into disease processes that could lead to new therapeutic methods.

Peter Stang, Distinguished Professor of Chemistry from the University of Utah and visiting Erskine Fellow was named as recipient of the ACS 2006 Linus Pauling Medal. Peter felt honored by the award '*particularly since it's associated with Linus Pauling, who was arguably one of the pre-eminent chemists in the world*' he said. Previous recipients include Prof Robert Grubbs (CIT) who was an Erskine Fellow last year, who with twelve other awardees, have become Nobel Laureates.

Former student Dr **Chris Richardson** has returned as a postdoctoral fellow working on *molecular cages of controlled size and shape* with the

Steel group. Chris was a graduate of the Department under Peter Steel's supervision, then undertook post-doctoral research with Chris Reed (UC- Riverside) then in the Auckland Cancer Society Research Centre, followed by the University of Bath.

Erskine Fellows, Peter Stang and Antony (Fez) Fairbanks have completed their times with us. Both were extremely popular with both staff and students. **Philipp Kuegler**, an exchange student from Konstanz, has also departed.

The Department was one of five at UC that funded prizes in the Sanford Science and Technology Fair held in Timaru in September. The fair encourages Years 12 and 13 students to enter projects that are judged by postgraduates on site for the event. The \$650 first prize was awarded jointly to **Tom Kuperus** (Mountainview High) and **Nicole Jenkins** (Mt Hutt College). Tom examined the impact of humidity on the amount of ammonia given off by slaters, a study that included calculations of uncertainties, statistical analysis of results, controls, and reproducibility of experiments. Nicole investigated the dissolved oxygen content of five sources of water, impressing the judges with her enthusiasm and her articulate responses to questions.

Science Outreach News

The Outreach Programme, the Chemistry Department and Canterbury Chemistry teachers recently hosted over 120 Year 13 students for a day specifically designed to assist them in preparing for the Scholarship Chemistry examination. Sessions included strategies for approaching the examination questions, techniques to use, how to plan out answers, sample answers, how to gauge the length of an answer and problem solving. Students also carried out a number of relevant practical experiments. The feedback from the day was overwhelmingly positive.

MANAWATU

Gerald Smith gave the Manawatu October lecture at the Fonterra Research Centre on the chemistry of Heritage Materials. Gerald also took

the opportunity to promote a new graduate programme at Victoria University in the area of heritage materials chemistry.

Massey University

Peter Derrick (Warwick University) will be joining the Institute of Fundamental Sciences in April 2007 as its new Head. Presently Chairman of Chemistry at Warwick, he was one of the first scientists to promote and develop mass spectrometry for the characterization of proteins. He developed tandem time-of-flight mass spectrometry for macromolecules and pioneered applications of Fourier transform ion cyclotron resonance (FTICR) to peptides and proteins and currently researches the development of mass spectrometers and the study of protein interactions.

Viatcheslav Filitchev is a new lecturer in Chemistry. Coming from the Nucleic Acid Center, University of Southern Denmark (Odense), he obtained his PhD from St. Petersburg State Technological Institute. **Ashton Partridge** will become Director Nanomaterials Research (NRC) upon David Officer's departure. Ashton has most recently been with the Ministry of Research, Science and Technology, and spent a very successful period at IRL. The NRC also welcomes postdoctoral **Loretta Crowe**, a graduate of West Florida who did her PhD in organic chemistry with Laren Tolbert at the Georgia Institute of Technology. She will be working on the synthesis and polymerisation of indanone-substituted terthiophenes and the development of functionalized ITO glass electrodes.

Shane Telfer received a 2006 Fast Start Marsden Grant for his work on *A rational approach to catalytically active porous materials*, a project that focusses on use of metal-containing molecular and supramolecular building blocks for the fabrication of crystalline, porous, nanostructured materials. He will specifically target solid state materials that perform useful functions such as catalyzing reactions, storing gases such as H₂, or separating enantiomers. **Paul Plieger** shared the CoS Emerging Career Research Award for his work in inorganic chemistry.

Congratulations to **Karen Bang** on gaining her PhD, to **Fabio Lodato** who has submitted his PhD dissertation *Synthesis and Properties of Fully Conjugated Porphyrin Arrays for Light Harvesting*, and to **Leyton Gapper** who has completed an MSc with David Harding. **Celia Webby** presented her PhD work in a seminar on the structure and function of Shikimate pathway enzymes. Celia is leaving for a postdoctoral position at the University of Oxford.

Martin Schwalbe, a recent PhD candidate in IFS, has been awarded a Vice Chancellor's doctoral scholarship. Martin will be working with Steve Pascal applying protein-NMR techniques to a Marsden-funded project linked to cancer and Alzheimer's disease.

OTAGO

Chemistry Department – OU

The inaugural PhD student symposium was held in late October when senior PhD students chaired and presented lectures on their research. Each talk was followed by enthusiastic discussion. The first year PhD students assisted **Heather Hannagan** in organizing the social side of the activities and ensured that the day had an appropriately celebratory feel to it. An enjoyable time was had by all. Prof **Sally Brooker**, **Theresa Renault** and **Rose Harrison** have been busy organising the one day *Supramolecular Chemistry and Nanoscience - Towards Functional Nanostructures* symposium to be held on Saturday March 3 2007 as advised previously (This Journal, 2006, 70, 105) Newly confirmed plenary lecturers include A/Prof **Peter Boyd** (Auckland) Prof **Geof Jameson** (Massey University), A/Prof **Richard Blaikie** (Canterbury) A/Prof **Keith Gordon** (Otago), and Dr **Stephen Sowerby** (Australo Limited, Dunedin). Prizes for the best student/postdoctoral talk and poster will be presented by Professor Lehn. For more details and to register online see: www.otago.ac.nz/conferences/supramolecular

In addition to the visit by Professor Lehn, visits by Prof **Jane Nelson** (Belfast) and Dr **Grace Morgan** (Dublin) in the new year until the

above conference, are eagerly anticipated.

Across in the Biochemistry Department Prof **Warren Tate** received the University of Otago's highest research honour, the Distinguished Research Medal, while Dr **Julian Eaton-Rye** received the Applied Biosystems/NZSBMB award for excellence in research at this year's ComBio Conference in September in Brisbane.

WAIKATO

Keith Gordon gave his Presidential Address in late September.

Waikato University

ChemQuest 2006, the annual quiz for Year 12 students, was held in mid-October. The fun night packed chemical questions on: *Periodic Puzzlers*, *Sensing the Senses*, *The Wide World of Chemistry* and *Demon Demos* to 57 teams from 19 schools all around the greater Waikato region. The James and Wells trophy, medals and cash prizes were up for grabs! After each of the four rounds of questions, it became *Teachers' Turn* (four teachers per round competing for a small prize for themselves and a textbook for their school donated by the Chemistry Department). Yet again it proved a most enjoyable night. Prizes were awarded as follows:

1st Tauranga Boys College *Incredibles* (Michael Kim, Nicholas Smith, James Bridgewater)

2nd Forest View High School *CCT* (Craig Pilott, Tung Huynh, Caren August)

3rd Fairfield College *Boron Bandits* (Stefan Smith, Gareth Jones, Kim Wigmore)

4th St Paul's Collegiate *Chem-i-cool 'X'* (George Hickmott, Natasha Khouri, Chris Cho)

5th Forest View High School *CHK*, (Hayden Whittaker, Cameron Whittaker, Naomi Stairmond)

Teachers' Turn winners were Duncan Smith (St Pauls Collegiate), Mary Thomas (Trident High), Lynn Muirhead (Waikato Diocesan) and Martyn Owen (Rotorua Girls High).

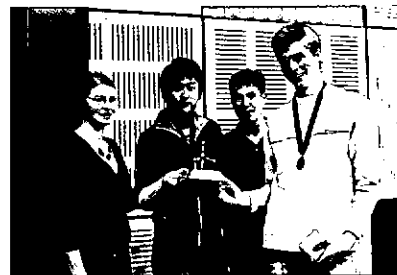


Photo caption: 1st prize presented by Sandra Wilcocks (James and Wells) to the Incredibles (Tauranga Boys College).

The quiz was presented by **Richard Coll** and **Michèle Prinsep**, with **Brian Nicholson** running the *Demon Demos*. Numerous other people contributed to the success of the occasion including many of the staff and students from Chemistry, and Waikato's School of Science & Engineering, assisted with organisation, marking and publicity. Waikato graduate **Sandra Wilcocks** presented the prizes. Sponsorship came from School of Science & Engineering (Waikato) Hill Laboratories, and James and Wells-Intellectual Property Lawyers

Mahima Senanayake, **Gordon Rajendram** and **Brendan Waugh** have completed their degrees, the last an MSc in collaboration with DEC Manufacturing (Te Rapa). The recent graduation ceremony saw a bumper crop of Chemists. **Lucia Ying**, **Sally Gaw** and **Grant Mathieson** each gained their PhD, **Sarah Devoy**, **Bevan Jarman**, **Kelly Kilpin**, **Karen Love**, **Chin-Fen Lee**, **Daniel van de Pas** and **Jessica Zhu** graduated MSc and **Sunita Jeram** Grad. Dipl. Appl. Sci. The same ceremony saw Sir Edmund Hillary receive his first honorary doctorate from a NZ University. Chin-Fen Lee plans to continue to PhD with Alistair Wilkins (on fern metabolites) while Jessica Zhu is now working for her father's paint company in Beijing. Bevan Jarman has begun his PhD with Marilyn Manley-Harris, Bill Henderson and Brian Nicholson.

Richard Coll and **Allan Harrison** (Central Queensland University) are finalising their edited book on teaching with analogies. The book focuses on helping teachers to make good use of analogies in the classroom by drawing on years of research. Analogies are extremely useful teaching tools, but research has shown that

if used inappropriately they can become a *double-edged sword* and introduce further misconceptions. The book contains a model that should be used when teaching with analogies and a compilation of over 50 of them from biology, chemistry, physics and the earth sciences. The book is to be published by published by Corwin.

A custom-designed HPLC centre is being built in the Chemistry Department to house the instrumentation valued at \$250,000.

WELLINGTON

September saw relative newcomer to Chemical and Physical Sciences at VUW Dr **Gerald Smith** talk on his subject the *Chemistry of Heritage Materials*. He outlined processes of degradation, particularly those of organic origin. He showed why knowledge of the chemistry of these processes is crucial in developing ways to preserve the visual art and objects that form part of our cultural heritage. In October the design, synthesis and manufacture of glycotherapeutics was presented by Dr **Richard**

Furneau (Acting General Manager, GlycoSyn, IRL). These compounds are small synthetic molecules that target biological processes involved in the use of natural carbohydrate components for therapeutic benefit. Industrial Research now has the largest Carbohydrate Chemistry enterprise worldwide, with a discovery team of 30 scientists and the GlycoSyn business unit with 23 staff that undertakes process development and cGMP manufacture of drug candidates for clinical trials. The lecture addressed progress in getting novel drugs into clinical trial for treatment of cancer, auto-immune disease, malaria and bacterial infections, and considered the prospects arising from current research activities. Richard is currently the Acting GM of GlycoSyn but will return to leading IRL Carbohydrate Chemistry team in December.

Victoria University

Chemistry staff of SCPS promoted in the 2006 round were NZIC Branch Chairman **Kenneth MacKenzie** to Professor in Inorganic Materials, and Drs **Thomas Borrmann** and **Richard**

Tilley to senior lectureships. School Chairman **John Spencer** has accepted a fractional (30%) appointment to the position of Deputy Dean of Science.

Recent visitors to the School have included Profs **Abhik Gosh** (Tromsø), **Peter Stang** (Utah), **Len Lindoy** (Sydney) and **Carl Schiesser** (Melbourne) all of whom gave excellent seminars for the graduate and undergraduate community.

Ben Murray has submitted his MSc *Controlling Calcium Carbonate Crystallisation* and his supervisor **Kate McGrath** attended the 12th International Conference on Surface and Colloid Science in Beijing where she presented *Emulsion microstructure and stability: Understanding and manipulating interfacial control*.

Council of the New Zealand Institute of Chemistry and Editor and Managing Editors of Chemistry in New Zealand would like to wish all readers and members a safe and happy holiday season.

Company Profile - Graham B Jackson

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Manapro12 – XII International Symposium on Marine Natural Products Queenstown 4 – 9 February 2007



The 12th International Symposium on Marine Natural Products will take place at the Millennium Hotel, Queenstown from the 4-9 February, 2007. It is the latest in a long running series of symposia that continue to attract an international audience to discuss all aspects of marine natural product chemistry and biology. You are cordially invited to attend.

The current symposium programme has been organised around six themes:

1. **DISCOVERY** (including methodology) will be opened with a plenary lecture from **Ray Andersen** (UBC) and will include invited lectures from Varian Associates Inc. and Bruker Biospin.
2. A session on **SOUTHERN OCEANS** will be highlighted through a plenary lecture from **Dennis Gordon** (NIWA) and will feature a distinguished list of Southern Hemisphere researchers.
3. Recent work on the **GENOMICS** of marine organisms will be presented in a plenary lecture by **Brad Moore** (SIO).
4. **ENVIRONMENTAL** (including ecological and marine toxins) will include a plenary lecture from **Nobuhiro Fusetani**.
5. The session on the **DEVELOPMENT** of marine natural products through synthesis, pharmacological studies, and nutraceutical investigations, will commence with a plenary lecture from **Chris Ireland** (Utah).
6. The final session, **NEW FRONTIERS**, has a plenary lecture from **Jon Clardy** (Harvard) and invited lectures from **Bill Gerwick** and **Amos Smith III**.

In addition, a further 25 scientists of eminent international standing will give talks across the themes and the conference will close with a keynote address from **Bill Fenical** (SIO).

Student participation is encouraged through a reduced conference fee and a selected number of younger invited speakers are included. We seek oral contributions from younger participants and will feature their posters through short oral presentations additional to the poster presentation; there are sponsored prizes for the best student posters.

Attendees have opportunities for contributed talks in areas 1-5 and poster presentation is also available. Three of the poster sessions will allow the key features of the works to be presented through a three minute PowerPoint display.

For programme and registration see: www.manapro12.co.nz

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