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PO Box 39-112
Harewood, Christchurch

Phone: +64 3 359 7275
Fax: +64 3 359 7248
Email: NZIC.Office@nzic.org.nz

Managing Editors and Publishers Advertising Sales

Fiona Summerfield and Rebecca Hurrell
PO Box 39-112
Harewood, Christchurch

Phone: +64 3 980 4809
Mobile: 021 075 4917
Email: fiona@thinkdifferent.co.nz

Scientific Editor

Professor B. Halton, FRSNZ, Hon, FNZIC
School of Chemical and Physical Sciences
Victoria University
PO Box 600
Wellington, New Zealand

Phone: +64 4 463 5954
Fax: +64 4 463 5241
Email: brian.halton@vuw.ac.nz

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Article

Structure Determination of New Algal Toxins using NMR Methods

Alistair L. Wilkins*,[a] and Christopher O. Miles[b,c]

[a]Chemistry Department, Waikato University (e-mail: a.wilkins@waikato.ac.nz)

[b]AgResearch Limited, Ruakura

[c]National Veterinary Institute, Oslo, Norway

Introduction

Shellfish are considered a delicacy by many consumers. In NZ, as in many overseas countries, there is a now thriving shellfish industry servicing both domestic and international markets. Periodically shellfish accumulate harmful levels of a variety of algal toxins, including domoic acid, yessotoxins, pectenotoxins, and brevetoxins. When this occurs, regulatory authorities may impose harvesting closures which have a consequential economic impact on both farmers and staff employed to harvest and market shellfish products.

Quantification of algal toxins in sea water or shellfish tissue is dependent on the prior identification and structure determination of the target toxin, and the subsequent availability of high purity reference material. Determination of the structure of an algal toxin, prior to its toxicity being established and its level regulated, requires the consideration of spectral data derived from a variety of techniques. UV spectroscopy can facilitate the identification of chromophoric groups, while IR data assist in identifying the presence of functional groups. However, these techniques rarely define the precise location or the stereochemical orientation of groups such as hydroxyl, acetoxyl, or sulfate.

Recent developments in mass spectrometry (MS), especially improvements in the design and sensitivity of electrospray ion trap and time-of-flight (TOF) spectrometers and the interfacing of liquid chromatography (LC) columns to MS systems, have dramatically improved the ability of scientists to detect and monitor the level of potentially harmful algal toxins in shellfish. LC-MS^n techniques can be used to define both the molecular weight of a target toxin, and characterize its fragmentation pattern. A particularly common approach is to determine the masses of a series of fragment ions generated by the progressive cracking of daughter ions generated by fragmentation of a parent ion. Ion trap and triple quad mass spectrometers are well suited to this approach, and while useful MS^n, for n = 2, 3, 4, *etc*., can be generated and used to define similarities or differences in structures of related algal toxins, mass spectrometry alone is rarely able to define the stereochemistry of chiral carbons, or in many cases the specific site of attachment of a functional group.

Thus, while a comparison of MS^n data (Fig. 1) determined for yessotoxin (YTX) and a new homoyessotoxin analogue **2** (Chart 1) showed that an additional 14 units were associated with ring B–C region of the new analogue **2**, it did not differentiate between, *e.g.* the replacement of a proton by a methyl group, the presence of a seven- rather than a six-membered ring, or replacement of a CH_2 group by a C=O group.[1]

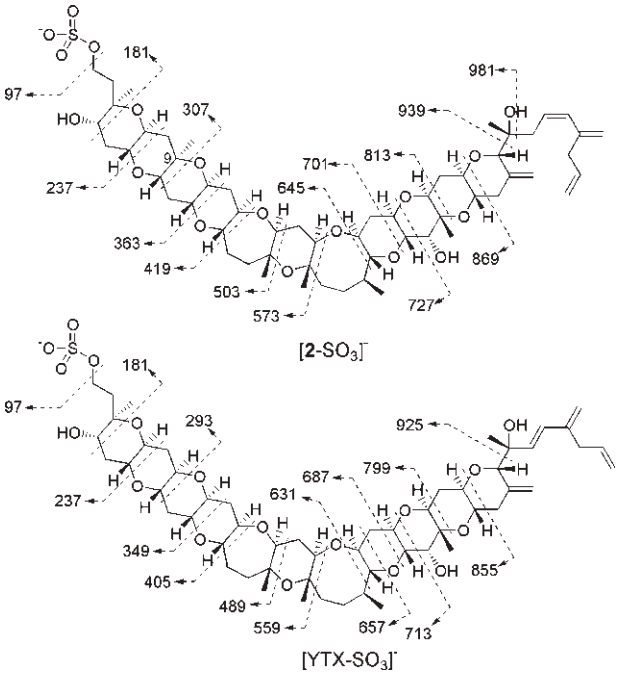

Fig. 1. MS^3 fragmentations observed for YTX and homoyessotoxin analogue **2** - see ref. 1.

Notwithstanding the power of modern MS techniques, NMR spectroscopy remains the method of choice for defining both atom connectivities and the three-dimensional stereochemistry of a molecule. The quantity of material required for the successful structure determination of algal toxins with molecular weights in the range 750–1250 Daltons has progressively decreased from more than 5 mg a decade or two ago, to less than 100 µg, even when using only moderate-field (400–500 MHz) instruments fitted with ambient temperature gradient shielded 5 mm probes. The sensitivity of state-of-the-art 750–900 MHz instruments fitted with cryogenically cooled microprobes is even better.

Raw power (highest possible field combined with the best hardware design) is always advantageous. However, careful attention to parameter setting, especially in two dimensional experiments, particularly the number of increments, repetition rate, number of scans per increment, and choice of transform conditions, can lead to the acquisition of data from a 400–500 MHz system, that approaches or sometimes even exceeds the quality and signal-to-noise of spectral data obtained from a less appropriately set up higher-field instrument, other than for factors related directly to field, *e.g.* spectral resolution. In our experience, there is considerable merit in optimizing the signal-to-noise ratio of spectral data that can be obtained in overnight or weekend experiments using known reference toxins, *e.g.* PTX-2 and yessotoxin, prior to embarking on

the more demanding task of defining the three dimensional structure and deriving a complete assignment of the ^{1}H and ^{13}C NMR resonances of a new algal toxin analogue.

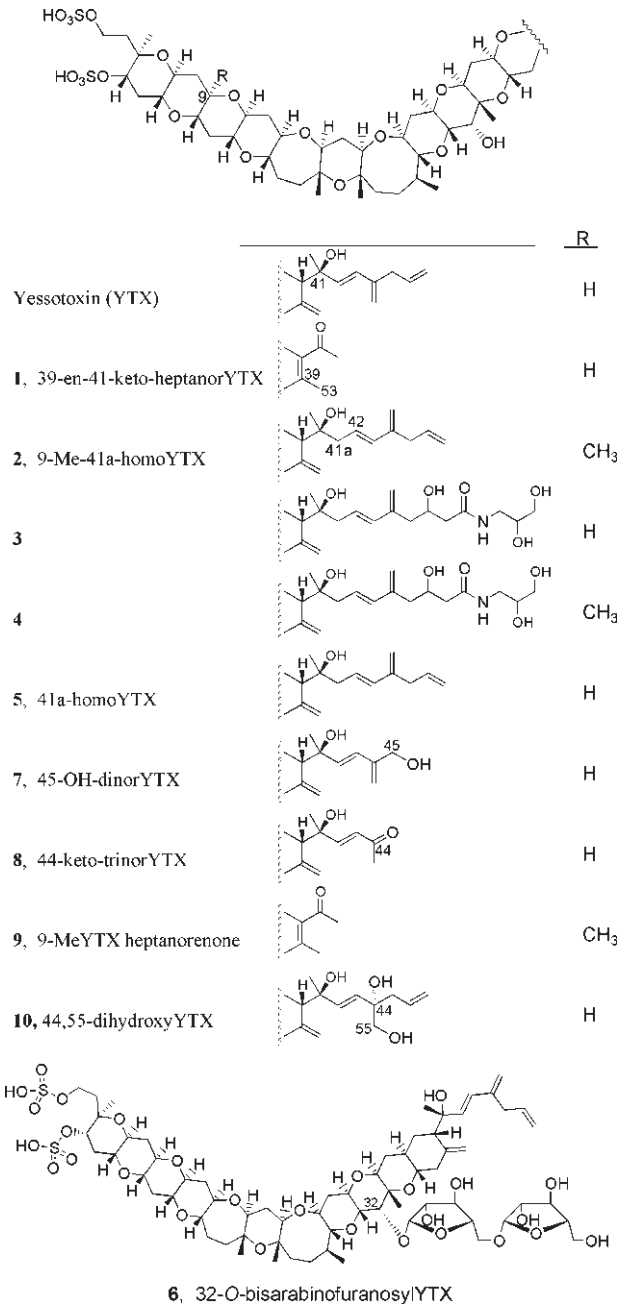

Chart 1. Structures of yessotoxins shown in their sulfonic acid forms.

Prior to a commitment being made in our laboratories in *ca.* 1996 to pursue the isolation and structural determination of sub-milligram quantities of new algal toxins, potentially harmful substances isolated from extracts of NZ shellfish have, with the notable exception of the determination of the absolute stereochemistry of gymnodimine,[2] been predominantly undertaken in Japanese or Canadian laboratories. Working collaboratively with other NZ and overseas scientists, we have reported the isolation and structure elucidation of numerous new yessotoxins, pectenotoxins, and several other algal toxins.[1,3-10] Recently, these studies have been aided greatly by access to a 600 MHz spectrometer equipped with microprobe and cryoprobe hardware, as part of a collaborative research agreement between the Chemistry Department of Oslo University, The National Veterinary Institute (NVI), Oslo, AgResearch at Ruakura (Miles) and a secondment agreement between the NVI and The University of Waikato (Wilkins).

^{1}H NMR Spectra

Despite the wide range of NMR experiments now available, a core group of 6–8 one- and two-dimensional NMR experiments frequently affords sufficient spectral data to define the structure of a new algal toxin. A standard approach is to firstly determine the ^{1}H NMR spectrum of the target compound. Invariably there is a substantial degree of overlap amongst methylene and methine proton signals in algal toxins with molecular weights in the range 800–1300 Daltons, as is apparent in the ^{1}H NMR spectrum (Fig. 2) of 42,43,44,45,46,47,55-heptanor-39-en-41-oxoyessotoxin (**1**) which was recently isolated from extracts of cultured *Protoceratium reticulatum*.[3] When solvent (or HOD) lines are excessive relative to target compound signals, they can be suppressed using single- or double-presaturation techniques that saturate the more slowly relaxing (long T_1) solvent (or HOD) lines, while not attenuating more rapidly relaxing target compound signals. Alternatively, this can be achieved using the WATERGATE technique. Modern spectrometer software allows these and other advanced NMR experiments to be set up and recalled by less experienced users as essentially *black box* experiments, other than for frequency setting and, if required, saturation power level adjustment.

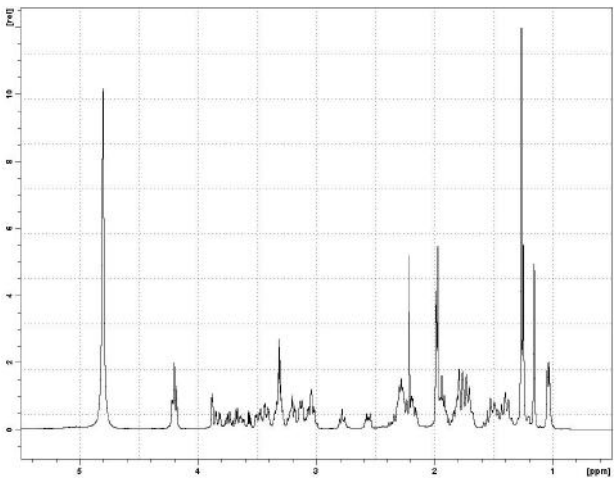

Fig. 2. ^{1}H NMR spectrum of 42,43,44,45,46,47,55-heptanor-39-en-41-oxoyessotoxin (**1**).

COSY and TOCSY Spectra

Thereafter, proton chemical shifts can be correlated in two dimensional correlation spectroscopy (COSY) and total correlation spectroscopy (TOCSY) experiments, or variants of these experiments, including double quantum filtered COSY, long range COSY, or COSY with solvent line presaturation. COSY data typically identify short range connectivities (^{2}J and ^{3}J couplings) whereas the spin-locked TOCSY experiment, also known as the HOHAHA experiment (Homonuclear Hartmann-Hahn Spectroscopy), can be optimized to detect short, medium, or long range correlations. Generally, in TOCSY experiments, a spin locked correlation (or mixing) time of the

order 15 msec affords a COSY-like spectrum whereas a mixing time of 150 msec enables connectivities for protons within 5–6 bonds of each other to be defined in vertical or horizontal columns appearing in the two dimensional spectra. The TOCSY spectrum of **1** is shown in Fig. 3 and detailed analyses of the multitude of correlations observed in the spectra of such medium to high molecular weight algal toxins is a time consuming, but rewarding task.

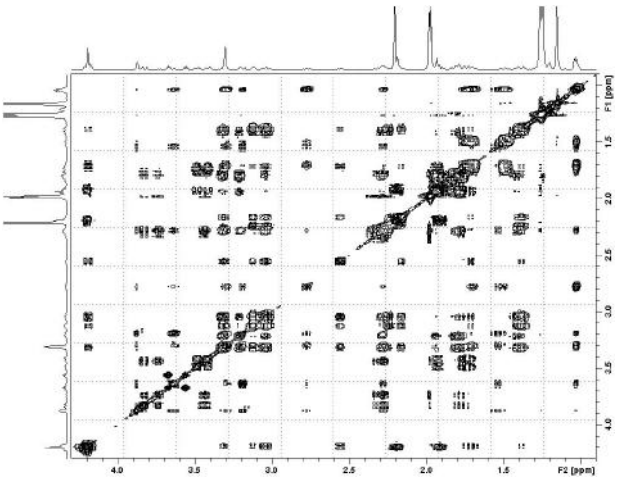

Fig. 3. TOCSY spectrum of **1**.

1D SELTOCSY

A powerful variant of the TOCSY experiment is the 1D-SELTOCSY (selective excitation TOCSY) experiment, a one dimensional selective excitation version of the more time-consuming two-dimensional experiment. Where knowledge of the correlations arising from only a limited number of protons is required, as is often the case for a substance known to differ from a known compound only in a single region of the structure, it may well be the method of choice. Advantages of the 1D-SELTOCSY experiment, compared to a conventional TOCSY experiment, include greater proton signal resolution (thereby allowing for coupling constant determination and the interpretation of vicinal couplings in six-membered rings using the Karplus equation), excitation only of a narrow region of the original ^{1}H NMR (typically 5–30 Hz), and a reduction in spectrometer time where only limited spectral data are required to define the location and stereochemical disposition of a particular group. Like TOCSY experiments, 1D-SELTOCSY experiments can be optimized for the detection of either short range (COSY-like) or long range correlations.

Selective excitation effectively eliminates solvent and impurity signals lines from these spectra. Despite ones best efforts at purification, detectable levels of phthalate and various tap grease components, surfactants and solvent stabilizers, are periodically encountered in precious samples that one is reluctant to subject to further cycles of clean-up and purification (particularly for samples that show a tendency to degrade during purification) pending initial establishment of the compound's structure. Provided target signals are not concealed by impurity signals, selective excitation techniques eliminate these impurity signals from consideration when setting up acquisition parameters such as receiver gain, and more importantly from plots of the resulting spectra.

Proton-Carbon Correlations

HMBC and HSQC Spectra

Having established short- and long-range proton connectivities, ^{1}J and longer range ^{2}J and ^{3}J proton–carbon correlations can be defined in gradient-selected heteronuclear single quantum correlation (HSQC) and heteronuclear multiple bond connectivity (HMBC) experiments, respectively, or variants of these experiments. Using gradient-selected inverse ^{1}H detection techniques, HMBC and HSQC spectra can now be obtained more readily than is the case for a conventional ^{1}H-decoupled ^{13}C NMR spectrum. Figs. 4 and 5 show the HSQC and HMBC spectra of **1**.

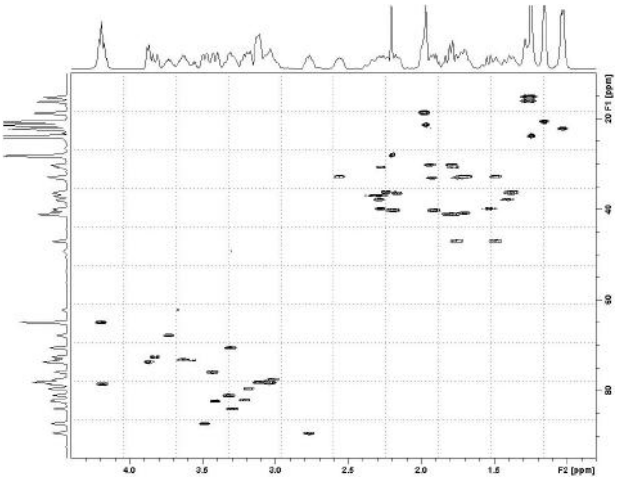

Fig. 4. HSQC spectrum of **1**.

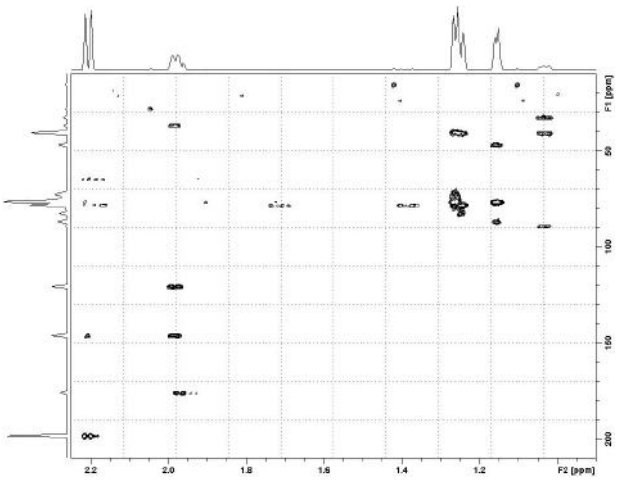

Fig. 5. Partial HMBC spectrum (CH_3 region) of **1**.

The resolution in the ^{1}H NMR axis of slices taken from the phase-sensitive HSQC spectrum of **1** was such that axial or equatorial orientation of methylene and methine protons in 6-membered ring systems could be defined. Typically, large ^{3}J axial-axial and ^{2}J vicinal couplings are resolved, whereas smaller ^{3}J axial-equatorial and ^{3}J equatorial-equatorial couplings are not resolved. Thus, the resonances of the axially and equatorially oriented $C(37)H_2$-protons can be readily distinguished (Fig. 6).

While ^{1}H-detected HSQC and HMBC experiments indirectly identify ^{13}C shifts with a precision of order 0.5–0.8 ppm, it is preferable to determine ^{13}C shifts directly with a precision of 0.1 ppm, and to define carbon types (C, CH, CH_2 or CH_3) using the distortionless enhancement by polarization transfer using a 135 degree selection pulse

(DEPT135) sequence. Frequently the acquisition of a ^{13}C spectrum requires 2–3 times more spectrometer time than is required to obtain good quality ^{1}H-detected HSQC and HMBC spectra.

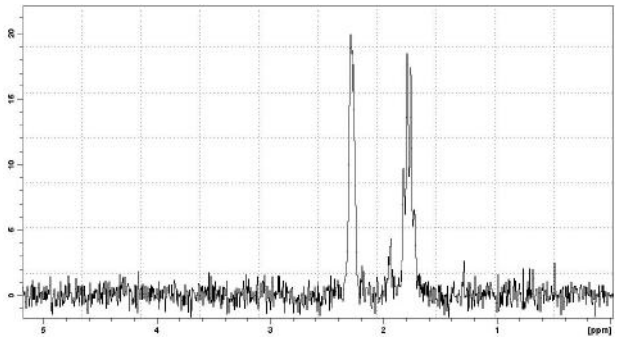

Fig. 6. HSQC slice showing the -C(37)H_2- methylene proton signals of **1**.

NOESY or ROESY Spectra

Careful consideration of a combination of ^{1}H, ^{13}C, DEPT135, COSY, TOCSY, HSQC and HMBC spectral data almost invariably enables a complete assignment of the ^{1}H and ^{13}C NMR assignments of new pectenotoxins, yessotoxins or other algal toxins to be derived, especially when considered alongside NMR data for known reference compounds. These data do not, however, allow for definition of the stereochemical relationship between specific functional groups. Data from nuclear Overhauser effect spectroscopy (NOESY) or the rotating frame variant ROESY, or from 1D-SELNOESY or 1D-SELROESY variants of these experiments, or the classic NOE-DIFFERENCE technique, can be utilized for this purpose. The spatial disposition of protons in ketone **1** was defined by correlations observed in its ROESY spectrum (Fig. 7).

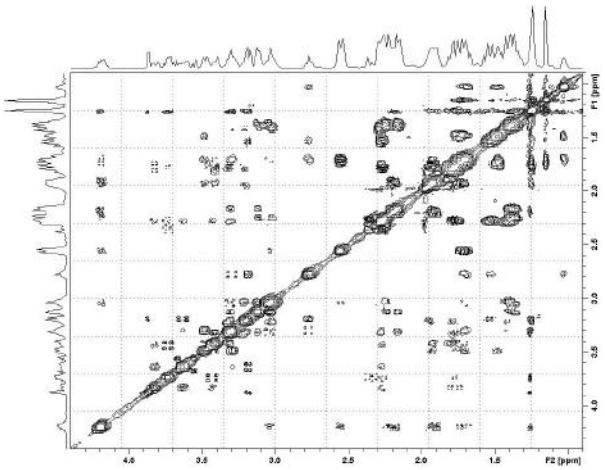

Fig. 7. ROESY spectrum of **1**.

We have used the NMR techniques described here to identify a number of new algal toxins, including a series of new yessotoxins, pectenotoxins and some gymnodimine and okadaic acid analogues. Some of the recently identified[1,3,4] yessotoxins are depicted by **1-10** (Chart 1) and we have also reported evidence for numerous other minor yessotoxins.[5] We anticipate that LC-NMR-MS[3] data will facilitate the identification of some of the minor components when considered alongside NMR spectral data for known YTX analogues. Arrangements are in place for LC-NMR investigations of the multitude of minor yessotoxins to be conducted collaboratively with our Norwegian colleagues.

Recently identified pectenotoxins include[6] **11-14** depicted in Chart 2 and a series of predominantly 37-*O*-acyl fatty acid esters of PTX-2 seco acid **15**.[7] Spectral data for PTX-11 **(11)** were determined collaboratively with Canadian workers while the structures of PTX-12 **(12)**, and the location of the acyl group in a series of PTX-2 seco acids esters, were determined collaboratively with Norwegian associates. Complete assignments of the ^{1}H and ^{13}C NMR assignments of PTX-2 SA **(15)** and 7-*epi*-PTX-2 SA **(16)** have also been achieved,[8] as has the structure elucidation of a number of other algal toxins including an okadaic acid *cis*-diol ester **(17)**[9] and gymnodimines B **(18)** and C **(19)**.[10]

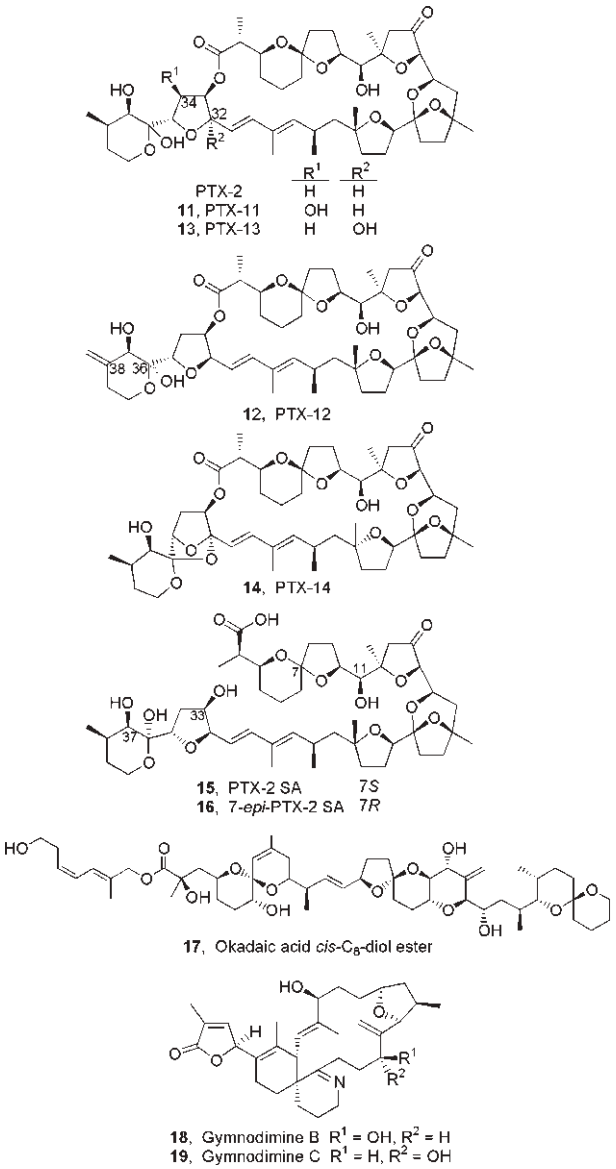

Chart 2. Structures of the pectenotoxins, okadaic acid derivatives, and gymnodimines.

Conclusion

The structure determination of sub-milligram quantities of newly isolation algal toxins using one- and two-dimensional NMR techniques, notably COSY, TOCSY, NOESY, ROESY, HSQC, HMBC, 1D-SELTOCSY, SELNOESY and SELROESY experiments, is now well es-

tablished. NMR analyses, in combination with MS^n data, have proved to be the cornerstone techniques for defining the structures of new algal toxins. It is likely that this will continue to be the case for the foreseeable future, since no other spectroscopic technique with the exception of X-ray crystallography (suitable crystals are rarely available) offers the same degree of insight into structural and stereochemical issues as does NMR spectroscopy.

Acknowledgements

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Faecal Sterols and Fluorescent Whiteners as Indicators of the Source of Faecal Contamination

Megan Devane,* Darren Saunders and Brent Gilpin

Institute of Environmental Science and Research Ltd (ESR), Christchurch
(E-mail: Megan.Devane@esr.cri.nz).

Human health risks due to infectious diseases in potable or recreational water are traditionally measured by assays for indicator organisms such as faecal coliforms, *Escherichia coli* and enterococci. These groups of organisms are common in most faecal material and their detection, which is relatively easy to establish, is usually a good indicator that water is contaminated by faecal material. However, the ubiquitous nature of these indicators in faecal material from humans, farmed animals, wild animals, and birds can make it difficult to identify the actual source of faecal pollution, particularly when there are multiple potential inputs. Replication of faecal coliforms in aquatic environments has also been reported and this could provide misleading results indicating a faecal source when the biological indicator is persisting in the environment long after the pollution event.[1,2]

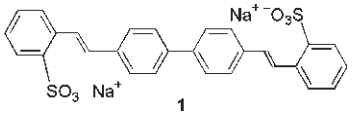
Chemicals associated with faecal material have long been attractive candidates for assisting with identification of the source of faecal pollution. Human faecal pollution is often the primary concern and caffeine, bile acids, human hormones, faecal sterols, and components of washing powders have all been utilised to varying degrees of success. Our experiences with two of these chemical indicators – fluorescent whitening agents and faecal sterols is surveyed below.

Fluorescent Whitening Agents

Fluorescent whitening agents (FWAs), also called *optical brighteners*, are fluorescent organic compounds that absorb ultraviolet light and re-emit most of the absorbed energy as blue light. They are used in manufacturing textiles and paper to improve whiteness, and are also added to most washing powders to replace those FWAs lost from clothing during wear and washing where they adsorb to the fabric and brighten clothing. Laundry detergents contain approximately 0.10-0.15% (w/w) FWA between 20-95% of which binds to the fabric during washing with the remainder be-

ing discharged with the washing liquor.[3,4] Most household plumbing mixes effluent from toilets with this *grey water* from the washing machine. As a consequence, in both septic tanks and community wastewater systems, FWAs are usually associated with human faecal contamination.

There exits a range of FWAs, but only one, 4,4'-bis(2-



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sulfostyryl)biphenyl (**1**) is used in NZ.[5] The key features of FWAs include:

- They are not known to occur as in nature.
- They are highly polar adsorbing strongly to the polysaccharides of paper and clothing.
- Irradiation by sunlight causes them to bind irreversibly to cellulose of protein, enabling binding to cotton and nylon fabrics.
- They are highly water soluble.
- They undergo photochemical degradation; τ½ is several hours under summer noon sun.
- They adsorb to soil but only photo-degrade in topsoil; they are assumed *persistent* below the photic zone.
- They are not readily biodegradable.
- They accumulate on sewage sludge with removal rates of 55-98% in sewage treatment plants.
- There are no known health effects of FWAs at levels seen in effluent or water.

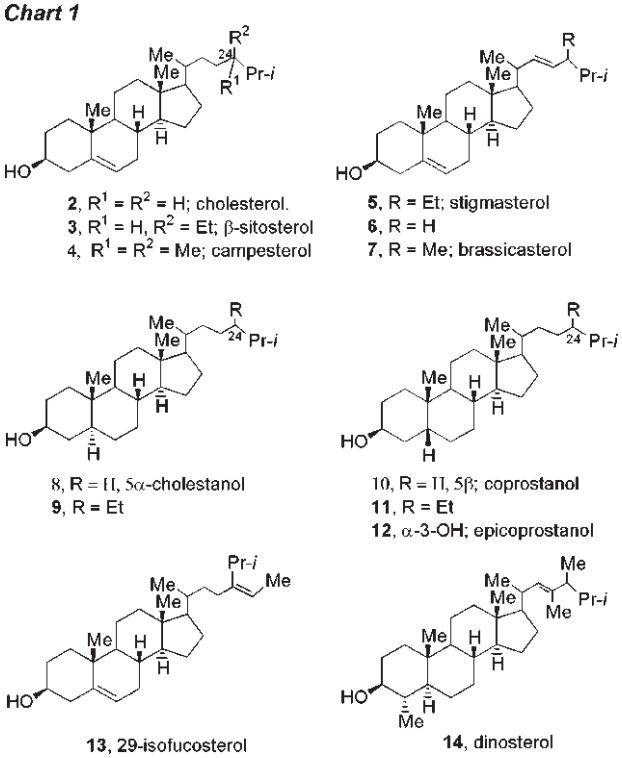
Analytical Methodology

FWA **1** was determined in water samples using HPLC with fluorescence detection after extraction from water (100 mL - and centrifuging to remove particulates when necessary) using a C-18 Sep-pak (an extract-clean column) (300 mg) pre-wet with methanol followed by deionised water. FWA **1** was eluted by the mobile phase (5 mL) and then injected (100 µl) on to the HPLC column.[6] Samples obtained from a local fresh water stream were spiked with the equivalent of 0.5 µg/L of **1** and sub-samples stored frozen at -20°C, refrigerated at 4°C in the dark, and at room temperature in ambient light, prior to analysis; none of **1** could be detected following storage at room temperature in ambient light for 48 hours. Samples stored at 4°C in the dark or frozen were found to be stable for at least a month.

Analysis of FWAs in septic tank and community wastewater consistently identified levels between 10 and 70 µg/L; with a detection limit of 0.01 µg/L, this allows for dilution by a factor of perhaps 1,000.

In surveys of streams and stormwater drains, we have detected low levels (<0.01 to 0.06 µg/L) of FWAs in many samples without any clear supporting evidence of human pollution. This probably reflects the low levels of human effluent which may or may not have health implications. Low levels of FWAs may also reflect upstream events with the FWAs surviving transport over large distances. Levels greater than 0.1 µg/L suggest a more significant degree of human sewage input. As a general recommendation, a level >0.2 µg/L is a strong indication of human sewage. Higher

Chart 1



levels of FWAs also generally contained high levels of *E. coli* but a direct linear relationship between the two is not always evident.

In our hands, FWAs are the best indicator of potential human effluent, and provide a focal point for attention. They do not, however, indicate whether human pathogenic (or even indicator bacteria such as *E. coli*) are also transported with the FWAs and contribute to the microbial population in the river. Currently, FWAs are the most practical indicator of human faecal pollution, and studies of their movement and degradation, relative to microbial pathogens and indicators, are required.

Faecal Sterols

Sterols are neutral lipids that have important biological functions in plants and animals, including cell membrane structures. Faecal sterols are C24-functionalized cholestane-based sterols found in animal faeces. The sterols present in an animal's faeces are determined by three factors, diet; synthesis by the animal (humans synthesize cholesterol), and transformations mediated by micro-organisms resident in the animal's digestive tract. Sterols eaten by animals include cholesterol (**2**) (an important membrane component in animals), and a range of plant-derived compounds that include 24-ethylcholesterol (β-sitosterol) (**3**) and stigmasterol (**5**) (Chart 1).[7] Upon entering the digestive tract some sterols are hydrogenated to stanols of various isomeric configurations by anaerobic bacteria. For example, cholesterol is the C_{27} precursor to 5α- and 5β-C_{27} stanols such as 5α-cholestanol (**8**) and 5β-coprostanol (**10**), hereafter referred to as cholestanol and coprostanol, respectively.

Coprostanol (**10**) is of particular interest in the detection of human faecal pollution as it is the principal sterol identified in human faeces and comprises *ca*. 60% of the total sterol concentration.[8] However, it and other sterols are also found in faeces from a range of other animals, and also

Table 1. Microbial and chemical analyses of water samples.

	Sample			
Faecal Indicator	1	2	3	4
Total coliforms[a]	65,000	2800	>2,400	11,000
E. coli[a]	6,200	2800	>2,400	2,200
FWA	0.31	<0.01	0.03	<0.01
Sterol/stanol (ppt)[b]				
Coprostanol (**10**)	1285	362	<70	1110
Epicoprostanol (**12**)	45	63	<70	630
Cholesterol (**2**)	8775	1914	5250	14890
24-Ethylcoprostanol (**11**)	405	1425	90	4380
Cholestanol (**8**)	960	296	760	5640
24-Ethylcholestanol (**9**)	160	1095	<70	8490
β-Sitosterol (**3**)	5510	1712	2000	31920
Ratios				
Total sterols	21090	8056	9330	81870
10:8	1.34	1.22	NA	0.20
11:9	2.53	1.30	NA	0.52
% **10:total sterols**	6%	4%	NA	1%
10/(**8**+**10**)	0.57	0.55	NA	0.16
10:12	28.56	5.75	NA	1.76
10:11	3.17	0.25	NA	0.25
Estimate % human sterols	100%	0%	NA	0%

[a]MPN/100mL. [b]Sterol in parts per trillion.
Note: Ratios for site 3 not calculated as **10** falls below detection limit.

in phytoplankton, zooplankton, aquatic plants, and protozoa.[9] Fortunately, they are generally at lower levels and, most importantly, are present in different ratios thereby allowing sterols from these sources to be distinguished. The major plant sterols are β-sitosterol (**3**), campesterol (**4**) and stigmasterol (**5**) (Chart 1), with **3** reported to be the most abundant sterol in plants.[10] The sterols found in higher concentrations in algae are 22-dehydrocholesterol (**6**), brassicasterol (**7**), isofucosterol (**13**), and dinosterol (**14**) (Chart 1).[7] Differentiation of human from herbivore faecal pollution relies on the high production of C_{29} stanols, such as 24-ethylcoprostanol (**11**) in herbivore faeces compared to human faeces. This is the result of herbivore consumption of plant material, which contains predominantly C_{29} sterol precursors. In comparison to **10**, which requires transformation via anaerobic bacteria residing in an animal intestine, **8** is the thermodynamically more stable isomer and commonly occurs in pristine environments where it is biosynthesized by phytoplankton, zooplankton and aquatic plants.

Analytical Method

Faecal sterol analysis is performed by filtering two or more litres of water through glass fibre filters that are then stored frozen until analysed. An internal standard is added and solvent extraction performed prior to hydrolysis, which is followed by back-extraction into hexane. The sterol fraction is eluted into methanol and silylated prior to analysis by GC-MS.[5] Each sterol and stanol result is expressed as parts per trillion (ppt).

With the advent of GC-MS technology there has been a resurgence in the analysis of faecal sterols because of lower detection limits and the ability to identify and quantify a wider range of sterols that co-elute and are inseparable by gas chromatography alone. Comparative analyses have indicated that sterols in samples collected from surface waters begin to degrade after 24 hours at 4°C, however, three cycles of freezing and thawing the samples could be performed without detection of sterol degradation. The recommendation, therefore, is to freeze samples after collection, prior to analysis as they are stable to freeze/thaw cycles.[11]

Practical Examples of the Use of FWAs and Faecal Sterol Data Analysis to Evaluate Water

Table 1 provides analytical results from three different water samples. Samples 1 and 3 are urban streams or stormwater drains, sample 2 is a rural stream, and sample 4 is a duck pond. Interpretation is only undertaken where >2000 ppt of total sterols is identified in a sample. The first ratios considered are coprostanol:cholestanol (**10:8**) and 24-ethylcoprostanol:24-ethylcholestanol (**11:9**), which when greater than 0.5 suggest faecal contamination (preferential reduction of sterol by gut microbiota), whereas a ratio less than 0.3 may suggest environmental reduction by, *e.g.* anaerobic bacteria in sediments. Higher ratios in the range 6-10 are more likely to be due to human pollution as reports on undiluted human faeces give ratios of >10, whereas undiluted sheep and cow faeces have values ranging from 1.5 to 3.0.[12] Sample 3 contains low levels of key sterols thereby preventing further analysis. Interpretation of the results is for faecal sterols not to support a faecal source of the *E. coli* present in the water. This contrasts with the duck pond sample (4) where significant levels of all sterols are present, but low ratios recorded do not support a human, and only marginally support a ruminant faecal source. In contrast, samples 1 and 2 are clearly above 0.5 and support a faecal source.

The ratio coprostanol:24-ethylcoprostanol (**10:11**) (**11** is the main herbivore sterol) is the primary indicator of the amount of pollution contributed by human faecal sources compared with the herbivores that have lower levels of coprostanol present. The ratio was >1.0 in site 1 (3.17) suggesting a human source of sterols, and «1.0 for site 2 (0.25), suggesting herbivore faecal contamination was most likely. Further support can be inferred from the ratios of **10**:total sterols and **10**/(**8** + **10**). If coprostanol (**10**) comprises greater than 5-6% of the total sterols, then it suggests human sewage as the source of the pollution.[13,14] Only sample 1 fulfils this criterion. Grimault *et al*.[15] suggested that the if the ratio **10**/(**8** + **10**) is >0.7 it indicates urban sewage, <0.3 unpolluted sediments, and 0.4-0.6 a complex intermediary. Of the samples examined, the duck pond ratios suggest non-human/herbivore faecal sources, while the others complex intermediaries.

Epicoprostanol (**12**) is found in low levels in fresh sewage and at higher levels in treated sewage due to the microbial conversion **2** → **10** → **12** during the treatment. Therefore, a high ratio of **10** to **12**, as shown by sample 1, suggests untreated faecal pollution.

Leeming *et al*.[12,16] have estimated the contribution from human sterols where a mixed pollution event with humans and herbivores is suspected using the formula:

***10/(10** + **11)** x 100%.*

A ratio >75% indicates a solely (100%) human source (sample 1, Table 1) while a ratio <30% indicates a solely herbivore source. A ratio between 75% and 30% with herbivore and human contamination suspected requires further calculation to take into account the 45% difference between % **10** and % **11**. This equates to a factor of 2.22 (100/45). Therefore, for every 1% of ***coprostanol*** that is below 75%, the proportion of faecal contamination due to humans is 2.2% less, as shown in the calculation below:

*[% **coprostanol**-30] x 2.22 = % human contribution*

For example, a sample containing 45% **10** and 55% **11** has as a contribution from humans: *(45 – 30) x 2.22 = 81.5%*. This implies, therefore, an 18.5% (100-81.5%) contribution from herbivores. Sample 1 has a ratio of 76% suggesting that the faecal pollution is 100% human derived, whereas sample 2 with 20% faecal contribution indicates 100% herbivore contamination.

Taken together with FWA analysis (Table 1), sample 1 supports the conclusion that the *E. coli* detected in this water sample are likely to have a human source. The water for this sample was derived from an open concrete-bottomed stormwater drain that flowed through an area surrounded by residential housing. Sample 2 contains significant sterols consistent with faecal origin, but clearly not human derived; together with the absence of FWAs herbivore inputs are suggested. This sample was collected from a stream that ran through farmland where cows and sheep were grazing.

Significant levels of *E. coli* in sample 3 are not supported by the presence of sterols, which for most are at the very low levels indicative of non-faecal sources. The low level of FWAs (0.03 ppt) may indicate events considerably further upstream making the source of the high faecal coliform concentrations unknown. Explanations include the controversial possibility that faecally-derived bacteria harboured by sediments are replicating in the environment,[17-19] or that they come from contribution by wild birds or dogs as the faeces of these species contain either none or only low levels of coprostanol and 24-ethylcoprostanol.[8]

Sample 4, from a duck pond, contains significant sterols highlighting the danger of detecting just coprostanol – the primary human sterol. Analysis of the sterol ratios is inconsistent with either a human or herbivore source, suggesting duck inputs will not, on the basis of sterols, be confused with human or herbivore sources.

Conclusion

The sources of faecal pollution can be difficult to ascertain requiring alternative methodologies. Analytical chemistry has much to offer biology on issues of microbial water quality, with faecal sterols and FWAs able to assist in identifying the source of the contamination. Where sufficient sterols are present, analysis can identify the faecal material in a water sample and indicate whether it is consistent with a human or herbivore source. Some assessment of proportionality is also possible providing ratio analyses of faecal sterols collate all ratios rather than be based on a single result. Careful site assessments are also essential.

In addition to source potential, chemical markers can offer advantages over microbial indicators. Toxic pollutants, *e.g*. chemical disinfectants and heat, may lead to the death of biological indicators, *e.g*. faecal coliforms, while some pathogens may still be present. Faecal sterols are relatively resistant to physical and chemical degradation and can, therefore, be useful indicators where levels of microbes are low but faecal contamination is still suspected. Furthermore, the persistence of sterols in anaerobic sediments makes them candidates for a long-term signature of faecal contamination.

Future study on extending faecal sterol analyses to contributions from dog, cat, avian, and feral animal sources, and to evaluation of survival and transport of chemical indicators relative to both indicators and pathogens is to be undertaken.

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Article

The Curious Case of Phosphate Solubility

Andrew J. Pratt

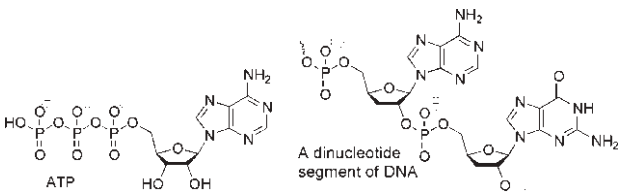
Chemistry Department, Canterbury University, Christchurch (e-mail: andy.pratt@canterbury.ac.nz)

Introduction

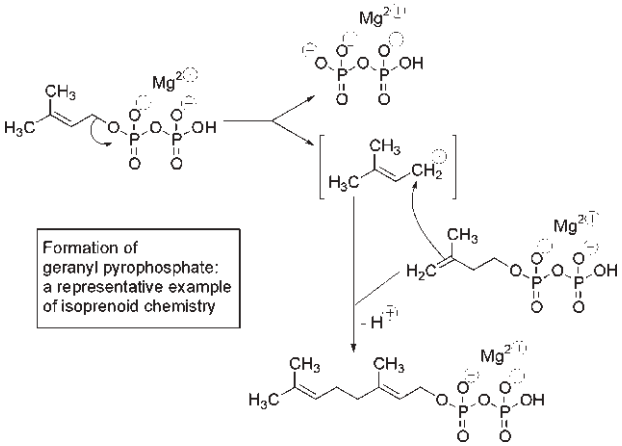
Phosphate is an essential chemical for life. In many marine environments it is a biolimiting macronutrient. The limitations in phosphate availability are related to the insolubility of important phosphate salts. Indeed, the relative solubilities of iron(II) and iron(III) phosphates have been widely considered as a key determinant in the phosphate cycle. The importance of understanding phosphate availability for addressing contemporary environmental issues, such as lake eutrophication (nutrient pollution), has led to more sophisticated analyses of phosphate sedimentation. The dynamics of iron phosphate solubility carry implications beyond contemporary environmental issues. It is likely that the interaction of iron and phosphate, along with sulfide and other species, has been important throughout the evolution of the biosphere. It is suggested that the sparingly soluble nature of iron(II) phosphate has played a key role in the biosphere from the emergence of life to the present day.

Why Nature Chose Phosphates

In an excellent review, Westheimer[1] laid out the chemical basis of the utilization of phosphates by living systems. Phosphate, a strong, tribasic acid, is ionized at neutral pH in aqueous environments. It can link up to two groups, as esters, *e.g.* in nucleic acids, and remain ionized. All these ionized species are retained within cells because of the inability of charged species to traverse non-polar cell membranes readily.



Phosphate esters and anhydrides, *e.g.* ATP, are thermodynamically unstable with respect to hydrolysis, but their negative charge repels nucleophiles and renders them kinetically stable. The combination of thermodynamic instability coupled to kinetic stability is a hallmark of life. Nucleic acids are polyesters that are sufficiently durable in water to house and transmit genetic information, but sufficiently labile thermodynamically to allow their subsequent recycling—polyphosphates such as ATP accomplish the impressive job of being water-compatible dehydrating agents for life! When needed, these kinetically stable species are activated by appropriate enzymes acting in concert with multivalent metal ions. Finally, phosphate derivatives, as the conjugate bases of strong acids, are good leaving groups, *e.g.* they are utilized as carbocation precursors in isoprenoid chemistry. Pyrophosphate, complexed to magnesium ions, is a ubiquitous leaving group in biochemistry.



The Hassle with Choosing Phosphates: Solubility

The many desirable chemical features of phosphate come with a cost: the limited solubility of phosphates in the presence of many multivalent metal cations. As Williams has pointed out, this factor has been a major issue in the evolution of phosphate biochemistry[2] and raises interesting questions about how phosphate came to play such an integral part in core metabolism.

The chemistry of phosphate within cells is primarily mediated by magnesium ions as the corresponding salts are soluble in aqueous media. By contrast, calcium phosphate is insoluble. Cells maintain low levels (10^{-7} M) of intracellular calcium, in part, because they must avoid the adventitious precipitation of calcium phosphate salts. Having adapted to export excess calcium ions, organisms have gradually evolved the ability to exploit the corresponding concentration gradients and solubilities. With higher concentrations of calcium outside cells, the temporary influx of calcium ions is now exploited as a biochemical signalling device. Furthermore, animals deposit extracellular calcium phosphate as bone: not just a useful material but also a dynamic store and buffer of both calcium ions and phosphate. Calcium phosphate, as apatite minerals, is a major sink of phosphate. The insolubility of this and other phosphate salts, control phosphate availability in many aqueous habitats.

The Phosphate Cycle: Interactions with Iron

The phosphate cycle plays a key role in governing the productivity of the planet.[3] As such, phosphate availability has a critical impact on the environment. Control of phosphate levels in the environment is the subject of ongoing discussion. Thus, it has been suggested that fertilizing the oceans with phosphate might be used to stimulate algal growth and hence to reduce carbon dioxide levels in an effort to address climate change issues.

Phosphate levels are controlled by solubility processes: continental weathering is the most important source of bio-

available phosphate, whilst the steady state levels of phosphate are subsequently controlled by mineral deposition. For example, it has been known for many decades that oxic lake sediments retain phosphate more efficiently than anoxic sediments, and that oxic sediments release large amounts of phosphate when they become anoxic. These observations led Einsele[4] and Mortimer[5] to develop a model for the phosphate cycle in lakes, in which the redox chemistry of iron species in sediments is coupled to phosphate availability. In this model, phosphate is sequestered by adsorption onto the surface of iron(III) oxide hydroxide (Fe(O)OH) in aerobic sediments. When these sediments are buried, the iron(III) is reduced to iron(II). Iron(II) phosphates have a greater solubility than those of the corresponding iron(III) species and it is assumed that this differential solubility leads to the release of soluble phosphate.

All chemists in NZ are aware of the incredible impact of superphosphate on agricultural productivity. The downside of this has been the environmental impact of enriched phosphate levels in waterways due to fertilizer run-off. This has generated a pressing, international environmental issue: the excess phosphate accelerates growth and is an important factor in anthropogenic eutrophication of rivers and lakes. Efforts are being made to control phosphate levels in waterways both by decreasing inputs, through more careful fertilizer use and irrigation, and by maximizing the trapping of phosphates by sedimentation processes. Thus, there has been a long standing effort to address the eutrophication of Lake Sempach in Switzerland, both by decreasing phosphate inputs and decreasing phosphate release from sediments. Based on the iron phosphate redox cycling model of Einsele and Mortimer, the latter issue was addressed via artificial oxygenation of the hypolimnion (bottom waters) in an effort to minimise anaerobic release of phosphate from sediments. After a 15 year study, it is clear that diminishing phosphate inputs has reduced eutrophication. However, hypolimnion oxygenation has not resulted in a lowering of lake phosphate levels.[6] The problem is likely due to an oversimplified notion of iron phosphate solubilities. It is important to understand the limitations of the Einsele and Mortimer model in order to inform detailed analyses of the cycling of phosphate in such lake environments, and in the wider biosphere.

Why is phosphate released when an iron(III) phosphate-containing sediment becomes anaerobic? It is not a simple case of the relative solubilities of iron phosphates. Although iron(II) phosphate is formed in such sediments, and is significantly more soluble than its iron(III) counterpart, it is still only sparingly soluble. Unless iron is precipitated as an even less soluble mineral it can easily accumulate to levels that lead to efficient precipitation of iron(II) phosphate. The solubility product of vivianite, $Fe_3(PO_4)_2.8H_2O$ ($\log Ks_0 = 36$), is sufficient for μM levels of iron(II) to deplete phosphate to μM levels also. The most likely mineral to trap iron(II) in anaerobic sediments is sulfide, which is generated in such sediments by microbial reduction of sulfate. Iron(II) sulfide is significantly less soluble that iron(II) phosphate and so can sequester iron(II) that is formed by reduction. It is likely that it is the combination of iron(III) reduction and sulfate reduction that leads to the sequestration of iron as iron(II) sulfides and the liberation of phosphate. From this perspective, the observed uptake of phosphate by aerobic sediments is likely to be due to diminished sulfide levels, rather than surface iron oxidation. Based on these ideas it has been proposed that the ratio of iron(II), phosphate and sulfide in the anoxic sediment controls phosphate retention and not the oxic sediment surface.[7]

This type of analysis illustrates the complexities of dealing with environmental issues when dealing with complex chemical equilibria. They also illustrate the shifting of environmental processes that can occur by perturbing the solubility of sparingly soluble salts. However, the relevance of these analyses go far beyond the contemporary environment; they inform us of constraints facing the adoption of phosphate as a key metabolite for life.

Phosphate, Iron, and Sulfide in the Origins of Phosphate Metabolism

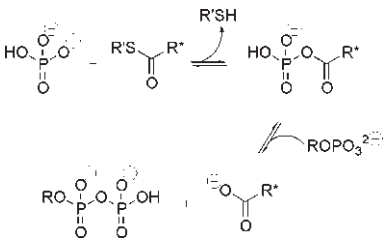
Soluble phosphates are present in cells at mM concentrations. By contrast, only μM concentrations of phosphate are present in the sea, due to phosphate mineral deposition. This is a first indication of the challenge facing the adoption of phosphate as a core metabolite. However, the discussion of phosphate release from anaerobic sediments hints at a much more substantial problem facing the origin of life. The most plausible habitats for the emergence of life (hydrothermal systems) are awash with iron. Not surprisingly, given the previous discussion, these environments are denuded of soluble phosphate. Furthermore, magnesium, phosphate's partner in contemporary biochemistry, is also scavenged from the hydrothermal fluids to form silicate minerals.[8] How could phosphate-dependent life arise in such an environment? In order to answer this question we have to back-track a little and examine why hydrothermal systems are plausible habitats for early life, and to evaluate whether the biochemistry of phosphate is compatible with such conditions. Understanding the opportunities and constraints of phosphate chemistry under these conditions has the potential to inform our understanding of the emergence of life on earth.

One of the most plausible scenarios for the origin of life is that it emerged more than three billion years ago at hydrothermal vent systems on an anaerobic earth.[9] At these mid-ocean ridge sites seawater percolates into a fragmentary crust and is heated to more than 300 °C. Once superheated, the water leaches minerals from the crustal rocks and deposits them in mineral mounds at the surface. These unlikely sites are often luxuriant oases in the middle of an almost sterile deep ocean. The iron sulfide minerals provide a continuous input of redox energy to fuel the ecosystems.[10] Iron sulfide can spontaneously form porous micro-compartments that have the capacity to act as reaction chambers, fulfilling many properties of cells such as redox and pH gradients, and compartmentalization.[11] Iron sulfide systems have also been found to catalyze a range of biomimetic transformations[12] including carbon[13] and nitrogen fixation.[14] These processes mimic contemporary iron/sulfur-dependent processes of anaerobic metabolism.[15]

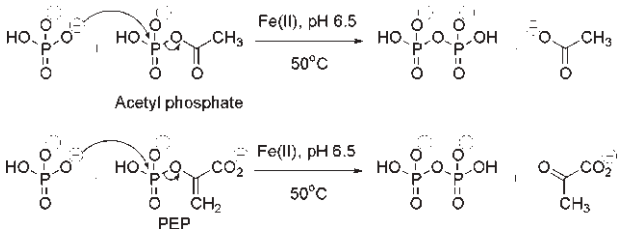
Phosphate is only present at vanishingly low levels in hy-

drothermal fluids, but it is not absent from the hydrothermal environment. It is present, admixed with iron, sulfide, and other prebiotic chemicals, as a precipitate rather than free in solution. Precipitation of phosphate species at hydrothermal vent sites[16] provides a possible concentration mechanism. Hence, one possible way in which phosphate could have been incorporated into an emergent iron/sulfur-based life is via heterogeneous chemistry. We have undertaken a study of key biomimetic phosphate chemistry under such conditions which lends support to this possibility.

Our studies have focused on the biomimetic generation of polyphosphates in aqueous media.[17] As indicated above, phosphate anhydrides, notably ATP, are used in biochemistry as dehydrating agents in water. Once made, polyphosphates are ubiquitous phosphoryl donors for metabolism. Simple inorganic polyphosphates, such as pyrophosphate, can be utilized in an analogous way to ATP.[18] In contemporary biochemistry ATP is generated both by exploiting concentration gradients at cell membranes and via direct *substrate-level* phosphorylation, involving phosphate transfer to phosphoryl donors, notably acyl phosphate and phosphoenolpyruvate (PEP). Acyl phosphates are, in turn generated from thioesters produced via primary metabolism. Thioesters, acyl phosphates and PEP are all plausible prebiotic molecules.



Phosphate and activated phosphoryl donors are efficiently precipitated from aqueous solution by the addition of iron salts at mM levels. In contrast to simple solution chemistry, the resulting co-precipitates facilitate the efficient production of pyrophosphate from inorganic phosphate and activated phosphoryl donors; pyrophosphate being formed from acetyl phosphate and PEP in yields of up to 25 and 14%, respectively. Pyrophosphate formation is most efficient at pH 6.5 and 50 °C, conditions that are compatible with many biochemical processes.



The co-precipitation of both phosphate and a phosphoryl donor on iron(II) diminishes electrostatic repulsion between the reactants, in much the same way as magnesium ions in phosphoryl-transfer enzymes. As is required in hydrothermal systems, the catalysis of pyrophosphate formation is tolerant of, but not insensitive to, the presence of sulfide ions, *e.g.* pyrophosphate is produced from acetyl phosphate in 12% yield in the presence of equimolar amounts of sulfide. These reactions mimic the extant biosynthesis of ATP from acetyl phosphate or phosphoenolpyruvate. Interestingly, under similar conditions, these minerals also retard the hydrolysis of pyrophosphate; allowing the accumulation of polyphosphates in aqueous media – a key requisite for foundational phosphate metabolism. Perhaps then, it is the sparingly soluble nature of iron(II) phosphate that was initially important in its biochemical exploitation. Co-precipitation of iron(II) phosphate species concentrates them, brings them into close proximity, and alleviates electrostatic repulsion. However, because the resulting salts are still sparingly soluble, a dynamic interaction with the aqueous environment is maintained; the products can then be utilized by other (bio)chemical processes in the surroundings.

Iron(II) Phosphate and the Importance of Being Sparingly Soluble

Phosphate solubility has been a key issue for life since its origins. The interplay of phosphate with iron has been a dynamic issue throughout life's history and, for all the changes in the environment of the earth from anaerobic to aerobic, it continues to the present. The sparingly soluble nature of iron(II) phosphates makes them fascinating, dynamic, components of the biosphere, a fact that life may have recognized from the very start.

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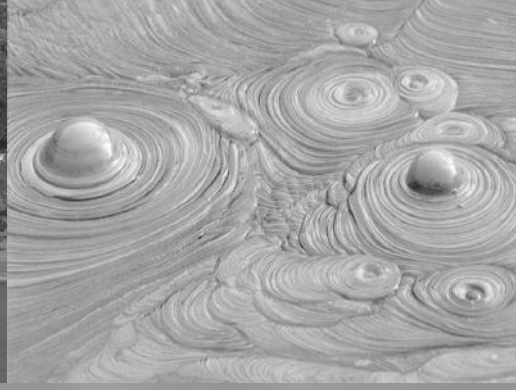

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Article

Water Oxidation by Ruthenium Dimers

Matthew I. J. Polson

Chemistry Department, Canterbury University, Christchurch
(E-mail: matthew.polson@canterbury.ac.nz).

Introduction

Hydrogen is generally considered the best fuel for the future due to its ease of application in fuel cells and clean burning properties. This fuel could be used to replace oil is the source of electricity, heat and transportation to give us a *hydrogen economy*. This future has many issues to be overcome before it can be realized, but the most pressing is the production of this most desired gas. Currently most hydrogen is produced from fossil fuels, and offers little advantage over oil.[1]

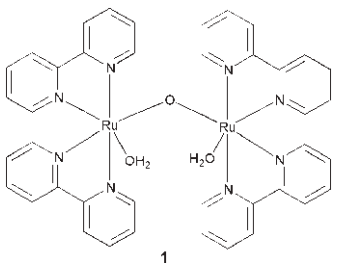
Transformation of water into hydrogen and oxygen (Eq. 1) requires an energy input of about 120 kJ/mol which is equivalent to that of four 1008 nm photons. This implies that most of the energy which is incident on the earth from the sun could be capable of contributing to the production of hydrogen. Calculations that take into account energy loses from higher energy photons, and quantum efficiencies less than unity, give a theoretical efficiency of about 30% for light of wavelength 770 nm or longer, presupposing a system involving only one light absorbing unit; a system involving two light absorbing units of different energies can have a theoretical efficiency of *ca*. 41%.[2] Thus, an attractive system would use catalysts to produce H_2 and O_2 from H_2O with sunlight driving the process. Although there are acceptable methods of catalyzing H_2 production, O_2 has received much less attention and for the process to be catalytic, it must be produced at the same time as hydrogen. In nature, the process is accomplished though the O_2-evolving centre (OEC) in Photosystem II which, while not fully understood, is known to comprises of four manganese atoms driven by light absorption from a series of porphyrin arrays.[3] Attempts have been made to use Mn-containing complexes to mimic this system but this approach is yet to yield a complex capable of producing O_2 from water.[4] On the other hand, in 1982 one ruthenium complex, a relatively simple dimer, was found to produce O_2 in the presence of a strong sacrificial electron acceptor.[5]

$$2H_2O_{(l)} \rightarrow 2H_{2(g)} + O_{2(g)} \text{ .....(Eq. 1)}$$

An overview of the catalyst used to decompose water and the mechanisms that could apply follows, although the work has yet to evolve to the stage of providing O_2 using only light energy. It focuses on the advances of the past five years and the nature of O_2-producing complexes. These compounds act as the catalyst for the oxygen-producing half cell of redox equation (1), freeing protons to be used for the desired hydrogen production; the energy for the catalytic process comes from an oxidant. The oxidation state of Ru is referred to using the notation: 3.3 for Ru(III)-O-Ru(III), 4.5 for Ru(IV)-O-Ru(V), *etc*.; the mixed valance state 3.4 mostly likely is delocalised extensively over the two metal atoms.

$[(bipy)_2Ru(H_xO)ORu(OH_x)(bipy)_2]^{n+}$

Ruthenium dimer (**1**) catalyses H_2O decomposition when supplied with an excess of oxidising agent, typically cerium(IV) ammonium nitrate . It is isolated from the synthesis in the 3.3 state and can be oxidized with the loss of four electrons to the 5.5 complex. The final step releases O_2 and regenerates the starting 3.3 complex from addition of two water (solvent) molecules.[6] The X-ray structure of the 3.3 complex shows the coordinated H_2O molecules at 90º to each other but free to rotate about the Ru-O-Ru bond.[7] The H_2O molecules can protonate/deprotonate depending on the solvent pH in processes that are influenced by the redox states of the Ru atoms which, in turn, have a redox potential influenced by the pH of the solution. This means that for those processes in which the redox potential is pH dependant, a change in protonation must accompany the change in the redox state.



1

Electrochemically, the 3.3 state is oxidized to the 3.4 state by one electron.[8] Then follows a complex process with three possible interpretations: i) 3 x one-electron processes occurring at similar potentials, ii) a two-electron process to the 4.5 state followed closely by one-electron oxidation,[7] and iii) a one electron process to a 4.4 state followed by a two electron process directly to the 5.5 state.[9] Mixing equimolar samples of the catalyst in the 3.3 and 5.5 states produces only one compound presumed to be 4.4. Path (i) would provide a complex mixture of all three states (3.4, 4.4 and 4.5). The two electron process of path (ii) implies the intermediate 4.4 state to be unstable and to disproportionate to an equimolar mix of 3.4 and 4.5.The distinct electronic spectrum of the 3.4 compound was not detected during the experiment making path (iii) the most likely. Moreover, calculations indicate any redox process involving a 4.5 state would have to be proton-linked to give the necessary potential in the region of 1.4 V.[9] This is in conflict with the experimental evidence which shows the process at this voltage to be pH independent. The work is further complicated by the precipitation of a highly oxidized species as its perchlorate salt.[7] Stoichiometric addition of the oxidising agent has led to isolation of the reactive 3.4 state that, over the 10-30 min of the O_2-producing experiment, did not undergo water ex-

change; its half-life exceeds 80 days. The key experiment used to elucidate the mechanism of the reaction employs ^{18}O-enriched water. The early experiment[10] has now been repeated[8] with continuous sampling and O_2-monitoring by mass spectroscopy. The amount of ^{18}O-^{18}O produced solely from the $H_2{}^{18}O$-containing catalyst is negligible. In the initial stages, an approximate 1:1 ratio of ^{16}O-^{18}O and ^{16}O-^{16}O is formed.

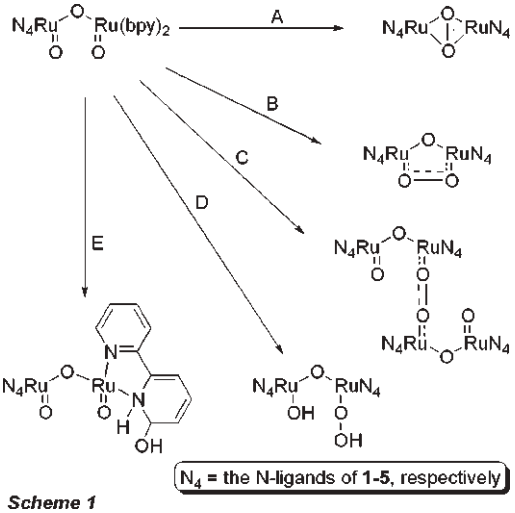
When the bipyridyl ligands of **1** are 6, 6'-disubstituted dimerization becomes impossible and the complexes fail to evolve O_2 under the reaction conditions.[11] Thus, there is a requirement for a second ruthenium atom, or at least some motif which can reproduce its hydrogen bonding ability.

Other catalysts

For nearly 15 years **1** was the only ruthenium complex known to catalyze *water to oxygen* although one group working in this area used the simpler $(NH_3)_5RuORu(NH_4)ORu(NH_4)_5$. This compound does provide O_2 but it also gives N_2 from the decomposition of the amine ligands. Encapsulation of the complex in plastic membranes helps to control this,[12,13] but the newer complexes **2-5** (Chart 1), developed over the past few years, show more promise (see below). The most important factors that relate to the catalyst are the Turnover Number (TN) (which describes catalyst stability in terms of the number of cycles the molecule can survive) and the rate of O_2 production ($k_{O\text{-}O}$). For bipyridyl dimer **1** the TN ~7-10 and the $k_{O\text{-}O} = 2.3 \times 10^{-3}$ s^{-1} at 25 ºC in 0.5 M acid with a 100 fold excess of oxidant.

The literature has recorded five pathways by which oxygen production from the fully oxidized Ru 5.5 state could occur. The final step of each is shown in Scheme 1. These are broadly classified as intra- or bi-molecular[14] and are shown in Scheme 1 where the stylized N_4 represents each of the ligand types in **1-5**. Path A requires the bridging oxygen to bond to one of the pendant Ru=O oxygens to form a symmetrically bridged species and then expel water. Raman studies[15] have shown only small changes to the Ru-O-Ru stretching vibration occur during the course of the reaction and these are ascribed to oxidation state changes of the ruthenium atoms. The lack of major change in the frequency implies the moiety not to be altered during O_2 production, and recent evidence from exchange of water and formation of mononuclear by-products make this pathway even less likely; isotopic labelling shows no substitution at the bridging oxygen.[8] Path B received much support until recently. Here, the pendant oxygens bond to give a peroxy bridge prior to rapid O_2 expulsion and replacement by water. Initial isotopic labelling experiments supported this mechanism but recent more accurate results discussed below argue against it.

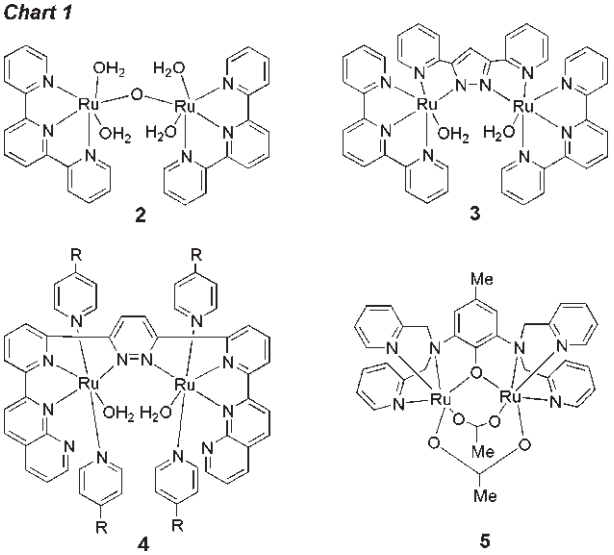
Like path B, bimolecular path C is discounted by the labelling experiments as both the oxygen atoms necessarily come from the catalyst and require the interaction of two catalyst molecules—but it does have relevance for O_2 production from a mononuclear complex. Paths D and E involve radicals and have gained support in recent times. Path D equates to the original explanation for O_2 formation, with O—O bond formation on one ruthenium atom by the attack of a radical Ru-O on a (solvent) water



Scheme 1

molecule. It gains strong support from DFT calculations[9] that provide a low energy pathway for O_2 formation and a simple explanation for ^{18}O-^{16}O production. However, it fails to account for the ^{16}O-^{16}O oxygen.[16] Path E offers an explanation[14] for ^{16}O-^{16}O formation. Reportedly, it is possible for water to add to bipyridine coordinated to ruthenium as well as other metal complexes.[17,18] More than one water may be attached to the complex at any time thereby allowing for the formation of unlabelled oxygen. However, the details of this route have been called into question repeatedly, and it must be viewed with suspicion.[19,20]

Chart 1



Of the new catalysts **2-5**, Meyer produced analogue **2** of **1** that carries a terpyridine ligand on each Ru atom leaving two of each six coordination sites for water ligands.[21] Oxidation of this complex is facile but oxygen production is quantitative per mole of complex, not catalytic. This stems the formation of mononuclear complexes and the incorporation of perchlorate ions, both of which terminate the catalytic cycle. In the work of Llobet, *et al*.[22,23] the bridging oxygen of **2** is replaced by a bridging 3,5-dipyridylpyrrazole moiety as **3**. Here the pyridines co-ordinated to provide for two water ligands as in **1**, but the stability of the complex is improved.The removal of H^+ provides for favourable -O•••H-O- bridging. However, the stability of the complex is only modestly improved even though TN increases to 20 with $k_{O\text{-}O}$ rising by a factor of six to

1.4×10^{-2} s^{-1}.[24]

A more substantial structural change has come from the laboratory of Thummel[25,26] with the synthesis of **4**. Here the bridging unit is a pyridazine ring bonded through positions 3 and 6 to separate 2-(2-pyridyl)-1,8-naphthyridines as the critical ligands. These latter bidentate ligands are held such that they point into the cavity that holds the coordinated water and each can, through the available N atom, H-bond to water such that the latter is held in an appropriate orientation for oxygen formation. The co-ordination sphere is completed with two 4-substituted pyridines per Ru. Substituent (R) has been varied from weakly donating (-Me) to strongly withdrawing ($-CF_3$) to elicit the effect on catalysis whereby an increased stability in **4** is reflected by TN which increases to 100 (CF_3) and 3200 (CH_3); the rate increases to $k_{O\text{-}O} = 7.7 \times 10^{-2}$ s^{-1} (**4**; R = Me). This is seen more clearly in the case of the similar mononuclear complexes. Here, the bulky ligands prevent dimer formation as demonstrated by Sauvage[11] for 6,6'-disubstituted derivatives of **1**. Thus there can be no requirement for one water on each of the two ruthenium atoms because pre-organization is controlled by the naphthyridine rings. Interestingly, $k_{O\text{-}O}$ is much lower for mononuclear complexes thereby implying that there is only one pathway for O_2 formation rather than the two for a binuclear complex.[26]

The binuclear complex **5** has been prepared by Sun.[27] Its design follows extensive study of corresponding Mn complexes that, unfortunately, fail to produce O_2. This complex again uses bridging oxygen but here it is phenolic in nature.[4] The ligands also differ through use of the nitrogen of an aryldialkylamino moiety that acts both as ligand and structural motif for two picoline units. The remaining two Ru vacancies are occupied by acetate as bridging ligands incorporated during synthesis. No data on O_2 production from **5** have been reported, but a further important step has seen incorporation of the light absorbing $Ru(bipy)_3$ unit. Preliminary electron transfer experiments indicate that this addition provides for extraction an electron from the catalytic unit upon excitation with visible light.

Conclusions

This brief overview indicates directions being taken in this blossoming field of research. To date, this has relied on chemical oxidants driving O_2-production but it is now ready to move to the next step and use light as the energy source. When coupled with a similar hydrogen producing unit an excellent source of cheap, clean energy can be expected. As energy becomes more expensive from the demands of a higher quality of life by more people, the traditional energy sources are becoming depleted; there is a clear demand for new and more economic options. Recent resurgence in technologies for storage and usage of hydrogen suggests that H_2 production from water using light will revolutionize the world's energy market.

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Fluorinated Analogues of Biological Molecules: Accessing New Chemical, Physical and Biological Properties

Michael Edmonds[a] and Victoria Peddie[b]

[a]School of Applied Science, Christchurch Polytechnic Institute of Technology, Christchurch (e-mail: edmondsm@cpit.ac.nz).
[b]Department of Chemistry, University of Canterbury, Christchurch.

Introduction

The introduction of fluorine into biological molecules often results in significant changes in their chemical, physical, and biological properties. As such, fluorinated analogues of biological molecules provide useful tools for probing and modifying the functions of biological systems. Where such modifications are beneficial to humans the fluorinated analogue becomes a potential therapeutic agent.

The potent effect of introducing fluorine is demonstrated here by describing the unique properties of a number of fluorinated biological compounds (amino acids, peptides and sugars). In particular, a focus on compounds that possess a single fluorine atom at a chiral centre serves to demonstrate how even a single F atom can have profound effects on the properties of a biologically active molecule. However, before discussing specific examples let us first consider some of the common effects that the introduction of fluorine can have on an organic molecule.

• As the most electronegative element, fluorine introduction has a potent electronic effect, particularly on nearby functional groups, *e.g.* the acidity of an adjacent carboxylic moiety is increased.

• Fluorine is similar in size to hydrogen and is often treated as a steric isostere of hydrogen. This assumption has been disputed due to the difference in C-H and C-F bond lengths (106 and 134 pm, respectively) which does affect the size of fluorinated molecules, especially those containing more than one fluorine atom, *i.e.* -CF_3 is now considered to be a steric isostere of the –$CH(CH_3)_2$ group.

• The replacement of H with F generally increases lipophilicity, a useful property in the design of medicinal agents.

• The C-F bond strength is relatively high and, in combination with its small size, allows it to be a suitable replacement for labile or oxidizable C-H bonds. Such substitutions can circumvent metabolism issues in the pharmaceutical industry.

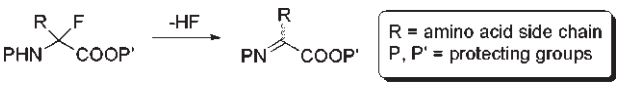
• The presence of fluorine in organic molecules can have a significant effect on the preferred conformation, and when strategically placed they may also influence the preferred conformations of amides and peptides.

• The use of ^{19}F NMR spectroscopy provides an analytical tool that can aid complex organic structure determination.

Fluorinated Amino Acids, Peptides, and Proteins

α-Amino acids

α-Amino acids are the basic building blocks of proteins and peptides. As such, fluorinated analogues of α-amino acids would provide valuable tools in the study of peptide and protein structure and function. Early research, however, revealed that amino acids fluorinated at the α position are unstable, undergoing immediate dehydrofluorination (Scheme 1).[1] Consequently, little use has been found for α fluorinated α-amino acids. Fluorination of the side chain is still possible and can result in derivatives with unique properties, particularly when the fluorinated amino acid is incorporated into a peptide or protein. A notable example of this can be seen in the use of 4-fluoroproline to produce fluorinated analogues of collagen.[2]



Scheme 1

Fluorinated Collagen

Collagen is an extremely well studied protein, no doubt due to its important biological properties and its unusual structure. The stability of its triple helix is due to the high percentage of proline and hydroxyproline residues, which have long been regarded as providing stability by hydrogen bond formation between the hydroxyl groups of the latter and amide carbonyls in the collagen backbone. However, recent work has shown that replacement of the (4*R*)-hydroxyproline residues with their (4*R*)-fluoroproline analogue actually *increases* triple helix stability.[2] Furthermore, incorporation of the diastereomeric (4*S*) isomer greatly destabilises the triple helical structure of the fluorinated collagen analogue. As fluorine rarely participates in H-bond formation (and only then as acceptor), it is now proposed that at least part of the stabilisation in collagen must be attributed to a stereoelectronic effect whereby a (4*R*)-fluorine (or hydroxyl) force the proline residues to adopt a conformation conducive to helix structure.

As well as the insight that this work provides into the formation of the secondary/tertiary structure of collagen, it is also proposed that these new fluorinated (hyperstable) forms of collagen may have potential applications as biomaterials for use in wound healing and tissue repair.

β-Amino acids

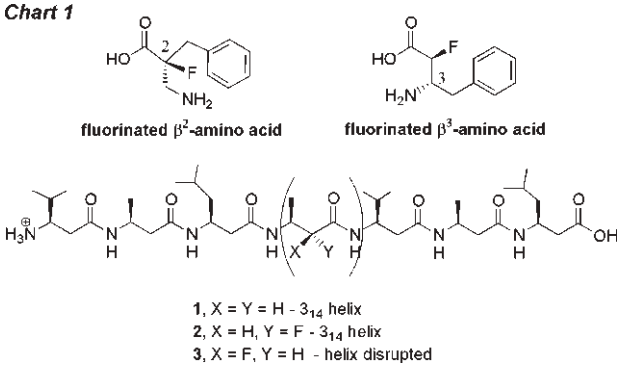
β-amino acids demonstrate many similarities to their α-analogues. For instance β-peptides, oligomers of β-amino

acids, have an ability to form secondary structures such as helices and turns. Hence they have been used as tools for studying peptide structures and functions. β-Peptides also have the advantage of being metabolically much more stable than peptides derived from α-amino acids, making them of great interest to medicinal chemists.

The presence of the CH_2 spacer group in the backbone also allows fluorine to be incorporated into the β-amino acid backbone without the problem of dehydrofluorination, *i.e.* so that it is not adjacent to the amine functionality.

There are two types of β-amino acids, β^2- and β^3-amino acids as shown by the fluorinated phenylalanine analogues in Chart 1. Fluorinated β^3-amino acids have been used to examine the effect of fluorine on secondary structure formation in β-peptides. In 2005, Seebach *et al*.[3] prepared the β-heptamers **1-3** (Chart 1) and examined their secondary structure using NMR spectroscopy. While the non-fluorinated **1** and fluorinated **2** adopt stable 3_{14} helixes, it was found that the presence of the fluorine atom in the non-axial position of **3** is enough to disrupt the 3_{14} helix. While fluorinated β^2 amino acids are not easy to obtain, recent work in our laboratory has provided a new methodology for their preparation. We are now working to see if these compounds can be incorporated into β-peptides and produce similar effects to those observed for fluorinated β^3 peptides.

Chart 1



Conformational effects – amide bonds

Fluorine is known to produce two conformational effects in organic amides. When positioned α to the carbonyl group of an amide it preferentially adopts a conformation *anti* to the carbonyl and *syn* to the C-N bond.[4] On the other hand, when β to the N atom of an amide the fluorine favours a conformation in which the C-F and C-N bonds are *gauche* with a dihedral angle of approx. 63º (Fig. 1).[5]

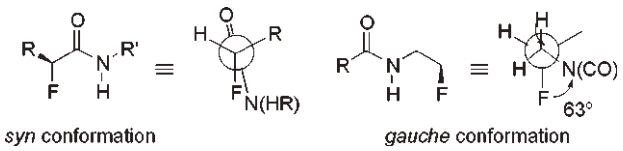


Fig. 1. Conformations of α- and β-fluoroamides.

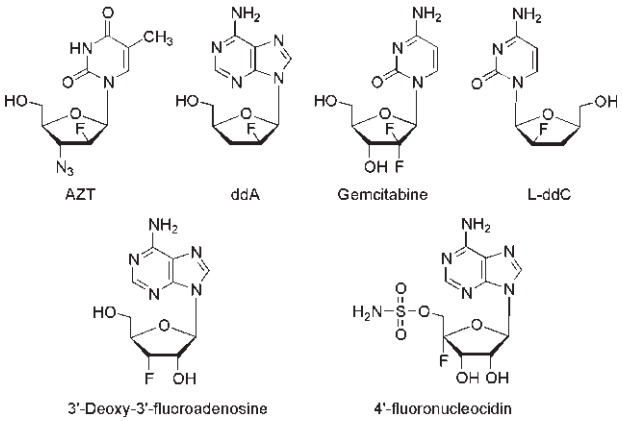
The ability of fluorine to influence the conformation of amide bonds has potential applications in medicinal chemistry where the design and control of the conformation of bioactive compounds is highly desirable. The *gauche* effect of fluorine has also been used to explain the unusual properties of fluorinated analogues of collagen.[2]

Fluorinated Sugars

The many roles of sugars in biological systems make them a key target for modification in the development of new tools for studying biological systems and new medicinal agents.

Nucleosides

Chart 2



The incorporation of fluorinated sugar residues into nucleosides has provided a number of potent therapeutic agents (mainly anticancer and antiviral),[6] as well as additional information on nucleoside function. The location of fluorine in the sugar is a major determinant with regards to its biological and medicinal effect. Fluorination at C2 to give a β-oriented fluorine has provided a number of potent antivirals such as AZT and ddA (Chart 2), both powerful inhibitors of HIV. The glycosylic bond is stabilized against hydrolysis by this adjacent fluorine and the tendency to undergo enzymatic deamination is reduced. The stereoelectronic effect of the F atom also locks the molecule into a preferred conformation. While α-fluorination at C'2 does not usually produce sugars of therapeutic value, the difluorinated C2' compound *Gemcitabine* (Chart 2) is a potent anticancer agent approved by the FDA for the treatment of pancreatic cancer. A further interesting approach to therapeutic C2' fluorosugars has been through synthesis of the unnatural L-configuration such as in L-ddC. These fluorinated L-nucleosides are reported to have strongly antiviral and anticancer properties, but possess lower toxicities than their D-counterparts.

Fluorination of nucleosides at positions other than C2' also introduce some beneficial stabilizing and conformational effects, and has been used to prepare compounds of medicinal and biological interest. 3'-Deoxy-3'-fluoroadenosine, for example, is active as an antiviral and anticancer compound, while fluorination at C4' has been used to produce a fluorinated analogue of the antitrypanosomal antibiotic, nucleocidin.

Enzyme probes and inhibitors

Sugars play important roles in many biological systems. Their role in immunological recognition and as components of genetic material also identifies them as suitable targets for developing therapeutic agents. Consequently, there are many enzymes that use sugars as substrates.

In order to better understand how enzymes process sug-

ars the substrate is often modified and the subsequent changes in enzyme function recorded. Incorporation of fluorine into the sugar analogues provides a strong electron-withdrawing effect expected to alter the mechanism of enzyme action. This has recently been demonstrated by Coward *et al*.[7] who, in initial studies, demonstrated that the 5-fluoro analogue of *N*-acetylglucosamine completely blocks epimerisation by a 4-epimerase enzyme, and also significantly alters the kcat/Km value in catalysis by a glycosyltransferase enzyme.

Conclusions

The incorporation of fluorine into biological molecules is a powerful way of modifying the properties of these molecules. At present the number of methods for incorporating fluorine into organic molecules is quite small, but a recent resurgence in organofluorine chemistry now promises new methods for synthesis. With the development of such methods one can expect an increase in the number of novel fluorinated analogues of biological molecules used to elucidate enzyme mechanisms and develop novel therapeutic agents and biopolymers.

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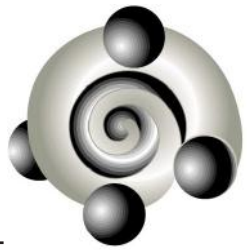

Held every two years, the conference has a broad base that attracts a mix of chemists, physicists and engineers, and has increasing components of interest to biologists. The three plenary speakers are **Profs. Sir John Pendry** (Imperial College; metamaterials and negative refraction), and Nobel Laureates **Sir Harry Kroto** (Sussex UK & Florida State USA; fullerenes, nanotubes and nanowires) and **Stephen Chu** (Lawrence Berkeley National Laboratory (optical tweezers, laser spectroscopy).

The programme consists of 2½ days of single session plenary and invited lectures across the range of topics by international leaders in the fields (see below) followed by 2 days of parallel specialized sessions, including the very popular breakfast posters. It commences with a welcome in the Wellington Town Hall on Sunday evening, Monday evening will see a special function to mark the visits of Nobel Laureates and Korean delegates; the conference dinner is on Tuesday evening. Wednesday afternoon is free for relaxation and excursions around the greater Wellington region. Thursday evening will see a MoRST sponsored public lecture *Science, Sustainability and Society* by **Sir Harry Kroto** as part of a one-day *Foundations for Success* symposium.

Session topics include advanced composite materials, biomolecular assembly, clusters and quantum dots, conducting polymers, nanolithography, soft condensed matter, spintronics, superconductors, materials modeling and many more.

Invited speakers include: John Abrahamson (Canterbury University), Mike Arnold (IRL), Tom Autrey (Pacific Northwest Laboratory); Jerome Bibette (ESPCI, Paris), Mark Bowden (IRL), Bobert Buckley (IRL), Tony Burrell (Los Alamos Laboratory), Mike Butler (Unilever-Colworth), Mike Cates (Edinburgh University), Pablo Etchegoin (VUW), Richard Haverkamp (Massey University), Seunghun Hong (Seoul National University), Sung Woo Hwang (Korea University), David Jamieson (University of Melbourne), Mikael Kall (Chalmers University of Technology), Ric Kaner (UCLA), Walter Lambrecht (Case Western), Richard L. McCreery (Ohio State), Steven McKeever (Oklahoma State), Gerard Milburn (Quantum Computer Technology Centre), Daniel Morse (UC-Santa Barbara), Richard Palmer (Birmingham), Andrew Parker (Oxford), Gerald Pereira (VUW), Joan Redwing (Penn. State), John E. Scott (Manchester University), Nava Setter (ETH), Lubab Sheet (SEMI), James Slezak (Cornell University), Mark Smith (University of Warwick), Claudia Steinem, Institut für Analytische Chemie, Chemo- und Biosensorik, Ned Thomas (MIT), Richard Tilley (VUW), Joe Trodahl (VUW), Ian Vickridge, (SAFIR, Paris), Zurii Vlasov (IBM), Gordon Wallace (Wollongong), Bill Williams (Massey University), Hiroshi Yokoyama (NRI), Anvar Zakhidov (University of Texas-Dallas).

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Article

Drug Discovery in the New Millennium

Steven G. Aitken

Inotek Pharmaceuticals, Christchurch (e-mail: SAitken@inotekcorp.com).

Introduction

Over the years there have been numerous milestones in the development of what is now regarded as the modern day drug discovery process. Medicinal chemists recognise that their roots can be traced back to the late 1920s when Erlich[1] pioneered the use of synthetic sulfonamides as antibacterial agents. In the late 1930s the discovery by Alexander Fleming[2] of the penicillins heralded what would become the wide-spread exploitation of natural products as therapeutic agents. In early 1960s Snyder pioneered the use of grind and bind receptor binding assays[3] while many also investigated the now familiar biochemical principle of enzyme inhibition. This article will concentrate on developments in the field of drug discovery since the mid 1980s.

Today drug discovery is a truly interdisciplinary undertaking. While the focus of this article is the multidisciplinary nature of the science behind modern day drug discovery, it is important first to consider the current economic and regulatory environment within which pharmaceutical companies operate. The key issue for financial success is a recognition that drugs cost billions of dollars to develop; it is estimated that $US 49.3 billion was invested in drug development in 2004 and it is important to appreciate that the release of every new drug is preceded by years of expensive (and time consuming) laboratory work and clinical testing, the latter representing the greatest cost. Thus pharmaceutical companies expect and require a significant payback from each new drug to compensate for the vast sums invested in its development.[4]

The Drug Discovery Process

In principle the drug discovery process is relatively simple with overall success dependent upon the correct choice of biological target, the correct disease association for the chosen target, and the correct choice of a drug development candidate for successful human clinical trials. In practice the process of drug discovery uses just five steps i) selection of the biological target of interest, ii) identification of a lead chemical compound (*hit*), iii) optimization of the lead structure, iv) animal trials to ensure the drug is efficacious in animal disease models and is safe for human clinical trials v) human clinical trials that prove the drug is efficacious and safe for use in the general patient population.

The record $US 49.3 billion invested in drug R&D in 2004 suggests that successful drug discovery is a much more complicated and difficult undertaking than appears from this simple analysis. In reality, research and development is a lengthy process requiring 10+ years from concept to clinic. Let us consider each of the drug discovery process steps in turn.

Selection of the biological target

The key question in selecting a biological target is: *Will therapeutic intervention have a positive effect on managing the disease(s) in question?* This forms the first phase of drug discovery, and improved success here would markedly reduce failure rates.

Nowadays this phase is absolutely critical to the drug discovery process. The human genome project has yielded *ca*. 35,000 potential targets for treating disease, a huge increase from the *ca*. 3,000 at the turn of the millennium. However, only a fraction of the 35,000 biological targets can currently be exploited because much of the human genome function is unknown. This vast amount of new information has provided, and continues to provide, new and exciting opportunities for novel therapeutic design.

Lead generation

Traditional medicinal chemistry identified a lead compound by screening collections of naturally occuring or laboratory synthesized compounds. Over time, computerization catalysed the development of *high throughput screens* (HTS) which allowed hundred of molecules to be tested in the time previously required for one. The development of HTS in turn drove medicinal chemists to develop methodology which would allow more compounds to be synthesized in a shorter time. As such the 1990s witnessed the widespread use of combinatorial chemistry to create *libraries* of compounds.

Library generation generally involves attaching a *skeleton* to an insoluble polymer support that is then subjected to sequential reactions (excess reagents drive the reactions to completion) and purification (excess reagents and by-products removed by washing). This methodology generates a large number of product molecules, or *library*, in which all possible combinations of a series of reactants have been obtained. The name *combinatorial chemistry* was coined to describe this process and today combinatorial chemistry is most easily defined as *the synthesis of chemical compounds as ensembles (libraries) in the form of mixtures or discrete compounds*.[5] Typically compounds are stored in a 96-well plate and the *library* screened by a high throughput procedure.

During the 1990s combinatorial chemistry was perceived by many to be the ultimate *drug discovery factory* and its introduction was embraced with unprecedented enthusiasm. Initially, synthesis of combinatorial mixtures was achieved relatively easily and quickly using a process of *mix and split* (or *split and pool*) strategies. For example, the preparation of all possible tripeptides from the 20 naturally occurring amino acids using solid phase synthesis (Fig. 1) involves coupling an *N*-protected amino acid [A] to a solid phase resin, deprotection, addition of a second

N-protected amino acid [B], removal of excess reagents (repeated washing) followed by deprotection of function [B], and addition of a third *N*-protected amino acid [C]. Repeated washing of the resin, followed by cleavage of the peptide-resin bond then affords unprotected tripeptide [A] [B] [C] in solution. By using *split and mix* techniques, the method can be adapted give all possible combinations of the 20 amino acids, *i.e*. A-A-A, A-A-B, A-B-A, B-A-A, *etc*., leading to a 20 x 20 x 20 array of 8000 tripeptides.

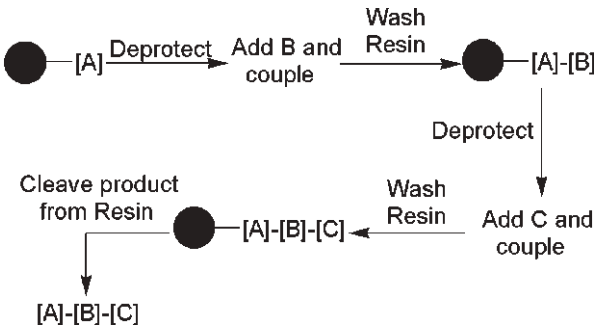


Fig. 1. Synthesis of a tripeptide by solid phase synthesis.

These early manual combinatorial strategies were very reaction- and vessel-efficient processes. However, the product library could not be rescued by purification when chemical conversion was incomplete or when side-products were generated. Moreover, a biologically active synthetic mixture required time consuming deconvolution to determine which compound was responsible for the activity. Even worse was the fact that combinatorial mixtures tended to give false positive results such that the labour- and time-consuming deconvolution process did not yield a single active compound responsible for the biological activity. These problems all but consigned this method of lead generation to the history books. Nonetheless, combinatorial chemistry is still an integral part of the lead generation process. However, only libraries of discrete compounds are now prepared for screening using modern combinatorial chemistry; the most successful applications of which pay great attention to the essentials of high throughput purification.

It is now approximately a decade since the large scale roll-out of combinatorial chemistry occurred and, given that that most drugs take approximately this time to reach the market, the significance of combinatorial chemistry should now be evident. This is clearly not the case as only 21 new drugs were approved by the FDA in 2004.

It should come as no surprise to most scientists that blind screening of large combinatorial libraries for drugs has had few successes. The libraries of the 1990s focused on increasing the number of compounds available for screening based on the naive assumption that this would result in more chemical leads being generated. Sadly, few chemicals make suitable drugs, and the ones that do are not uniformly distributed throughout *chemical space*. To counter this numerous models have been, and currently are being, developed to define the *drug-like* characteristics of a particular compound. The best-known, and most utilized,[6] model is the so-called *Lipinski rule of 5*. It derives its name from Pfizer employee Christopher A. Lipinski who, with others, decided that the relevant cut-offs for a *drug-like* compound were all multiples of 5. While the rule excludes most *undrug-like* compounds it does not guaranteed a *drug-like* one will succeed. The model assumes that most chemicals will not be suitable as oral drug candidates if they lack bioavailability. Accordingly, the rule states that for a compound to be absorbed through biological barriers it must not contravene more than two of the following:

- It should have no more than 10 hydrogen bond acceptors.
- It should have no more than 5 hydrogen bond donors.
- Its relative molecular mass (M_r) should be below 500.
- Its log P value[7] should be less than 5.

Despite exceptions (notably for antibiotics), approximately 90% of the top 200 drugs follow the rule. In light of this, scientists at GlaxoSmithKline studied the Lipinski properties of both the top 200 selling drugs and the lead compounds generated by high throughput screening of their combinatorial libraries from the late 1990s and early 2000s. From this analysis it was concluded that both the leads and the top selling 200 drugs follow the rule, especially with respect to M_r and the numbers of hydrogen bond donors and acceptors. However, and most significantly, leads generated by HTS tended to have higher log P values. Although the differences were small, it is widely acknowledged by medicinal chemists that in the process of transforming a chemical lead into a selective orally active drug, both the M_r and log P tend to increase; to undertake lead optimisation on a chemical that has higher than average log P is unwise.

As a solution to this problem, GSK, and many other companies now use computer-based virtual screening of virtual libraries (VSVL)[8] to identify the best compounds for combinatorial synthesis. Much of the detail is proprietary with few examples of VSVL in the open literature. However, computational chemists confirm that the methods work and a glut of start-up companies specializing in virtual screening now exist.

The potential and success of combining VSVL, combinatorial chemistry and HTS is best illustrated by GlaxoSmithKline. Table 1 shows the improvement in screening success rates, numbers of lead compounds generated per screen, and the potency of the lead from 1998-2004. The success is attributed largely to use of VSVL in the design of the combinatorial libraries for HTS screening.

Table 1. GlaxoSmithKline HTS scorecard.[a]

	1996	1999	2003	2004
Compounds screened	100,000	430,000	615,000	1,050,000
Average lead potency	3,000 nM	400 nM	10 nM	10 nM
Screen success	20%	50%	58%	65%
Leads per target	1.0	1.7	1.9	2.0

[a]Data taken from: *http://pubs.acs.org/cen/coverstory/8230/8230drugdiscovery.html*

Lead Optimisation

Perhaps the most challenging stage in drug development is to take to full development that compound with appropriate biological and chemical properties. Formally, the objective of lead optimisation is the design, synthesis and selection a drug development candidate that has the best balance of potency, selectivity and ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) characteristics.

For most drugs the best route of administration is oral. Thus, even if a compound is very potent against its biological target *in vitro*, translation of this into *in vivo* activity in a human patient requires the understanding and optimisation of a number of biological processes. Firstly, the drug has to be taken into the blood stream and then carried to its effector site where it is then adsorbed by the target organ or cell. For example, if the target is in the central nervous system (CNS) the natural blood-brain barrier has to be crossed. Even when the drug reaches its target, its rate of metabolism has to be appropriate and it must be sufficiently stable to remain there long enough for the desired biological effect to be achieved. In some cases a prodrug approach is required. Here, chemical modifications taking place within the organism are pre-requisites for the biological activity of the chemical compound. Additionally, once metabolised, compounds have to be excreted to minimise bioaccumulation in organ or tissue.

A lead optimisation program needs to ensure that correct physicochemical properties are imparted to the potential molecule for the drug to be both efficacious and safe in humans. Lead optimisation still relies heavily on traditional medicinal chemistry techniques. Examples include quantitative structure activity relationships (QSAR), conformation constraint, pharmacophores, isosteres/bioisosteres, and heterocyclic similarity; the most commonly used strategies in lead optimisation, by far, are the last two. Isosteres are substituents or groups with similar molecular size and/or volume. A bioisostere extends this principle to groups with similar pK_a values, lipophilicity, and electrostatic properties. Each bioisostere within a group is expected to have similar interaction (and hence biological activity) with the target. Heterocyclic similarity can be thought of as a further extension of bioisosterism where one heterocycle is replaced by another with comparable pK_a, lipophilicity, and electrostatic properties.

The major change to lead optimisation over the last decade or so is the introduction of focused combinatorial chemistry. Synthesis of mini-libraries facilitates expeditious synthesis of closely related analogues. This form of combinatorial chemistry is more reliant on feedback and less on force of numbers in defining a quantitative structure-activity relationship (QSAR); it uses the principles of isoseteres/bioisosteres/heterocyclic similarity to define the synthetic targets.

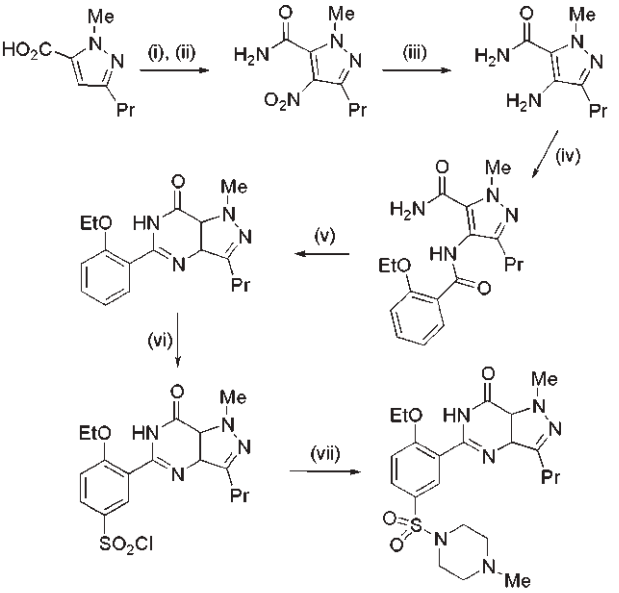
Chemical development

A very important stage of the drug discovery process that is often overlooked is that, after selection of a drug candidate for clinical trials, a commercial synthesis must be designed and implemented.[9] As can be seen from Table 2 the objectives and priorities for laboratory and chemical development syntheses are very different.

Table 2. Priorities for laboratory and commercial synthesis.

Laboratory synthesis	Commercial synthesis
Scale < 100 g	Scale > 100 kg
Cost of synthesis not relevant	Cost of synthesis vital in maximising potential profit
Overall yield not so important	Overall yield critical as above
Synthetic scheme designed to maximize diversity	Convergent synthetic scheme
Any reagent/reaction	Potentially dangerous/toxic reagents avoided if possible
Environmental impact not considered	Environment impact assessed

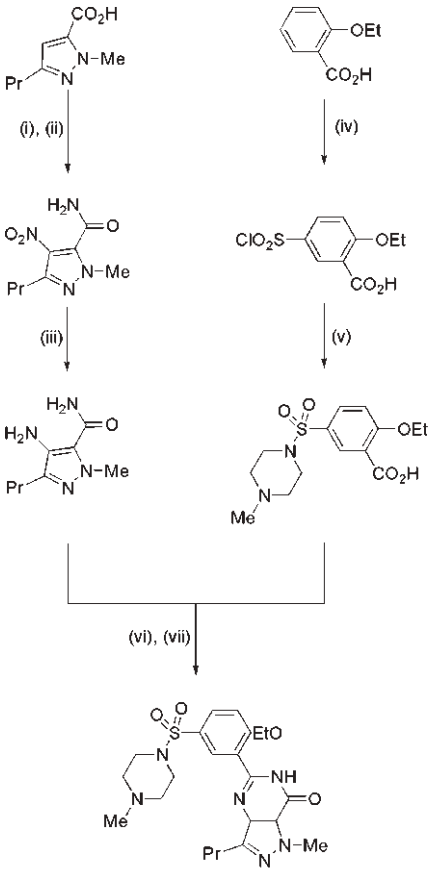
A classic example of this difference in priorities is illustrated by the development of a commercial route to Sildenafil (Viagra). The laboratory synthesis (Scheme 1) had several commercial disadvantages in that (i) it was linear with a low overall yield (7.5%), (ii) toxic materials were used in the final bond-forming step that was difficult to scale up, and (iii) the $SnCl_2$ used for nitro group reduction is too toxic for large scale use.



Reagents: (i) HNO_3, H_2SO_4; (ii) a) $SOCl_2$, b) NH_3; (iii) $SnCl_2$, HCl, EtOH; (iv) 2-ethoxybenzoyl chloride, Pyr, DCM; (v) NaOH; (vi) $ClSO_3H$; (vii) *N*-Methylpiperazine. Overall yield – 7.5%

Scheme 1. Laboratory synthesis of Viagra

In contrast, the commercial route (Scheme 2) is convergent and higher yielding (75.8%) with a *clean* cyclization as the final step and all potentially toxic materials used early in the synthesis. The $SnCl_2$ reduction has been replaced by catalytic hydrogenation. An added bonus is that the commercial route uses *ca*. 10% of the organic solvents required for the laboratory synthesis, making it both more environmentally friendly and cheaper; two solvents replace the previous six (Table 3).



Reagents (i) HNO_3, H_2SO_4; (ii) a) $SOCl_2$, toluene b) NH_3; (iii) Pd/C, H_2, EtOAc; (iv) $SOCl_2$, $ClSO_3H$; (v) *N*-Methylpiperazine, NaH, H_2O_2; (vi) DCC, EtOAc; (vii) *t*-BuOH, *t*-BuOK. Overall yield - 75.8%

Scheme 2. Commercial synthesis of Viagra

Table 3. Solvent volumes (L) required to produce 1000 kg of Viagra.

Solvent	Laboratory Route (L)	Commercial Route (L)
Toluene	39,000	2,800
Dichloromethane	37,000	
Ethyl acetate	19,000	10,700
Acetone	18,000	
Butan-2-one	10,000	
Pyridine	2,000	
Total	125,000	13,500

Clinical trials

Once a drug development candidate is identified clinical trials must be conducted so as to demonstrate to the regulatory authorities that the drug is safe, efficacious, and can be manufactured to acceptable quality standards. However, before such trials, a company performs careful cost/benefit exercises to ensure the potential for profit outweighs the risk (Fig. 2). Even at this stage development of a drug demonstrating promise as an effective therapeutic agent will be terminated if it is not seen to be profitable.

If the cost/benefit analysis indicates a profitable product full clinical trials will be instigated.[10] This phase of the discovery process is known to be comprised of four separate parts. However, in addition to these (and before candidate selection is made) animal studies are conducted—the pre-clinical phase. To illustrate this, the case history of Avandia follows.

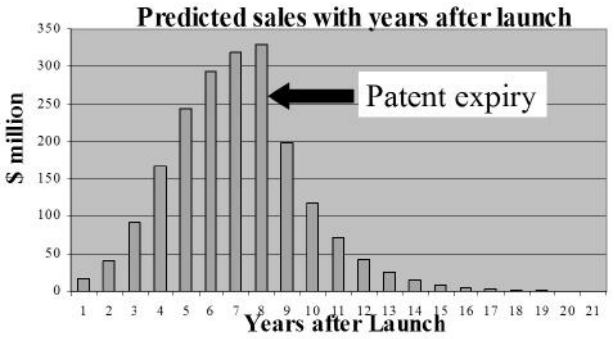


Fig. 2. Drug profitability time-line.

The pre-clinical phase

Typically taking about a year and involving several potential development candidates (*pre-candidates*) this is relatively cheap and can help to ensure that the best of a number of closely related leads is chosen. The phase is essential before the FDA (or other regulatory body) allows human trialling and involves at least two different animal species. The level at which toxicity develops and those organs most susceptible are established; the treated animals are sacrificed and autopsies performed. The studies involve a single high dose to define the gross toxic effect, and repeated dosage at various levels and durations to determine toxic effects. These provide the gross toxicity of the particular compound class or the specific candidate, and lead to an initial understanding of the drug metabolism in the animal species and whether such metabolism is likely to be harmful in human trials. The cost to this point is *ca*. $NZ 600,000, but the likelihood of the drug eventually reaching the market is still below 10%.

Phase I trials

Typically taking about a year and usually consisting of three separate studies, a *single dose* study in healthy male volunteers, a repeat *dose rising* study in healthy volunteers, and a *food interaction* study in healthy volunteers. The aim is to ensure that the drug is well tolerated in healthy humans with those safety issues identified from pre-clinical animal experiments appropriately assessed. The cost to this point is $NZ 5.4 M while the probability of the drug reaching the market is now 15%!

Phase II trials

Taking up to two years, this is much more expensive than the first studies and it is often separated into phases IIa and IIb. Phase IIa is a *proof of concept* stage where carefully selected patients are used to demonstrate that the compound is efficacious. Phase IIb is similar but uses larger patient groups, generally with multiple dosing arms. The data gathered from these studies are used to refine dosages and the parameters for the even more expensive phase III study. Several such pilot trials may be necessary to establish optimal dosage but these also help define the best way to administer the product and the best way to measure its benefits.

The aims of the phase II trials are to demonstrate efficacy and safety in patients with the medical condition for which the drug is designed, and to gain appropriate data to define the most efficacious way for drug administration and how to best measure the benefits obtained. This information allows for the design of a larger phase III trial with sufficient patients to determine if the benefits provided outweigh the risks of toxicity. The total costs to this point are *ca*. $NZ 80 M but the probability of success is close to 50%.

Phase III

Before commencing this, the most expensive phase, a further cost/benefit exercise is performed using updated information to ensure that the potential for profit still outweighs the risk. Even though vast amounts of money have been spent and the probability of success is now high, the development of a potentially non-profitable drug can be terminated at this point. Phase III trials typically take a further one-to-two years and are conducted on large patient populations. Usually the format consists of at least two global trials at two dose strengths with approximately two thousand patients per trial. They are almost always double-blind, placebo-controlled and are the *gold standard* for substantiating product effectiveness; these trials may also contain a drug that is already on market so as to demonstrate that the new drug is better, in someway, than the one currently on the market.

The ultimate objective here is to obtain sufficient data that the regulatory authorities accept that the drug works and is safe. There is no guarantee that marketing approval will be granted and the FDA review may take 18 months. By now a total of $NZ 1.1 billion has been spent with a 90+% probability of the drug reaching the market.

Phase IV

In this final phase the risk-to-benefit ratio is evaluated in the marketplace to ensure that the drug performs as expected, after all the marketplace is the ultimate test of product value. The system is not perfect and the FDA has withdrawn several drugs because their demonstrated toxicity could not counterbalance their benefits; the withdrawal of Vioxx last year provides a well published example.

Is drug discovery financially worthwhile?

One may wonder whether the huge financial costs involved can be justified. The R&D costs of Avandia was $NZ 1.1 billion, it took some 12 years to get to the market, and, with exclusive patent rights of 20 years, approximately 8 years remained for the drug to recover its R&D costs and return a profit. For a blockbuster drug such as Avandia with sales of NZ 2.5 billion in 2003 it has to be worthwhile. However, it needs to be remembered that only 3% of compounds that make it to clinical trials reach the market place.

Summary

Drug discovery appears to have moved full circle. In the 1960-1970s molecules were painstakingly synthesized and only slowly screened with structure-activity relationships guiding further synthesis. In the late 1980s and early 1990s high throughput screening and combinatorial chemistry made possible the testing of tens of thousands of compounds per year. This led to enormous volumes of biological data, but left large numbers of inactive compounds. Lacking an effective way to analyse these data and provide the necessary structure-activity relationships for further syntheses, the anticipated increase in new drug approvals did not eventuate. However, the turn of the millennium saw chemists focus on structure-activity relationships by employing computational and artificial intelligence techniques. VSVL is showing an impact in the drive for intelligent selection of the compounds that will form the targets of the vast combinatorial libraries of the future. It remains to be seen whether or not this promising technique to new drugs will be faster and more effective than before.

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4 For background on the pharmaceutical industry and annual reports see the PhRMA website: *http://www.phrma.org*.

5. For background and further information on combinatorial chemistry see: *The world of combinatorial chemistry: http://combichem.net/home/index.aspx.*

6 For background and further information on the *Lipinski rule of 5* and VSVL see: Lipinksi, C.A. *et al. Adv. Drug Del. Rev.* **1997**, *23*, 3-25.

7. Log P is a measure of the partition coefficient of a compound between octanol and water and may be regarded as a measure of its hydrophobicity/hydrophilicity. Hydrophobicity relates to key drug properties such as absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism, and toxicity. Log P is one of the most critical properties to be optimised to develop a suitable drug candidate.

8. For an excellent review on virtual screening of virtual libraries see: Green, D.V.S. *Prog. Med. Chem*. **2003**, *41*, 61-97.

9. For an excellent review on property distributions: differences between drugs, natural products, and molecules from combinatorial chemistry see Feher, M.; Schmidt, J.M. *J. Chem. Inf. Comp. Sci*. **2003**, *43*, 218-227.

10 For further information on clinical trials see the US and Canadian clinical trials registry: *http://www.clinicaltrials.com*.

Addendum

The article on NZ contributions to IUPAC (*CiNZ*, **2006**, *70*, 58) inadvertently omitted the contribution of Prof. Keith Hunter (Otago) to Division VI (Chemistry and the Environment) concerning iron in the ocean through a joint IUPAC-SCOR working group. The outcome was a treatise on *The Biogeochemistry of Iron in Seawater*.

Details can be found at: *www.iupac.org/publications/books/author/turner*

Post codes

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2006 NZIC Salary Survey Summary

By Fiona Summerfield

In the first quarter of 2006, 600 Salary Survey forms were posted out to waged members of NZIC. 224 replies were received. Not every respondent answered all the questions, thus the sample sizes shown in this summary may not add up to 224 in each case.

The median age group of respondents was 51–60. The median base salary was $77,000 and the median remuneration package was $83,910. The median base salary for full-time employed respondents was $80,000 and the median remuneration package was $87,500. The median salary increase over 2005 was 3.5%. This was in step with the Consumer Price Index (CPI) that rose 3.4% between the March 2005 and 2006 quarters.[1]

The most common chemistry qualification was a PhD, which was held by 57% of respondents. The most common workplace was a university where 32% of respondents worked. The split between the islands was 70% North Island, 30% South Island, which was close to the overall New Zealand population split of 75%, 25%.[2]

The results of the survey were also compared with professionals throughout New Zealand and the results from a survey carried out by The Royal Australian Chemical Institute (RACI) in 2005. An attempt was made to do a comparison across several countries and professions, however comparative data was difficult to obtain and it was felt the results were so subjective as to be meaningless. The huge variance in job descriptions, qualifications, experience, and remuneration packages meant it was difficult at any kind of level to compare salaries across different countries.

Gender Variation

185 males and 39 females answered the gender question.

Table 1 shows the median and lower and upper quartile results for both salary and remuneration packages according to gender. The median base salary for males was $80,330 and the median base salary for females was $57,000.

While the sample size of females is small, this large difference in median salary warranted some further investigation. The highest salary received by a female was 45th overall. Looking at the status of the employment of women, it was found a much higher percentage worked part-time with 23% part-time female respondents and only 9% part-time male respondents.

Age Variation

57% of respondents were over fifty. The youngest chemists received the highest median salary increase over the previous twelve months. The group with the highest median base salary were the 51-60 year olds, see table 2. The percentage increase between the groups was varied and showed a noticeable stabilising after fifty. Has a person in their fifties reached the pinnacle of their earning potential? It will be interesting if this changes in later surveys.

Table 3. Percentage increase in median salary by age group.

Age Group	Increase in median base salary over previous age group (%)	Increase in median remuneration over previous age group (%)
20-30		
31-40	20	22
41-50	32	31
51-60	6	5
>60	-2	1

Regional Variation

The regional variation produced some unexpected results with Christchurch the lowest ranked main centre, see table 4. Dunedin had the highest median salary and the highest median salary increase over 2005. Auckland had the higher median remuneration package. Overall the main centres had higher median salaries and remuneration packages than the regional locations. A possible reason for the lower median in Christchurch could be the greater number of respondents from Christchurch who worked part-time. 32% of respondents in Christchurch were part-time, while the next highest percentage of part-time respondents in main centres was Auckland and Hamilton with 9% each.

Chemistry Qualification Variation

57% of respondents had a doctorate qualification. The respondents with Masters degrees or Master degrees with honours did not have a higher median salary than the Bachelor degree holders as expected, see table 5. The median base salary and remuneration packages were around a similar amount for NZCS, Bachelor and Masters qualified respondents. There was substantial jump to that of doctorate holders. The qualification statistics correspond to the respondents' highest chemistry qualification. 4% of respondents had doctorates in other subjects.

Variation by Employment Sector

The group with the highest median salary were those that worked in universities, though the highest median remuneration package was with those who worked for the government either at a local or national level, see table 6. Owner/Directors were well down the list in median salary indicating perhaps the reward for owning your own business was not a higher salary. 58% of this group were self-employed. Employees of universities, government, CRIs and the private sector all received a median salary increase above the CPI and this may reflect the tight labour market.

Table 1. Gender variation.

Gender	Sample Size	Median Salary	Lower Quartile Salary	Upper Quartile Salary	Median Remuneration	Lower Quartile Remun.	Upper Quartile Remun.
Female	36	$57,000	$49,375	$64,703	$59,000	$51,875	$69,752
Male	173	$80,330	$65,000	$98,459	$89,000	$66,928	$105,500

Table 2. Variation by age.

Age Group	Sample Size	Median Salary	Lower quartile salary	Upper quartile salary	Median remun.	Lower quartile remun.	Upper quartile remun.	Median salary increase
20-30	7	$50,000	$45,500	$55,750	$53,500	$52,500	$57,000	7%
31-40	27	$60,000	$51,850	$75,500	$65,000	$53,600	$79,250	4%
41-50	56	$78,992	$60,700	$90,000	$85,000	$61,000	$97,861	4%
51-60	69	$84,000	$66,928	$101,927	$89,000	$69,850	$107,500	3%
>60	51	$82,000	$59,500	$103,500	$89,500	$59,500	$109,000	3%
All ages	210	$77,000	$59,200	$96,363	$83,910	$60,000	$102,875	4%

Table 4. Variation by location.

Location	Sample Size	Median Salary	Lower Quartile Salary	Upper Quartile Salary	Median Remun.	Lower Quartile Remun.	Upper Quartile Remun.	Median Salary Increase
Main centres	159	$80,000	$60,000	$97,650	$84,466	$62,500	$104,750	3%
Regional centres	51	$72,000	$54,500	$89,000	$82,000	$55,000	$97,200	4%
Dunedin	18	$83,733	$71,576	$95,250	$85,742	$76,576	$99,750	5%
Auckland	44	$81,500	$60,000	$100,000	$90,750	$64,250	$111,250	4%
Hamilton	22	$80,000	$63,963	$96,361	$85,000	$67,713	$97,450	1%
Wellington	44	$76,160	$60,000	$96,000	$79,000	$62,500	$107,750	3%
Other South Island	13	$77,000	$54,000	$84,000	$82,000	$59,000	$104,000	5%
Christchurch	31	$74,000	$51,500	$93,000	$75,000	$55,250	$101,316	3%
Other North Island	38	$71,000	$55,000	$92,250	$80,000	$55,000	$96,050	3%

Table 5. Variation by qualification.

Qualification	Sample Size	Median Salary	Lower Quartile Salary	Upper Quartile Salary	Median Remun.	Lower Quartile Remun.	Upper Quartile Remun.	Median Salary Increase
NZCS	8	$64,988	$48,750	$93,750	$72,488	$53,400	$97,500	5%
BSc & BSc(hons)	40	$62,085	$55,000	$87,000	$68,335	$55,000	$101,375	3%
MSc & MSc(hons)	27	$60,000	$49,250	$78,160	$67,000	$50,750	$86,910	3%
PhD	121	$84,000	$69,800	$100,000	$90,000	$70,000	$105,000	4%

Table 6. Variation by employment sector.

Sector	Sample Size	Median Salary	Lower Quartile Salary	Upper Quartile Salary	Median Remun.	Lower Quartile Remun.	Upper Quartile Remun.	Median Salary Increase
University	67	$90,000	$66,000	$101,214	$92,000	$67,250	$105,480	4%
Central & Local Govt.	7	$88,560	$70,750	$121,000	$96,060	$74,500	$133,500	8%
Private employee	60	$78,150	$56,875	$97,250	$86,000	$60,000	$108,500	4%
CRI	39	$75,000	$59,000	$84,000	$80,000	$64,000	$89,250	4%
Owner/ Director	21	$65,000	$60,000	$80,000	$72,000	$60,000	$95,000	0%
Secondary	12	$60,500	$58,750	$64,685	$62,469	$59,750	$67,180	0%

The box and whisker plot illustrates the comparison between the main workplace groups with maximum, minimum, upper and lower quartiles and median results shown.

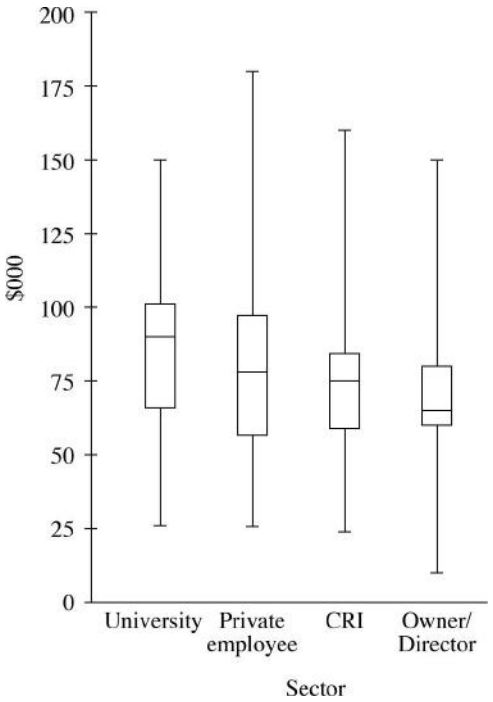

Fig. 1 Box and Whisker plot of base salaries by workplace

Variation by Job Function

The job function categories were broadened to see if this had an impact on salary and remuneration. Jobs that involved administration, management, sales or marketing were broadly labelled as deskwork. Those involved in analysis, research and development were broadly labelled as bench work. Separate categories were maintained for those involved in both research and teaching because this was a substantial group and those involved only in teaching. The research and teaching category had the highest median salary and remuneration package.

Influence of Variables on Salary

To investigate what factor influenced base salary a data subset was taken of full-time respondents with chemistry qualifications that included Bachelors degree (including those obtained with honours), Masters degree (including those with honours) and PhD. The subset numbered 166 and the variables looked at were age, years of chemistry experience, place of work and chemistry qualification.

Linear regression was used with salary as the continuous variable. A backward selection type procedure was used with variables dropped that were not associated with the salary outcome once the other variables were controlled. It was found while age alone was strongly associated with salary once the other variables were taken into account, it no longer influenced the salary so was removed from the model.

Years of experience working chemistry, chemistry qualification, and workplace all independently had a statistically significant association with salary.

Five years increase in work experience in chemistry equated to approximately $4,850 higher salary with a 95% confidence interval of $3,020–$6,670, $p < 0.01$.

Qualifications were ranked as Bachelors degree, Masters and Doctorate. Each qualification was associated with approximately $7,290 higher salary, 95% confidence interval $1,900–$12,670 $p = 0.008$.

Workplaces were looked at individually. Crown Research Institutes (CRIs) were used as the baseline. Working in a university compared to a CRI meant approximately a $9,680 higher salary, 95% confidence interval of -$1,350–$20,710. Working for a private company as an employee meant approximately $10,390 higher salary than a CRI, 95% confidence interval of -$1,610–$22,400. Owner/Directors received approximately $9,640 less salary than working for a CRI, 95% confidence interval of -$25,870–$6,590. $p = 0.002$ for each of the workplace variables.

Promotion

Less than a fifth of respondents had received a promotion in the last twelve months. 78% of these respondents had received a salary increase with their promotion and the median increase was 5%. Only 44% of respondents who had changed employers in the last twelve months had experienced a salary increase with the change. This possibly fits with other survey results on why people change jobs, with career progression the most common motivator rather than salary.3,4 49% of respondents who had received a new job description in the last twelve months, received a salary increase with this change and the median increase was 7%.

Other Employee Benefits

57% of respondents who answered the questions in this section received a benefit. The benefits received were quite varied but 20% of those who did receive one, did not consider it part of their overall salary package. If additional benefits were to help keep employees happy, then this survey would indicate one in five employees did not perceive their value. The most common benefit was superannuation, with 60% of those receiving benefits having it. The median value of extra benefits was the under $5,000 category.

65% of respondents had received funded training in the last twelve months with 58% of this training being conference attendance. Respondents that attended conferences, 29% also received some other form of training.

2000 NZIC Survey Comparison[5]

The last NZIC salary survey was completed in 2000 and reported in CINZ in November 2001. The plot below compares the overall remuneration results from the two surveys. The percentage change in the median base salary between 2000 and 2006 was 17%. The change in the consumer price index over this same time frame was 17%, while the decline in purchasing power over the time frame was 14.4%.6 This means the median base salary in 2006 provides the earner with a better ability to purchase than in 2000.

Table 7. Variation by job function

Job Function	Sample Size	Median Salary	Lower Quartile Salary	Upper Quartile Salary	Median Remun.	Lower Quartile Remun.	Upper Quartile Remun.	Median Salary Increase
Research & Teaching	55	$93,000	$68,900	$103,500	$95,000	$71,400	$109,000	4%
Desk	50	$84, 250	$73,500	$102,000	$93,500	$76,049	$114,500	3%
Bench	76	$71,041	$55,000	$84,117	$74,612	$56,500	$93,240	3%
Teaching	18	$60,500	$56,500	$66,180	$61,000	$58,250	$67,685	0%

Table 8. Comparison of results with Statistics New Zealand data.[7]

Survey	Year	Sample size	Median Salary	% change between years
NZIC survey	2000	261	$66,000	
NZIC survey[5]	2006	210	$77,000	17%
Legislators, Administrators & Managers[7]	2000	159,000	$41,392	
Legislators, Administrators & Managers[7]	2005	172,800	$51,844	25%
Professionals (holding a university degree)[7]	2000	206,100	$36,920	
Professionals (holding a university degree)[7]	2005	280,000	$46,280	25%

Table 10. Comparison between RACI and NZIC survey results.

Survey	Median base salary	Median total package	Average salary increase over previous 12 mths	CPI increase over previous 12 mths	Big Mac price 2006[11]
NZIC 2006	$77,000	$83,820	4.2%	3.3%	$4.45
RACI 2005	AU$81,000	AU$94,019	4.6%	2.5%	AU$3.25

Compared to 2000, there was an 80% drop in respondents earning a remuneration package over $200,000. Regional variation has also changed with Christchurch dropping to the bottom and Auckland leap-frogging Wellington. The main cause for this would appear to be Christchurch median base salary in 2000 was $74,500 and in 2006 was $74,000. This could be caused by the higher percentage of respondents in Christchurch who work part-time as described earlier in this summary. In both surveys education had the higher base salary over other sectors. Both surveys had a similar percentage of respondents with doctorate degrees.

Both found similar differences between median base salaries and remuneration packages by qualification. In 2000 the MSc and MSc(hons) respondents had higher median results than the Bachelor degree holders. The variation by age has changed slightly with 49% being over 50 in 2000 compared to 57% of respondents in 2006. The percentage of respondents under forty has declined between the two surveys with 22% in 2000 compared to 16% in 2006.

The box and whisker plot illustrates the remuneration comparison between the two surveys with maximum, minimum, upper and lower quartiles and median results shown.

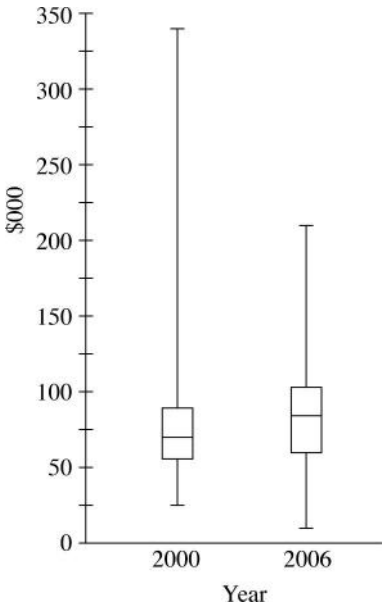

Fig. 2 Box and whisker plot of comparison between NZIC salary survey remuneration.

Comparison with other professions in New Zealand

It is a commonly heard saying, that science is a poorly paid career in New Zealand. The data from the salary survey was compared with data from Statistics New Zealand and other salary surveys in the tables below to see if the facts matched this sentiment. The first table shows comparative median salary data to the two surveys carried out by the NZIC to see if chemists salaries were keeping pace with others in society. The second table compares average remuneration results with other surveys carried out in New Zealand.

Table 9. Comparison of results with other salary survey data.

Survey	Year	Average Remuneration
NZIC survey	2006	$85,512
Senior Qualified Accountant – Finance Manager (turnover up to $50M)[8]	2006	$80,000
Senior Associate Lawyer[8]	2006	$95,000-$140,000
GP[9]	2005	$93,000
Civil Structural Engineer[8]	2006	$55,000-$100,000

Comparison with RACI Survey 2005[10]

The table below shows the results from the RACI survey compared to the New Zealand results. The Australian figures have been left in Australian dollars. It is important to note the questions used to establish the total package figure was quite in depth in RACI survey resulting in a more accurate figure than the NZIC survey, which did not go into so much detail. This maybe something that needs to be considered for the next NZIC salary survey. The annual salary increase shown here is the average to give a comparison to the RACI result. One indicator of purchase-power parity is also given in this table with the MacDonald's Big Mac price in the two countries.

The job responsibility questions proved difficult to assess. The very helpful suggestions by many respondents have been noted for future surveys. Customized summary data information is available for NZIC members and can be requested via the NZIC administration. *nzic.office@nzic.org.nz*

Thanks to Fiona Ewings and Ben Joyce for working out the statistics showing the influence of the variables, Richard Rendle for the box and whisker plots, Biolab and MEP Instruments Ltd for the prizes for the returned forms and all the respondents that took the time to correctly fill in forms.

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New President of the Royal Society of New Zealand

The Council of the Royal Society of New Zealand is pleased to announce that Neville Jordan BE CNZM will take over as President of the Royal Society of New Zealand when Dr Jim Watson's term ends in mid June 2006. Neville Jordan is a strong supporter of science in New Zealand and will bring considerable knowledge and experience to his leadership of an organisation whose focus is the promotion of excellence in science and technology.

"It's a both privilege and honour to be able to serve science and technology through being President of the Royal Society of New Zealand," says Neville. "We have a rich heritage of science in New Zealand with large economic gains achieved by successfully applying many discoveries made continually over the last hundred years or so. The dramatic success of our primary industry is an example of this."

After graduating in electrical engineering from the University of Canterbury, Neville worked in the civil aviation industry and for IBM in various management positions. In 1976 he founded MAS Technology Ltd, a telecommunications company. In 1997, as Chief Executive, he led MAS Technology's successful float on the United States NASDAQ stock exchange. He later pooled the company with another US-listed enterprise. Neville has served on the boards of AgResearch, the Foundation for Research, Science and Technology, and the Prime Minister's Growth and Innovation Advisory Board. He is a Distinguished Fellow of the Institute of Professional Engineers NZ (IPENZ) and has been awarded the UK IEE Kirby medal for "outstanding eminence and distinction in advanced technology." He received the Governor General of New Zealand Supreme Award for Exporting in 1997 and was inducted into the New Zealand Hi-Tech Hall of Fame in 2004. In 1999 he was made a Companion of the New Zealand Order of Merit in recognition of his substantial contribution to international telecommunications and exports. Neville is now a venture capital investor, Endeavour Capital Ltd, and is the founder or chairman of several advanced technology and science-based companies.

"My academic and professional life is centred on science and engineering and I have been very fortunate in my career. It's now an exciting prospect to help blaze new trails for those that follow." In the 139 year history of the Royal Society of New Zealand, Neville is only the second engineer to be President of the Society.

"Over the next three years I would like to enhance public understanding of the great importance of science and technology to our general wellbeing. I would also like to find ways to establish a focal point for pure and applied science, as well as social science, to aid this understanding. Excellence in New Zealand science is not an indulgence - it's an imperative"

Chemical Processes In New Zealand – Where To From Here?

Now that the second edition (1998) of *Chemical Processes in New Zealand* is online on the NZIC website, *www.nzic.org.nz*, there is an opportunity to develop the CPNZ project further. The event that initiated the project in 1975 was a question asked of me by a secondary school teacher, "could the NZIC help teachers by making information on chemical processes carried out in New Zealand available to them?" Volume one was published in 1978 and demand led to it being reprinted three times with 1800 copies being produced. Besides its intended school educational purpose it was widely used in tertiary institutions, bought by many industries for an overview of the New Zealand scene and as a good introduction for non-chemists such as lawyers and accountants. Copies in public libraries were also extensively consulted. Volume two with new articles on different processes followed in 1988, and eventually NZIC was able to give a copy of this volume in every secondary school. It was hoped to have the 1998 second edition online with a search engine by about 2002, but this project foundered. The 101 articles of 1998 edition now online were scanned from the printed copy and are as jpg files. At the moment one goes to the contents, clicks on the article of interest and this comes up. The first improvement that Rebecca Hurrell and I plan is to take the user first to the summary box of the article rather than the full article, and where this is too long, to a brief introduction/summary before proceeding to the box. If more detail is required the user will then bring up the full article.

If one were to follow the ten year intervals between volume 1, volume 2 and the 2nd edition there should be a 3rd edition in 2008! But so much has changed in the field of information technology that producing a printed 3rd edition would not seem sensible.

So the question *Where to from here?*

The 1998 publication is still the most comprehensive account of New Zealand's chemistry and chemical technology, but in so many areas it is now dated. The research and technology part of WRONZ is now Canesis; the dairy industry has undergone major changes with the formation of Fonterra, the Kinleith and Kawerau paper mills have undergone changes in ownership; the surface coating of car bodies (with some fascinating chemistry) in Thames stopped three weeks after the 2nd edition was printed; petroleum is no longer produced from natural gas and methanol production is under threat; just a few examples.

Having the publication online means articles could now be updated and new articles added at any time. But again is this the right approach? Might it be better to leave the 2nd edition essentially as it is and gradually build up a third edition online. I believe one important function of NZIC is to preserve aspects of the history of chemistry in New Zealand. But I do not believe NZIC has any archives. The 1940 NZIC publication *Chemistry in the Development of New Zealand Industry* (reproduced as the final article of the 2nd edition and which could be regarded as the original CPNZ) could so easily have been lost. This, the 1978, 1988 and 1998 publications of CPNZ, together with P.P. Willliams *Chemistry in a Young Country* and D. Hogan and B. Williamson's *New Zealand is Different* provide a fairly comprehensive account. It could be sensible to scan in the 1978 and 1988 volumes to preserve them in electronic form.

Building up a 3rd edition from scratch on the website could lead to a much more attractive and informative product. Colour photos of plant, colour illustrations and figures can be introduced. Links could be made to the websites of companies and organizations whose activities are described in articles. More statistical information on the output and value could be included. The site could be the first place anyone seeking information on some aspect of chemistry or chemical technology in New Zealand turns to.

For secondary schools a list of articles that illustrate topics covered in the curriculum could be created with links to the articles, (or sections in new of revised articles in html format).

An ambitious development as outlined above would be possible if a few enthusiastic individuals could be found to take on its organisation. One would hope that the spirit New Zealand's chemists is as enthusiastic and willing and it was in the 1970's, 80's and 90's. In the 1970's bright first year university students made a major contribution by going out to industries and writing first drafts. 3rd year Chemical Engineering students at Auckland in the 1990's did projects which had the potential to be used. The brilliant 2nd year PhD students seminars on a general topic, and which appear frequently in CHEM NZ, show how course work built into many degree structures could be a source of articles.

Perhaps Council, the newly re-established Chemical Education Section, Branch Committees of NZIC, and Chemistry and Chemical Engineering Departments in our tertiary institutions might like to consider *where to from here?* also. I would also ask any professional chemists who think they could provide articles, update articles, provide information which could be incorporated or offer any ideas on *where to from here?* to contact the NZIC secretary (*Secretary@nzic.org.nz*).

How might it be financed? There is over $3000 in the bank at the moment. Some of our large industries and CRI's might make a contribution.

John Packer, Editor of CPNZ to date.

Patent Ownership: Why You Need to Get it Right the First Time

By Blair Hesp

When it comes to filing a patent application for a new invention there are a number of considerations to take into account because of the commercial nature of patents. One consideration is the inventorship/ownership issue. A recent situation in Australia has highlighted how important it is to have the particulars of inventorship for a patent application in order from the very beginning, starting with who is actually entitled to file and own the patent application/granted patent.

Patent Ownership

As a general rule, the true and first inventors are entitled to the invention in the absence of other constraints. However, if the invention has been created during the normal course of employment, or using the resources of an employer, then the employer will be the rightful owner of the invention and entitled to apply as the applicant. In turn, ownership can then be assigned to a third party, if the owner so desires. However, it is important to note that in the absence of an agreement in New Zealand, joint owners of patents cannot act unilaterally when it comes to assigning (or licensing) their share of a patent, but must do so with the consent of all other owners of the patent.

Why Do You Need To Get It Right?

Patent specifications are dynamic documents and are often modified to meet the requirements of each jurisdiction. For example, this may result in the deletion of method of medical treatment claims from a specification in New Zealand which would otherwise be valid in an application in the US. These modifications may result in one or more inventors no longer being entitled to an ownership stake in the patent because their contribution to the invention is no longer within the scope of the modified patent specification.

So what happens if the inventor/owner details are not recorded correctly? The Australian Federal Court recently decided that if any of the inventor and/or ownership details are incorrect then the patent should be revoked (see Conor Medsystems, Inc v The University of British Columbia and Angiotech Pharmaceuticals, Inc. (No2) [2006] FCA 32). In this case, the University of British Columbia (UBC) claimed part ownership of a patent following two of the "original inventors" assigning their interest in the patent to UBC. It was later pointed out by a third party that the inventors who assigned their interest in the patent to UBC did not contribute to the development of the invention, as the specification stood in Australia, and were therefore not entitled to assign ownership of an interest in the patent application. Meanwhile, the true inventors assigned their interests in the patent to Angiotech Pharmaceuticals.

The issue here is that a patent may be invalidated or revoked in many jurisdictions, including New Zealand, if the patent applicant or inventor is not the true and first inventor. For example, if a person effectively "steals" someone else's idea the patent may be revoked, if challenged by a third party, because the applicant is not the true and first inventor. In this case, even though Angiotech was the assignee of the true and first inventors and entitled to apply for a patent, it was found that UBC was not entitled to apply because their interest had not been assigned to them by the true and first inventors. When challenged the granted Australian patent was revoked because UBC was not entitled to apply for the patent.

Because the patent had already been granted the Judge ruled that the application as a whole had been granted on false grounds. Angiotech was legally entitled to an interest in the patent by assignment from the true and first inventors but the Courts declined to validate Angiotech as sole owner of the patent on the grounds that the patent application was granted under false circumstances.

Therefore, because inventorship/ownership was not confirmed prior to filing a patent application in Australia both UBC and Angiotech came out as big losers. This case serves to remind us that it is important to have your house in order before filing a patent application because any discrepancies between the information declared in a patent application and the facts can be fatal during patent revocation or infringement proceedings.

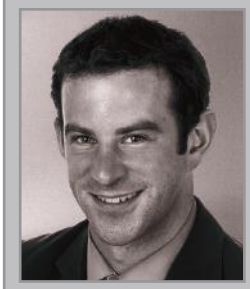
A reminder: if you have any queries regarding patents, or indeed any form of intellectual property, please direct them to:

Patent Proze

Baldwins

PO Box 852, Wellington

Email: *email@baldwins.com*



Blair Hesp of Baldwins specialises in chemistry and biotechnology patents. Blair joined Baldwins in 2006. He has a PhD in pharmacology from the University of Otago as well as a NZDipBus with a management focus. Blair is currently studying towards a law degree and registration as a patent attorney.

Book Review

CHASING THE MOLECULE: Discovering the building blocks of life. By John Buckingham. Sutton Publishing, 2005, ISBN 0 7506 3346 1. Reviewed by John Packer.

This paperback of 229 pages is an absolute gem. It traces the development of organic chemistry up to the time of establishing the correct number of atoms in a molecule, which atoms are connected to which and their geometrical arrangement in space; i.e. what we might now call the ball and stick model of molecules. By the end of the 1870's most chemists accepted this model and it allowed organic chemistry to advance at a great rate even although the structure of the atom had not yet to been discovered and there was no theory of what held the atoms in molecules in place – no theory of chemical bonding.

The book is written for the lay-person, with simple explanations of the modern basic ideas of chemical structure introduced in appropriate places so that the reader can appreciate the thoughts and problems facing chemists of the 1700's and mainly 1800's as they struggled to make sense of theirs and others experimental observations and results. Anyone with Year 12 knowledge (UE or 6th form for those over 30!) of chemistry would feel right at home.

As well as following the developments of the ideas, the author gives us wonderful insights to personalities, problems, circumstances and rivalries of the main players in the saga, and attempts to proportion the proper recognition of the contribution various individuals deserve. The main protagonists (in alphabetical rather than chronological order) in the story from 1800 are Berzelius, Couper, Dumas, Gerhardt, Hofmann, Kekule, Laurent, Liebig, Pasteur, Wöhler and Wurtz. The ideas and contributions of other chemists and physicists (Avogadro, Biot, Butlerov, Bunsen, Cannizzaro, Crum Brown, Dalton, Davy, Faraday, Frankland, Gay-Lussac, Kolbe, Lavoisier, Loschmidt, Odling, Priestley, Scheele, Williamson) are woven into the story.

The obstacles and difficulties that held up more rapid development are discussed in an entertaining way – the confusion of the atomic weights of the elements, the rise and fall of the vitalism, the conservatism of senior players and their reluctance to accept new theories, nationalistic pride, the vendetta of Kolbe against Kekule.

I found the progress from Berzelius's radicals to Dumas' type theory and its development by Laurent and Gerhardt to the idea of functional groups particularly interesting. The place of Kekule, and the authenticity of his dreams are fully explored.

In the last chapter the author describes the organic chemistry of today, with its emphasis on natural products and synthesis, and its relationship with the pharmaceutical industry.

Even New Zealand appears in the story! It relates to an Italian myth and chirality. Perhaps this will whet the appetite and encourage people to read this book. It should be in the library of all schools with students genuinely interested in chemistry; it should be compulsory reading for any BSc student majoring in chemistry, and a prized possession of all professional chemists. Perhaps NZIC could accept orders and put in for a bulk order.

I repeat my first sentence. *This book is an absolute gem.*

Open Access Online to Chemistry papers

A new service publishing peer-reviewed, open access research in chemistry was launched in August.

Chemistry Central is a website that currently features chemistry related articles published in BioMed Central. In the near future a peer-reviewed general chemistry title, Chemistry Central Journal will be launched. One of the first to join the Editorial Advisory Board of this new journal was Professor David Williams from the University of Auckland.

The site has been developed by the same team behind BioMed Central, which was the first open access publisher. It was launched in May 2000. It is the largest open access publisher in the world.

Bryan Vickery, BioMed Cental Deputy Publisher, said "the time seemed right for BioMed Central to create an open access publishing website to meet the needs of chemists".

Since the chemistry site has been launched, Mr Vickery said the response "has been very encouraging."

The costs of the publishing is mostly covered through Article Processing Charges (APCs). Mr Vickery said "these costs are generally paid by the author's institution or funder, just as it is the institution or funder that currently pays for subscriptions to traditional journals." He also said some of the journals are fully funded by the organizations that run them. BioMed Central has yet to break even.

Chemistry Central and BioMed Central are part of the Science Navigation Group. This is a group of independent companies that collaborate to publish and develop information and services for the professional biomedical community and the consumer market.

The chairman of the group is Vitek Tracz, He was born on the border between Russian and Poland in 1940. He studied mathematics and film before eventually becoming involved in scientific publishing.

The web address for the site is *chemistrycentral.com*.

NZ Team Wins 3 Silver medals and 1 Bronze at the 38th International Chemistry Olympiad in Korea

PhotoCaption: The NZ team with their medals and mentors

The 38th International Chemistry Olympiad (IChO), covering 67 countries, was held at Yeungnam University (Gyeongsan, Korea) in July. It was an enormous thrill when, for the first time in 15 years involvement, the NZ team came away with 3 silver medals and 1 bronze medal, bettering the performance of their traditional rivals from Australia, the UK, and other countries. This truly outstanding performance reflects the calibre of the students, both in terms of their knowledge of chemistry and their willingness to put in the many extra hours to attain the high level needed. Silver medals were won by **Joshua Baker** (Newlands College, Wellington), and **Kuan-Lun Huang** and **James Park** (Auckland Grammar), and the bronze medal by **Richard Stebbing** (Northcote College, Auckland).

Head Mentor, **Dr Jan Giffney** (St Cuthbert's College, Auckland) accompanied the team together with mentor **Dr David Salter** (Auckland University). For years the NZ Chemistry Olympiad Trust has worked hard to develop a sound training programme and the contributions of **Drs Robert Maclagan** (Canterbury University) and **Sheila Woodgate** (Auckland University) are notable and here acknowledged.

The IChO is not just a competition but rather a festival. It gives students a chance to meet and enjoy the company of many others from around the world, to meet in a spirit of peace and friendship, and to have fun! The four NZ students said the trip was the most memorable experience of their lives.

The exams that the students sat were, not surprisingly, challenging and long! For the 5 hour practical each student was provided with a set of brand new equipment including a computer to take absorbance readings. There were three parts to the practical i) use of a column to chromatographically separate 2 dyes, construct a calibration curve for one, then determine its concentration in a mixture of both, ii) use a column to separate two acids and, using pre-standardized NaOH, determine the acid concentration in *each* of 20 samples collected, and thence the concentration of each acid in the original mixture, and iii) identify 7 organic unknowns each with multifunctional groups employing 9 tests on each sample –63 test-tube tests! Credit must go to Joshua Baker who recognized the structure of vanilla and used the odour as a clue to its identification - not that smell was supposed to be a test used. Almost no students completed the tasks in the allocated 5 hours, a fact that is hardly surprising.

Two days later the students sat the 5 hour theory exam. Although the international jury (the mentors from the 67 countries involved) had managed to delete ~20% of the questions in the original paper, the exam was still long. There was emphasis on physical chemistry, and any student hoping to make it at this level had to have a high mathematical competency.

Our Korean hosts could not have been more hospitable. They gave us the opportunity to experience their culture—notably an amazing series of performances by groups playing Korean drums—a visit to the Hyundai car factory that produces one car every 12 seconds(!), and many trips to Korean temples, villages, museums, and amusement parks. That July is the rainy season in Korea and we hardly saw the sun simply did not matter.

The NZ Chemistry Olympiad acknowledges financial support from Auckland, Canterbury and Victoria Universities, and sponsors Talent Development Initiative—Ministry of Education, Talented Students Travel Awards—RSNZ, The MacDiarmid Institute, Unilever Ltd., Douglas Pharmaceuticals, Thomson Publishers, ABA Books and Crescendo Enterprises. Apart from this, the advice and guidance that teachers, mentors, and various NZIC members have given to the students in the team and those involved in the Olympiad training programme is appreciated.

Dr Jan Giffney
St Cuthbert's College

New Zealand Institute of Chemistry

supporting chemical sciences

September News

NEW ZEALAND INSTITUTE OF CHEMISTRY
2006 Annual General Meeting
Novotel Convention Centre, Rotorua
Sat. 2 Dec. 2006, 16.30 – 17.30

Nomination for NZIC Offices

Nominations are called for the Offices of President, First Vice-President, Second Vice-President, Honorary General Secretary, and Honorary Treasurer. The 1st Vice-President is automatically nominated for the position of President and the 2nd Vice-President is automatically nominated for the position of 1st Vice-President.

Nominations can be made by any Branch or by any *six* members and should reach the Hon. Gen Secretary by 31 October 2006.

The address for nominations is: *nzic.secretary@nzic.org.nz* or Freepost 96, PO Box 39-112, Harewood, Christchurch 8005, New Zealand.

Should any election be needed it be advised *via* and conducted on the NZIC web site (www.nzic.org.nz) from 6 November 2006.

R. Rendle
Honorary General Secretary

Executive

PAST-PRESIDENT ELECTED COMPANION OF RSNZ

Council offers its congratulations to **Doug Wright**, CNZM, CRSNZ, JP, Hon FNZIC, MSc (Hons.), PhD, DSc, NZIC President 1981-1982, on his election as a Companion of RSNZ. Doug has made long and significant contributions to science and industry in NZ. His professional career spanned more than 50 years - he entered the Department of Agriculture as a technical trainee and exited as chairman of national and international science and technology committees.

He became a scientist in the Departments of Agriculture and Scientific and Industrial Research, was a flight lieutenant, RNZAF in the NZ Defence Science Corps, a senior lecturer in Biochemistry at Canterbury University, a postdoctoral at McGill University (Canada) and then University of California-Davis. At the Ruakura Animal Research Station he became a section leader, and eventually Asst. Research Director [Animals] in the Ministry of Agriculture and Fisheries. In 1987 he was appointed Director of the Meat Research Institute of NZ (MIRINZ) from which he retired in 1992.

Doug held leading roles as President of the NZ Institute of Chemistry, Nutrition Society, and represented the Member Bodies on the RSNZ Council; he also served on the Waikato Polytechnic Institute Council. He was a member of the committee which established the Meat Research and Development Council (now with Meat and Wool New Zealand), he co-authored the McGregor Report on the funding of Public Good Science through FRST, and was Acting Chief Scientist in MoRST pending the appointment of a new Chief Scientist.

He has actively promoted science to industry and to the public with talks that include *The Importance of Ernest* - a talk on Ernest Rutherford, *A mouth full of Ps - possums, poisons and pestilence in New Zealand*, and *It may be natural but is it good for you?*

IUPAC Poster Prizes for Students at Rotorua Conference

IUPAC have authorised the award of up to *two* student poster prizes at the NZIC Rotorua conference. The prizes, which consist of a certificate and a 1-year subscription as an IUPAC Affiliate to *Chemistry International*, will judged by a panel appointed by the Organizing Committee.

Chemical Education Specialist Group

Council provided partial support to allow Suzanne Boniface (Convener)

to attend the IUPAC sponsored 19th ICCE conference in Seoul in August as the sole NZ representative.

BRANCH NEWS

AUCKLAND

The Branch hosted **Prof. Brynn Hibbert** (University of New South Wales) in July at the start of his NZ tour as RSC/NZIC/RACI Australasian lecturer. He gave his anecdotal view of work in the courts that included bogus health products, unsuccessful defences of murderers and racehorse trainers, and highly lucrative patent cases jointly to the NZ Forensic Science Society. Those present enjoyed the relaxed, entertaining and yet highly informative discourse that also included a brief but highly relevant discussion of statistics (lies, damned lies and …). This role of the expert witness was made clear and the need for professional societies, such as NZIC, to maintain standards of professionalism stressed. His lecture followed one on his work with self-assembled monolayers in the Chemistry Department during the afternoon.

Chemistry Department UA

The Medicinal Chemistry Group recently celebrated the beginning of human clinical trials of a drug developed in the laboratories. The Department has purchased a new liquid chromatograph–mass spectrometer with a grant of $120,000.00 from Lottery Grants Board Health 9 (led by **Margaret Brimble**) and the balance from the University. **Tilo Soehnel** has received a $30,000 University Early Career Research Excellence Award for work entitled *The Chemical Transport of Ternary and Quaternary Cu-Sb-Oxides and Halides*.

Together with the Faculty, the Department hosted thousands of children and accompanying adults for *Incredible Science Day* on July 3. The Slime won the day with the Magic show and glassblowers again packed.

Auckland Cancer Society Research Centre - 50 Years of Research

It is 50 years since the Auckland Cancer Society Research Centre was founded by the Auckland Cancer Society. A small team of researchers led by Drs. Bruce Cain and Jack Burton began a programme of research that focused on isolation and testing of extracts from NZs native flora for anticancer activity. Initial results showed ~12% of compounds with a response in experimental tumour models but further analysis indicated polyphenolic tannins to be largely responsible for the toxicity; only ~0.2% of extracts had convincing antitumour activity. Further disappointment followed when Cain found the active agents to be related to known compounds. As progress in discovering new anticancer drugs by natural products chemistry was painstakingly slow, Cain reasoned that greater progress might ensue from systematic modification of the structures of anticancer agents of known chemical composition to increase activity. Once the structure of DNA was known he became interested in designing and developing drugs that would interact with it. His studies were rewarded by the 1970s development of the clinical antileukaemic drug Amsacrine and with its development came the discovery of a new class of anticancer drugs – the topoisomerase poisons. With Cain's sudden death in 1981, the research programme was advanced by the new directors Drs. Bruce Baguley and Bill Denny with the aim of developing a topoisomerase agent with activity against solid tumours. Four new agents from the amsacrine analogue programme were advanced to clinical trial over the next 20 years [*Asulacrine* (1986), *DACA* (1995), *XR-11576* (2001), and *MLN-944* (2003)].

A major problem with topoisomerase inhibitors is that they target not only tumour cells, but also dividing normal cells, and their use is limited by these undesirable side effects. Through Baguley and Denny's leadership ACSRC has sought to exploit particular features of tumour cells or their environment and to design drugs that specifically target tumour tissue. The first drug to be developed from this strategy was *DMXAA* which targets tumour vasculature and induces a host cytokine storm; it is soon to enter Phase III clinical trial. *Canertinib*, an irreversible inhibitor of the epidermal growth factor receptor, followed. The activation of this receptor is important in many common solid cancers; developed with Pfizer, it is in Phase II clinical trial. Recently, a 15-year programme to produce bioreducible drugs that are activated in low oxygen regions of solid tumours has yielded *PR-104*, and this is now in Phase I clinical trial.

To celebrate its 50th anniversary, ACSRC is hosting a 2-day symposium **Patience, Patents, Patients** (20-21 November) that will showcase drug discovery highlighting the work of medicinal chemists, molecular and cellular biologists, pharmacologists and clinicians with internationally renowned invited speakers. Further information and registration details can be found at *www.health.auckland.ac.nz/cancer*

CANTERBURY

Recent Branch events have been well attended and extremely well received. In June **Darren Saunders** (ESR) gave an entertaining talk on food safety *Food Forensics; CSI without the bodies*. The question session resulted in a further investigation of one of the cases covered. The July talk was the, *Scientist versus the Law* by **Prof. Brynn Hibbert**. August saw the annual ***Trivia and Truffles*** evening. This year a record 23 teams entered and as **Don McNickle** accepted 1st prize on behalf of the team ***We Will Let You Know Next Week*** (**Jan Wikaira, Bryce Williamson** and **Don**) he was heard to mutter 'About time too - I've been doing this for years'. The win was controversial since Bryce is Head of Chemistry and Jan is the Chair of the local Branch. 2nd place went to ***The Ether Bunnies*** (**Alan Downward, Reuben Jane** and **Neroli Ayling**) and 3rd third was ***Shelf Five, Policemen and Cows*** (**Ben Perston, Paul Wilson** and **Sam Edwards**).

Great concentration at the Trivia and Truffles evening

Chemistry Department UC

Andrew Abell and **Matt Jones** are the recipients of Growth Industry Pilot Initiative (GIPI) funding that includes a 3-year Science Entrepreneur Research Associate (SERA) position for Matt. **Gregory Francis** has been named runner-up in the *Science in our Communities* category of the MacDiarmid Awards. Greg is undertaking a PhD under the supervision of **Murray McEwan** in association with Syft Technologies on the development of a device capable of identifying the presence and concentration of chemical weapons agents. **Alison Downard** has been awarded $119 K from the MoRST NZ/France S&T Support Programme; it will enable Alison to take part in an exchange project at Universite de Rennes. **Joshua Lehr**, working with **Alison Downard** on covalently modified carbon surfaces with the aims of developing components for use in bio-fuel cells, has been awarded a Top Achiever Doctoral Scholarship.

Nathan Alexander, Uma Adash, Anna McCarthy and **Ramin Zibaseresht** have completed their PhD studies. Nathan worked with **Andrew Abell** on *Molecular Switches: The Design, Synthesis and Biological Applications of Photoactive Enzyme Inhibitors*; Uma's research was on *Synthesis and Kinetic Investigations into Free-radical Polymerisation used in the Preparation of Polymer Therapeutics* (supervisor **Greg Russell**); Anna's thesis was entitled *Biological Activity of Steroid Analogues: Synthesis and Receptor/Enzyme Interactions* for work conducted under the joint supervision of **Profs. Ian Shaw** and **Andrew Abell**; Ramin's work on *Approaches to Photoactivated Cytotoxins* was supervised by **Richard Hartshorn**. **Mutita Klanchantra** has been awarded her MSc with 1st class Honours for work (supervisor **Andrew Abell**) concerning the *Design and Synthesis of β-strand Conformationally Constrained Calpain Inhibitors for Cataract Treatment* via *Metathesis Ring Closing*. **Sean Devenish** has been awarded a NZS&T Postdoctoral Fellowship for the project *Disruption of protein oligomerisation as a novel strategy in drug design* with **Juliet Gerrard** in the School of Biological Sciences. **Xianming Li** has started a postdoctoral position with **Alison Downard** on the aspects of CVD synthesis, and electrochemical and biological applications of carbon nanotubes. **David Tran** (**Emily Parker**) and **Omar El-Hadad** (**Greg Russell**) have started PhD studies. **Scott Walker, Aidan Harrison** and **Hemi Cumming** have moved from Massey to join **Emily Parker**. Visiting student **Anna-Skrollan Geiermann** (Germany) is working with **Profs. Murray Munro** and **John Blunt** in the Marine Group, and **David Cho** (IC-London) is with **Ward Robinson**. June saw **Sonia van der Sar** go to Germany to take part in the Lindau Nobel Laureate Meeting as one of two PhD students chosen by RSNZ. Currently **Jennifer Burgess, Justine Cottam** and **Jennifer Zampese** (the *women of Steel*) attended the 37th *International Conference of Coordination Chemistry* in Cape Town where Jennifer won the student poster competition.

Ther first Oxford-Canterbury Exchange Fellow, **Antony Fairbanks** is visiting for four months. Fez, as he is known, is an organic chemist with interests in synthetic carbohydrate chemistry with emphasis on biological applications. Dumont d'Urville Fellow, **Frédéric** (Fred) **Barrière**, is visiting for two months in **Alison Downard's** group and working on electrode surface modifications for bio-fuel cell applications. **Prof. Richard Keene** (James Cook-Townsville) spent three weeks continuing his research collaboration with **Peter Steel**. **A/Prof. Muna Al-Mandhary** (Sultan Qaboos University, Oman) made her fourth visit continuing work with **Peter Steel**. **Greg Jackson** has completed his Erskine stay and returned to Canberra and **Chris Pursell** has returned to San Antonio. **Dr. Michael Mautner**, who has been affiliated with the Department since 1986, has been appointed Adjunct Professor for three years; he has collaborated with several staff members but particularly with **Murray McEwan**. **Dr. Michael Lever's** appointment as an Adjunct Senior Fellow has been extended for three more years. **Prof. Peter Stang** (University of Utah) has been in the Department since late August; specializing in physical organic, organometallic, polyvalent iodine, and metallosupramolecular chemistry, he is Chief Editor Journal of the American Chemical Society and was recently awarded the 2006 Linus Pauling Medal.

Caption: Bryce Williamson making the presentation to Ward Robinson.

July saw a retirement function for **Ward Robinson**. There was a very large turnout that included Emeritus Professors and staff from Waikato and Otago universities who came along to pay their tributes. Accolades came from all over the world and it took some time to read them all. The words expressed by visitors and passed on by email were wonderfully reflective of Ward's local, national, and international standing as a scientist, teachers, colleague, and friend. Ward was thankful some speakers, who were in a position to divulge sensitive information, felt restrained by the certain knowledge they would not have the last say. Ward, elected to Emeritus Professor by the University, was presented with a camera and a GPS as a farewell present.

In the last few weeks of August three girls have been born to staff members: **Owen Curnow** and his wife **Catherine** welcome **Carolyn, Sunny Hu** and her husband **Nathan** welcome **Shachia**, and **Rachael Hocking** and her partner **Riegan** welcome **Rhiannon**.

Canterbury and Westland Science Fair

Three Branch judges (**Jan Wikaira, Sarah Lundy** and **Darren Saunders**) attended the Lincoln University Canterbury-Westland S&T Fair as judges. The number of entries, up on 2005, had the judges were hard pressed to get around in the time allotted. Quality was impressive to the point where the original two NZIC prizes were expanded to include honourable mentions.

The Senior Prize was awarded to **Niamh Peren** (St Margaret's, Christ-

church) while **Yun-Joo So** and **Erica Li** (Christchurch Girl's High school) won the Junior Prize for their investigation into methods of controlling crying when peeling onions.

MANAWATU

Landcare Research

Benny Theng attended the 18th World Congress of Soil Science (in Philadelphia in July) where he gave an introductory lecture on the absorption of non-ionic organic compounds by soils and clay-humic complexes. Well over 2000 soil scientists from more than 100 countries came together to present thousands of posters and hundreds of oral papers on soil science topics, ranging from the molecular scale to the global dimension. The plenary address was given by **Jeffrey D. Sachs** (Director, Earth Institute-Columbia University and special adviser to **Kofi Annan**) on the Millennium Development Goals. Dr. Sachs emphasized the role of soil science in sustaining soil fertility and crop yields with special reference to Africa, the continent that the green revolution has apparently by-passed.

Massey University

Welcome to **Padmesh Anjukandi** who arrived in NZ last month to take up a PhD studentship with **Bill Williams** on calculating the mechanical behaviour of biopolymer chains and networks. This will add a theoretical aspect to the current experimental programmes in single polysaccharide stretching and the micro-rheological investigation of soft materials.

The International Conference on the Science and Technology of Synthetic Metals (ICSM), held at Trinity College Dublin in early July, brought together over 1000 leading materials scientists and engineers, including **David Officer, Pawel Wagner** and **Sanjeev Gambhir**. The conference covered the diverse area of synthetic metals (conducting polymers, carbon nanotubes etc) with Noble Laureate **Alan MacDiarmid** presenting the plenary lecture in a programme that included nine keynote presentations from the likes of **Sir Harry Kroto** and **Sir Richard Friend. David Officer** was an invited lecture, while Pawel and Sanjeev both presented posters.

Pawel Wagner also attended a conference on Hybrid and Organic Solar Cells (ECHOS) in Paris. The conference was organized by the French Ministry of Sciences and MOLYCELL (whose members comprises all European scientific groups working on photovoltaics - PVs). Although attended mainly by European scientists, Australasia was also represented by **Paul Dastoor** (University of Newcastle and a Massey NRC collaborator) who gave an oral presentation.

Carol Taylor's productive time at Massey has come to an end with her appointment at Baton Rouge. Carol won the Easterfield Medal in 2001 and has been very successful in gaining Marsden grants. An article in Massey's glossy included, *"Dressed in jeans and sneakers, surrounded by books and papers, the diminutive chemists ..."* but there is nothing diminutive about Carol's stature as a chemist. NZIC wishes her well in her future career.

Emily Parker has returned to Canterbury University where she started her academic life. An impressive feature of Emily's time in Massey was the collaborations she established both with other members of IFS and with IMBS, such that her work spanned the range from intricacies of organic mechanisms and synthesis to site-directed mutagenesis and other techniques of chemical biology; she has been awarded an Honorary Research Fellowship to continue this relationship. Emily gained Marsden Awards, the Massey University Women's award in 2005, and the NZIC Easterfield Medal in the same year; *Mrs. Curly Arrow* will be sorely missed. Emily's post-doctoral fellows **Linley Schofield** and **Fiona Cochrane**, along with PhD students **Ben Mulchin, Celia Webby, Amy Pietersma, Jenness Guthrie** and **Meekyung Ahn** who are all in the final throes of completing their PhD theses, and **Leonardo Negron** (who successfully jumped the Confirmation of Registration hurdle) remain at Massey University. Celia has just accepted a post-doctoral position at Oxford University. **Karl Shaffer** has been awarded a Top Achiever Doctoral Scholarship to enable him to undertake his PhD with **Paul Plieger**.

Te Manawa, the local museum, hosted this years Science Week under the theme *Health, Fitness and the Human Body*. **Eric Ainscough** delighted his audience with an illustrated talk entitled *A Voyage into the Gastrointestinal Tract*.

OTAGO

Prof. Warren Tate, a world-leading biochemist and molecular biologist, has been awarded Otago University's distinguished Research Medal. Warren is an exceptional researcher, training younger researchers as an unselfish colleague, and making an enormous contribution to science in New Zealand. Warren's achievements include the Alexander von Humboldt Fellowship, Pharmacia Research Prize and the Howard Hughes International Research Scholar Award.

Prof. Sally Brooker recently hosted a flying visit from **Prof. Cameron Kepert** (Sydney) during which he presented a 400-level lecture course. Sally is organizing a one day conference for ***Sat. 3 March 2007*** (8.30 am – 11 pm including a conference dinner) on *Supramolecular Chemistry and Nanoscience – Towards Functional Nanostructures* to mark the visit of 1987 Nobel Laureate **Prof. Jean-Marie Lehn** (University Louis Pasteur, Strasbourg). **Prof. Paul Callaghan** (Victoria) will present the closing plenary lecture. Please register your interest in this conference by e-mail to *trenault@chemistry.otago.ac.nz*

Three new PhD students have joined **A/Prof. Keith Gordon's** group. **John Earles**, [BSc (Hons) Otago] is working on porphyrin maquette assemblies jointly with **Prof. David Officer** (Massey), **Louise Ho** (BPharm) on THz spectroscopy and imaging of pharmaceutical systems jointly with **Profs Mike Pepper** (Cambridge) and **Thomas Rades** (Otago, Pharmacy) and spending much of her time in with Pepper's associated instrument company *Teraview*, and **Destari Pratiwi Clarke** (Tiwi) on a TIF-funded PhD also with Thomas Rades. Her project, part-based at Lactose NZ with **Dr Gorrey Chui**, is on the prediction of tablet quality using spectroscopic techniques.

Keith has spent time at conferences

and meetings this year; he gave an invited talk *Modular design and construction of new electroactive materials: multi-component Re(I) complexes for application in OLEDs* at the 2nd International Workshop of NANO Systems Institute (Seoul) in May. Keith also attended the NZ-German Workshop on Functional Nanostructures and Nanomaterials, organized by Uli Zuliche (Massey, Physics) and held at VUW.

Keith has been appointed by the FRST as the NZ Focal Point Co-ordinator for Advanced Materials and Nanotechnology for interactions with Korea. To this end Keith helped organise, the *NZ & Korea Workshop for Advanced Materials and Nanotechnology*, and the subsequent visits by the Korean delegation to Victoria and Massey; Keith spoke at the workshop on *Modular design and construction of new electroactive materials for application in OLEDs*. Keith also attended the Synthetic Metals Conference (ICSM) in Dublin in July together with a number of other NZ delegates.

Dr. Sarah Howell, (Keele, UK) visited to work on pharmaceutical materials and solar cell dyes using Raman spectroscopy. **Penny Walsh** went to Korea to work with **Prof. Chang Hee Lee** (Oganic Semiconductor Lab., Seoul National University) on OLEDs with materials that had been made by **Natasha Lundin**.

Cushla McGoverin, a FRST Top Achiever Awardee, visited the Clandeboye Fonterra plant in August as part of her research into the analysis of milk products using Raman spectroscopy and chemometrics.

Dr. Garth Irwin joined theGordon group at the beginning of the year for a 2-year postdoctoral position. Garth, an Otago graduate who completed his PhD in inorganic photochemistry at the Victoria (British Columbia) in 1999 has held a variety of teaching posts since that time. He is working on on the synthesis and properties of metal complexes containing discotic polypyridyl ligands.

WAIKATO

Brynn Hibbert presented his entertaining seminar RSC/NZIC/RACI *Scientist versus the Law* lecture to the Branch in July.

University

The University hosted *SciCon2006-Celebrating Science through Innovation* in July involving a number of Chemistry staff both on the organising committee (**Michèle Prinsep**) and giving talks (**Michèle Prinsep, Brian Nicholson**) or running workshops (**Bill Henderson, Merilyn Manley-Harris**).

The ***Waikato Mass Spectrometry Facility*** (*www.mass-spec.co.nz*) had its public launch in late July and saw representatives of the local AgBio industrial cluster, CRIs, and representatives from industry and research centres in other parts of the North Island. Organiser and academic manager (**Merilyn Manley-Harris**) outlined the different instruments and their research applications. Other speakers included **Dr. George Slim** (Director, Emerging Technologies,MoRST) and **Mark McMorran** (Business Manager, Technology New Zealand) as several local dignitaries. Maximization of the research dollar through centres of this type was emphasised by Dr. Slim.

Lyndsay Main and **Michèle Prinsep** presented a session *Coming to Our Senses: Chemicals of Smell, Taste and Colour* in the Science/Engineering ***Café Scientifique*** programme. A sizeable crowd enjoyed smelling, tasting and seeing a wide range of chemicals, and hearing all about their properties.

Sally Gaw and **Lusha Kodikara** have now gained their doctorates and Sally has taken up a position in Christchurch. **Kelly Kilpin** has been awarded a Top Achiever Doctoral Scholarship.

WINTEC

Chromatography courses, in conjunction with the NZ Chromatography Group and offered at WINTEC, have trained some 1200 scientists and technicians from throughout NZ since 1981. The next course will run Nov 28 - Dec 1 and details are available from: *Beverly.Langmore@wintec.ac.nz*

WELLINGTON

The June meeting, held jointly with the Wellington Branch of the NZ Forensic Science Society, was addressed by **Dr. Gordon Miskelly** (Deputy Director, Forensic Science Programme, Auckland University) on *Enhanced Visualisation of Forensic Evidence*. With an ideal balance between image and chemical detail Gordon was able to keep the 40 strong audience fascinated with his recent investigations into ways of increasing the sensitivity and selectivity of methods for enhancing forensic evidence such as blood, sweat, and soil. The work in improving imaging and image analysis techniques provided the highlight and this lecture followed on from an equally successful seminar in the VUW School earlier in the day.

In mid-June the annual titration competition preceded the schools' evening ***Chemistry Quiz***. In the afternoon **David Weatherburn** and **Jackie King** (with a little help) hosted 35 young chemists competing in the annual NZIC/SCPS titration competition. David set a challenging EDTA back-titration with a difficult end-point, but as usual, the best students managed it easily. The joint winners were **Joshua Baker** (Newlands College) and **Hana Christenson** (Wellington Girls' College), with **Tony Zheng** (Upper Hutt College) in third place.

In the evening **Brendan Burkett** welcomed 220 secondary students from 22 schools and colleges around the region to the annual NZIC/VUW Chemistry Quiz, held in the Union Hall. The quiz continues to grow in popularity which has meant some headaches for **Wendy Popplewell** and **Joanna Wojnar** who organized the event, assisted by a large team of Happy Helpers (mostly SCPS postgraduates). The questions were compiled by **Mina Razzak**, and were best answered by a team from **Newlands College**, with teams from **Scots College** in second and third place. While the students were having fun, the accompanying teachers and parents were entertained by Pablo Etchegoin who enlightened them on the potential of Raman spectroscopy as a diagnostic tool in medicine, over a cup of coffee or tea. It was good to see several of our graduates amongst the attending teachers. Thanks go to the Science Faculty (Platinum Sponsor), NZIC, VUWSA, Student Recruitment, and Holey Bagels for their sponsorship of the events.

July saw two Branch meetings, the first an excellent informal mid-winter dinner at the Istanbul Cafe that saw some 20 members having a very pleasant evening together and the second, later in the month, the RSC/RACI/NZIC lecturer **Brynn Hibbert** (University of New South Wales) giving his anecdotal view of work in the courts that included bogus health products, unsuccessful defences of murderers and racehorse trainers, and highly lucrative patent cases. AA group of about 35 enjoyed the relaxed, entertaining and yet highly informative discourse that also included a brief but highly relevant discussion of statistics (lies, damned lies and …). This role of the expert witness was made clear and the need for professional societies, such as NZIC, to maintain standards of professionalism stressed. Sadly, our Branch Chairman (**Ken MacKenzie**) was unable to attend the meeting following his hospitalization in the UK and subsequent delayed return to NZ – we wish him well in his recovery.

August saw the President address *New electroactive materials for application in OLEDs & solar cells* when electronic materials made from molecular compounds with new solutions in a variety of important technologies, including display and lighting (using organic light emitting diodes, OLEDs) and energy capture (with non-silicon solar cells) were explained. The key intermediates charged and excited state species,examined using time-resolved and electrochemical spectroscopic experiments, were shown o be more than plausible. The use of computational chemistry and spectroscopy to understand the reactivity and conduction mechanisms of thiophene oligomers was elegantly.

The Wellington Regional Science Fair, held at Victoria University, led to the award of the junior Branch prize for *Biodiesel* to **Daniel Friar** (Wellington College) and (the senior award to **Georgina Hampton** (Queen Margaret College) for *Iodised Salt Heating Up*.

Victoria University

Dr. Joanne Harvey gave birth to her and husband Adrian's first child, Miriam Jean, on July 3. This is a first for VUW female chemists since the Department was established at the turn of the last century.

Recent visitors to the School have included **Dr. Mark Coster** (Sydney) who spoke on *Anti-cancer and anti-HIV natural products* and **Prof. Bryn Hibbert** (New South Wales) who, apart from his RSC lecture, addressed the School on *All that SAMs is not gold*.

James Crowley who did a Masters with **David Weatherburn** and a PhD with Bryce Bosnich (Chicago) is now in Edinburgh on a 2008-08 Ramsay Fellowship with Prof. David Leigh. **Fern Kelly** (Jim Johnston supervisor) has been awarded a Top Achiever Doctoral Scholarship and ***five*** current graduate students have received financial support from the Branch to attend the national conference in Rotorua in December.

ESR

Barbara Thompson was a prize-winner at the 39th Annual Australian Institute of Food Science and Technology (AIFST) Convention held in Adelaide for her poster entitled *Too much salt - not enough iodine*.

IRL

GlycoSyn, IRL's small molecule process development and GMP manufacturing business unit, has nearly completed the manufacture of the key ingredient for a new drug designed to slow the progression of Parkinson's Disease, thanks largely to the efforts of **Drs. Paul Benjes** and **Tony Davidson**. Initially invented by scientists at Otago University, Antipodean Pharmaceuticals Ltd. is now trialling the drug, MitoQ®, and has been working closely with GlycoSyn to advance the drug further. In an agreement between IRL and Antipodean, GlycoSyn is manufacturing sufficient amounts of MitoQ® for human clinical trials in NZ, Australia and the US. Phase II clinical trials are already underway and the potential impact of the drug is far-reaching - four million people affected by Parkinson's worldwide. GlycoSyn have also installed a new 60 L reactor train to compliment their 250 L reaction vessel, both of which operate under GMP.

Dr. Peter Tyler (Carbohydrate Chemistry) presented a bid to the Medicines for Malaria Venture in Washington DC in July. The MMV is funded by Bill and Melinda Gates and has fielded over 200 applications in the current funding round; only a small percentage of applicants made it to the interview stage. Several members of the Carbohydrate Chemistry Team attended the recent XXIIIrd International Carbohydrate Symposium (Whistler, Canada) presenting several posters one of which won a student prize for **Gary Ainge; Peter Tyler** provided an oral presentation on the *Potent and Selective Inhibition of Adenosine Deaminase from* Plasmodium falciparum. During a client meeting on a local golf course, **Drs. Tyler** and **Painter and Yorke** (NZP) discovered that in Canada, black bears are a hazard on par with sand-traps and rough! During his North American travels, **Peter Tyler** visited the new San Diego-based Biotech Amira Pharmaceuticals Inc. founded by former VUW graduate Dr. Peppi Prasit as CSO with former Auckland graduate Dr. Jilly Evans as Head of Biology; it and provides further evidence, were any needed, that NZ develops world class scientists.

Prof. Sir David Lane (Director, Molecular and Cell Biology Institute at A*Star) visited IRL in June to evaluate the capability and capacity to participate in a collaborative research; presentations were made by **Drs. Ruth Falshaw, Wayne Severn** and **Richard Furneaux**, and **Tim Boyd**. Sir David toured CarboChem and GlycoSyn. **Dr. Cees Lensink** has resigned from IRL to join BDGlobal at Gracefield.

BioCryst Pharmaceuticals Inc. (Nasdaq: BCRX), who license two drugs designed and synthesized at IRL, announced the receipt of a Special Protocol Assessment (SPA) from the US FDA that allows the initiation of a pivotal clinical trial for the company's lead anti-cancer compound Fodosine™ (forodesine hydrochloride). Fodosine™ will be trialled in patients who have failed two or more previous induction therapies for acute lymphoblastic T-cell leukemia/lymphoma. The multicenter, open-label, non-randomized, repeat-dose pivotal trial, expected to commence by the

end of the year, will enroll approximately 100 patients with relapsed or refractory precursor T-lymphoblastic leukemia/lymphoma who have failed two or more prior treatment regimens. The study is designed to determine the rate of complete remission achieved with this regimen of Fodosine™. Secondary endpoints include assessing the safety and tolerability of extended daily treatment with this regimen, determining the effects of this regimen on survival endpoints and, evaluating the maintenance of response with this regimen.

Materials & Energy Group leader **Dr. Ian Brown** has been appointed Adjunct Professor in the School of Chemical and Physical Sciences at Victoria University. Ian recently delivered a presentation to NZ Parliamentarians on ***New Energy Technologies for New Zealand: Options and Opportunities*** in the Speakers Science Forum in the Grand Hall. The recently funded FRST IIOF programme, *Hybrid Solid State Hydrogen Storage Materials*, features strong collaboration with US National laboratories at Los Alamos and Pacific Northwest. Dr. Mark Bowden visited LANL and PNNL during a sponsored research visit in June and also attended the US DoE hydrogen energy reviews in Washington. He also presented a US-NZ collaborative paper on amine borane hydrogen storage materials at the MRS Spring Meeting in San Francisco. A collaborative IRL-LANL-PNNL research proposal titled *Combination of Amine Boranes with MgH_2 & $LiNH_2$ for High Capacity Reversible Hydrogen Storage* has recently been approved as a formal collaborative programme by the International Partnership for the Hydrogen Economy (IPHE – see: *www.iphe.net*); additional partners are the National University-Singapore and the University of Oxford. As part of the hybrid hydrogen storage project, VUW student **Hayley Woolf** is undertaking her MSc with **Drs. Ian Brown** and **Mark Bowden** while Waikato student **Kathryn Benge** is with **Dr. Tim Kemmitt**. The group is currently hosting two intern students from Imperial College; **Donat Fatet** is working with **Dr. Stuart Smedley** to develop new electrodes for alkaline fuel cells and **Naser Al-Mufachi** is with **Dr. Alex Kirchner** to fabricate nanostructured ceramic membranes for gas separation. **Dr. Susan Edwards** and **Mr. Vlatko Materic** have recently been appointed chemical engineers with Stuart Smedley and Ian Brown to develop new CO_2 capture technologies.

Conference Calendar

Nature Chemical Biology Symposium, Boston, USA, 10-11 November 2006

This symposium will explore how chemists and biologists are contributing concepts and tools to the understanding of the molecular basis of cell biology. For more information see: *http://www.nature.com/nchembio/meetings/2006symposium/index.html*

6th Annual Functional Foods Symposium, Auckland, November 16 2006

This years' focus is "lipids for lifestyle and profit". The programme includes the latest scientific developments in functional food research and also covers the business of creating new functional foods and getting them into the marketplace. For more details see: *http://www.health.auckland.ac.nz/ffood/index.htm*

NZIC Conference Royal Lakeside Novotel, Rotorua, December 2-6 2006

Back to the Basics: From Small Molecules to Materials and Surfaces See full page advertisement elsewhere in this journal. Also a special symposium titled "Showcase, Industrial Chemistry in New Zealand". For more information see *www.massey.ac.nz/~nzic/*

Hill Laboratories Waikato Science Summer School, 3-8 December 2006

A unique week long residential course at Waikato University for Year 12 students interested in science who will be going on to further science study in Year 13. It will be an opportunity for the students to experience the wide range of science subjects. For an application form and further information see: *http://sci.waikato.ac.nz/student_info/highschool_info/HillSummerSchool.shtml*

4th International Conference on Advanced Materials and Processing, Waikato, 10 - 13 December 2006

Presentation topics include advanced polymers and composites, novel materials processing technologies and advanced metallic materials. For more information see *http://mape.waikato.ac.nz/icamp/*

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:

- 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: *http://www.colloid-oz.org.au* or email *acis@pco.com.au*

AMN-3 Third International Conference on Advanced Materials and Nanotechnology, 11-16 February 2007, Wellington, New Zealand

The conference will be covering the latest findings in the areas of nanotechnology and advanced materials. It will be 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*