Sulfur Chemistry:

Thiolates, disulfides, thioethers and thiones:

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A thesis submitted to the Department of Pure & Applied Chemistry, University of Strathclyde, in fulfilment of the requirements for the degree of Doctor of Science

April 2015

To the other love of my life

Declaration of Copyright

Acknowledgements

I wish to express my gratitude to everyone who had contributed to my research over the past 35 years. The list of names is extensive and it is impossible to record them all here. I would ask that, when you are reading a specific paper that you take a moment to look at the names and remember that research today is all about collaboration.

Throughout my career I have had the great fortune to have had excellent technical support. In this regard my colleagues in the Department of Chemistry at Strathclyde University have provided sterling service over the past 30 years. It is appropriate that I quietly apologise here to Margret Adams and Pat Keating for all the samples which failed to be what I said they would be.

Four co-workers at Strathclyde deserve a special mention. David Armstrong, who patiently carried out the theoretical calculations which underpinned most of my best work; Alan Kennedy, who tried to teach me how to refine crystal structures and ended up doing all the dirty work, finding space groups, fixing disordered solvents and nailing down atoms which can't quite decide where they are supposed to be, and Corinne Spickett who fixed my poor biology etc (!!). Mark Spicer deserves a special mention. Mark was a co-conspirator in the design and development of soft scorpionate chemistry. He, more than anyone, has tolerated my ramblings and fixed my poor English.

A special mention goes out Bill Cullen at UBC who taught me that an academic career did not mean that you had to give up your sense of humour and that it was possible to both enjoy doing chemistry and continue doing chemistry for yourself.

Finally I need to thank my wife Susan who has shared my journey. From the start 32 years ago when I took my doctoral thesis on our honeymoon she has tolerated my habit of writing in the evenings and while on holiday. One day it will stop and she will have to put up me with me 24/7.

Abstract

The thesis brings together my efforts in research over the past 35 years. The work has been collected together under a number of themes and not in chronological order. An overview and full list of publications are given in Chapter 1.

Research commenced with a study of the nitroprusside anion as a vasodilator (Chapter 2). Although nitric oxide never became a central theme of my research it has been incorporated it my work on occasions and these efforts are brought together in this section. These studies, however, did highlight the importance of sulfhydryl compounds which did become a central theme of my research. Thus, Chapter 3 details studies on the bio-organometallic chemistry of arsenic and the importance of thiolates in arsenic reduction and the formation of thioarsinites. Chapter 4 changes emphasis focusing on the use of small molecule (glutathione, N-acetylcysteine) and protein sulfhydryl groups as a redox buffers in clinical science. Studies detailing the ability of sulfhydryl functions to bind and modify therapeutic complexes are also discussed.

A re-alignment in my research lead to three new areas of research. Chapter 5 discusses efforts to design a redox sensitive MRI contrast agent using thio-ether macrocycles. This continues the theme of oxidative stress in disease. The design, synthesis and reactivity of soft scorpionates ligands (thione donors) is discussed in Chapter 6. This work marks a return to mainstream coordination chemistry. The combination of the topics discussed in Chapter 5 and 6 generated a final research theme on multi metallic complexes.

The connections between these topics is discussed which in turn explains how it is possible to drift across themes (anaesthesia, microbiology, rheumatology) while engaging in chemistry from all areas of the periodic table.

Contents

Chapter 1

John Reglinski 1981-2014

An overview

Graphical Abstract

Comment

Research is a journey. As chemistry, skills and knowledge develop new opportunities present themselves, ideas form and directions change.

1.1. Opening remarks.

The roles metals play in biology was an early fascination in my academic life which subsequently became an underlying theme of my research career. The fact that biology can carry out difficult chemical transformations (nitrogen fixation, methane oxidation) in an environment which is still essentially aerobic and aqueous is a constant reminder to chemists of what can be achieved using the lighter transition metals coupled to a limited range of donor species. The manner in which biology synthesises and controls reactive, cell messengers, such as nitric oxide (NO) or hypochlorous acid (HOCl), can be both a demonstration of chemical elegance and stubbornness. Interest in signalling molecules naturally leads to an interest in what occurs when the balance and control of these reactive species e.g. hydrogen peroxide (H_2O_2), is lost during disease, such as rheumatoid arthritis, which leads to their highly deleterious effects on sensitive molecules distributed within the cell.

1.2. Background

From the beginning of my studies the applied aspect of research has always had an allure. However, initially I was self conscious about my approach to chemistry having drawn criticism from my peers that my first contribution to research was made in the British Journal of Anaesthesia [1]. As my career developed I have come to realise that this was an inspired decision as it has defined my career. Instead of expecting readers to find my work, efforts have been made to reach readers directly through their preferred journals. The adage that people publish widely is commonly applied too lightly. In this respect I can confidently claim a wide readership having published papers as senior author in inorganic chemistry (obviously), organic chemistry [46, 47], physical chemistry [88, 108], physics [34], analysis [36, 38], nanoscience [48, 79], microbiology [6, 19], environmental science [24], geology [87], cell biology [16] and medicine (rheumatology [22], cancer [12], endocrinology [33], pregnancy [61] and clinical chemistry [29]).

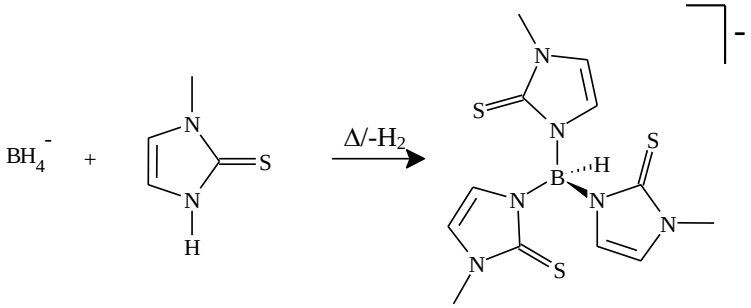
The study of inorganic biochemistry offers an opportunity to have a broad church approach to chemistry. Thus, having completed a successful doctorate studying an organometallic vasodilator used in anaesthesia (the nitroprusside anion and nitric oxide: Chapter 2) a decision was made to widen my experience by moving

to a completely new area of the periodic table, i.e. the main group, and also engage in research in a different sphere of inorganic biochemistry namely the microbial bio-transformation of arsenic (Chapter 3). A thorough study of the synthesis and mechanism of reduction of arsenicals was conducted [4, 5] followed by an analysis of these species as substrates in biological methylation [19, 20]. These efforts produced a highly respected piece of applied science where mechanistic chemistry was mapped directly onto microbiological studies [4, 5]. This work remains relevant today having found an outlet in modern environmental chemistry and unexpectedly, in the understanding of the activity of dimethylarsino moieties as putative anticancer therapies.

Studies in arsenic chemistry confirmed my interest in sulfur as a donor atom and reducing agent in biology. Crucially, the importance of the redox status of species such as glutathione had been identified in these earlier studies which when combined with my understanding of erythrocyte biochemistry allowed me to commence work on the redox balance in erythrocytes from patients suffering from rheumatoid arthritis using NMR methods [32]. Thus began a long interest in medicinal sulphydryl chemistry which encompasses redox status [16, 37], metal binding sites [30, 48] and membrane proteins [31, 41] (Chapter 4). These studies required strong links with medical departments and although the original funding was secured for a project in rheumatoid arthritis the work expanded to include other conditions e.g. cancer [59], endocrinology [33], pregnancy [61]. This work was extended further to encompass the effects of therapy *in-vitro* and *in-vivo* [8, 32].

A natural re-alignment of research took place *circa* 1994 as funding for medicinal inorganic projects became more difficult to obtain. A specific decision was taken not to follow the funding into bio-organic chemistry. However, the interest in oxidative stress had not dulled. Consequently, the focus of the research shifted from measuring oxidative stress *ex-vivo* to trying to sense it *in-vivo*. Discussions with clinicians during earlier studies (Chapter 4) had identified a need to able to measure redox status *in-vivo* such that disease severity can be assessed and therapy can be tailored to a patients need. Thus began a programme which sought to synthesis active redox sensors using first row transition metals [118]. This is still a current research theme (Chapter 5).

The role of sulfur donors in coordination chemistry had also remained an area of great interest. Initially research had focused on these as reducing agents. Latterly an interest developed in understanding metal binding sites in proteins which were redox active [96] and which typically contained cysteinyl residues but which were themselves ostensibly redox inert. Metal complexes, especially copper based, which model metalloproteins of this type were difficult to produce because of the conflict between the sulfurs behaviour as a donor atom and as a reducing agent [90]. Studies on penicillamine [8] had however, indicated that it was possible to moderate this behaviour. While attending ICBIC 13 (San Diego) I became re-acquainted with the poly-(pyrazolyl)borate anions and their use in biomimetic chemistry. Combining these observations led to the synthesis of the soft scorpionate anion, the hydro-tris(methimazoly)borate anion [53, 67] (Scheme 1.1, Chapter 6). This was synthesised by replacing pyrazole by methimazole in Trofimeko's celebrated synthetic approach.[1] Work commenced in 1993 with the first report appearing in 1996 [53]. The area has expanded greatly in the intervening years. The report opened new avenues of research and there are currently about 25 groups working in this area which can be traced back to our initial report [53]. What was a single soft ligand has been augmented by other species and the philosophy proposed by the group at Strathclyde lead to a huge expansion in interest in other tripodal soft scorpionates [105].



Scheme 1.1

A final area of research has developed more recently by combining the studies on soft tripodal ligands with the work on redox sensors. Here we are trying to construct redox active metalloligands and multimetallic complexes [111] (Chapter 7). A major reason for the development of this area of research is that it has allowed me an opportunity to indulge in chemistry first hand again. This area is still

developing and has recently led to the design of di-cerium complexes for DNA hydrolysis and by a circuitous route into the design of ruthenium complexes for light harvesting and water oxidation [108].

1.3. Order of material

The research discussed here has a variety of interweaving and developing topics. Consequently it is best that the material contained herein is presented as a series of thematic chapters and not in a strict chronological order. Finally, research continues on the topics discussed in Chapters 5, 6 and 7 and hints at the directions these are is taking are presented in the form of posters which have been on view at various conferences and it is hope that the maxim "the best is yet to come" has an element of the truth.

1.4 Referencing

Three methods of referencing are employed in this document in an attempt to lead the reader through the material.

(i) Square brackets are used to identify my personal work as listed in **section 1.5**

(ii) The Harvard system (Reglinski et al. 2010) is used to indicate that a copy of that specific paper can be found in the primary literature for review at the end of the relevant chapter

(iii) Superscripts are employed for literature references from sources out with this document which are needed to support the narrative.

1.5. Peer reviewed publications.

1. *Sodium nitroprusside and cyanide release: reasons for re-appraisal*. W.I.K. Bisset, A.R. Butler, C. Glidewell and J. Reglinski. **Brit. J. Anaesth., 53**, 1015-1018 (1981)

2. *Photochemistry of the nitroprusside ion and the consequences for the detection of cyanide in mixtures of nitroprusside and blood: Use of sodium nitroprusside as a hypotensive agent.* W.I.K. Bisset, M.G. Burdon, A.R. Butler, C. Glidewell and J. Reglinski. **J. Chem. Res.,** 299, (M) 3501-3515 (1981)

3. *Ferrocenyllithium derivatives: Lithiation of α-N,N,-dimethylaminoethyl-ferrocene and the single crystal X-ray structure of* $((n^5\text{-}C_5H_4Li)Fe(n^5\text{-}C_5H_3LiCH(Me)\text{-}NMe_2))_4\ (LiOEt)_2\ (TMEDA)_2$. I.R. Butler, W.R. Cullen, J. Reglinski and S.J. Rettig. **J. Organomet. Chem., 249**, 183-194 (1983)

4. *The reduction of trimethylarsine oxide to trimethylarsine by thiols: A mechanistic model for the biological reduction of arsenicals.* W.R. Cullen, B.C. McBride and J. Reglinski. **J. Inorg. Biochem., 21**, 45-60 (1984)

5. *The reaction of methylarsenicals with thiols: Some biological implications.* W.R. Cullen, B.C. McBride and J. Reglinski. **J. Inorg. Biochem., 21**, 179-194 (1984)

6. *The wood preservative chromated copper arsenate is a substrate for trimethylarsine biosynthesis*. W.R. Cullen, B.C. McBride, A.W. Pickett and J. Reglinski. **Appl. Environ. Microbiol., 47**, 443-444 (1984)

7. *The pentacyanonitrosylferrate ion. part 1. Reactions with various amines.* A.R. Butler, C. Glidewell, J. Reglinski and A. Waddon. **J. Chem. Res.,** 279, (M) 2768-2783 (1984)

8. *Changes in glutathione in intact erythrocytes during incubation with penicillamine as detected by* ^1H *spin echo NMR spectroscopy.* C.N.N. McKay, D.H. Brown, J. Reglinski, W.E. Smith, H.A. Capell and R.D. Sturrock. **Biochim. Biophys. Acta., 888**, 30-35 (1986)

9. *Nuclear magnetic resonance in living systems.* J. Reglinski and W.E. Smith. **Trends in Anal. Chem., 5,** 190-196 (1986)

10. *A* ^1H *spin echo NMR study of the HeLa tumour cell.* J. Reglinski, W.E. Smith, C.J. Suckling, M.J. Stewart, I.D. Watson and M. Al-Kabban. **FEBS lett., 214**, 351-356 (1987)

11. *Spin echo* ^1H *NMR detected response of ergothioneine to oxidative stress in the intact erythrocyte*. J. Reglinski, W.E. Smith and R.D. Sturrock. **Magn. Reson. Med., 6**, 217-223 (1988)

12. *The use of ^{1}H spin echo NMR and HPLC to confirm Doxorubicin induced depletion of glutathione in the HeLa cell.* M. Al-Kabban, I.D. Watson, M.J. Stewart, J. Reglinski, W.E. Smith and C.J. Suckling. **Brit. J. Cancer, 57**, 553-558 (1988)

13. *Doxorubicin induced altered glycolytic patterns in the leukemic cell studied by proton spin echo NMR.* J. Reglinski, W.E. Smith, C.J. Suckling, M.J. Stewart, I.D. Watson and M. Al-Kabban. **Clin. Chim. Acta., 175**, 285-290 (1988)

14. *The oxidation of glutathione by nitroprusside: Changes in glutathione in intact erythrocytes during incubation with sodium nitroprusside as detected by ^{1}H spin echo NMR spectroscopy*. A.R. Butler, A.M. Calsey-Harrison, C. Glidewell, I.L. Johnson, J. Reglinski and W.E. Smith. **Inorg. Chim. Acta., 151**, 281-286 (1988)

15. *Exchange reactions between disulphides and Myocrisin: An in-vitro model for a mechanism in chrysotherapy*. J. Reglinski, S. Hoey and W.E. Smith. **Inorg. Chim. Acta., 152**, 261-265 (1988)

16. *Cellular response to oxidative stress at sulphdyryl group receptor sites on the erythrocyte membrane* J. Reglinski, S. Hoey, W.E. Smith and R.D. Sturrock. **J. Biol. Chem., 263**, 12360-12366 (1988)

17. *The action of Captopril at a cellular level.* J. Reglinski, W.E. Smith and J.J.F. Belch. **J. Chem. Res**., 316-317 (1989)

18. *The detection of malignancy by proton nuclear magnetic resonance spectroscopy of plasma: A reappraisal*. R.F. McKee, J. Reglinski, W.E. Smith and D.C. Carter. **Surg. Res. Comm., 6**, 131-136 (1989)

19. *The metabolism of methylarsine oxide and sulphide*. W.R. Cullen, B.C. McBride, H. Manji, A.W. Pickett and J. Reglinski. **Appl. Organomet. Chem., 3**, 71-78 (1989)

20. *The effect of arsenicals on cell suspensions of the madagascar periwinkle (Catharanthus roseus).* W.R. Cullen, D. Hettipathirana and J. Reglinski. **Appl. Organomet. Chem., 3**, 515-521 (1989)

21. *The action of Myocrisin on membrane bound sulphydryl groups*. F. McCrae, J. Reglinski, W.E. Smith, M. Brezski and R.D. Sturrock. **Clin. Chim. Acta., 195**, 41-46 (1990)

22. *The concentration and reactivity of the sulphydryl group population on the membranes of intact human erythrocytes in patients with rheumatoid arthritis.* C. Chillis, M. Mulheron, F. McCrae, J. Reglinski, W.E. Smith, M. Brzeski and R.D. Sturrock. **Ann. Rheum. Diss., 49**, 668-671 (1990)

23. *A cellular based, NMR compatible model for solid tumour.* J. Reglinski, W.E. Smith, M. Al-Kabban, M.J. Stewart and I.D. Watson. **J. Pharm. Biomed. Anal., 8**, 721-724 (1990)

24. *Speciation of antimony in natural waters: The determination of Sb(III) and Sb(V) by continuous flow hydride generation atomic absorption spectrometry*. B. Mohammad, A.M. Ure, J. Reglinski, and D. Littlejohn. **Chem. Speciation. Bioavail., 3**, 117-122 (1990)

25. *The action of sodium gold(I) thiomalate on the erythrocyte membrane.* S. Hoey, J. Reglinski, D.H. Brown, W.E. Smith and R.D. Sturrock. **Inorg. Chem., 29**, 5190-5196 (1990)

26. *The effect of doxorubicin on the glutathione content and viability of cultured human lung cancer cell lines A549 and GLC$_4$210.* M. Al-Kabban, M.J. Stewart, I.D. Watson and J. Reglinski. **Clin. Chim. Acta., 194**, 121-130 (1990)

27. *^{1}H spin echo nuclear magnetic resonance (NMR) spectroscopy: A novel approach to studying the cellular effects of carbimazole therapy*. R. Wilson, J. Reglinski, W.E. Smith, J.H. McKillop, L.M. Buchanan and J.A. Thomson. **Quart. J. Med., 77**, 1092 (1990)

28. *The use of nuclear magnetic resonance (NMR) spectroscopy in following changes in cellular metabolism in Graves' disease*. R. Wilson, J. Reglinski, L.M. Buchanan, J.H. McKillop, W.E. Smith and J.A. Thomson in The Thyroid Gland, Environment and Autoimmunity (H.A.Drexhage, V.J.M de Vijler and W.M.Wiersinga eds) **Exerceptia Medica,** 249-251 (1990)

29. *Clinical analysis in intact erythrocytes using ^{1}H spin echo NMR.* J. Reglinski, W.E. Smith, R. Wilson, L.M. Buchanan, J.H. McKillop, J.A. Thomson, M. Brezski, M. Marabani and R.D. Sturrock. **Clin. Chim. Acta., 201**, 45-57 (1991)

30. *Gold drugs used in the treatment of rheumatoid arthritis.* W.E. Smith and J. Reglinski. **Persp. Bio-inorg. Chem., 1**, 183-208 (1991)

31. *The action of sodium gold(I) thiomalate on the erythrocyte membrane II*. J.M. Campbell, J. Reglinski, W.E. Smith, D. Porter and R.D. Sturrock. **Ann. Rheum. Diss., 51**, 969-971 (1992)

32. *Clinical analysis using ^{1}H spin echo NMR II: Oxidation of intracellular glutathione as a consequence of Penicillamine therapy*. J. Reglinski, W.E. Smith, M. Marabani, M. Brzeski and R.D. Sturrock. **J. Med. Chem., 35**, 2134-2137 (1992)

33. *Spin echo NMR studies on intact erythrocytes: Changes in cellular metabolism as a consequence of Carbimazole therapy*. J. Reglinski, W.E. Smith, R. Wilson, L.M. Buchanan, J.H. McKillop and J.A. Thomson. **Clin. Endocrinol., 37**, 319-324 (1992)

34. *Direct spectroscopic determination of functional sulphydryl groups on intact cell surfaces by Surface Enhanced Resonance Raman Scattering*. B.N. Rospendowski, J.M. Campbell, J. Reglinski and W.E. Smith. **Eur. Biophys. J., 21**, 257-261 (1992)

35. *The oxidation state of glutathione in the erythrocyte*. M. Garner, J. Reglinski, W.E. Smith and J. McMurry. **Clin. Sci., 83**, 637 (1992)

36. *Selenium in Graves' disease.* J. Reglinski, W.E. Smith, R. Wilson, D.J. Halls, J.H. McKillop and J.A. Thomson. **Clin. Chim. Acta., 211**, 189-190 (1992)

37. *Studies of oxidative stress in cellular systems; The interaction of monocytes and erythrocytes.* P.E. McGowan, J. Reglinski, W.E. Smith, R. Wilson and R.D. Sturrock. **FEBS Lett., 314**, 455-457 (1992)

38. *The interaction of sodium nitroprusside with peripheral white blood cells in vitro: A rationale for cyanide release in-vivo.* J.M. Campbell, F. McCrae, J. Reglinski, R. Wilson, W.E. Smith and R.D. Sturrock. **Biochim. Biophys. Acta., 1156**, 327-333 (1993)

39. *Quantitaive ^{1}H NMR analysis of amniotic fluid.* P.E. McGowan, J. Reglinski, R. Wilson, S. Wisdom and J.J. Walker. **J. Pharm. Biomed. Anal., 11**, 629-632 (1993)

40. *The effect of sodium gold (I) thiomalate on sugar translocation across the erythrocyte membrane* P.E. McGowan, J.M. Campbell, J. Reglinski and W.E. Smith. **Inorg. Chim. Acta., 210**, 1-3 (1993)

41. *Site of action for the inhibition by gold sodium thiomalate of rabbit platelet activation.* K.M.S. McKague, C.J.L. Lock, F. McCrae, W.E. Smith, H. Buchanan, W.F. Kean and J. Reglinski. **J. Pharm. Sci., 82**, 174-178 (1993)

42. *^{1}H spin echo NMR: A probe of the chemistry of living cells.* J. Reglinski and W.E. Smith. **Life Sci. Adv. – Oncology, 12**, 101-112 (1993)

43. *Resonance and Surface Enhanced Raman Scattering and ^{1}H spin echo NMR as probes of the chemistry of living cells.* W.E. Smith and J. Reglinski. Proc. 5th Inter. Conf. Spec. Biol. Mol. T.Theophanides (ed), **Kulwar Academic Pub**., pp 227-234 (1993).

44. *Metal nitrosyl complexes as a source of new vasodilators: Strategies derived from systematic chemistry and nitrosyl ligand reactivity.* J. Reglinski, A.R. Butler and C. Glidewell. **Appl. Organomet. Chem., 8**, 25-32 (1994)

45. *The selenium mediated de-iodination of iodophenols; A model for the mechanism of 5' thyronine de-iodinase*. C. Beck, S.B. Jensen and J. Reglinski. **Biomed. Chem. Lett., 4**, 1353-1356 (1994)

46. *The structure of methimazole and its consequences for current therapeutic models of Graves' disease.* M. Garner, D.R. Armstrong, J. Reglinski, W.E. Smith, R. Wilson and J.H. McKillop. **Biomed. Chem. Lett., 4**, 1357-1360 (1994)

47. *Alteration of the erythrocyte glutathione redox balance by N-acetylcysteine, captopril and exogenous glutathione*. J. Russell, C.M. Spickett, J. Reglinski, W.E. Smith, J. McMurray and I.B. Abdullah. **FEBS Lett., 347**, 215-220 (1994)

48. *The interaction of colloidal metals with erythrocytes.* M. Garner, J. Reglinski, W.E. Smith and M.J. Stewart. **J. Inorg. Biochem., 56**, 283-290 (1994)

49. *Distribution and reactivity of myocrisin.* W.E. Smith and J. Reglinski. **Metal Based Drugs, 1**, 497-507 (1994)

50. *A comparative study of the interaction of myocrisin with albumin and γ-globulin*. C. McDonald, P. Mortimer, G. McAllister, P.E. Gardiner, J. Reglinski and W.E. Smith. **J. Pharm. Biomed. Anal., 13**, 99-102 (1995)

51. *Surface enhanced Resonance Raman Scattering from cyano cobalamin and 5-deoxy-adenosyl-cobalamin* L. Quaroni, J. Reglinski and W.E. Smith. **J. Raman Spec., 26**, 1075-1076 (1995)

52. *The interaction of nitric oxide with cytochrome P-450 monitored by Surface Enhanced Raman Scattering* L. Quaroni, J. Reglinski, W.E. Smith and C.R. Wolf. **Biochim. Biophys. Acta., 1296**, 5-8 (1996)

53. *Hydrotris(methimazolyl)borate, a soft analouge of hydrotris(pyrazolyl)borate. Preparation and crystal structure of a novel zinc complex.* M. Garner, J. Reglinski, I. Cassidy, M.D. Spicer and A.R. Kennedy. **J. Chem. Soc. Chem. Commun.,** 1975-1976 (1996).

54. *Proton NMR studies of oxidative stress in disease.* C.M. Spickett, W.E. Smith and J. Reglinski. in Advances in Spectroscopy Vol 25, Clark and Hester eds 267-294 (1996)

55. *An analytical perspective of NMR spectroscopy of biological fluids and cells*. J. Reglinski and I.D. Watson. **Ann. Clin. Biochem., 33**, 290-397 (1996)

56. *The interaction of nitric oxide with cobalamins.* J. Reglinski and J. Naismith. in the Biology of Nitric Oxide Pt 5, Vol 10, 177. Portland Press. (1996)

57. *HPLC determination of biologically active thiols using pre-column derivatisation with 5,5'-dithio (bis-2-nitrobenzoic acid).* J. Russell, J.A. McKeown, C. Hensman, W.E. Smith and J. Reglinski. **J. Pharm. Biomed. Anal., 15**, 1757-1763 (1997)

58. *Resistance of erythrocytes to oxidation by vanadate as studied by ^{1}H spin echo and ^{51}V NMR spectroscopy.* M. Garner, J. Reglinski, W.E. Smith, J. McMurray, I. Abdullah and R. Wilson. **J. Biol. Inorg. Chem., 2**, 235-241 (1997)

59. *Menadione-resistant chinese hamster ovary cells have an increased capacity for glutathione synthesis.* K.A. Vallis, J. Reglinski, M. Garner, M.M.E. Bridgeman and C.R. Wolf. **Brit. J. Cancer, 76**, 870-877 (1997)

60. *Myocrisin mediated oxidative stress*. J. Reglinski, D.E. Paterson, S. Latimer, J.M. Campbell, R. Wilson, D. Porter, R.D. Sturrock and W.E. Smith. **Clin. Chim. Acta., 268**, 85-99 (1997)

61. *Erythrocyte glutathione balance and membrane stability during preeclampsia.* C.M. Spickett, J. Reglinski, W.E. Smith, R. Wilson, J.J. Walker and J. McKillop. **Free Radical Biol. Med., 24,** 1049-1055 (1998)

62. *Evidence for carbimazole as an antioxidant?* R. Wilson, L. Buchanan, W.D. Fraser, C. Jenkins, W.E. Smith, J. Reglinski, J.A. Thomson and J.H. McKillop. **Autoimmunity, 27,** 149-153 (1998)

63. *Oxidation of erythrocyte glutathione by monocytes stimulated with interleukin-6 - Analysis by H-1 spin echo NMR.* C.M. Spicket, W.E. Smith, J. Reglinski, R. Wilson and J.J. Walker. **Clin. Chim. Acta., 270**, 115-124 (1998)

64. *Environmental and medicinal; chemistry of arsenic, antimony and bismuth* J. Reglinski in "Chemistry of Arsenic antimony and bismuth" N.C.Norman ed, Blackie Academic, Chapman & Hall, 403-440 (1998)

65. *N-Nitrosohydroxylamine-N-sulfonate: A re-determination of its X-ray crystal structure and an analysis of its formation from NO and SO_3^{2-} using ab-inito molecular orbital calculations*. J. Reglinski, D.R. Armstrong, K. Sealey, and M.D. Spicer. **Inorg. Chem., 38**, 733-737 (1999)

66. *The structural consequences of the use of hard and soft tripodal ligands during metathesis reactions: The synthesis of the [bis-(hydrotris(methimazolyl)-borato]-bismuth(III) [bis-(hydrotris(pyrazolyl)-borato]-sodiate.* J. Reglinski, M.D. Spicer, M. Garner and A.R. Kennedy **J. Amer. Chem. Soc., 121**, 2317-2318 (1999)

67. *Sodium hydrotris(methimazolyl)borate, a novel soft, tridentate ligand: preparation, structure and comparisons with sodium hydrotris(pyrazolyl)borate.* J. Reglinski, M. Garner, I.D. Cassidy, P.A. Slavin, M.D. Spicer, and D.R. Armstrong. **J. Chem. Soc. Dalton Trans.,** 2119-2126 (1999)

68. *^{1}H NMR as a non-invasive probe of amniotic fluid in insulin dependant diabetes mellitus.* P.E. McGowan, W.C. Lawrie, J. Reglinski, C.M. Spickett, R. Wilson, J.J. Walker, S. Wisdom, and M.A. Maclean. **J. Perinat. Med., 27**, 404-408 (1999).

69. *The modulation of cell membrane structure and fluidity by endogenous agents: A ^{1}H-NMR approach.* J. Reglinski, S.K. Tunnah, W.C. Lawrie and R. Wilson. Proc. 8th Inter. Conf. Spec. Biol. Mol. J.Greve (ed), **Kulwar Academic Pub**., 437-440 (1999)

70. *Preparation and crystal structure of the [bis-{hydrotris(methimazolyl)borato}-thallium(III)] cation: modulated chemistry resulting from the use of soft and hard tripodal ligands.* P.A. Slavin, J. Reglinski, M.D. Spicer and A.R. Kennedy. **J. Chem. Soc. Dalton Trans.,** 239-240 (2000)

71. *The synthesis of soft tripodal ligands: Restrictions on the synthesis of hydrotris-(thiazolyl)-borate anions from borohydride melts.* J.F. Ojo, P.A. Slavin, J. Reglinski, M. Garner, M.D. Spicer, A.R. Kennedy and S.J. Teat. **Inorg. Chim. Acta., 313**, 15-20 (2001)

72. *Soft (S3) Scorpionate complexes of molybdenum and tungsten.* M. Garner, M-A. Lehmann, J. Reglinski, and M.D. Spicer. **Organometallics, 20**, 5233-5236 (2001)

73. *N,N'-bis(salicylidene)-1,4-butanediamine.* A.R. Kennedy and J. Reglinski. **Acta. Crystallogr., E57**, O1027-O1028 (2001)

74. *The preparation and structures of group 12 (Zn, Cd, Hg) complexes of the soft tripodal ligand hydrotris(methimazolyl)borate (Tm).* I. Cassidy, M. Garner, A.R. Kennedy, G.B.S. Potts, J. Reglinski, P.A. Slavin, and M.D. Spicer. **Eur. J. Inorg. Chem.,** 1235-1239 (2002)

75. *1,1,1-tris(2-hydroxybenzylideneamino)-methylpropane iron(III) chloroform solvate*. J. Reglinski and M. Patykiewicz. **Acta. Crystallogr., E58,** m543-m544 (2002)

76. *Supporting conformational change at metal centres. Part 1: octahedral systems.* J. Reglinski, S. Morris and D.E. Stevenson. **Polyhedron, 21,** 2167-2174 (2002)

77. *Supporting conformational change at metal centres. Part 2 Four and five coordinate geometry.* J. Reglinski, S. Morris and D.E. Stevenson. **Polyhedron, 21,** 2175-2182 (2002)

78. *Structural and spectroscopic characterisation of iron(II), nickel(II) and nickel(III) complexes of the hydrotris(methimazolyl)borate anion: soft donors in a weak ligand field.* M. Garner, K. Lewinski, A. Pattek-Janczyk, J. Reglinski, B. Sieklucka, M.D. Spicer and M. Szaleniec**. Dalton Trans**., 1181-1185 (2003)

79. *Altering the surface characteristics of coated silver surfaces. Soft donors allow the direct detection of isolated porphyrins using SERRS.* J. Reglinski, M.D. Spicer, J.F. Ojo, G.D. McAnally, A. Skórska, S.J. Smith, and W.E. Smith. **Langmuir, 19,** 6336-6338 (2003)

80. *From metalloproteins to coordination chemistry: A non-contact learning exercise to support the teaching of transition metal chemistry.* J. Reglinski, D. Graham, A.R. Kennedy and L.T. Gibson. **J. Chem. Ed., 81**, 76-82 (2004)

81. *Pushing the frontiers of hard and soft scorpionate chemistry.* C.A. Dodds, A.R. Kennedy, J. Reglinski and M.D. Spicer. **Inorg. Chem., 43**, 394-395 (2004)

82. *Soft scorpionate complexes of the fourth and fifth row elements arsenic and tin.* C.A. Dodds, M. Jagoda, J. Reglinski and M.D. Spicer. **Polyhedron, 23**, 445-450 (2004)

83. *N,N-Bis-(2-methoxybenzylidene) adducts of 1,2-ethanediamine, 1,3-propanediamine and 1,4-butanediamine.* J. Reglinski, M.K. Taylor, and A.R. Kennedy. **Acta Crystallogr., C60**, o169-o172 (2004).

84. *[N,N'-Bis-(o-sulfidobenzylidene)-1,3-diaminopropane]nickel(II) 1,4-dioxane solvate.* M.K. Taylor, J. Reglinski and D. Wallace. **Acta. Crystallogr., Section E60**, m850-m851 (2004).

85. *Cobalt half sandwich, sandwich and mixed sandwich complexes with soft tripodal ligands.* C.A. Dodds, M-A. Lehmann, J.F. Ojo, J. Reglinski and M.D. Spicer. **Inorg. Chem., 43,** 4927-4934 (2004)

86. *Coordination geometry of nickel complexes with tetradentate Schiff's base ligands: The effects of donors, backbone length and hydrogenation.* M.K. Taylor, J. Reglinski and D. Wallace. **Polyhedron, 23**, 3201-3209 (2004)

87. *The long-term environmental behaviour of strontium and barium released from former mine workings in the granites of the Sunart region of Scotland, UK.* C.M. Davidson, M.D. Gibson, E. Hamilton, B.H. MacGillivray, J. Reglinski and E. Rezabal. **Chemosphere, 58,** 793-798 (2005)

88. *Dimethylsulfoxide oxidizes glutathione in vitro and in human erythrocytes: kinetic analysis by ^{1}H-NMR* N.Z. Homer, J. Reglinski, R.J. Sowden, C.M. Spickett, R. Wilson and J.J. Walker. **Cryobiology, 50**, 317-324 (2005)

89. *Lower main group element complexes with a soft scorpionate ligand: the structural influence of stereochemically active lone pairs* C.A. Dodds, J. Reglinski and M.D. Spicer. **Chem. Eur. J., 12**, 933-941 (2006)

90. *Modelling the impact of geometric parameters on the redox potential of blue copper prote*ins. M.K. Taylor, D.E. Stevenson, L.E.A. Berlouis, A.R. Kennedy and J. Reglinski. **J. Inorg. Biochem., 100**, 250-259 (2006)

91. *[Bis(2-chloro-5-sulfonyl benzaldehyde)hexaaqua]Ca(II)monohydrate*. D. Wallace, J. Reglinski, M.K. Taylor and A.R. Kennedy. **Acta. Crystallogr., E62,** m339-m341 (2006).

92. *Coinage metal complexes of a boron substituted soft scorpionate ligand.* C.A. Dodds, M. Garner, J. Reglinski and M.D. Spicer. **Inorg. Chem., 45**, 2733-2741 (2006)

93. *The effect of donor groups and geometry on the redox potential of copper Schiff base complexes.* M.K. Taylor, L.E.A. Berlouis, A.R. Kennedy and J. Reglinski. **Inorg. Chim. Acta., 359,** 2455-2464 (2006)

94. *Schiff base ligands: Towards the controlled organisation of open metal frameworks.* J. Reglinski, M.K. Taylor and A.R. Kennedy. **Inorg. Chem. Commun., 9,** 736-739 (2006).

95. *Unlocking knowledge we know the students know.* J. Reglinski. **J. Chem. Ed., 84,** 271-272 (2007).

96. *[Mo(Tm^{Me})O$_2$Cl]: An improved model of Sulfite Oxidase*. D. Wallace, J. Reglinski, M.D. Spicer and L.T. Gibson. **Inorg. Chem., 46**, 3804-3806 (2007)

97. *Structural and theoretical insights into metal-scorpionate ligand complexes.* M. Schwalbe, P.C. Andrikopoulos, D.R. Armstrong, J. Reglinski and M.D. Spicer. **Eur. J. Inorg. Chem.,** 1351-1360 (2007)

98. *Bis(dimethylformamido hydrotris(methimazolyl)borato sodium): A complex where sodium exhibits a preference for sulfur over oxygen.* A. Biernat, M. Schwalbe, D. Wallace, J. Reglinski and M.D. Spicer. **Dalton Trans.,** 2242-2244 (2007)

99. *Multidentate ligands for the synthesis of multi-metallic complexes.* A. Mustapha, K. Busch, J. Reglinski, A.R. Kennedy and T.J. Prior. **Polyhedron, 27**, 868-878 (2008).

100. *Copper N_2S_2 Schiff base macrocycles: The effect of structure on redox potential.* M.K. Taylor, K.D. Trotter, J. Reglinski, L.E.A. Berlouis, A.R. Kennedy, C.M. Spickett, R.J. Sowden. **Inorg Chim. Acta., 361**, 2851-2862 (2008).

101. *On-Site determination of formaldehyde: New low cost measurements for museum environments.* L.T. Gibson, W.J. Kerr, A. Nordon, J. Reglinski, C. Robertson, L. Turnbull, C.M. Watt, A. Cheung and W. Johnstone. **Anal. Chim. Acta., 623**, 109-116 (2008)

102. *The use of hydrogenated Schiff base ligands in the synthesis of multi-metallic compounds.* A. Mustapha, J. Reglinski and A. R. Kennedy. **Inorg. Chim. Acta., 362,** 1267-1274 (2009)

103. *Structural Studies of trans-N_2S_2 Copper Macrocycles.* K.D. Trotter, J. Reglinski, K. Robertson, J.C. Forgie, J.A. Parkinson, A.R. Kennedy, D.R. Armstrong, R.J. Sowden and C.M. Spickett. **Inorg Chim. Acta., 362**, 4065-4072 (2009).

104. *The bioinorganic chemistry of methimazole based soft scorpionates.* J. Reglinski and M.D. Spicer. **Curr. Bioact. Cmpds., 5**, 264-276 (2009)

105. *Soft scorpionates based on imidazole-2-thione donors.* M.D. Spicer and J. Reglinski. **Eur. J. Inorg. Chem**. 1553-1574, (2009)

106. *Surface Science of Soft Scorpionates.* D. Wallace, E.J. Quinn, J. Reglinski, M.D. Spicer and W.E. Smith. **Inorg. Chem., 49,** 1420-1427 (2010)

107. *The structural and electrochemical consequences of hydrogenating Copper N_2S_2 Schiff base macrocycles.* K.D. Trotter, M.K. Taylor, J.C. Forgie, J. Reglinski, L.E.A. Berlouis, A.R. Kennedy, C.M. Spickett and R.J. Sowden. **Inorg. Chim. Acta., 363,** 1529-1538 (2010)

108. *A simple, novel method for preparing an effective water oxidation catalyst* A. Mills, P.A. Duckmanton and J. Reglinski. **Chem. Commun., 46**, 2397-2398 (2010)

109. Metal complexes as potential ligands: The deprotonation of aminephenolate metal complexes. A. Mustapha, J. Reglinski and A.R. Kennedy. **Inorg. Chem. Commun., 13,** 464-467 (2010)

110. *Multidentate ligands for the synthesis of multi-metallic complexes II. Formation of a planar Cu_4OH motif.* A. Mustapha, J. Reglinski, A.R. Kennedy, D.R. Armstrong, J. Saßmannshausen and M. Murrie. **Inorg. Chem., 49**, 5350-5352 **(**2010).

111. *N-donor ligand complexes of nickel, zinc and copper: Comparisons with tetradentate N-donor ligands derived from Schiff bases.* A. Mustapha, J. Reglinski and A.R. Kennedy, **Polyhedron, 29**, 2590-2594 (2010)

112. *The use of hydrogenated Schiff base ligands in the synthesis of multi-metallic compounds II.* A. Mustapha, C. Busche, J. Reglinski and A.R. Kennedy. **Polyhedron,** 30, 1530-1537 (2011)

113. *Importance of the nanoparticle size in colorimetric and SERS-based multimodal trace detection of Ni(II) ions by functional gold nanoprobes. Z.* Krpetic, L. Guerrini, I.A. Larmour, J. Reglinski, K. Faulds and D.Graham. **Small 8,** 707-714 (2012)

114. *Reactions of Copper Macrocycles with Antioxidants and HOCl: Potential for Biological Redox Sensing.* R.J. Sowden, K.D. Trotter, L. Dunbar, G. Craig, O. Erdemli, C.M. Spickett and J. Reglinski. **Biometals 26**, 85-96 (2013)

115. *The S-alkylation of soft scorpionates.* R. Rajasekharan-Nair, D. Moore, K. Chalmers, D. Wallace, L.M. Diamond, L. Darby, D.R. Armstrong, J. Reglinski and M.D. Spicer. **Chem. Eur. J., 19**, 2487-2495 (2013)

116. *Soft Scorpionate anions as platforms for novel heterocycles.* R. Rajasekharan-Nair, A. Marckwordt, S.T. Lutta, M. Schwalbe, A. Biernat, D.R. Armstrong, A.J.B. Watson, A.R. Kennedy, J. Reglinski and M.D.Spicer. **Chem. Eur. J., 19,** 13561-13568 (2013)

117. *The nickel, copper and zinc complexes of potentially heptadentate nitrogen-sulfur donor ligands.* G. Steel, A. Mustapha, J. Reglinski and A.R. Kennedy. **Polyhedron, 67**, 360-367 (2014)

118. *Nitric oxide species as oxidizing agents and adducts for soft scorpionates*. R. Rajasekharan-Nair, L. Darby, J. Reglinski, M.D. Spicer and A.R. Kennedy **Inorg. Chem. Commun. 41,** 11-14 (2014)

119. *The reactivity of complexed thiolates with Ellmans reagent: An NMR spectroscopic study.* N.Ullah, M.Mukhitar, M.F.Kahn, J.Reglinski, **Polyhedron 78,** 104-111 (2014)

120. *The thermal stability of soft scorpionates and their germanium complexes.* D. Wallace, K. Chalmers, C.A. Dodds, D.R. Armstrong, L.E.A. Berlouis, J. Reglinski and M.D. Spicer. **Eur J. Inorg Chem.** 2569-2575 (2014)

121. *Soft scorpionate coordination at alkali metals.* R. Rajasekharan-Nair, S.T. Lutta, A.R. Kennedy, J. Reglinski and M.D.Spicer. **Acta Cryst. C**., **C70,** 421-427 (2014)

122. *The Stability of Mercaptobenzothiazole Based Soft Scorpionate Complexes.* R. Rajasekharan-Nair, D. Moore, A.R. Kennedy, J. Reglinski, M.D. Spicer. **Inorg. Chem., 53,** 10276–10282 (2014)

123. *Tetradentate Schiff base beryllium complexes.* J. Reglinski, A.R. Kennedy and G. Steel. **New J. Chem. 39**, 2437-2439 (2015)

124. *Chemistry of the p-block element with anionic scorpionate ligands.* J.Reglinski, M.D.Spicer. **Coord Chem. Revs. 297-298**, 181-207 (2015)

125. *Copper complexes as a source of redox active MRI contrast agents.* L. Dunbar, R.J. Sowden, K.D. Trotter, M.K. Taylor, D. Smith, A.R. Kennedy, J. Reglinski and C.M. Spickett. **Biometals 28**, 903-912 (2105)

126. *Determination of metal ion concentration by SERS using 2,2'bipyridyl complexes*. J.Docherty, S.Mabbott, W.E.Smith, J.Reglinski, K.Faulds, C.Davidson, D.Graham. **Analyst 140**, 6538-6543 (2015)

127. *Observations on the steric influence of N- and S-donor scorpionate ligands.* G.Steel, R.Rajasekharan-Nair, I.Stepek, A.r.Kennedy, J.Reglinski, M.D.Spicer. **Eur. J. Inorg. Chem** DOI 10.1002/ejic.201500924

128. *The first structurally characterized example of silicon in an S6 coordination sphere. A.Marckworrdt,* R.Rajasekharan-Nair, G.Steel, A.r.Kennedy, J.Reglinski, M.D.Spicer. **Eur. J. Inorg. Chem** submitted

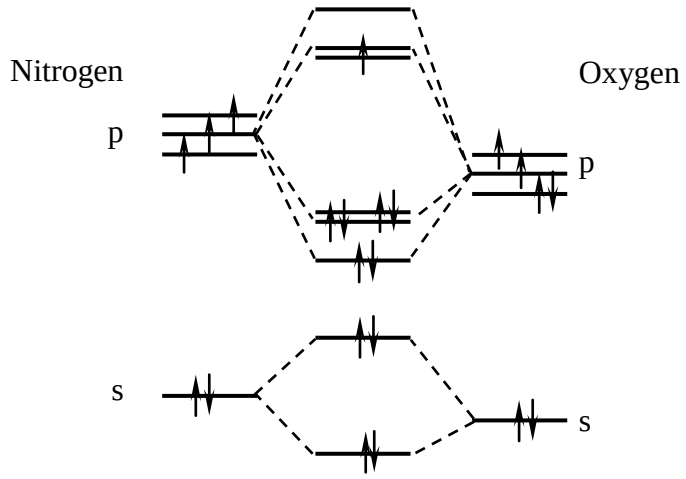
Book Reviews

1. *NMR in the life sciences,* E.M. Bradbury and C. Nicolini eds, NATO ASI Series, Series A: Life Science Vol. 107, (1986), Trends in Anal. Chem. **6**, XXI, (1987)
2. *Biological Magnetic Resonance 7,* L.J. Berliner and J. Reubens eds, Plenum Press (1987) New York.,Trends in Anal. Chem. **7**, 187, (1988)
3. *Two dimensional NMR spectroscopy - Applications for chemists and biochemists,* W.R. Croasmun and R.M.K. Carlson eds, VCH Verlagsgesellschaft, Weinheim (1987), Trends in Anal. Chem. **8**, 78, (1989)
4. *Biological Magnetic Resonance 9,* L.J. Berliner and J. Reubens eds, Plenum Press (1990) New York., Trends in Anal. Chem. **10**, 187, (1991)
5. *NMR applications in biopolymers: Basic life sciences* Vol 56, J.W. Finley, S.J. Schmidt and A.S. Serianni eds, Plenum Press (1990) New York. Trends in Anal. Chem. **11**, X, (1992)
6. *Bioorganometallics,* G. Jaouen, Wiley VCH GmbH & Co KgaA, Weinheim, Chemistry World 3, 60, (2006)

Chapter 2

Sodium Nitroprusside and nitric oxide

Graphical Abstract



Comment:

At the start of an academic career we know so little its embarrassing. Many choose areas of chemistry to study by a chance; the result of a successful project or an inspirational lecturer. While an undergraduate at Dundee University, R.F. Jameson delivered a series of lectures on inorganic biochemistry. Despite my previous difficulties with him I opted for a project in his laboratory on the copper catalysed oxidation of thiols using molecular oxygen. On this choice turned my entire academic career.

On graduating I looked for an opportunity in the area of inorganic biochemistry and secured a postgraduate postition at St. Andrews University studying the nitroprusside anion and its use as a vasodilator (A.R. Butler & C. Glidewell). The work was funded by the Scottish Hospitals Endowment Research Trust Fund (SHERT).

2.1. Background

Studies leading to my doctorate were based on the use of the nitroprusside anion ($[Fe(CN)_5NO]^{2-}$) as a vasodilator. These studies commenced (1978-81) ten years before the role of nitric oxide in biology was appreciated; this despite the fact that the importance of this nitrosyl complex in vasodilation was already accepted.[2,3] Sadly we never made the link between the nitroprusside anion, Endothelial Derived Relaxing Factor and nitric oxide.

Similar to many young researchers, work conducted during a PhD can remain an enduring feature of future research. However, a decision was made not to return to the chemistry of nitric oxide as a main research theme, but to include it in future research on occasions where appropriate. Consequently, post 1985, studies were conducted on the interaction of nitroprusside with intact human erythrocytes (Butler et al. 1988) and lymphocytes (Campbell et al. 1993). There followed a brief interest in the interaction of nitric oxide with cobalamins (Quaroni et al. 1995; Reglinski & Naismith 1996) and p450 (Quaroni et al. 1996). Some work outstanding from my doctoral studies on the reactivity of alternative nitrosyl complexes was completed at Strathclyde University (Reglinski et al. 1994) which led to a retrospective contribution on nitric oxide coupling (Reglinski et al. 1999). The enduring fondness for nitric oxide continues and there remain a number of papers which utilize this species which are best presented later chapter in Chapter 6.

2.2. Primary Literature for review

2.2.1 Published from St Andrews University (Doctoral studies).

Sodium nitroprusside and cyanide release: reasons for re-appraisal. W.I.K. Bisset, A.R. Butler, C. Glidewell and J. Reglinski. **Brit. J. Anaesth.,** 53, 1015-1018 (1981)

Photochemistry of the nitroprusside ion and the consequences for the detection of cyanide in mixtures of nitroprusside and blood: Use of sodium nitroprusside as a hypotensive agent. W.I.K. Bisset, M.G. Burdon, A.R. Butler, C. Glidewell and J. Reglinski. **J. Chem. Res.,** 299, (M) 3501-3515 (1981)

The pentacyanonitrosylferrate ion. part 1. Reactions with various amines. A.R. Butler, C. Glidewell, J. Reglinski and A. Waddon. **J. Chem. Res.,** 279, (M) 2768-2783 (1984)

2.2.2 Published from Strathclyde University

The oxidation of glutathione by nitroprusside: Changes in glutathione in intact erythrocytes during incubation with sodium nitroprusside as detected by ^{1}H spin echo NMR spectroscopy. A.R. Butler, A.M. Calsey-Harrison, C. Glidewell, I.L. Johnson, J. Reglinski and W.E. Smith. **Inorg. Chim. Acta.,** 151, 281-286 (1988)

The interaction of sodium nitroprusside with peripheral white blood cells in vitro: A rationale for cyanide release in-vivo. J.M. Campbell, F. McCrae, J. Reglinski, R. Wilson, W.E. Smith and R.D. Sturrock. **Biochim. Biophys. Acta.,** 1156, 327-333 (1993)

Metal nitrosyl complexes as a source of new vasodilators: Strategies derived from systematic chemistry and nitrosyl ligand reactivity. J. Reglinski, A.R. Butler and C. Glidewell. **Appl. Organomet. Chem.,** 8, 25-32 (1994)

Surface enhanced Resonance Raman Scattering from cyano cobalamin and 5-deoxy-adenosyl-cobalamin. L. Quaroni, J. Reglinski and W.E. Smith. **J. Raman Spec.,** 26, 1075-1076 (1995)

The interaction of nitric oxide with cobalamins. J. Reglinski and J. Naismith. in the **Biology of Nitric Oxide** Pt 5, Vol 10, 177 Portland Press. (1996)

The interaction of nitrogen monoxide with cytochrome P-450 monitored by Surface Enhanced Raman Scattering. L. Quaroni, J. Reglinski and W.E. Smith and C.R. Wolf. **Biochim. Biophys. Acta**., 1296, 5-8 (1996)

N-Nitrosohydroxylamine-N-sulfonate: A re-determination of its X-ray crystal structure and an analysis of its formation from NO and SO_3^{2-} using ab-inito molecular orbital calculations. J. Reglinski, D.R. Armstrong, K. Sealey, and M.D. Spicer. **Inorg. Chem.,** 38, 733-737 (1999)

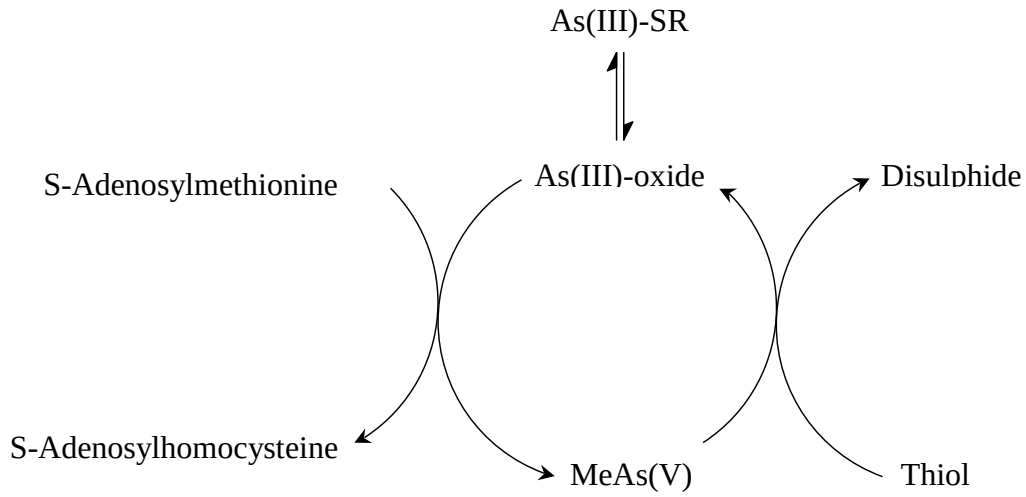
Sodium Nitroprusside and nitric oxide

Reprints

Chapter 3

The bio-organometallic chemistry of arsenic

Graphical Abstract



Comment:

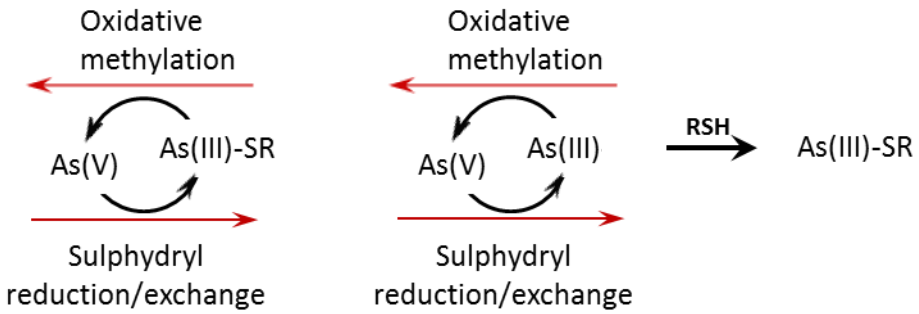
There are two simple routes into an academic career. Remain with an area you are comfortable with or choose something new and expand your horizons. The latter is the case here. For my postdocotoral work I chose to move from transition metal chemistry to main group chemistry and furthermore swap medicinal chemistry for microbiology. This approach brought new skills and new perspectives. I also decided to swap the UK for Canada

3.1. Background

The mechanism by which inorganic arsenic is converted into trimethylarsine (eq 1) was central to an understanding of the mobility of arsenic in the environment. A reaction cycle which involved metalloid reduction and oxidative methylation had been proposed based on that discussed by Challenger *et al.* in 1948 (Scheme 3.1, eq 3.2).[4] However, there was some debate about the role of thio-arsenites in the cycle as these are plausible products of arsenic reduction *in-vivo*.

$$[AsO_4]^{3-} \xrightarrow{\textit{Candida humicola}} Me_3As \qquad (3.1)$$

Inorganic Salt — "Organic" Gas



Scheme 3.1

$$Me_xAs^{(V)}O(OH)_{(3-x)} + (5-x)RSH \longrightarrow Me_xAs(SR)_{(3-x)} + RSSR + H_2O \qquad (3.2)$$

The study looked at the reduction of arsenicals by thiols and the synthesis of thio-arsenites (eq 2, Cullen et al., 1984a 1984b). The ability of thio-arsenites to act as substrates for trimethylarsine production was also tested using microbiological methods (Cullen et al 1989). The work was a combination of inorganic chemistry and microbiology. Despite modest interest in this area of chemistry during 1983 – 1988, the main mechanistic reports published in 1984 have assumed a wider audience (Figure 3.1) as concerns about arsenic in the environmental increased and once dimethylarsino-thiols were identified as potent anti-cancer compounds.[5]

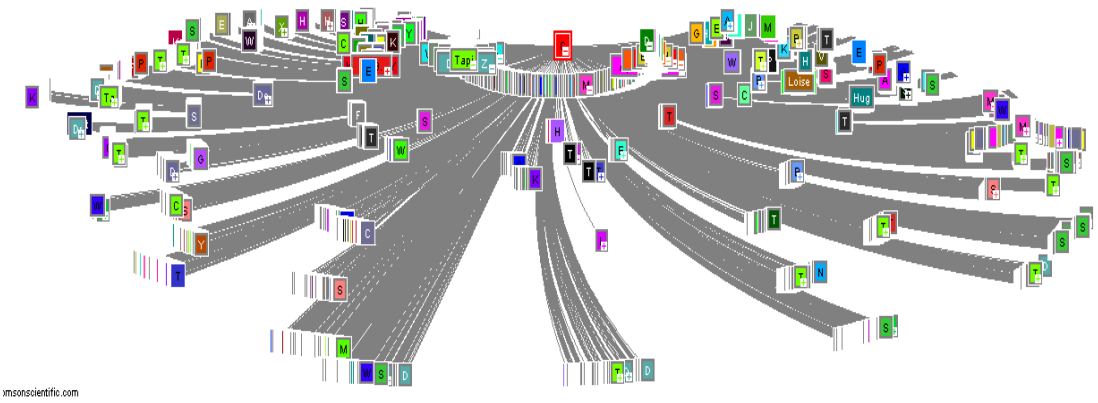


Figure 3.1. The citation map for Cullen, McBride and Reglinski, J. Inorg. Biochem. 1984b downloaded Dec 2011.

I have maintained a passing interest in environmental chemistry since my appointment at Strathclyde. A mine site in the vicinity of Eskdalemuir in the Scottish borders was identified for study (Mohammad et al. 1990). From 1988 to 2004 capable students were available from our environmental chemistry stream (M.Sc) and project work was offered initially in the chemistry of antimony.[6-8] The foot and mouth epidemic in 2001 ended this work prematurely and my attention turned to the environmental chemistry of the strontium deposits in the Strontian granites above the village of Sron-an-t-Sithein (translated as Point of the Fairy Hill) from where the metal takes its name (Davidson et al. 2005). The study follows the migration of strontium from the granite at the head waters of the strontian river via the river water and sediments to one of of its final destinations, the shells of the mussels and cockles sourced at the rivers entrance into the sea loch. This study is a model for the long term fate of strontium effluent such as that produced in nuclear reactors.

3.2 Primary Literature for review

The reduction of trimethylarsine oxide to trimethylarsine by thiols: A mechanistic model for the biological reduction of arsenicals W.R. Cullen, B.C. McBride and J. Reglinski. **J. Inorg. Biochem.** 21, 45-60 (1984)

The reaction of methylarsenicals with thiols: Some biological implications. W.R. Cullen, B.C. McBride and J. Reglinski. **J. Inorg. Biochem.** 21, 179-194 (1984)

The wood preservative chromated copper arsenate is a substrate for trimethylarsine biosynthesis. W.R. Cullen, B.C. McBride, A.W. Pickett and J. Reglinski. **Appl. Environ. Microbiol.** 47, 443-444, (1984)

Spin echo ^{1}H NMR detected response of ergothioneine to oxidative stress in the intact erythrocyte. J. Reglinski, W.E. Smith and R.D. Sturrock. **Magn. Reson. Med.** 6, 217-223 (1988)

The metabolism of methylarsine oxide and sulphide. W.R. Cullen, B.C. McBride, H. Manji, A.W. Pickett and J. Reglinski. **Appl. Organomet. Chem.** 3, 71-78 (1989)

The effect of arsenicals on cell suspensions of the madagascar periwinkle (Catharanthus roseus). W.R. Cullen, D. Hettipathirana and J. Reglinski. **Appl. Organomet. Chem.** 3, 515-521 (1989)

Environmental and medicinal; chemistry of arsenic, antimony and bismuth J. Reglinski in "Chemistry of Arsenic antimony and bismuth" N.C.Norman ed, Blackie Academic, Chapman & Hall, 403-440 (1998)

Speciation of antimony in natural waters: The determination of Sb(III) and Sb(v) by continuous flow hydride generation atomic absorption spectrometry. B. Mohammad, A.M. Ure, J. Reglinski, and D. Littlejohn. **Chem. Speciation. Bioavail.** 3, 117-122, (1990)

The long-term environmental behaviour of strontium and barium released from former mine workings in the granites of the Sunart region of Scotland, UK. C.M. Davidson, M.D. Gibson, E. Hamilton, B.H. MacGillivray, J. Reglinski and E. Rezabal. **Chemosphere 58,** 793-798 (2005)

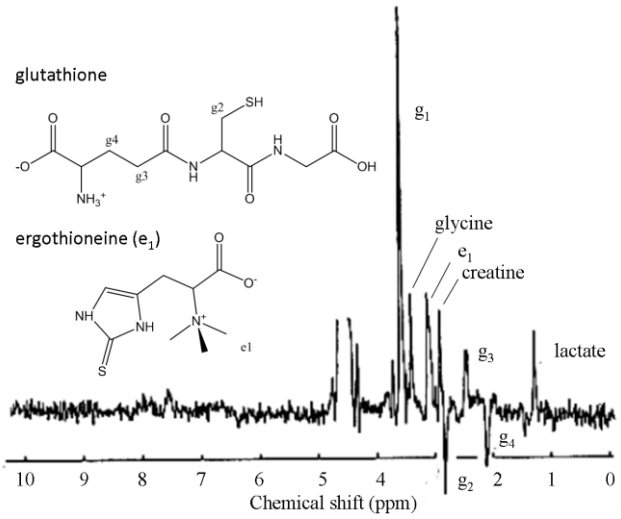
The bio-organometallic chemistry of arsenic

Reprints

Chapter 4

Medicinal inorganic chemistry

Graphical Abstract



Comment:

A meeting with Dallas Rabenstein at the 66th Chemical Institute of Canada in Calgary in 1983 identified the possibility of studying the chemistry of arsenic (Chapter 3) in human red blood cells. Unfortunately my time in Canada was at and end and I had to give up the opportunity to look at this process *ex-vivo*. In 1985 a position came free at Strathclyde University to use the techniques developed by Rabenstein *et al.* to study the clinical implications of thiophilic drugs and their use in the treatment of rheumatoid arthritis. My previous interest in the area made the position irresistible.

4.1 Introduction

The concept of oxidative stress in medicine was topical during the mid-1980's. Medical departments were actively seeking collaborations with chemistry departments to access novel instrumentation especially those that could be applied non-invasively. I joined the project when funding was made available from the Scottish Home & Health Department to investigate the redox balance in erythrocytes obtained from patients suffering from Rheumatoid Arthritis (RA) using non-invasive techniques (^{1}H spin echo NMR, resonance Raman spectroscopies). Over the intervening 20 years the program developed but at its core remained the ability to use the seminal work of Dallas Rabenstein on the ^{1}H spin echo NMR spectrum of the intact and viable erythrocyte (Figure 4.1) to estimate the glutathione/digutathione (GSH/GSSG) ratio using the relative intensities of the glutamyl and cysteinyl resonances.[9] The program at Strathclyde University ultimately took the form of a number parallel studies.

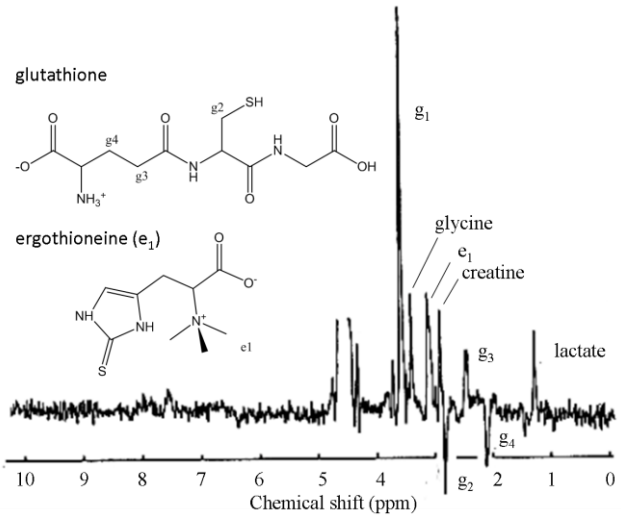


Figure 4.1: The 250 MHz ^{1}H spin echo NMR spectrum of the intact and viable human erythrocyte. The g2 resonance arises from the -CH_2- group adjacent to the sulfur. The strong negative value confirms that the intracellular glutathione is 100% in its reduced form.

4.2. Monitoring erythrocyte redox balance in clinical samples.

A clinical study on the use of penicillamine therapy in the treatment of rheumatoid arthritis using ^{1}H spin echo NMR lay at the heart of the initial program

(Reglinski *et al*. 1992a). However, the main study required a number of base line studies on the *in-vitro* behavior of penicillamine on the erythrocyte (McKay *et al*. 1986) and the general application of spin echo NMR in clinical chemistry (Reglinski *et al*. 1991). The clinical study (Reglinski *et al*. 1992a) was a blind study which tracked a number of patients through their therapy in an attempt to correlate clinical outcome to redox status. The novelty of the method attracted interest from other clinical groups and a parallel study on thyroid disease commenced (Reglinski *et al*. 1992b). The program also expanded to include heart disease (Reglinski 1990) and pre-eclampsia (Spickett *et al*. 1998). The outcome of these studies was positive and we were able to identify a shift in the redox balance (oxidation) of patients who responded to therapy. In contrast, the non-responders showed no change in redox status. Although the studies were a success other analytical methods (e.g mass spec) were becoming simpler and more powerful. The limitations of studying erythrocytes using proton NMR were becoming apparent.

4.3 Direct ^{1}H NMR for the analysis of biological fluids

A number of clinical co-workers were interested in simpler fluids which did not require the use of pulse sequences.

A report had appeared in the New England journal of Medicine which claimed to correlate the line width of plasma proteins in the ^{1}H NMR spectrum of Human plasma with a diagnosis of cancer.[10] This report generated immense interest globally and many NMR spectroscopists were contacted by clinical departments with requests to conduct parallel studies. Although a number of preliminary reports quickly appeared which placed the initial report in doubt, Prof Carter (Dept. of Surgery) requested that a study be conducted. As with many of the papers in this area we were unable to confirm the original claims of Fossel el al.[10] (McKee *et al*. 1989).

Contact with the maternity unit gave rise to a study of diabetic pregnancy. Two studies were conducted; a baseline study investigating the ^{1}H NMR observable contents of amniotic fluid and their quantitation (McGowan *et al*. 1993) and a more sophisticated study on the effect of these metabolites in diabetic pregnancy (McGowan *et al*. 1999).

4.4. Compounds that affect the redox balance of cells

An interest in anti-oxidant therapies (section 4.2) naturally led to an interest in the *in-vitro* analysis of the structure and function of therapeutic compounds and their effect on redox balance of the cell. Studies using Captopril, N-acetylcysteine, Myocrisin, Vanadate and colloids led to the general observation that treatment of the erythrocyte with these compounds shifted the redox balance of the intracellular environment to a more oxidized state. We were also able to show how stimulated white cells can induce the oxidation of erythrocyte glutathione (McGowan *et al*. 1992). The ability to interrogate the intracellular redox status was transferred to cultured cells (Reglinski *et al*. 1987). Studies here focused on the use of anthracyclines in cancer chemotherapy (Reglinski *et al*. 1988, Vallis *et al*. 1997).

These studies initiated an interest in membrane bound sulfhydryl groups. We were able to show that membrane impermeable species such as Ellmans reagent were able to influence the redox status of the intracellular environment (Reglinski *et al*. 1988). This effect was postulated to occur through the membrane, thus stimulating and interest in the distribution of sulfhydryl groups on the membrane proteins of the cell and their ability to act as potential binding sites for drugs.

4.5. Membrane sulfhydryl status.

The study using Ellmans reagent stimulated an interest in non-soluble thiolates on the proteins embedded in the cell membrane (Chillis, *et al*. 1990). Our interested extended to their distribution and specifically which membrane proteins were affected in disease and by therapy (McCrae, *et al*. 1990). Both disease and therapy lowered the availability of sulfhydryl groups on membrane proteins which in turn could be linked to changes in cell activity.

4.6. In vitro studies

All of the work mentioned above was supported by parallel studies on erythrocytes, cultured cells and experimental methods. Exploratory studies were carried out to identify new avenues of research. These included two studies on selenium (Reglinski *et al*. 1992; Beck *et al*. 1993) and a foray into embryology (Homer *et al*. 2005)

4.7 Natural demise

This work came to a natural end due to a mixture of reasons. The clinical partners became more interested in molecular biology and funding became difficult to secure. However the number of targets for an inorganic chemist was limited and a stark choice presented itself – allow the research to become dominated by bio-organic chemistry or change emphasis. A decision was taken to return to alternative lines of research based on inorganic biochemistry and coordination chemistry and the work was allowed to come to a natural end.

4.8 Publications in Refereed Journals

4.8.1 Pre-clinical and Clinical Studies

Changes in glutathione in intact erythrocytes during incubation with penicillamine as detected by ^{1}H spin echo NMR spectroscopy. C.N.N. McKay, D.H. Brown, J. Reglinski, W.E. Smith, H.A. Capell and R.D. Sturrock. **Biochim. Biophys. Acta., 888**, 30-35 (1986)

Demonstration of oxidative stress across cell membrane in chronic heart failure using ^{1}H spin echo NMR spectroscopy of intact erythrocytes. J. Reglinski, M. Chopra, J. McMurray, H. Dargie and W.E.Smith. **Mol. Cell Cardiol.** 22, Supll II, S99, (1990)

Clinical analysis in intact erythrocytes using ^{1}H spin echo NMR. J. Reglinski, W.E. Smith, R. Wilson, L.M. Buchanan, J.H. McKillop, J.A. Thomson, M. Brezski, M. Marabani and R.D. Sturrock. **Clin. Chim. Acta., 201**, 45-57 (1991)

Clinical analysis using ^{1}H spin echo NMR II: Oxidation of intracellular glutathione as a consequence of Penicillamine therapy. J. Reglinski, W.E. Smith, M. Marabani, M. Brzeski and R.D. Sturrock. **J. Med Chem., 35**, 2134-2137 (1992)

Spin echo NMR studies on intact erythrocytes: Changes in cellular metabolism as a consequence of Carbimazole therapy. J. Reglinski, W.E. Smith, R. Wilson, L.M. Buchanan, J.H. McKillop and J.A. Thomson. **Clin Endocrinol., 37**, 319-324 (1992)

The oxidation state of glutathione in the erythrocyte. M. Garner, J. Reglinski, W.E. Smith and J. McMurry. **Clin. Science, 83**, 637 (1992)

An analytical perspective of NMR spectroscopy of biological fluids and cells. J. Reglinski and I.D. Watson. **Ann. Clin. Biochem**., **33**, 290-397 (1996)

Proton NMR studies of oxidative stress in disease. C.M. Spickett, W.E. Smith and J. Reglinski in Advances in Spectroscopy Vol 25 Clark and Hester eds vol 25, 267-294 (1996)

Erythrocyte glutathione balance and membrane stability during preeclampsia. C.M. Spickett, J. Reglinski, W.E. Smith, R. Wilson, J.J. Walker and J. McKillop. **Free Radical Biol. Med., 24,** 1049-1055 (1998)

4.8.2 Direct ^{1}H NMR for the analysis of biological fluids

The detection of malignancy by proton nuclear magnetic resonance spectroscopy of plasma: A reappraisal. R.F. McKee, J. Reglinski, W.E. Smith and D.C. Carter. **Surg. Res. Comm., 6**, 131-136 (1989)

Quantitaive ^{1}H NMR analysis of amniotic Fluid. P.E. McGowan, J. Reglinski, R. Wilson, S. Wisdom and J.J. Walker. **J. Pharm. Biomed Anal., 11**, 629-632 (1993).

^{1}H NMR as a non-invasive probe of amniotic fluid in insulin dependant diabetes mellitus. P.E. McGowan, W.C. Lawrie, J. Reglinski, C.M. Spickett, R. Wilson, J.J. Walker, S. Wisdom, and M.A. Maclean. **J. Perinat. Med., 27**, 404-408, (1999).

4.8.3 Ex-vivo modeling using NMR

A ^{1}H spin echo NMR study of the HeLa tumour cell. J. Reglinski, W.E. Smith, C.J. Suckling, M.J. Stewart, I.D. Watson and M. Al-Kabban. **FEBS lett. 214**, 351-356 (1987)

Exchange reactions between disulphides and Myocrisin: An in-vitro model for a mechanism in chrysotherapy. J. Reglinski, S. Hoey and W.E. Smith. **Inorg. Chim. Acta. 152**, 261-265 (1988)

Cellular response to oxidative stress at sulphdyryl group receptor sites on the erythrocyte membrane J. Reglinski, S. Hoey, W.E. Smith and R.D. Sturrock. **J. Biol. Chem., 263**, 12360-12366 (1988)

The use of ^{1}H spin echo NMR and HPLC to confirm Doxorubicin induced depletion of glutathione in the HeLa cell. M. Al-Kabban, I.D. Watson, M.J. Stewart, J. Reglinski, W.E. Smith and C.J. Suckling. **Brit. J. Cancer, 57**, 553-558 (1988)

The action of Captopril at a cellular level. J. Reglinski, W.E. Smith and J.J.F. Belch. **J. Chem. Res**., 316-317 (1989)

The action of sodium gold(I) thiomalate on the erythrocyte membrane. S. Hoey, J. Reglinski, D.H.Brown, W.E.Smith and R.D.Sturrock. **Inorg. Chem., 29**, 5190-5196 (1990)

Gold drugs used in the treatment of rheumatoid arthritis. W.E. Smith and J. Reglinski. **Perspectives on Bio-inorganic Chemistry 1**, 183-208, (1991)

Studies of oxidative stress in cellular systems; The interaction of monocytes and erythrocytes. P.E. McGowan, J. Reglinski, W.E. Smith, R. Wilson and R.D. Sturrock. **FEBS Lett., 314**, 455-457 (1992)

Alteration of the erythrocyte glutathione redox balance by N-acetylcysteine, captopril and exogenous glutathione. J. Russell, C.M. Spickett, J. Reglinski, W.E. Smith, J. McMurray and I.B. Abdullah. **FEBS Lett.. 347**, 215-220 (1994)

The interaction of colloidal metals with erythrocytes. M. Garner, J. Reglinski, W.E. Smith and M.J. Stewart. **J. Inorg. Biochem., 56**, 283-290 (1994)

Menadione-resistant chinese hamster ovary cells have an increased capacity for glutathione synthesis. K.A. Vallis, J. Reglinski, M. Garner, M.M.E. Bridgeman and C.R. Wolf. **Brit. J. Cancer, 76**, 870-877 (1997)

Resistance of erythrocytes to oxidation by vanadate as studied by ^{1}H spin echo and ^{51}V NMR spectroscopy. M. Garner, J. Reglinski, W.E. Smith, J. McMurray, I. Abdullah and R. Wilson. **J. Biol. Inorg. Chem., 2**, 235-241 (1997)

Oxidation of erythrocyte glutathione by monocytes stimulated with interleukin-6 - Analysis by H-1 spin echo NMR. C.M. Spicket, W.E. Smith, J. Reglinski, R. Wilson and J.J. Walker. **Clin. Chim. Acta., 270**, 115-124 (1998)

The modulation of cell membrane structure and fluidity by endogenous agents: A ^{1}H-NMR approach. J. Reglinski, S.K. Tunnah, W.C. Lawrie and R. Wilson. Proc. 8th Inter. Conf. Spec. Biol. Mol. J.Greve (ed), **Kulwar Academic Pub**., 437-440 (1999).

4.8.4. Membrane and protein sulfhydryl chemistry

The concentration and reactivity of the sulphydryl group population on the membranes of intact human erythrocytes in patients with rheumatoid arthritis. C. Chillis, M. Mulheron, F. McCrae, J. Reglinski, W.E. Smith, M. Brzeski and R.D. Sturrock. **Ann. Rheum. Diss.. 49**, 668-671 (1990)

The action of Myocrisin on membrane bound sulphydryl groups. F. McCrae, J. Reglinski, W.E. Smith, M. Brezski and R.D. Sturrock. **Clin. Chim. Acta., 195**, 41-46 (1990)

The action of gold(I) thiomalate on the erythrocyte membrane II. J.M. Campbell, J. Reglinski, W.E. Smith, D. Porter and R.D. Sturrock. **Ann. Rheum. Diss., 51**, 969-971 (1992)

Direct spectroscopic determination of functional sulphydryl groups on intact cell surfaces by Surface Enhanced Resonance Raman Scattering. B.N.Rospendowski, J.M.Campbell, J.Reglinski and W.E.Smith. **Eur. Biophys. J. 21**, 257-261 (1992)

The effect of sodium gold (I) thiomalate on sugar translocation across the erythrocyte membrane P.E. McGowan, J.M. Campbell, J. Reglinski and W.E. Smith. **Inorg. Chim. Acta., 210**, 1-3 (1993)

Distribution and reactivity of myocrisin. W.E.Smith and **J.Reglinski. Metal Based Drugs 1**, 497-507, (1994)

A comparative study of the interaction of myocrisin with albumin and globulin. C. McDonald, P. Mortimer, G. McAllister, P.E. Gardiner, J. Reglinski and W.E. Smith. **J. Pharm. Biomed. Anal., 13**, 99-102 (1995)

4.8.5. In-vitro studies

Doxorubicin induced altered glycolytic patterns in the leukemic cell studied by proton spin echo NMR. J. Reglinski, W.E. Smith, C.J. Suckling, M.J. Stewart, I.D. Watson and M. Al-Kabban. **Clin. Chim. Acta. 175**, 285-290 (1988)

The effect of doxorubicin on the glutathione content and viability of cultured human lung cancer cell Lines A549 and GLC_4210. M. Al-Kabban, M.J. Stewart, I.D. Watson and J. Reglinski. **Clin. Chim. Acta. 194**, 121-130 (1990)

Selenium in Graves' disease. J. Reglinski, W.E. Smith, R. Wilson, D.J. Halls, J.H. McKillop and J.A. Thomson. **Clin. Chim. Acta., 211**, 189-190 (1992)

Site of action for the inhibition by gold sodium thiomalate of rabbit platelet activation. K.M.S. McKague, C.J.L. Lock, F. McCrae, W.E. Smith, H. Buchanan, W.F. Kean and J. Reglinski. **J. Pharm. Sci. 82**, 174-178 (1993)

The selenium mediated de-iodination of iodophenols; A model for the mechanism of 5' thyronine de-iodinase C. Beck, S.B. Jensen and J. Reglinski. **Biomed. Chem. Lett., 4**, 1353-1356 (1994)

HPLC determination of biologically active thiols using pre-column derivatisation with 5,5'-dithio (bis-2-nitrobenzoic acid). J. Russell, J.A. McKeown, C. Hensman, W.E. Smith and J. Reglinski. **J. Pharm. Biomed. Anal.,15**, 1757-1763 (1997)

Myocrisin mediated oxidative stress. J. Reglinski, D.E. Paterson, S. Latimer, J.M. Campbell, R. Wilson, D. Porter, R.D. Sturrock and W.E. Smith. **Clin. Chim. Acta., 268**, 85-99, (1997)

Evidence for carbimazole as an antioxidant? R. Wilson, L. Buchanan, W.D. Fraser, C. Jenkins, W.E. Smith, J. Reglinski, J.A. Thomson and J.H.McKillop. **Autoimmunity** 27, 149-153, (1998)

Dimethylsulfoxide oxidizes glutathione in vitro and in human erythrocytes: kinetic analysis by ^1H-NMR N.Z. Homer, J. Reglinski, R. Sowden, C.M. Spickett, R. Wilson and J.J. Walker. **Cryobiology 50**, 317-324 (2005)

The reactivity of complexed thiolates with Ellman's reagent: An NMR spectroscopic study. N. Ullah, M. Mukhitar, M.F. Kahn and J.Reglinski. **Polyhedron 78**, 104-111 (2014)

Medicinal inorganic chemistry

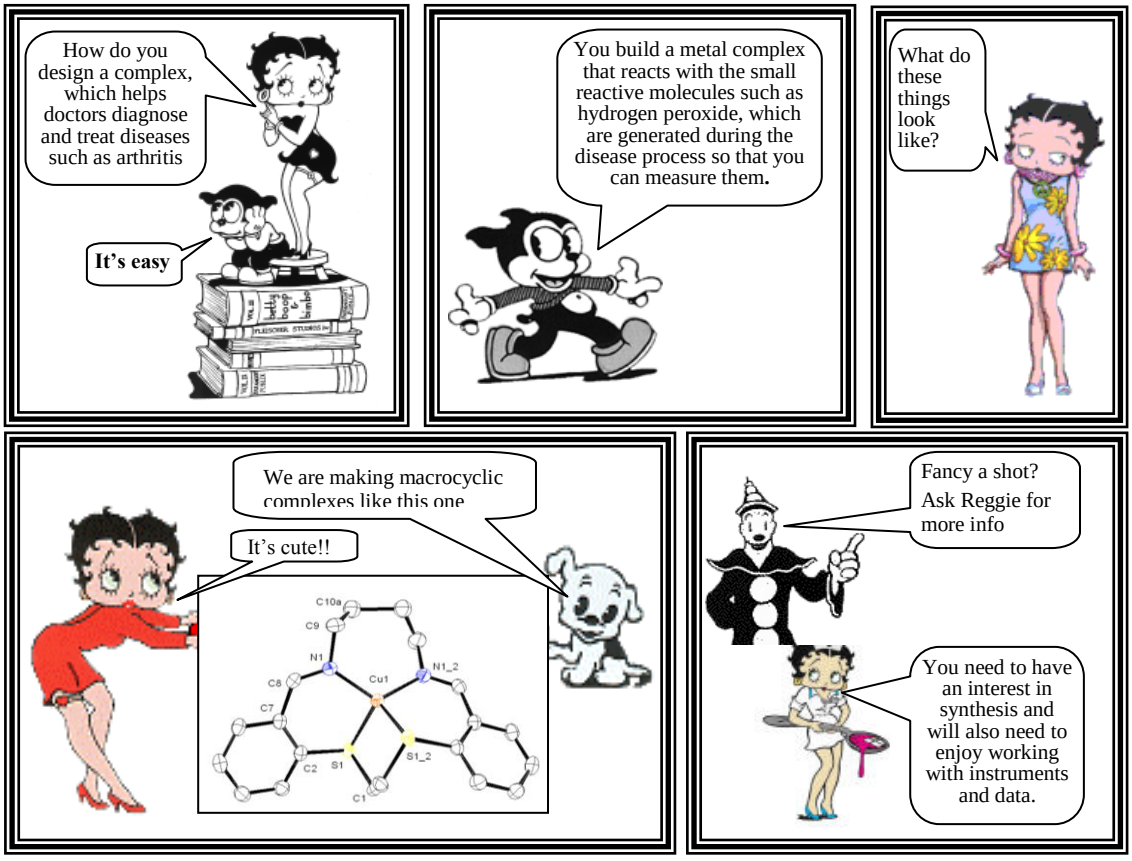
Reprints

Pre-clinical and Clinical Studies

Chapter 5

Sensors for the detection of oxidative stress

Graphical Abstract



Apologies to Betty, Bimbo and Koko

Comment

As a result of previous work on the spectroscopic analysis of diseases which include oxidative stress in their pathology (chapter 4), it had become apparent that there were significant problems with early diagnosis and treatment. A program was started to try and use the small molecules responsible for oxidative stress to score disease severity *in-vivo* by developing a redox sensitive contrast agent for MRI.

5.1. Background:

Many diseases of major clinical importance are of inflammatory origin, where the pathology is caused by acute or chronic stimulation of the immune system, resulting from exogenous damage, autoimmune responses or infection [54]. Diseases with an accepted inflammatory aetiology include atherosclerosis, rheumatoid arthritis, pre-eclamptic toxaemia, diabetes, systemic lupus erythamatous, and some bowel disorders. Unfortunately, the diagnosis of some of these diseases is difficult until the pathology is well advanced, thus limiting the possibility of prevention and making therapy more complicated and less successful. It would be of enormous clinical benefit to develop a straightforward and noninvasive imaging approach, which is able to detect the occurrence of localised inflammatory processes within the body at an early stage of the disease process. This would also allow more precise identification of the site(s) of pathology in advanced disease stages, and hence more targeted and suitable therapy.

In addition to the release of many inflammatory mediators, degradative enzymes and antimicrobial proteins, inflammation involves the production of reactive oxygen species by phagocytic cells, such as macrophages and neutrophils [63]. Although microbiocidal, they are nonspecific and can damage host tissue if inappropriate or excessive production occurs. Superoxide is generated by the respiratory burst, and then converted to hydrogen peroxide. Hypochlorous acid (HOCl) is a product of the enzyme myeloperoxidase, which has been detected in atherosclerotic plaques. HOCl levels may reach as high as 340 μM in localized inflammatory sites [60]. Levels of hydrogen peroxide in the μM range are also thought to occur. Overall, the generation of oxidants at an inflammatory site shifts the local redox balance to a more oxidizing state, this is normally referred to as oxidative stress. This enhanced oxidative status provides the basis for a novel method for monitoring the process of inflammation.

Metal complexes such as diethylenetriaminepenta-acetic acid gadolinium(III) dihydrogen salt dihydrate (GdDTPA) are licensed for use as contrast agents in Magnetic Resonance Imaging (MRI), where they assist the T_1 relaxation of water in the body.[11] This increases the ability of MRI to differentiate between unbound and

tissue-bound water in the T_1 weighted image. The degree of water binding by tissues allows inferences to be made regarding the likelihood of malignancy. However, these compounds cannot provide information on the pathology caused by oxidative stress in inflammatory diseases. Imaging a biochemical process such as oxidative stress can be achieved by metal complexes that are diamagnetic when infused into the body in the reduced form, but are oxidised to a paramagnetic form at the site of inflammation. The paramagnetic complexes will generate a localised alteration in the T_1 of water at these sites, allowing the extent of the inflammation there to be measured directly from the MRI image contrast.

Many of the design principles required for this work were well understood and supported the concept. In summary, the properties required of complexes suitable for imaging of oxidative stress are as follows:

(a) the complexes must have two available oxidation states and be prepared in the reduced form, they must have an oxidation potential tuned to that of biologically relevant oxidants (0.7-0.9 V),

(b) they must be diamagnetic in their reduced form but paramagnetic in their oxidised form,

(c) they must change charge and/or shape on oxidation but not release the metal ion,

(d) they should not be able to redox cycle catalytically

(e) ideally, they should be less membrane permeable in the altered, more charged form.

5.2. Progress.

The design philosophy began by considering a number of metals. Although some work was carried out using iron attention turned to copper as its change in oxidation state operated in tandem with the required change in magnetic properties. Based on the behavior of blue copper proteins, work commenced by confirming that an N_2S_2 coordination set was the most appropriate for copper for this application (Taylor *et al.* 2006). This was achieved using a structural and electrochemical study on a series of Schiff base ligands (figure 5.1). The aqueous solubility and stability of these complexes was poor and the motif was reinforced by joining the sulfur donors

thus completing the ring and then by reducing the imines (Trotter *et al.* 2010). The ability of the compounds to influence the T_1 of water was assessed by ^{1}H NMR indicating that these species did have the potential to act as contrast agents (figure 5.2).

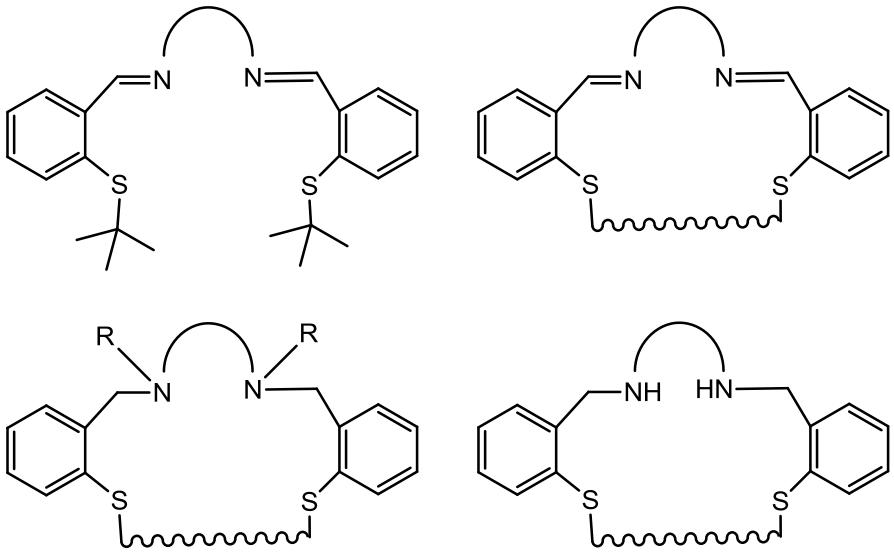


Figure 5.1 The evolution of the ligand platform used in the development of redox sensitive copper based contrast agents

5.3 Future work

Thus far our synthetic efforts have not generated a suitable copper(I) complex and all the compounds generated which are water stable and soluble are copper(II). However, although we have yet to produce a copper(I) complex which is sensitivity to oxidizing conditions, we have been able to demonstrate the reverse behavior i.e. sensitivity to reducing conditions. The final step in the design is to generate copper(I) complexes which are stable under biological conditions which are susceptible to stoichiometric oxidation by hydrogen peroxide and hypochlorous acid. Work continues to realize this aim,.

5.4. Primary literature for review

N,N'-bis(salicylidene)-1,4-butanediamine. A.R. Kennedy and J. Reglinski. **Acta. Crystallogr., E57**, O1027-O1028 (2001)

Supporting conformational change at metal centres. Part 1: octahedral systems. J. Reglinski, S. Morris and D.E. Stevenson. **Polyhedron 21,** 2167-2174 (2002)

Supporting conformational change at metal centres. Part 2 Four and five coordinate geometry. J. Reglinski, S. Morris and D.E. Stevenson. **Polyhedron 21,** 2175-2182 (2002)

N,N-Bis-(2-methoxybenzylidene) adducts of 1,2-ethanediamine, 1,3-propanediamine and 1,4-butanediamine. J. Reglinski, M.K. Taylor, and A.R. Kennedy. **Acta Crystallogr. C60**, o169-o172, (2004).

[N,N'-Bis-(o-sulfidobenzylidene)-1,3-diaminopropane]nickel(II) 1,4-dioxane solvate. M.K. Taylor, J. Reglinski and D. Wallace. **Acta. Crystallogr. Section E60**, m850-m851, (2004).

Coordination geometry of nickel complexes with tetradentate Schiff's base ligands: The effects of donors, backbone length and hydrogenation. M.K. Taylor, J. Reglinski and D. Wallace. **Polyhedron 23**, 3201-3209 (2004)

[Bis(2-chloro-5-sulfonyl benzaldehyde)hexaaqua]Ca(II)monohydrate. D. Wallace, J. Reglinski, M.K. Taylor and A.R. Kennedy. **Acta. Crystallogr. E, 62,** m339-m341, (2006).

*Modelling the impact of geometric parameters on the redox potential of blue copper prote*ins. M.K. Taylor, D.E. Stevenson, L.E.A. Berlouis, A.R. Kennedy and J. Reglinski, **J. Inorg. Biochem. 100**, 250-259 (2006)

The effect of donor groups and geometry on the redox potential of copper Schiff base complexes. M.K. Taylor, L.E.A. Berlouis, A.R. Kennedy and J. Reglinski. **Inorg. Chim. Acta., 359,** 2455-2464 (2006)

Copper N_2S_2 Schiff base macrocycles: The effect of structure on redox potential. M.K. Taylor, K.D. Trotter, J. Reglinski, L.E.A. Berlouis, A.R. Kennedy, C.M. Spickett, R.J. Sowden. **Inorg Chim. Acta** 361, 2851-2862, (2008).

Structural Studies of trans-N_2S_2 Copper Macrocycles. K.D. Trotter, J. Reglinski, K. Robertson, J.C. Forgie, J.A. Parkinson, A.R. Kennedy, D.R. Armstrong, R.J. Sowden, C.M. Spickett **Inorg Chim. Acta** 362, 4065-4072 (2009).

The structural and electrochemical consequences of hydrogenating Copper N_2S_2 Schiff base macrocycles. K.D. Trotter, M.K. Taylor, J.C. Forgie, J. Reglinski, L.E.A. Berlouis, A.R. Kennedy, C.M. Spickett, R.J. Sowden. **Inorg Chim Acta 363,** 1529-1538 (2010)

Reactions of Copper Macrocycles with Antioxidants and HOCl: Potential for Biological Redox Sensing. R.J. Sowden, K.D. Trotter, L. Dunbar, G. Craig, O. Erdemli, C.M. Spickett and J. Reglinski. **Biometals 26**, 85-96 (2013)

Copper complexes as a source of redox active MRI contrast agents. L. Dunbar, R.J. Sowden, K.D. Trotter, M.K. Taylor, D. Smith, A.R. Kennedy, J. Reglinski and C.M. Spickett. **Biometals 28**, 903-912 (2015)

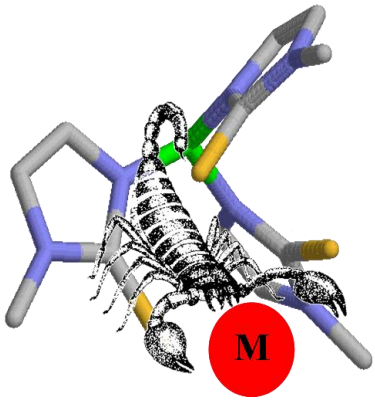
Sensors for the detection of oxidative stress

Reprints

Chapter 6

Soft Scorpionate Chemistry

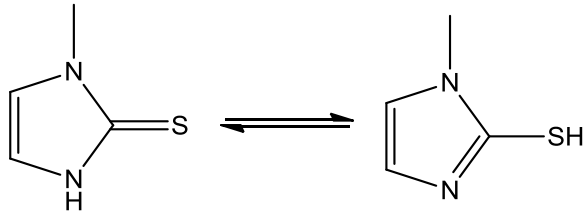
Graphical Abstract



Comment:

The worth of a research publication is typically measured externally using impact factors and citation indexes. However, in some instances a paper is generated which seeds an idea in the authors but attracts no attention within the scientific community. Unassuming contributions of this nature can be important as they are the source of the stimulus which generates a new area of chemistry.

6.1 Background.



Scheme 6.1

Studies on methimazole and its action in Graves' disease [28] (chapter 4) identified a difference of opinion between the chemists and the medical practitioners regarding the structure of the therapeutic agent itself. The medical literature and commercial suppliers commonly present the molecule as a thiolate. However, ^{1}H, ^{13}C and ^{15}N NMR spectroscopy clearly shows that the molecule is best represented as its thione tautomer (scheme 1). To reinforce this view within our clinical partners and conclude the argument (win a bet) this observation was published (with them as co-authors) in Biomed. Chem. Lett. in 1994 [46]. Concurrent with this work, reports were appearing which used metal complexes of the pyrazolylborate ligand system (Tp, Figure 6.1) to model the behaviour of metalloproteins.[1] These ligands are commonly referred to as scorpionates due to the manner in which the donors atoms bind to metal centres.[1] Many of the biological systems being modelled were soft in nature (i.e. naturally containing sulfurs donors) despite the fact that the hydrotris(pyrazolyl)borate anion (Tp) proffers an N_3 donor set. It was obvious that there was a requirement for a soft tripodal scorpionate which could better model this class of enzymes.

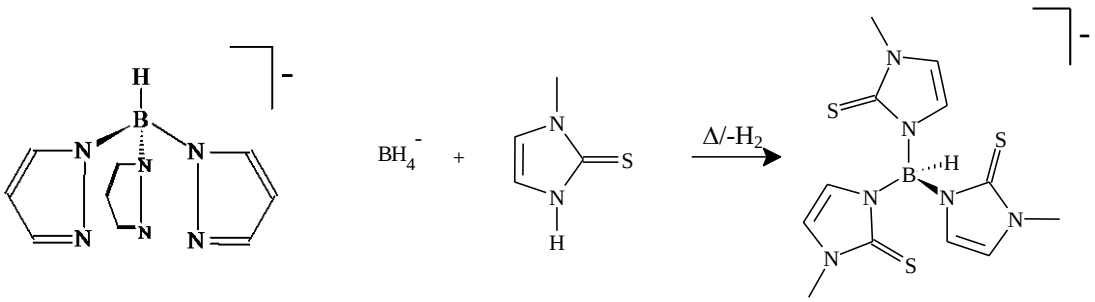


Figure 6.1. Left: The hydrotris(pyrazolyl)borate anion (Tp). Right the synthesis and schematic diagram of the hydrotris(methimazolyl)borate anion (Tm^{Me}).

The synthesis of Tp involves the direct coupling of pyrazole with sodium borohydride in a melt reaction. The realisation that methimazole was a thione which contained an acidic proton on the nitrogen (Scheme 1) suggested that it would replace pyrazole in the synthetic protocol.[1] The subsequent reaction produced a new ligand, the hydrotris(methimazolyl)borate anion (Tm^R: R = Me) in high yield [53, 67]. The anion was quickly adopted and modified by the wider chemistry community.[1]

The chemistry of these soft scorpionate has produced a steady stream of reports from our laboratory at Strathclyde University (*vide infra*). How these reports have influenced the output from other groups world wide is evident from a review of the wider literature. The specific impact of the initial reports in Chemical Communication [53] and Dalton Transactions [67] can be seen in the citation maps taken from the Web of Knowledge (Figure 6.2).

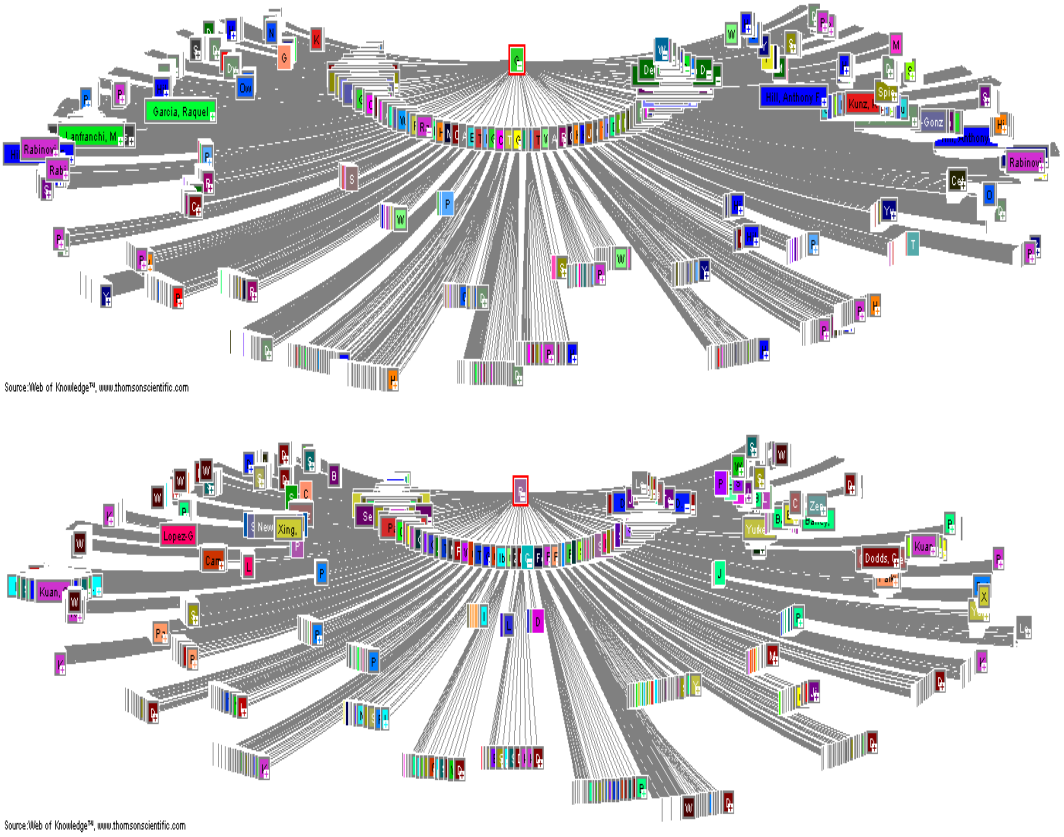


Figure 6.2. The citation maps for Garner et al. Chem Commun 1996 (above) and Reglinski et al Dalton Trans 1999 (below).

6.2. Highlights of this area of chemistry

Our efforts in this area of research from the outset have been to explore the influence of the sulfur donor atoms on the chemistry of the scorpionates. Principally we have used a combination of structural analysis, spectroscopy and theoretical chemistry to unlock our understanding of these compounds.

The chemistry in this area is still expanding rapidly. There remain many questions and avenues of a fundamental nature. Much use is made of the word serendipity and it is evident that there are further surprises to come (figure 6.5).

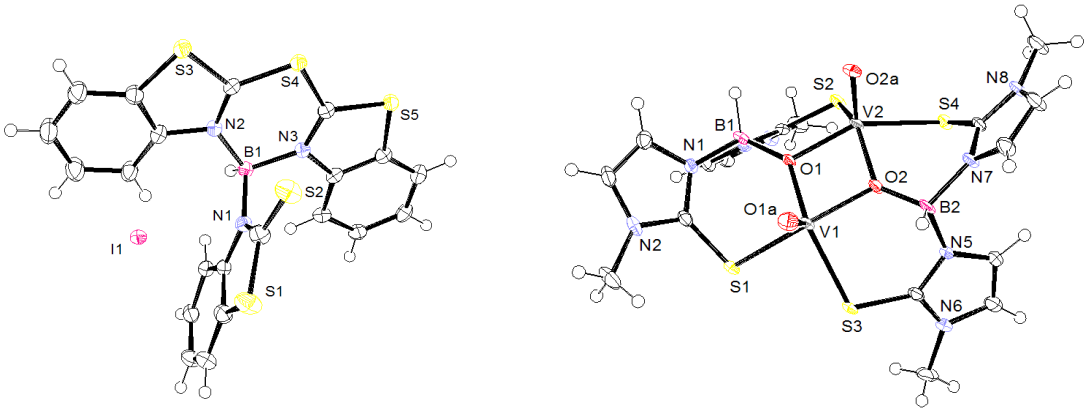


Figure 6.3. Left: A pentacyclic heterocycle derived from the oxidation of the soft scorpionate derived from mercaptobenzothiazole. Right: An product from a reaction involving vanadate.

6.7. Primary literature for review

The structure of methimazole and its consequences for current therapeutic models of Graves' disease. M. Garner, D.R. Armstrong, J. Reglinski, W.E. Smith, R. Wilson and J.H. McKillop. **Biomed. Chem. Lett. 4**, 1357-1360 (1994)

Hydrotris(methimazolyl)borate, a soft analouge of hydrotris(pyrazolyl)borate. Preparation and crystal structure of a novel zinc complex. M. Garner, J. Reglinski, I. Cassidy, M.D. Spicer and A.R. Kennedy. **J. Chem. Soc. Chem. Commun.** 1975-1976 (1996).

Sodium hydrotris(methimazolyl)borate, a novel soft, tridentate ligand: preparation, structure and comparisons with sodium hydrotris(pyrazolyl)borate. J. Reglinski, M. Garner, I.D. Cassidy, P.A. Slavin, M.D. Spicer, and D.R. Armstrong. **J. Chem. Soc. Dalton Trans.** 2119-2126 (1999)

The structural consequences of the use of hard and soft tripodal ligands during metathesis reactions: The synthesis of the [bis-(hydrotris(methimazolyl)borato] bismuth(III) [bis-(hydrotris(pyrazolyl)-borato]-sodiate. J. Reglinski, M.D. Spicer, M. Garner and A.R. Kennedy **J. Amer. Chem. Soc. 121**, 2317-2318 (1999)

Preparation and crystal structure of the [bis-{hydrotris(methimazolyl)borato}-thallium(III)] cation: modulated chemistry resulting from the use of soft and hard tripodal ligands. P.A. Slavin, J. Reglinski, M.D. Spicer and A.R. Kennedy. **J. Chem. Soc. Dalton Trans.** 239-240 (2000)

The synthesis of soft tripodal ligands: Restrictions on the synthesis of hydrotris-(thiazolyl)borate anions from borohydride melts. J.F. Ojo, P.A. Slavin, J. Reglinski, M. Garner, M.D. Spicer, A.R. Kennedy and S.J. Teat. **Inorg. Chim. Acta 313**, 15-20, (2001)

Soft (S3) Scorpionate complexes of molybdenum and tungsten. M. Garner, M-A, Lehmann, J. Reglinski, and M.D. Spicer. **Organometallics 20**, 5233-5236, (2001)

The preparation and structures of group 12 (Zn, Cd, Hg) complexes of the soft tripodal ligand hydrotris(methimazolyl)borate (Tm). I. Cassidy, M. Garner, A.R.

Kennedy, G.B.S. Potts, J. Reglinski, P.A. Slavin, and M.D. Spicer. **Eur. J. Inorg. Chem.** 1235-1239 (2002)

Structural and Spectroscopic Characterisation of iron(II), nickel(II) and nickel(III) complexes of the hydrotris(methimazolyl)borate anion: soft donors in a weak ligand field. M. Garner, K. Lewinski, A. Pattek-Janczyk, J. Reglinski, B. Sieklucka, M.D. Spicer and M. Szaleniec**. Dalton Trans**. 1181-1185 (2003)

Altering the surface characteristics of coated silver surfaces. Soft donors allow the direct detection of isolated porphyrins using SERRS. J. Reglinski, M.D. Spicer, J.F. Ojo, G.D. McAnally, A. Skórska, S.J. Smith, and W.E. Smith. **Langmuir 19,** 6336-6338 (2003)

Pushing the frontiers of hard and soft scorpionate chemistry. C.A. Dodds, A.R. Kennedy, J. Reglinski and M.D. Spicer. **Inorg. Chem. 43**, 394-395, (2004)

Soft scorpionate complexes of the fourth and fifth row elements arsenic and tin. C.A. Dodds, M. Jagoda, J. Reglinski and M.D. Spicer. **Polyhedron 23**, 445-450, (2004)

Cobalt half sandwich, sandwich and mixed sandwich complexes with soft tripodal ligands. C.A. Dodds, M-A. Lehmann, J.F. Ojo, J. Reglinski and M.D. Spicer. **Inorg. Chem. 43,** 4927-4934, (2004)

Lower main group element complexes with a soft scorpionate ligand: the structural influence of stereochemically active lone pairs C.A. Dodds, J. Reglinski and M.D. Spicer **Chemistry - A European Journal 12**, 933-941 (2006)

Coinage Metal Complexes of a Boron Substituted Soft Scorpionate Ligand. C.A. Dodds, M. Garner, J. Reglinski and M.D. Spicer. **Inorg Chem 45**, 2733-2741 (2006)

[Mo(Tm^{Me})O$_2$Cl]: An improved model of Sulfite Oxidase. D. Wallace, J. Reglinski, M.D. Spicer and L.T. Gibson. **Inorg. Chem. 46**, 3804-3806, (2007)

Structural and theoretical insights into metal-scorpionate ligand complexes. M. Schwalbe, P.C. Andrikopoulos, D.R. Armstrong, J. Reglinski and M.D. Spicer. **Eur. J Inorg. Chem.** 1351-1360, (2007)

Bis(dimethylformamido hydrotris(methimazolyl)borato sodium): A complex where sodium exhibits a preference for sulfur over oxygen. A. Biernat, M. Schwalbe, D. Wallace, J. Reglinski and M.D. Spicer. **Dalton Trans.** 2242-2244, (2007)

The bioinorganic chemistry of methimazole based soft scorpionates. J. Reglinski and M.D. Spicer **Current Bioactive Compounds 5**, 264-276, (2009)

Soft scorpionates based on imidazole-2-thione donors. M.D. Spicer and J. Reglinski **Eur. J. Inorg. Chem**. 1553-1574, (2009)

Surface Science of Soft Scorpionates D. Wallace, E.J. Quinn, J. Reglinski, M.D. Spicer, W.E. Smith. **Inorg Chem. 49,** 1420-1427 (2010)

The S-alkylation of Soft Scorpionates. R. Rajasekharan-Nair, D. Moore, K. Chalmers, D. Wallace, L.M. Diamond, L. Darby, D.R. Armstrong, J. Reglinski and M.D. Spicer. **Chem. Eur. J. 19**, 2487-2495 (2013)

Soft Scorpionate anions as platforms for novel heterocycles. R. Rajasekharan-Nair, A. Marckwordt, S.T. Lutta, M. Schwalbe, A. Biernat, D.R. Armstrong, A.J.B. Watson, A.R. Kennedy, J. Reglinski and M.D.Spicer. **Chem. Eur. J**. **19,** 13561-13568 (2013)

Nitric oxide species as oxidizing agents and adducts for soft scorpionates. R. Rajasekharan-Nair, L. Darby, J. Reglinski, M.D. Spicer and A.R. Kennedy **Inorg. Chem. Commun. 41,** 11-13 (2014)

The thermal stability of soft scorpionates and their germanium complexes. D. Wallace, K. Chalmers, C.A. Dodds, D.R. Armstrong, L.E.A. Berlouis, J. Reglinski and M.D. Spicer. **Eur J. Inorg Chem.** 2569-2575 (2014)

Soft scorpionate coordination at alkali metals. R. Rajasekharan-Nair, S.T. Lutta, A.R. Kennedy, J. Reglinski and M.D.Spicer. **Acta Cryst. C**., **C70,** 421-427 (2014).

The Stability of Mercaptobenzothiazole Based Soft Scorpionate Complexes. R. Rajasekharan-Nair, D. Moore, A.R. Kennedy, J. Reglinski, M.D. Spicer. **Inorg. Chem., 53,** 10276–10282 (2014).

Chemistry of the p-block elements with Scorpionate Ligands. J. Reglinski and M.D. Spicer, **Coord. Chem. Revs** 297-298, 181-207, (2015).

Observations on the impact of N- and S- donor scorpionate ligands. G. Steel, R. Rajasekharan-Nair, I. A. Stepek, A.R. Kennedy, J. Reglinski, M.D. Spicer. **Eur. J. Inorg. Chem.** In press Doi.org/10.1002/ejic.201500924

The first structurally characterised example of silicon in an S6 coordination sphere. A. Marckwordt, R. Rajasekharan-Nair, G. Steel, A.R. Kennedy, J. Reglinski, M.D. Spicer. . **Eur. J. Inorg. Chem.** submitted

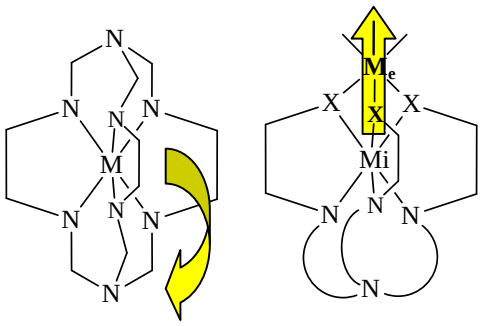
Soft Scorpionate complexes

Reprints

Chapter 7

Multimetallic complexes

Graphical Abstract



Comment:

An interest in Schiff base ligands commenced very early in my academic career. Indeed the program to develop copper based imaging agents began with studies on Schiff base ligands. The cross pollination of these studies (Chapter 5) and those on soft scorpionate chemistry (Chapter 6) led to this interesting aside. Crucially the ability to work on Schiff base chemistry has offered me an opportunity to conduct practical work on occasions.

7.1 Background

The internalisation of metal cations within ligands is easily achieved using a wide variety of cyclic polydentate systems otherwise known as cryptands or sepulchrates.[13] These species are designed in such a manner that donor atoms (O, N, S) can be directed inwards to satisfy the coordination geometry of the metal while folding the bridging organic framework outwards towards the supporting medium and its contents. Modifying the complex structure in this way makes it possible to solvate simple salts in non-polar media.[14] Not only do cryptand species alter the behaviour of metal cations, they modulate their reactivity patterns. For example transition metals undergo redox processes via two simple mechanisms namely inner and outer-sphere electron transfer. However, once encapsulated inner sphere electron transfer is effectively stopped, thus forcing any redox driven process to operate via the alternative outer-sphere mechanism (Figure 7.1). In effect these species provide a definitive method by which chemists control electron transfer processes.

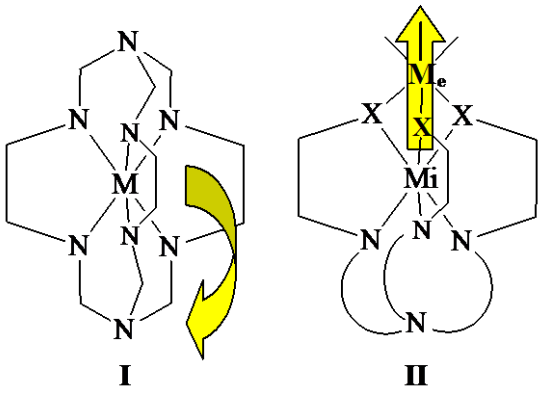


Figure 7.1: A typical sepulchrate (cyptand) complex[12] and an analogue that has a second metal cation embedded in the cap (X = O, N, S). The pathways by which electrons leave (and enter) the metal centre are depicted (arrows) i.e. outer-sphere electron transfer (left) and channeled inner sphere electron transfer (right).

Viewing transition metal sepulchrate complexes from an alternative perspective, they can be considered as repositories for electrons which are held on internalised, low valent metal cations (e.g. M = Co^{II}, Ru^{II}, Ir^{I}; Figure 7.1).[13] Considering the ease with which many of these established complexes can be oxidized,[12] it is clear that they would have immense value if they could be re-

designed as facially capping tripodal ligands which act as an additional source of redox capacity. One method of generating such crypts would be to create a hexadentate podand system which encapsulates one metal ($M_{internal}$: M_i) within the ligand and facilitates the complexation of a second metal ($M_{external}$: M_e) at the site(s) normally occupied by the capping unit (**II**, Figure 7.1). This design allows the electrons on the internalised metal to travel through the donor bridges (X = O, N, S) into the cap in a controlled manner. Placing a reactive metal fragment (e.g. M_e-halide) into the cap would allow us to decouple substrate selectivity (binding; M_e) from the metal undergoing redox change (source of chemical potential; M_i). Thus it would allow us to engender redox behaviour in metals (M_e) such as zinc and the lanthanides. Furthermore, using this design it should be possible to supplement the redox capacity of a metal such as copper (M_i, $M_e = Cu^{I/II}$) or transfer three or more electrons (M_i, $M_e = Ir^{I/III}$) through a single site.

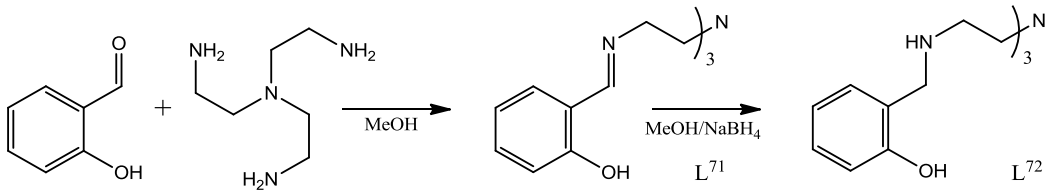


Figure 7.2: The synthesis of L^{71} and L^{72}

This working hypothesis initiated an interest in multidentate ligands. Previous experience with Schiff base ligands (Chapter 5) suggested that they were an appropriate system from which to construct the necessary multidentate ligands [76, 77]. Initially, salicylaldehyde was selected because there was an extensive literature on this salicylidene Schiff based ligands. However, the work was quickly expanded to include o-^{t}butylthiobenzaldehyde and o-aminobenzaldehyde. To date we have constructed complexes which contain a varying number of metal atoms from simple monometallic species to complex octametallic clusters (Mustapha et al. 2010a, 2010c, 2011).

7.2. Unexpected asides.

Our survey of the chemistry of L^{72} (figure 7.2) led us to the synthesis of a novel Ce_2-μO_2 complex (Mustapha et al 2009). Of particular note was the presence

of a bridging oxygen in our complex. This is a common moiety in cerium based nucleases,[15] which suggested that we should test our species for its ability to hydrolyse DNA. The results suggest that this is a highly efficient catalyst operating at room temperature and at low concentrations (Reglinski 2011; Mustapha et al. 2008).

Our ability to generate sophisticated motifs led to a collaboration with Andrew Mills on photolytic water oxidation. The production of energy (hydrogen) from the photolysis of water is restricted by the low efficiency of the oxidation step which furnishes the electrons required to produce the hydrogen (equation 7.1).

$$H_2O \longrightarrow O_2 + 2e + 2H^+ \qquad \text{- (7.1)}$$

A system is being developed which is based on a TiO_2 semiconducting support augment with an oxidation catalyst. Initially we used oxides of ruthenium as the oxidation catalyst (Duckmanton et al 2010). Although these performed in a satisfactory manner, long term issues with corrosion and loss of ruthenium as RuO_4 suggested that we refocus our attention on iridium(IV) dioxide. Currently we are studying the properties of co-catalysts which are designed to harvest light. Work employing picolinic acid complexes is in an advanced stage (Steel et al 2013b). These compounds are being used in an attempt to isolate the crucial features required of a co-catalyst (e.g. Molar absorbtivity, redox potential).

7.3. Primary literature for review.

1,1,1-tris(2-hydroxybenzylideneamino)-methylpropane iron(III) chloroform solvate. J. Reglinski and M. Patykiewicz. **Acta. Crystallogr,** E58, m543-m544 (2002)

Schiff base ligands: Towards the controlled organisation of open metal frameworks. J. Reglinski, M.K. Taylor and A.R. Kennedy. **Inorg. Chem. Commun.** 9, 736-739, (2006).

Multidentate ligands for the synthesis of multi-metallic complexes. A.Mustapha, K.Busch, J.Reglinski, A.R.Kennedy and T.J.Prior. **Polyhedron** 27, 868-878 (2008).

The use of hydrogenated Schiff base ligands in the synthesis of multi-metallic compounds. A. Mustapha, J. Reglinski and A.R. Kennedy. **Inorg Chim. Acta** 362, 1267-1274 (2009)

Metal complexes as potential ligands: The deprotonation of aminephenolate metal complexes. A. Mustapha, J. Reglinski, A.R. Kennedy. **Inorg. Chem. Commun.** 13, 464-467 (2010)

Multidentate ligands for the synthesis of multi-metallic complexes II. Formation of a planar Cu_4OH motif. A. Mustapha, J. Reglinski, A.R. Kennedy, D.R. Armstrong, J. Saßmannshausen, M. Murrie. **Inorg. Chem.** 49, 5350-5352 (2010).

N-donor ligand complexes of nickel, zinc and copper: Comparisons with tetradentate N-donor ligands derived from Schiff bases. A. Mustapha, J. Reglinski, A.R. Kennedy. **Polyhedron** 29, 2590-2594 (2010)

A Simple, Novel Method for Preparing an Effective Water Oxidation Catalyst A. Mills, P.A. Duckmanton, J. Reglinski. **Chem. Commun.** 46, 2397-2398 (2010)

The use of hydrogenated Schiff base ligands in the synthesis of multi-metallic compounds II. A. Mustapha, C. Busche, J. Reglinski, A.R. Kennedy. **Polyhedron.** 30, 1530-1537, (2011)

The nickel, copper and zinc complexes of potentially heptadentate nitrogen-sulfur donor ligands. G. Steel, A. Mustapha, J. Reglinski, A.R. Kennedy. **Polyhedron** 67, 360-367, (2014)

Tetradentate Schiff base beryllium complexes. J. Reglinski, A.R. Kennedy, G. Steel. **New J. Chem.** 39, 2437-2439, (2015)

7.3.1 Conference presentations.

Cerium complexes for DNA hydrolysis. (Poster) A. Mustapha, R. Stevenson, J. Reglinski, D. Graham, K. Faulds. 2nd EuChemS Congress Turin 2008

Cerium complexes for DNA hydrolysis. (Oral) J. Reglinski, 15th International Conference on Biological Inorganic Chemistry (ICBIC 15) Vancouver 2011

Tunable dyes for water oxidation based on dipicolinic acid complexes of ruthenium. G. Steel, J. Reglinski, M.D. Spicer, K.D. Trotter. USIC Edinburgh 2013

Multimetallic complexes

Reprints

Chapter 8

Scholarship

Graphical Abstract

Comment:

During an academic career there is an expectation that there is a contribution to teaching which goes beyond delivering classes. This can come in many forms. Two that are important to my career are undergraduate research training and the development of teaching methods.

8.1. Research as teaching

Undergraduates who have good manual skills can generate quality data. Significantly, in a subject such as chemistry it can be the case that a student of lesser academic ability can excel in practical science. When done successfully, patiently and in combination, the efforts of undergraduates can generate data which can appear in print. A number of the papers cited in my record include a contribution from undergraduates. Within this group a small number of papers arise solely from the efforts of undergraduates [45, 50, 76, 77]. In many cases this output will be their only impact on science.

8.2. Teaching practice

In my time at Strathclyde I have tried to be innovative in an effort to change working practice. Two activities have led to the publication of papers in teaching journals.

Circa 2002/2003 there was a drive to introduce computers into teaching in such that it properly supported a theme. Typically coordination chemistry is introduced to undergraduates using the periodic table, ligand field theory and the spectrochemical series. The concept published in 2004 (Reglinski et al.) was an attempt to reverse engineer coordination chemistry using the protein crystal data bank as a starting point. I co-opted colleagues from the section to cover the key disciplines required, basic biochemistry (D. Graham), crystallography (A.R. Kennedy) and analysis (L.T. Gibson). This exercise is still used in the department today under the title “information retrieval”.

Under the old curriculum the final examination included a question which was based on general chemistry and chemistry taught in the earlier years. Invariable the performance of the class in this question was poor. This was frustrating. The staff held the view that these questions were “easy” and we were convinced that the students knew the answers but lacked the ability to source the information under the pressure of the exam. A decision to experiment with visual questions which contained no words was taken. To say the concept was original would be unfair as it is a hybrid of the inkblot tests used in psychology and flash cards used to teach young children. The paper published (Reglinski 2007), however, really arose due to

a disagreement between the external examiner and myself. He held the view that the approach would not work (the question is reproduced below). In reality it was a real success. It has been some time since an entire question has been set using this approach but it is still regularly used in part by myself and another member of staff.

8.3 Primary literature for review

From metalloproteins to coordination chemistry: A non-contact learning exercise to support the teaching of transition metal chemistry. J. Reglinski, D. Graham, A.R. Kennedy and L.T. Gibson **J. Chem. Ed. 81**, 76-82 (2004).

Unlocking knowledge we know the students know. J. Reglinski, **J. Chem. Ed. 84**, 271-273 (2007).

Question 7, Paper C, degree examinations, Pure & Applied Chemistry, Strathclyde University 2005

Scholarship

Reprints

Chapter 9

Miscellaneous

Graphical Abstract

Comment:

It is impossible to be in academic life for 30 years and not get involved in projects that produce publishable results but which have no future. These either result from collaborations with colleagues (favours) or result from orphan projects which just fail to realize any potential.

There is no narrative for these papers as they do not have a proper place in my research. They are here because I like them

Chapter 9

Miscellaneous

Reprints

Chapter 10

Conclusion and closing remarks

Graphical Abstract

Comment:

That was fun!

10.1 A concluding overview

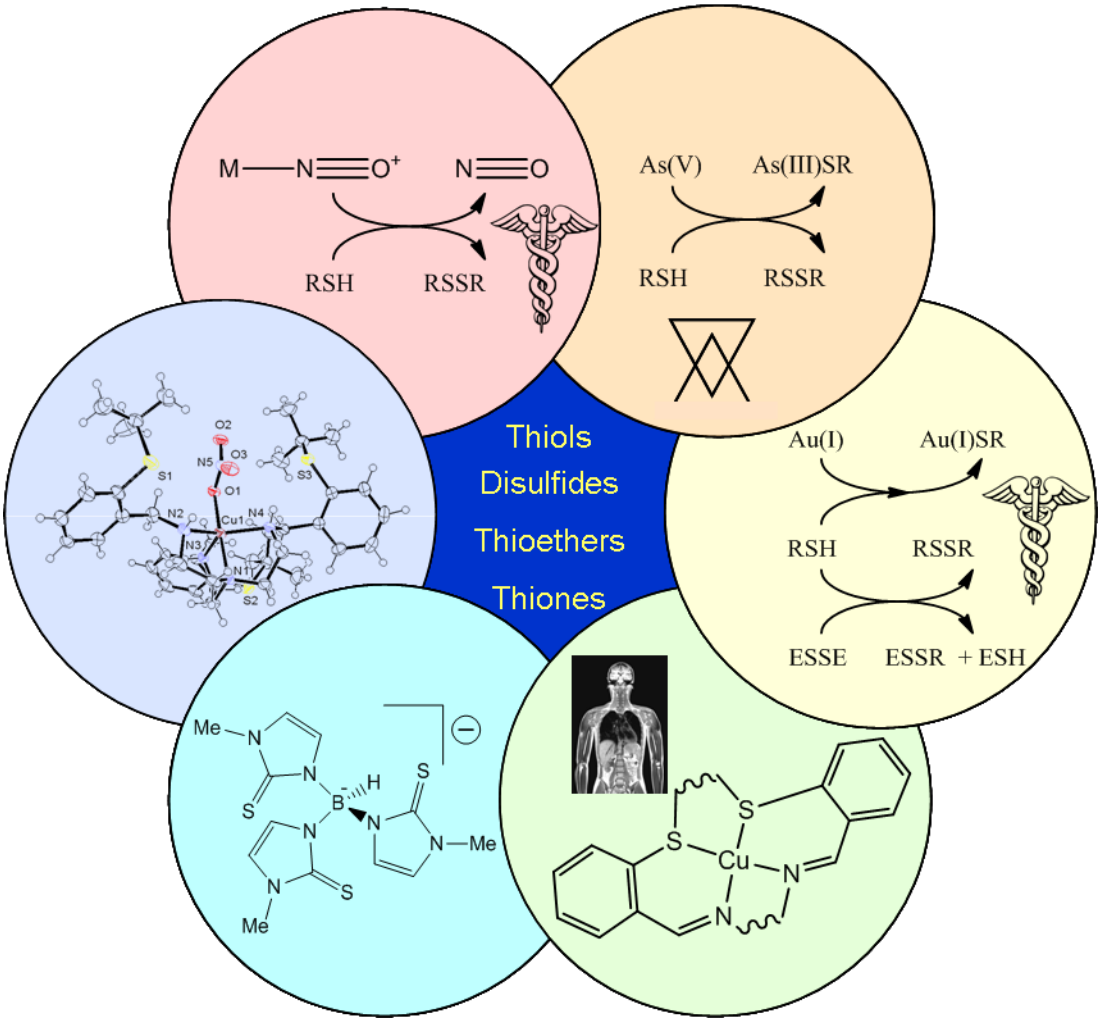


Figure 10.1. An integrated view of my research.

The unifying theme in my research to date has been the compounds of sulfur (Figure 10.1). My introduction to sulfur chemistry came via its ability to act as a mild, biologically relevant reducing agent in the presence of nitrosonium complexes. This role was expanded during a period in Canada where its ability to act as a "ligand" (Me_2AsSR) came to the fore. Until this point the disulfides were viewed as uninteresting by-products. However, these species assumed greater importance during my studies on the medicinal chemistry of sulfur and oxidative stress. My time in clinical chemistry instigated an interest in contrast agents and consequently thio-ether macrocycles and multidentate thio-ether ligands. Clinical chemistry also exposed me to the thiones which thus far had escaped my attentions. Research was

coming full circle. Having started as a sythetic chemist preparing nitrosyl complexes for medicinal purposed, medicinal chemist identified the thione moiety as a potential donor group in coordination chemistry. This led to the development of soft scorpionates.

10.2 Academic research – a subtext

I have unashamedly used my academic position to pursue chemistry and ideas which I found attractive. On occasions the output of this labour has attracted little attention. Other efforts have had a significant impact on chemistry. This approach has, however, allowed me to work in a variety of topics across many disciplines, across the entire (within reason) periodic table and, rather selfishly, enjoy myself. From an early stage as an academic I set myself the frivolous challenge of publishing a paper on every inorganic element in the periodic table (figure 10.2). Safety concerns have rendered certain areas of chemistry (e.g. uranium, thorium) "off-limits" for casual chemistry. Some elements are too rare (e.g. Tc, Po, At) or have chemistry in which is outside my skill set (e.g. Nobel gases). A number of papers have appeared which include the lanthanoids. It is unlikely that I will complete this series. Bending an old adage; when you have done chemistry with one lanthanoid you have done chemistry of them all (cerium apart).

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Th		U											

Figure 10.2 The chemistry accessible periodic table. The elements shaded blue are the subject or a major component of a published paper. Those in white remain to be completed. Those in yellow will probable never appear in one of my publications for the reasons mentioned.

Unlike many academics, 35 years after graduating for the first time, I still find time to work at the bench making new compounds; I still do chemistry. My H index (24) is lower than it should be, but this is undoubtedly due to the fact that I have not restricted myself to research in one area of chemistry during the past 30 years. Ultimately, we each hope that we will leave our mark in our chosen area. I have been fortunate to make a significant contribution in two areas; biomethylation of arsenic (Chapter 3) and soft scorpionate chemistry (Chapter 5). However, every time a paper appears in print we hope it will stimulate interest in the community. Recent efforts to design a redox sensitive contrast agent are just such a contribution.

Additional references

1. in Scorpionates II: Chelating Borate Ligands, C. Pettinari Imperial College Press (2008).
2. D.E. Koshland. Science, 1861, 258 (1992)
3. J.H. Tinker and J.D. Michenfelder. Anesthesiology, **45**, 340 (1976)
4. M.L. Bird F. Challenger, P.T. Charlton and J.O. Smith Biochem. J. **43**, 78 (1948).
5. S-dimethylarsino-thiosuccinic acid, S-dimethylarsino-2-thiobenzoic acid, S-(dimethylarsino)glutathione as treatments for cancer. H. Dukale, E.L. Freireich, H. Kantarjian, M. Sotelo-Lerma, S. Verstovsek and R.A. Zingaro. US 6911471 B2 June (2005)
6. Antimony in the environment. V Shanmugam, M.Sc. Strathclyde University 1994
7. Towards the speciation of antimony in the environment by indirect photometric chromatography. K. Mohamed, M.Sc. Strathclyde University 1996.
8. Towards the biospeciation of antimony in the environment. S. Forster M.Sc. Strathclyde University 1997
9. D.L. Rabenstein J. Biochem. Biophys Meth. 9, 277-306 (1984)
10. E.T. Fossel, J.M. Carr and J. McDonagh New Engl. J. Med. **315**, 1369-1376 (1986)
11. J. Reedijk Curr. Opin. Chem. Biol .**3:** 236-240 (1999)
12. A. Al-Harbi, Y. Rong, G.Parkin Dalton Trans **42**, 1117-1127 (2013)
13. P. Osvath, A.M. Sargeson, A. McAuley, R.E. Mendelez, S. Subramanian, M.J. Zaworotko, L. Broge. Inorg. Chem. **38**, 3634 (1999).
14. in Bioinorganic chemistry: Inorganic elements in the chemistry of life. W. Kaim and B. Schwederski. P 237 Wiley
15. M.E. Branum, A.K. Tipton, S. Zhu and L. Que J. Amer. Chem. Soc. **123** 1898 (2001).