Designer ligands: The search for metal ion selectivity

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The paper reviews research conducted at Rhodes University towards the development of metal-selective ligands. The research has focused on the rational design, synthesis and evaluation of novel ligands for use in the formation of copper complexes as biomimetic models of the metalloenzyme, tyrosinase, and for the selective extraction of silver, nickel and platinum group metal ions in the presence of contaminating metal ions. Attention has also been given to the development of efficient, metal-selective molecular imprinted polymers.

Introduction

South Africa has rich metal ore deposits and isolation of the high value metals represents a significant component of the country's economy.[1] Particular challenges are presented in: the isolation and purification of such metals; the recovery of precious metals from ore leachates; and their use in value-added products. As organic chemists with interests in computer modelling and synthesis, the design, preparation and evaluation of customised ligand systems for selective chelation presented new and challenging research opportunities. Our contributions in this area have included the development of: (1) biomimetic ligands for the construction of copper complexes as tyrosinase models; (2) platinum group metal (PGM)-selective ligands and molecular imprinted polymers (MIPs); (3) silver-selective ligands; and iv) nickel-selective ligands and MIPs.

Biomimetic ligands for the construction of transition metal complexes as tyrosinase models

Tyrosinase, a polyphenol oxidase metalloenzyme, catalyses the *ortho*-hydroxylation of phenolic systems to catechols (phenolase activity) and their subsequent oxidation to quinones (catecholase activity)[2] – a process responsible for the browning of injured fruit and vegetables. The active site is believed to contain two appropriately coordinated copper(I) atoms[3] approximately 3.55 Å apart[4] and is activated, following binding of molecular oxygen, with the formation of a dioxygen-bridged dicopper(II) complex (Figure 1). A multidisciplinary PhD project[5] on biocatalytic and biomimetic studies of polyphenol oxidase was followed by an investigation into the *de novo* design and synthesis of ligands and their dinuclear copper complexes with a view to developing biomimetic models of the tyrosinase active site.[6]

Attention was given to the use of various spacer groups, including Schiff-base,[7] biphenyl[8] and 1,10-phenanthroline[9] moieties, and synthetic pathways developed to access the polydentate 1,10-phenanthroline-based ligands from neocuproine (2,9-dimethyl-1,10-phenanthroline) and their capacity to form bis-copper(II) and bis-cobalt(II) chelates are illustrated in Scheme 1.[10] With the various ligands available, complexes with other transition metals, namely manganese(II), nickel(II) and zinc(II) were also explored.[11,12] As crystals suitable for single crystal X-ray analysis were only obtained in isolated cases, the complexes were typically characterised using elemental analysis and appropriate spectroscopic techniques, and their possible structures were explored using computer modelling at the molecular mechanics level.[13]

Modelling of complex 10 revealed a remarkably organised potential binding pocket, containing the copper(II) atoms separated by 4.5 Å; following introduction of the dioxygen bridge, the Cu-Cu distance was observed to decrease to 4.1Å for *trans* μ-1,2 and 2.5Å for μ-η^2:η^2 bridging (Figure 2).[14]

Evaluation of the phenolase and catecholase activity of such complexes typically involves the use of 3,5-di-*t*-butylphenol (DTBP) and 3,5-di-*t*-butylcatechol (DTBC) as the respective substrates.[15] DTBP is oxidised to DTBC, which is oxidised, in turn, to 3,5-di-*t*-butyl-*o*-quinone (DTBQ); if formed, the oxidation products may be readily detected by nuclear magnetic resonance (^{1}H-NMR) analysis. Whereas all of the Co(II) complexes tested and all but one of the Cu(II) complexes tested catalysed the conversion of DTBC to DTBQ, the Co(II) complexes exhibited more efficient

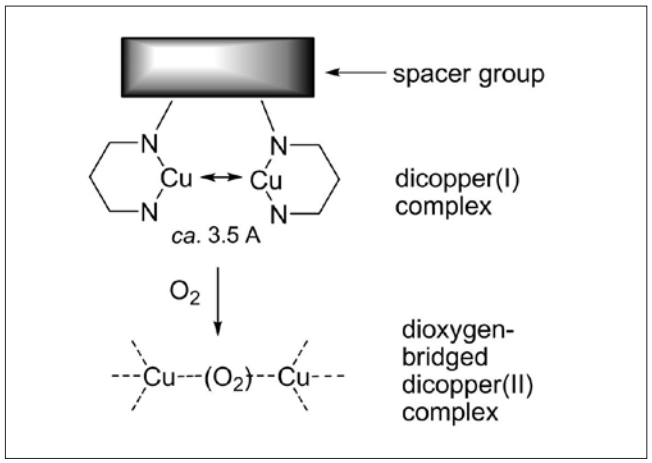


FIGURE 1: Design objectives for biomimetic tyrosinase models.

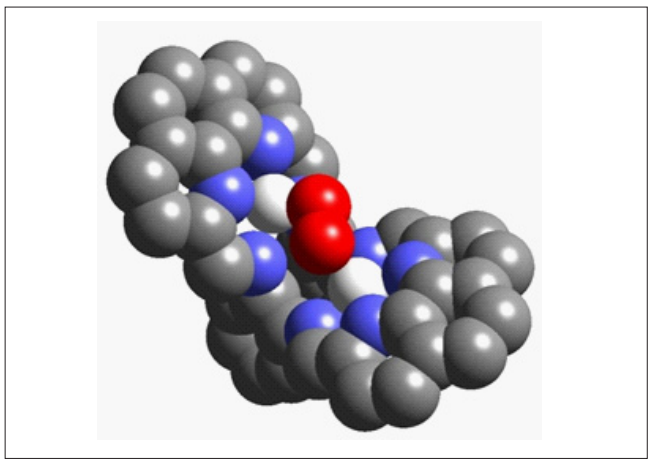
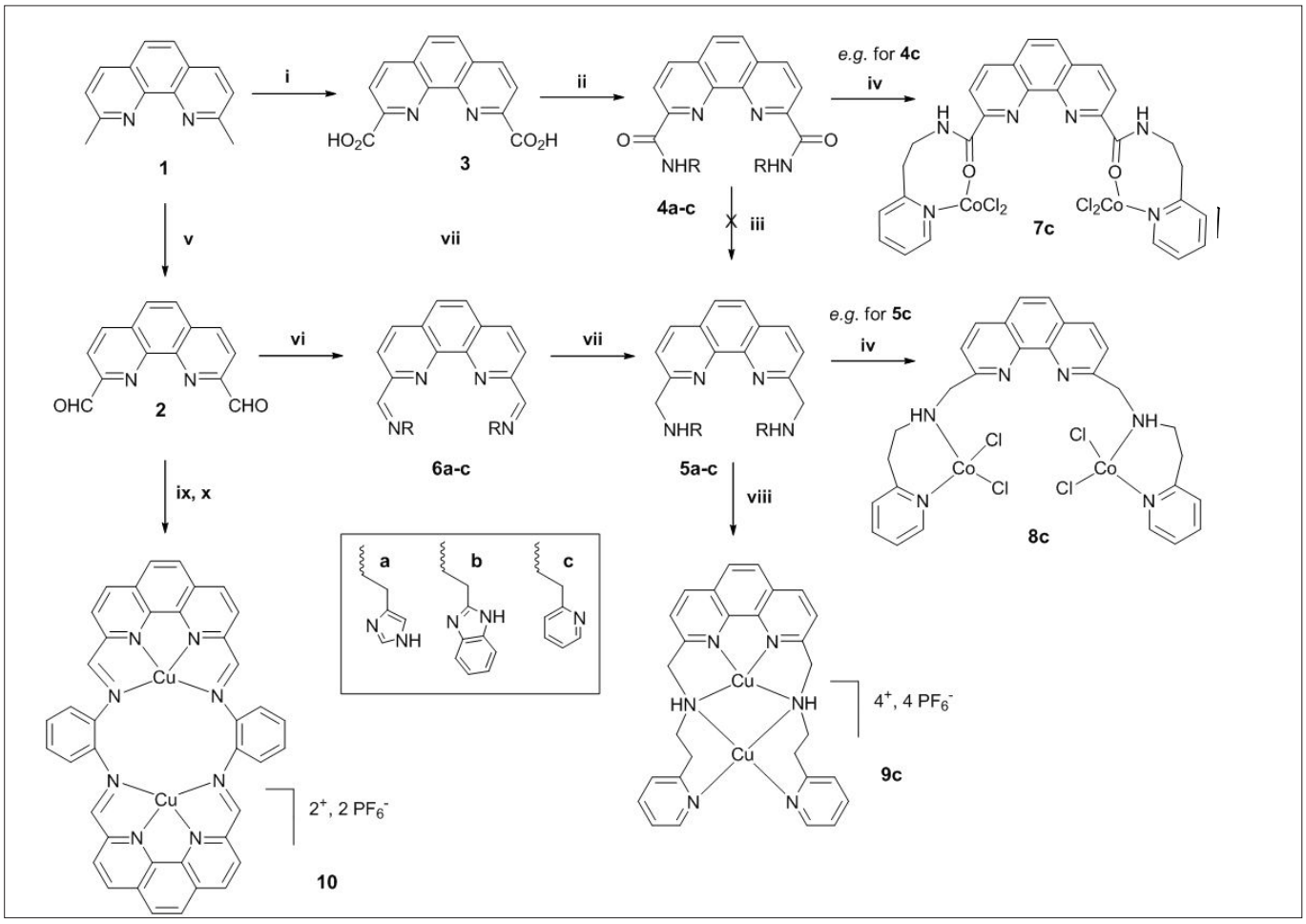


FIGURE 2: Computer-modelled structure of the *trans*-μ-1,2-dioxygenated complex 10.



Reagents: (i) 80% HNO_3; (ii) RNH_2, CDI; (iii) $LiAlH_4$, THF; (iv) $CoCl_2 . 6H_2O$, DMF; (v) SeO_2, 1,4-dioxane; (vi) RNH_2, $CHCl_3$; (vii) $NaBH_4$, MeOH; (viii) $Cu(MeCN)_4PF_6$, DMF; (ix) 1,2-diaminobenzene, MeOH; and (x) $Cu(MeCN)_4PF_6$, DMF, N_2.

SCHEME 1: Synthesis of 1,10-phenanthroline-based ligands.

conversion and, generally, excellent recyclability (when fresh substrate, dimethylformamide and Et_3N were added to the residue from the initial reaction, and the mixture was stirred for 24 h).[10] Interestingly, Co(II) complexes have been observed to form metal-oxygen adducts,[16] and have been used to model biological processes.[17] With the exception of complex 9c, the Cu(II) complexes appeared to be polymeric, and their catalytic activity suggests that, in these cases at least, the copper ions are sufficiently close to permit dioxygen bridging and subsequent substrate binding.

While our research interests had, since the late 1980s, focused on synthetic and physical organic aspects of heterocyclic systems and challenges in asymmetric synthesis, our work on biomimetic models of the tyrosinase active site, coupled with a developing interaction with MINTEK, prompted expansion of our programme to include the development

of novel ligands designed to selectively chelate, and hence extract, strategically important metal ions from mixtures containing metal ion contaminants.

PGM-selective ligands and MIPs

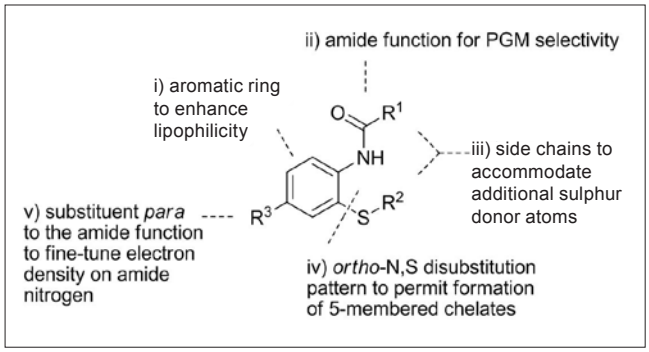
The use of the platinum complexes, cisplatin[18] and carboplatin,[19] as anti-cancer agents and the need for rescue agents to remove nephrotoxic platinum from the body[20] has highlighted the importance of platinum-selective ligands in medicine. At an industrial level, separation of the valuable PGMs from base metals, such as iron, copper, nickel and cobalt,[21] is typically achieved by solvent extraction, using PGM-selective ligands. Our research has included the synthesis of novel platinum-selective ligands; the development of platinum-selective MIPs; and evaluation of their PGM extraction potential. The ligands were designed to incorporate the features illustrated in Figure 3, namely (i) an aromatic ring to increase lipophilicity; (ii) an amide function for platinum and palladium selectivity; (iii) additional sulphur donors for multidentate coordination with the metal centre; (iv) S- and N-donor atoms for metal chelation; and (v) substituents (R^1 and R^3) to fine-tune N-donor capacity.[22,23]

The preparation of polydentate ligands incorporating these features is outlined in Schemes 2 and 3.[22,23] Thus, the bidentate and tridentate ligands 12 and 13 were obtained from the anilines 11 via the corresponding benzothiazole intermediates, while access to the tetradentate ligands 16 was achieved by the use of disulphide linkages as a protection strategy. The structure and size distribution of the polymeric intermediates represented by structure 15 were not material factors, as reductive cleavage of *all* the disulphide links afforded the desired tetradentate ligands 16 as the sole monomeric unit in each case.

Preliminary solvent extraction studies[24] using some of these and other related ligands indicated, in general, significant selectivity for palladium(II) over copper(II), nickel(II) and cobalt(II) and, in subsequent studies,[25] attention was given to the application of MIP technology in the construction of PGM-selective MIPs (Scheme 4).

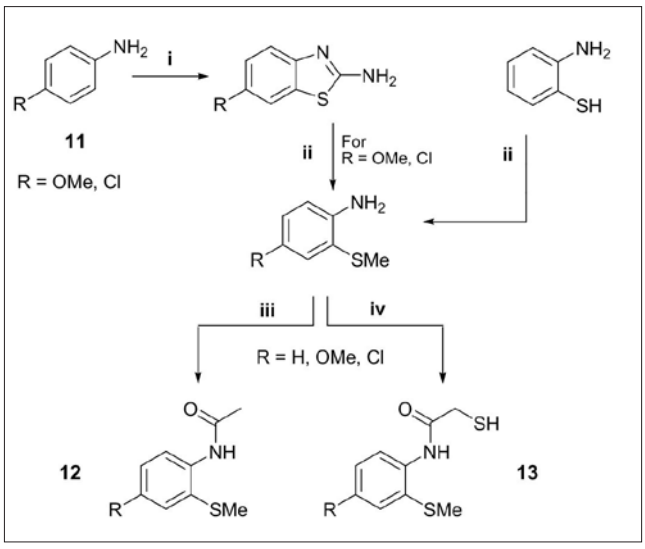
Reaction of ligand 17 with 1,2-dibromoethane afforded the novel diallylated system 18 as the functional monomer (Scheme 4) for construction of a platinum-selective MIP. Rosatzin et al.[26] explored the use of MIPs to separate calcium(II) from magnesium(II) and alkali metal ions, and our preparation of platinum-selective MIP 20 involved the following five steps[26]:

(I) *Mixing* solutions of the functional monomer with a print molecule (K_2PtCl_4) to afford the corresponding platinum(II) complex as the template.
(II) *Co-polymerisation* of the platinum(II) complex with the cross-linking agent, ethylene glycol dimethyl acrylate, in the presence of the initiator, azoisobutyronitrile.
(III) *Washing* the crude co-polymer to remove unreacted functional monomer.
(IV) *Grinding* the dried co-polymer to obtain granules.
(V) *Leaching* the print molecule (K_2PtCl_4) from the co-polymer granules to afford the MIP.



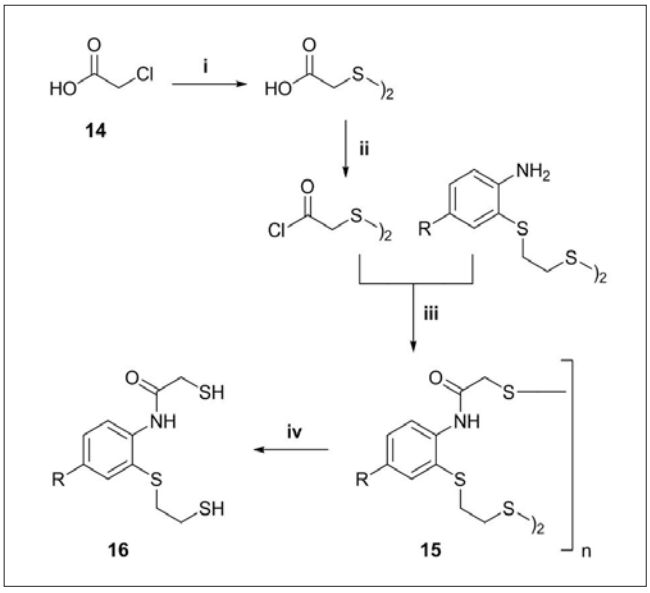
Sources: Hagemann and Kaye[22,23]

FIGURE 3: Design criteria for the polydentate, platinum group metal selective ligands.



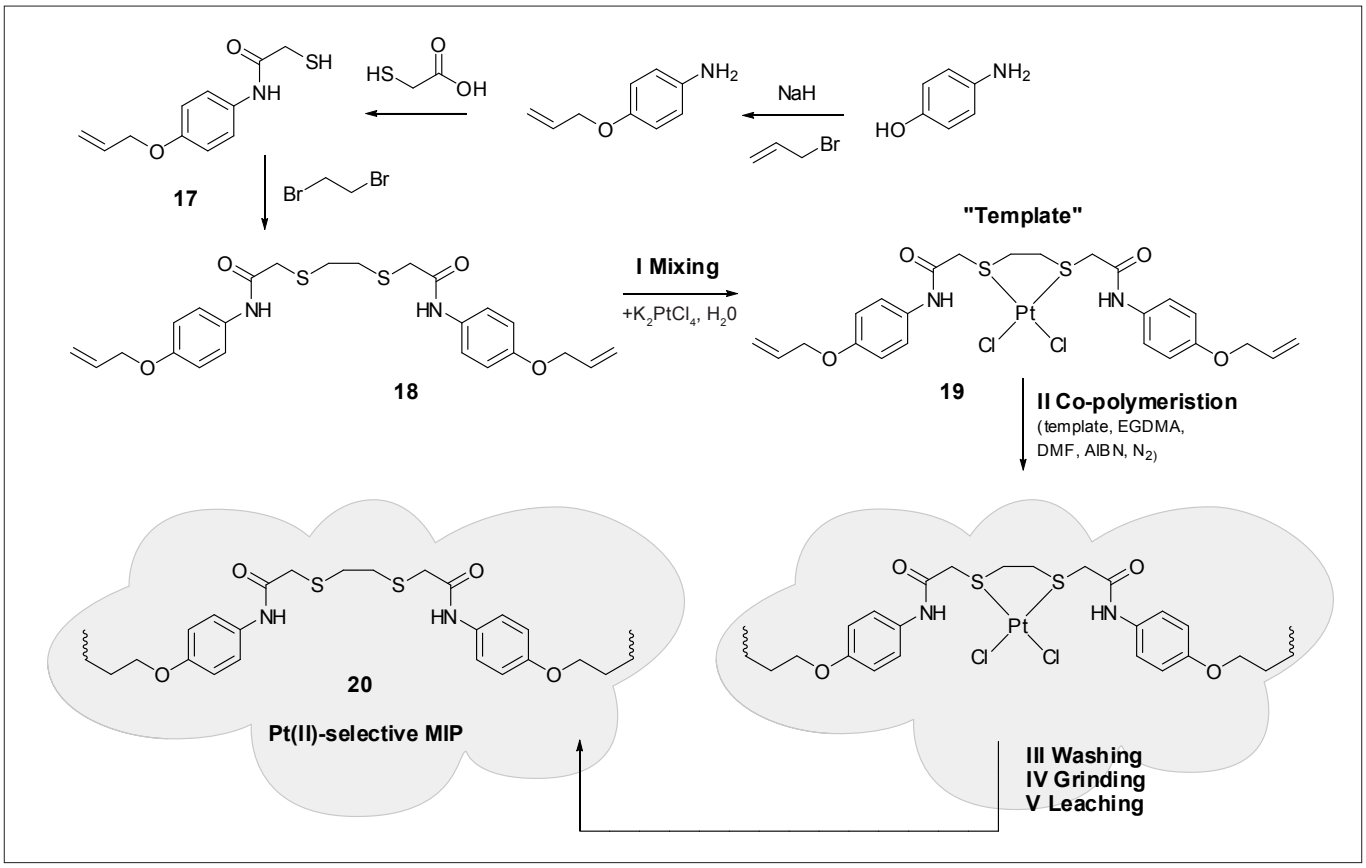
Reagents: (i) NaNCS or NH_4NCS, Br_2, AcOH; (ii) KOH, MeI; (iii) Ac_2O; and (iv) $HSCH_2CO_2H$, N_2.

SCHEME 2: Synthesis of bidentate and tridentate platinum group metal selective ligands.



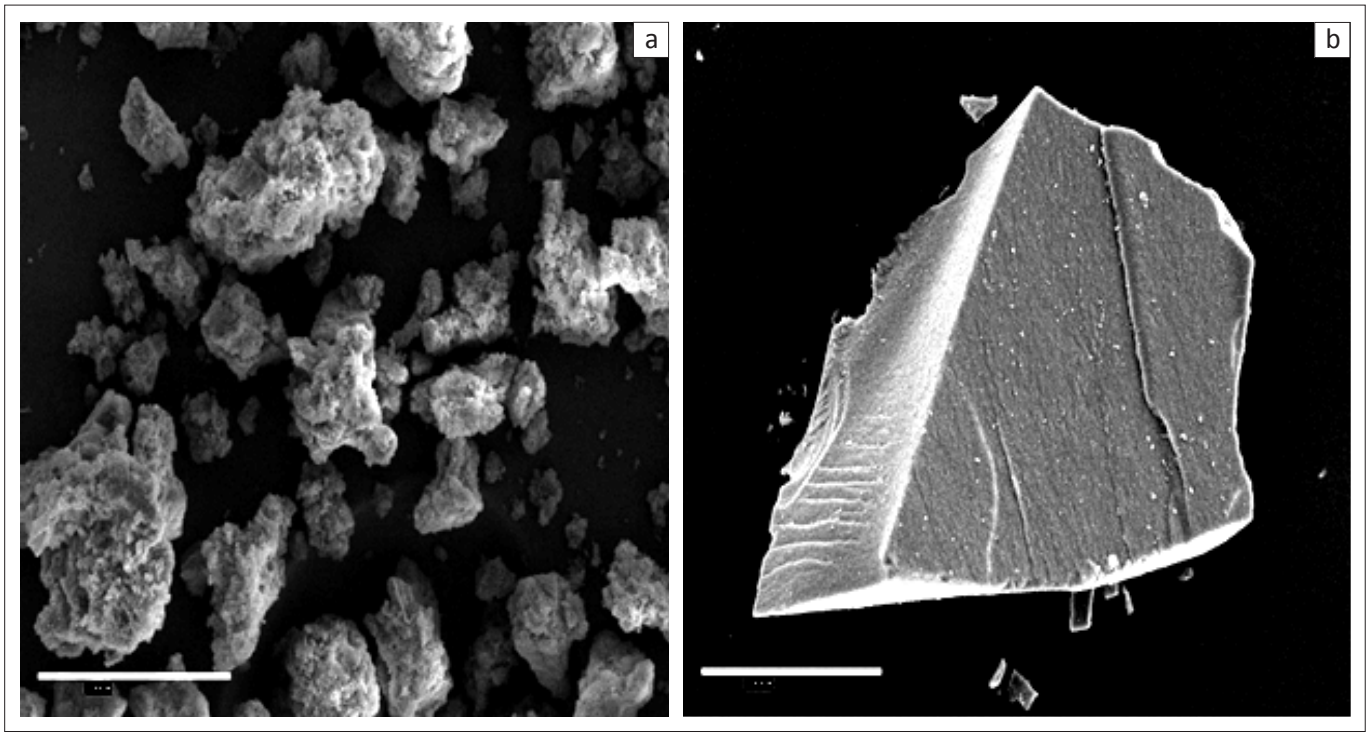
Reagents: (i) $Na_2S_2O_3$, Na_2CO_3, I_2; (ii) $SOCl_2$; (iii) Et_3N; and (iv) Ph_3P, H_2O-MeOH.

SCHEME 3: Synthesis of tetradentate platinum group metal selective ligands.



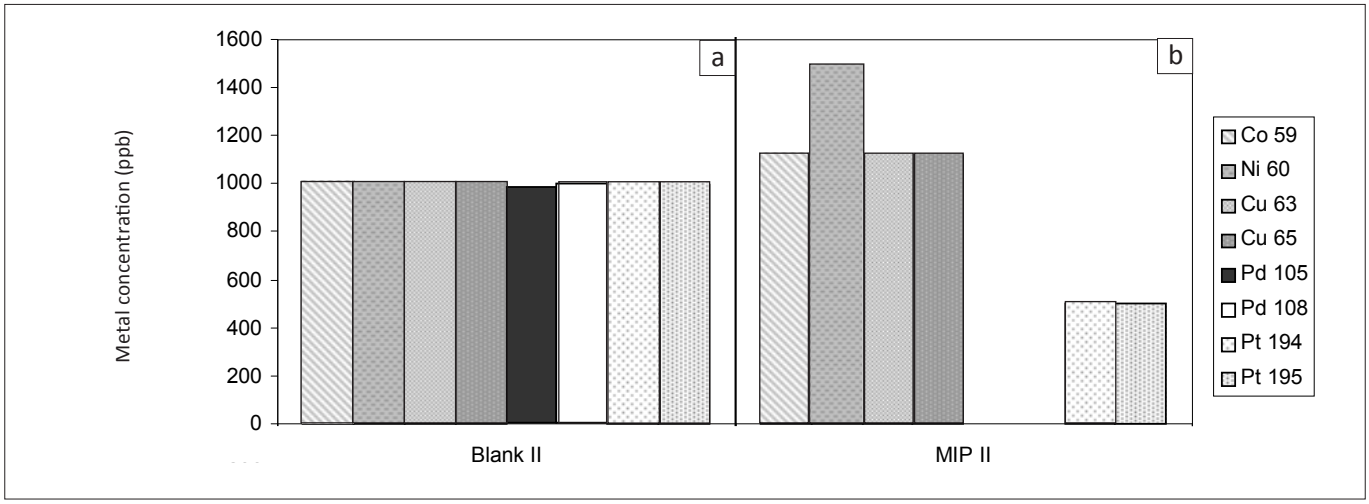
EGDMA, ethylene glycol dimethyl acrylate; DMF, dimethylformamide; AIBN, azoisobutyronitrile.

SCHEME 4: Synthesis of a platinum group metal selective molecular imprinted polymer (MIP).



Source: Kaye et al.[27]

FIGURE 4: Scanning electron micrographs of the polymer particles: (a) molecular imprinted polymer II granules; and (b) blank co-polymer granules.



Source: Kaye et al.[27]
With the use of molecular imprinted polymer II, the residual Pd(II) concentrations could not be detected.

FIGURE 5: Inductively coupled plasma mass spectrometry data showing the metal ions present in the metal ion solution after passage through: a) the reference polymer blank II and b) molecular imprinted polymer (MIP) II.

In the particular case illustrated in Scheme 4, the grinding step (IV) was not necessary as MIP 20 (MIP I) was precipitated in granular form. A second MIP (II) was prepared using the allylated ligand 17 as the functional monomer. Blank co-polymers were prepared similarly using the functional monomers but excluding the print molecule in each case. Scanning electron micrographs clearly reveal the morphological differences between MIP II and the corresponding blank (Figure 4).[27]

Elution of a solution containing Co(II), Cu(II), Ni(II), Pd(II) and Pt(II) ions in 2% aqueous HCl through granules of MIP II in a semi-microscale 'column' resulted in complete removal of Pd(II) and partial removal of Pt(II) (Figure 5); the corresponding blank co-polymer exhibited no selectivity for either Pd(II) or Pt(II). Under these conditions, however, MIP I (20) exhibited significantly less selectivity for either Pd(II) or Pt(II) than MIP II.[27]

Silver-selective ligands

Silver(I), a soft-metal centre, is capable of forming linear or tetrahedral complexes with N,S and N,O donor atom combinations. A range of potential silver(I)-selective ligands, such as compounds 21 and 22, which meet the design criteria identified in Figure 6 were prepared using both conventional heating and microwave-assisted methods as illustrated in Scheme 5.[28] The latter provided significant improvements in reaction time and yield. Ligand 22, for example, was obtained in 66% yield after boiling the reaction mixture under reflux for 48 h, whereas the product was formed in comparable yield under microwave-assisted conditions in 4.5 min.

Metal extraction studies of solutions containing copper(II), lead(II) and silver(I) ions revealed that all of the synthesised ligands exhibited some selectivity for silver over the base metals.[28] Ligand 21, for example, was found to extract

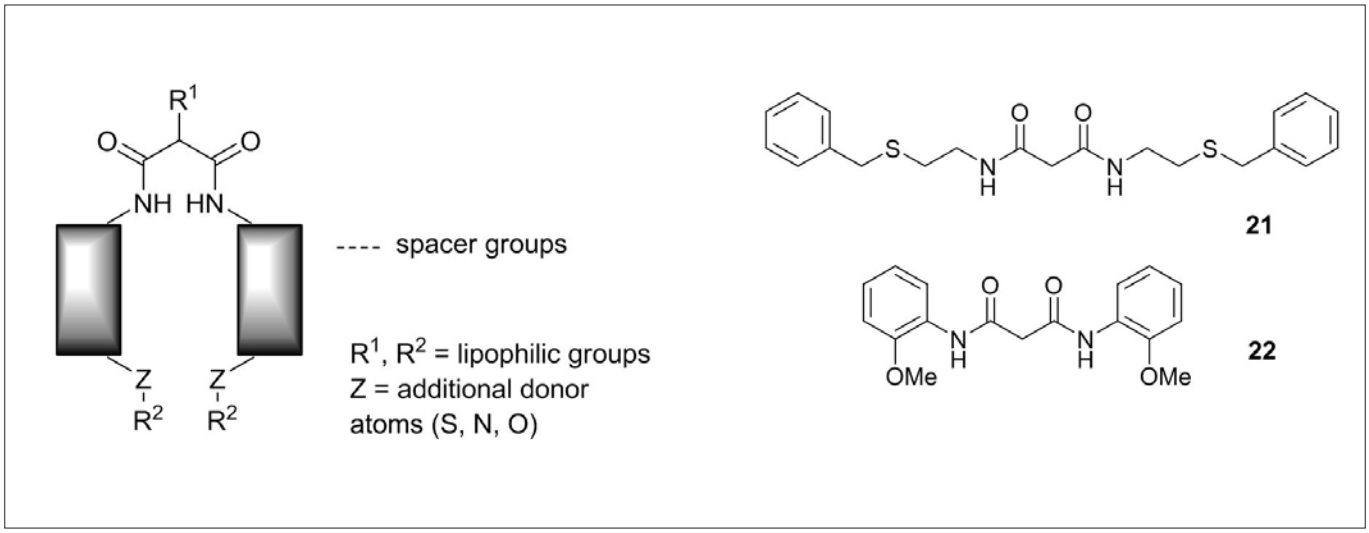
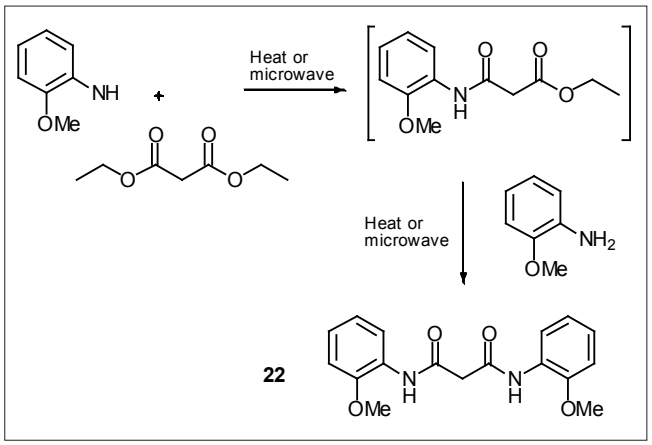


FIGURE 6: Design features and examples of silver(I)-selective ligands.



SCHEME 5: Synthesis of the silver(I)-selective ligand 22.

silver(I) with remarkably high extraction efficiency (97%) and selectivity as determined by inductively coupled plasma mass spectrometry (ICP-MS) analysis of the residual metal ions in the aqueous phase following extraction (Figure 7). Computer modelling, using the Cerius2 software package,[13] indicated a flattened tetrahedral (almost square planar) coordination of the two sulphur and two nitrogen donor atoms to the silver(I) cation. Interestingly, Modder et al.[29] have reported bis(thienyl ketimine) silver(I) complexes exhibiting similar coordination geometry.

Nickel-selective MIPs

Although various nickel-complexing agents had been reported previously,[30] industrial extraction of nickel had yet to be satisfactorily achieved.[31] Attention was therefore given to developing novel and effective nickel-selective ligands, which exhibited high nickel-stripping efficiency and were stable at the low pH values that characterise particular ore-streams (Green B, personal communication, date unknown), cost-effective to synthesise and selective for nickel(II) in the presence of iron(III).

Various ligands that contain nitrogen donors (especially pyridyl) and that are capable of forming five-membered chelates, are known to form stable, four-coordinate nickel(II) complexes.[30] These factors were taken into account and nickel(II)-selective bidentate ligands were designed to contain: (1) pyridyl and amino nitrogen donors, located to permit the formation of five-membered metal chelates; (2) substituents to fine-tune donor capacity and steric demand; and (3) a vinyl group for co-polymerisation to generate MIPs (Figure 8). The ligands 25a-g, which incorporate these features, were obtained following the general synthetic pathway outlined in Scheme 6.

The preparation of the MIPs containing nickel(II)-selective cavities involved the typical five phases, which have been described above and which are illustrated for this series in Scheme 7. In the *mixing* (or pre-arrangement) step, solutions of the nickel(II) salts (the print species) with two equivalents of each of the bidentate ligands 25a-g (the functional monomers) in methanol (the porogenic solvent) were stirred overnight – the colour of the solutions typically changed from light-yellow to light-green.[32] MIPs were prepared using each of the seven ligands 25a-g and then subjected to preliminary evaluation of their relative extraction efficiencies, equilibration times, and mesh-size and counter-ion effects.[31]

Residual nickel(II) and iron(III) concentrations following extraction were determined initially by atomic absorption spectroscopy. Four MIPs were selected, based on these preliminary studies, for final evaluation, using ICP-MS analysis. The results, illustrated in Figure 9, clearly demonstrate preferential extraction of nickel(II) in the presence of iron(III).

Conclusions

Several series of novel ligand systems were thus successfully developed for: (1) the formation of metal complexes as

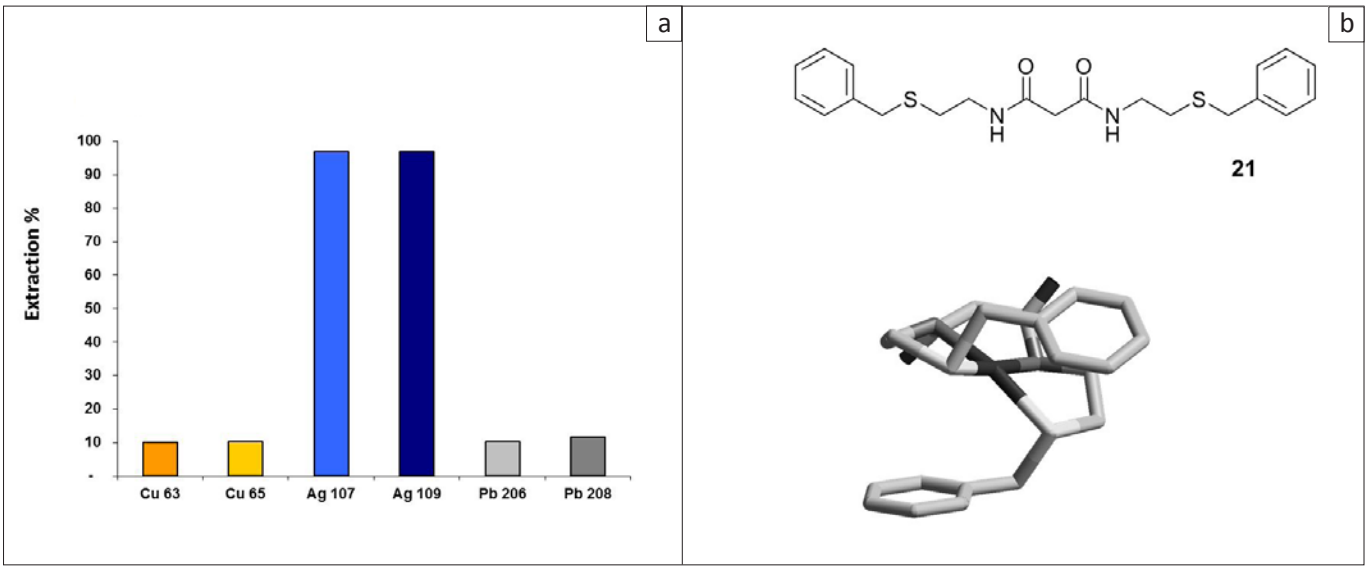


FIGURE 7: (a) Metal extraction efficiencies observed using ligand 21 and (b) the computer-modelled structure of the corresponding silver(I) complex.

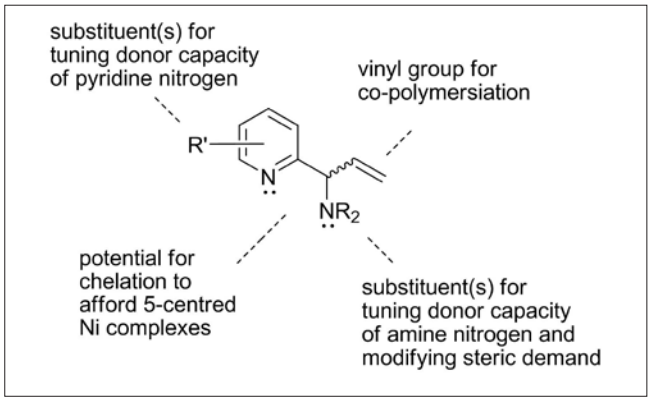
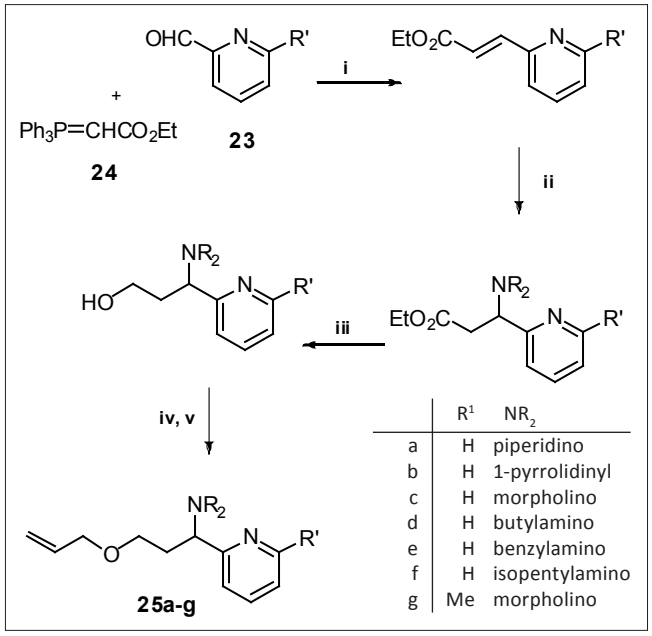
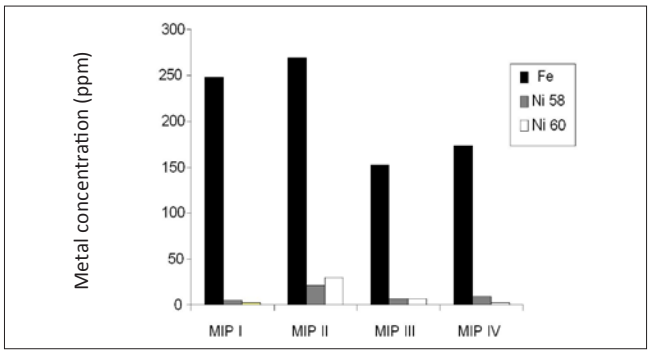


FIGURE 8: Design features of proposed nickel-selective ligands.



Reagents and conditions: (i) CH_2Cl_2, reflux; (ii) R_2NH, THF, reflux; (iii) $LiAlH_4$, THF, N_2; (iv) NaH, THF, N_2; and (v) CH_2=$CHCH_2Br$.

SCHEME 6: Synthesis of nickel-selective ligands.



MIP I, Ni(II) tetrafluoroborate–25c; MIP II, Ni(II) acetate–25a; MIP III, Ni(II) acetate–25g; MIP IV, Ni(II) chloride–25c.

FIGURE 9: Inductively coupled plasma mass spectrometry data for analysis of residual metal ion concentrations following molecular imprinted polymer (MIP) extraction (using fine particles) of standard 300 ppm solutions containing Ni(II) and Fe(III) ions.

biomimetic models of the tyrosinase active site; and (2) for the selective extraction of silver, nickel or PGM metals from mixtures containing contaminating metals. The latter ligands have exhibited encouraging selectivity, amply rewarding the efforts of the postgraduate students who worked in this area of our research programme. Future developments could include the use of electrospinning techniques to produce MIP-derived nanofibres, thus increasing access to ligand sites and enhancing extraction efficiency.

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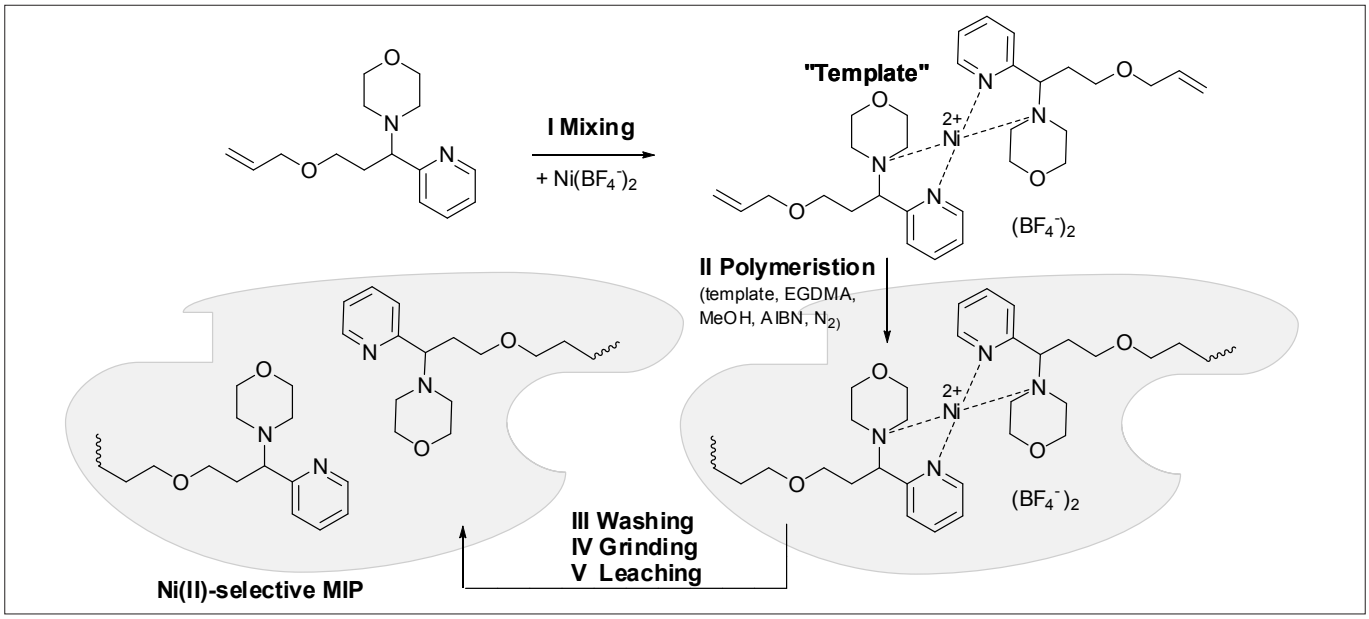

EGDMA, ethylene glycol dimethyl acrylate; AIBN, azoisobutyronitrile.

SCHEME 7: Synthesis of a Ni-selective molecular imprinted polymer, using compound 25c.

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