Electron Transfer Reactivity, Synthesis, Surface Chemistry and Liquid-Membrane Transport of Sarcophagine-Type Poly-Aza Cage Complexes

A Thesis

Submitted for the Degree of

Doctor of Philosophy

of the

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by

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Canberra, ACT

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Declaration

The work presented in this thesis is
the original work of the candidate,
except where otherwise indicated.

Glen William Walker

21 February 1997

Acknowledgments

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Contents

Appendix A

Appendix B

Abbreviations

General

anal.	analysis
AR	analytical reagent
calcd	calculated
CMC	critical micelle concentration
CoN_6	complex with cobalt bound to six nitrogen donors
L	litre
M	moles per dm^3
mmol	millimole
mol	mole
mL	millilitre
W	watt
λ	wavelength
κ	conductivity
ϕ	trigonal twist angle

Spectroscopy

A_l (A_r)	absorbance of left (right) circularly polarised light
AAS	atomic absorption spectroscopy
br	broad
CD	circular dichroism
c	concentration
deg	degrees
ΔA_λ	differential absorbance of circularly polarised light
$\Delta\varepsilon_\lambda$	differential molar absorptivity of circularly polarised light
d	doublet
e. e.	enantiomeric excess
HETCOR	heteronuclear correlation

l	path length
$[M]_{\lambda}^{T}$	molecular rotation
m	multiplet
NIR	near infra-red
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
ORD	optical rotatory dispersion
ppm	parts per million
quat	quaternary
s	singlet
sh	shoulder
t	triplet
UV	ultra-violet
vis	visible
α_{λ}^{obs}	measured optical rotation
$[\alpha]_{\lambda}^{T}$	specific rotation
ε	molar absorptivity
ε_l (ε_r)	molar absorptivity for left (right) circularly polarised light
♦	internal standard

Kinetics

K_{12}	equilibrium constant for an electron transfer cross reaction
k_{12}^{calc}	calculated second-order cross-reaction rate constant
k_{12}^{obs}	measured second-order cross-reaction rate constant
k^{obs}	measured pseudo first-order rate constant
k_{11}, k_{22}	second order electron self-exchange rate constants
Z	collision frequency of uncharged molecules in solution
κ_{11}, κ_{22}	electronic transmission factor in electron self-exchange reaction
κ_{12}	electronic transmission factor in electron-transfer cross-reaction

Electrochemistry

ΔE_p	peak-to-peak separation
$E_p^a\left(E_p^c\right)$	anodic (cathodic) peak potential
$E_{1/2}$	half-wave potential
$E_{1/2}^{obs}\left(E_{1/2}^{calc}\right)$	measured (calculated) half-wave potential
F	Faraday
$i_p^a\left(i_p^c\right)$	peak anodic (cathodic) current
K	equilibrium constant for the Hammett standard reaction
mV	10^{-3} volts
n	number of electrons
SCE	saturated calomel electrode
SHE	standard hydrogen electrode
ρ	Hammett reaction constant
σ_E	electrochemical polar substituent constant
σ_I	inductive polar substituent constant

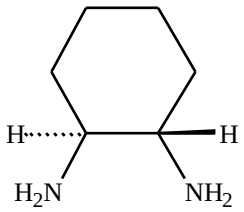
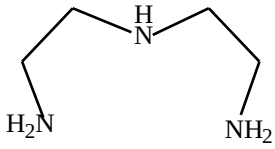
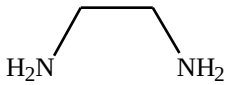
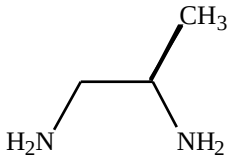
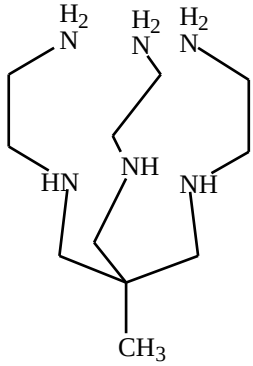
Parasites

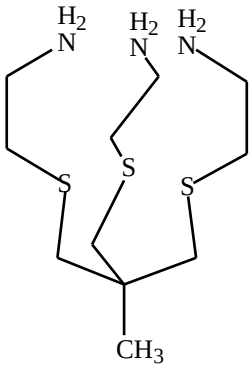
H. diminuta	*Hymenolepis diminuta*
T. vaginalis	*Trichomonas vaginalis*
T. foetus	*Tritrichomonas foetus*

Transport and Extraction

J_{av}	average flux
K_{ex}, ($K_{ex}^{'}$)	equilibrium constant for two-phase liquid-liquid extraction of $[CoL_6]^{3+}$ from H_2O (aqueous NH_4Cl)
K_{ex}^{Δ}, (K_{ex}^{Λ})	equilibrium constant for two-phase liquid-liquid extraction of Δ-$[CoL_6]^{3+}$ (Λ-$[CoL_6]^{3+}$) from H_2O

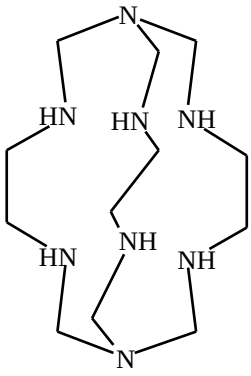
Ligands

Structure	**Trivial Name (Systematic Name)**
	chxn (*trans*-1,2-cyclohexanediamine)
	dien (Bis(2-aminoethyl)amine)
	en (1,2-ethanediamine)
	pn (1,2-propanediamine)
	sen (4,4',4''-ethylidynetris(3-azabutan-1-amine))



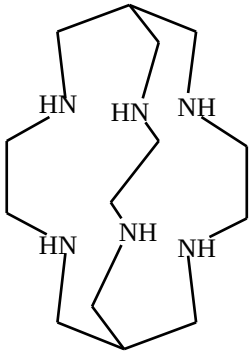
ten

(4,4',4''-ethylidynetris(3-thiabutan-1-amine))



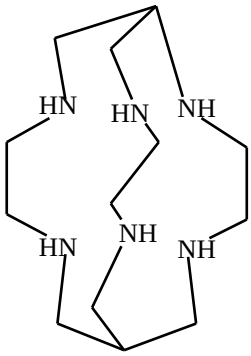
(di-AZA)-sar

(1,3,6,8,10,13,16,19-octaazabicyclo[6.6.6]icosane)



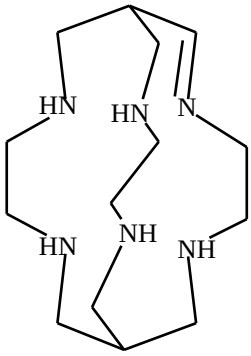
sar

(3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane)



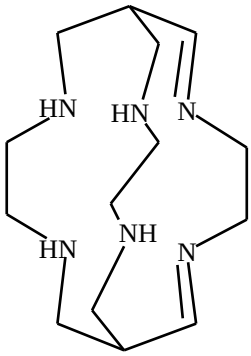
absar

(3,6,10,13,15,18-hexaazabicyclo[6.6.6]nonadecane)



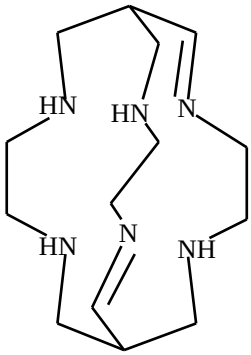
sar-2-ene

(3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosa-2-ene)



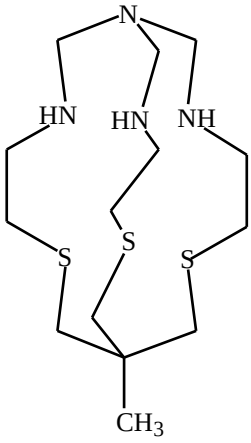
sar-2,6-diene

(3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosa-2,6-diene)



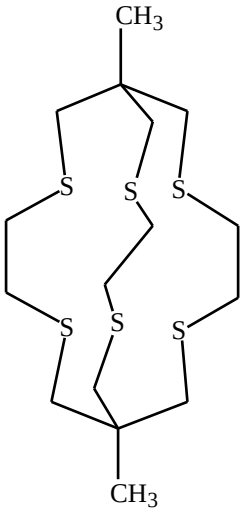
sar-2,9-diene

(3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosa-2,9-diene)



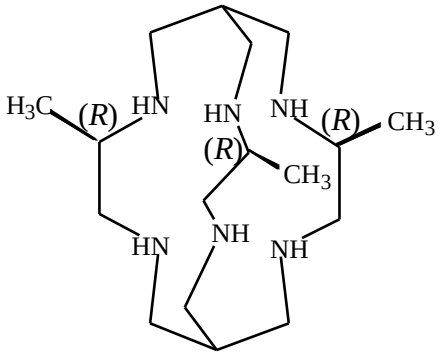
(AZA, CH_3)-N_3S_3-sar

(8-methyl-1,3,13,16-tetraaza-6,10,19-trithiabicyclo[6.6.6]icosane)



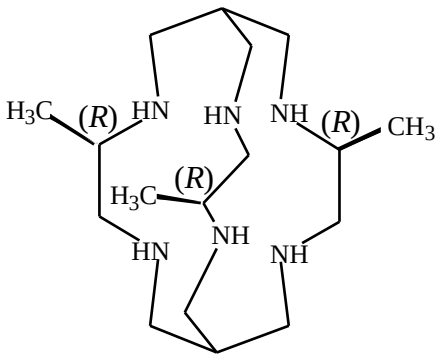
$(CH_3)_2$-S_6-sar

(1,8-dimethyl-3,6,10,13,16,19-hexathiabicyclo[6.6.6]icosane)



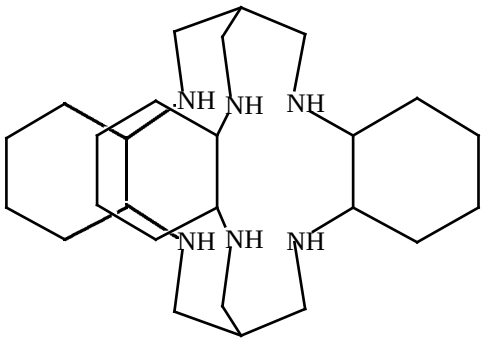
(4*R*,12*R*,17*R*)-pnsar

(4*R*,12*R*,17*R*)trimethyl-3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane



(4*R*,11*R*,17*R*)-pnsar

(4*R*,11*R*,17*R*)trimethyl-3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane

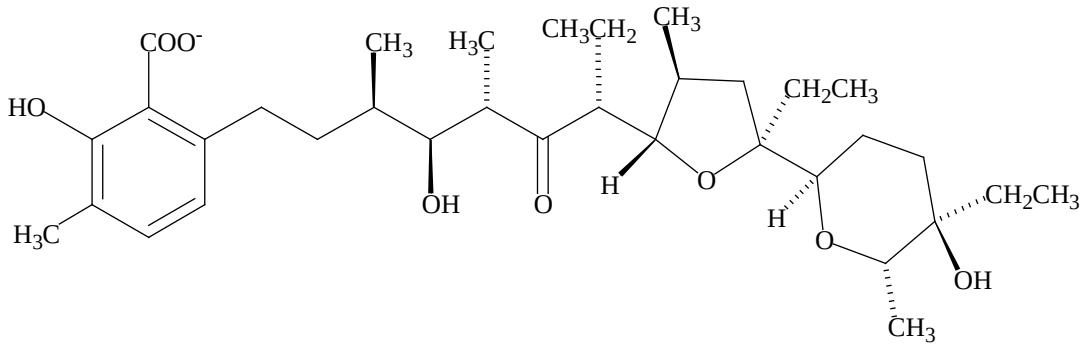


char

(3,10,14,21,24,31-hexaazapentacyclo-[10.10.10.$0^{4,9}$0.$^{15,20}0^{25,30}$]dotriacontane)

LAS$^-$

(conjugate base anion of lasalocid A)



Abstract

The kinetics for outer-sphere electron transfer between a series of cobalt(II) poly-aza cage ligand complexes and the iron(III) sarcophagine-type hexa-aza cage complex, $[Fe(sar)]^{3+}$ (sar = 3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane), in aqueous solution have been investigated and the Marcus correlation is used to deduce the electron self-exchange rate constant for the $[Fe(sar)]^{3+/2+}$ couple from these cross-reactions. The deduced electron self-exchange rate constant is in relatively good agreement with the experimentally determined rate constant ($k_{ex}^{calc} = 4 \times 10^5$ M^{-1} s^{-1}; $k_{ex}^{obs} = 8 \times 10^5$ M^{-1} s^{-1}). The successful application of the Marcus correlation to the electron transfer reactions of the Fe cage complex is consistent with the trend for the Co, Mn, Ni and Ru cage complexes which all follow the pattern of outer-sphere electron transfer reactivity expected from the Marcus-Hush formalism. A comparison of predictions based on the Marcus correlation with the experimentally determined kinetics of an extended series of cross reactions involving cobalt cage complexes with low-spin–high-spin cobalt(III)/(II) couples shows that electron transfer reactions involving large spin changes at the metal centre are not necessarily anomalous in the context of the adiabatic Marcus-Hush formalism. The results of this study also show that for suitable systems, the Marcus correlation can be used to reliably calculate the rates of outer-sphere electron transfer cross-reactions, with reaction free-energy changes spanning the range -6 to -41 kJ mol^{-1} and many different combinations of initial electronic configurations. Together, these results provide a coherent and internally consistent set of experimental data in support of the Marcus-Hush formalism for outer-sphere electron transfer. The results with the caged metal-ion systems also highlight the special nature of the mechanism of electron transfer in reactions of metal-aqua ions.

A new range of symmetrically disubstituted hexa-aza sarcophagine-type cage ligand complexes are prepared in this study by the base-catalysed co-condensation of formaldehyde and α-methylene aliphatic aldehydes with cobalt(III) tris(1,2-diamine) precursors in acetonitrile solution. Encapsulation reactions based on the condensation of the weak carbon di-acids propanal and decanal with formaldehyde and the cobalt(III)

tris(1,2-diamine) precursors, $[Co(en)_3]^{3+}$ (en = 1,2-ethanediamine) and Δ-*lel*$_3$-[Co((*R*, *R*)-chxn)$_3$]$^{3+}$ (chxn = 1,2-cyclohexanediamine), yield unsaturated cobalt(III) cage complexes with an *endo*-cyclic imine function in each cap. The Co^{III}-coordinated *endo*-cyclic imine units of the cage ligands are reactive electrophiles that are readily reduced by the BH_4^- ion to give the corresponding symmetrically di-substituted hexaamine macrobicyclic cage ligands. The nitromethane carbanion is also shown to add at the *endo*-cyclic imine function to yield a novel nitromethylated cage ligand complex. The latter reaction introduces a new method for the regioselective functionalisation of cage ligands at sites removed from the more commonly substituted bridgehead positions. The capping of cobalt(III) tris(1,2-diamine)-type complexes with weak CH-acids developed in this study introduces a new and more direct route to symmetrically di-substituted cage ligand complexes.

A new range of cobalt(III) surfactant cage complexes, with linear octyl, dodecyl and hexadecyl hydrocarbon chains built directly into the bridgehead structure of the cage ligand, have been prepared by the base catalysed co-condensation of formaldehyde and long chain aliphatic aldehydes with the tripodal cobalt(III) hexaamine complex, $[Co(sen)]^{3+}$ (sen = 4,4',4''-ethylidynetris(3-azabutan-1-amine)), in acetonitrile solution. Chiral surfactant cage complexes are obtained by capping reactions beginning with the optically pure Λ-$[Co(sen)]^{3+}$ precursor complex. The cobalt(III) cage complexes with octyl to hexadecyl substituents are surface active and reduce the surface tension of water to levels approaching those of organic solvents. The dodecyl substituted cage complex forms micelles in aqueous solution when the concentration of cage complex is $> 1 \times 10^{-3}$ mol dm^{-3} at 25 °C. The cobalt(III) cage head-group of these surfactants undergoes an electrochemically reversible one-electron reduction to the corresponding cobalt(II) cage complex. The reduction potential of the surfactant head group can be tuned to more positive potentials by replacing the bridgehead hydrocarbon chain substituent with an ether linked hydrocarbon chain. The cobalt(III) surfactant-cage complexes are biologically active and are lethal to the tapeworm *Hymenolepis diminuta*, and the vaginal parasites, *Trichomonas vaginalis* and *Tritrichomonas foetus.* The surfactant cage complexes also cause lysis in red-blood cell membranes at

concentrations as low 10^{-5} mol dm^{-3}. Their biological activity is linked to the high head-group charge (3+) and size which cause distortions in biological membranes when the membrane is treated with these molecules. The combination of the chemically reversible outer-sphere redox properties of the cobalt cage head-groups and the chirality of the head group introduces a new and possibly unique series of chiral surfactant coordination complexes which are also redox active.

The chiral carboxylic-acid ionophore, lasalocid A, has been used to promote the selective supramolecular transport and extraction of cobalt(III) hexa-aza cage cations and related tripodal cobalt(III) complexes. The conjugate base anion of lasalocid A forms stoichiometric outer-sphere complexes with the cobalt(III) cage and tripod complexes. These outer-sphere complexes are highly lipophilic and partition strongly from water into a chloroform phase. The extraction of the dissymmetric cobalt(III) complexes by the chiral polyether anion is enantioselective for many systems and results in the partial resolution of initially racemic complexes in the aqueous phase. A strong structural preference was demonstrated by the ionophore for symmetrically disubstituted cobalt(III) hexa-aza cage cations with a Δ-absolute configuration of the ligand about the metal-ion and an *R* configuration of the coordinated secondary amine N—H groups. The lasalocid A anion was also shown to promote the transport of the complexes, intact, across a chloroform bulk-liquid membrane against an NH_4^+ concentration gradient. The transport of the cobalt(III) complexes was also enantioselective and resulted in partial resolution of the initially racemic aqueous phase. The most efficiently transported enantiomer of each complex was also the most efficiently extracted isomer in all systems examined, consistent with a transport process limited by interfacial diffusion. The magnitude of the enantiomer separation obtained in some systems was sufficient to indicate that lasalocid A mediated extraction and transport may become a practical method for the resolution of particular types of kinetically-inert chiral metal-amine complexes.