Pure & Appl. Chem., Vol. 65, No. 3, pp. 521–526, 1993.
Printed in Great Britain.

Supramolecular transport of metal amine complexes through liquid membranes by the ionophore lasalocid A

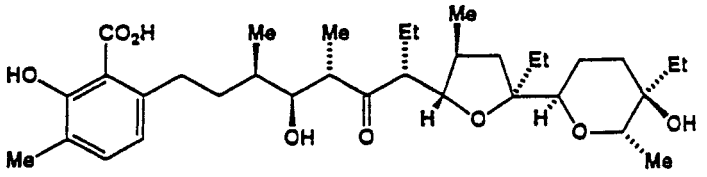
Peter S. K. Chia,[1] Leonard F. Lindoy,[2*] Glen W. Walker,[3] and Grover W. Everett[4]

[1]School of Chemistry, University of New South Wales, Kensington NSW, 2033, Australia. [2] Department of Chemistry and Biochemistry, James Cook University of North Queensland, Townsville, 4811, Australia. [3]Research School of Chemistry, Australian National University, Canberra ACT 2601, Australia. [4]Department of Chemistry, University of Kansas, Lawrence, Kansas 66045, USA.

Abstract - The naturally occurring antibiotic lasalocid A acts as an ionophore for the extraction and membrane (chloroform) transport of a series of sarcophagine cobalt(III) complexes. The process has been shown to be enantioselective resulting in the partial resolution of selected cage complexes. Factors underlying the observed behaviour are discussed.

INTRODUCTION

Carrier mediated transport of metal ions through bulk liquid membranes has been extensively studied in a range of synthetic (including biomimetic) systems (ref. 1). Lipophilic derivatives of crown ethers, cryptands, macrocyclic amines and some naturally occurring polyether antibiotics have all been used as ionophores in such studies (ref. 2). Macrocycles of these types have well established host-guest properties which include the ability to form hydrogen bonds with small organic substrates (ref. 3). The resulting supramolecular assembly can facilitate the transport of species across otherwise impermeable membranes (ref. 4). An elegant example of such behaviour is the enantioselective transport of asymmetric amines by chiral crown ethers (ref. 5).



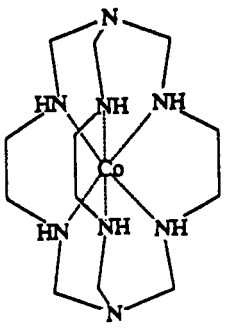
1. Lasalocid A

The polyether antibiotic, lasalocid A **1**, is produced stereospecifically by bacteria and is a versatile ionophore; for example, it mediates the transport of simple amines across lipid bilayer membranes (ref. 6). Recently, we described one of the first examples of the supramolecular transport of co-ordination compounds across bulk liquid membranes (ref. 7). In this study we demonstrated that inert metal (III) and (IV) ammine complexes can be efficiently transported and extracted by lasalocid A which was also used as the ionophore for the enantioselective transport of metal ammine and amine complexes across a chloroform membrane. It is believed that the lasalocid anions form hydrophobic host guest adducts with the cationic coordination compounds in which charge neutralization and hydrogen bonding plays an analogous role to that found in the adduct between three molecules of (deprotonated) (**1**) and $[Co(NH_3)_6]^{3+}$ in the solid state (ref. 8). Such a hydrophobic assembly is able to be transferred across the

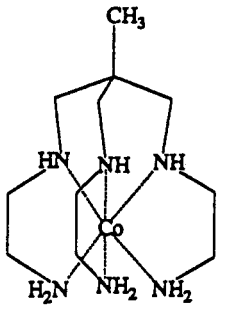
membrane to an aqueous receiving phase interface where the adduct dissociates and the intact metal complex partitions into the aqueous phase. Similar behaviour has been proposed for the membrane transport of labile cobalt(II) and nickel(II) ammine complexes by proton-ionizable crown ether ionophores (ref. 9).

The above transport exhibits a parallel with the iron concentrating mechanism proposed for *E. coli* (ref. 10); the latter involves the active transport of an iron(III)-siderophore complex across the outer cell membrane using a specific transport protein (ref. 11). The interaction between the siderophore complex and the transport protein has been shown to be stereoselective in some instances (ref. 12).

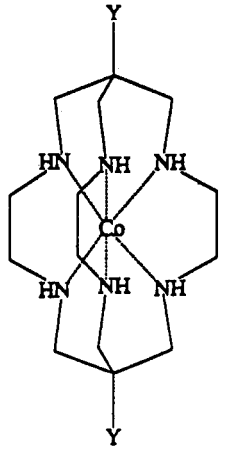
In our earlier study the cage complex, Δ-$[Co(sep)]^{3+}$ (see **2**), was shown to be extracted and transported preferentially by the lasalocid A anion (ref. 7). In the present study the generality of this phenomenum was probed using the related tripodal complex **3** and the sarcophagine complexes **4-8**. The sarcophagine ligands make available a range of systems with a variety of apical substituents and the hydrogen bonding abilities of these systems are expected to vary significantly (ref. 13). In addition, these cobalt(III) complexes have well characterised chiro-optical properties and are extraordinarily resistant to racemisation (ref. 14) - both these characteristics have aided the use of these systems in the present investigation.



2. $[Co(sep)]^{3+}$



3. $[Co(sen)]^{3+}$



4, Y=H, $[Co(sar)]^{3+}$

5, Y=CH_3, $[Co((CH_3)_2\text{-sar})]^{3+}$

6, Y=NO_2, $[Co((NO_2)_2\text{-sar})]^{3+}$

7, Y=Cl, $[Co((Cl)_2\text{-sar})]^{3+}$

8, Y=NH_2, $[Co((NH_2)_2\text{-sar})]^{3+}$

EXPERIMENTAL

Compounds All complexes were prepared as their racemic chloride salts using literature methods (ref. 13). The $(NH_2)_2$-sar complex **8** was initially obtained as its dihydrochloride salt and then neutralized with 5% NaOH. All complexes gave satisfactory microanalyses (C, H, N) and their ^1H and ^{13}C nmr spectra were in accord with the corresponding published spectra. The sodium salt of **1** was obtained from the Aldrich Chemical Co.

Extraction experiments The partitioning of a metal complex from an aqueous phase (deionised water or 0.1 mol dm^{-3} NH_4Cl) into a chloroform phase containing Na.LAS was determined by gently shaking the two phases in sealed glass vials on a horizontally oscillating platform for 6 h at 25 °C. Experiments were performed in duplicate or triplicate. No extraction was observed for any of the system investigated in the absence of LAS^-.

Isolation of [Co(cage)](LAS)$_3$ adducts Stable adducts between lasalocid A anion and three cage complexes were obtained using the method described previously (refs.7 and 8). Microanalyses of the orange crystalline products in each case indicated a stoichiometry of one cage cation for every three lasalocid anions. Anal. Calcd for $[Co\{(NO_2)_2\text{-sar}\}](LAS)_3.1.5H_2O$: C, 62.48; H, 8.68; N, 5.03. Found: C, 62.55; H, 8.55; N, 5.05. Calcd for $[Co\{(Cl)_2\text{-sar}\}](LAS)_3$: C, 63.86; H, 8.73; N, 3.85. Found: C, 63.71; H, 8,78; N, 3.56. Calcd for $[Co(sar)](LAS)_3.H_2O$: C, 65.39; H, 9.13; N, 3.94. Found: C, 65.57; H, 9.14; N, 4.46. The

^{1}H nmr spectra of the adducts in $CDCl_3$ show peaks arising from both the lasalocid anions and the cage ligands with broadening of the latter being evident relative to the spectra of the free complexes in D_2O.

Transport experiment The lasalocid A mediated transport of the cobalt(III) cage complexes across a chloroform membrane is represented schematically in Fig. 1.
The average flux rates (J_{av}) for the transport of the cobalt(III) complexes across such a membrane were determined using a concentric cylinder cell of the type shown in Fig. 2; the design in based on one reported by Bartsch *et al.* (ref 9) and differs from the cell employed in our previous study (ref. 7). The volumes of the aqueous source and receiving phases were 10 mL and 30 mL, respectively, while the chloroform phase volume was 50 mL. The area of the receiving phase/membrane interface was 4.9 cm^2. The moles of complex passing across this unit area of interface in a 24 h period were used to calculate J_{av} for each system.

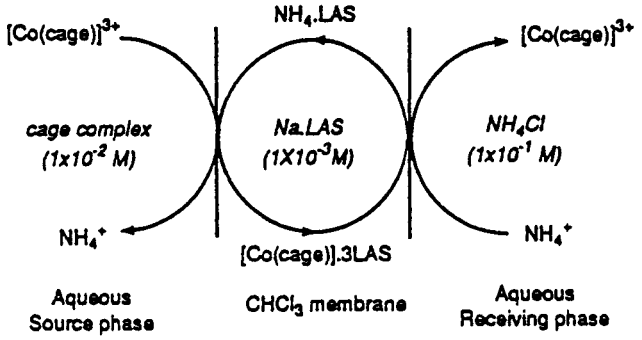


Fig. 1. Schematic illustration of a typical transport experiment.

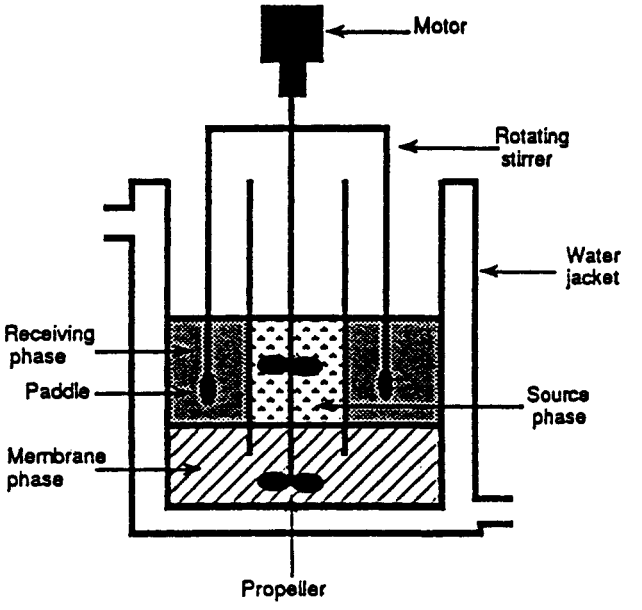


Fig. 2. The transport cell.

RESULTS AND DISCUSSION

Extraction of metal amine complexes The extraction of cobalt(III) cage complexes and an open chain analogue from aqueous solution into a chloroform phase containing the lasalocid A anion (LAS^-) is comparable for all systems (in the absence of ammonium chloride) (Table 1). The values for $[Co(NH_3)_6]Cl_3$ and $[Co(en)_3]Cl_3$ (en is 1,2-diaminoethane) are also similar. The uniform results are consistent with an extraction mechanism in which all of the available lasalocid anions are associated with the respective complexes to form 3:1 supramolecular adducts (the maximum expected extraction under the present conditions is 83%). The

TABLE 1. Extraction of cobalt(III) amine and ammine complexes from aqueous solution water or 0.1 mol dm^{-3} NH_4Cl solution into a chloroform phase containing lasalocid A[a]

Complex	% Extraction of complex 0.1 mol dm^{-3} NH_4Cl	water	Aqueous phase enantiomeric ratio (Λ/Δ)[b]
$[Co(NH_3)_6]Cl_3$	57	80	-
$[Co(en)_3]Cl_3$[c]	23	84	1.2 : 1
$[Co(sen)]Cl_3$	46	84	0[d]
$[Co(sep)]Cl_3$	69	80	1.5 : 1[e]
$[Co(sar)]Cl_3$	69	85	2.4 : 1
$[Co\{(CH_3)_2\text{-sar}\}]Cl_3$	70	79	1.4 : 1
$[Co\{(NH_2)_2\text{-sar}\}]Cl_3$	46	82	3.7 : 1
$[Co\{(NO_2)_2\text{-sar}\}]Cl_3$	82	82	2.7 : 1
$[Co\{(Cl)_2\text{-sar}\}]Cl_3$	85	83	1.9 : 1

[a]In a typical experiment, 5 mL of a 5.0×10^{-3} mol dm^{-3} aqueous solution of a cobalt(III) complex and 5 mL of a 12.5×10^{-3} mol dm^{-3} solution of Na.LAS in chloroform were shaken together for 6 h at 25 °C; the cobalt(III) amine complexes were present (initially) as racemic mixtures. [b]Data refers to extractions from water only. [c]Where en is 1,2-diaminoethane. [d]No optical activity was detected in the aqueous phase at the end of the experiment. [e]This result refers to extraction of the complex (total initial concentration = 5.0×10^{-3} mol dm^{-3}, from 0.1 mol dm^{-3} NH_4Cl solution (5 mL) into a chloroform phase containing Na.LAS (5 mL, 25×10^{-3} mol dm^{-3}), over 6 h at 25 °C.

successful isolation of particular solid 3:1 adducts provides additional evidence for the existence of such assemblies in chloroform.

In our previous study it was shown that the extraction of inert metal ammine complexes is inhibited by the presence of ammonium chloride in the aqueous phase (ref. 7) . Such behaviour is in accord with the ammonium ion competing with the metal complex for the ionophore via hydrogen bond formation (the NH_4LAS adduct species has been isolated) (ref. 15). In view of this, an investigation of the extraction of the present complexes from 0.1 mol dm^{-3} ammonium chloride solution was instigated. The results are summarised in Table 1. The extraction of most of the cage cations and of $[Co(sen)]^{3+}$ decreased in the presence of ammonium ion relative to their extraction from water; however, exceptions are $[Co\{(Cl_2)\text{-sar}\}]^{3+}$ and $[Co\{(NO_2)_2\text{-sar}\}]^{3+}$.

The aqueous phases from the extraction experiments were analysed for optical activity at the completion of each run (Table 1). Substantial enantiomeric selectivity was observed in the case of the cage complexes - in all cases the Δ isomer was preferentially extracted from the racemic mixture initially present. However, in the case of $[Co(sen)]^{3+}$, no optical activity was detected at the end of the run.

The above behaviour needs to be considered against the component equilibria involved in the extraction process. Factors to be considered include: (i) the association constants for adduct formation by the respective enantiomers and (ii) the degree of aqueous phase/organic phase partitioning of the adducts, carrier and starting metal complexes. A similar set of considerations apply to equilibria involving the competing ammonium ion.

In the present study, no partitioning of the starting complexes into the organic phase was observed in the absence of the carrier (from water or 0.1 mol dm^{-3} ammonium chloride solution). Similarly, no carrier was detected in the aqueous phase. The LAS adducts formed with the cage complexes are readily soluble in chloroform but very sparingly soluble (if at all)

in water. Association constants for the formation of the 3:1 adducts undoubtedly depend on the hydrogen bonding network which is set up and will be a function of the detailed structure of individual complexes. The consistent preference (over such a variety of complexes) for enantiomers with a Δ configuration (with respect to their C_3-axes) suggests a common structural influence across all these species; however, in the absence of structural data for of the adducts, it is inappropriate to comment further on the nature of this influence.

Transport of metal amine complexes The transport fluxes for the cobalt complexes across the receiving phase/membrane interface are listed in Table 2. It is noted that the fluxes reported here (J_{av}) are each a time averaged quantity and do not refer to the (instantaneous) flux at a given time. However, the amount of complex transported to the receiving phase (expressed as a percentage of the amount initially present in the source phase) is a measure of the overall transport efficiency for each complex (see Table 2).

TABLE 2. The lasalocid A mediated transport of cobalt(III) amine complexes through a chloroform bulk liquid membrane and the resulting enantiomeric enrichment in the aqueous receiving phase[a]

Complex[b]	$J_{av}/10^{-7}$ mol h^{-1} cm^{-2}[c] (% transport of complex)		Receiving phase enantiomeric ratio (Λ/Δ)
$[Co(NH_3)_6]Cl_3$	1.8	(21)	-
$[Co(en)_3]Cl_3$	1.1	(13)	1 : 1.2[d]
$[Co(sen)]Cl_3$	1.6	(18)	0[e]
$[Co(sep)]Cl_3$	1.6	(20)	1 : 1.4[d]
$[Co(sar)]Cl_3$	1.5	(17)	1 : 1.6[d]
$[Co\{(CH_3)_2\text{-sar}\}]Cl_3$	1.0	(12)	1 : 1.4[d]
$[Co\{(NH_2)_2\text{-sar}\}]Cl_3$	1.7	(21)	1 : 2.6[d]
$[Co\{(NO_2)_2\text{-sar}\}]Cl_3$	0.4	(5)	0[e,f]
$[Co\{(Cl)_2\text{-sar}\}]Cl_3$	0.4	(5)	0[e,f]

[a]Each run lasted for 24 h at 25 °C. [b]Complexes initially present as racemic mixtures. [c]Average flux across the receiving phase/membrane interface; no transport occurred in the absence of carrier. [d]Aqueous source phase was enriched in the Λ isomer at the end of the experiment. [e]No optical activity was detected in the receiving phase at the end of the experiment. [f]The source phase was slightly enriched in the Λ isomer at the end of the experiment owing to preferential loss of the Δ isomer into the chloroform phase.

As well as the differences in the transport efficiencies between systems, most of the systems also show the selective transport of one enantiomer relative to the other. That is, for the majority of cases the aqueous receiving phases were enriched in the Δ isomer at the end of each run: the aqueous source phases (initially racemic) were enriched in the Λ isomer. The lack of detectable optical activity in the receiving phases from the transport of $[Co\{(Cl_2)\text{-sar}\}]^{3+}$ and $[Co\{(NO_2)_2\text{-sar}\}]^{3+}$ may have been due to the low concentration of the complexes in this phase after 24 h.

The tripod complex, $[Co(sen)]^{3+}$, shows no detectable resolution in either aqueous phase despite efficient transport (18% in a 24 h period). The absence of chiro-selectivity in the transport of this complex is consistent with the extraction result; no enantiomeric enrichment was observed in the extraction experiments. For the cage complexes, the most extracted isomer is also the most efficiently transported. This observation confirms and extends an earlier trend which showed the preferential transport of the most extracted isomer (ref. 7).

CONCLUDING REMARKS

The present systems may prove useful for testing the relationship between extractability and transport proposed earlier (ref. 16) since a wide variety of substrates with differing extractabilities is available. Selectivity phenomena may also be able to be subtly probed by means of the chiral discrimination between enantiomers.

Acknowledgement

We thank the ANU microanalytical service for C, H and N analyses. The authors are grateful to Professor A. M. Sargeson and Drs. R. J. Geue and P. Osvath [Research School of Chemistry (ANU)] for helpful discussions and the provision of some compounds used in this study. We acknowledge A. J. Leong and Associate Professor F. R. Keene (James Cook University) for assistance and the Australian Research Council for support.

REFERENCES

1. For reviews on facilitated transport, see (a) J.M. Lehn, *Pure Appl. Chem.*, 1979, 51, 979-997. (b) G. R. Painter and B. C. Pressman, *Top. Current Chem.*, 1982, 101, 83-110. (c) B. G. Cox and H. Schneider, "Coordination and Transport Properties of Macrocyclic Compounds in Solution" in studies in physical and theoretical chemistry, Vol. 76, pp. 1-420, Elsevier (1992)
2. (a) J. D. Lamb, R. M. Izatt and J. J. Christensen, *Prog. Macrocyclic Chem.* 1981, 41-90. (b) J. W. Westley, "Polyether Antibiotics - Naturally Occurring Acid Ionophores" in J. W. Westley, (ed.) Vol. 1, pp. 103-184, Marcel Dekker, Inc. (1982). (c) S. Shinkai and O. Manabe, *Top. Current Chem.* 121, pp. 67-104 (1984). (d) H. Tsukube, *J. Coord. Chem.*, 1987, 16, 101-129.
3. For a summary of the host-guest binding properties of macrocycles, see (a) D. J. Cram, *Angew. Chem.*, 1988, 27, 1009-1020. (b) L. F. Lindoy, "The Chemistry of Macrocyclic Ligand Complexes" Cambridge University Press, Cambridge, pp. 1-269 (1989). (c) G. W. Gokel, "Crown Ethers and Cryptands" in Monographs in Supramolecular Chemistry No. 3, Royal Society, pp. 1-208, (1991).
4. (a) R. M. Izatt, B. L. Nielsen, J. J. Christensen, and J. D. Lamb, *J. Membr. Sci.*, 1981, 9, 263-267. (b) H. Tsukube, *Tetrahedron Lett.*, 1983, 24, 1519-1522. (c) K. Maruyama, H. Sohmiya, and H. Tsukube, *J. Chem. Soc., Chem. Commun.*, 1989, 864-865. (d) W. F. Nijenhuis, A. R. Van Doorn, A. M. Reichwein, F. de Jong, and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1991, 113, 3607-3608.
5. M. Newcomb, J. L. Toner, R. C. Helgeson, and D. J. Cram, *J. Am. Chem. Soc.*, 1979, 101, 4941-4947.
6. J. F. Kinsel, E. I. Melnik, S. Lindenbaum, L. A. Sternson, and Y. A. Ovchinnikov, *Biochimica et Biophysica Acta.*, 1982, 684, 233-240.
7. P. S. K. Chia, L. F. Lindoy, G. W. Walker, and G. W. Everett, *J. Am. Chem. Soc.*, 1991, 113, 2533-2537.
8. F. Takusagawa, J. Shaw, and G. W. Everett, *Inorg. Chem.*, 1988, 27, 3107-3112.
9. J. Strzelbicki, W. A. Charewicz, Y. Liu, and R. A. Bartsch, *J. Incl. Phen.*, 1989, 7, 349-361.
10 R. C. Hider, *Structure and Bonding* 58, pp. 25-87, Springer-Verlag, Berlin (1984).
11. D. J. Ecker, B. F. Matzanke, and K. N. Raymond, *J. Bacteriol.*, 1986, 167, 666-673.
12. J. B. Neilands, J. Erickson, and W. H. Rastetter, *J. Biol. Chem.*, 1981, 3831-3832.
13. (a) R. J. Geue, T. W. Hambley, J. M. Harrowfield, A. M. Sargeson, and M. R. Snow, *J. Am. Chem. Soc.*, 1984, 106, 5478-5488. (b) A. H. Höhn, R. J. Geue, and A. M. Sargeson, *J. Chem. Soc., Chem. Commun.*, 1990, 1473-1475.
14. A. M. Sargeson, *Chem. Br.* 1979, 23-27.
15. R. C. R. Gueco, and G. W. Everett, *Tetrahedron*, 1985, 41, 4437-4442.
16. J.-P Behr, M. Kirch, and J.-M. Lehn, *J. Am. Chem. Soc.*, 1985, 107, 241-246 .