



Original article

Recognition and transport of amphiphilic molecules by a new class of inorganic ditopic receptors. The synthesis of $M-tBu_4$ -salphen-3*n*-cr-*n* complexes and their use ($M = Mn, Fe, n = 6$) in the transport of tryptophan and serotonin across bulk liquid membranes

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Abstract

A new class of ditopic receptor molecules have been synthesized and structurally characterized. The unique structural features of these molecules are: (a) a very lipophilic unit that consists of two 3,5-di-*t*-butylsalicylideneimine moieties that form a square O_2N_2 coordination site and (b) a relatively hydrophilic benzo-18-crown-6 unit capable of binding to alkali metal ions and hydrogen bonding with ammonium functional groups. These molecules are totally insoluble in water but very soluble in non-polar solvents. By virtue of their hydrophilic end, they are able to invade the water-organic solvent interface and retrieve hydrophilic molecules from water solution that subsequently are extracted into the organic solvent. Procedures are described for the syntheses of the $\{H_2-tBu_4$ -salphen-18-cr-6 and also 15-crown-5 and 12-crown-4 derivatives. With dibenzo-crown ethers 2:1 tBu_4 -salphen:crown ether molecules have been obtained with 18-crown-6, 24-crown-8 and 30-crown-10 'bridges'. A variety of metal ions (Mn^{3+} , Fe^{2+} , Fe^{3+} , Co^{2+} , Ni^{2+} and Cu^{2+}) have been incorporated within the N_2O_2 cavity of the salphen subunits in the 18-crown-6 and 24-crown-8 hybrids. An account of structural features and transport characteristics for some of these molecules are reported. The results of a detailed study of the transport of tryptophan and serotonin across $CHCl_3$ bulk liquid membranes are discussed for these processes that follow Michaelis–Menten kinetics. **To cite this article:** D. Coucouvanis *et al.*, *C. R. Chimie* **6** (2003).

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Résumé

Les membranes cellulaires qui protègent les cellules et permettent en même temps le transport de petites molécules biologiques importantes à travers la frontière cellulaire sont des bicouches de lipides qui contiennent un intérieur hydrophobe flanqué de surfaces hydrophiles. Une nouvelle classe de récepteurs ditopiques a été synthétisée et caractérisée du point de vue structural. Les caractéristiques uniques de ces molécules sont : (a) une unité très lipophile, qui consiste en deux unités

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3,5-di-*t*-butylsalicylideneimine, qui forment un site de coordination O_2N_2 carré, et (b) une unité benzo-18-crown-6 relativement hydrophile, capable de se lier à des métaux alcalins et de former des liaisons hydrogène avec des groupes ammonium fonctionnels. Ces molécules sont totalement insolubles dans l'eau, mais très solubles dans des solvants polaires. Grâce à leur terminaison hydrophile, elles sont capables d'envahir l'interface eau-solvant organique et de récupérer des molécules hydrophiles de la solution aqueuse, qui sont extraites ultérieurement dans le solvant organique. Des procédures sont décrites pour les synthèses des dérivés du H_2 - t -Bu₄-salphen-18-cr-6 du 15-crown-5 et 12-crown-4. Avec les dibenzo-crowns, des molécules 'Bu₄-salphen:crown éther (2:1) ont été obtenues, qui présentent des « ponts ». Une variété d'ions métalliques (Mn³⁺, Fe²⁺, Fe³⁺, Co²⁺, Ni²⁺ et Cu²⁺) a été incorporée dans la cavité N₂O₂ des sub-unités salphen dans les hybrides 18-crown-6 et 24-crown-8. Les caractéristiques structurales et de transport pour certaines de ces molécules sont décrites. Les résultats d'une étude détaillée du transport du tryptophane et de la sérotonine à travers des membranes liquides massives de CHCl₃ sont discutés pour ces processus, qui suivent des cinétiques de type Michaelis–Menten. **Pour citer cet article : D. Coucouvanis et al., C. R. Chimie 6 (2003).**

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1. Introduction

Cell membranes that protect the cell and at the same time allow for the transport of biologically important small molecules across the cell boundary are lipid bilayers that contain a hydrophobic interior flanked by hydrophilic surfaces. The partitioning of hydrophilic solutes into these bilayers is an important process intimately involved in events such as drug uptake and metabolite transport and may be important in the mechanism of anesthetic drug action.

A great number of biomolecules and drugs are water-soluble species, often insoluble in lipid membranes. As a result, their transport across membranes must be facilitated by specific carriers. A great number of naturally occurring carriers are known for amino acids, neurotransmitters, nucleosides, sugars etc. Usually these are proteins mostly of unknown structures. Synthetic carriers for the facilitated transport of hydrophilic biomolecules and drugs across cell membranes are rare and the design and synthesis of such molecules are important, and of vital concern to biology and pharmacology.

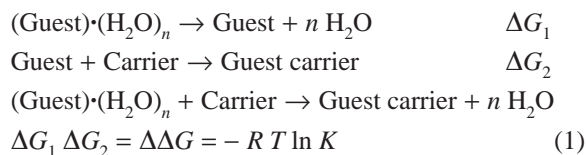
The transport of amino acid derivatives or nucleotides by synthetic carriers across CH₂Cl₂ or CHCl₃ bulk liquid membranes, BLMs, has received considerable attention and has been the subject of numerous reports. Among them are included: (a) the pH-gradient-driven transport of amino acids by positively or negatively charged hydrophobic carriers [1]; (b) the transport of hydrophobic amino acids from aqueous solution at the isoelectric point using Kemp's triacid-

acridine 2:1 condensate [2]; (c) the transport of phenylalanine in a neutral pH transport system facilitated by cooperative ditopic interactions between the amino acid, and non-bound arylboronic acid and crown ethers [3]; (d) the simultaneous transport of anions and cations by a neutral bifunctional receptor that contains calix[4]phosphate and an appended uranyl salophene unit [4]; (e) the ditopic fixation and transport of amino acids with a bifunctional metalloporphyrin receptor [5]; (f) the proposed ditopic transport of amino acids by lanthanide (III) tris(β-diketonate) complexes [6]; (g) the use of phenylboronic acid/trioctylmethylammonium bromide as a carrier of amino acids through a ClCH₂CH₂Cl BLM [7]; (h) the transport of amino acid derivatives by certain hydrophobic, neutral LM(Cl)₂ complexes (M = Co²⁺, Cu²⁺, L = a macrocyclic polyamine ligand) in basic aqueous solutions. This transport is assisted by the concomitant transport of antiport halide ions [8–10]. The recognition of thymidine nucleotides by the zinc(II)-bis(cyclen) ditopic receptors also has been reported [11].

In the majority of these biological transport studies, the bulk liquid membranes, BLMs, are non-aqueous, hydrophobic solvents and, in transport experiments, they contain the carrier and also serve as barriers between the aqueous source and receiving phases.

The concentration gradient between the source compartment (containing the transportable guest) and the receiving compartment (initially pure water) is the thermodynamic driving force for transport. Transport occurs at various rates, subject to solubility properties of the host-guest complex and kinetic constraints. It is

optimally effective when the $\Delta\Delta G$ of the dehydration/complexation steps (equation (1)) is such that the complex formation constant, K , is of a magnitude that will facilitate extraction of the guest from water but will also allow for its release:



Major drawbacks in most of the previous studies have been either slow rates of transport or carrier instability.

Our interest in supramolecules containing individual subunits with unique structural and reactivity properties has led us to the synthesis of a new class of crown-functionalized salicylaldimine ligands [12–15]. In this paper we report on the metal complexes of these

multinucleating ligands and their use in the recognition and transport of zwitterions and amphiphilic molecules across hydrophobic barriers

2. Results and discussion

2.1. Synthesis of ${}^t\text{Bu}_4$ -salphen-crown ether ligands and complexes

The general procedures employed in the synthesis of the $\{\text{H}_2\text{-}{}^t\text{Bu}_4\text{-salphen-18-cr-6}\}$ ligands and complexes have been reported [13–15] and also have been used in the synthesis of the 15-crown-5 and 12-crown-4 derivatives (Fig. 1) [16].

With dibenzo-crown ethers, 2:1 ${}^t\text{Bu}_4$ -salphen:crown ether molecules have been obtained (Fig. 2) with 18-crown-6, 24-crown-8 [13–15] and 30-crown-10 ‘bridges’ [16].

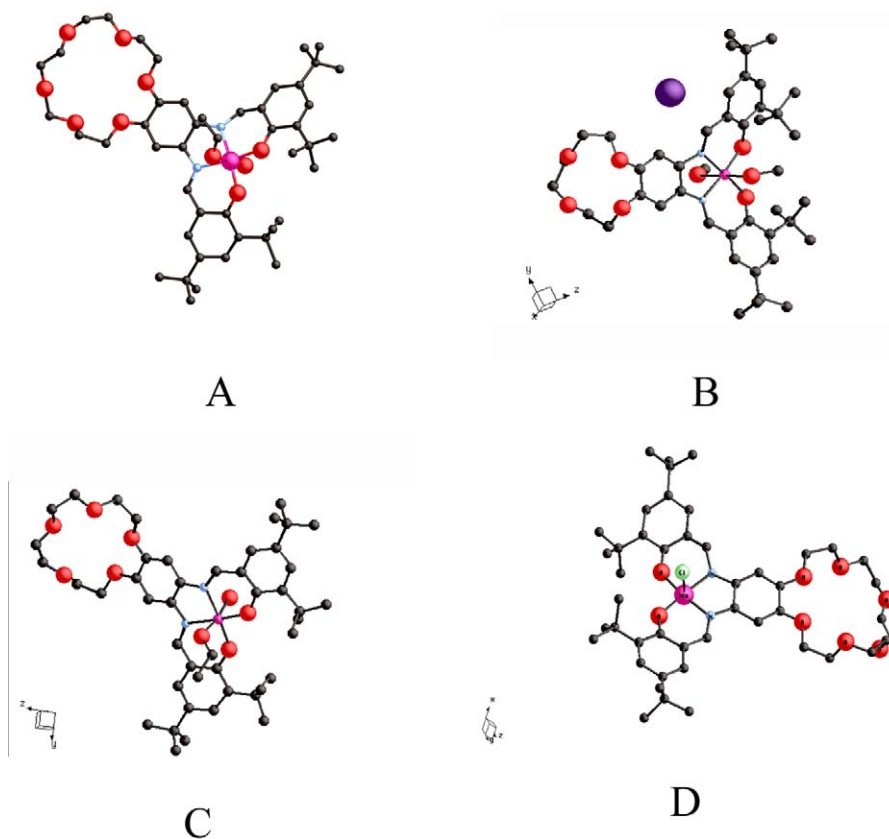


Fig. 1. The structures of complexes: (A) $\{(\text{EtOH})(\text{H}_2\text{O})\text{Mn}^{3+}\text{-}{}^t\text{Bu}_4\text{-salphen-3 } n\text{-cr-}n\}^+ \Gamma$, $n = 6$ [12–14]; (B) $\{(\text{MeOH})_2\text{Mn}^{3+}\text{-}{}^t\text{Bu}_4\text{-salphen-3 } n\text{-cr-}n\}^+ \Gamma$, $n = 4$ [16]; (C) $\{(\text{MeOH})(\text{H}_2\text{O})\text{Mn}^{3+}\text{-}{}^t\text{Bu}_4\text{-salphen-3 } n\text{-cr-}n\}^+ \Gamma$, $n = 5$ [16]; (D) $\{(\text{MeO})\text{Fe}^{3+}\text{-}{}^t\text{Bu}_4\text{-salphen-3 } n\text{-cr-}n\}^+ \Gamma$, $n = 6$.

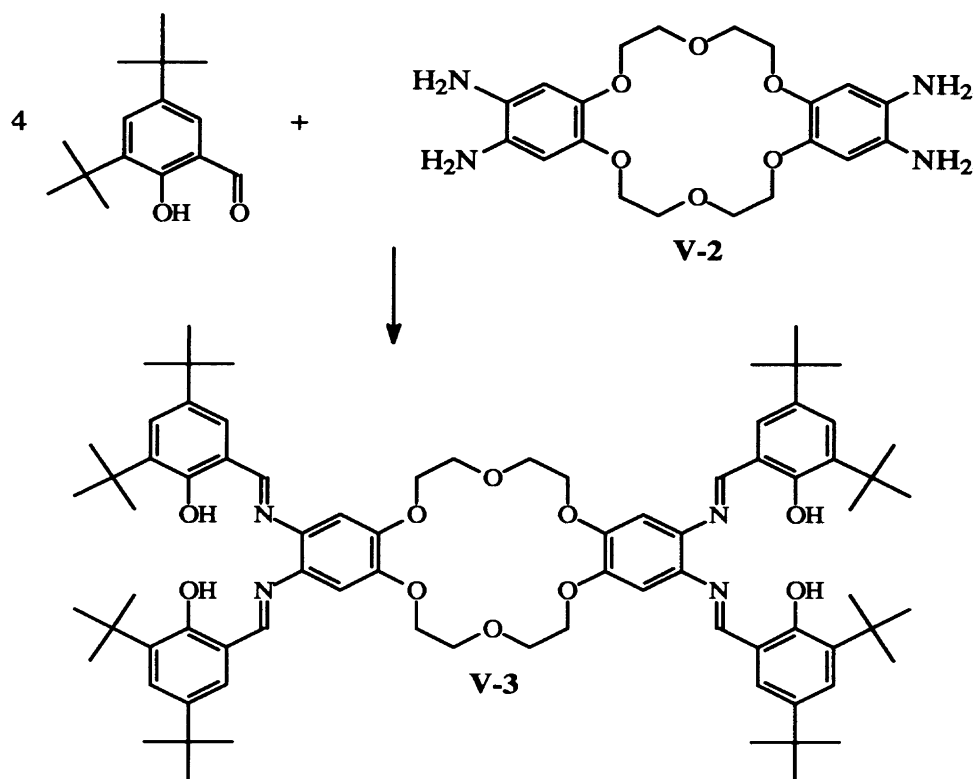


Fig. 2. General synthesis of the $\{[H_2\text{-}^t\text{Bu}_4\text{-salphen}]_2\text{318-cr-6}\}$ hybrid ligands [12,13].

Various metal complexes have been synthesized with these ligands and the structures of the $\{[Ni^{2+}\text{-}^t\text{Bu}_4\text{-salphen}]_2[24\text{-cr-8}]\}$ and $\{[Ni^{2+}\text{-}^t\text{Bu}_4\text{-salphen}]_2[24\text{-cr-8}]\text{Cs}\}$ complexes demonstrate the structural flexibility of the 24-crown-8 bridge (Fig. 3).

The tertiary butyl groups in the salicylaldehyde subunits of the ligands serve two purposes: (1) they impart highly lipophilic character to one end of the ditopic molecule and (2) they preclude short intermolecular interactions of the coordinated oxygen atoms with Lewis acids. A variety of metal ions (Mn^{3+} , Fe^{2+} , Fe^{3+} , Co^{2+} , Ni^{2+} , Cu^{2+}) have been incorporated within the N_2O_2 cavity of the salphen subunits in the 18-crown-6 and 24-crown-8 hybrids [13]. The $\{Ni^{2+}\text{-}^t\text{Bu}_4\text{-salphen-3 } n\text{-cr-}n\}$ complexes, **I**, are neutral molecules [12,13] and the $\{M^{3+}\text{-}^t\text{Bu}_4\text{-salphen-3 } n\text{-cr-}n\}$ complexes ($M = Mn, Fe, Co$) are monocations.

The $\{(\text{EtOH})(H_2O)Mn^{3+}\text{-}^t\text{Bu}_4\text{-salphen-18-cr-6}\}^+\text{Cl}^-$, **II**, and $\{(\text{MeO})Fe^{3+}\text{-}^t\text{Bu}_4\text{-salphen-18-cr-6}\}$, **III**, complexes (Fig. 1A and D) contain six-coordinate

Mn^{3+} and five-coordinate Fe^{3+} ions, respectively, and are obtained in high yield by air oxidation of the corresponding divalent complexes. Both **II** and **III** are very soluble in non-polar organic solvents and totally insoluble in water. It is worth emphasizing that the Cl^- counterion that accompanies **II** is not directly coordinated to the oxophilic Mn^{3+} ion, which instead is coordinated by a water molecule and an ethanol molecule. Similar coordination is observed with the 12-cr-4 and 15-cr-5 ether analogs (Fig. 1B and C). The $\{[Ni^{2+}\text{-}^t\text{Bu}_4\text{-salphen}]_2[24\text{-cr-8}]\}$ complex, **IV** (Fig. 3A and B) contains a four-coordinate Ni^{2+} ion and shows both linear and 'hairpin' structures that demonstrate the flexibility of the 24-crown-8 unit. The bending that places the two Ni^{2+} ions within 11.6 Å from each other is further enhanced ($Ni\text{-}Ni = 4.1$ Å), when Cs^+ is added to the 24-crown cavity.

The $\{[(Cl)Fe^{3+}\text{-}^t\text{Bu}_4\text{-salphen}]_2[24\text{-cr-8}]\}$ complex **V** (Fig. 4) also has a 'hairpin'-type structure, with a Fe-Fe separation of 6.05 Å. It undergoes hydrolysis under

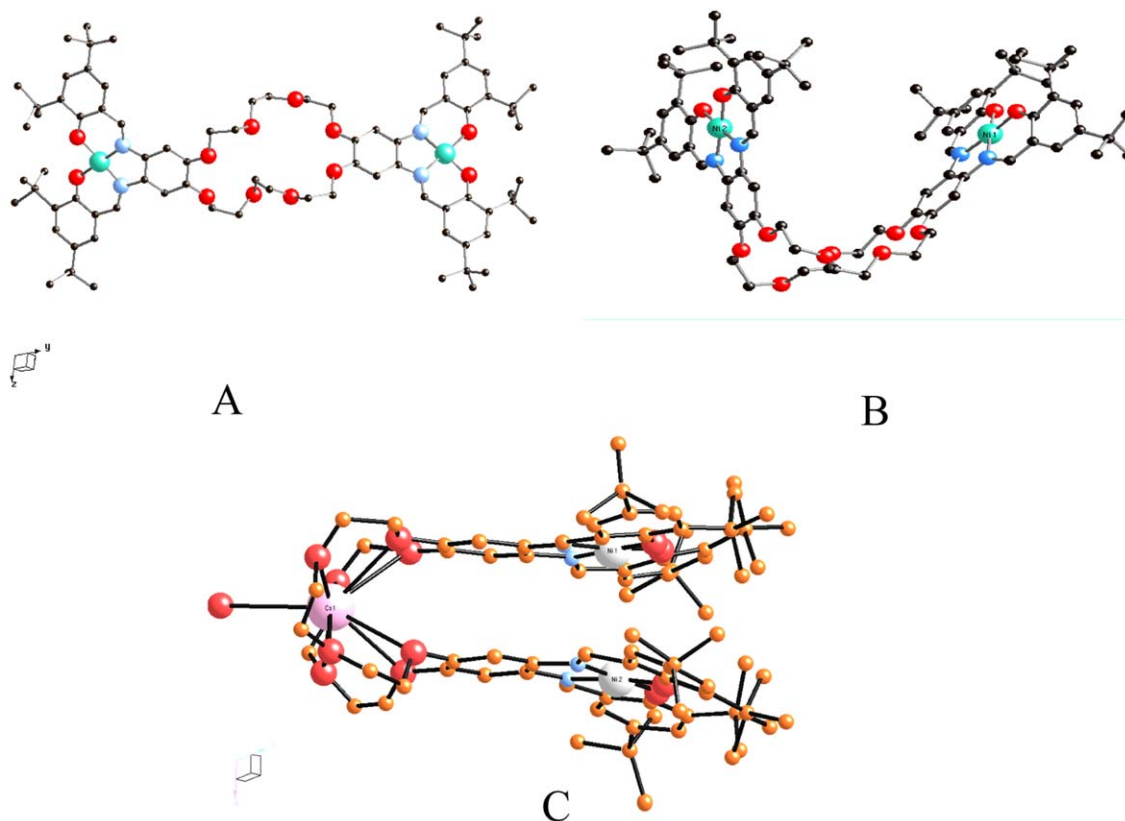


Fig. 3. Two forms of the $\{[\text{Ni}^{2+}\text{-}^t\text{Bu}_4\text{-salphen}]_2[24\text{-cr-}8]\}$ complex, **IV**, both found in the same asymmetric unit [13] (**A**, **B**), and the Cs adduct of the same complex (**C**). In the latter, the Cs^+ ion is nine-coordinate bound to the 24-cr-8 ether and to a water molecule. The Ni–Ni distances in (**A**), (**B**), and (**C**) are 17.5, 11.6, and 4.1 Å, respectively.

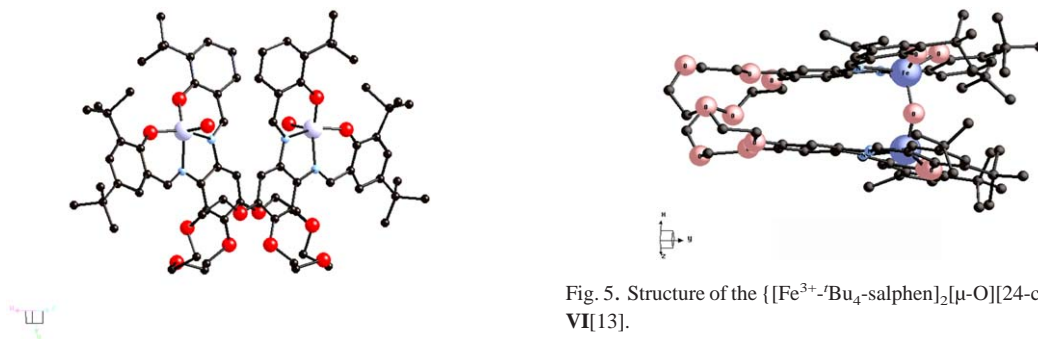


Fig. 4. Structure of the $\{(\text{Cl})[\text{Fe}^{3+}\text{-}^t\text{Bu}_4\text{-salphen}]_2[24\text{-cr-}8]\}$, **V**[13].

Fig. 5. Structure of the $\{[\text{Fe}^{3+}\text{-}^t\text{Bu}_4\text{-salphen}]_2[\mu\text{-O}][24\text{-cr-}8]\}$ dimer, **VI**[13].

basic conditions to give the oxo bridged dimeric complex $\{[\text{Fe}^{3+}\text{-}^t\text{Bu}_4\text{-salphen}]_2[\mu\text{-O}][24\text{-cr-}8]\}$ **VI** (Fig. 5).

2.2. Transport studies through bulk liquid membranes

2.2.1. Tryptophan, serotonin

The facilitated transport of zwitterionic, lipophilic amino acids, dipeptides tripeptides, serotonin, dopamine and the nucleosides adenosine, guanosine, thym-

ine, and cytosine was investigated across CHCl_3 BLM and found effective to various extents with different $\{\text{M}'\text{Bu}_4\text{-salphen-18-cr-6}\}$ complexes. In this paper, we report on our transport studies with tryptophan and serotonin. The cell shown in Fig. 6 was used.

The Ni^{2+} complex, **I**, and its derivatives, the corresponding Cu^{2+} complex and the benzo-18-C-6 crown ether, that was investigated as a control, were equally ineffective in the transport of tryptophan [15]. In contrast, the Mn^{3+} complex, **II**, readily transported tryptophan (Fig. 7) by a process driven by the tryptophan concentration gradient [12,14]. The concentrations of tryptophan in the receiving and source compartments asymptotically reach equal values as the transport

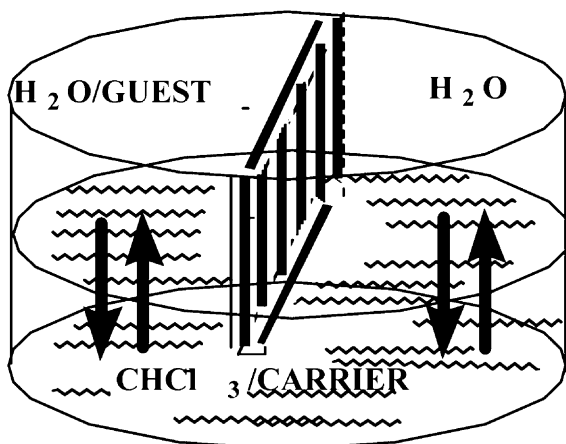


Fig. 6. The cell used in the transport studies across bulk liquid membranes, BLM [5].

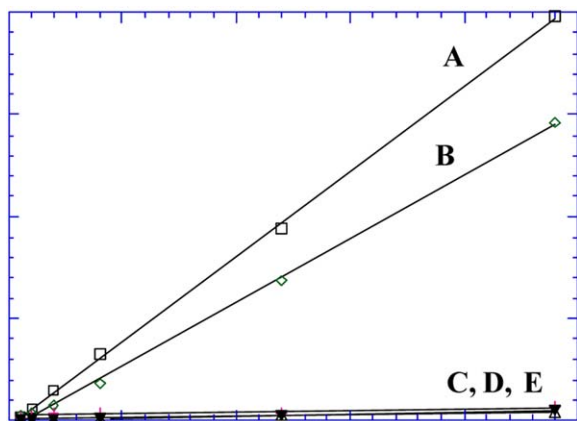


Fig. 7. Transport of tryptophan by: (A) $\text{Mn}'\text{-Bu}_4\text{-salphen-18-cr-6}^+ \text{I}^-$; (B) $\{[\text{Fe}^{3+}\text{'Bu}_4\text{-salphen-18-cr-6}]_2[\mu\text{-O}]\}$; (C), (D) the $\{[\text{M}'\text{-Bu}_4\text{-salphen}]\text{-[18-cr-6]}\}$ carriers $\text{M} = \text{Ni, Cu}$; (E) benzy18-cr-6 [12,14].

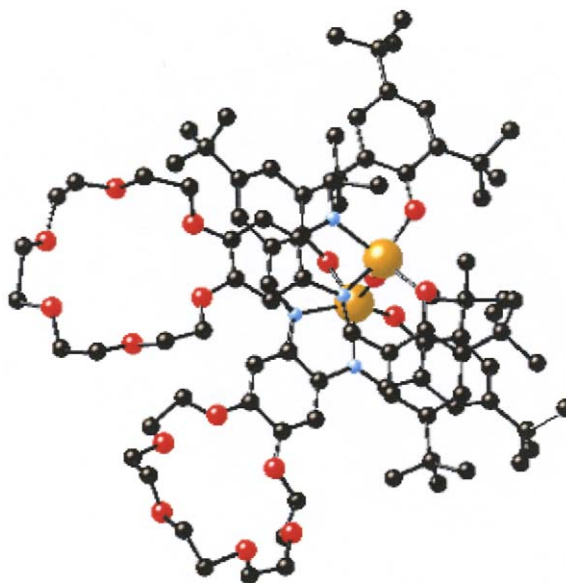


Fig. 8. Structure of the $\{[\text{Fe}^{3+}\text{'Bu}_4\text{-salphen-18-cr-6}]_2[\mu\text{-O}]\}$ complex [13].

progresses. Nearly as effective in transport was the neutral $\{[\text{Fe}^{3+}\text{'Bu}_4\text{-salphen-3n-cr-n}]_2\text{O}\}$, $n = 6$, complex (Fig. 8).

We have attributed the poor transport performance of **I** and of the Cu^{2+} analog to the stability of the square planar Ni^{2+} and Cu^{2+} ions and their inability to bind axial ligands.

The importance of the unencumbered crown ether unit in **II** becomes apparent when the transport properties of **II** are compared to those of the $\{[\text{Mn}'\text{-Bu}_4\text{-salphen}]_2\text{-[18-cr-6]}\}^{2+} \cdot 2 \text{I}^-$ carrier with two $\text{Mn}'\text{-Bu}_4\text{-salphen}$ units surrounding the 18-cr-6 unit (Fig. 9). The inferior performance of the latter may be due to the fact that in this carrier the hydrophilic part of the molecule is flanked by two very hydrophobic units and is not free to assist in retrieving the tryptophan molecule from the water solution. It is possible that the observed difference in transport rates is due to the presence of only two aliphatic ether oxygen donors in the $\{[\text{Mn}^{3+}\text{'Bu}_4\text{-salphen-X}]_2\text{[18-cr-6]}\}$ carrier and the consequent weaker interactions possible with the dibenzo-crown unit. This possibility can be tested using derivatives of **II** that also contain two aliphatic ether donors.

Various modes of interaction can be envisioned between the carrier and the zwitterionic form of tryptophan. They may involve such interactions as: (a) carboxylate coordination to the Mn^{3+} center, (b)

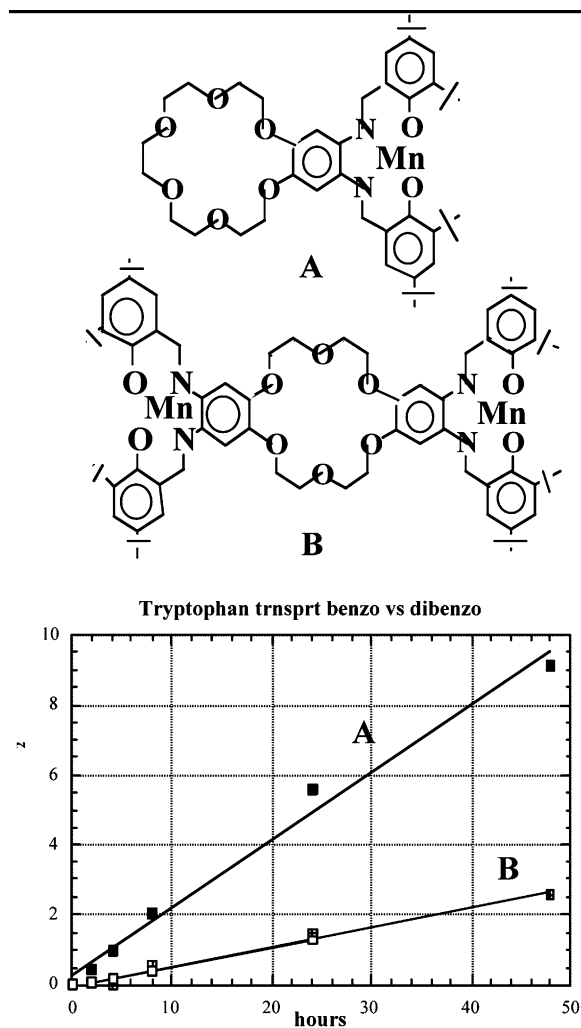


Fig. 9. Transport of tryptophan by: (A) $\text{Mn}^{\text{III}}\text{-Bu}_4\text{-salphen-18-cr-6}^+ \Gamma^-$ and (B) $\{[\text{Mn}^{\text{III}}\text{-Bu}_4\text{-salphen}]_2\text{-[18-cr-6]}\}_2 \Gamma^-$ carriers across a CHCl_3 BLM [12–14].

H-bonding of the $-\text{NH}_3^+$ to the crown ether cavity of the carrier, (c) carboxylate coordination to an alkali metal bound in the crown ether cavity, and (d) H-bonding interactions between the indole NH proton and a hydrogen bond accepting site within the carrier. There is no apparent difference in the tryptophan transport rate when the 18-cr-6 unit in **II** is replaced by a 24-cr-8 unit.

The bathochromic shifts of the 470-nm band, caused by axial ligand coordination to the Mn(III) center, in derivatives of **II** with various counterions, indicate that this electronic absorption is very likely

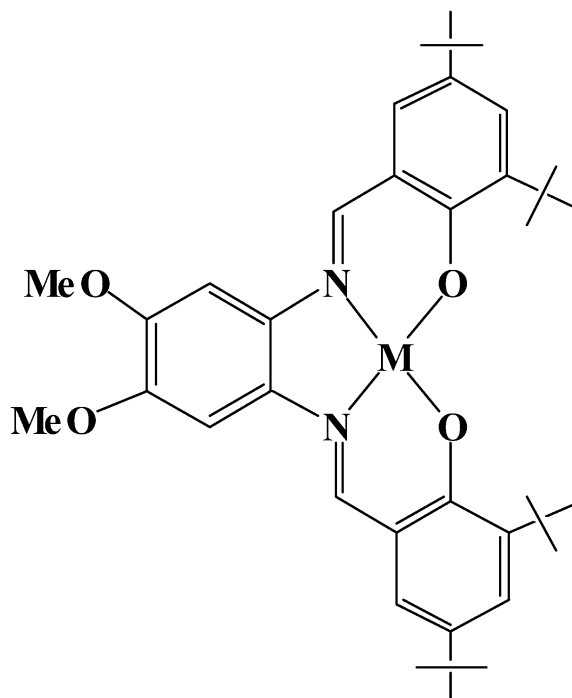


Fig. 10. The $\text{M}^{\text{III}}\text{-Bu}_4\text{-salphen veratrol}$ complexes

due to a M-ligand charge transfer, MLCT, process. The relative substrate transport rates decrease as the bathochromic shift of the MLCT band (at 470 nm in the BPh_4^- anion) increases. The differences in the bathochromic shift of the CT absorption reflect differences in the magnitude of Mn(III)-axial-ligand interactions. Generally, the transport data indicate [12] that the weakly coordinating anions give carriers that transport amino acids more effectively in the order: $\text{B(Ph)}_4^- > \Gamma^- = \text{Piv}^- > \text{Cl}^- > \text{Ac}^-$.

Transport studies were conducted to determine whether the ditopic receptors are more efficient transporters than an equimolar mixture of two similar monotopic half-receptors. The transport properties of a 1:1 mixture of the Mn-veratrol complex (Fig. 10) and benzo-18-crown-6 were compared to those of $\{\text{Mn}^{\text{III}}\text{-Bu}_4\text{-salphen-18-cr-6}\}^+ \text{X}^-$ or $\{\text{Mn}^{\text{III}}\text{-Bu}_4\text{-salphen veratrol}\}^+ \text{X}^-$. The results show [1] that, in an equimolar mixture, the two carrier components function synergistically. The rate of transport observed with **II** however was still about 30% faster and indicates moderate ditopic cooperativity. The same experiments carried out with serotonin show greater ditopic cooperativity and can be attributed to a better dimensional matching

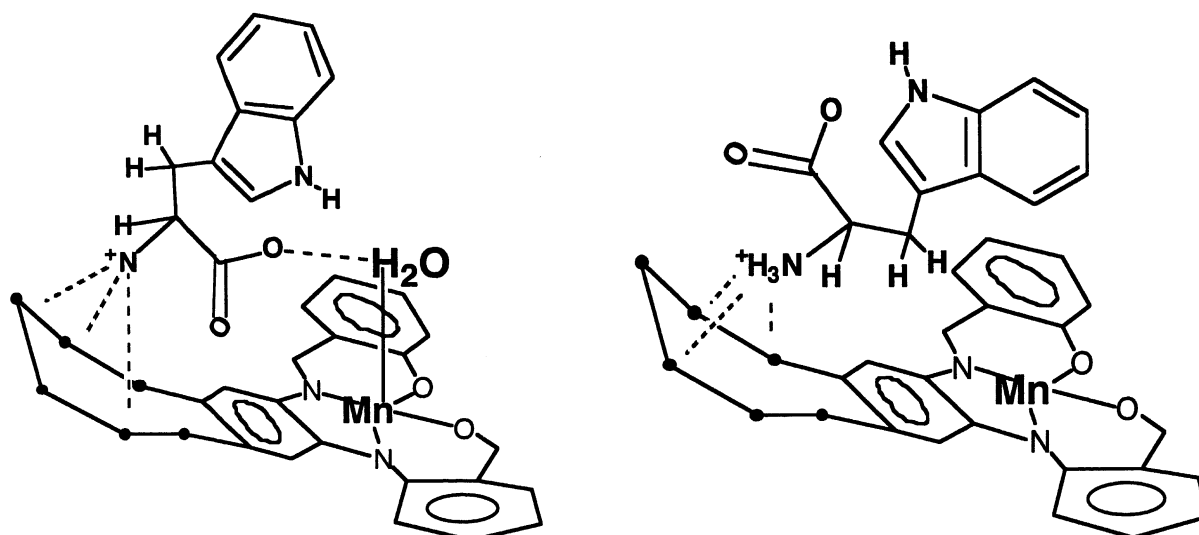


Fig. 11. Schematic illustrations of the energy-minimized structures of the tryptophan- $\{Mn^{3+}\text{-}tBu_4\text{-salphen-18-cr-6}\}^+$ complexes: (A) the lower energy complex with Mn-coordinated water and (B) the higher energy complex without Mn-coordinated H_2O [12].

between the donor–acceptor pairs within the serotonin-**II** complex. In **II** the acidic and basic sites are closely spaced such that the simultaneous binding of the tryptophan zwitterion by both the carboxylate group (to the Mn^{3+}) and the ammonium group (to the crown ether) is not possible unless the crown ether unit bends severely (to a right angle or more) towards the salphen unit. The ditopic cooperativity shown in the transport of substrates has been reported previously [17] for the crown-ether-functionalized boronic acids in the facilitated transport of catecholamines. The synergism displayed by the mixture of the two separate carrier components of **II** in the transport of tryptophan has been reported previously [17], for equimolar mixtures of arylboronic acids and crown ethers, in the transport of L-phenylalanine through $CHCl_3$.

Molecular mechanics calculations [12] on the tryptophan-**II** complex (Fig. 11) support this contention and show that when tryptophan is placed in the pocket of the carrier that contains a water molecule axially coordinated to the Mn(III) center, the relative energy of the guest–host complex decreases. In the energy minimized structure, in addition to RNH_3^+ hydrogen bonding with the crown ether appendix, short hydrogen bonds are found between the amino acid carboxylate group and the Mn(III)-bound water molecule (Fig. 11A). These hydrogen bonds ($N-H\cdots O$,

2.69 \AA ; $C\cdots H-O-H$, 2.51 \AA) are to be contrasted with those found in the energy-minimized structure without the Mn(III)-bound water molecule (Fig. 11B). In the latter case, the only hydrogen bonding interaction is between the RNH_3^+ unit and the crown ether ($N-H\cdots O$, 2.69 \AA ; $C-O\cdots Mn$, 3.79 \AA).

The same type of calculation was carried out with serotonin. With a water molecule axially bound to the Mn(III) ion in **II**, the energy-minimized structure (Fig. 12A) shows the relative energy of the serotonin-**II** complex much higher than that of the complex without an axially bound water molecule (Fig. 12B). The lower energy of the latter is not unexpected considering the close distance matching of the two donor–acceptor pairs [12].

Thus far the transport data suggest that the initial carrier–amino acid contact is the rate-determining step and occurs between the crown ether unit of the carrier and the $-NH_3^+$ unit of the zwitterion. This suggestion also is supported by the observed inhibition of transport in the presence of the crown-blocking K^+ ion. The slow transport rate by the benzo-18-crown-6 molecule shows that a crown ether interaction with the amino acid alone is not sufficient for effective transport, although it should be recognized that the crown ether is less hydrophobic than the tBu -salphen-crown ether receptor.

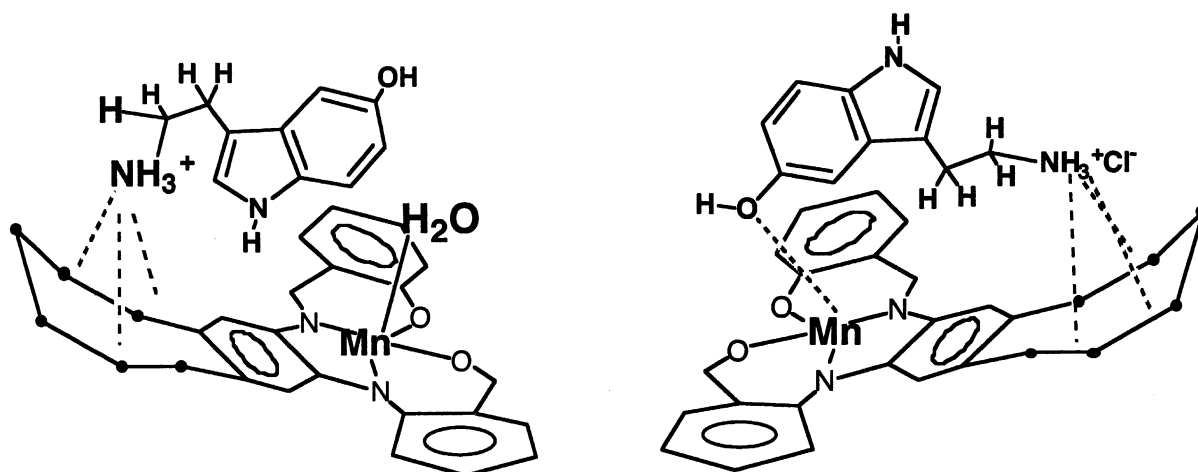


Fig. 12. Schematic illustrations of the, energy-minimized structures of the serotonin- $\{Mn^{3+}\text{-}^7Bu_4\text{-salphen-18-cr-6}\}^+$ complexes: (A) the higher energy complex with Mn-coordinated water and (B) the lower energy complex without Mn-coordinated H_2O [12].

For the facilitated transport of a given solute through a membrane (Fig. 13), the flux [18], J_{solute} , is defined as [19]:

$$J_{\text{solute}} = \frac{D_{CS} C_0 K_{\text{ex}}}{L} \frac{S_s - S_r}{(1 + K_{\text{ex}} S_s)(1 + K_{\text{ex}} S_r)}$$

where D_{CS} = carrier–solute diffusion constant, C_0 = total concentration of carrier, S_s = concentration of solute at source interface, S_r = concentration of solute at receiving interface, L = membrane thickness, and $K_{\text{ex}} = \frac{[CS_m]}{[S_s][C_m]}$. When K_{ex} is not very small and S_s reasonably large (early in the transport process), $K_{\text{ex}} S_s \ll 1$, and the flux is given by $J_{\text{solute}} = \frac{D_{CS} C_0 K_{\text{ex}} S_s}{L} \frac{S_s}{(1 + K_{\text{ex}} S_s)}$, which is a form of the Michaelis–Menten equation for the process

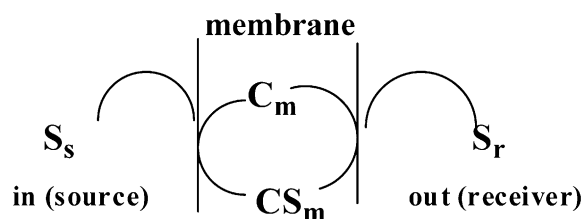


Fig. 13. Facilitated transport of a solute S through a membrane m by a membrane-residing carrier, C_m .

The Michaelis constant $K_m = \frac{[S_s][C_m]}{[CS_m]} = \frac{1}{K_{\text{ex}}}$ can be obtained from double-reciprocal Lineweaver–Burke plots (Fig. 14).

From the apparent Michaelis constants (K_m) of 25 mM and 245 mM, carrier-permeant extraction constants ($K_{\text{ex}} = 1/K_m$) of $40 M^{-1}$ and $4 M^{-1}$ were determined, respectively, for the tryptophan and serotonin carrier complexes. Theoretically, the transport of serotonin as the hydrochloride derivative should be more appropriately treated, as a symport-transport case [19]. The successful application of the same Michaelis–

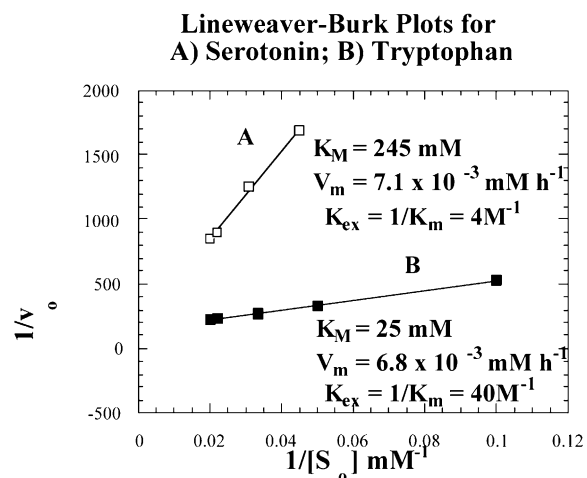


Fig. 14. Michaelis–Menten kinetics for serotonin and tryptophan transport by $\Pi\text{-I}$ [12].

Menten kinetics treatment for serotonin HCl, as that used for tryptophan, however suggests that the HCl derivative of serotonin in CHCl_3 behaves as a tight ion pair rather than as an electrolyte.

Rate studies as a function of temperature and Arrhenius plots were used to determine activation energies and activation parameters for the process of transport of tryptophan and serotonin [12].

The ΔE s of activation of 20 and 16 kcal mol⁻¹ indicate diffusion-controlled processes [19] through the Nernst layer at the CHCl_3 - H_2O interphase.

The transport of serotonin-HCl by II^+I^- proceeds at a respectable rate, but which is still half of that of tryptophan. The transport of dopamine (in a buffered solution at pH 7.2) by the same carrier is slower, but still much better than the transport observed with the benzo-18-cr-6 carrier) [1]. The difference in transport rates between serotonin and dopamine is probably due to differences in hydrophobicity between these two molecules. The distance between the electron-pair donor hydroxyl groups and the hydrogen-bond donor amino groups in both are very similar, and for both, $\{\text{Mn}^{3+}\text{-}^t\text{Bu}_4\text{-salphen-18-cr-6}\}^+$, **II**, can serve as a ditopic receptor. The flux [20] of the previously reported [19] transport of serotonin by the boronic-acid-functionalized crown-ethers is nearly 100 times smaller than that determined for **II**.

For the transport of tryptophan, through a CHCl_3 BLM, the dependence of transport rate on the stirring rate of the BLM (Fig. 15) unequivocally indicates a diffusion-controlled process [20]. An increase in the stirring rate is expected to reduce the thickness of the Nernst layer. With a hindered carrier (Fig. 9B), difficulty in rapidly penetrating the interphase may introduce a slow kinetic step that may in fact become the rate-determining step.

The lipophilicity of the amino acids is correlated to their solubility in water [2,3,21]. The transport rates of the three lipophilic amino acids, tryptophan, leucine and phenyl alanine (Table 1) roughly follow their insolubility in water and indicate that π interactions, possible with tryptophan but not with leucine, are not very important in the transport process. The faster transport rate observed with the less hydrophilic tryptophan again suggests that, for **II**, the pickup of the amino acid by the carrier (rather than the release) is the rate-determining step in the transport process. A comparison of the fluxes for the transport of these amino

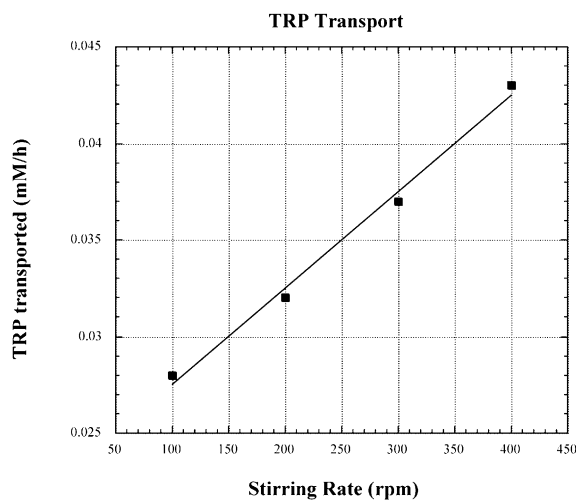


Fig. 15. Dependence of facilitated tryptophan transport through a CHCl_3 BLM by **II**-**I** on the stirring of the BLM.

Table 1

A comparison of tryptophan, phenylalanine and leucine transport^a, by different carriers across a CHCl_3 BLM.

Trp	Phe	Leu	Reference
0.03	0.03	0.01	^b
2.33	0.47	< 0.006	^c
N/A	0.01	0.006	^d
24.3	16.1	21.8 ^f	^e

^a Flux = mmol guest transported $\times 10^4$ (s) (cm²) (mmol carrier)

^b Source phase 0.1 N KOH; receiving phase 0.1 N HCl; carrier: tricaprylmethylammonium chloride [1].

^c source phase, H_2O ; receiving phase, H_2O ; carrier: Kemps triacid-acridine hybrid [2].

^d Source phase, H_2O ; receiving phase, H_2O ; carrier: lanthanide tris diketonate complexes [6].

^e Source phase, H_2O ; receiving phase, H_2O ; carrier: $\{(\text{EtOH})(\text{H}_2\text{O})\text{Mn}^{3+}\text{-}^t\text{Bu}_4\text{-salphen-18-cr-6}\}^+\text{I}^-$ (this work).

^f Source and receiving phases buffered at pH 7.2.

acids by different carriers across a CHCl_3 BLM is shown in Table 1 (flux is defined as: [mmol substrate transported] [mmol carrier]⁻¹ s⁻¹ cm⁻²).

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