Crown-Ether-Functionalized Mn(III) Salicylaldimine Complexes as Ditopic Carriers. Efficient Transport of Tryptophan and Serotonin across a $CHCl_3$ Barrier

Dell T. Rosa, Victor G. Young, and D. Coucouvanis*

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109-1055

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Our recent research interests in the chemistry of functionalized macrocyclic and salicylideneimine complexes[1] include the design and synthesis of crown-ether-containing ditopic receptor molecules. Related complexes have been reported previously;[2] however, their utility as sensors or transporting agents has not been evaluated. The development of carriers that can recognize and transport essential amino acids as well as specific physiologically important molecules is an area of great importance in biology. In this work specific emphasis is placed on the transport of tryptophan and neurotransmitters such as serotonin and dopamine. The active uptake of tryptophan is the first step in the synthesis of serotonin in the brain and is facilitated by a carrier that also transports other large neutral and branched-chain amino acids. Serotonin influences a multitude of brain functions including sleep, cognition, sensory perception, motor activity, temperature regulation, appetite, sexual behavior, and hormone excretion.[3]

Pioneering studies by Behr and Lehn[4a] have examined the pH gradient driven transport of amino acids across organic solvent "membranes" by positively or negatively charged hydrophobic carriers. Similarly, Newcomb et al. have reported[4b] on the chiral recognition and transport of amino acids by chiral, functionalized crown ether molecules. Since then, numerous other reports have appeared and include the transport of hydrophobic amino acids from aqueous solution at the isoelectric point across a $CHCl_3$ solution that contained a Kemp's triacid−acridine 2:1 condensate;[5] the transport of phenylalanine in a neutral pH transport system facilitated through a chloroform "membrane" by cooperative ditopic interactions between the amino acid, arylboronic acid, and crown ethers;[6] ditopic facilitated transport of catecholamines across bulk and polymer supported membranes by hydrophobic boronic acid−crown ether condensates;[7] the simultaneous transport of anions and cations by a neutral bifunctional receptor that contains calix[4]phosphate and an appended uranyl salophene unit;[8] interactions of ω-aminocarboxylates with a ditopic receptor that consists of a macrotricyclic quaternary ammonium unit bridged via a xylyl bridge to an aza crown ether;[9] and the ditopic fixation and transport of amino acids with a bifunctional metalloporphyrin receptor.[10]

In this communication we report on the synthesis, structure, and zwitterion-transport properties of the easily synthesized, crown-ether-functionalized $[Mn^tBu_4salphen(H_2O)(EtOH)18\text{-crown-}6]^+Cl^-$, **I**, complex. This molecule belongs to a new, general class of hybrid $[MR_nsalphen\text{-crown}]$ complexes that combine the electron pair donor characteristics of the crown ether component with the metal-dependent electron pair acceptor properties of the $R_nsalphen$-bound metal ions.

In a recent communication we reported[11] synthetic and structural studies of the $Ni^tBu_4salphen$-18-crown-6 complex, **II**, and its K^+, Cs^+ and $C_6H_{13}NH_3^+$ derivatives and preliminary studies on amino acid transport by these molecules. The slow rate of amino acid transport observed with **II** and derivatives is comparable to that observed with the simple benzo-18-crown-6, **III**. In **II**, the Ni(II) site is inert to base adduct formation and very likely does not serve as an electron pair acceptor in the transport of guest molecules. The similarity in transport properties between **II** and **III** must be attributed solely to the 18-crown-6 group, which is a common, guest-binding, feature in both molecules. Consistent with these observations is the inability of the $Ni(^tBu_4salphen)$-veratrole complex, **IV**, to facilitate transport of tryptophan. In **IV**, the benzo-18-crown-6 unit has been replaced by a 1,2-dimethoxy phenyl group (veratrole).

The synthesis of **I** is accomplished when an equimolar mixture of 4,5-bis(3,5-ditertiarybutylsalicylideneimine)benzo-18-crown-6[11,12] and $MnCl_2$ are allowed to reflux in air for 18 h in an EtOH/CH_2Cl_2 solution. Crystallization of the crude product from an acetone/ethanol mixture affords dark brown crystals of **I** that are isolated in 70% yield.[12] The structure of **I** has been determined[13] and shows (Figure 1) the Mn(III) ion in the salphen cavity, coordinated axially by water and ethanol molecules. The water molecule is also hydrogen bonded to three oxygen atoms of the crown ether unit of another molecule in an interaction that results in centrosymmetric dimers. The Mn-bound ethanol ligand trans to the water ligand ($Mn-O_{eth} = 2.215(3)$ Å) is hydrogen bonded to the Cl^- ion ($Cl-O_{eth} = 3.025(4)$ Å; $Mn-Cl = 4.541(1)$ Å). The magnetic moment of **I** ($\mu_{corr}^{eff} = 4.85\ \mu_B$ at 300 K) is typical for a high-spin d^4 ion.

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(11) Rosa, D. T.; Coucouvanis, D. *Inorg. Chem.* **1998**, *37*, 2328−2329. The transport properties of the K^+I^- and Cs^+I^- derivatives of Bz-18-C-6, **III**, were virtually identical to the alkali metal ion "free" crown.

(12) Satisfactory elemental analyses, mass spectroscopic data, infrared spectroscopic data, and electronic spectroscopic data are available as Supporting Information.

(13) Crystal data for **I**: space group $P\bar{1}$, $a = 10.9387(2)$ Å, $b = 14.3794(2)$ Å, $c = 18.4478(4)$ Å, $\alpha = 104.958(1)°$, $\beta = 104.245(1)°$, $\gamma = 99.140(1)°$, $Z = 2$, $R = 0.059$.

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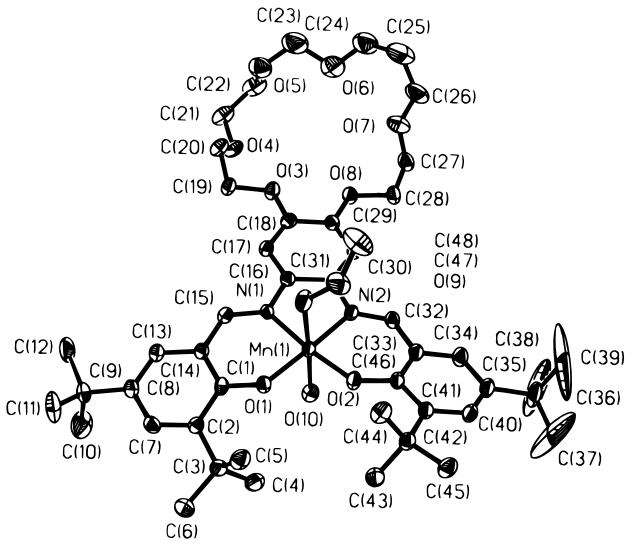

Figure 1. Structure and labeling of [Mn^{t}Bu$_4$salphen (H_2O)(EtOH)18-crown-6]$^+$Cl$^-$, **I**. Selected distances: Mn$-$O$_{salph}$ = 1.866(2) Å, 1.874(2) Å; Mn$-$O$_{H2O}$ = 2.289(3) Å; Mn$-$O$_{Et}$ = 2.214(3) Å; Mn$-$N, 1.990(2) Å, 1.992(3) Å; Mn$-$crown-ether centroid = 8.570 Å.

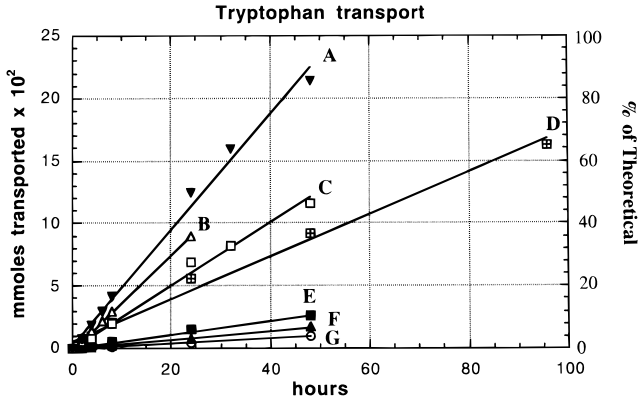

Figure 2. Transport of tryptophan by **A**, Cs$^+$-(**I**)$_2$; **B**, K-**I**; **C**, Cs-**I**; **D** [Mn^{t}Bu$_4$salphen(H_2O)(EtOH)18-crown-6]$^+$Cl$^-$, **I**; **E**, [Mn^{t}Bu$_4$salphen-(H_2O)(EtOH)24-crown-8]$^+$Cl$^-$; **F**, Bz-18-crown-6, **III**; **G**, [Ni^{t}Bu$_4$salphen-(H_2O)(EtOH)18-crown-6], **II**. The concentration of tryptophan was monitored by electronic spectroscopy, and the experiments were run in triplicate. Reproducibility was within 7%. As the system approaches equilibrium, the concentration in both aqueous compartments asymptotically should reach the same level at 0.25 mmol of tryptophan. The initial transport data are displayed as linear plots for all experiments, although the expected onset of curvature is apparent in **A.** With **A** as a carrier 86% of the theoretically expected 25 mmol of tryptophan was transported after 48 h. Excellent fits of the data were obtained using the equation $[Trp](t) = [Trp](t=\infty)(1 - \exp^{-kt})$, which describes first-order kinetics (where [Trp] = concentration of tryptophan).

The rate of transport of tryptophan from aqueous solution (isoelectric point, pH 5.89) was determined using **I** and its alkali metal derivatives as "carrier" molecules.[14] The transport properties of **I** and derivatives were found (Figure 2) far superior to those observed for **II** or **III** and the K^+ or Cs^+ derivatives of **II**.[11]

The cationic Mn(^{t}Bu$_4$salphen)-veratrole complex, **V** (used as a I$^-$ salt), which like **IV** does not contain a crown ether group, was found active in the transport of tryptophan, albeit at a much slower rate and an initial flux value of 5.5×10^{-5} mol·m^{-2}·s^{-1}·mol$^{-1}_{carrier}$. A similar flux was obtained for **III**. The marginal transport properties of **V** must be due entirely to the Mn^{III} axial sites that can be made available for interactions with electron donors (possibly the carboxylate group of tryptophan). The flux obtained from an equimolar mixture of **III** and **V**, at 1.0×10^{-3} mol/(m^2·s), is 30% less than that obtained for **I**.[14] These results[15] suggest that in **I** *both the Mn(III) and the 18-crown-6 sites contribute to the transport of tryptophan in a synergistic rather than an additive fashion.*

The transport rates of dopamine and serotonin·HCl using **I** as carrier were measured, and initial flux values of 2.2×10^{-4} mol·m^{-2}·s^{-1}·mol$^{-1}_{carrier}$ and 5.5×10^{-4} mol·m^{-2}·s^{-1}·mol$^{-1}_{carrier}$ were obtained, respectively.[14] These values are smaller than the flux obtained with the same carrier and tryptophan (1.4×10^{-3}, Figure 2D) but 4$-$5-fold larger than values obtained with **III** as a carrier.

The introduction of K^+ or Cs^+ in the crown-ether cavity of **I** results in tryptophan transport rates even better than those shown by **I** alone. This contrasts with the transport rates observed with the alkali metal derivatives of **II**, which were found considerably slower than those of alkali metal free **II**. The alkali metal complexes of **I** probably are structurally similar to the crystallographically characterized derivatives of **II**[10] (**II**:K^+, **II**:Cs^+, and (**II**)$_2$:Cs^+). The importance of the crown-ether size in the transport process is underscored by the observation that the 24-crown-8 analogue of **I** (**C**, Figure 2) is approximately 4 times slower than **I** (**E**, Figure 2). Preliminary kinetic studies show the transport of either tryptophan or serotonin to be first order in guest and first order in host concentrations.

In **I** possible binding sites for the Lewis acid or Lewis base groups of guest molecules include the Mn(III)$-$OH$_2$ center, which can serve either as an electron pair acceptor (following dissociation of the kinetically labile H_2O ligand) or a hydrogen bond acceptor (via a coordinated H_2O molecule). The 18-crown-6 group may serve as a hydrogen bond accepting site but upon addition of an alkali metal ion (K^+, Cs^+) is converted to an electron pair acceptor. The bridging phenyl group also could serve as a $\pi-\pi$ interaction site. The transport of a particular zwitterion by **I** shows variations that depend not only on the different alkali metal ions (K^+, Cs^+) but also on the halide ions (Cl^-, I^-) present. Systematic studies currently in progress are investigating the factors that influence the transport process.

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Supporting Information Available: Detailed synthesis and characterization of the compounds and transport data; tables containing listings of positional parameters, thermal parameters, and selected distances and angles of **I** (16 pages). Ordering information is given on any current masthead page.

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(14) The transport studies were carried out at ambient temperature in systems where a compartment containing 10 mL of an aqueous, 50 mM solution of tryptophan is separated from a compartment containing 10 mL of pure water by a layer (50 mL) of a 7.2 mM $CHCl_3$ solution containing the carriers The cell used was similar to one described previously,[5] and the surface area of contact between the phases is 22 cm^2. The fluxes reported are expressed as mol·m^{-2}·s^{-1}·mol$^{-1}_{carrier}$ and were calculated after 24 h of transport. The concentration of the transported tryptophan was monitored by electronic spectroscopy at 278 nm (ϵ = 5000 M^{-1}·cm^{-1}).

(15) The appropriate data and rate plots have been deposited as Supporting Information.