

## ABSTRACT

## Synthetic Ion Transporters: Membrane Activity of Amphiphilic Cobalt-cage Complexes with Aza-crown Spacer.

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This dissertation examines the field of synthetic ion transport systems which span an extensive array of structural archetypes that have dramatic effects on membrane permeability. It investigates a novel class of cobalt-cage metallosurfactant, with appended diaza-18-crown-6 ether moiety and varying alkyl tail lengths; specifically designed as potential synthetic ion transporters. The research focused on characterizing the molecular interactions between these amphiphilic cobalt-cage complexes and an array of membrane mimetic systems, to gain insight into their suprastructural membrane activity and mechanisms of action.

Electrochemical studies in planar bilayers reveal varying mechanisms of action depending on the concentration and lipophilicity of the amphiphile. The short-chain analogue formed transient pores and exhibited detergent-like activity; whereas low concentrations of long-chain amphiphiles formed stable, high-conductivity “pores”, and higher concentrations led to a detergent-like solubilization of the membrane. Non-linear concentration dependence and Hill coefficients suggested the possible formation of dimeric membrane-active species.

Comparative lipid monolayer studies at the air-water interface and DSC analyses of mixed amphiphile/DPPC liposomes demonstrated the formation of non-ideal, miscible systems, over the composition range investigated. Thermodynamically stable mixed monolayers were formed at low concentration and high packing density due to attractive intermolecular forces and geometric accommodation. However, at high concentrations, increased Coulombic repulsions and steric forces, led to more expanded monolayers and disruption of monolayer packing. Similarly, the impact of surface charge density and steric hindrance on membrane packing and permeability was reflected in the DSC data which showed abolition of the pretransition peak, linear depression of the main transition temperature and decreased cooperativity of the main transition, with increased amphiphile concentration. The fluidizing effects on bilayer packing were more pronounced with long-chain compared to short-chain amphiphiles, suggesting augmented partitioning into the bilayer and membrane-activity due to the hydrophobic effect (partition coefficients decreased with hydrophobicity). Both Langmuir and DSC studies suggest electrostatic interactions between amphiphile/lipid headgroups leading to reorientation of the phosphocholine moiety perpendicular to the membrane surface (at low concentration), and formation of an interdigitated state.

In conclusion, it was postulated that a toroidal-pore mechanism was operative at low concentrations, based on the mismatch between the intrinsic geometries of the single-chain surfactants and phospholipids, the observation of high-conductivity, dimeric “pores”, and prevalent amphiphile-lipid electrostatic interactions.

**Keywords:** Lorele Jeanine Lalgee; cobalt-cage complexes; differential scanning calorimetry (DSC); Langmuir monolayer; liposomes; model membranes; planar lipid bilayers; synthetic ion transport; voltage clamp.