



Synthetic ion transporters: Pore formation in bilayers via coupled activity of non-spanning cobalt-cage amphiphiles



Lorale J. Lalgee^a, Lebert Grierson^a, Richard A. Fairman^a, Gina E. Jaggernauth^a, Albert Schulte^{a,1}, Roland Benz^b, Mathias Winterhalter^{b,*}

^a The Department of Chemistry, The University of the West Indies, St. Augustine, Trinidad and Tobago

^b School of Engineering and Science, Jacobs University Bremen, Germany

ARTICLE INFO

Article history:

Received 24 August 2013

Received in revised form 7 January 2014

Accepted 27 January 2014

Available online 7 February 2014

Keywords:

Cobalt-cage metallosurfactant

Aza-crown spacer

Synthetic ion transporter

Lipid bilayer membrane

Liposomes

ABSTRACT

Three amphiphilic cobalt-cage congeners bearing a diaza-crown bridge and varying alkyl chains (**1:2:3**; $n = 12, 16, 18$) have been assessed for their ion transport across planar lipid bilayer membranes. In symmetrical electrolyte solutions, a range of ion transport activity is provoked: **1** disrupts painted (fluid) bilayers in a detergent-like mode of action; **2** forms conducting “pores” in folded (rigid) membranes with long open lifetimes (>2 min) while **3** requires the larger auxiliary solvent volume and lower lateral stress of painted membranes to effect ion transport via long-lived pores. Hill analysis of the conductance variation with monomer concentration yields coefficients (**2:3**; $n = 2.3, 1.9$) in support of dimeric ($n = 2$) membrane-active structures, for which the derived “pore” radii are correlated with charge-density of the transported cations and their affinity for the crown moiety. A toroidal-pore model is invoked to account for the flux of guest ions through planar bilayer membranes without a fast-diffusing intermediary or direct membrane-spanning structure.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Natural ion channels constitute a large group of membrane proteins that allow the passive diffusion of ions across biomembranes. Their importance to the vitality of living organisms is evident in their ubiquity and their crucial role in physiological processes such as propagation of electrical signals in the nervous system, coordination of muscle contraction and transport in all tissues [1]. Consequently, the function of transmembrane ion channels is one of the most extensively studied areas in modern biological chemistry and validates a growing thrust to investigate synthetic systems capable of regulating ion flow across biological membranes. Current mimics of natural ion channels span an extensive array of structural archetypes [2–9] and transmembrane functional activity; from well-defined ion channels with ion-selectivity and gating properties [2–9] to membrane disrupting agents with non-specific activity [10]. These model systems not only contribute to our fundamental understanding of the behavior of naturally occurring ion channels, but are also pertinent to the development of non-natural antimicrobials [11], catalysts and sensors [12,13], as well as potential therapeutic agents [14].

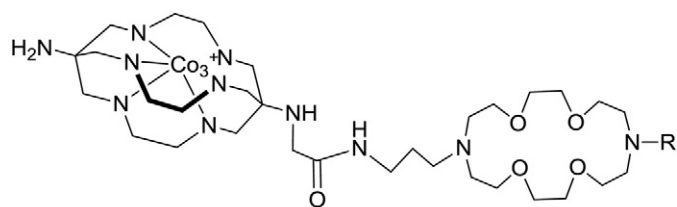
Some common designs of synthetic ion transporters feature combinations of [2]: (a) a single [5] or self-assembled [7–9] membrane spanning moiety, (b) an embedded relay or selectivity region and (c) hydrophobic segments for membrane solubility and branching interactions with the membrane. Nevertheless, measured ion transport across bilayer membranes by synthetic carriers may be uncorrelated to these specifications, due to the diversity of kinetic, ionic, pseudophase aggregation behavior and interfacial phenomena that, in concert, defy practical trending of structure–activity relationships. We therefore aim to extend the range of available synthetic ion transporters which may usefully probe these variables by combining (1) an inert, yet highly charged head group, (2) a metal-coordinating midsection (guest cavity or ionophore) and (3) an aliphatic tail of variable chain length (Scheme 1).

Other groups have explored binary permutations of these factors, ranging from head groups with molecular recognition capability [15] to *n*-tailed metallo-surfactants [16,17] and geminis [2,18,19] (double-headed groups, bolaamphiphiles). However, the simplicity of components in our ternary molecular configuration affords control of (i) hydrophobicity; through chain length variation, (ii) strength of host–guest interactions; variable by macrocycle ring size and donor atoms, and (iii) headgroup charge-density; limited or enhanced by the amide linker between the ionophore and the highly-charged pendant cage. Such a “stacked functionality” surfactant is at once a well-defined probe for modeling interactions at the interface, bilayer membrane interior, and aqueous environments of surfactant-lipid assemblies where host–guest interactions engender molecular recognition and ion transport.

* Corresponding author at: Jacobs University Bremen, School of Engineering and Science, Research II, Campus Ring 1, 28759 Bremen, Germany. Tel.: +49 421 200 3248.

E-mail addresses: lorale.lalgee@sta.uwi.edu (L.J. Lalgee), lebert.grierson@sta.uwi.edu (L. Grierson), richard.fairman@sta.uwi.edu (R.A. Fairman), gina.jaggernauth@sta.uwi.edu (G.E. Jaggernauth), schulte@sut.ac.th (A. Schulte), r.benz@jacobs-university.de (R. Benz), m.winterhalter@jacobs-university.de (M. Winterhalter).

¹ Biochemistry–Electrochemistry Research Unit, School of Chemistry and Biochemistry, Institute of Science, Suranaree University of Technology, Thailand.

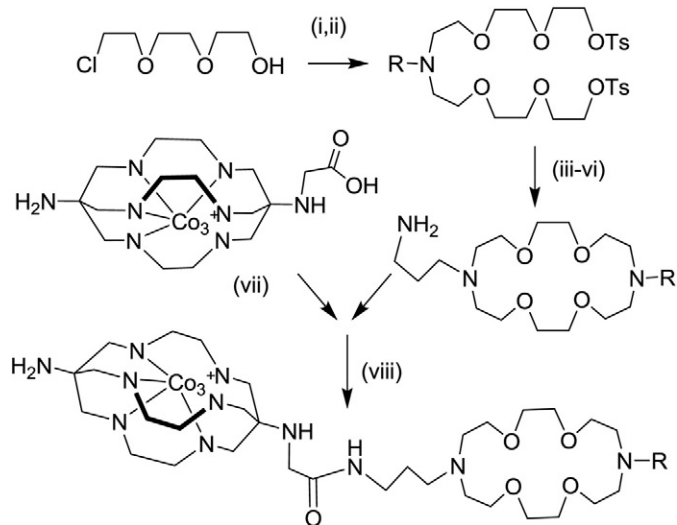


1, R = C₁₂H₂₅; **2**, R = C₁₆H₃₃; **3**, R = C₁₈H₃₇

Scheme 1. Structure of compounds **1–3** used in this study.

The large biological activity of amphiphiles such as **1–3** with the cobalt-cage headgroup [20–23] is attributed to two deterministic factors. The first is the electrostatic affinity of a negatively charged cell membrane for the highly charged cage, which ensures a high rate of membrane binding. Secondly, the embedded surfactants impose positive-curvature strain on the planar membrane [24,25] which is relieved by inward movement of the amphiphiles to maintain electrical neutrality. Ultimately, intracellular osmotic pressure increases and the cell ruptures. For supported bilayer membranes, a more detailed toroidal pore formulation is relevant. In this treatment the alien surfactant forces the membrane lipids to tilt relative to the bilayer normal, forming a well-defined, water-filled core that is lined by both alien and native lipid headgroups. Having a macrocyclic auxiliary, compounds **1–3** should enhance solubilization of guest ions in the bilayer, resulting in high rates of transmembrane ion flux. In related studies of **1** [26], a dramatic increase in the effective mean molecular area of the headgroup occurred with Mg²⁺ ions, indicative of high selectivity by the crown and also that changes in orientation of the molecule at the interfacial region are triggered by coordination of the guest. We apply the voltage clamp technique [1,27] in this work to directly assess the ion transport properties of **1–3** in the presence of different cations in the aqueous phase.

Given the new combined features of **1–3**, whether their aqueous aggregation behavior conforms to the standard packing parameter model (PPM) [28] is intriguing. According to the PPM, the nature of aggregate structures in water depends on hard-sphere type repulsive interactions of the head group (a = area), its size relative to the tail (l = length) and the total solvated volume of the amphiphile, V , through $p = V/al$. Limiting values of p are strongly correlated with aggregates shaped as spheres ($<1/3$) or cylinders ($<1/2$), vesicles (<1) planar lamellae (≈ 1)



Scheme 2. Synthesis of cobalt cage amphiphile. (i) DMF, K₂CO₃, 4d; (ii) p-TsCl, NaOH/THF, 0 °C; (iii) BzNH₂, MeCN, Na₂CO₃, 3d; (iv) H₂, Pd/C 50 °C, 8 h; (v) CH₂CHCN, 12 h; (vi) = (iv), (vii) SOCl₂, 3 h; (viii) K₂HPO₄, RT, 12 h. **2**, R = C₁₆H₃₃; **3**, R = C₁₈H₃₇.

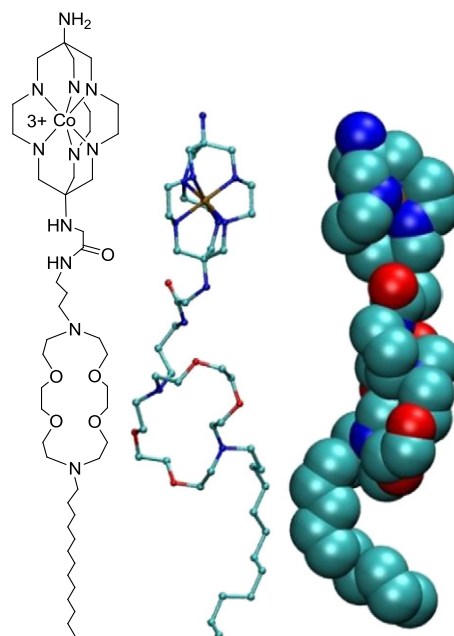


Fig. 1. Chemical and semi-empirical energy minimized structures of **1** (PM6 method [29]; COSMO [30] solvation; Mopac9 [29,31]).

and inverse micelles (>1). We utilize molecular modeling, surface tension measurements of the critical micelle concentration, and compared these estimates to atomic force microscopy previously reported [26] to test the PPM model for this class of novel surfactant.

A further geometrical consideration is that unimolecular **1–3** are unlikely to span the entire bilayer membrane in a manner which establishes a stable channel. We therefore posit that ion transport typical of channel formation can only originate through cooperative effects between monomers [8,9,32–37].

We conclude this report by interpreting the combined results according to the precepts of a toroidal pore model and hypothesize on the proximal interactions that are likely to establish such pores in the bilayer when **1–3** and their guest ions interact with the membrane.

2. Experimental section

2.1. Materials and methods

1,2-Diphytanoyl-*sn*-glycero-3-phosphocholine (DPhPC) and 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) were purchased

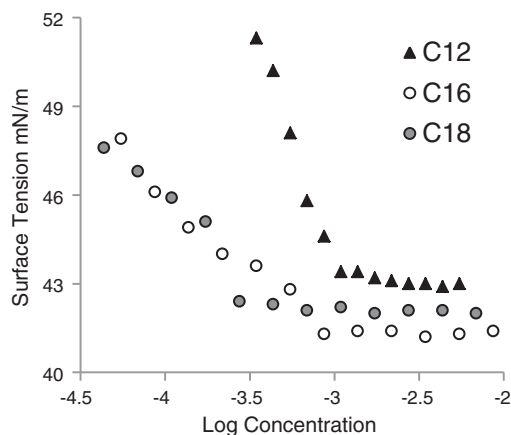


Fig. 2. Critical micelle concentration by discontinuity in surface tension for **1–3** (C₁₂, C₁₆, C₁₈).

Download English Version:

<https://daneshyari.com/en/article/10796864>

Download Persian Version:

<https://daneshyari.com/article/10796864>

[Daneshyari.com](https://daneshyari.com)