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Influence of the lipid environment on valinomycin structure and cation complex formation

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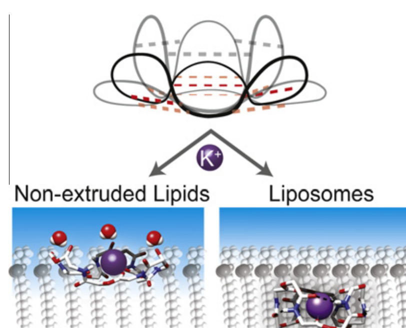
HIGHLIGHTS

- ▶ DUVRR can monitor protein dynamics during peptide solvation in lipid bilayers.
- ▶ Partially open and closed forms of valinomycin are sampled dynamically in lipid.
- ▶ The transient ion binding state is trapped with more hydrated lipid environments.

GRAPHICAL ABSTRACT



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ABSTRACT

Carrier-type molecular ionophores, such as the cyclic dodecadepsipeptide valinomycin, often must undergo structural changes during the binding and transport of a cation across the lipid membrane. Observing the structural fluctuations that occur during this process experimentally has proven extremely difficult due to the complexities of spectroscopic analysis of protein structure/dynamics in native lipid bilayer environments. Currently, our understanding of how valinomycin selectively transports ions across membranes is derived from atomic structures solved of the cyclic macromolecule solvated in various organic solvents and complimentary *in silico* dynamics experiments. We have shown recently that deep-UV excited resonance Raman spectroscopy (DUVRR) has a unique ability to characterize secondary structure content and simultaneously provide information about the relative solvation of the probed peptide backbone C.M. Halsey, J. Xiong, O. Oshokoya, J.A. Johnson, S. Shinde, J.T. Beatty, G. Ghirlanda, R.D. JiJi, J.W. Cooley, Simultaneous observation of peptide backbone lipid solvation and a-helical structure by deep-UV resonance Raman spectroscopy, ChemBioChem 12 (2011) 2125–2128, [16]. Interpretation of DUVRR spectra of valinomycin in swelled lipid and unilamellar lipid bilayer environments indicate that the uncomplexed valinomycin molecule dynamically samples both the open and closed conformations as described for the structures derived from polar and non-polar organic solvents, respectively. Upon introduction of potassium, the structure of valinomycin in swelled lipid environments resembles more closely that of the open conformation. The shift in structure upon complexation is accompanied by a significant decrease in the valinomycin DUVRR spectral amide I intensity, indicating that the open conformation is more water solubilized and is seemingly “trapped” or predominantly located close to the lipid–water interface. The trapping of the valinomycin in the act of complex of potassium at the bilayer-solvent interface and its analysis by DUVRR represents the first spectroscopic description of this state. Conversely, an opposite trend is observed in the amide I intensity upon potassium complexation in unilamellar (or extruded) vesicles, implying the predominant conformation upon potassium binding in native bilayers

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is one where the peptide backbone of valinomycin is desolvated as would be expected if the molecule were more readily able to traverse a bilayer interior. Interpretation of the DUVRR spectral features is also consistent with the loss or formation of hydrogen bonds observed in the open and closed structures, respectively. Valinomycin must then sample several conformations in the absence of appropriate ions depending upon its locale in the lipid bilayer until potassium causes a greater degree of closure of the open conformer and an increased residency within the more non-polar interior. The potassium induced decreased solubility enables diffusion across the membrane where potassium release can occur by equilibration at the opposite lipid water interface.

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Introduction

The ionophore valinomycin (Val) belongs to a broad class of antimicrobial peptides that alter the function and integrity of lipid bilayers. Val itself is a potent K^+ ion transporter, which has been used extensively in a variety of studies to collapse membrane potentials ($\Delta\psi$) during investigations of membrane trafficking and enzyme catalysis [1,2]. The simplicity of Val's molecular architecture has facilitated its use as a model for how selective membrane transport is achieved by antimicrobial peptides. Val is a dodecadepsipeptide comprised of a repeating, cyclic trimer of alternating peptide and ester bonds whose formula can be written as cyclo-(D-valine-L-Lac-L-valine-D-Hyv)$_3$ where Lac is lactic acid and Hyv is hydroxyvaleric acid. The valine residues alternate between the D and L conformations and, thus, the stereochemistry lends itself to a general tennis ball seam appearance, moderated by breaking and forming hydrogen bonds intramolecularly or with polar solvent (Fig. 1). The six amide carbonyls are all oriented towards the metal cation forming a near ideal octahedral environment for complexation, selective for potassium based on ionic radius [3].

The mechanism of the potassium-selective ionophore has been a target of biophysical spectroscopic efforts dating back to its initial isolation from *Streptomyces fulvissimus* in 1955 and total synthesis in 1963 [4–6]. Historically Val was the first ionophore whose structure was derived from spectroscopic methods prior to obtaining an atomic structure [7]. The uncomplexed state is highly sensitive to solvent polarity while the complexed state is only weakly so. Three conformations of the uncomplexed state vary from fully hydrogen bonded valine residues to no intramolecular hydrogen bonding. In general, Val adopts a relatively rigid structure in non-polar medium and a more flexible structures in more polar organic media [8]. Of these conformations, previously [9] named the A, B, and C states, the structures solved in non-polar (*n*-octane) (Fig. 1A) and medium polarity (dimethyl sulfoxide) (Fig. 1B) are thought to represent the most biologically relevant. Of particular note when examining the structure of the solved structures is differing hydrogen bonding of the amide backbone. Specifically, conformation A features six $4 \rightarrow 1$ type intramolecular hydrogen bonds between an amide (Am) N–H and carbonyl oxygen (Fig. 1A). In the more flexible conformation B, only three intramolecular hydrogen bonds remain and are formed by the D-valine NH group to the Am carbonyl (Fig. 1B). The consequence is an open conformation on one side of the ring. Upon complexation, the ester carbonyls coordinate a central potassium atom while maintaining the hydrogen bonding motif similar to that of conformation A (Fig. 1C), regardless of solvent polarity. All that is known about the structure of Val and its changes with K^+ binding are presently derived from studies carried out in organic solvent environments, which lack the amphiphilic and ordered phase geometries of a lipid bilayer or membrane.

Determination of biomolecular conformation within lipid membranes has improved dramatically in terms of the complexity and size of the structures capable of being solved [10]. X-ray diffraction or NMR methods have not generally been amenable to samples of Val solubilized in lipid bilayers due to its rapid structural dynamics and the atomic complexity associated with the lipid milieu. However, lower resolution techniques like CD, IR, and Raman spectroscopy have been invaluable for the structural characterization of Val, especially in solution. To date, no single technique has been successful in interrogating Val's structure while it is present in dilute

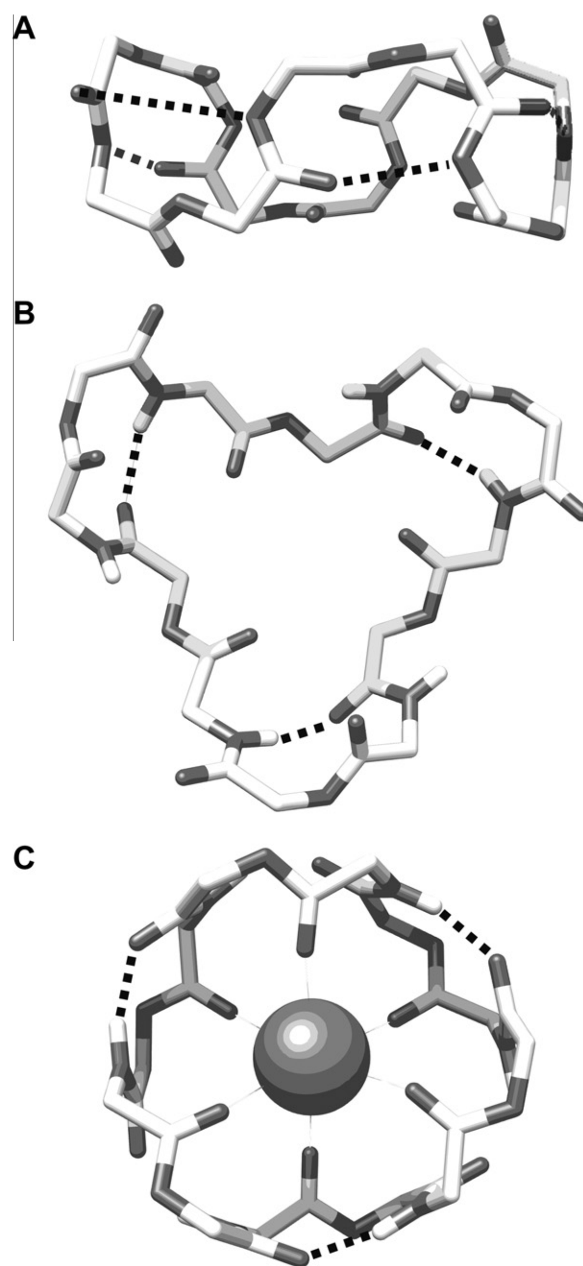

Fig. 1. Various structural forms of Val. Representations of the crystal structures derived from (A) non-polar (Cambridge Database ID: VALINM30), (B) polar solvent (GEYHOH), and (C) complexed to potassium (purple) (VALINK). Dashed lines represent hydrogen bonds, with the two planes of bonds indicated as black or gray. Structures are taken from references [29–31]. To be reproduced in color online only.

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