Light-induced generation of the active chloride-phosphate anionophore from its inactive proanionophore

Oindrila Biswas,† Priyanka Mazumder,§ Avigyan Naskar,‡ Soumya Srimayee† Sachin Kumar,+ Niladri Patra,‡ and Debasis Manna\*,†§

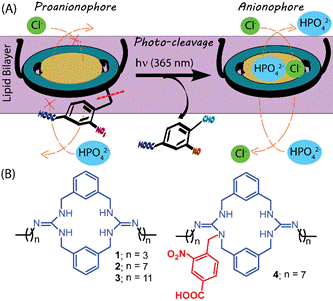
†Department of Chemistry, Indian Institute of Technology Guwahati, Assam 781039, India. §Centre for Environment, Indian Institute of Technology Guwahati, Assam-781039, India. ‡Department of Chemistry, Indian Institute of Technology (Indian School of Mines) Dhanbad, Jharkhand 826004, India. +Department of Bioscience and Bioengineering, Indian Institute of Technology Guwahati, Assam-781039, India

\*E-mail: [dmanna@iitg.ac.in](mailto:dmanna@iitg.ac.in)

**ABSTRACT**

Protein ion channels form an integral part of every living cell. Their mimics play an essential role in investigating the functions of these ion channels and provide an insight into the related biological events. Misregulation of transport of highly biologically abundant ions like Cl─, HCO3−, HPO42−, and SO42− results in channelopathies.1-3 Phosphate and phosphorylated molecules serve as the building block for various essential substances used by the cell for important biological purposes. Sodium-dependent phosphate transporters such as type II (SLCA34) and type III (SLC20) are primarily accountable for the influx of extracellular phosphate transport.4 However, disruption of the natural protein machinery responsible for the transport of phosphate ions causes phosphate imbalance in the body, resulting in hyperphosphatemia or hypophosphatemia. Recently, several conventional synthetic ion transporters like prodigiosin, calix[4]pyrroles, and others have been developed to mimic the functions of natural protein machinery and also to induce apoptosis in cancer cells.1, 3 However, ion transport-promoted unwanted death of normal cells remains a major concern for ion therapy. So, to minimize the apoptosis of the normal cells and selectively target the cancer cells, biomimetic stimuli-responsive systems are being used, which are triggered in the presence of any external or natural stimuli like a ligand, mechanical force, and light, specifically in the cancer cells. The use of light-triggered ion transporters can give site-selective precise control over the functioning of the ion transporters. Lately, “optochemical genetics” has integrated natural protein channels with various photoswitches to achieve optical control.7, 8 Therefore, a strategically placed photocleavable or photoisomerisable moiety tethered to the main anionophore can serve the purpose well.

Herein, we synthesized C2 symmetric guanidine-based macrocycles conjoined with hydrophilic alkyl chains of varying lengths. Fork-like guanidium moiety was installed in the macrocycle because of its selective interaction with phosphate ions. The alkyl chains were installed in the macrocycle to bridge the hydrophilicity and hydrophobicity of the anionophore and to provide an anchor for the anionophore in the membrane. The ion binding scaffold and the hydrophobic domain impart lipophilicity to transport the ions. The guanidinium macrocyclic pore contained the much-needed array of H-bond donors for oxyanion recognition. To further explore the concept of a photocleavable proanionophore, we attached the *o*-nitrobenzyl (ONB) group with the guanidium-N moiety. On shining light (365 nm), the ONB group easily cleaves off, paving the way for the anionophore to carry its ion transport function. The ONB group has been immensely exploited in numerous applications to cleave under photoirradiation. However, in ion transport, the use of the ONB group has been rare except for a few examples.



**Figure 1.** Schematic representation of the photomediated generation of ionophore from ONB-linked proanionophore (A). Structures of the synthesized compounds (B).

**References:**

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