European Journal of Medicinal Chemistry 45 (2010) 1799–1804

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

# Mechanistic aspects of transport antibiotics

A. Banerjee, A. Yadav*

*Department of Chemistry, University Institute of Engineering and Technology, CSJM University, Kanpur 208024, India*

ARTICLE INFO

*Article history:*
Received 4 November 2009
Accepted 7 January 2010
Available online 15 January 2010

*Keywords:*
Transport antibiotic
Nactins
Ion carriage
Valinomycin

ABSTRACT

Ab initio molecular orbital calculations at the Hartree Fock level have been performed on transport antibiotics. Conformational aspects together with electrostatic interactions play a role in determining efficient transport properties of these compounds. Our results indicate that cytotoxicity of nactins may be related to their highly reorganized ionophore in presence of ion leading to tightly bound ion that cannot be delivered at site of action. Mechanistic aspects discussed in this study will enable efficient designing of compounds with more drug like features and prospective usage as immunosuppressants.



## 1. Introduction

Nactins are macrotetrolide antibiotics [1]. They are antibacterial agents that act by making the bacterial cell more permeable towards ions. Poly nactins refers to group of antibiotics produced by streptomyces aureus. The biological activity of nactins grows as their 'number' grows. Structures of nactins are shown in Fig. 1. Nonactin, the parent compound is the least potent. Tetranactin is the most abundant and most potent [2]. However nactins have not been clinically used as antibiotics due to cytotoxicity problems at higher concentrations. They have been used to study cation transport through biomembranes [3–5]. Recently, tetranactin has been shown to possess immunosuppressive properties analogous to cyclosporine A [4–6]. Recent developments have led to increased interest in these compounds for their prospective use in development of new and improved immunosuppressive drugs [6,7]. Tetranactin has been observed to be immunosuppressive at concentrations as low as 1 ng/ml [8,9]. It is not toxic at such low concentrations. Interest in macrolide antibiotics, cyclic ionophores and cyclic peptidic/peptidomimetic compounds is multifold [10]. They are transport antibiotics impairing mitochondrial functions due to ion uptake by mitochondria. Some of them can act as electrodes in pure form or as ion carriers across natural or artificial membranes. Tetranactin has been used as $K^+$ ion detector due to its high selectivity towards $K^+$ ions as compared to $Na^+$ ions [11]. Tetranactin also has potential use in therapy of diseases associated with increased group II phospholipase $A_2$ activity [12]. They also show channel or tubular formation to some extent depending on the structure/conformational aspects [13]. However due to complexity of possible conformations in these systems very few conformational studies have been undertaken in the past [14,15]. They also carry potential to be used in removing ion toxicity from body.

In this study ab initio quantum mechanical calculations have been performed on various nactins to understand variations in conformations and its impact on transport properties of nactins and their selectivity towards cations, potency etc. These calculations will help us understand mode of action of these compounds.

Calculations have also been performed on a clinically used antibiotic valinomycin which is also transport antibiotic to understand features that make it clinically usable. Chemical structures of compounds studied are shown in Fig. 1. An attempt has been made to design some cyclic peptidomimetic lead compounds with more 'drug like features'.

## 2. Methodology

Ab initio Hatree Fock molecular orbital calculations [16] have been performed for various transport antibiotics. Complete geometry optimizations have been performed utilizing Berny's algorithm [17] at 6–31G basis set [18]. Ion carriage by these compounds has been studied utilizing intermolecular interaction calculations.

Interaction energies between compound and ions have been calculated by supermolecule approach i.e. $\Delta E_{int} = E_{AB}^{supermolecule} - (E_A^{ion} + E_B^{compd})$. Ions have not been allowed to be covalently linked with the ionophore as we want to study carriage of ions not complexation. This study is directed towards understanding mode of action of these drugs. Ion is held inside drug by non bonded

* Corresponding author. Tel.: +91 9415405636; fax: +91 512 2590007.
*E-mail addresses:* antaraemails@gmail.com, arpitayadav@yahoo.co.in (A. Yadav).

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doi:10.1016/j.ejmech.2010.01.012

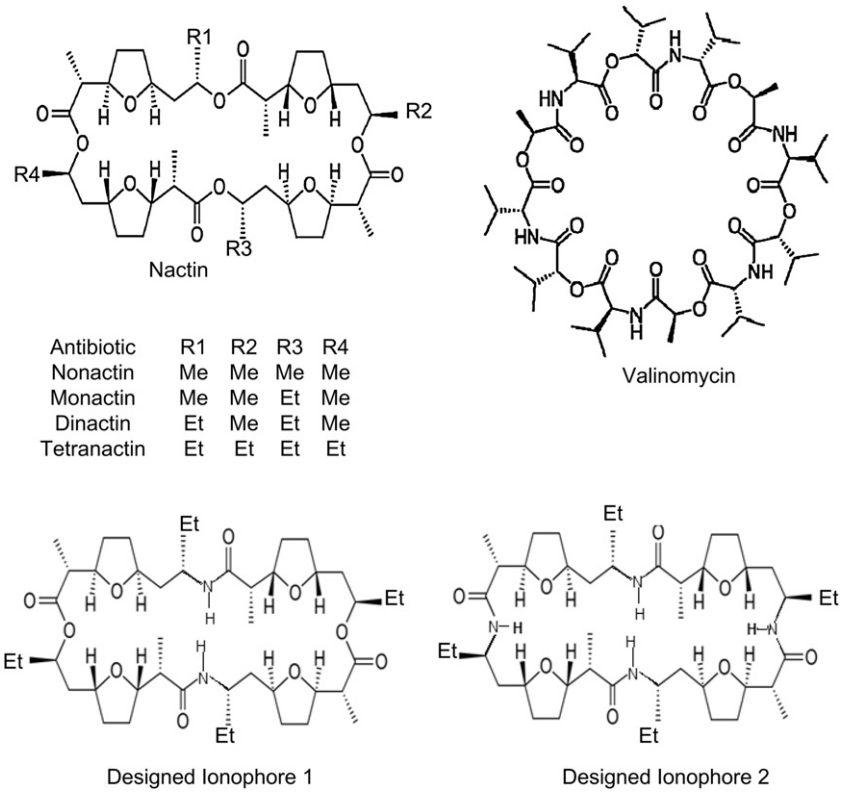


**Fig. 1.** Chemical structures of various transport antibiotics.

interactions so that it can be emptied inside bacterial cell. We have studied possible locations where ion can be held and carried. Possibilities of multiple ion carriage have been explored. Reorganization of ionophore in presence of ion has also been estimated. Conformational and electrostatic contributions towards facile ion carriage have been estimated.

Recent study on valinomycin has indicated little possibility of conformational reorganization in ionophore [19] on capturing ions. Present study is directed towards accurate estimation of electrostatic and conformational contributions for facile ion carriage in nactins. Large accurate ab initio calculations at the Hartree Fock level have been undertaken so that relative potencies of different nactins can be explained mechanistically. These calculations have been compared with results on valinomycin to understand characteristics rendering it qualities of a drug.

All calculations have been performed utilizing GAUSSIAN '03 [20] software. GAUSSVIEW [21] has been used for all graphical representations.

## 3. Results and discussion

Top and side views of optimized conformations of prototype nonactin are shown in Fig. 2 which forms the basis of their classification. Top view of these forms gives an idea of the space available for ion carriage. It is interesting to note that in all these forms most of the hydrophobic substituents are disposed outwards which is essential for the antibiotic to cross bacterial cell membrane. Bloated and donut conformations corresponding to stretched backbone are higher in energy. Fig. 3 shows optimized conformations (in top view) for monactin and dinactin. In monactin energy difference between different forms is considerably increased due to introduction of one large substituent and disturbed symmetry. In dinactin cradle and donut forms are somewhat equivalent. Bloated

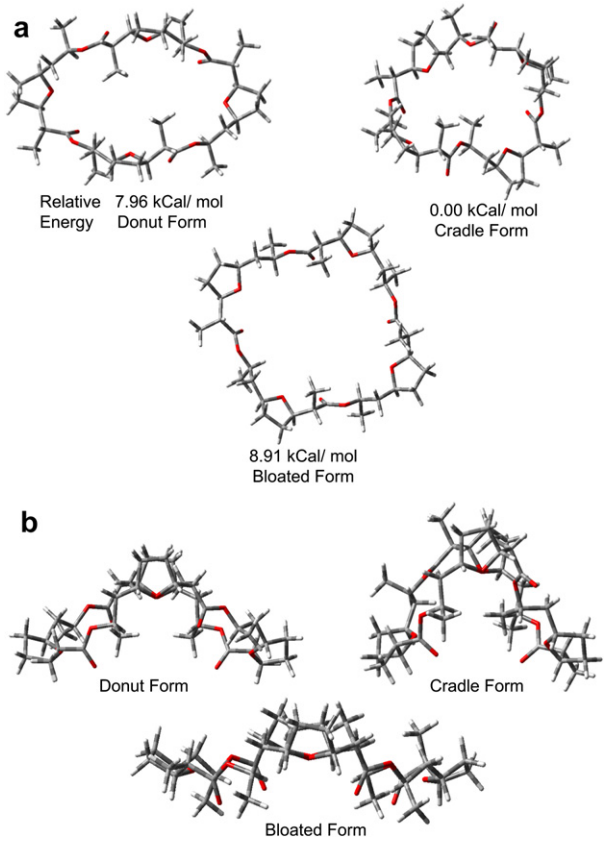


**Fig. 2.** a. Top views of optimized conformations of Nonactin. b. Side views of optimized conformations of Nonactin.