

Low Toxicity β -Cyclodextrin-Caged 4,4'-Bipyridinium-bis(siloxane): Synthesis and Evaluation

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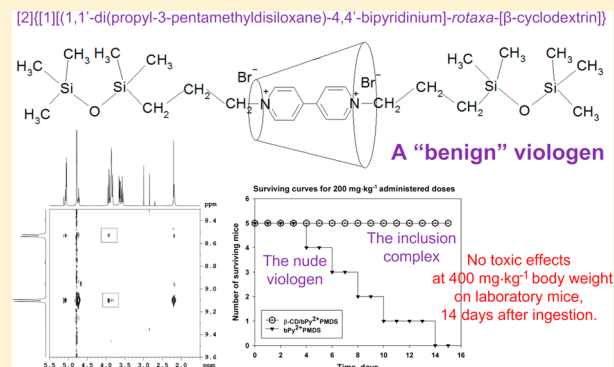
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S Supporting Information

ABSTRACT: The toxicity of viologens can be significantly reduced by including them in tight [2]rotaxane structures alongside β -cyclodextrin, thus turning them into candidates of pharmaceutical interest. Here, we report a synthesis pathway for a benign viologen, by capping a small β -cyclodextrin-caged molecule, the 4,4'-bipyridine, with minimal-length presynthesized axle-stopper segments of the propyl-3-pentamethyldisiloxane type. After 90 min from the oral administration to laboratory mice, the product concentration in the bloodstream reaches a value equivalent to 0.634% of the initial dose of 800 mg·kg⁻¹. As compared to the nude viologen having the same structure, which proved to be lethal in doses of 40 mg·kg⁻¹, the product induces reversible morphological changes in the liver, kidney, lung, and cerebellum, up to a dose of 400 mg·kg⁻¹, with higher dosages giving rise to a chronic slow evolution.



1.0. INTRODUCTION

Through appropriate chemical architecturing, toxic compounds like viologens can be transformed into pharmacologically active species.^{1,2} As we will further demonstrate, the toxicity of viologens (1,1'-di(hydroxycarbyl)-4,4'-bipyridinium salts, according IUPAC nomenclature) is significantly diminished by host–guest complexation, which turns them into candidates of pharmaceutical interest.

Viologens became interesting to the scientific world in 1933 when Michaelis reported his first study on their electrochemical properties.³ Surprisingly for those early studies, viologens showed the lowest redox potential as compared with any other organic compound, together with a significant degree of redox reversibility. Shortly after that, they became the “parents” of a whole herbicide family, mainly because of their redox potential.⁴ It has been also demonstrated that electrochemically reduced viologens can further reduce compounds that are not electroactive by themselves.^{4,5} Recently, viologens were involved in advanced applications such as electrochromic display devices,⁶ molecular wires in molecular electronic devices,⁷ and prooxidants in oxidative stress testing.⁸ Viologens also revealed antibacterial efficiency⁹ toward *Escherichia coli*,

due to their ability to accomplish DNA strand scission.¹⁰ Methyl viologen (Paraquat) has been extensively used as a herbicide,^{11–13} and numerous works were done to evaluate its action on the human body because of the severe suspicions about its toxicity against mammals,¹⁴ induced by its low redox potential.^{15–17} Hatcher et al.¹⁸ have proved the ability of several pesticides, including those from the class of viologen herbicides, to increase the incidence of Parkinson's disease. Once ingested, 4,4'-bipyridyl viologens (bPy²⁺) can be enzymatically reduced to form a radical cation (bPy^{•+}) which, in the presence of O₂ and/or H₂O₂, generates highly reactive radicals (e.g., HO[•]), causing the oxidation of some species of biochemical importance, like cell membrane lipids, proteins, and nucleic acids.⁸ In this context, scientists are trying to develop new strategies for the treatment of viologen poisoning but also to capitalize its redox potential in pharmacological purposes. Of current interest is the host–guest complexation with cyclodextrins (CDs), which can be evidenced by spectroscopic methods based on the changes of spectra upon complexation.¹⁹

Received: November 5, 2013

Published: February 24, 2014