STRUCTURE/FUNCTION STUDIES OF ATROPINE: CUCURBITURIL COMPLEXES

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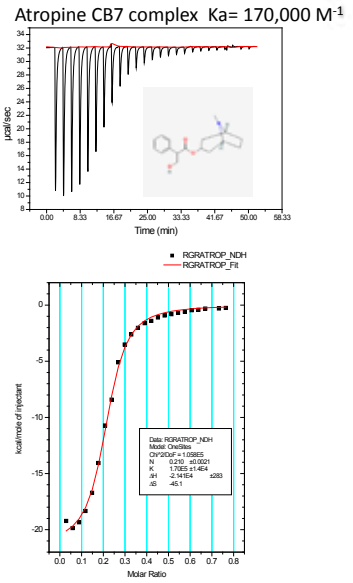
Introduction: There are over one million accidental exposures to organophosphate insecticides annually. Weaponized organophosphates (sarin) released in a Tokyo subway caused many casualties. The antidote, atropine, is difficult to titrate and overdose leads to an anticholinergic toxidrome. We are investigating whether excess atropine can be chelated with a readily available macrocycle to help control its side effects.

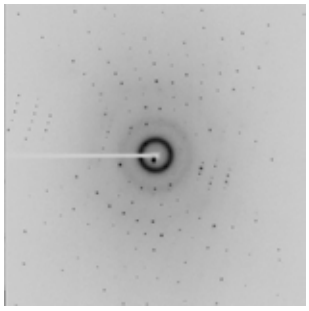
With over 5 million Americans abusing cocaine, it is not uncommon to have to provide anesthesia for patients requiring emergency surgery who are cocaine toxic. Decades of attempts to modify cocaine's structure to make a receptor blocker, similar to naloxone for morphine, have been futile. We are studying the structure of atropine with cucurbituril to determine if a macrocycle-cocaine inclusion complex can be created.

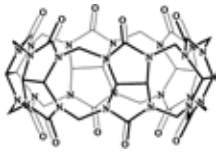
Methods: The binding constant of atropine to cucurbit[7]uril (CB7) was measured using isothermal titration calorimetry. Crystallization of the complex was achieved by controlled evaporation and X-ray diffraction data were measured at the Advanced Photon Source, Life Sciences Collaborative Access Team (LS-CAT) beamline 21-ID-D. The crystals are orthorhombic and diffract to 0.97Å resolution.

Results: The binding constant of atropine to cucurbit[7]uril (CB7) was determined to have a Ka= 170,000 M-1. The crystal structure reveals that the portal carbonyls of the cucurbituril interact with the nitrogen of the atropine tropane ring.

Significance: These studies will help design new drug antidotes. In the interest of homeland security, anesthesiologists and other first responders will have additional tools in their armamentarium to reverse the effects of weaponized chemicals. Drug abuse may be treated with a modified macrocycle that can scavange and encapsulate cocaine.







Cucurbit[7]uril