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Project Title: **Managing Tight-binding Receptors for New Separations Technologies**

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MANAGING TIGHT-BINDING RECEPTORS FOR NEW SEPARATIONS TECHNOLOGIES

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RESEARCH OBJECTIVE

The research objective of this project is to exploit extremely tight-binding ligands for new separations technologies by gaining control over the properties that militate against such applications. The main advantage of these ligands is in the feats they can accomplish not accessible to ordinary ligands, such as binding in extremely dilute solutions and extracting metal ions from mineralized deposits. Their main limitation is that, as the affinity increases, the rates of binding and dissociation decrease very greatly. Thus the best tight-binding ligands react too slowly to be useful in most known separations and remediation technologies. The subject program aims at solving this basic problem through three specific goals:

1. Make tight-binding ligands that bind fast using the new concept of "switch-binding" instead of equilibration.
2. Make tight-binding ligands that dissociate fast using the new concept of "switch-release".
3. Develop a "soil poultice" as a slow technology for remediation of contaminated soils.

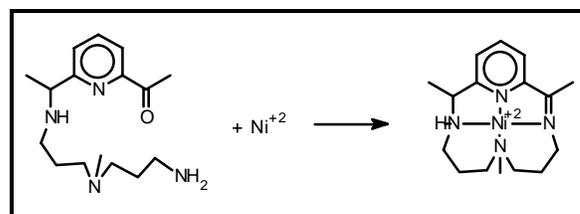
RESEARCH PROGRESS AND IMPLICATIONS--as of 32nd month of a 3 year grant

Ligands Designed for Switch-binding

First Demonstration of Concept. Hypothesis: *if a linear chelating agent can convert to a macrocyclic ligand during the course of binding a metal ion, the reaction can be fast, but the stability can be great.* First verification was achieved with a system composed of 2,6-diacetyl pyridine, 3,3'-diaminodipropylamine, and nickel(II) ion, which behaves as if a single organic reagent were present the initial organic reaction is allowed to precede prior to addition of the metal ion. Further, the reaction then proceeds to the desired macrocyclic product rapidly and quantitatively. As expected, reactions between switch-binding ligand and metal ion are observed in two time regimes; the linear ligand binds to the metal ion on the millisecond time scale, followed by a macrocyclic ring closure on the seconds time scale. The latter reaction confers on the product the stability and lethargy of a macrocyclic ligand. Further, the rates we observed are much faster than the slow rates observed for macrocycles.

Generation 1 "Switch-binding" Ligands. The first ever family of switch-binding ligands has been specifically designed. Such a ligand is a linear tetradentate molecule with functional groups at its extremities that will condense with each other in the presence of a complementary metal ion to produce a macrocycle that encompasses the metal ion (**equation**).

Physical studies proving the switch-binding concept are nearing completion. Because in the absence of metal ions the ligand reacts with itself to form a variety of

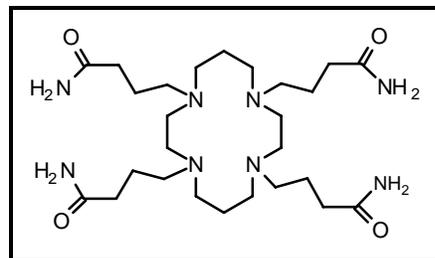


products at most pH values, two closely related “stand-in” molecules have been used to estimate pK values and speciate ligand solutions. We deduce that most of the ligand is diprotonated near pH 5.5, and mostly in the monoprotonated form near pH 8. The two species are about equal in concentration at pH 7. Subsequent kinetic studies reveal almost identical behavior on the parts of the switch-binding ligand and its “stand-in” despite the contrasting final structures of the complexes. The overall macrocyclization reaction is about as fast as the rate of chelation of the simple tetradentate ligand, proving that switch-binding can bring the rates of formation of tight-binding ligands into the same time regime as that of ligands with relatively moderate binding affinities.

Ligands Designed for Switch-release. Approaches to macrocycles and cryptates possessing phototriggerable side chains, or attached directly to a macrocycle bridge, are in progress. We have constructed a protected 1,4,7-triazaheptane for coupling with a diacid chloride in the closure process for the synthesis of a functionalized macrocycle. The yields were low (20%) and work is in progress to improve these to useful levels. We have also constructed the macrocycle, 4,7,10-tris(*p*-toluenesulfonyl)-4,7,10-triaza-1-oxacyclotetradecanylemethanol, by a Grubbs olefin metathesis in 32% from its bis-allyl precursor. This will serve as the basis for incorporating the phototrigger via an *o*-nitrophenyl ethylene glycol unit. We have appended substituted benzoyl derivatives to the amine function on 7,16-aza-1,4,10, 13-tetraoxocycloicosane through the reaction of the acid. These amide linkages are models for the desired cinnamate derivatives, and synthesis of the trans *o*-hydroxycinnamic acid analogue is in progress.

Macroporous Polymers.

Synthesis and Characterization of polymers. These studies featured the nickel(II) complex of a cyclam derivative having amide terminals on pendant arms (**Structure**) to hydrogen-bond to polymer sites. The macroporous polymer was templated to match this molecule. To produce highly crosslinked polymers with mesopores (20-500Å diameter), ethylene glycol dimethacrylate, EGDMA, was used as a two point crosslinking agent. The active monomer was acrylamide, with acetonitrile as the porogen. Polymers **P1** and **P2a** were imprinted with perchlorate salts. Polymer **2b** used the vinylsulfonate salt. A control polymer (**P3**) with no imprint was also synthesized. Following polymerization, the imprinting complex was removed and the new polymers were characterized by infrared spectroscopy, polymer swelling, and surface area/porosity measurements. Even though the porogen and crosslinker were the same in all polymers, polymer morphology varied. **P2a** and **P3** gave surface areas of slightly greater than 200m²g⁻¹, in the range expected for macroporous resins (50-1000m²g⁻¹), but **P1** and **P2b** have both much reduced surface area (about 10m²g⁻¹) and less swelling.



Complex Rebinding Studies. The rebinding of the nickel(II) tetramide macrocyclic complex with the four polymers was evaluated in this first proof of concept study. The chemical literature reports 15-20% rebinding of the imprinted sites for polymers featuring hydrogen bonding. For our polymer **P2a**, complex rebinding was found to fill 21% of the sites, at the top end of the previously observed range. Further, comparison with the untemplated polymer (**P3**) showed that the templated polymer binds over 2½ times more complex. This bodes well for the success of this entirely new methodology and its important proposed applications. Further, we hold high hopes for greatly increasing the rebinding capacity by templating the counter ion into the selective site and polymer **P2b** was designed for this purpose. Despite the unfortunate fact that our sample **P2b** is not highly porous, the rebinding of the complex filled 25% of the available sites, actually exceeding the rebinding to our nicely macroporous baseline polymer **P2a**.

PLANNED ACTIVITIES

A no-cost extension has been requested to permit completion of two aspects of the work: (1) Complete synthesis of tetraazamacrocycles from which metal ions can be released by photoswitching; this will strongly complement the more complete work on switch-binding. (2) Maximizing the selective binding of the templated macroporous polymers; here strong leads suggest the bold new technology may work, especially if counter ions can be brought into the binding process of highly macroporous templated polymers.