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Managing Tight-binding Receptors for New Separations Technologies

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Research Objective

Whereas such traditional separation methodologies as ion exchange and solvent extraction require rapid interaction between ligands and metal ions, the most strongly binding ligands invariably bind slowly; e.g., cryptates bind and dissociate more slowly than macrocycles, which are slower than open-chain chelating ligands. This project seeks to maximize the binding and dissociation rates for tight-binding receptors in order to make them more useful to separations science. An alternative slow-binding technology is also under exploration.

Research Progress and Implications

Acceleration of Binding: Sixteen months into this 3 year project, seminal examples of a new class of ligands have been designed and synthesized, and the basic premise of the project has been confirmed. This work involves the design and synthesis of very special ligands that seek to capture the best properties of open-chain chelates and macrocycles. The ligands must begin as open-chain structures so they can bind fast, but they must have reactive groups that close the structures into macrocycles upon chelation to metal ions. There exists no literature precedent for such ligands, putatively because of the great tendency of the two ends of the molecule to react with each other. Synthetic challenges were indeed encountered en route to our first generation ligand **1**, a molecule in which the ligand extremities are carbonyl and amine groups that can condense to form a C=N linkage. The ligand has now been properly characterized and is available for detailed studies. Solution studies on the binding of ligand **2**, which is generated in solution, have confirmed the basic hypothesis that the rate of macrocyclic complex formation can be quite rapid when metal ion templated ring closure is involved. Solution studies have also shown that the Schiff base condensations like those involved in forming macrocyclic complexes with **1** and **2** can be reversed. Second generation ligands **3** and **4** are sought; the first to provide a macrocycle with no fused pyridine ring and the second to utilize a different ring closure reaction, ester exchange. **4** has been synthesized in high yield and characterized.

Figure 1

Planned Activities: Detailed equilibrium and kinetic studies of **1** will be conducted. Conditions for ring closure will be found for **4** and its derivatives. Synthesis of **3** will be completed. **3** and **4** will be subject to detailed study when appropriate. Third generation ligands will be designed and synthesized. Kinetic data will be compared with literature data on open-chain chelates and macrocycles.

A Biomimic as a Possible Slow Separations Technology: Certain single cell organisms secrete powerful sequestrants (siderophores) for iron and then absorb the iron complexes back through their membranes. Imprinted macroporous polymers¹ may provide the equivalent of the cellular membrane

for selective adsorption of complexes of tight-binding ligands. Separation by such a process need not be rapid and could exploit the full selectivity and strength of binding of the strongest ligands. N,N',N'',N'''-tetrasubstituted 1,4,8,11-tetraazacyclotetradecanes (substituted cyclams) were investigated to test this concept. The substituents varied from those capable of covalent bonds (amines for Schiff base formation), good hydrogen bonders (amides) to moderate dipoles (nitriles). The mode of association also included incorporating anions (vinyl sulfonate) into the polymer. Complexes were incorporated into the matrix showing some promise, but work was discontinued to focus on other aspects of the project.

Photorelease of Metal Ions from Tightly Bound Adducts: Macrocycles capable of rapid release of tightly bound ions by photolytic fragmentation of the macrocyclic ring have been designed and are being synthesized. Two strategies for the synthesis of photolabile macrocycles have been pursued. In the first strategy, a substituted triazadioxo-15-crown-5 (**5**) has been synthesized by coupling 3-benzyloxy triethylene glycol ditosylate with a protected triazaundecane diol. This nine step synthesis to an intermediate macrocycle (see Appendix on web site) provides a general route to monosubstituted macrocycles. Conversion of the side chain into a photoactive ligand is in progress. Because of the lengthy procedure and low yields encountered using our earlier strategy, a second, more efficient synthesis for the substituted macrocycle was designed and carried out. In this second strategy (Appendix), the ring closure is accomplished by a Grubbs olefin metathesis using phenylmethylene bis(tricyclohexylphosphine)ruthenium dichloride. The 4-oxy-7,10,13-triazahexadeca-1,15-diene was closed to 2-hydroxymethyl-1-oxo-4,8,12-triazatetradecane (**6**) in excellent yield (94%). Reduction of the double bond and hydrogenolysis of the protecting benzyl group has provided a much more efficient entry into an analogous hydroxymethyl substituted macrocycle which can be further elaborated into the photoactive macrocycle. Exploratory photochemistry of bis-7,16-(di-p-methoxybenzoyl)-1,4,10,13-tetraoxo-7,16-diazacyclooctadecane (**7**) has also been examined. No fragmentation of the crown ether was observed during irradiation either at 254 or 300 nm as anticipated for amides.

Figure 2

Planned Activities

Included above.