

PROGRESS REPORT NUMBER 1

Managing tight-binding Receptors for New Separations Technologies a DOE EMSP Research Project DOE Award Number DEFG0796ER

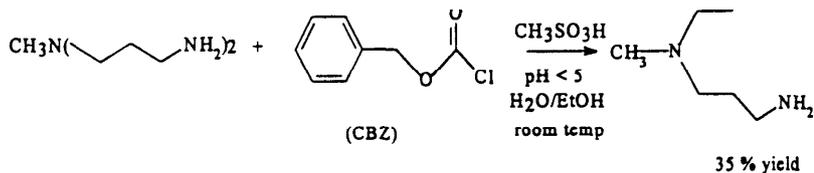
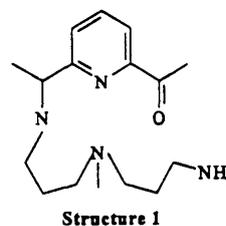
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PERIOD OF REPORT: from September 15, 1996, to June 10, 1997

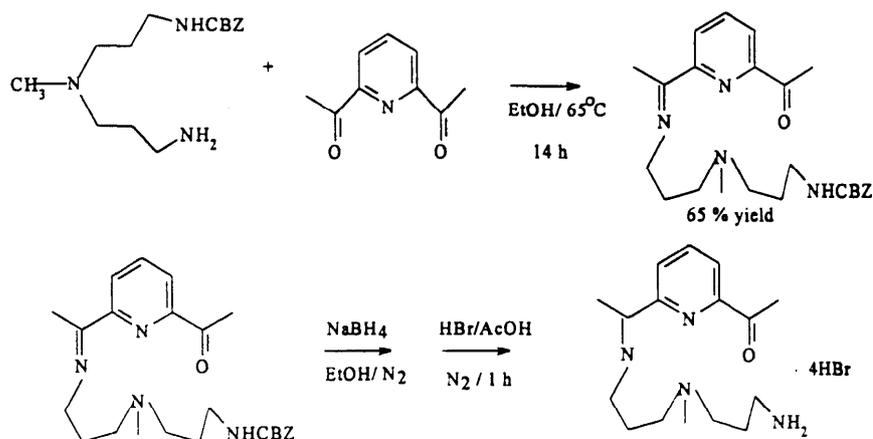
This program is fully staffed and all proposed investigations are proceeding as outlined in the Task Schedule of our original proposal. The program aims remain unchanged and excellent progress is reported below. We anticipate no substantial unexpended funds from the first year's budget at the end of the first year of support. Any such remaining funds will certainly be less than 10% of the budget; less than 5% is expected.

Three projects make up this program and each focuses on a single aspect of the major problem of overcoming the inherent slow reaction rates of tight-binding ligands. In a logical order, Project 1 addresses the rates of formation of metal complexes using tight-binding ligands; Project 2 addresses the rate of release of metal ions from complexes with tight-binding ligands; and Project 3 provides the possibility of a new technology that should be unimpeded by the inherent dilatory rates.

Project 1: Accelerated Binding Rates for Tightly-Bound Adducts. In the study of rapid macrocyclic chelation of polydentate linear ligands in the coordination sphere of target metal ions, the first generation ligand having **Structure 1** was proposed to be best example that might be synthesized by template methods. Although synthesis of the corresponding tetradentate monomethine complex with Ni(II) was previously reported, the literature preparation did not give a significant yield and, further, led to a mixture of products with varying numbers of azomethine linkages. Thus, an alternative synthesis was designed, involving the initial protection of one end the diamine (**Scheme 1**). Ligand synthesis and

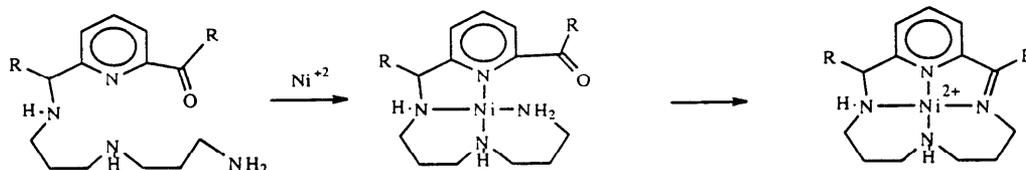


Scheme 1. Schiff Base Synthesis of Ligand Using a Protecting Group



characterization was completed well before the nine month target date. Movement toward the design of second generation ligands is being made.

Potentiometric and spectrophotometric measurements to understand the equilibrium and kinetics of binding between **1** and nickel(II) to form the complex of structure 1 have begun (**Scheme 2**). pK_a values for



Scheme 2. Reaction of templating ligand with nickel(II) ion

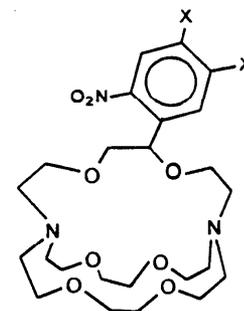
the protonated ligand species and stability constants for complex formation have been determined from potentiometric titrations. The ligand appears to form moderately stable nickel(II) complexes with $\log \beta=8.93$, a value comparable to those reported for other tetra-azamacrocycles.² Species distribution curves indicate that the desired complex is dominant at $pH \geq 8$. With these evaluations of pH conditions for complex formation complete, effects of both aqueous (buffered) and nonaqueous media have been studied. Nonaqueous solvents are preferred as they appear to improve solubility and, consequently, consistency of measurements. Preliminary kinetic measurements have been made on ligand to metal complexing using single wavelength UV/VIS scans (extended time) and stopped flow spectrophotometric (millisecond range) experiments, under pseudo first order conditions with respect to ligand in ethanol at room temperature. The data reveal two moderately slow rate processes, one on the second time scale and the other on the minute time scale. Determination of the exact nature of these processes is the focus of present efforts. Solution infrared analyses under complexation conditions are indicative of template ring closure; i.e., the carbonyl stretching frequency from the linear starting material disappears and a band assignable to an azomethine function (from closure of the macrocycle) appears during the course of reaction in the presence of the metal ion.

References

- (1) Barefield, E.K.; Lovecchio, F.; Tokel, N.E.; Ochiai, E.; Busch, D.H. *Inorg. Chem.*, **1972**, *11*, 283
- (2) Boeyens, J.C., et al. *Inorg. Chim. Acta.*, **1996**, *246*, 321-29.
- (3) Bormans, G.; et al. *Inorg. Chem.*, **1996**, *35*, 6240.
- (4) Dey, B.; et al. *Inorg. Chem. Acta*, **1993**, *214*, 77.
- (5) Hay, R.W.; et al. *J. Chem. Soc., Dalton Treans.*, **1987**, 2605.

Project 2: Photorelease of Metal Ion from Tightly Bound Adducts. As noted in our proposal, several published studies on o-nitrobenzyl photochemistry of a variety of EDTA analogues have established the photoactivated release of common alkaline earth and alkali metal cations, such as Ca^{+2} , Na^+ , etc.¹ A recent preliminary report by Grell and Warmuth² extending the o-nitrobenzyl photochemistry to a series of cryptates (e.g., NC222 and DMN222, **structure 2**), from which K^+ , Na^+ , Ca^{+2} , and Tl^+ were released, has established the proof of concept that we sought in Tasks A and B (pg 25 of proposal) and further indicated that Task C would not be essential. Therefore, we have begun the synthesis of the macrocyclic ligands containing the active chromophores.

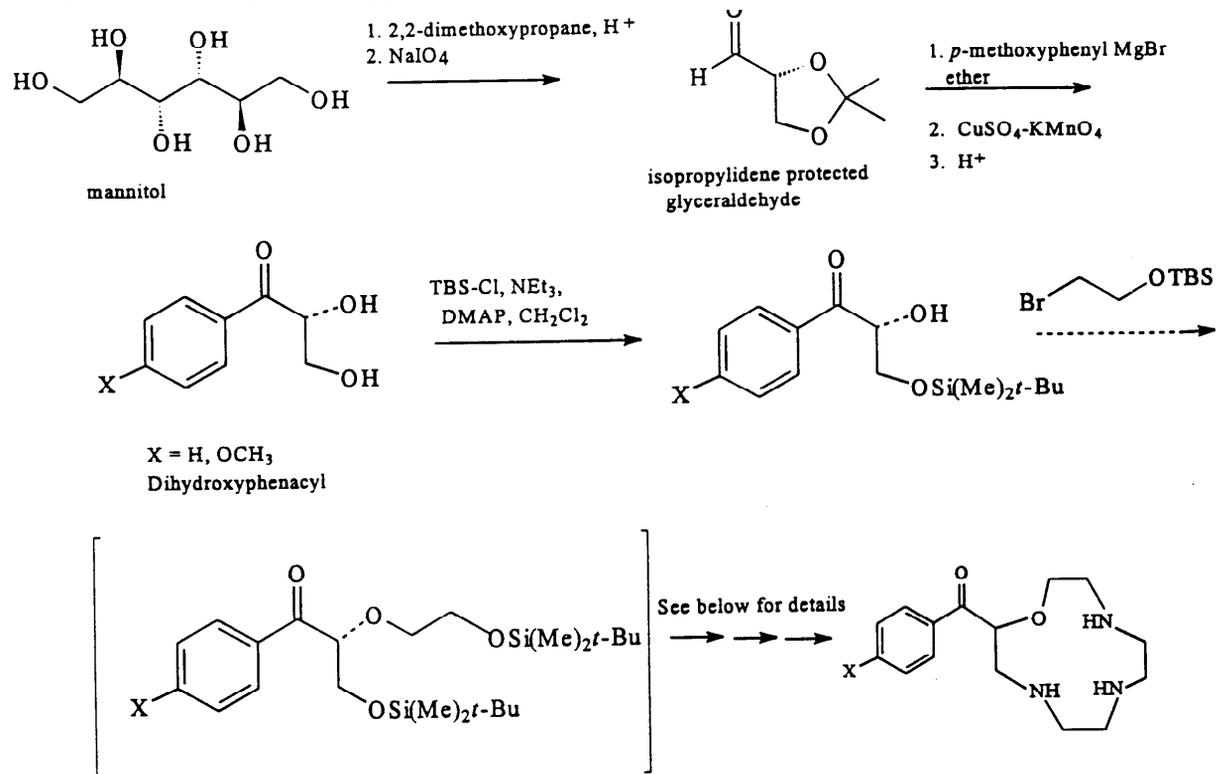
As shown in **Scheme 3**, two strategies to the phenacyl substituted macrocycle are being pursued. The goal is to develop a general synthesis of a substituted triazaocyclododecane **1** that will allow the introduction of any one of the photoactive appendages we have proposed. A second advantage of these approaches is the variety of macrocycles they may produce. In the first strategy, the hydroxyl groups in glyceraldehyde were protected as their isopropylidene ketal.



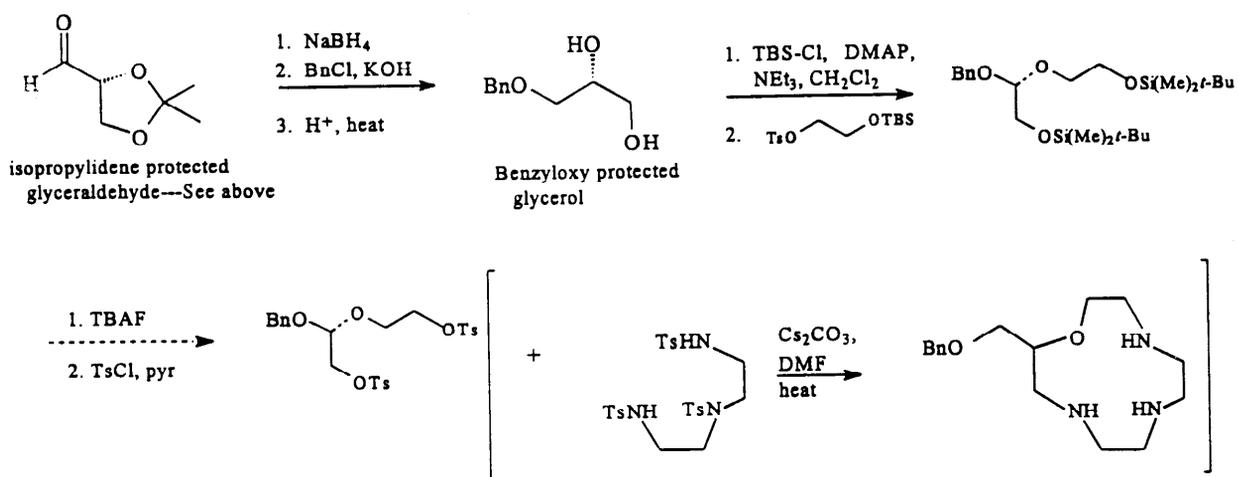
X = H, NC222
X = OCH₃, DMN222
Structure 2

Scheme 3: Strategies toward photoactive oxotriaza-2222 macrocycles.

Strategy 1. Dihydroxyphenacyl approach:



Strategy 2. Benzyloxy approach:



p-Methoxyphenyl Grignard was added to the aldehyde carbonyl and the resulting alcohol was oxidized with $\text{CuSO}_4\text{-KMnO}_4$ to yield the *p*-methoxybenzoyl 1,3-dioxolane. Removal of the ketal with H_2SO_4 (1%) gave 4'-methoxy-1,2-dihydroxypropiophenone. We then have protected the primary hydroxyl group as its *t*-butyldimethylsilyl ether and are exploring the manipulation of the secondary hydroxyl to prepare the left hand side of the macrocycle. The parallel strategy focuses on the synthesis of the right hand portion of the macrocycle.

In that second strategy, the synthesis begins with the natural sugar, mannitol, which is converted to the 1,2,5,6-protected ketal by reaction with 2,2-dimethoxypropane/ H^+ . Oxidation with HIO_4 gives the protected D-glyceraldehyde. Reduction with NaBH_4 and treatment with benzyl chloride gives monobenzyl glycerol. Treatment with *tert*-butyldimethylsilyl chloride selectively protects the primary hydroxyl. Further elaboration to produce the desired coupling portion A is in progress.

References

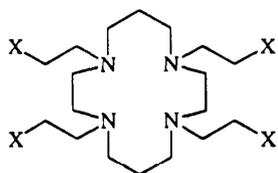
1. See original proposal, references 20, 27, 29-31
2. Grell, E.; Warmuth, R. *Pure & Appl. Chem.* **1993**, 65, 373-379.

Project 3: A Slow Separations Methodology

Preliminary investigations have been made into the use of molecularly imprinted macroporous polymers for the selective binding of macrocyclic metal complexes (e.g., **Scheme 4**) Our original schedule did not envision beginning this project during the first year of support, however support from other sources facilitated an early start. The strategy adopted is to evaluate the roles of different types of interactions for rebinding of a metal complex to an imprinted polymer; and their contributions to efficient extraction of the complex. Types of interactions under evaluation include hydrogen bonding, easily hydrolyzed covalent bonds (e.g. Schiff base), and electrostatic interactions.

The literature shows the application of imprinting to molecular recognition in two categories--rebinding via covalent interactions or non-covalent interactions. Non-covalently interacting polymers (mainly hydrogen bonded) has been extensively applied to chromatography. Although high selectivities were achieved, reoccupation of the imprinted cavities was lowered. In the case of covalent interactions 80-90% of the empty cavities can be re-occupied as compared to 10-15% in polymers imprinted with non-covalent template interactions. Some of this was attributed to the relaxation of strain on template removal and matrix swelling inducing change of shape in some of the cavities.

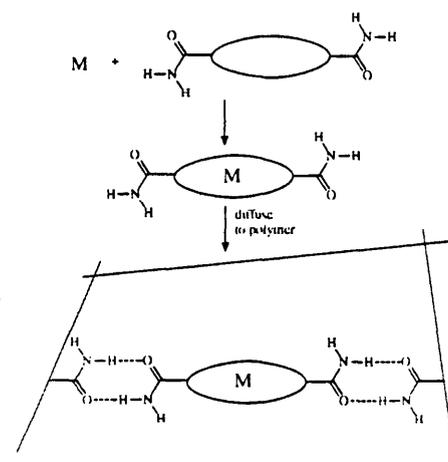
The current work consists of three stages: the synthesis of appropriate imprint complexes and interacting monomers; polymerization; analysis of imprinted polymer and re-binding potential. The system selected for initial investigations was based on N-functionalized 1,4,8,11-tetraazacyclotetradecane (cyclam),



Structure 3: X= CH_2NH_2 , CN, CONH_2

Structure 3. Varying the pendent functionalities introduced interactions appropriate to active monomers. Nickel complexes are under study because suitable examples have been characterized. Complexes containing amide, amine and cyano pendent arms were synthesized. The amide group provides the potential for hydrogen bonding to an active monomer such as acrylamide; the amine group can be used to form a hydrolyzable Schiff base linkage to a polymerizable group; and the cyano derivative can be used to evaluate electrostatic interactions with a polymerizable anion (in the absence of other interactions), and as a control in re-binding experiments.

Apparatus was modified to permit photoinitiation of the polymerization reactions at lowered temperature (0°C), to reduce the disruption of hydrogen bonded interactions during the imprinting process.



Scheme 4: Schematic for metal extraction

Initial selection of the other polymerization components, cross-linking agent, porogen and initiator, was based on literature data. Blank polymerizations with no imprint and with nickel cyclam dichloride were initially run to demonstrate the effectiveness of the system and to evaluate the use of some analysis techniques; for example: CHN elemental analysis, i.r., DRIFT i.r. diffuse reflectance UV-vis. and atomic absorption spectroscopy. The use of additional techniques such as electron microscopy to identify the macroporous nature of the synthesized polymers is being considered. Insufficient data is available at this time to comment on the effectiveness of the re-binding and potential for metal extraction. To our knowledge no other work is currently being carried out on the reversible binding of metal complexes (as opposed to metal ions) to an imprinted macroporous polymer, and no systematic study has previously been reported on this subject. The task schedule has been exceeded with the first range of templating adducts prepared and imprinted polymer synthesis in progress.