01 Apr 1991

# Synthesis and Characterization of an 18-Membered Macrocyclic Ligand Containing 2,2-Biimidazole for Selective Binding of Transition Metal Ions

Mark Barnett

# SYNTHESIS AND CHARACTERIZATION OF AN 18 MEMBERED MACROCYCLIC LIGAND CONTAINING 2,2 -BIIMIDAZOLE FOR SELECTIVE BINDING OF TRANSITION METAL IONS

*Mark Barnett*

## Abstract

A description of the synthetic approach to the preparation of an 18 membered macrocyclic ligand containing 2,2'-biimidazole is presented. A diol derivative of 2,2'-biimidazole is tosylated with p-toluene sulfonyl chloride making it susceptible to bimolecular substitution with a disodium salt of tetratosylated triethylenetetraamine. The final desired product is an 18N6 macrocycle, 4,7-(1,1'-(2,2'-biimidazolo))-1,4,7,10,13,16-hexaazacyclooctadecane, potentially capable of binding transition metal ions in various combinations with three chelating sites. Initial characterization includes NMR and IR spectroscopic analysis.

## Introduction

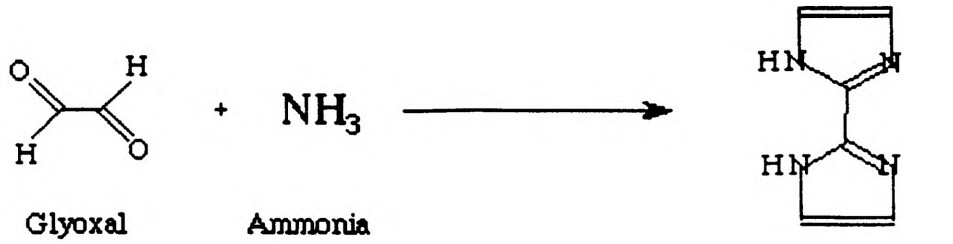
Natural biological chemical systems that contain macrocyclic chemical units can be extremely complicated molecules and characterization to discern their structure and function is very difficult. Thus, whenever possible, it is desirable to chemically prepare and characterize very basic macrocycles as models that may allow understanding the more complex nature of such entities found in naturally occurring species. These models may typically imitate behaviors related to structure, molecular interaction, or chemical reactivity found in natural systems. Studies that are of interest today include reversible reactions with small molecules, such as that demonstrated with reversible dioxygen binding by the heme macrocycle of hemoglobin; roles as active sites in catalytic processes (30% of enzymes contain transition metal complexes of macrocyclic ligands that provide catalytic activity); and selective metal ion binding that is useful in studying chelation processes. The characteristic properties of macrocyclic complexes, i.e., after metal complexation, include marked kinetic inertness, stabilization of high oxidation states of bound metal ions, and high thermodynamic stability.

The goal of this project is to investigate the synthesis of a unique 18-membered macrocyclic ring system containing 2,2'-biimiddazole and characterize it via the application of electronic spectral analysis before and after metal ion complexation. The use of electrochemical, elemental, and magnetic characterization methods will ultimately be used to provide a more thorough investigation of this ligand.

## Experimental

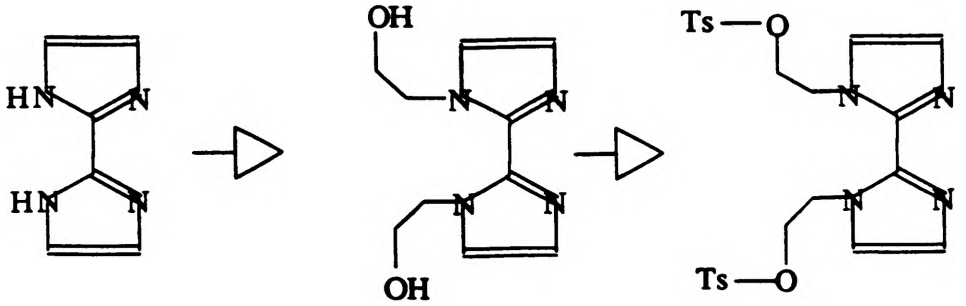
### Preparation of 1,1'-Dihydroxyethyl-2,2'-biimidazole Ditosylate

The preparation of the macrocycle which this paper describes begins with the synthesis of 2,2'-biimidazole, first reported in 1856 by Debus. The formation of 2,2'-biimidazole is achieved via the exothermic and spontaneous reaction of glyoxal and ammonia. Glyoxal, usually obtained as a 40% solution in water, is added to an equal volume of concentrated aqueous ammonia with constant stirring. The reaction results in a mixture of dark brown liquid and a brown biimidazole precipitate. The solid biimidazole is collected by filtration and recrystallized several times from boiling water producing an off-white or light tan crystalline solid. Typical yields ranged from 10 to 20%.




Glyoxal Ammonia 2,2'-Biimidazole

The biimidazole is then transformed into 1,1'-dihydroxyethyl-2,2'-biimidazole (HEB) by replacing the protons on the nitrogen atoms with hydroxyethyl groups. For this preparation, a 5.0 gram quantity (0.0373 mol) of biimidazole is placed in a three-necked, 500 mL round-bottom flask. A 200 mL portion of ethanol and 50 mL portion of water are added to the flask and slowly heated to 50 degrees C. Then a solution of 5.96 grams of NaOH in 25 mL of wtaer is added to the mixture and stirred for four hours. An additional 2.25 grams (0.017 mol) of biimidazole is added during the first hour. After four hours, 7.34 mL (d-1.201 g/mL, 0.108 mol) of 1-chloro-2-ethanol is carefully added over a one-hour period. The mixture is then neutralized with dilute HCl, roto-evaporated to one-third the initial volume and then filtered. To the collected yellow-orange solution is added successive amounts of acetone followed by azeotropic roto-evaporation of the solvents and filtration to remove precipitated salts. The sample is then dried and redissolved in boiling acetone and filtered again. The acetone solution contained both HEB and mono-HEB (a side product in which only one of the biimidazole protons is substituted with an hydroxyethyl group). This solution is roto-evaporated to approximately one-third its initial volume and allowed to stand at room temperature for several days to permit crystallization of the mono-HEB derivatives. The HEB enriched solution is decanted, leaving the red-orange crystals of mono-HEB behind. Thin layer silica-gel chromatography analysis was used to confirm the purity of the soluble portion obtained. The enriched soluble component can be further purified by a redissolved dried sample in metahnol and treating the mixture on a flash chromatographic column. The mono-HEB followed by HEB (distinct yellow band) are eluted using a 3:8:1 solvent mixture of propanol:hexane:ethanol to give a 20-25% yield of the pure HEB derivative.




2,2'-Biimidazole HEB Tos-HEB

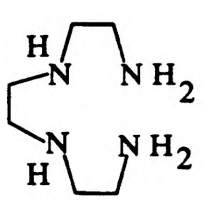
In order to make the diol reactive, it is tosylated with p-toluene sulfonyl chloride. To a chilled solution of 0.2 g HEB ($8.8 \times 10^{-4}$ mol) dissolved in approximately 10 mL pyridine, 0.34 g GsCl ($1.76 \times 10^{-3}$ mol) was added in small portions; the solution was maintained around 20 degrees C, as the reaction is extremely exothermic, giving off HCl which is adsorbed by the pyridine. The resultant solution was stirred for an additional three hours and after unsuccessful attempts to remove the pyridinium hydrochloride, the mixture was allowed to set several days while the solvent evaporated. The reaction went mostly to completion. In this form, the

tosylated HEB is susceptible to bimolecular substitution by strong base, the preparation os which is described next.

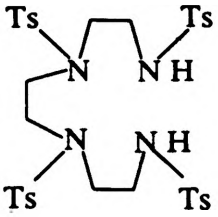
**Preparation of DiSodium Salt of TetraTosTETA**

4.4 Grams of triethylenetetraamine (0.03 mol TETA) was dissolved in a solution of 7.2 grams of NaOH in 25 mL water. While this was vigorously stirred, a solution of 22.9 g p-toluene sulfonyl chloride (0.12 mol) dissolved in 60 mL diethyl ether was added dropwise resulting in the white precipitate tetratosylated triethylenetetraamine, tos-TETA, and stirred for one hour. This tosylation was to deter undesired attack on the non-terminating nitrogen atoms. The tos-TETA was washed with ethanol/water, filtered, and dried. The yield was approximately 40%.

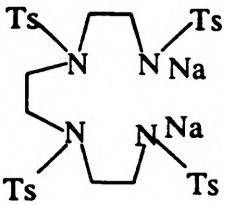
86.7 Grams of tos-TETA was reflused in ethanol for two hours. To this was added dropwise an ethanol solution of sodium (0.63 g Na in 18.25 mL ethanol). The solution was refluxed for an additional two hours, filtered, and the filtrate was rotoevaporated to about half its initial volume. Upon standing a day or two, a white crystalline precipitate formed. The salt was filtered and washed with an ethanol, giving a typical yield of 40%.




TETA



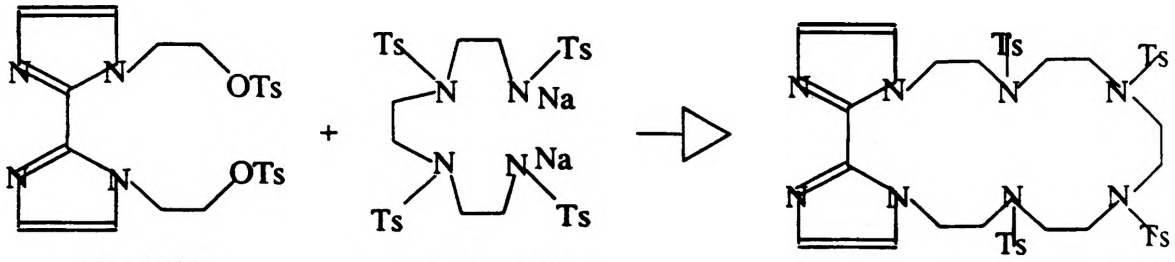

tos-TETA




tos-TETA-diNa

**Preparation of Macrocycle**

The macrocycle is formed by the reaction of the tosylated diol, tos-HEB, and tosylated disodium salt of TETA, tos-TETA-diNa. Each of these materials was dissolved in N,N-dimethylformamide (DMF) to form very dilute solution; 0.62 g tos-HEB (0.0012 mol) in 20 mL DMF was added dropwise over a period of four hours at 110 degrees C to 0.946 g tos-TETA-diNa (0.0012 mol) in 50 mL DMF and stirred for an additional hour. However, it was discovered that this dibase reacted mostly with the troublesome pyridinium hydrochloride to form tos-TETA and NaCl. So, another stoichiometric equivalent of dibase was added under the same conditions to form the macrocycle. The macrocycle is believed to form via a bimolecular nucleophilic substitution, where one end of the base displaces the tosylate, which is an excellent leaving group. The solutions are dilute so as to minimize the possibility of another base molecule substituting the remaining tosylate of the tos-HEB. The other end of the base then displaces the other tosylate leaving group, forming the macrocycle. Most of the DMF was removed by azeotropic distillation with water under reduced pressure using rotoevaporator. In aqueous solution, the unreacted amine becomes insoluble tos-TETA, leaving the macrocycle in solution. Yields are around 20%.




Tos-HEB tos-TETA-diNa macrocycle

**Discussion and Conclusions**

**Nomenclature**

In general, macrocycles are classified according to the size of the ring and number of nitrogen atoms contained in the ring structure. The macrocycle discussed in this paper is an 18N6; the first number represents the number of atoms composing the ring structure, N for nitrogen, and the last number represents the number of nitrogen atoms in the ring. Specifically, the completed macrocycle has the following formal name, in accordance with the nomenclature rules of the Union of International Pure and Applied Chemistry (UIPAC):

4-7-(1,1'-(2,2'-biimidazolo))-1,4,7,10,13,16-hexaazacyclooctadecane

**Initial Characterization by NMR and IR**

Initial spectroanalysis by proton NMR supports the formation of the tosylated macrocycle; for peak assignments refer to *Table of NMR Assignments* at the end of this paper. Without detosylation, the final macrocycle was complexed with copper (II) chloride resulting in a maize colored material. It was found that the IR peaks of the complexed macrocycle were shifted towards higher energies when compared to the non-complexed material. This evidence indeed, supports the formation of the macrocycle, see *Table of IR Assignments* at the end of this paper.

**Future Investigation**

Initial evidence supports the formation of the tosylated macrocyclic ligand. The next step is to detosylate and characterize the macrocycle. After this, the ligand will be exposed to a variety of metal cationic salts for binding studies. There are potentially three binding sites in this macrocycle. It is desirable to gain insight as to which chelating cavity is preferred by the metal cation or whether the cavities have priorities for the binding of various metals simultaneously. Ultimately, characterization of this specific macrocycle wil not only help us gain insight into more complex naturally occurring macrocycles, but may lead to exciting new applications in microelectronics as a molecular semiconducting material.

**Result**

| Material | Mol. Wt (g/mol) | Exp. Yield | Description |
|---|---|---|---|
| Biimidazole | 134.0 | 20% | Lt tan-off white, crys. |
| HEB | 226.3 | 20% | Yellow solid (pure) |
| Tos-HEB | 530.5 | 99% | Yel-brown cryst. |
| tos-TETA | 763.1 | 38% | White solid |
| tos-TETA-diNa | 807.0 | 40% | White crys. solid |
| tos-Macrocycle | 949.1 | 20% | Pumkin orange residue |

**Table of IR Assignments**

NMR Characterization of 18-Membered Macrocyclic Ligand

| Group Assignment | Tos-Mac (ppm) |
|---|---|
| C-H (Biimazole) | 7.8 - 8.8 |
| Ar-H (Tosyl) | 7.2 - 7.7 |
| D2O (solvent) | 4.7 |
| C-H (Triene) | 3.7 - 4.5 |
| CH3 (Tosyl) | 2.3 |
| TMP (zero std) | 0.0 |

IR Characterization of 18-Membered Macrocyclic Ligand and Complexed Ligand

| | Frequencies, $cm^{-1}$ | |
|---|---|---|
| Group Assignment | Tos-Mac | Complex |
| S-N (tosyl) | 1399 | 1399 |
| Ar-C-H (tosyl) | 3038 | 3038 |
| para subst Ar (tosyl) | 814 | 814 |
| C=N (biimidazole) | 1599 m | 1599 vw |
| C-N (aliph) | 1638 | 1638 |
| C-N (biim) | 1668 | - |
| C-H (asym/sym str, triene) | 2921 | 2921 |
| In-plane C-H bend (biim) | 1044 | 1049 |
| Out-of-plane C-H bend (biim) | 955 | - |
| Ring Torsional vibr (biim) | 683 | 696 |

**REFERENCES**


Sugimoto, M.; Nonoyama, M.; Ito, T.; Fujita, J. Inorg. Chem. 22, 950 (1983).

Melloni, P.; Metelli, R.; Bassini, D.; Confalonieri, C.; Logemann, W.; de Carneri, I. Arzneim-Forsch (Drug Res.) 25, Nr.1, 9 (1975).

Melloni, P.; Bassini, D.; Dradi, E.; Confalonieri, C. J. of Heter. Cyl. Chem. 11, 731 (1974).

Debus, H. Ann. Chem. 607, 199 (1856).