

SIMPLE METHODS FOR THE SYNTHESIS OF CRYPTANDS AND SUPERCRIPTANDS

KRZYSZTOF E. KRAKOWIAK
IBC Advanced Technologies
P.O. Box 98
American Fork, UT 84003, USA

Abstract. The preparation of cryptands, supercryptands and macropolycyclic cylindrical compounds is reviewed.

Key Words. Cryptands, supercryptands, macropolycyclic ligands, bisazacrown ethers.

1. Introduction

The field of macrocyclic chemistry has been growing very rapidly both in scope and quality in recent years. Originally this field included mainly crown ethers. More recently, supercryptands, calixarenes, and other families of macrocyclic compounds have become important [1]. Currently, many companies synthesize and sell some of these macrocyclic ligands. Catalogs from Aldrich and ACROS (Jansen) each list approximately 50 macrocyclic ligands. Many other companies such as Fluka, TCI, Strem, and Lancaster also sell some macrocyclic compounds. The popularity of this field is obviously growing. This is evident in a recently published ten-volume series [2] and two journals [3] which are devoted to macrocyclic chemistry. Each year hundreds of chemists gather at the International Macrocyclic Chemistry Symposium. There are other meetings devoted to calixarene chemistry and inclusion phenomena where the main topics include macrocyclic compounds. A few companies, including IBC Advanced Technologies, Inc., manufacture and use crown ethers. Professors Jerald S. Bradshaw and Reed M. Izatt have collaborated in the macrocyclic chemistry field for many years. Professor Bradshaw's group has synthesized hundreds of

macrocyclic compounds while Professor Izatt's group has determined their complexation properties. This joint research has become the foundation on which IBC Advanced Technologies, Inc. has been built. This company specializes in finding applications for the macrocyclic compounds in separations.

I worked in Professor Bradshaw's laboratory for seven years. During this time, we developed many new methods for synthesizing macrocycles [4,5]. Short syntheses from inexpensive starting materials are very important for any application. I present here only the most recent topics from this collaboration.

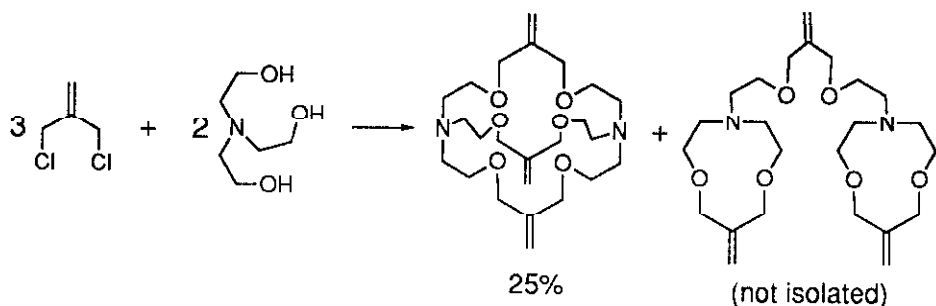
Cryptands and supercryptands are some of the most important classes of macrocycles because they can interact with many cations and anions with high selectivity and high stability constants [6,7]. These characteristics are very important in separating ions from solution. Why are some of these compounds called super? In the world, we have superman, supernova, and superstar to denote things beyond the normal. In chemistry, there are compounds which have characteristics that are well beyond the normal so they should have the "super" prefix. A few years ago, the scientific world became fascinated by the discovery of the buckminsterfullerene molecule which was the subject of the recent Nobel prize. What was most interesting to me was the way in which this molecule was prepared, a one-step reaction during the high temperature burning of graphite rods. There is a connection between buckminsterfullerene molecules and cryptands. They both have complicated structures, but nevertheless may be prepared in simple one-step reactions. This paper concerns the cryptand molecules which are defined by three ethyleneoxy units between two nitrogen atoms.

Professor J.-M. Lehn and his coworkers first prepared cryptands over 25 years ago [8]. Simmons and Park prepared molecules similar to cryptands at about the same time, but the nitrogen bridgehead atoms were connected by hydrocarbon chains [9]. The multistep synthesis of cryptands allowed the preparation of many different types including those that are symmetrical (each bridge the same) and asymmetrical (different bridges). After the initial synthesis by the Lehn group, Klstad and Malmsten tried to prepare cryptand [2.2.2] in a one-step bicyclization procedure. However, they obtained only 1,10-diaza-18-crown-6 [10]. They accomplished their cryptand synthesis in a 6% overall yield using a stepwise process starting with 1-iodo-8-chloro-3,6-dioxaoctane. Others tried a 2:1 synthetic procedure by reacting two equivalents of a dihalide with one equivalent of a diamine using rigid molecules containing aromatic rings. Aromatic rings were helpful in the bicyclization reaction because no unwanted by-products can form [11].

2. Synthesis of Cryptands

Our first work on the preparation of the cryptands started six years ago when we treated two equivalents of triethanolamine with three equivalents of 3-chloro-2-(chloromethyl)propene [12]. As shown in Scheme 1, we obtained the symmetric cryptand in a 25% yield. At the time, we realized that the same starting materials could produce a bis(aza-10-crown-3) (see Scheme 1), which would have the same molecular formula and molecular weight as the cryptand. We suspected that the cryptand and biscrown ether would have different ^1H and ^{13}C NMR spectra. For this reason, we prepared the biscrown ether in a different way by treating ethanolamine with the ditosylate of 5-methylene-3,7-dioxa-1,9-nonadiol to form the hydroxyethyl-

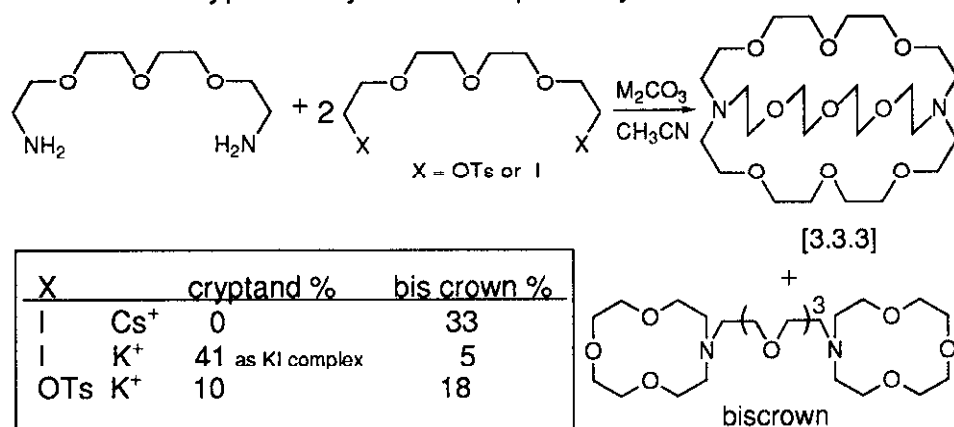
Scheme 1. Cryptands by a One-Step 3:2 Cyclization Reaction



substituted aza-10-crown-3 which was reacted with 3-chloro-2-(chloromethyl)propene to form the biscrown ether. Indeed, the ^1H and ^{13}C NMR spectra of the cryptand and the biscrown ether were different [13].

We discovered a simple method for the preparation of aliphatic cryptands using a 2:1 bicyclization of bisprimary amines and diiodides or ditosylates [14-16]. Biscrown ethers were also obtained in this reaction as shown by the example in Scheme 2. Using an appropriate template cation, we were able to manipulate the formation of products. In some cases, it was possible to obtain only the cryptand in yields approaching 50%. This one-step method for cryptand synthesis is very attractive because the starting compounds are commercially available and inexpensive. The purification process is simple and requires decomplexation by passage of the cryptand through an alumina column and crystallization; or instead of crystallization, separation on a silica gel column using a mixture of methanol and aqueous ammonia as eluent. We have not studied all of the variables for cryptand formation, but we know that high dilution is not needed. Acetonitrile and alkali metal

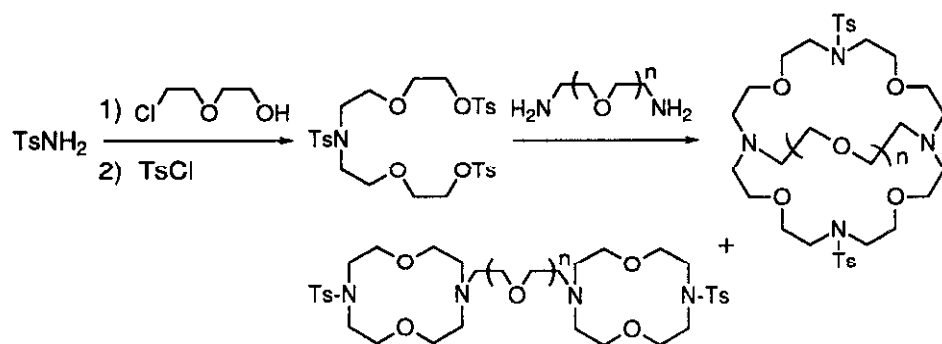
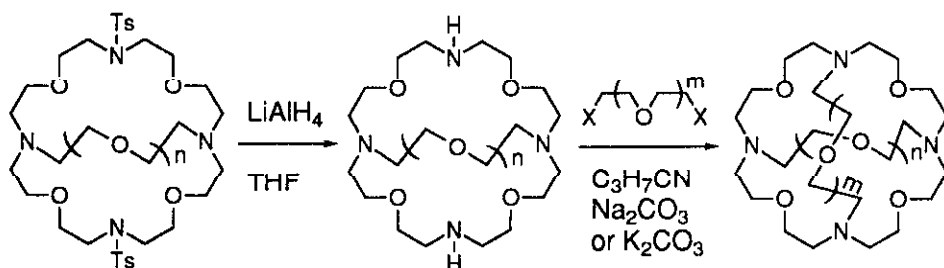
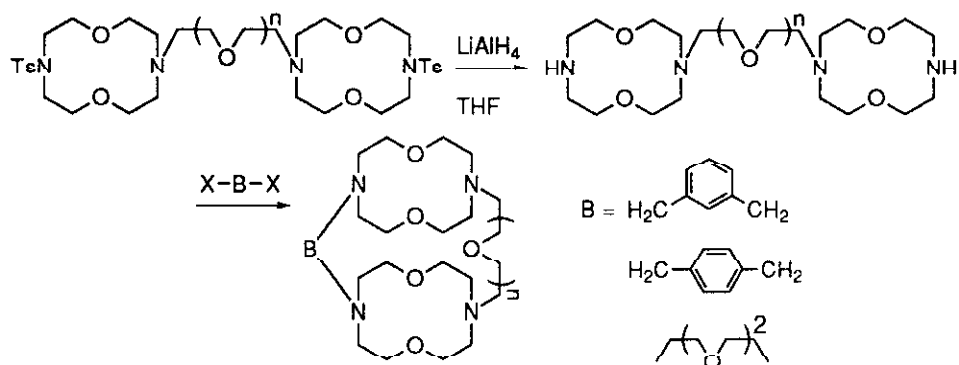
Scheme 2. Cryptands by a One-Step 2:1 Cyclization Reaction



carbonates are used. We studied the influence of a template cation on the one-step formation of cryptands in a few cases. The most surprising result was that, during the preparation of cryptand [3.3.3], cesium carbonate caused the bis-crown ether to form and the cryptand was not isolated (see Scheme 2). Potassium carbonate, on the other hand, afforded the cryptand as the major product. In general, higher yields in the preparation of the cryptands were observed using the diiodides rather than ditosylates which reduced the formation of the biscrown ether. However, cryptand [2.2.2] can only be prepared in good yields by this one-step method from the ditosylate [15].

3. Synthesis of Supercryptands and Cylindrical Ligands

We also prepared supercryptands and cylindrical macrotricyclic molecules. From *p*-toluenesulfonamide, diazacyptands were synthesized in a three-step reaction (Scheme 3). Separation of the diazacyptands from the biscrown ethers was easy and required only column chromatography on silica gel. It is important to note that both of these products are very useful for the preparation of supercryptands [17] and cylindrical macrotricycles [18]. After removal of the tosyl groups from the diazacyptand, it was treated with a diiodide to form the supercryptand (Scheme 4) [17]. Others had prepared supercryptands by a process of more than 10 steps [19]. The biscrown ether, which was a byproduct during the preparation of a supercryptand (Scheme 3), was used to prepare cylindrical molecules (Scheme 5). First, the tosyl groups were removed and the biscrown ether was treated with an appropriate dibromide or diiodide. Three different cylindrical molecules were

Scheme 3. Synthesis of Diazacryptands and Biscrown Ethers**Scheme 4. Synthesis of Supercryptands****Scheme 5. Synthesis of Cylindrical Ligands**

synthesized [18]. The structure of one cylindrical macrotricyclic was verified by an X-ray crystal structure analysis.

Working with Professors Bradshaw and Izatt has been a great pleasure for me. Our joint research has produced many exciting results. I would like to thank them for all the help that I have received over the years.

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