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The preparation of a Lewis-acid bearing cyclam ligands

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THE PREPARATION OF A LEWIS-ACID BEARING CYCLAM LIGANDS

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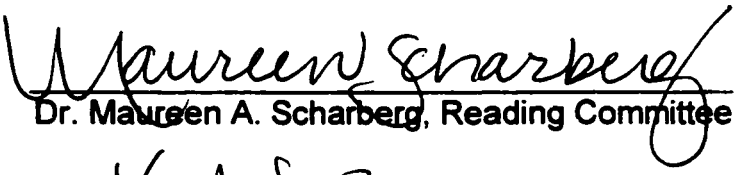

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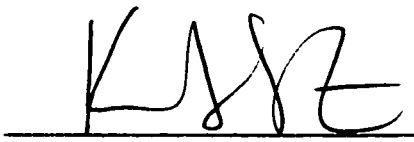

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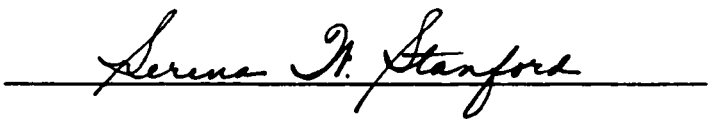

ABSTRACT

The mechanism of some metalloenzymes in the redox transformation of substrates consists of a push of electron density from a metal center to the substrate and / or a pull of electron density by a Lewis acid from the substrate. This project aims at mimicking such a system by synthesizing a cyclam ligand, (into which any first row transition metal can be inserted,) directly tethered to a Lewis acid. This simple system might bind and reduce the bond order of small substrates, CO and NO for example, and catalyze the reduction of such substrates.

Initial C-alkylation attempts of dioxocyclam were unsuccessful in spite of other similar alkylations in the literature. The aminolysis of a trimethyl stannyl substituted malonate ester produced the target molecule, 6(3-trimethylstannyl-propyl)-5,7-dioxo-1,4,8,11 tetraazacyclotetradecane, in 26% yield.

ACKNOWLEDGEMENTS

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CHAPTER 1

INTRODUCTION TO THE BIMETALLIC MODEL

1.1 Biochemical Energy and Enzyme.

It is generally agreed that one of the main themes in biochemistry revolves around the conversion of energy to biochemically useful forms. Much of the energy is furnished by the sun, captured by plants and low living organisms, then transferred to animals and humans in the food chain. In that biological chain, essential biochemical reactions necessarily occur. These reactions are catalyzed by specific enzymes. They involve the transformation of molecules along with the inter-conversion of energy and transfer of electrons.

For example, the majority of energy released from food digestion is conserved in the form of adenosine tri-phosphate (ATP), to be used later in other biochemical processes such as the biosynthesis of glycogens, amino acids and nucleotides. Most ATP is produced by oxidative phosphorylation, which is fueled mainly by the electron carrier nicotinamide adenine dinucleotide (NADH) through the oxidation-reduction (redox) chemistry, that is the electron and energy transfer process. The electrons released from the net oxidation of food molecules are transferred to NAD+ along with H^+ to form NADH,[1] as in equation 1.1.

$$\text{Energy} + NAD^+ + H^+ + 2e^- \longrightarrow NADH \quad (1.1)$$

NADH, formed in metabolic reactions, is oxidized by the respiratory electron transport chain along with the concomitant production of several ATP molecules.

$$NADH + \tfrac{1}{2} O_2 + H^+ \longrightarrow NAD^+ + H_2O \quad \Delta G^0 = -52.6 \text{ kcal/mol (free energy.)} \quad (1.2)$$

The metabolism goes on in such a pattern. Every time a redox reaction occurs, energy is gained or used for the transformation of another molecule.

These transformations could not possibly occur without enzymes due to the high activation energy of certain reactions caused by unstable intermediates or very stable reactants. Enzymes are indeed indispensable in metabolism.

1.2 Introduction to Metalloenzymes.

There are thousands of different enzymes in even the simplest living organism. Among all known enzymes, more than one third to one half of them are metalloenzymes[2] or metal-activated enzymes. Metal ions are involved in enzyme catalysis in several different ways.

1.2.1 Non-Redox Metalloenzymes.

In a non-redox role, metals help to stabilize the enzyme structure, bring the substrates into close proximity of catalytic site, enhance the binding of the substrates and catalyze their reactions by their flexible coordination.[3] Sometimes they induce conformational changes in the enzyme to either enhance or inhibit its catalytic activity.[4]

An illustration of a non-redox metalloenzyme is carbonic anhydrase which is a Zn(II) containing enzyme. Zn(II) is known as an active metal in over 100 enzymes in humans.[5] It is thought that the presence of Zn(II) in metalloenzymes reflects its ability to act as a Lewis acid (LA) without engaging in redox chemistry. Carbonic anhydrase catalyzes the hydration of CO_2 into HCO_3^- as shown in Figure 1.1.[6] Zn(II) is ligated to 3 N atoms from his 94, his 96 and his 119, and to a water molecule, in a distorted tetrahedral geometry. Zn acts as a Lewis acid, binding the O atom from CO_2 to form a five-coordinate Zn (II) intermediate (as

seen in step 1 of Figure 1.1.) Upon coordination to Zn(II) in step 2, the CO_2 carbon becomes more electrophillic than before, facilitating attack by the nucleophillic OH^- (or H_2O.) In the last steps, the bicarbonate formed leaves after the incorporation of another OH^- by Zn(II). Zn(II) returns to its original distorted tetrahedral geometry in the final stage.

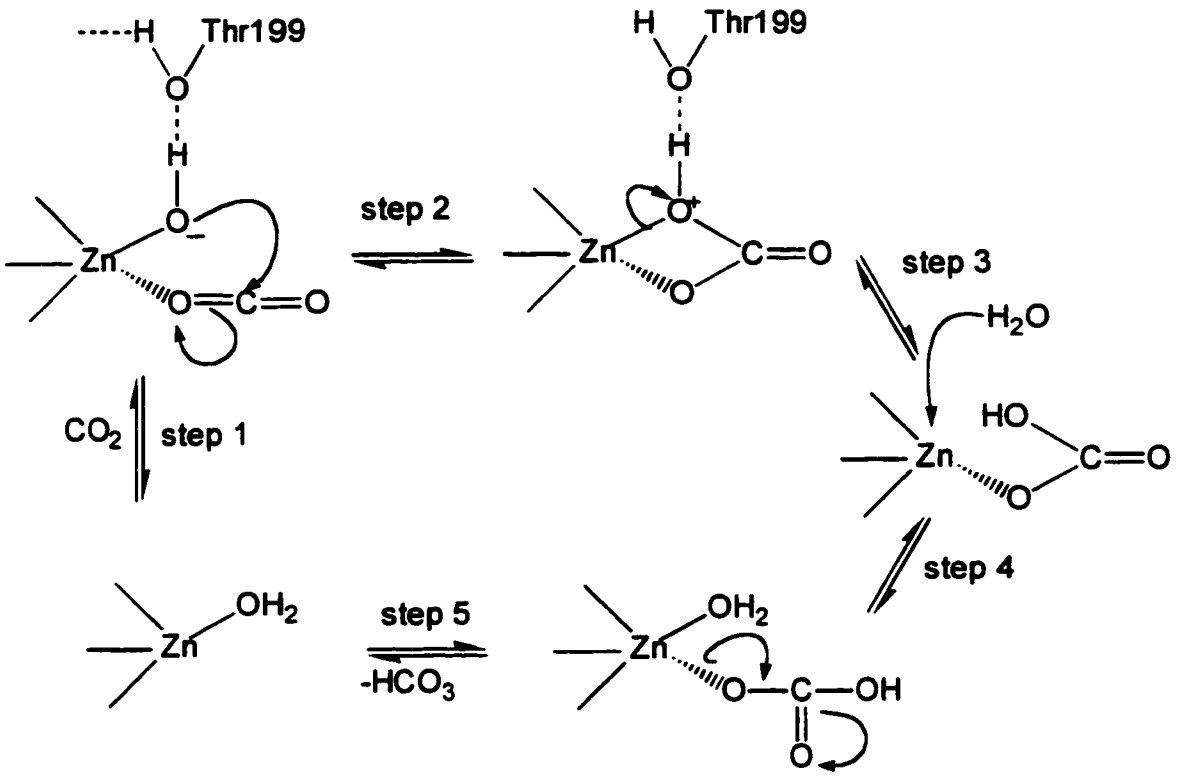


Figure 1.1: Suggested mechanism for carbonic anhydrase. [6]

In summary, the main function of Zn (II) in this enzyme is its Lewis acid role *to "pull" electron density from the substrate.*

1.2.2 Redox-Active Metalloenzymes.

Besides acting as Lewis acids, metal ions can play several important roles in metalloenzymes, especially in redox transformations of substrates. Transition metals play a key role in redox catalysis for the following reasons:

1) They have many accessible oxidation states; thus they can readily give electrons to or take electrons away from the substrate.
2) The redox potentials for such electron transfers can be "tuned" by variations of the metal's geometry or ligand type.

In addition, transition metals are valuable in metalloenzymes because of their ability to assist in atom transfer reactions (i. e., Co (II) in coenzyme B_{12} catalyzes C atom transfer reaction) and their ability to bind neutral as well as anionic ligands.[7]

A particularly thoroughly studied class of enzymes is the cytochrome P-450 enzymes.[7] This enzyme occurs as an Fe (III) porphyrin as shown in Figure 1.2:

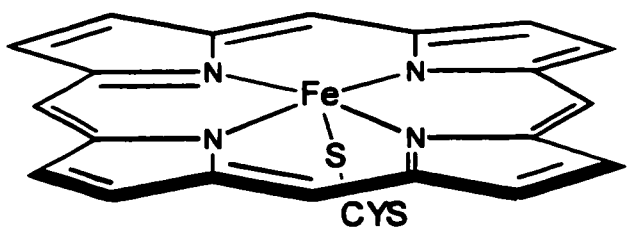


Figure 1.2: Fe (III) porphyrin in P-450.

The P-450s are known as monooxygenases because their function consists of incorporating one oxygen atom from O_2 into the substrate and reducing the other oxygen atom, with concomitant proton transfer. The oxygen atom may be transferred to a variety of substrates such as alcohols, alkenes, arenes, sulfides etc., i.e. $R\text{-}H + O_2 + 2H^+ + 2e^- \longrightarrow R\text{-}OH + H_2O$. (1.3)

The catalytic cycle of P-450 is depicted in Figure 1.3.

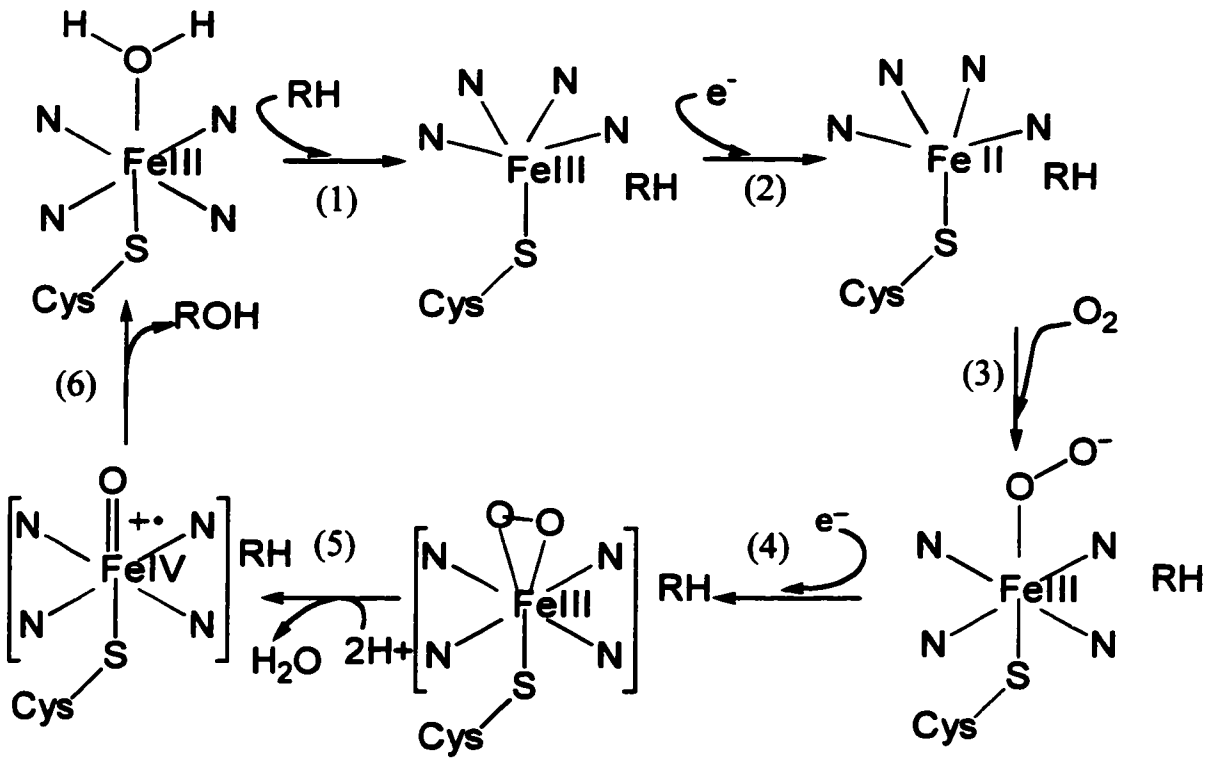


Figure 1.3: Catalytic cycle of P-450.

Upon binding the substrate (RH) in step 1, the known resting state of Fe (III) bound heme changes from low spin six-coordinate with a low reduction potential to high spin five-coordinate with a higher reduction potential to facilitate electron

transfer. After receiving an electron (step 2) and incorporating O from O_2 (step 3), oxy-P450 is a stable hexacoordinate species (Figure 1.4.) This state causes stronger binding of the substrate, preventing the loss of active intermediates.

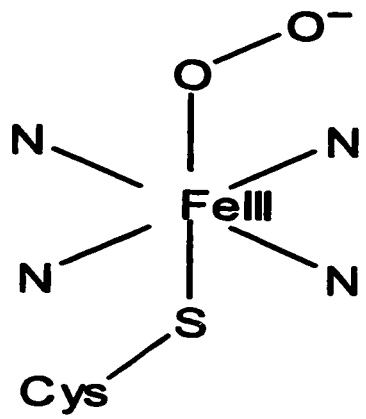


Figure 1.4: Hexacoordinate Oxy-P450.

Upon the addition of a second electron (step 4) and $2H^+$ (step 5), H_2O and ROH were formed from the cleavage of O-O bond. The cycle included the formation of a hypothetical intermediate heptacoordinated Fe III as shown in Figure 1.5.

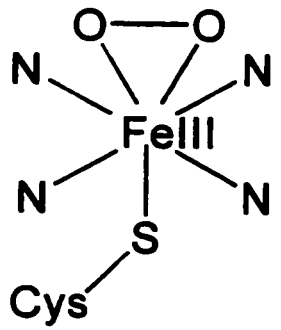


Figure 1.5: Hypothetical intermediate of heptacoordinated Fe III in P-450.

Most interesting was the discussion about the axial thiolate ligand of P-450 [8] in step 5. *This ligand is thought as a strong internal electron donor to push the electron density toward the peroxo bound iron such that O-O cleavage resulted.* In step 6, for specific alkane hydroxylation, intermediate Oxygen-bound -Fe(IV) abstracts a hydrogen atom from the substrate to form a carbon radical and iron-bound hydroxyl radical. Alcohol forms as a result of the radical recombination of the two radical species [8] in the last step of the cycle.

1.2.3. " Push-Pull" Effect.

The above example illustrates the "push" effect (i.e., the pushing of electron density onto a substrate) that a transition metal (and its axial ligand) may impose during substrate transformation. An isolated case of the "pull' effect of a Lewis acid was described above for Zn (II) carbonic anhydrase (section 1.2.1). It is more interesting to see that both push and pull effects come together in the action of horseradish peroxidase as analyzed by John Dawson[8] and illustrated in Figure 1.6. In cytochrome c peroxidase, the nitrogen from the proximal histidine is bound strongly to the Fe-porphyrin in an axial position. N-histidine is a strong electron (e^-) donor to the heme. It exerted a push of e^- density toward Fe-O. It also helped to stabilize Fe(IV) in its unstable high oxidation state, during the catalytic cycle. On the other side, the distal histidine acts as a proton donor, and together with a positively charged arginine residue, helps to pull apart the O-O bond and stabilize the separating charge formed during O-O bond cleavage.

(B = Arginine)

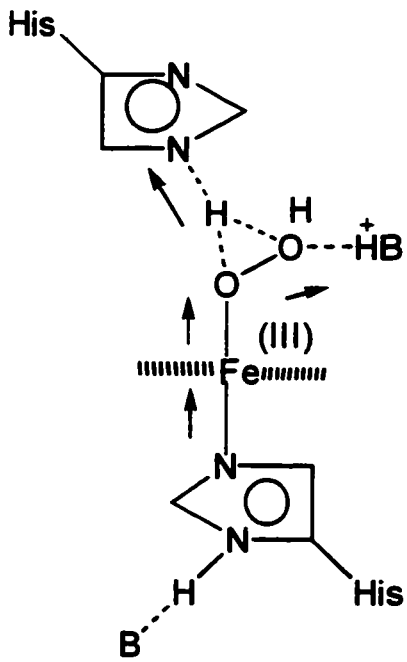
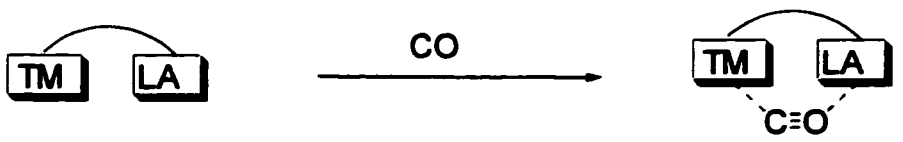


Figure 1.6: Push-pull mechanism in catalytic bond cleavage of cytochrome peroxidase.[8]

Thus, it can be concluded that both the push of electron density from the metal and the pull of electron density by the protons, aid in O-O bond cleavage.

1.3 Proposed Approach to a Bimetallic Model

The suggested push-pull effect is seen to facilitate bond cleavage in small substrates. Such an effect, if present in a catalyst, could promote the reduction of small substrates. Our group proposed to isolate this "pull" effect, that is, to determine the effect that proximal Lewis acids have on the binding and reduction of small substrates. We have proposed a bimetallic model in which a Lewis acid (LA) is directly attached to a transition metal (TM) binding site in one complete skeleton as shown in Figure 1.7.



Lewis acid attached directly to a transition metal.

Binding of substrate by the proposed bimetallic model

Figure 1.7: Proposed bimetallic model.

This bifunctional model is expected to improve the catalyst's ability to bind, activate and reduce the substrate (CO, for example) because:

1) Efficient bifunctional binding increases the substrate affinity toward the catalyst. For example, the nucleophillic O site is attracted to the Lewis acid, while electrophillic C to the transition metal.
2) A push-pull effect may be observed with Lewis acid metal exerting a strong pull while the transition metal exhibiting a strong push, resulting in bond weakening of the bound substrate.

One of the earliest bimetallic models involved cofacial diporphyrins.[9] This model consists of two porphyrins incorporating two different metals, covalently linked in a stacked or face to face manner. Other works included crown ethers bearing one or two pendant phosphines[10] and porphyrin-crown ether ligands.[11] Nevertheless, these complexes have encountered limited success due to:

1) Synthetic difficulty (many steps) in making functionalized porphyrins[11] and in inserting two different metals into the ligand.
2) Ease of dissociation of the ligand from the transition metal.[12]

3) Bi-functional binding is disfavored because of the large distance between the transition metal and the Lewis acid.[11, 12] (6 Angstrom distance or more from crown ether to porphyrin.)

To improve on some of these early models, our group proposed the synthesis and study of cyclams tethered directly to a Lewis acid. The target molecule would be of the type shown in Figure 1.8:

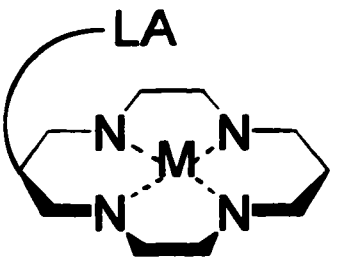


Figure 1.8: Lewis acid tethered cyclam.

Cyclam (1,4,8,11 tetraazacyclotetradecane) was chosen for the model because it is known to form stable complexes with transition metals, and its ring size fits to accommodate all first row transition metals.[13, 14] It also has a useful and versatile list of applications. Cyclam and its derivatives have been known as effective metal ion capturing[15] and separating[16] agents. They have been experimented as possible electrocatalysts in the reduction of water[17] and CO_2[18] and in the oxidation of olefins[19] and other substrates. In the medical field, a radioisotopically labeled metal-cyclam complex bound to biomolecules has been used as a labeling agent in cancer diagnosis and therapy[20, 21] due to its stability.

Our proposed model has the following advantages:

a) Stability of metal-ligand complex (quadridentate versus mono or bidentate) as it allows more tenacious binding of cyclam to the transition metal than in some earlier models.

b) Simplification of the synthetic methodology (shorter pathway.)

c) The distance between proximal Lewis acid and transition metal may be varied easily for favorable host / guest interaction.

1.4 Synthetic Methodologies.

There are two possibilities for connecting a Lewis acid to a cyclam. One can connect the tether to the carbon framework to prepare for a C-pivot scorpiand, or one can attach the tether to one of the nitrogens for an N-pivot one. C- and N- functionalized cyclams are shown in Figure 1.9.

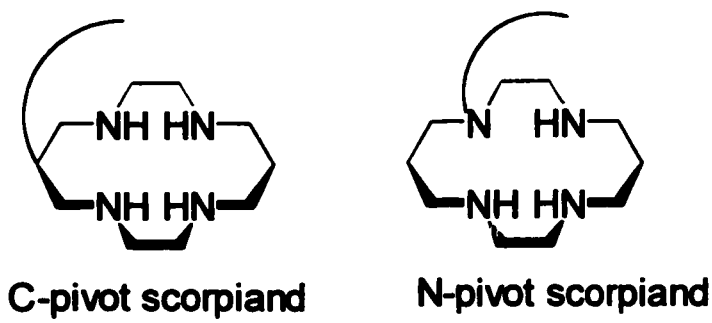


Figure 1.9: Tethered cyclams.

Available synthetic methods consist of 1)Tabushi's aminolysis of the malonate ester by the tetraamine,[15] 2) C-alkylation and 3) N-alkylation of dioxocyclam.[22] Each reaction is followed by reduction of the amide groups.

1.4.1 Tabushi's Synthetic Method.

Tabushi's method, first described in 1977, consisted of condensation of the N, N' (bis-2-aminoethyl) propane (tetraamine) with the appropriate R-substituted diethyl malonate [15] as in Figure 1.10.

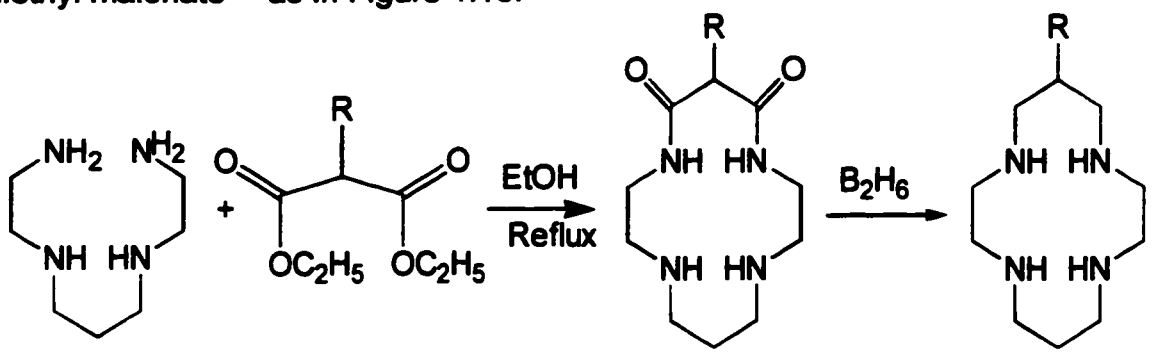


Figure 1.10: Tabushi's condensation.

This method is the most common scheme for preparing substituted cyclams in spite of its low yield. The highest yield reported by Tabushi was 40% in the aminolysis step where R was $-CH_2CH_2OH$. The average yield was about 25% as shown in Table 1.1.

YIELD (%)	R	YIELD (%)	R
30	-H	25	$-CH_2CH_2CH_2CH_3$
25	$-CH_2C_6H_5$	30	$-CH_2CH_2CH_2CN$
40	$-CH_2CH_2OH$	25	$-CH_2CH{=}CH_2$

Table 1.1 Reported yield in Tabushi's method with different functional groups.

Adaptation of Tabushi's method yielded mostly lower than 25% yield, sometimes with extreme modification of the reaction conditions.[23, 24] Other attempts to improve the yield of the aminolysis such as changing to high pressure, high dilution conditions or working with more reactive reagents were all futile.[25, 26] Nonetheless, this method appears to be much simpler and shorter than any other routes prior to 1977, such as the use of a metal template [27] or cyclization of the tetratosylated tetraamine by a dihaloalkane. [28]

1.4.2. C-Alkylation of Dioxocyclam.

Another option for the synthesis of the target molecule is the direct alkylation of the alpha carbon between the two carbonyls of dioxocyclam (5,7-dioxo-1,4,8,11-tetraazacyclotetradecane) as in Figure 1.11.

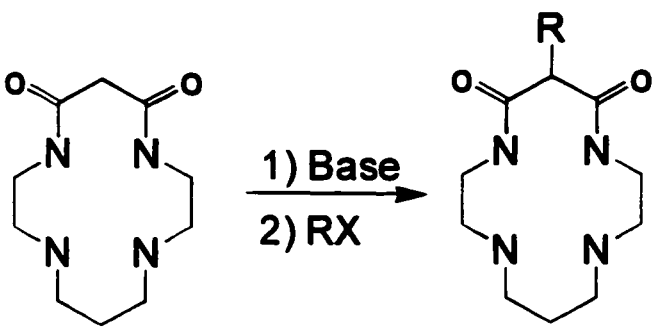


Figure 1.11: C-alkylation of dioxocyclam.

This would seem to be the simplest method if proper conditions can be found. However, to our knowledge, there is no report of the mono-alkylation to an alpha carbon of a diamide molecule, or to any similar compound (literature

search from 1950 to present.) C-alkylation remains a promising route considering the modest product yield of Tabushi's aminolysis method.

1.4.3. N-Alkylation of Dioxocyclam.

The last convenient route covers N-alkylation of dioxocyclam.

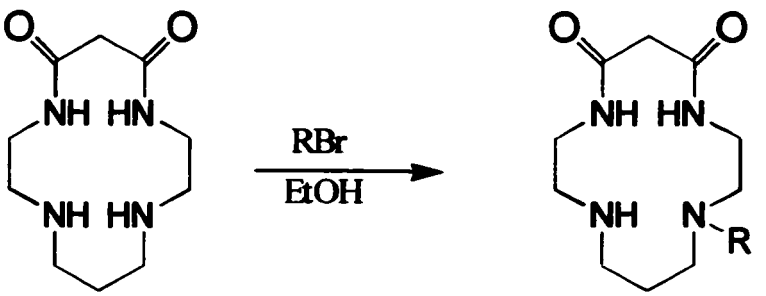


Figure 1.12: N-alkylation of dioxocyclam.

Previous work included the synthesis of N-cetyl dioxocyclam with 17% yield reported by Tabushi[29] as illustrated above in Figure 1.12. A more recent method in this category was the tosylation of unsubstituted cylam, then N-alkylation and detosylation to give N-substituted cyclam.[30, 31]

1.4.4. Other Synthetic Approach.

Another method included the direct ring closure by the tosyl derivatives developed by Richman and Atkins in 1974 [32] where extra steps involved the tetratosylation of tetraamine and ditosylation of the alkane diol. Even though the yield of the ring closure step was in the 70-80% of the tetratosylated cyclam,[33] the most delicate step was the detosylation one.[34, 35, 36] Free cyclam in that step

shrunk to a meager 40-50%. We might encounter difficulty in the detosylation step, due to possible disintegration of the tethered Lewis acid during the reflux process in hydrogen bromide/ acetic acid.

1.5 Conclusion.

With all these available synthetic schemes, we should be able to prepare cyclams tethered to Lewis acids to test the idea of a bimetallic model in the binding and reducing of small substrates. We look forward to finding out if the idea of a push-pull mechanism works in our simple system, and if so, to what extent.

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CHAPTER TWO

C-ALKYLATION OF DIOXOCYCLAM.

2.1 Introduction.

C-alkylated cyclams have attracted a great deal of attention since the late 1970's due to their popular application in transition metal chemistry relating to metal ions separation,[1] biomimetic catalysis[2] or biomedical usage.[3] In addition to this list of cyclam applications, our research group wishes to employ carbon-functionalized cyclams to explore the pull effect of a proximal Lewis acid on the bound substrate. The Tabushi method, established in 1977 and used since by many others in the study of cyclam and its derivatives, gave only modest product yield. Our group herein sets out to explore a simple direct C-alkylation of dioxo cyclam since none has been reported.

We hoped that the CH_2 group between the two amide carbonyls of dioxo cyclam (5,7-dioxo-1,4,8,11- tetraazacyclotetradecane) would be activated toward deprotonation. Upon treatment with a base, C-alkylation might be possible as shown below:

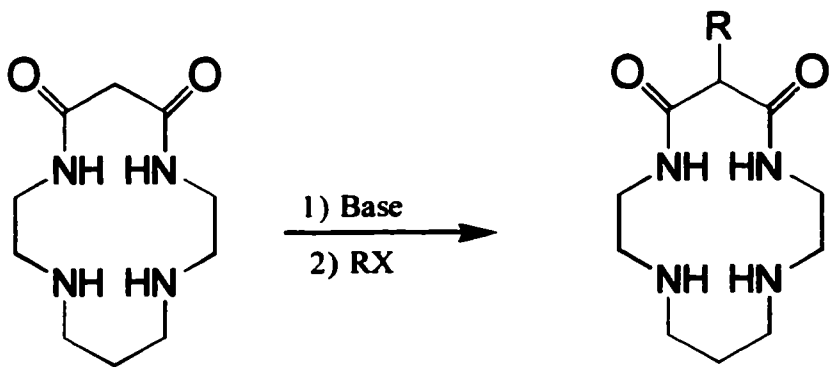


Figure 2.1: C-alkylation of dioxo-cyclam.

We believed this might work because the ease of carbanion formation of an α carbon from various carbonyl compounds decreases in the order of aldehydes >

ketones > esters> amides> acids[4]. If an amide is only one rank behind ester, then a methylene α to two amide carbonyls might be deprotonated as easily as an α carbon of an ester. Unfortunately, we were not able to find the dissociation constant of the methylene proton α to the two amide carbonyls. However, since the pKa of a CH_2 alpha to both carbonyls of the malonate is around 11, we hoped that the pKa of CH_2 α to both carbonyls of the amides would be less than 17, such that deprotonation by EtO^- would be possible as shown in Figure 2.2.

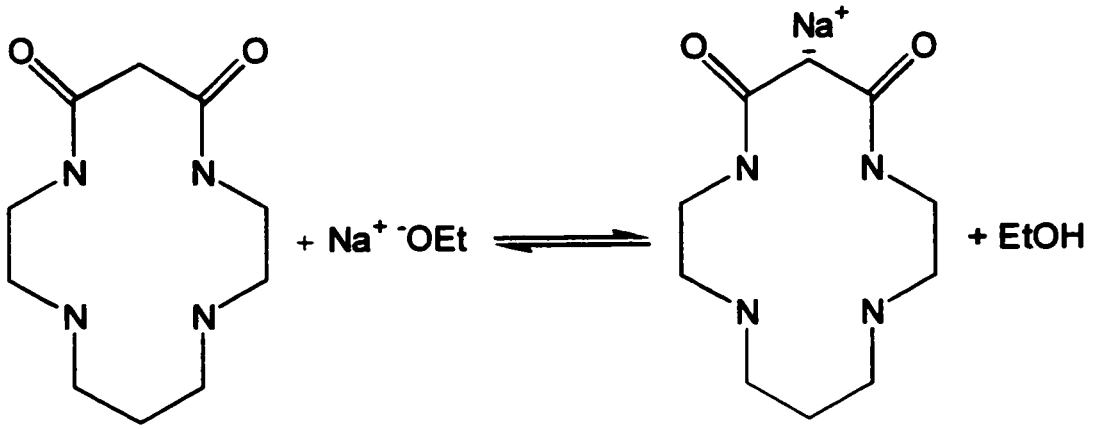


Figure 2.2: Deprotonation of dioxocyclam by EtO^-.

Once formed, the carbanion would be stabilized by its enolate resonance for further electrophillic attack as in Figure 2.3.

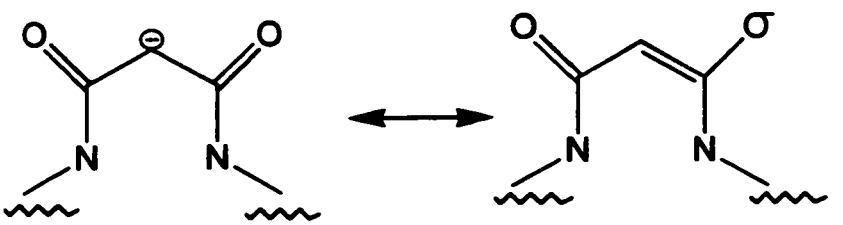


Figure 2.3: Enolate resonance of dioxocyclam.

As seen in Figure 2.3, the carbanion is much more reactive toward alkylation than the oxo-anion due to the less electronegative character of the carbon atom such that C-alkylation will be favored.

Our group had even more reason to explore this methodology since there have been instances where alkylation of carbon alpha to a carbonyl amide was successful, such as in β-lactam[5, 6] or N-phenyl acetamide[7] as shown in Figure 2.4:

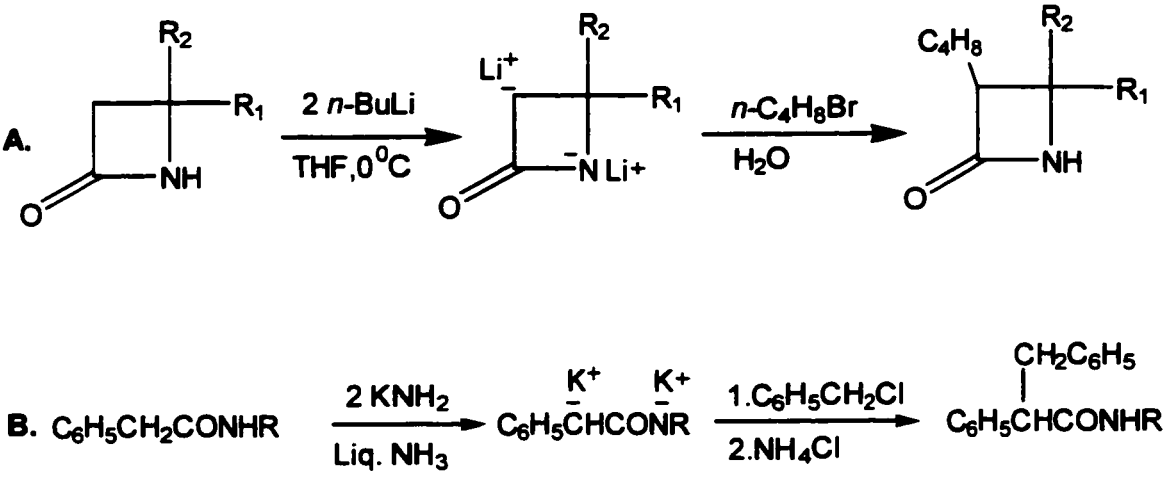


Figure 2.4: Instances of successful C-alkylation of α-carbon of amides.

For all the above reasons, the direct C-alkylation idea is reasonable to investigate. We herein report the result and discussion of our attempt of C-alkylation of dioxocyclam using *t*-butyl acrylate for Michael addition type reactions and ethyl bromide for substitution reactions.

2.2 Results and Discussion:

2.2.1 Alkylation of Dioxocyclam by Michael Addition.

C-alkylation of dioxocyclam might be performed by Michael addition of *t*-butyl acrylate to dioxocyclam treated with potassium *t*-butoxide as in Figure 2.5:

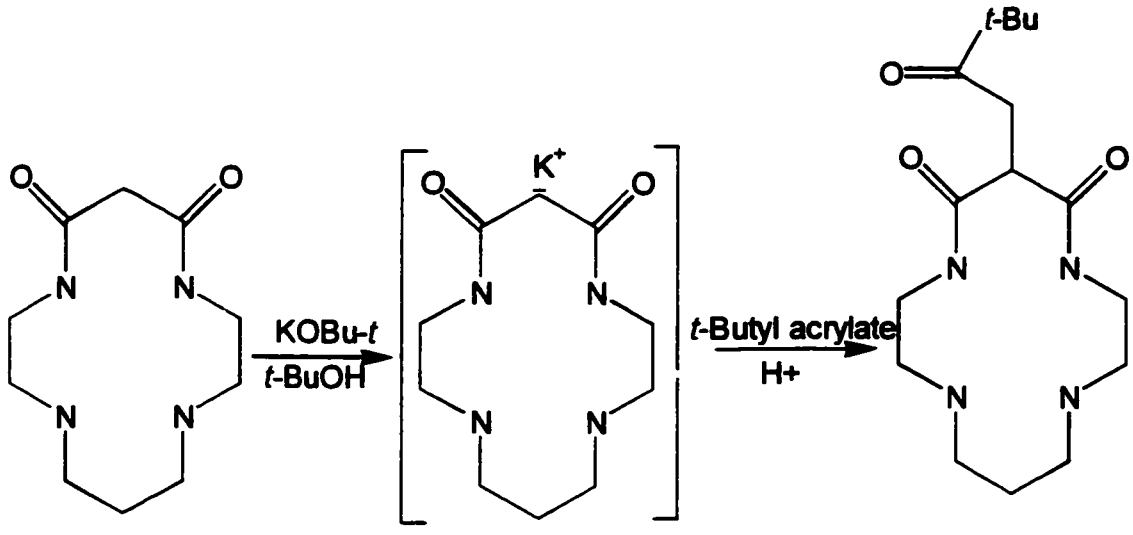


Figure 2.5: Michael addition of dioxocyclam .

The general procedure was adopted and modified according to the literature.[8, 9] This procedure gave at least three products. Four components were seen on TLC with unreacted dioxocyclam, being the darkest spot in the baseline. Although *t*-butyl acrylate was completely consumed, there was no sign of the desired product in proton NMR spectrum of the crude mixture because the desired product would be expected to have a triplet in place of the singlet at around 3.5 to 3 ppm. This preliminary result gave us reason to think that both amine groups in dioxocyclam were more active toward alkylation than the CH_2

alpha to the two amide groups. This was confirmed with similar results in subsequent routes (please, see discussion in 2.2.2.)

2.2.2 Alkylation of Dioxocyclam by Ethyl Bromide.

This reaction procedure was generally based on similar reaction of a diester with an alkyl bromide.[10] 1.3 equivalent of sodium ethoxide was used to deprotonate the methylene proton α to the carbonyls of the amides prior to the addition of 1.3 equivalent of ethyl bromide. We had hoped to get the desired product as shown in Figure 2.6:

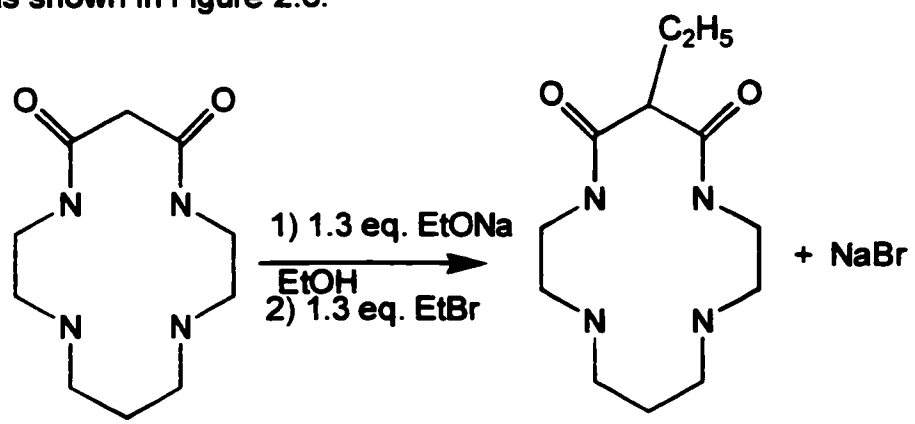


Figure 2.6: Desired alkylation of dioxocyclam with ethyl bromide.

After three hours or more of refluxing, the mixture was chilled down to precipitate more NaBr, which was filtered from the mixture. The crude mixture was chromatographed using Si gel and 16% MeOH in CH_2Cl_2 and trace amount of NH_3. N-ethyl dioxocyclam was instead obtained at 40% yield and N, N'-diethyl dioxocyclam at 12% yield as shown in Figure 2.7.

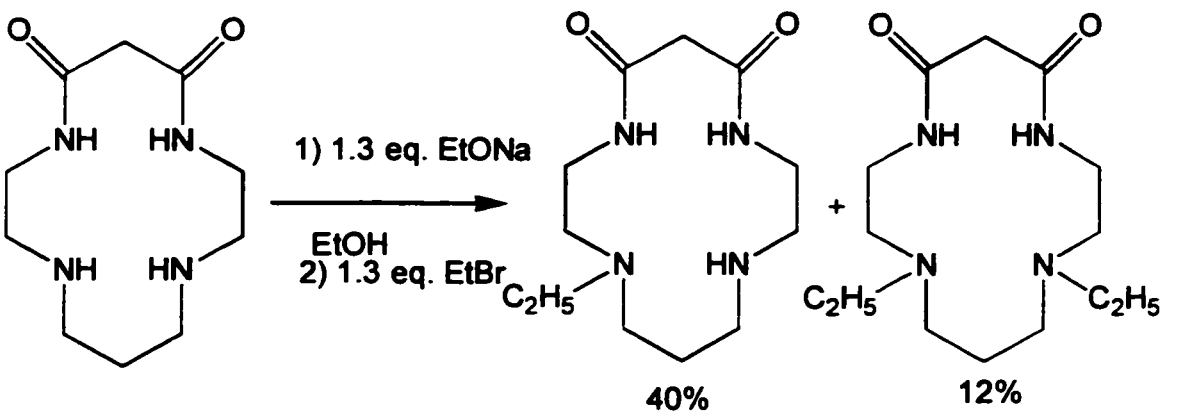


Figure 2.7: Actual alkylation of dioxocyclam with ethyl bromide.

Distinguishing dioxocyclam and its derivatives by ^{1}H-NMR is very easy. Whereas the spectrum of dioxocyclam is simple because of its high symmetry, that of N-ethyl dioxocyclam (shown on page 36) shows many more methylene proton resonances due to broken symmetry. On the other hand, N, N' diethyl dioxocyclam (spectrum on page 37) has high symmetry and a simple spectrum.

This result gives convincing evidence that both secondary amines in dioxo cyclam are more active than the methylene group alpha to the amide carbonyls. This suggests that deprotonation is not occuring at the carbon site but rather at the amide nitrogen site. Upon being deprotonated by the base, the anionic amide N may immediately hydrogen bond with the neighboring amine proton. This occurrence renders the neighboring amine nitrogen more susceptible to electrophillic attack due to its available lone pair of electrons as shown in Figure 2.8. It is thus necessary to protect both secondary amines each with a protective group before any C-alkylation can take place.

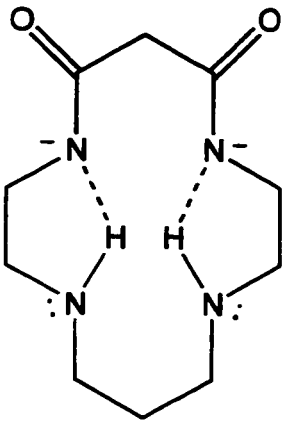


Figure 2.8: H-bonding of anionic amide N in dioxocyclam.

2.2.3 C-alkylation of 1,11-(bis *t*-butyl carbamyl)-5,7dioxo-1,4,8,11 tetraazacyclotetradecane.

Because amine nitrogens are more susceptible toward alkylation than the methylene carbon near the two (amide) carbonyls, we decided to protect them with *t*-butyl carbonate (*t*-boc in brief). Reaction of dioxocylam with di-*t*-butyl dicarbonate yields 75% of 1,11 bis *t*-butyl carbamyl-5,7dioxo-1,4,8,11 tetra-azacyclotetradecane[11,12] (^{1}H nmr on page 38) as shown in Figure 2.9:

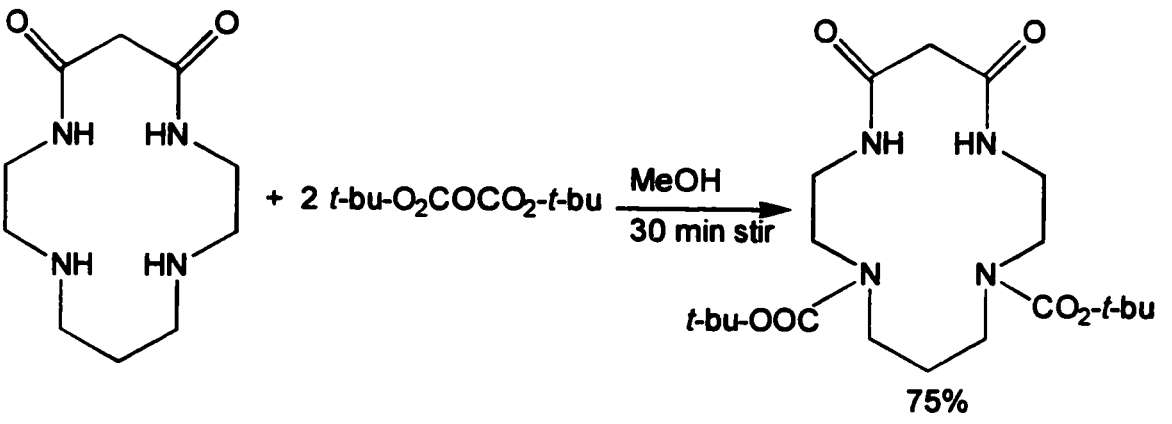


Figure 2.9: Protected dioxocyclam.

Having protected the amine nitrogens, we set out again to try the alkylation reaction of this diprotected dioxocyclam with ethyl bromide under the same condition as in 2.2.2 with overnight refluxing. Under these conditions, 77% of the starting materials were recovered.

The use of a stronger base such as LDA (lithium diisopropylamide) or *n*-butyl lithium did not help. LDA has been known to help alkylate an alkylacetic acid to form dialkyl-acetic acid through a putative intermediate lithiated acetic acid species[5, 6] as in reaction 2.1:

$$RCH(CH_3)CO_2H + 2\ LDA \longrightarrow RC(CH_3)CO_2^{-}Li^{+} \xrightarrow{R'X} R'RC(CH_3)COOH \quad (2.1)$$

89%, R'X = *n*-butyl iodide

It is quite a surprise that an α-substituted alkyl carboxylic acid can be formed while alpha-substituted alkyl diamide cannot be. This is because the formation of the carbanion of the carboxilic acid should be more difficult due to the greater resonance stability of its carboxylate anion form in comparison to the amide form as seen in Figure 2.10:

Figure 2.10: Resonance stability of carboxylate and amidate anions in the ease of formation of its carbanion.

As shown in Figure 2.10, if there is less of the enolate resonance form because of the greater competition of the other carboxylate form, then the methylene proton of the alpha carbon of the carboxylic acid is not acidic enough to be easily deprotonated.

As mentioned in the introduction, *n*-butyl lithium and LDA are known procedurally to successfully help the alkylation of β-lactam. Up to 77% yield was achieved with the alkylation of *n*-butyl bromide to β-lactam.[7, 13]

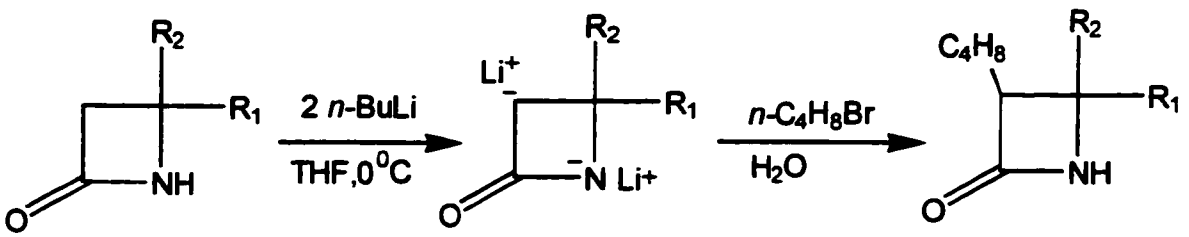


Figure 2.11: C-alkylation of β-lactam.

Other successful alkylations similar to this route include the formation of 90% 1-propyl-N, N'-Dimethylacetamide[14] or up to 86% of alpha-substituted phenylacetamide[15] as shown in figure 2.12.

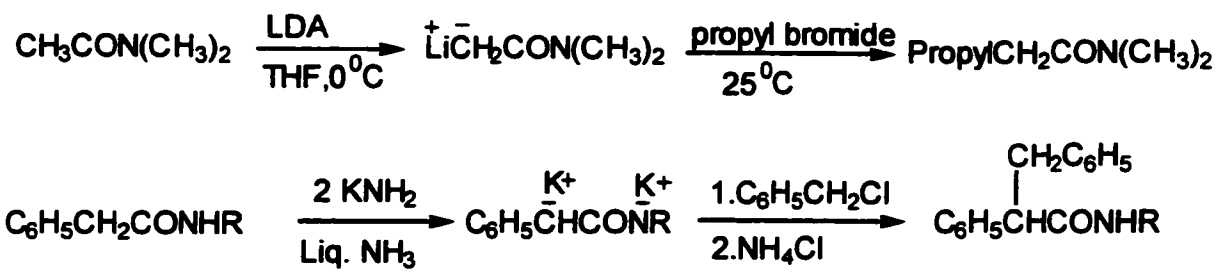


Figure 2.12: C-Alkylation of α-carbon of amides.

An effort to explain the above instances is that β-Lactam is a reactive molecule due to its strain geometry such that carbanion formation and electrophillic attack can be facilitated. As for acetamide, it is not surprising that a carbanion can be formed from the alpha carbon with a primary hydogen[13] in view of its higher acidity than its secondary analogue (in dioxocyclam.) Also, the presence of an inductive phenyl group to introduce and then stabilize the enolate resonance form helps in the essential formation of a carbanion before any alkylation can take place.

2.3 Conclusion.

It is concluded that direct C-alkylation to dioxocyclam is perhaps unattainable. We therefore gave up the idea of C-alkylation of dioxocyclam. N-alkylation product was instead obtained through this route, with a better yield than reported in the literature[16] owed perhaps to the presence of a base. An undergraduate research student, Endy Min has begun using this method in her N-alkylation project.

2.4 Experimental.

General procedure. Reactions were generally performed under a N_2 inert atmosphere. *tert*-butanol was dried over 4 Angstrom molecular sieves before use. Dry absolute ethanol was freshly prepared before use by dissolving 10% Na by weight in absolute ethanol, followed by vacuum transfer. Tetrahydrofuran was distilled from sodium benzophenone ketyl solution under N_2 and stored in the dry box. Ethyl bromide was dried with P_2O_5 for a day before being vacuum

transferred. Benzyl bromide was dried with 4 Angstroms molecular sieves one day before use.

Any reactions prepared under anhydrous condition were done in a Vacuum Atmospheres Co. dry box equipped with an HE493 Dri-train and operated under a N_2 atmosphere. Before introduction into the dry box, liquid reagents were degassed by three freeze-pump-thaw cycles performed on a bench top vacuum line in Schlenk flasks with o-ring vacuum adapter fittings. Solid reagents were also dried under vacuum. ^{1}H-NMR data were recorded on a GE QE Plus 300. $CDCl_3$ was carefully passed through a plug of anhydrous alumina (neutral activity) before use. Column chromatography was performed using a 250 ml capacity column, 1" in diameter, using Kieselgel 60 (230-400 mesh) silica gel and reagent grade solvents.

Attempt of Michael addition of dioxocyclam. To 5,7-dioxo-1,4,8,11-tetraazacyclotetradecane (100 mg, 0.438 mmol) treated with potassium *t*-butoxide (1/3 equivalent, 0.146 mmol) was added a solution of *t*-butyl acrylate (56.74mg, 0.438 mmol) in 1 ml butanol, over 20 minutes with stirring. After being stirred overnight at room temperature, the mixture was quenched with HCl (.1mmol) then 1ml $KHCO_3$ (saturated) and extracted with ethyl acetate (3x3ml). The organic layer was dried over anhydrous K_2CO_3 before being removed by rotary evaporation and dried under reduced pressure.

Alkylation of dioxocyclam by ethyl bromide. In the dry box, finely chopped sodium (69.4 mg, 3mmol) was added to 2 ml dry absolute ethanol with stirring

until all dissolved. Dioxocyclam (532 mg, 2.3 mmol) was added to the ethoxide mixture after which ethyl bromide (327 mg, 3.2 mmol) was also added dropwise. A reflux condenser was then attached and the apparatus was sealed and brought out of the dry box. The apparatus was put under a positive pressure of N_2 and heated to reflux for three hours. After filtering off the NaBr and evaporating the solvent, the crude product was chromatographed on a 1"x7" silica gel column using CH_2Cl_2: MeOH: NH_3 solvent in proportion of 25:4:0.25 respectively. Yield: 75 mg, (12%) N,N'diethyl dioxocyclam; 198 mg, (40%) N-ethyl dioxocyclam. (See appendix, pages 36-37.)

^{1}HNMR ($CDCl_3$,ppm): N,N'diethyl dioxocyclam: N<u>H</u>(COR) 7.04 (s,2H), C<u>H</u>$_2$(NCOR) 3.39 (q,4H), C<u>H</u>$_2$(CONR) 3.24 (s,2H), (CONH$_2$)C<u>H</u>$_2$(NR$_2$) 2.64 (t,4H), R$_2$N-C<u>H</u>$_2$CH$_3$ 2.60 (q, 4H), CH$_2$C<u>H</u>$_2$NR$_2$ 2.46 (t,4H), C<u>H</u>$_2$(CH$_2$NR$_2$) 1.58 (p, 2H), CH$_3$ 1.03 (t, 6H). N ethyl dioxocyclam: CONH 8.51 (t, 1H) and 8.21 (t, 1H), C<u>H</u>$_2$(NCO) 3.72 (q, 2H) and 3.44 (q, 2H), C<u>H</u>$_2$(CONR) 3.32 (s, 2H), C<u>H</u>$_2$(NHR) 3.46 (t, 2H) and 3.26 (t, 2H), C<u>H</u>$_2$(NR$_3$) 2.80 (m, 6H), C<u>H</u>$_2$(CH$_2$N) 1.98 (p,2H), CH$_3$ 0.90 (t, 3H).

C-Alkylation of the protected dioxocyclam with alkyl halide.

1) Preparation of 1,11 (bis *t*-butyl carbamyl) 5,7 dioxo-1,4,8,11-tetraaza-cyclotetradecane. Di-*t*-butyl dicarbonate (1.05 ml, 4.18 mmol) was added dropwise by syringe over 10 minutes to a solution of dioxocyclam (477 mg, 2.09 mmol) in 50ml methanol. The solution was allowed to stir at room temperature for 50 minutes after which MeOH was reduced to 2 ml. Crystallization in freezer

for two days resulted in a white powdery product, which was collected by filtration and rinsed with cold methanol. Yield: 78%, 695 mg. ^{1}HNMR ($CDCl_3$,ppm): CONH 7.00 (s,2H), CH_2NR_3 3.43 (s, 8H), CH_2CON 3.18 (s,2H), CH_2(NHCO) 3.11 (t, 4H), CH_3 1.50 (s,18H). MS (m+1)/z 429. (See p. 38-39.)

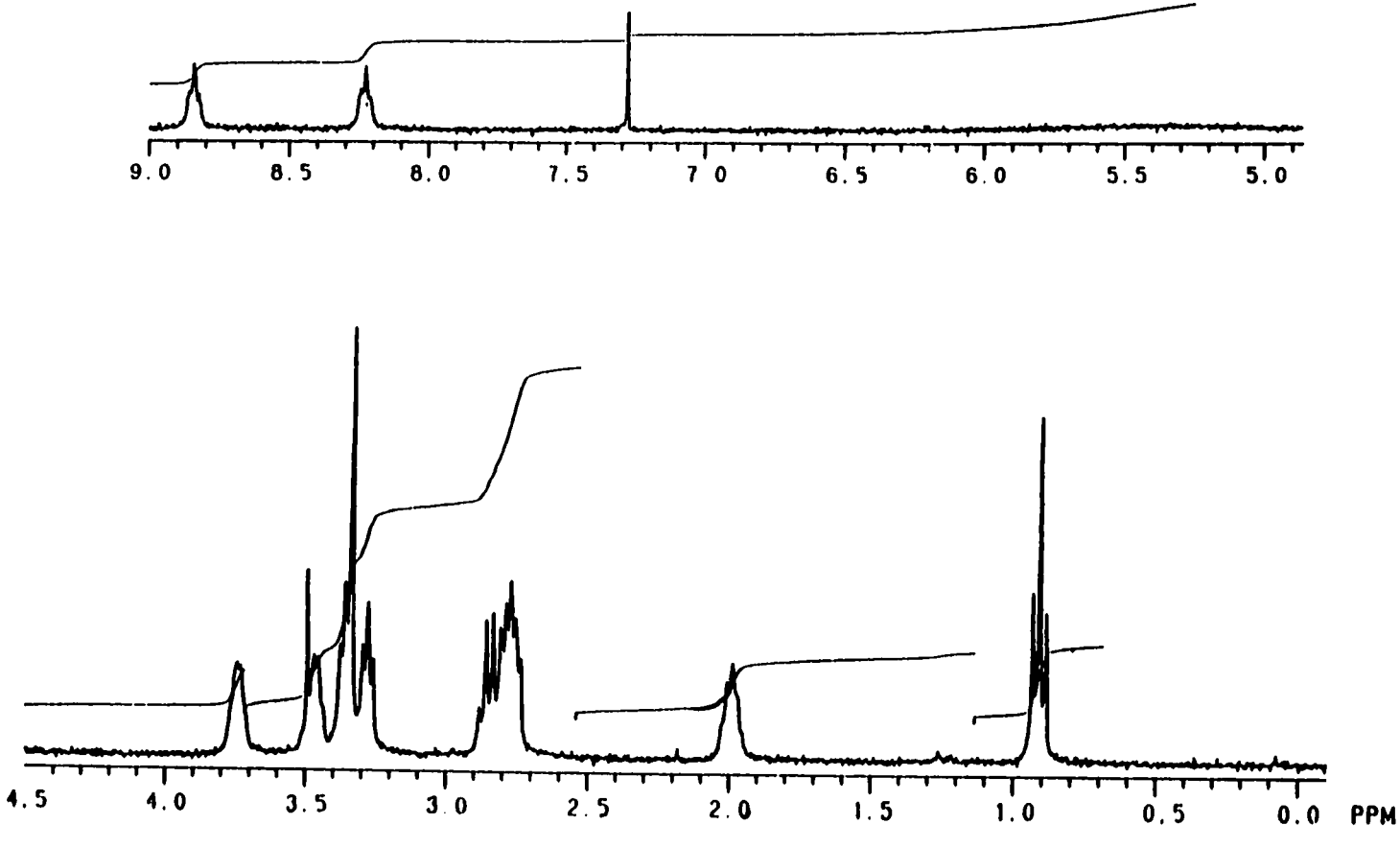
2) Attempted alkylation of 1,11-(bis *t*-butyl carbamyl) 5,7dioxo-1,4,8,11 tetraazacyclotetradecane:

a) Treatment with Na and ethyl bromide. 1,11 (bis N,N' *t*-butyl carbamyl) 5,7-dioxo-1,4,8,11 tetraazacyclotetradecane (404 mg, 0.95 mmol) was treated with Na (24.2 mg, 1.1 mmol) under anhydrous condition as above, except reflux was done overnight. 77% unreacted diprotected dioxocyclam was recovered. 14.8 mg of inconclusive material was obtained, which was not the desired product.

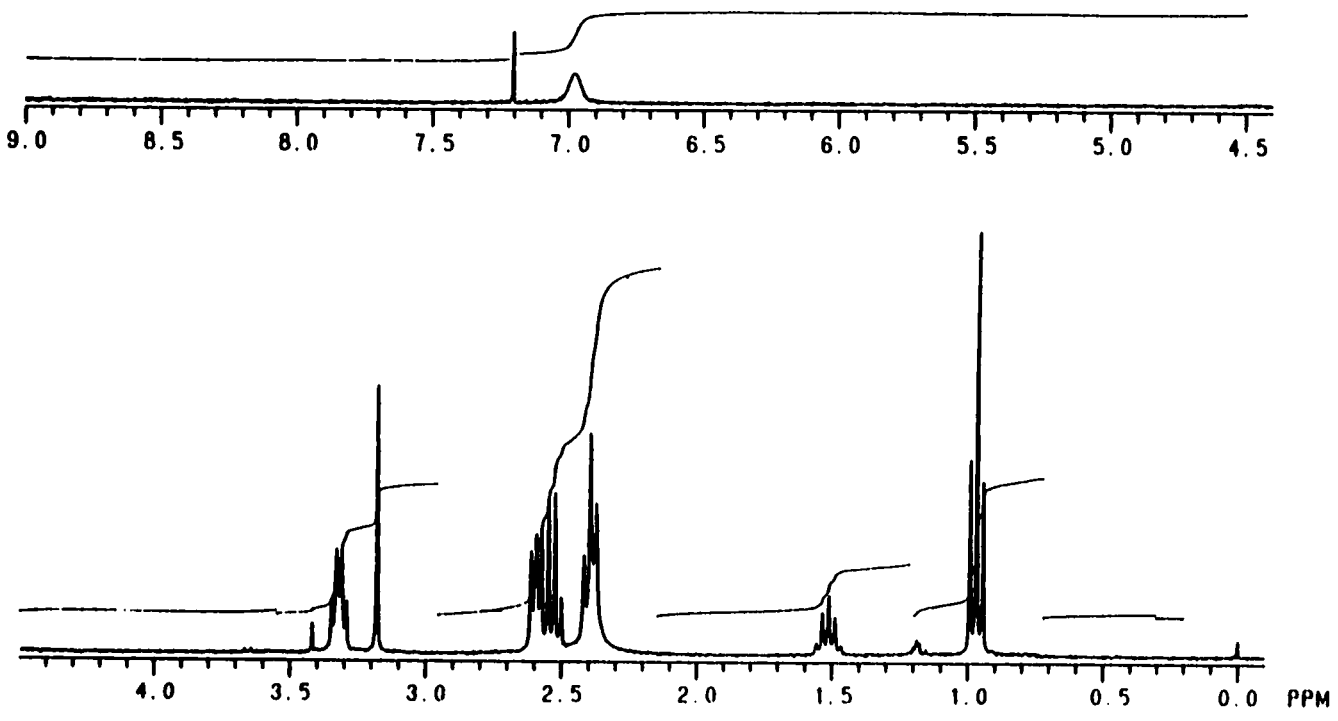
b) Treatment with LDA and benzyl bromide. To the solution of di-*t*-boc dioxo-cyclam (152 mg, 0.355 mmol) dissolved in 9 ml THF in a salt ice bath, LDA (1.17 mmol, 3 eq) was added dropwise. The clear brown mixture was stirred for an additional 30 minutes. Water was then added to the mixture and the solution was extracted with CH_2Cl_2 (3 x 4 ml). The organic layer was dried with $MgSO_4$ and the solvent was removed by rotary evaporation. Di-*t*-boc dioxocyclam (65% recovered) along with trace amount of other four components were obtained and identified by ^{1}HNMR. Resonance spectra of these four components were inconclusive due to poor resolution. None of them showed any alkylation at the carbon α to the amide carbonyls.

c) **Treatment with *n*-butyl lithium and benzyl bromide.** This reaction was done with the same procedure as in part b above. Again, there were five components with 37% recovered di-*t*-boc dioxocyclam. The other components were suspected to be decomposition products.

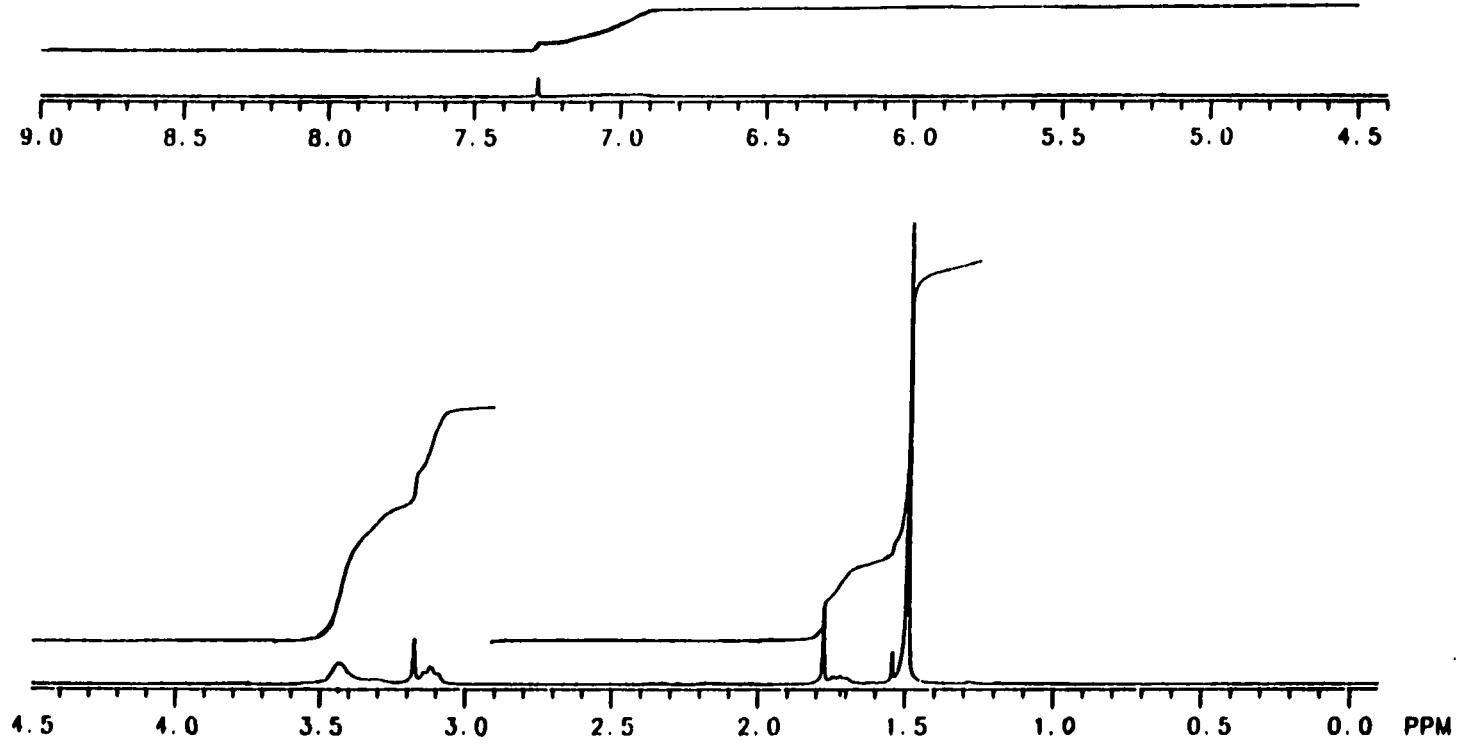
APPENDIX TO CHAPTER 2



^{1}H NMR of N-ethyl dioxo cyclam ($CDCl_3$, 300 MHz)

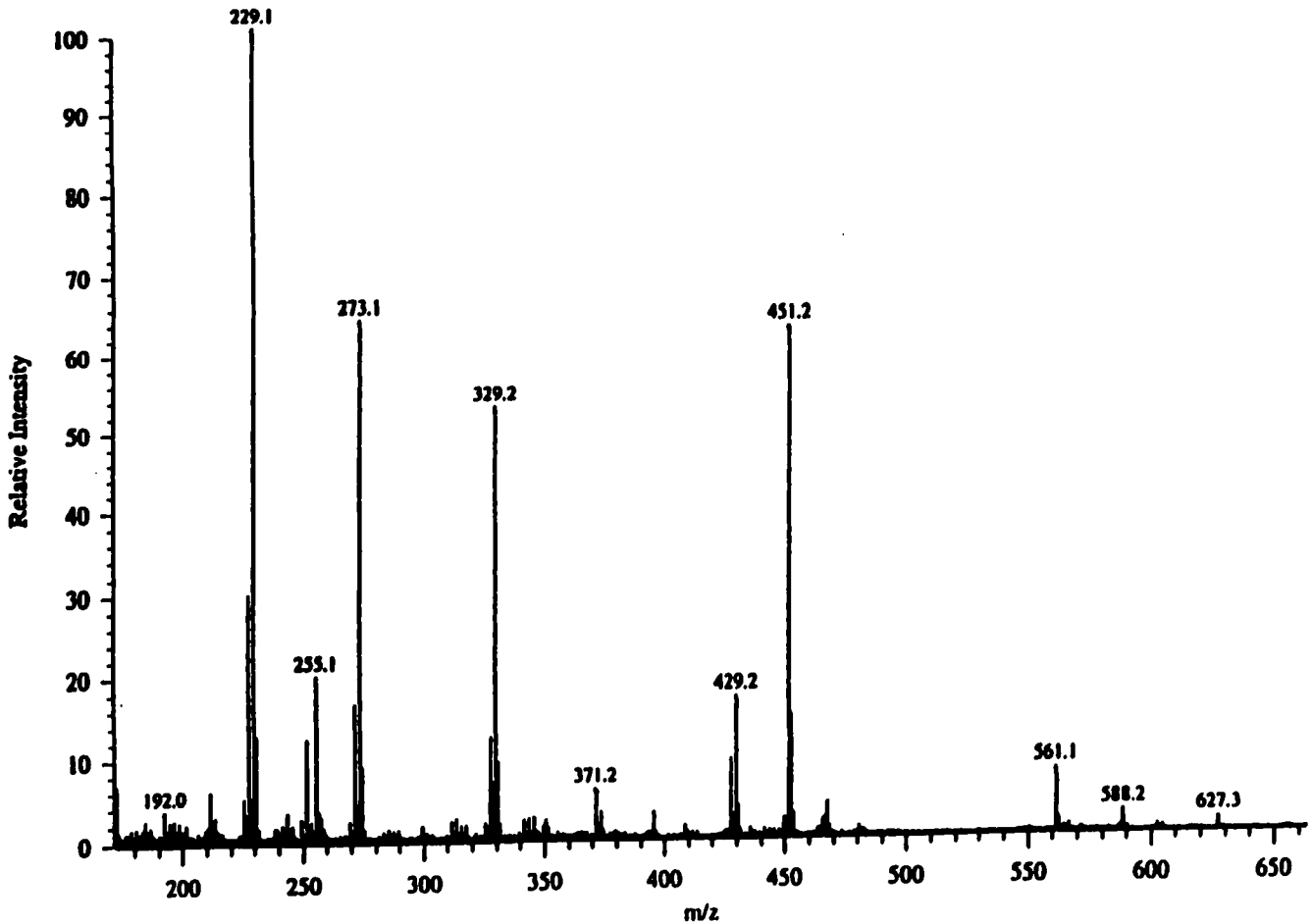


^{1}H NMR of N,N'-diethyl dioxo cyclam($CDCl_3$, 300 MHz)



^{1}H NMR of 1,11-(bis *t*-butyl carbamyl)-5,7dioxo-1,4,8,11 tetraazacyclotetradecane ($CDCl_3$, 300 MHz)

(diprotected dioxo cyclam)



Mass spectrum of 1,11-(bis *t*-butyl carbamyl)-5,7dioxo-1,4,8,11 tetraazacyclotetradecane

References

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CHAPTER 3

PREPARATION OF C-SUBSTITUTED DIOXOCYCLAM BY MALONATE AMINOLYSIS.

3.1 Introduction.

In 1977, Iwao Tabushi developed a convenient method of preparing cyclam[1]. This method employed the idea of preparing an amide from an ester and a primary amine. Substituted cyclams are obtained similarly by using a substituted ester as shown in Figure 3.1.

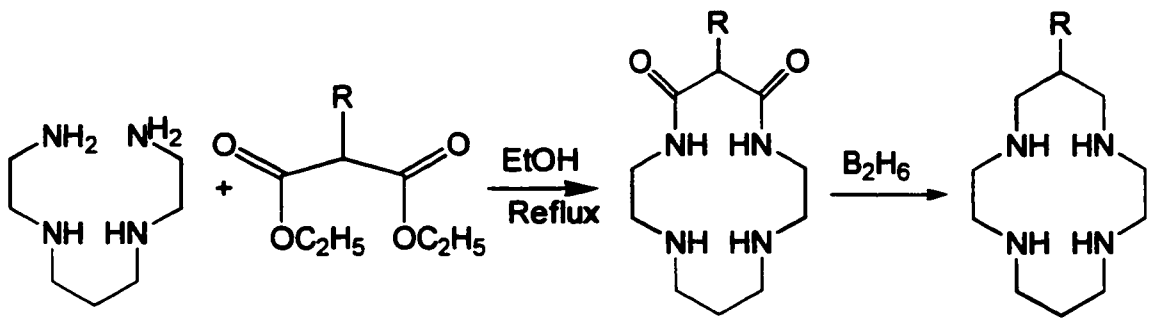


Figure 3.1. Tabushi's method for the preparation of substituted cyclams.

This method allows the preparation of a variety of substituted cyclams for diverse applications. For example, the introduction of a long alkyl chain onto cyclam to decrease its solubility in water makes it more useful to capture and recover heavy metals in waste water[2]. In the medical field, the incorporation of cyclam bearing labeled metals into monoclonal antibodies is made possible with carbon-functionalized cyclams[3]. These antibodies are for use in tumor imaging and therapy. Others synthesized pyridine pendant cyclam[4], phenolic cyclam[5], bi-cyclam etc[6,7,8]. Our group, likewise, aims at alkylating cyclam so that a Lewis acid can be covalently attached to this versatile ligand.

The advantage of this aminolytic method lies in its simplicity. It takes fewer steps to synthesize substituted cyclams using this method than the tosylation's [9] or crab-like cyclization's.[10] Importantly, it involves a carbon-carbon bond instead of an N-C tethering which can possibly reduce the cyclam 's chelating behavior toward metal ions.[7] Also, the preceding C-alkylation step of the malonate can be done using a variety of reaction types[4, 11] with moderate to good yield. Finally, it takes minimum effort to run this reaction with a simple reflux and crystallization procedure. The main disadvantage of this method is its long reaction time and its low yield due to polymerization.

Our initial attempt was to create an aza crown ether bearing dioxocyclam. This crown ether will later chelate a Lewis acid metal cation such as Na^+ or K^+ or even the alkaline earth metal ion (Mg^{2+} etc.) This attempt, however, was halted due to the difficulty in the last step of aminolysis and to other reasons that will be discussed. We therefore switched to another type of Lewis acid such as alkylstannane[12] with a direct Sn-C bond. Some alkyl stannanes are known to be good Lewis acids when one or more of the alkyl groups are replaced by an electronegative group, i.e. halogen or acyloxy.[13] This will increase tin's ability to form complexes with an electron donor group and increase its coordination number from 4 to 5 or 6[13]. This is exactly what our group wishes to examine after the synthesis of cyclam: to see if our tethered cyclam will complex well with small substrates as predicted and how strong its effect will be on the substrate. That

way, we can analyze the push-pull effect due to both Lewis acid and transition metal on the substrate.

The synthesis of Lewis acid-functionalized-cyclams consists of three steps: 1) Alkylation of the Lewis acid.

2) Alkylation of diethyl malonate with the above substituted Lewis acid.

3) Aminolytic condensation of the substituted malonate with the tetraamine.

The general scheme, shown in Figure 3.2, is:

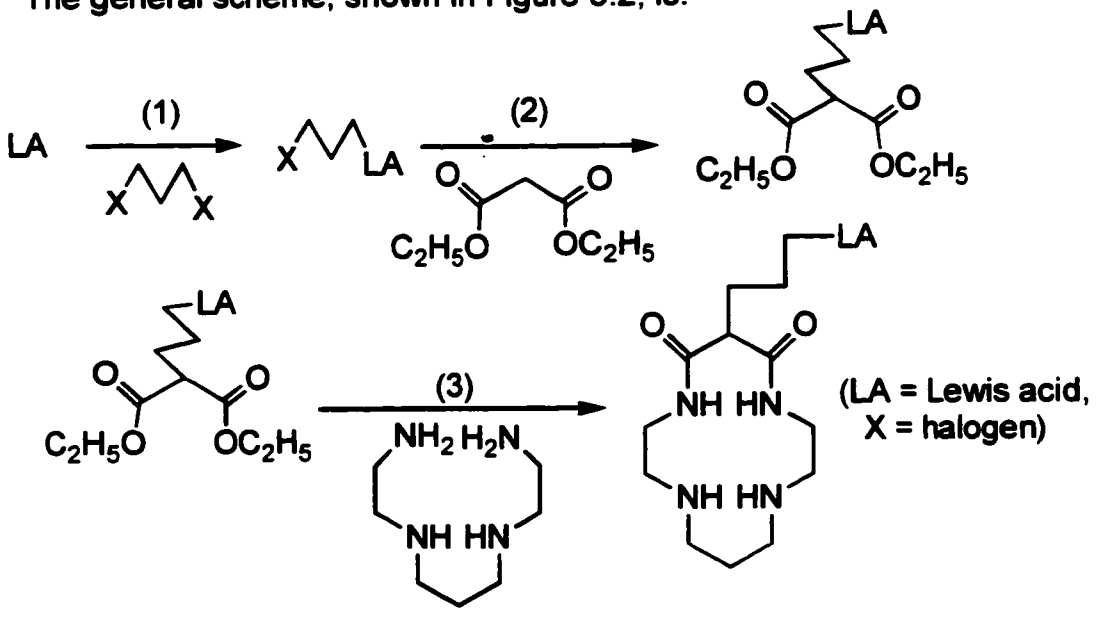


Figure 3.2. General synthetic scheme of Lewis acid functionalized cyclam.

The two carbonyl groups of dioxocyclam can be reduced smoothly by B_2H_6 in THF using established methods[1]. However, our group may first explore the push-pull effect of this bi-metallic dioxocyclam (upon chelating a transition metal and

binding a substrate) due to its numerous interesting behaviors with regard to our group's goal.

3.2 Results and Discussion.

3.2.1 Dioxocyclam Synthesis.

Preliminary experiments comprised of the synthesis of the unsubstituted 5, 7-dioxo-1,4,8,11 tetraazacyclotetradecane. This was done several times to probe the low yield and long reaction time problems of the method. Indeed, a reaction at the exact condition as Tabushi's (1M of each reactant, reflux 3 days) sometimes gave only 6% product. Other successful results obtained from this aminolysis included 41% yield at 0.05M concentration of one reactant with gentle reflux for 5 days; 10% product at 0.05M at room temperature reaction for 7 days. Sometimes, less than 5% product was obtained with 0.05M concentration of reactants at 5 days reflux. This series of probe reactions indicated that the product yield might not necessarily be simply a function of the concentration of the reactants and the reaction time (as will be discussed later). High dilution does help avoid polymerization [14,15] as far as dioxocyclam synthesis is concerned. We found that substituted malonates give higher yields under highly concentrated conditions. Polymerization can be visualized by the gradual coloration of the ethanolic mixture upon being refluxed. The color runs from yellow to orange to pink and purple. Crystals of dioxocyclam were simply filtered off from the ethanolic mixture with rinsing well in CH_2Cl_2 after several days of crystallization. They can also be collected from second or third batches.

3.2.2 Attempted Synthesis of 6(3-propanoyl-aza-18-crown-6) 5,7-dioxo-1,4,8,11 tetraazacyclotetradecane.

The synthetic plan for cyclam substituted with an aza crown ether is shown in figure 3.3 below:

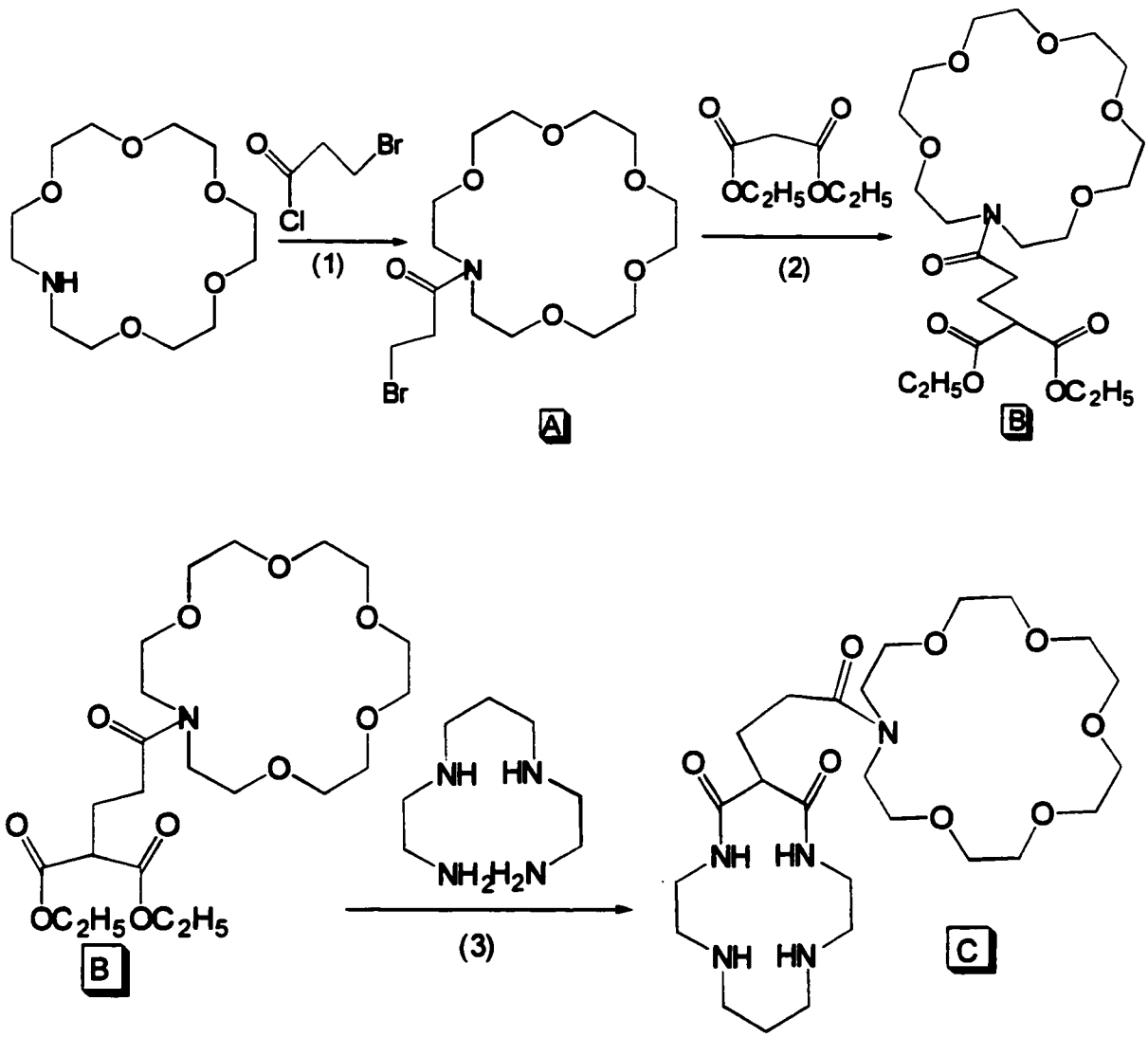
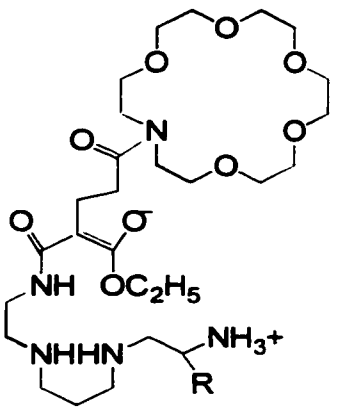


Figure 3.3. Synthetic plan for aza crown ether substituted dioxocyclam.

The acylation step 1 was a modification of a similar procedure by Gokel et al.[16] Acylation with acyl chloride is naturally superior to that with bromoalkyl. The reaction proceeded smoothly giving 76% yield of A (^1H, ^{13}C nmr and mass spectra are shown on pages 62-64) in three hours of reaction time at room temperature. Due to the mild conditions of the reaction, the bromide end of the alkyl chain remained intact for later alkylation in step 2. Step 2 represented another smooth reaction in which diethyl malonate and sodium ethoxide was heated to reflux with A for three hours. Up to 75% yield of B was obtained (spectrum data shown on pages 65-67.) This method was done by modifying established methods.[11] This procedure is simple and takes considerably less time to proceed than the two days reaction at milder condition done by E. Kimura et al.[4]

The last step, 3, was conducted as previously performed for dioxocyclam synthesis. After three days of refluxing in moderate dilution (0.15 M), 76% of aza crown ether substituted malonate was found unreacted. The ethanolic solution remained colorless as well (no polymerization.) The small amount of product was thought to be an open chain mono-amide. In other word, after three days of reflux, only a small amount of the tetraamine was able to attach to one side of the malonate, while the other end was left dangling. Wagler, Fang and Burrows[17] obtained the same result in their condensation of a di-substituted tetraamine (2,10-diisopropyl-tetraazaundecane) and dimethyl malonate (only 7.5% product.) They argue that the difficulty in the final ring closure may result from decreased

reactivity of a zwitterionic form or by an unfavorable conformational restriction such as illustrated in figure 3.4.



R = *iso*-propyl or H.

Figure 3.4: Zwitterionic form in the ring closure step of Tabushi's aminolysis.

This reaction was repeated once more with 9 days of refluxing the mixture under more dilute conditions (0.04M). After purifying the mixture by chromatography, about 60% of unreacted malonate **B** were recovered. Three other components were also present at minimum amount, none of which was the desired product. The first fraction was the starting material. The second was possibly an open chain mono-amide attached to a possibly decomposed ether (rf =0.16). The third fraction at rf = 0.13 appeared to be the desired product except that it has a C=C bond at the region 5.1 to 5.8 ppm (^{1}H and ^{13}C nmr spectrum shown on page 68-69.) The fourth fraction also appeared to be another type of open chain mono-amide.

As seen above, there was a possible decomposition or rearrangement of the aza crown ether due to extensive heating (yet, only 40% of the malonate **B**

had reacted.) Another possible reason for the failure of this aminolysis is that the bulky aza crown ether may present such a steric hindrance for the approach of the tetraamine. This may also explain the absence of polymerization. Fraction 3 might represent the result of a forceful acylation by an SN_2 mechanism (by the tetraamine), such that the substituted malonate has to rearrange intramolecularly to accommodate such change. Also, there was a possible difficulty in the isolation of the desired product due to the omni solubility of this type of molecule in all types of solvent. In view of the above factors, we decided to abandon the use of this Lewis acid chelator agent and opted for another type of Lewis acid, namely, alkylstannanes.[12]

3.2.3 Synthesis of 6(3-trimethylstannylpropyl)-5,7 dioxo-1,4,8,11 tetraazacyclotetradecane.

The general scheme of this route is as shown in Figure 3.5 below.

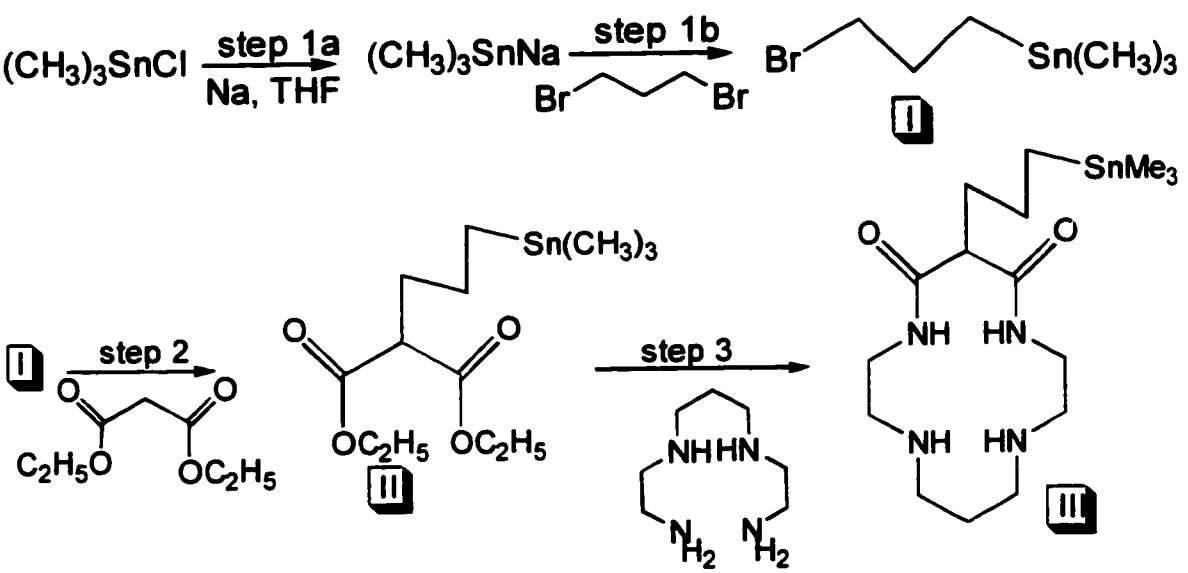


Figure 3.5. Synthetic scheme for alkylstannyl functionalized dioxocyclam.

Step 1a involves the formation of a trimethyl tin sodium salt. This salt is isolable, but unstable upon air exposure. It is very reactive toward compounds containing electronegative elements. It can be prepared in either THF solvent or liquid ammonia[18]. This salt is an important synthetic reagent because it makes possible the attachment of a trimethyl tin group to another compound.[18] Step 1b involves the dropwise addition of this salt in THF into a cold solution of 1,3-dibromopropane in THF. We obtained 30% yield of I (^{1}H nmr on page 70) under these conditions. The preparation of unsymmetrical organotin compounds, [19] steps 1a and 1b, is usually performed in liquid ammonia, but we chose to conduct it in cold THF[20] once. (Our team got about 80% yield using liquid NH_3 with 1,3-dichloropropane.) 3-bromo-1-trimethyl stannyl propane was obtained by distillation at reduced pressure and collected at around 80^{0}C at 10 torr.[21] The low yield of this process might be partly due to the formation of 1,3 bis-trimethyltin propane[16] and possible cyclopropane formation.

The alkylation of diethyl malonate with 3-bromo-1-trimethylstannyl propane progressed smoothly, similar to the procedure in section 3.2.2. This reaction type gives yields in the range of 60 to 80%, depending on the purity of reagents and the dryness of solvent.[11] The reaction in this particular section gave only 58% product, possibly due to the presence of 6% 1,3-dibromopropane impurity and the susceptibility of the electrophillic organotin toward the halogen. Upon purification by chromatography, four fractions were obtained with fraction 3 being the desired product II (^{1}H nmr on page 72.) Fraction 4 weighed the most

(1g collected.) This might be a poly-halogen-alkyl tin compound. Fraction 2 at 4% yield was identified as di-alkylation product $(Me_3Sn(CH_2)_3)_2C(COOC_2H_5)_2$, (^{1}H nmr shown on page 71.)

The last step, the aminolytic condensation of the tetraamine and II was difficult. Upon 7 days of reflux (at 0.07M concentration), 70% of II was recovered unreacted. Three other components were also present at minimum amount, barely enough to be characterized by ^{1}HNMR. The last constituent seemed to contain a small amount of the desired product III, although it was not clear in the ^{1}HNMR spectrum due to unresolved peaks. This reaction was therefore tried again. The recovered II (340 mg) was heated at reflux with the tetraamine in absolute ethanol for 13 days at higher concentration than before (0.47M) since it did not polymerize the last time. Upon cooling the mixture, some white solid was observed. After separation by chromatography with CH_2Cl_2 in the presence of 9% MeOH and 1% NH_3, 17% of II was recovered. Two other components in small amounts, 9 and 7 mg, with rf values of 0.29 and 0.18 respectively, were also present. The fourth fraction at 26% of the theoretical yield was the desired product III (^{1}H and ^{13}C nmr shown on pages 73-75) with rf value of 0.05. Hence, we succeed in synthesizing Lewis acid tethered dioxocyclam at reasonable yield. We believe that this yield may be increased by further optimization of the reaction conditions, such as increasing the refluxing time (to completely use up the 17% unreacted II as mentioned above), and purifying the product by crystallization

only (to avoid loss during chromatography since this was successfully done to the synthesis of dioxocyclam in increasing its yield.)

Thus, some of the synthetic difficulties along the path to our target molecule have been solved. We succeed in synthesizing a Lewis acid tethered dioxocyclam ligand in a reasonably high yield. We have yet to chlorinate the Sn and reduce the amides, but there are precedents for both of these reactions in the literature. We are more confident than ever that we will be able to realize our goal of studying the push pull effect with these simple compounds.

3.2.4 Discussion of the Aminolytic Condensation Reaction.

To account for the slowness of the reaction, it is helpful to evaluate factors that are involved in the mechanism of such reaction. This aminolytic condensation involves the acylation of an amine by an ester. The term acylation denotes the nucleophilic attack of a substrate (namely amine) toward the carbonyl carbon atom in an SN_2 mechanism, therefore steric hindrance is a significant factor. Alkyl and di-alkyl malonic esters are recognized as particularly resistant toward aminolysis due to the steric hindrance at their carbonyl sites[22]. Bunnett and Davis in their study of the aminolysis of ethyl formate with *n*-butylamine in ethanol solution reveals that this type of reaction is essentially base catalyzed.[23] Not only that, it also involves powerful intramolecular self-catalysis presented in the study of the reaction of a diamine with phenyl acetate by Bruice and Willis.[24] In light of such study, Tabushi's aminolysis involves likewise, a self-catalysis reaction where one end of the tetraamine served as a catalyst to

promote the nucleophillic attack at the other end amine in the rate determining step as in the following general equation shown in Figure 3.6:

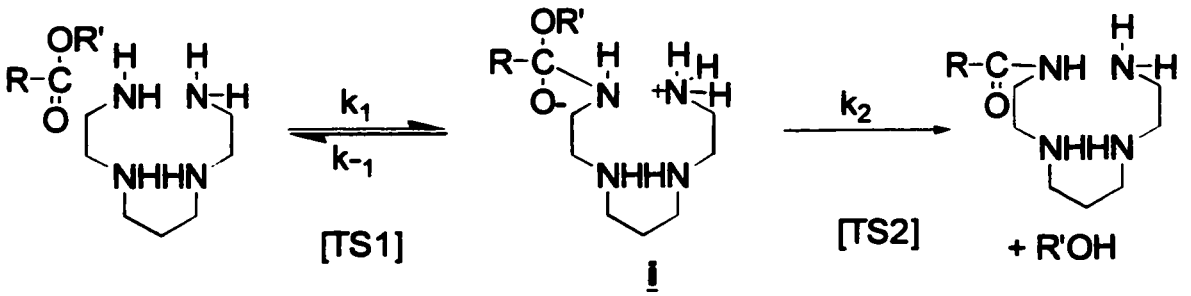


Figure 3.6 General self-catalysis acylation reaction of an amine.

In the formation of intermediate i, transitional state 1(TS1) necessarily involves partial bond formation of C-N as a result of the nucleophilic attack of the amine, which is being activated by its other primary amine end. Roughly, the mechanism leading to transitional state 1 and intermediate i is illustrated as in the following:

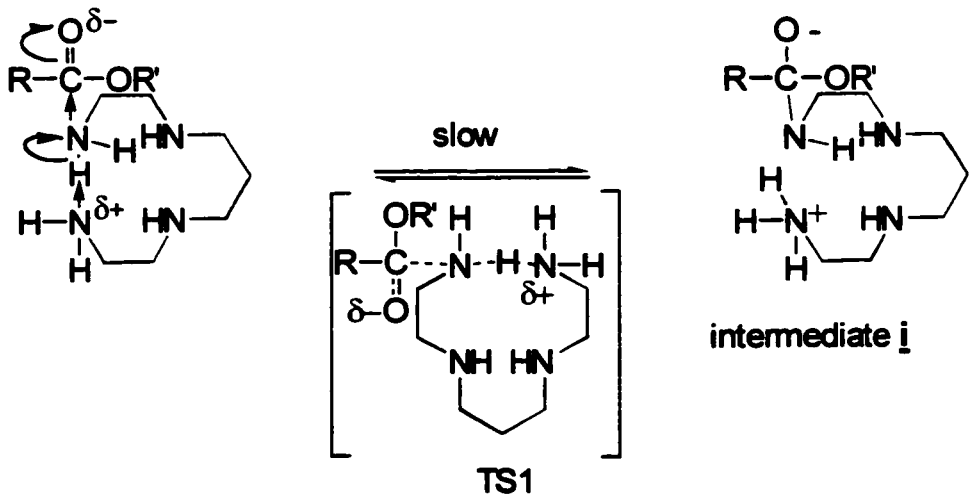


Figure 3.7 Mechanistic pathway leading to transitional state 1 and intermediate i.

Intermediate i essentially involves the bond breaking step of the leaving group to form the product. This step requires the assistance of a proton donor group, namely RNH_3^+ in a concerted manner. The mechanistic pathway can be depicted as following:

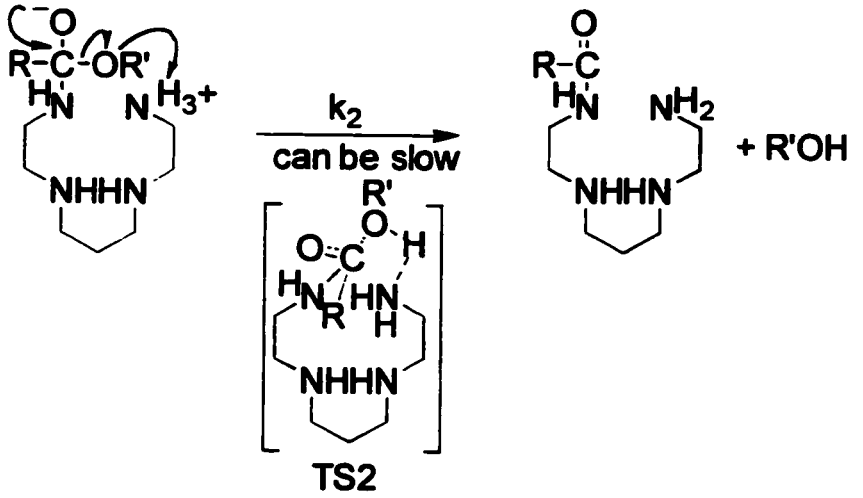


Figure 3.8 Mechanistic pathway for acid-catalyzed bond breaking of OR'.

The above step is acid-catalyzed. Under basic condition, this step can become rate determining step[25] because it involves a proton transfer from a nucleophillic atom. In fact, Jencks and coworkers believe that with a poor leaving group, k_2 is rate determining step whereas with a good leaving group, k_1 is.[22,26] In light of such mechanism, Tabushi's method comprises factors that are inherently unfavorable to both the bond formation step as well as the bond breaking steps of the product, namely the steric hindrance of the carbonyl carbon and the poor leaving group $^-OC_2H_5$. Even in cases where the leaving group is not a problem, i.e. replace the ester group by an acyl chloride, the yield and the

reaction rate do not improve[17] perhaps because the steric hindrance factor is still there.

As suggested by Wagler et al., the final ring closure step may be difficult due to the presence of a zwitterionic form that hindered the acylation of the other end of the tetraamine. This argument sounds possible to us since our result showed mono-amide formation many times. In addition, we suggest another reason for this difficulty in term of catalysis and dilution of the reactants in the mixture. We believe that the final ring closure step involves a less powerful intermolecular catalysis that is slower than intramolecular one. While low dilution conditions of the mixture facilitates intermolecular catalysis (because it increases the chance of a collision between two amines), it also magnifies the polymerization product, e.g., trimerization which is the condensation of two amine molecules with one malonate molecule as illustrated in figure 3.9.

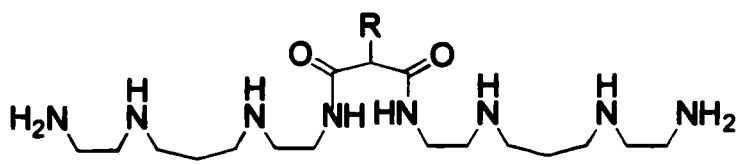


Figure 3.9: Polymerization product in aminolytic condensation.

This trimerization occurs preferentially over the cyclization in concentrated solutions. Although high dilution helps avoid polymerization, it may also make the second acylation more difficult if the reaction is catalyzed intermolecularly as discussed above. Intramolecular catalysis by the secondary amines within the

chain is difficult due to geometric constraints once it is attached to one end of the malonate.

In conclusion, the Tabushi aminolytic condensation has three inherent factors causing low yield and long reaction time, namely, the steric hindrance of the acyl carbon of the malonate, the poor leaving group with poor basic assistance for bond cleavage and the natural polymerization factor. One can choose to manipulate one or two latter factors but never about the geometric portion of the malonate. Nevertheless, this type of reaction remains a convenient and popular method in the synthesis of cyclam for more than two decades.

3.3 Experimental

General procedure. Most reactions were often run under a N_2 or argon inert atmosphere. Dry absolute ethanol was prepared before use by dissolving 10% by weight of Na in absolute ethanol followed by vacuum transfer. Dry benzene and tetrahydrofuran were distilled from benzophenone ketyl under N_2 and stored in the dry box. Diethyl malonate, 3-bromo1-propanoyl chloride, 1,3-dibromo-propane and N, N' bis-2aminoethyl-propane as well as the solid trimethyl stannyl chloride were of commercial reagent grade and used as is. Na_2CO_3 was dried by heating to 230^{0}C and stored in a dry dessicator. Metallic sodium was stripped of its oxide film before admission into the dry box. Reactions under dry conditions were prepared and / or performed in a Vacuum Atmospheres / inert N_2 atmosphere dry box equipped with an HE 493 Dri-train. Before admission to the dry box, liquid reagents / solvents were degassed by three freeze-pump-thaw

cycles using Schlenk flasks with o-ring vacuum adapter fittings. All glassware brought into the dry box was previously dried in the oven at 120^{0}C for 30 minutes or more. $CDCl_3$ was passed through a plug of neutral alumina before use. ^1H and ^{13}C-NMR data were recorded on a GE QE plus 300. Chromatography was performed using a chromatotron with a 1 or 2 mm thick plate of absorbosil plus P and 25% $CaSO_4.6H_2O$. Eluting solvents were usually of reagent grade.

3.3.1 Attempted synthesis of 6(3-propanoyl-aza-18-crown-6-ether)-5,7 dioxo-1,4,8,11 tetraazacyclotetradecane.

3-Bromo-1-propanoyl-N-aza-18-crown-6-ether (A). To a vigorously stirred solution of mono-N-aza-18-crown-6-ether (451 mg, 1.7 mmol) and anhydrous Na_2CO_3 (218 mg, 2 mmol) in dry benzene (25 ml) was added dropwise 3-bromo 1-propanoyl chloride (322 mg, 1.8 mmol) at ambient temperature. The mixture was stirred for three more hours at room temperature, then filtered and purified by chromatography with 3% MeOH in CH_2Cl_2 eluent. 514 mg of a transparent, faintly yellow oil was obtained (75%). ^{1}HNMR ($CDCl_3$, ppm) 3.68 (m,26H) and 3.01 (t, 2H). MS (FAB) (M+1)/z = 398.1 (100%), M+3 = 400.1 (95%). ^{13}CNMR ($CDCl_3$, ppm): 27.72, 36.22, 46.73, 48.96, 53.51, 69.42, 69.66, 70.22, 70.29, 70.39, 70.50, 70.62,70.90, 170.37. (See p. 62-64.)

Diethyl-2(1-propanoyl-3-aza 18-crown-6-ether) malonate (B). In the dry box, diethyl malonate (261 mg, 1.63 mmol) was added dropwise to a stirred solution of finely chopped Na (37 mg, 1.63 mmol) in 1.5 ml dry EtOH after which a solution of A (554 mg, 1.4 mmol) in 2.5 ml dry EtOH was added over 10 minutes.

Reflux condenser was then fitted, sealed and brought out of the dry box. The mixture was brought to reflux for three hours under N_2, then filtered and purified by chromatography with 5% MeOH in CH_2Cl_2 eluent. 480 mg of a faintly yellow, transparent thin oil was obtained as B (71%). ^{1}HNMR ($CDCl_3$, ppm): $CH_3C\underline{H}_2OCO$ 4.21 (q,4H), H(aza-crown-ether) 3.67 (m, 24H), $C\underline{H}(COOR)_2$ 3.50 (t, 1H), $C\underline{H}_2CONR_2$ 2.49 (t, 2H), $C\underline{H}_2CH(COOC_2H_5)_2$ 2.25 (q, 2H), $C\underline{H}_3CH_2OCO$ 1.29 (t, 6H). MS (FAB): (M+1)/z = 478.3 (100%). ^{13}CNMR ($CDCl_3$, ppm): 13.84, 23.93, 29.90, 46.49, 48.61, 50.72, 61.02, 69.21, 69.51, 70.01, 70.16, 70.25, 70.31, 70.38, 70.41, 70.44, 70.60, 168.98, 171.60.(See p. 65-67.)

Attempted condensation of the malonate B with tetraamine. To a stirred solution of malonate B (477 mg, 0.99 mmol) in 25 ml absolute EtOH was added dropwise N,N' bis-2-aminoethyl-propane (160 mg, 0.99 mmol). The mixture was refluxed for 9 days after which it was purified by chromatography with an eluent of CH_2Cl_2:MeOH: NH_3 in proportion of 10:1.5:0.2 respectively. 270 mg of B was recovered (57%). Three other components were also formed, none of which was the desired product. (See p. 68-69 for third fraction's spectra.)

3.3.2 Synthesis of 6(3-trimethylstannylpropyl)-5,7dioxo-1,4,8,11 tetraazacyclotetradecane.

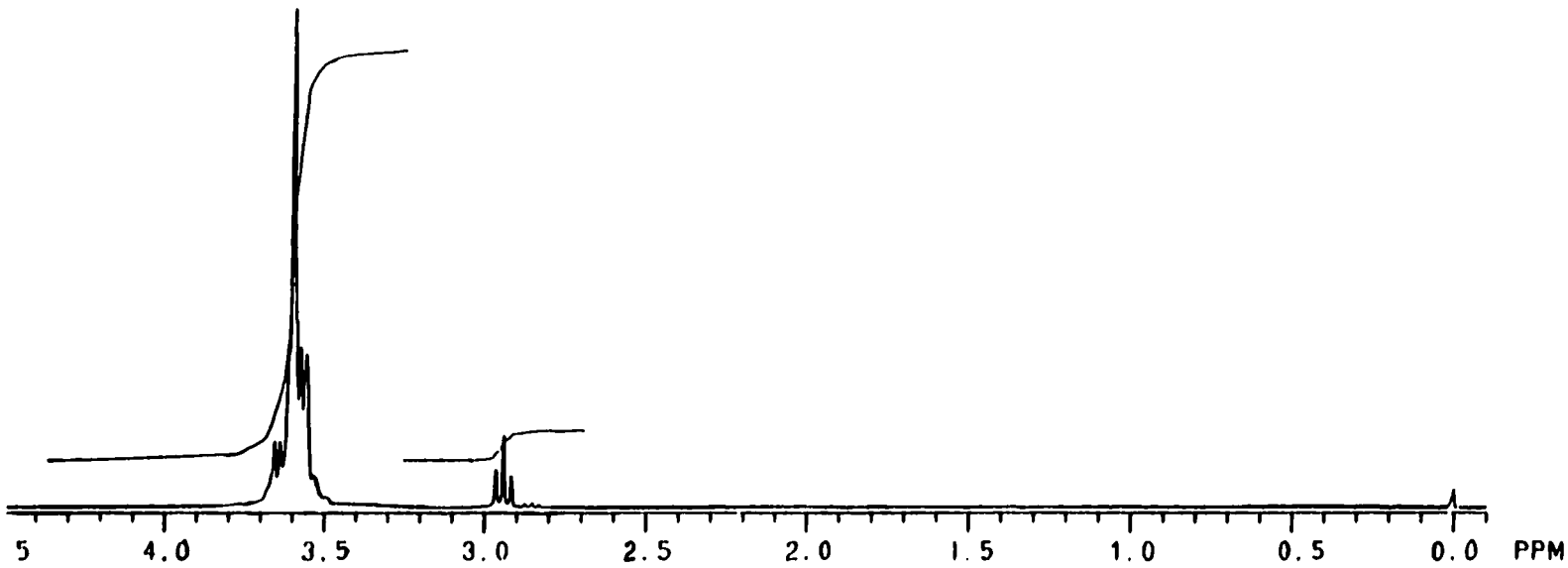
3-Bromo 1-trimethylstannyl propane (I). To a mixture of finely chopped Na (3.2 mg, 0.14 mmol) in 25 ml dry THF and 5 mg of napthalene,[27] was added dropwise overnight a solution of trimethyl tin chloride (5.06 g, 25.4 mmol) dissolved in 20 ml dry THF. The grayish mossy green mixture was stirred, then

filtered to give a transparent yellow liquid. To a stirred solution of 1,3-dibromopropane (4.8 mg, 23.8 mmol in 30 ml THF) at -78^0C was added dropwise the yellow solution of Me_3SnNa over 1 hour. After 15 minutes stirring at -78^0C, the cold bath was removed and the mixture was allowed to be stirred for 1 more hour at room temperature. The mixture was filtered and then NH_4Cl (5 ml, saturate) was added. THF was allowed to evaporate under reduced pressure and the aqueous layer extracted with CH_2Cl_2 (2 x 5ml) and dried with $MgSO_4$. CH_2Cl_2 was removed under reduced pressure to give a transparent oil. Distillation at 10 Torr, 80^0C afforded 1.6 g of I (26%) as a thin, colorless liquid. ^{1}HNMR ($CDCl_3$, ppm): $(C\underline{H}_3)_3SnR$ 0.10 (s, 9H), $C\underline{H}_2SnR_3$ 0.86 (m, 2H), $C\underline{H}_2CH_2Sn$ 2.00 (m, 2H), $C\underline{H}_2Br$ 3.36 (m, 2H).(Spectrum on p. 70.)

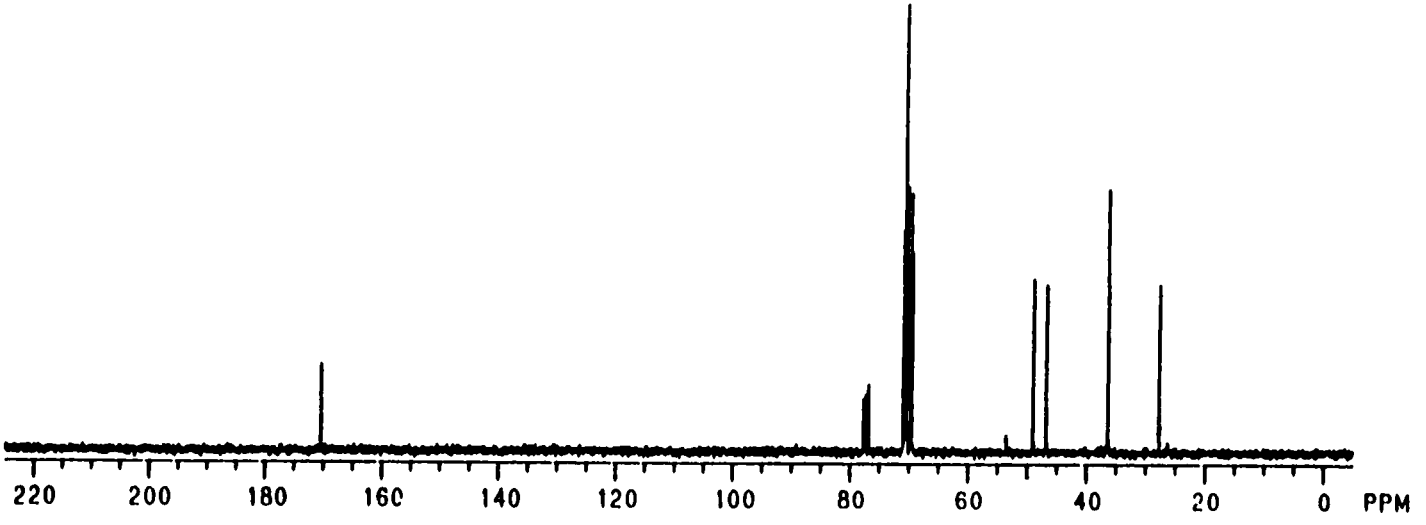
Diethyl 2-(3-trimethylstannylpropyl) malonate (II). The procedure was the same as in the preparation of B above. To a stirred solution of dry absolute EtOH (3ml) and finely chopped Na (75 mg, 3.4 mmol) was added diethyl malonate (495 µl, 3.4 mmol). After dropwise addition of I (789 mg, 2.8 mmol) over one half-hour, the mixture was refluxed for three hours, then cooled and filtered. After purification by chromatography with CH_2Cl_2, 581 mg of II was obtained (60%) as a thin colorless liquid at the third fraction with rf = 0.34. ^{1}HNMR ($CDCl_3$, ppm) $C\underline{H}_3Sn$ 0.08 (t, 9H), $C\underline{H}_2SnR$ 0.82 (t, 2H), $C\underline{H}_3CH_2OR$ 1.27 (t, 6H), $C\underline{H}_2CH_2SnR$ 1.50 (p, 2H) $C\underline{H}_2CHR$ 1.90 (q,2H), $C\underline{H}(COOR)_2$ 3.34 (t,1H), $C\underline{H}_2CH_3$ 4.20 (q, 4H). (Spectrum on p. 72.)

6(3-trimethylstannylpropyl)-5,7 dioxo-1,4,8,11 tetraazacyclotetradecane(III). To a stirred solution of II (340mg, 0.93 mmol) in 2 ml absolute EtOH was added dropwise N, N' (bis-2-aminoethyl) propane (156 μl, 0.93 mmol.) The mixture was slowly brought to reflux for 13 days after which the solvent was reduced to about 3 ml by rotary evaporation. Upon being condensed, some white solid was observed to crash out. The mixture was purified by chromatotron with 1mm plate and with an eluent of 9% MeOH and 1% NH_3 in CH_2Cl_2. 103 mg of III as a white solid was obtained (26%) in the last fraction, rf = 0.05. ^{1}HNMR ($CDCl_3$, ppm): $C\underline{H}_3Sn$ 0.02 (t,9H), $C\underline{H}_2Sn$ 0.79 (t, 2H), $C\underline{H}_2CH_2Sn$ 1.47 (m, 2H), $C\underline{H}_2CH_2N_{amine}$ 1.65 (p, 2H), $C\underline{H}_2CHCOO$ 1.85 (q, 2H), $\underline{H}_{amine}$ 2.23 (s, 2H), $C\underline{H}_2$ 2.60 (m, 2H), $C\underline{H}_2N_{amine}$ 2.72 (t, 4H), $C\underline{H}_2N_{amine}$ 2.79 (m,2H), $C\underline{H}COR$ 3.06 (t, 1H), $C\underline{H}_2$ 3.27 (m, 2H), $C\underline{H}_2$ 3.52 (m, 2H), $\underline{H}_{amide}$ 7.23 (s, 2H). (See spectra on pages 73-75.)

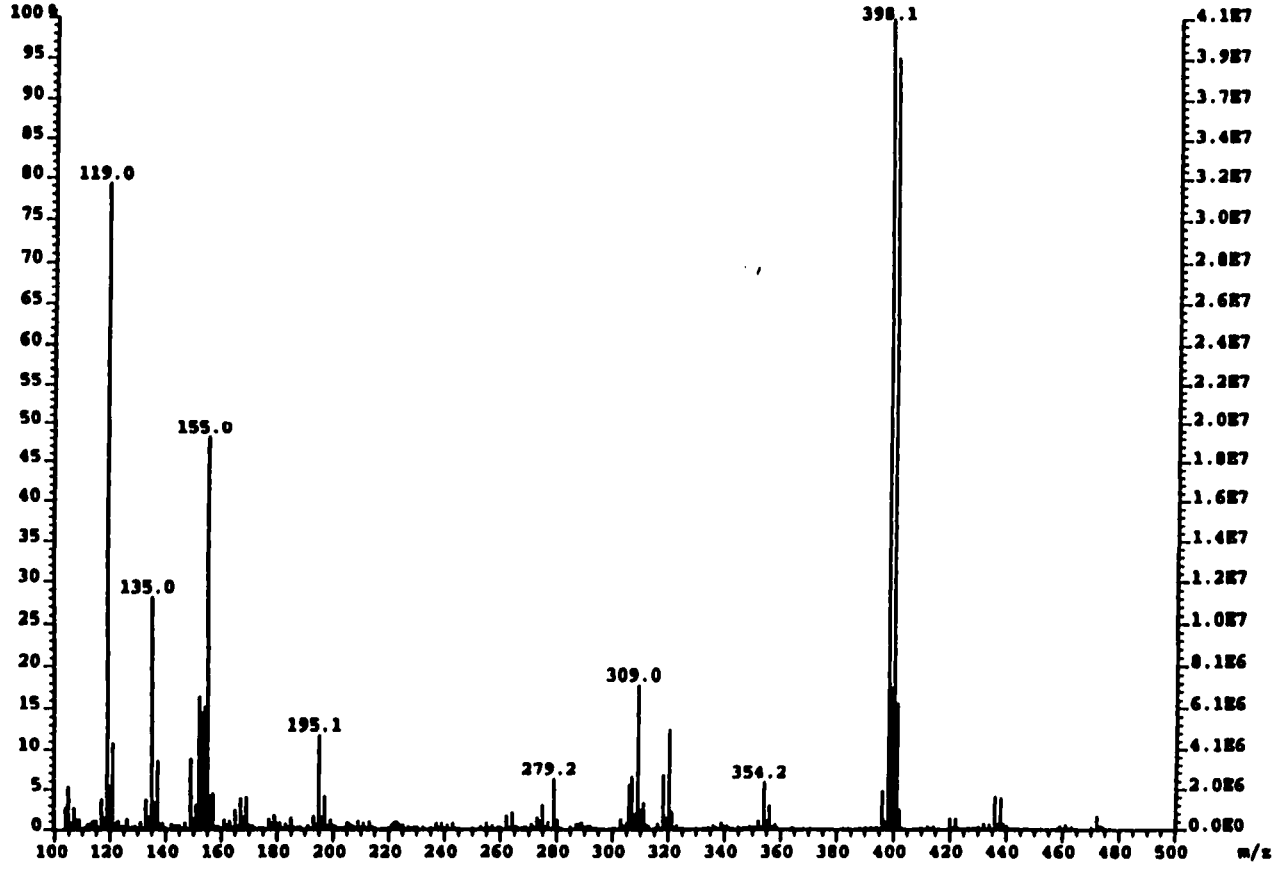
APPENDIX TO CHAPTER 3



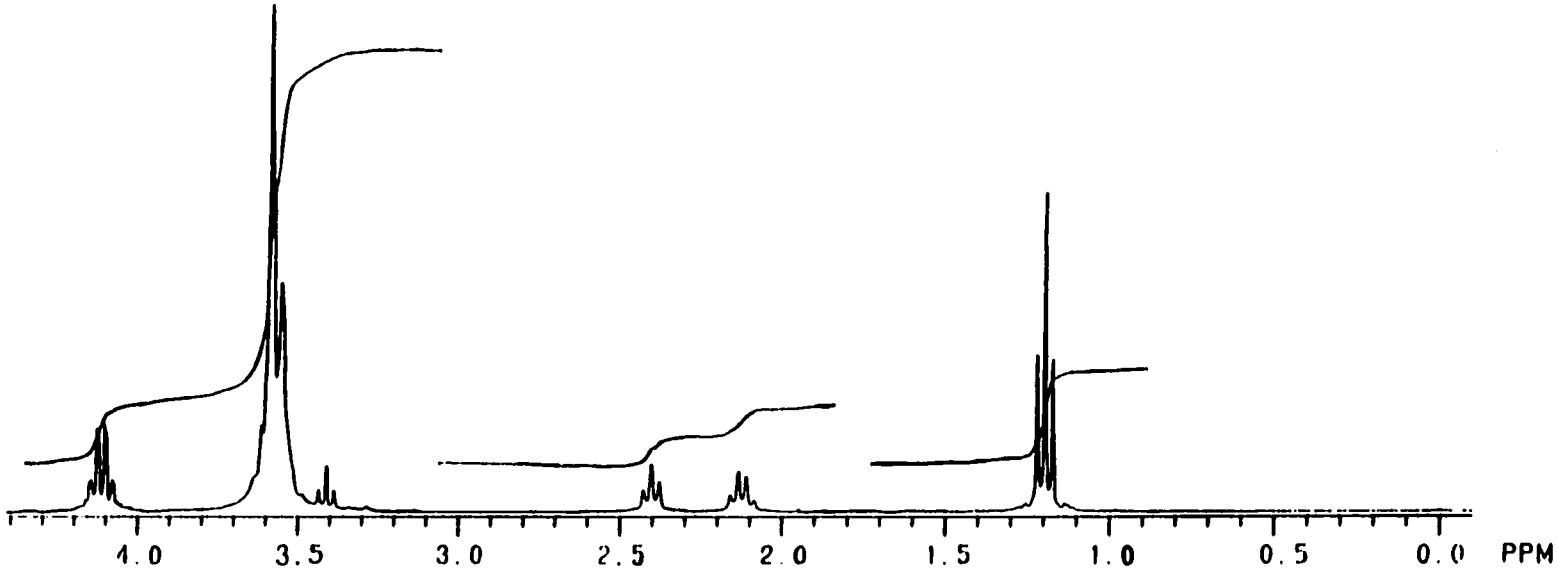
^{1}H NMR of 3-Bromo-1-propanoyl-N-aza-18-crown-6-ether (**A**) ($CDCl_3$, 300 MHz)



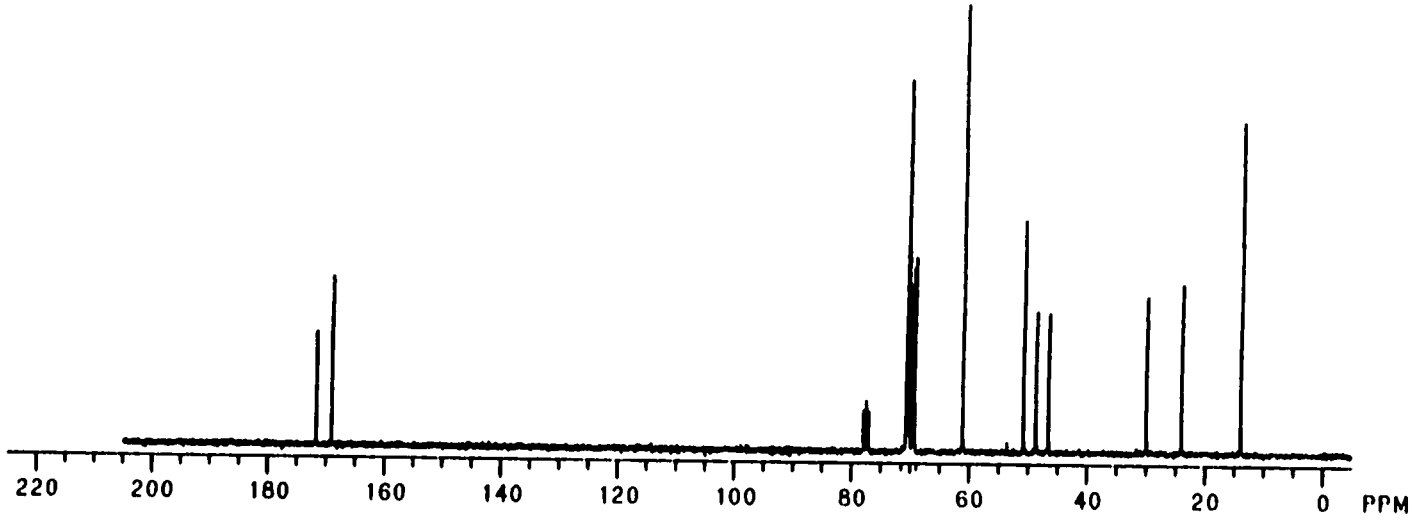
^{13}C NMR of 3-Bromo-1-propanoyl-N-aza-18-crown-6-ether (A) ($CDCl_3$, 300 MHz)



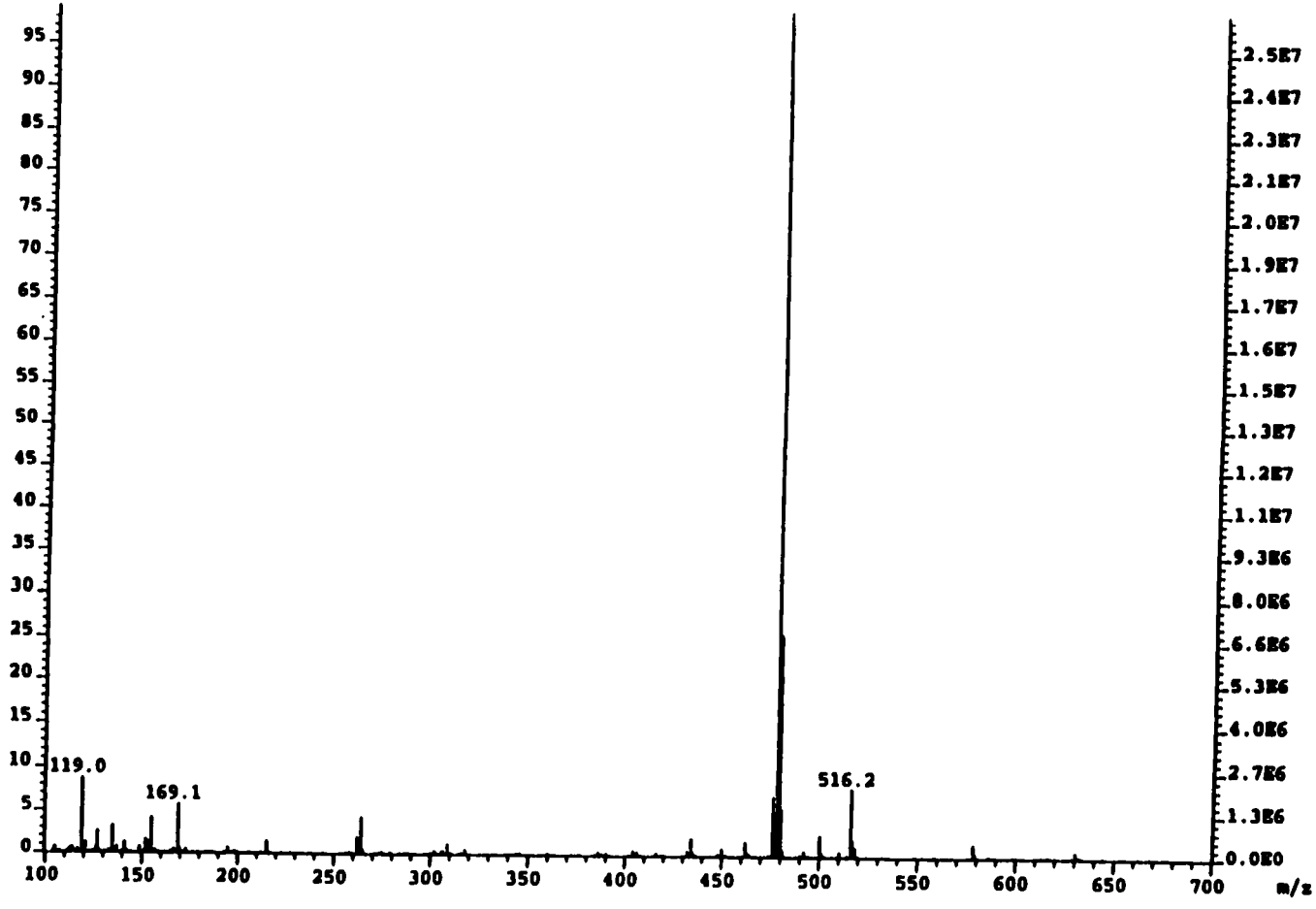
Mass spectrum of 3-Bromo-1-propanoyl-N-aza-18-crown-6-ether (A)



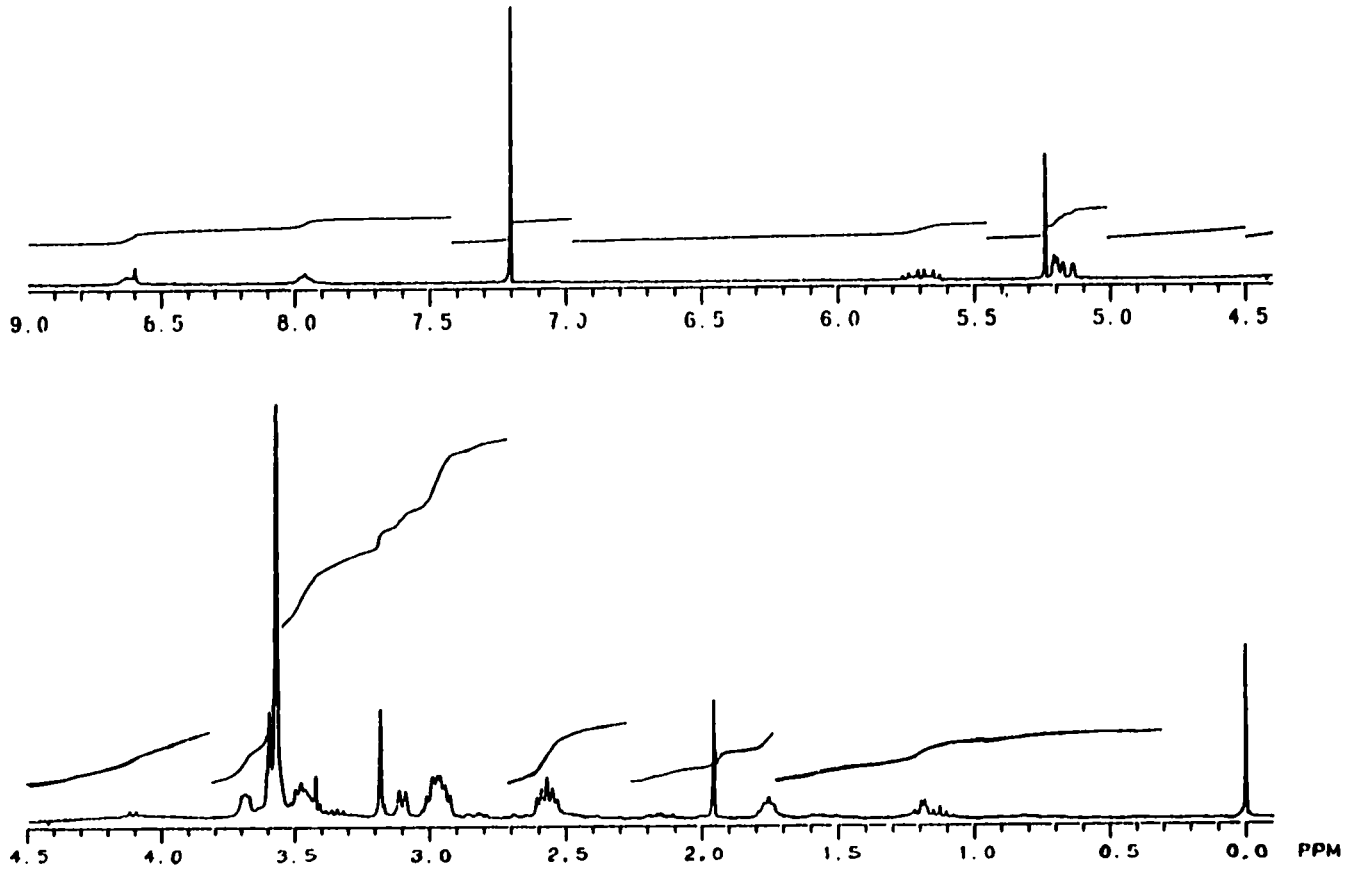
^{1}H NMR of diethyl-2(1-propanoyl-3-aza 18-crown-6-ether) malonate (B)



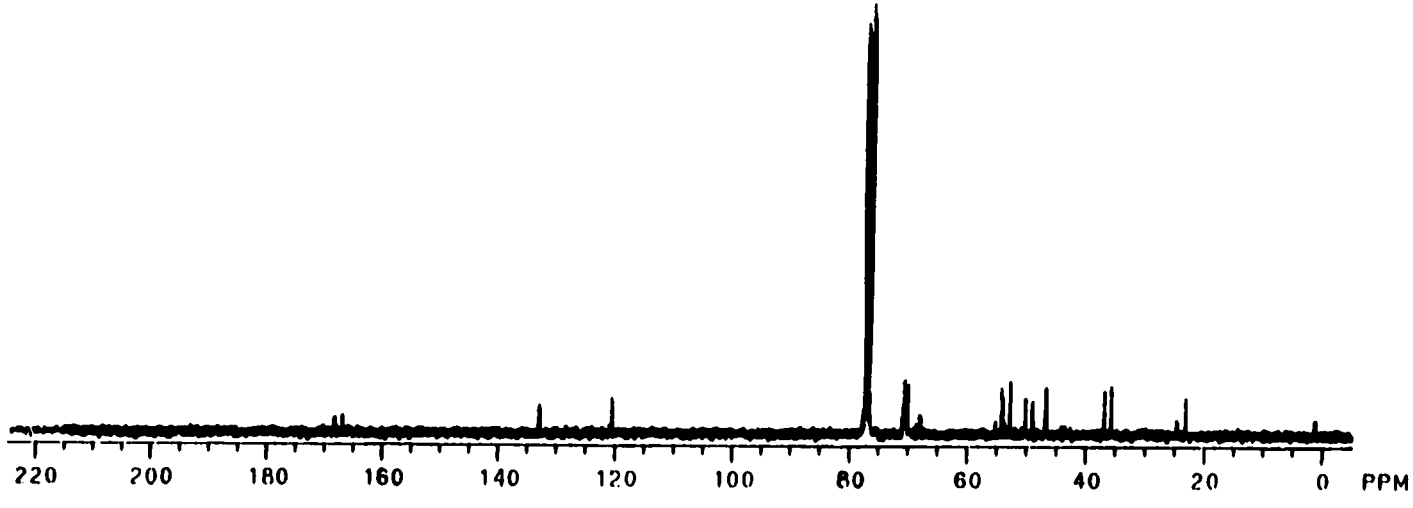
^{13}C NMR of diethyl-2(1-propanoyl-3-aza 18-crown-6-ether) malonate (B)



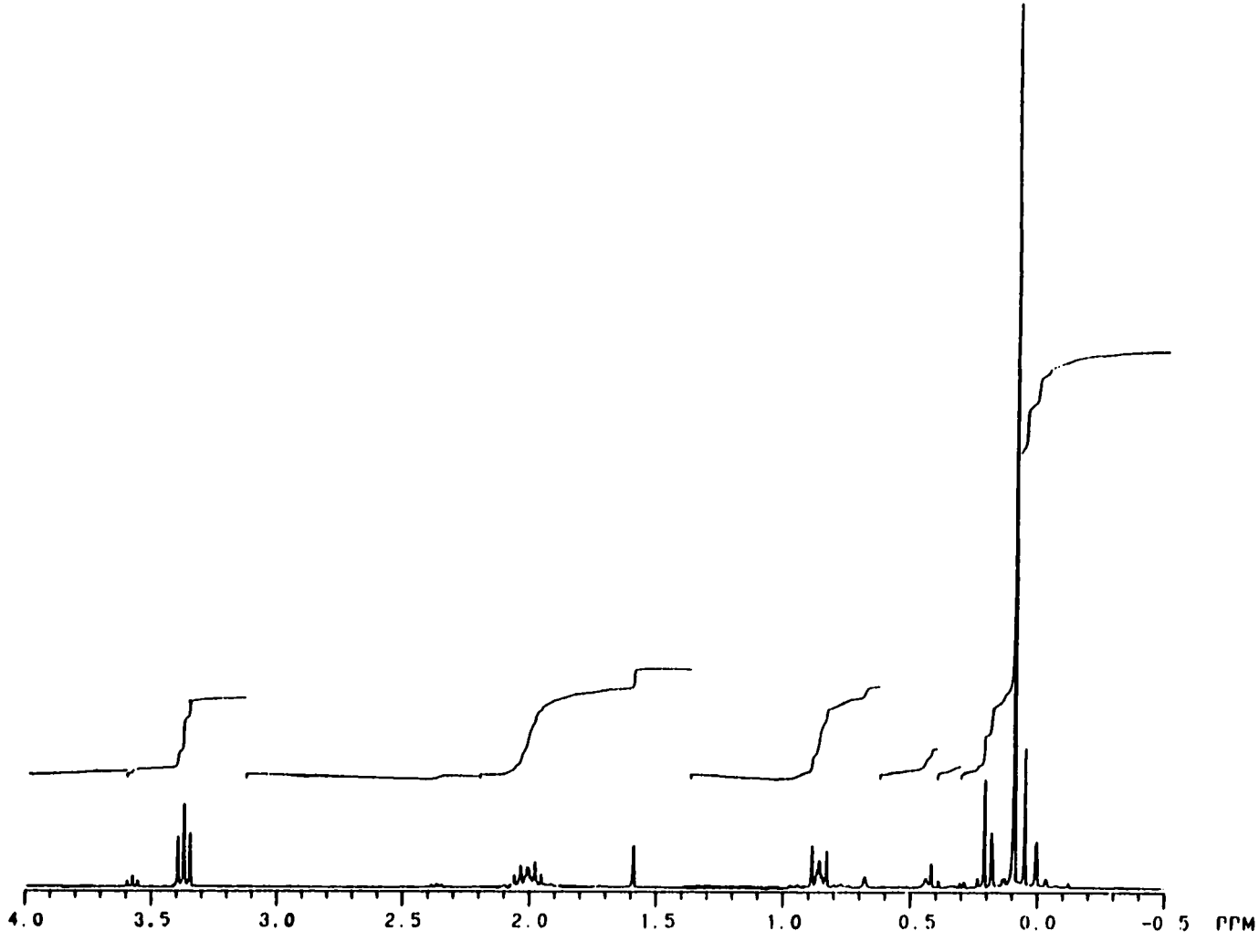
Mass spectrum of diethyl-2(1-propanoyl-3-aza 18-crown-6-ether) malonate (B)



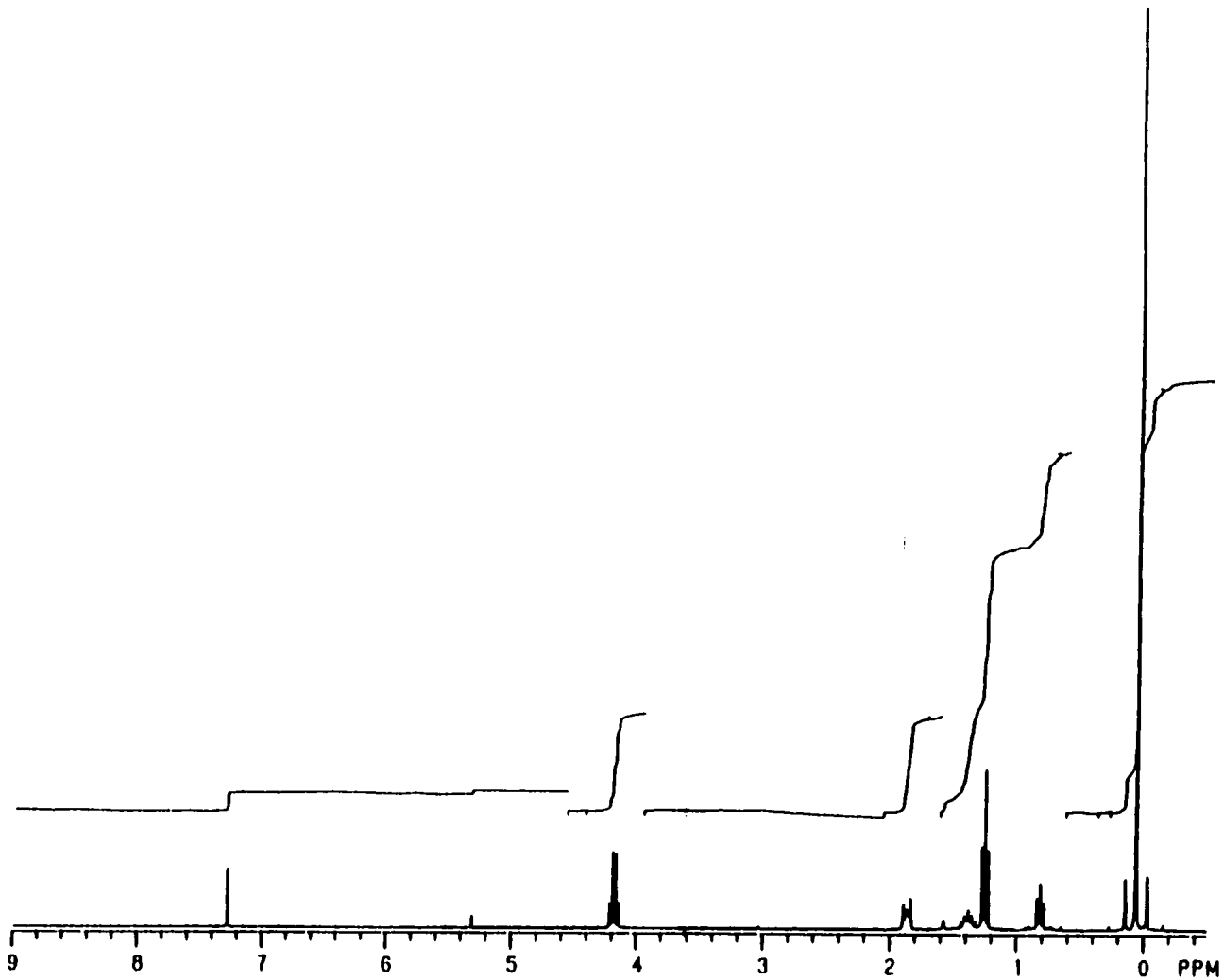
^{1}H NMR of fraction 3 in the attempted synthesis of 6(3-propanoyl-aza-18-c-6) 5,7-dioxo -1,4,8,11 tetraazacyclotetradecane (300 MHz, $CDCl_3$)



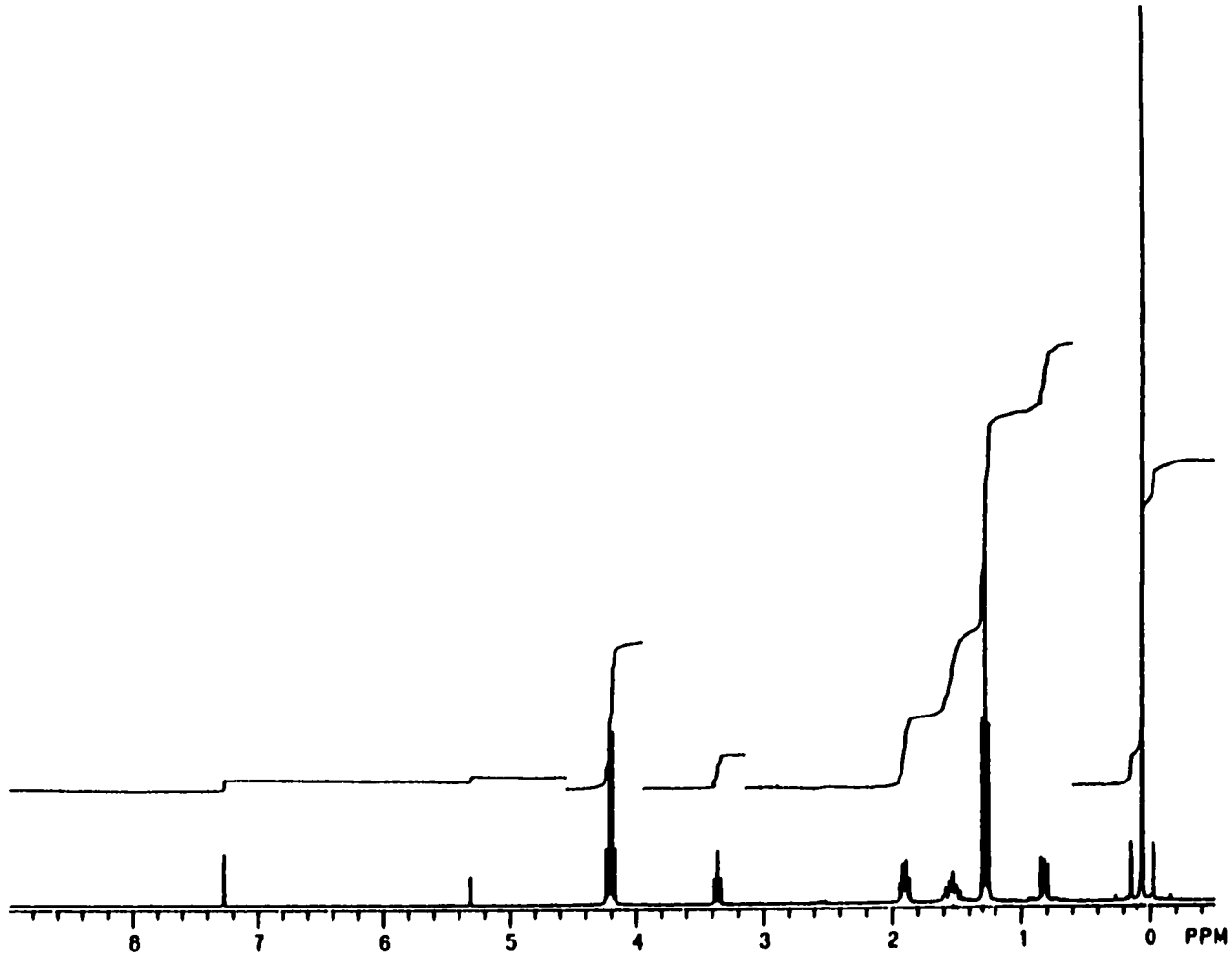
^{13}C NMR of fraction 3 in the attempted synthesis of 6(3-propanoyl-aza-18-c-6) 5,7-dioxo -1,4,8,11 tetraazacyclotetradecane (300 MHz, $CDCl_3$)



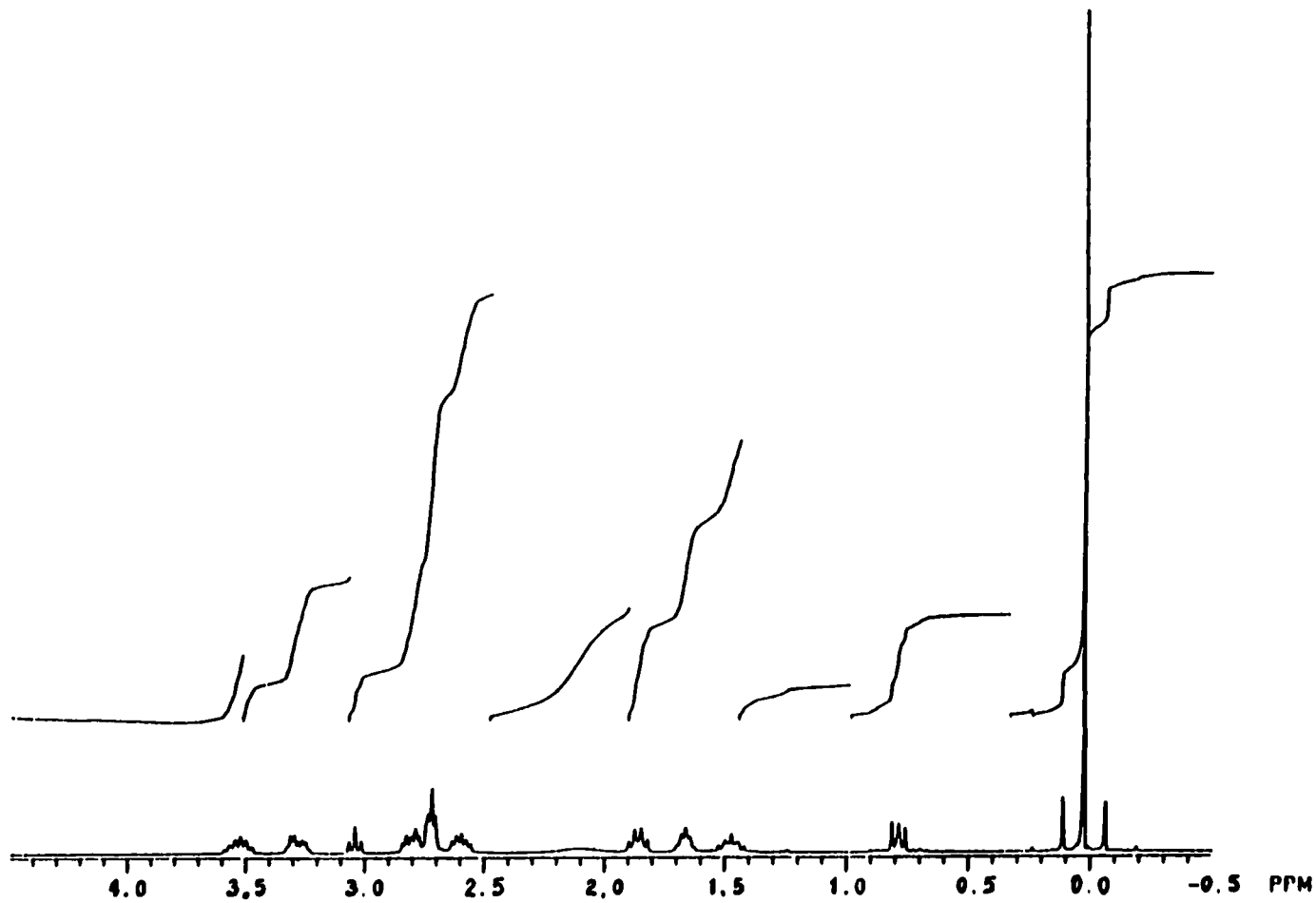
^{1}H NMR of 3-Bromo 1-trimethylstannyl propane (I) ($CDCl_3$, 300 MHz)



^{1}H NMR of diethyl 2-bis-(3-trimethylstannylpropyl) malonate ($CDCl_3$, 300 MHz)

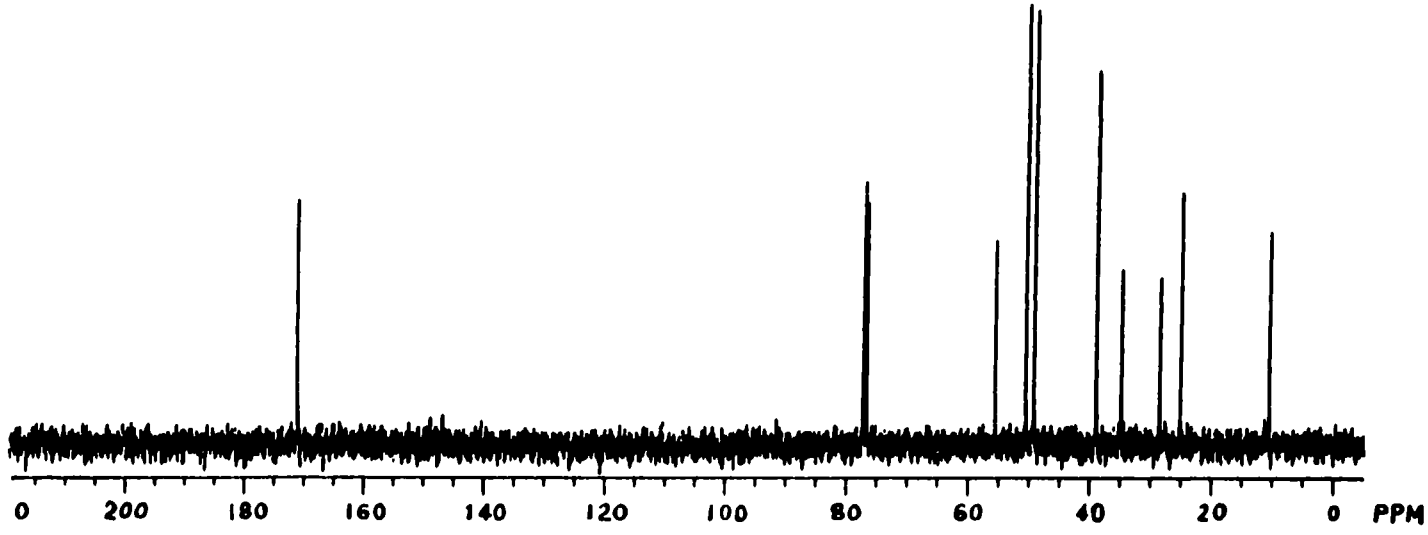


^{1}H NMR of diethyl 2-(3-trimethylstannylpropyl) malonate (II) ($CDCl_3$, 300 MHz)



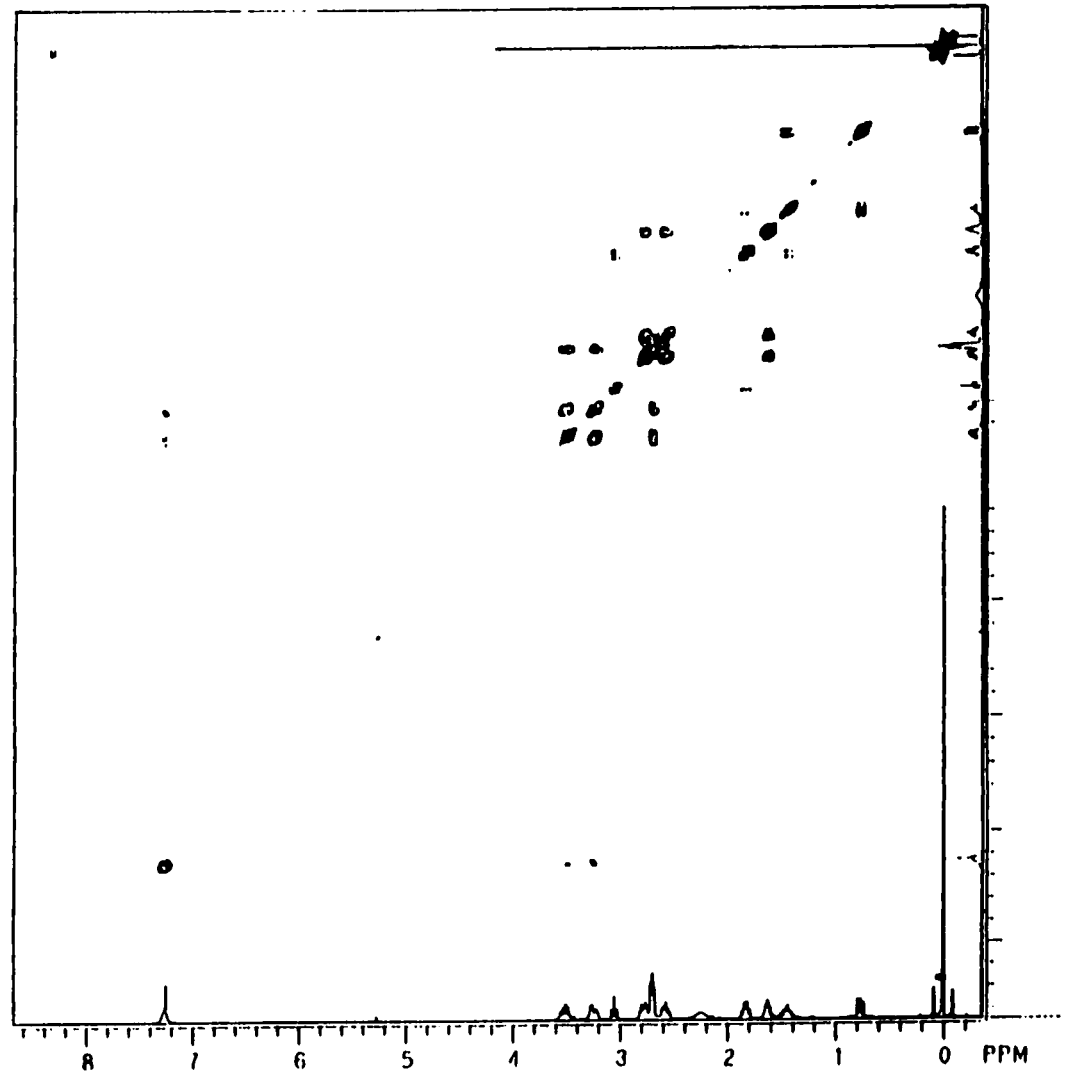
^{1}H NMR of 6(3-trimethylstannylpropyl)-5,7 dioxo-1,4,8,11 tetraazacyclotetradecane (III)

($CDCl_3$, 300 MHz)



^{13}C NMR of 6(3-trimethylstannylpropyl)-5,7 dioxo-1,4,8,11 tetraazacyclotetradecane (III)

($CDCl_3$, 300MHz)



2-D COSY ^{1}H NMR of 6(3-trimethylstannylpropyl)-5,7 dioxo-1,4,8,11 tetraazacyclotetradecane (III)

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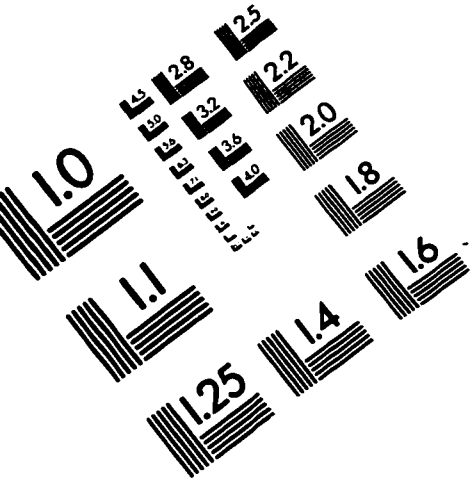
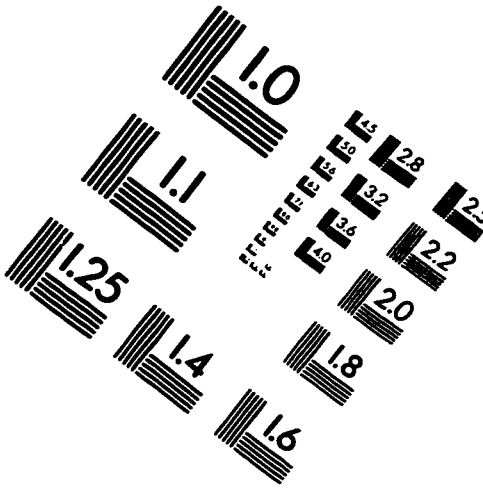
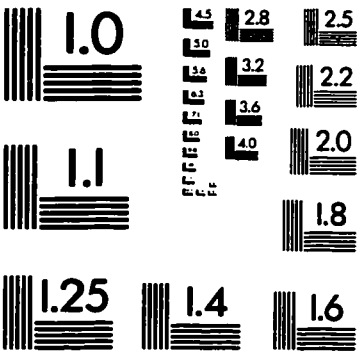
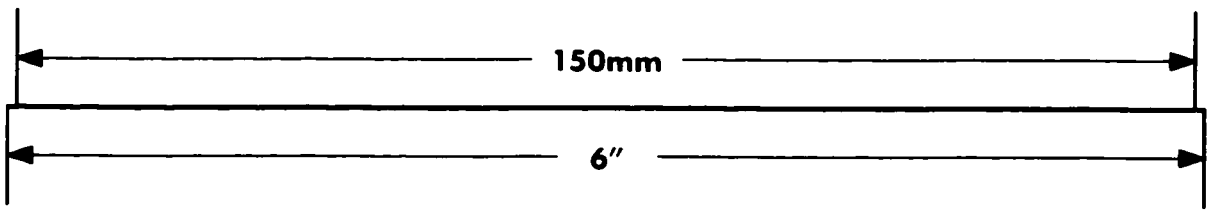
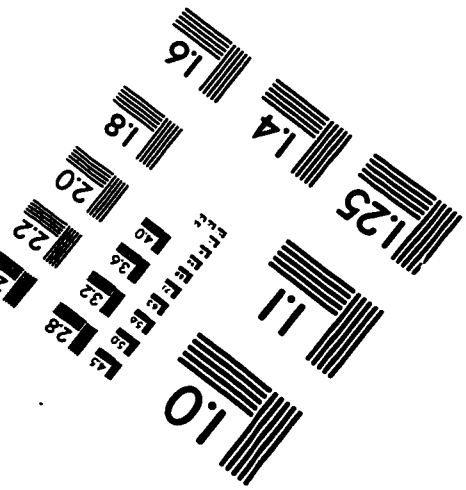
IMAGE EVALUATION TEST TARGET (QA-3)

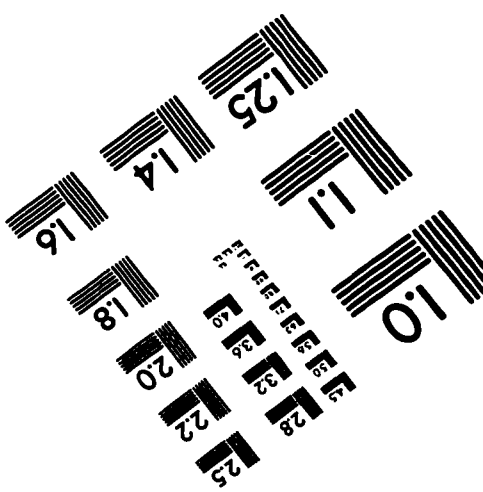












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